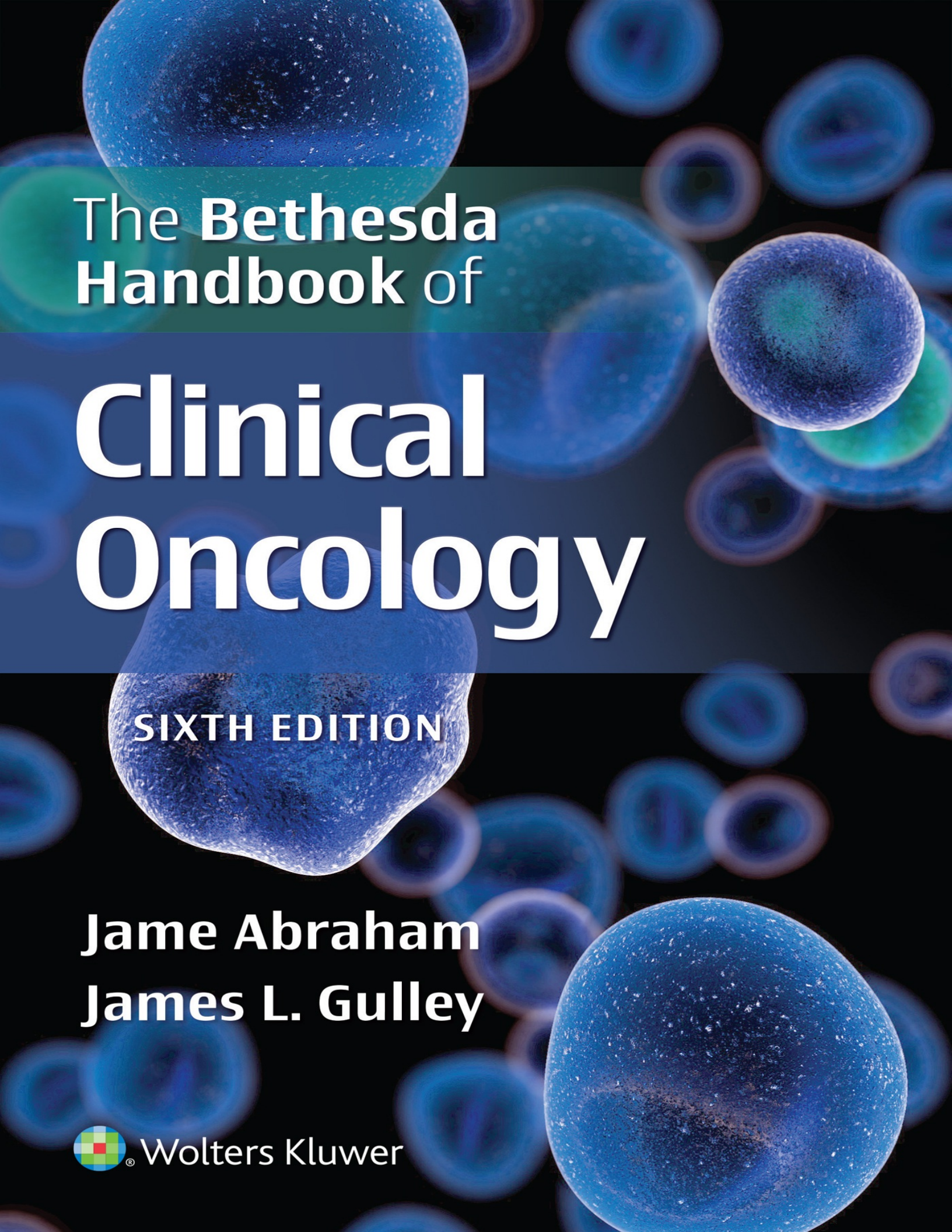
The Bethesda Handbook of
Clinical Oncology
SIXTH EDITION
Jame Abraham
James L. Gulley
Wolters Kluwer

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We dedicate this book to those lives that are touched by cancer and to their caregivers who spend endless hours taking care of them.

"May I never forget that the patient is a fellow creature in pain. May I never consider him merely a vessel of disease."
—Maimonides (*Twelfth-century philosopher and physician*)

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Preface

The Bethesda Handbook of Clinical Oncology is a clear, concise, and comprehensive reference book for the busy clinician to use in their daily patient encounters and for board review. The book has been compiled by clinicians who are working at the National Cancer Institute, National Institutes of Health, Cleveland Clinic, M.D. Anderson, Mayo Clinic as well as experts from other academic institutions. To limit the size of the book, less space is dedicated to etiology, pathophysiology, and epidemiology and greater emphasis is placed on practical clinical information. For easy accessibility to the pertinent information, long descriptions are avoided, and more tables, pictures, algorithms, and phrases are included.

The Bethesda Handbook of Clinical Oncology is not intended as a substitute for the many excellent oncology reference textbooks available that are essential for a more complete understanding of the pathophysiology and management of complicated oncology patients. We hope that the reader-friendly format with its comprehensive review of the management of each disease with treatment regimens, including dosing and schedule, makes this book unique and useful for hematology/oncologists, advanced practice providers, hematology and oncology fellows, residents, students, oncology nurses, and allied health professionals.

The landscape of oncology has changed substantially since we published the first edition of this book more than 21 years ago. For the sixth edition, we have updated all chapters and given importance to genomics, immune-oncology, and targeted therapies.

As always, we have attempted to capture the advances in the field and listened to the feedback from readers to improve this edition.

We hope that anyone needing a comprehensive review of oncology will find *The Bethesda Handbook of Clinical Oncology* to be an indispensable resource.

Jame Abraham and James L. Gulley

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Our sincere thanks to all our esteemed colleagues and friends who contributed to this book.

We thank our publisher, Wolters Kluwer, and dedicated staff members at the company who have been supporting this book for more than 21 years. We would like to thank Nicole Dernoski, Acquisitions Editor; Stacey Sebring, Senior Development Editor; and Priyanka Alagar, Editorial Coordinator.

We thank our wives, Shyla, and Trenise, for their encouragement and support in this endeavor.

Above all, we thank you for your support and feedback.

Contents

1

Head and Neck Cancer

Nikhil Joshi, Jessica Geiger, James R. Broughman, Brian Burkey

EPIDEMIOLOGY AND RISK FACTORS

The overwhelming majority of head and neck cancers are squamous cell cancers (HNSCC). HNSCC continues to increase in incidence with 890,000 new cases reported worldwide in 2018 along with 450,000 deaths. Head and neck cancer accounts for about 4% of all cancers in the United States. Most patients are older than 50 years, incidence increases with age, and the male-to-female ratio is 2:1 to 5:1. The age-adjusted incidence is higher among black men, and, stage-for-stage, survival among African Americans is lower overall than in whites. Death rates have been decreasing since at least 1975, with rates declining more rapidly in the past decade. Human papillomavirus (HPV)-related oropharyngeal cancer is a subset of head and neck cancers that is increasing in number and is associated with a better prognosis, in part due to better response to treatment. The most common sites of head and neck cancer in the United States are the oral cavity, pharynx, larynx, and hypopharynx. Nasal cavity, buccal, paranasal sinus cancers; salivary gland malignancies; and various sarcomas, lymphomas, and melanoma are less common. This chapter will limit its discussion to the more common tumors found in the head and neck region, namely squamous cell carcinomas and related histologies. Lymphomas, sarcomas,

cutaneous malignancies including melanoma, and thyroid gland cancer will not be discussed.

Common risk factors include tobacco (smoking tobacco and other forms) and alcohol intake. Heavy alcohol consumption increases the risk of developing squamous head and neck cancer 2- to 6-fold, whereas smoking increases the risk 5- to 25-fold, depending on gender, race, and the amount of smoking. Both factors together increase the risk 15- to 40-fold. Smokeless/chewing tobacco and snuff are associated with oral cavity cancers. Use of smokeless tobacco, or chewing betel nut with or without tobacco and slaked lime (common in many parts of Asia and some parts of Africa), is associated with premalignant lesions and oral squamous cancers. Chronic dental irritation due to ill-fitting dentures, sharp teeth, or inflammatory lesions like oral lichen planus also predispose to oral cavity cancers.

Multifocal mucosal abnormalities have been described in patients with head and neck cancer ("field cancerization"). There is a 2% to 6% risk per year for a second head and neck, lung, or esophageal cancer in patients with a history of a tobacco-related cancer in this area. Those who continue to smoke have the highest risk. Second primary cancers represent a major risk factor for death among survivors of an initial squamous carcinoma of the head and neck.

Epstein-Barr virus (EBV) has been detected in almost all nonkeratinizing and undifferentiated nasopharyngeal cancers in North America but less consistently in the keratinizing squamous nasopharyngeal cancers. HPV infection is associated with up to 70% of cancers of the oropharynx (base of tongue and tonsil), and some squamous nasopharyngeal cancers. The incidence of HPV-related oropharyngeal cancers is increasing in several countries, and HPV positivity is more common in cancers in nonsmokers. Disorders of DNA repair (eg, Fanconi anemia, dyskeratosis congenita) as well as organ transplantation with immunosuppression are also associated with increased risk of squamous head and neck cancer.

ANATOMY AND PATHOLOGY

A simplified depiction of extracranial head and neck anatomy is presented in Figure 1.1. The major regions and subsites of the upper aerodigestive tract are divided into the nose and paranasal sinuses; nasopharynx; oral cavity (lips, gingiva, buccal areas, floor of mouth, hard palate, and tongue anterior to the circumvallate papillae); oropharynx (soft palate, palatine tonsils, base of tongue and lingual tonsils, and pharyngeal wall between palate and vallecula); hypopharynx (posterior pharyngeal wall between vallecula and esophageal inlet, piriform sinuses, post cricoid space); and larynx (supraglottis, glottis, and subglottis). The supraglottic larynx comprises the epiglottis, aryepiglottic folds, false vocal cords, and ventricles. The glottis comprises the true vocal cords (including the underside of the cords, termed the infraglottis), anterior commissure and posterior commissure. The subglottis extends from the infraglottis to the bottom of the cricoid cartilage and then ends at the trachea.

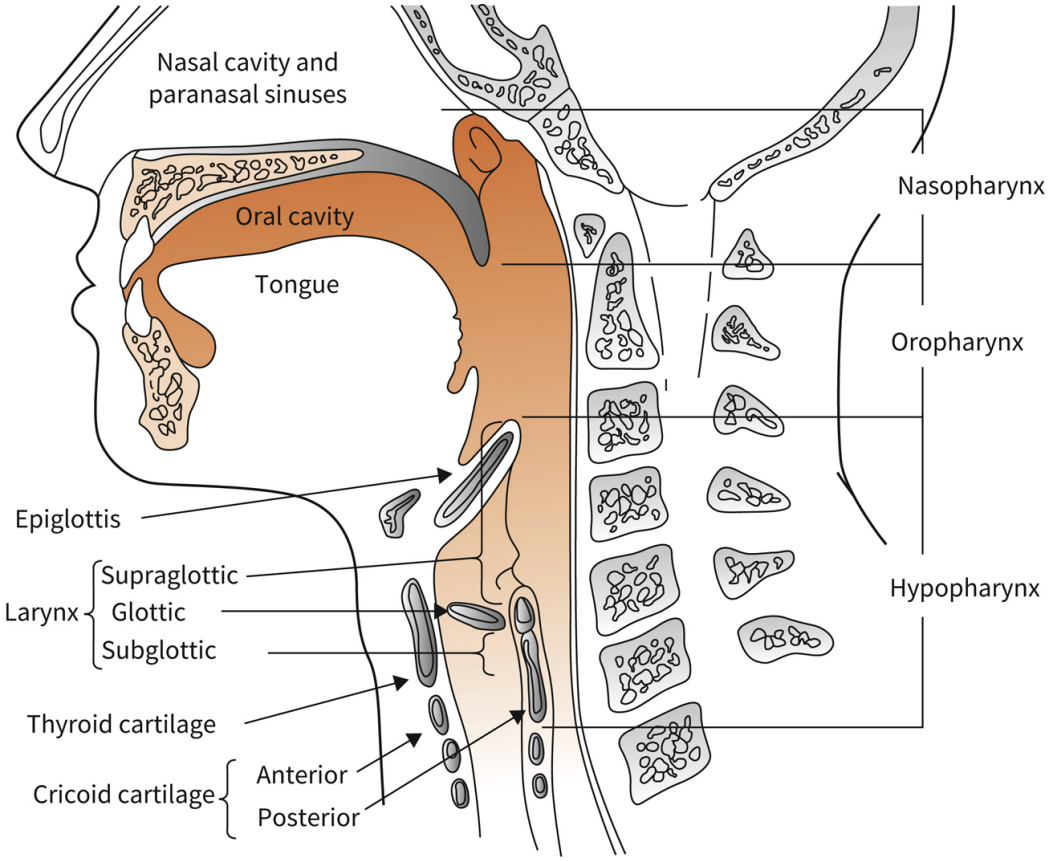

FIGURE 1.1 Sagittal section of the upper aerodigestive tract.(Adapted with permission from Oatis CA. *Kinesiology*: The Mechanics and Pathomechanics of Human Movement. Lippincott Williams & Wilkins; 2004.)

Knowledge of the lymphatic drainage of the neck assists in identification of the site of a primary tumor when a palpable lymph node is the initial presentation, and in staging metastatic spread, enabling the surgeon or radiation oncologist to plan appropriate treatment of both primary and neck disease. The patterns of lymphatic drainage divide the neck into several levels (Figure 1.2). Level I includes the submental and submandibular nodes, which are most often involved with lesions of the oral cavity, nasal cavity, or submandibular salivary gland. Level II (upper jugular lymph nodes) extends from the skull base to the hyoid bone and is frequently the site of metastatic presentation of naso- or oropharyngeal primaries. Level III (middle jugular lymph nodes between the hyoid bone and the lower border of the cricoid cartilage) and level IV (lower jugular lymph nodes between the cricoid cartilage and the clavicle) are most

often involved by metastases from the hypopharynx, larynx, or above. Level V is the posterior triangle including cervical nodes along cranial nerve XI, frequently involved along with level II sites in cancers of the naso- and oropharynx. Level VI is the anterior compartment from the hyoid bone to the suprasternal notch bounded on each side by the medial carotid sheath and is an important region for spread of laryngeal and thyroid carcinomas. The site of the superior mediastinum mostly portends distant metastasis except for thyroid cancers.

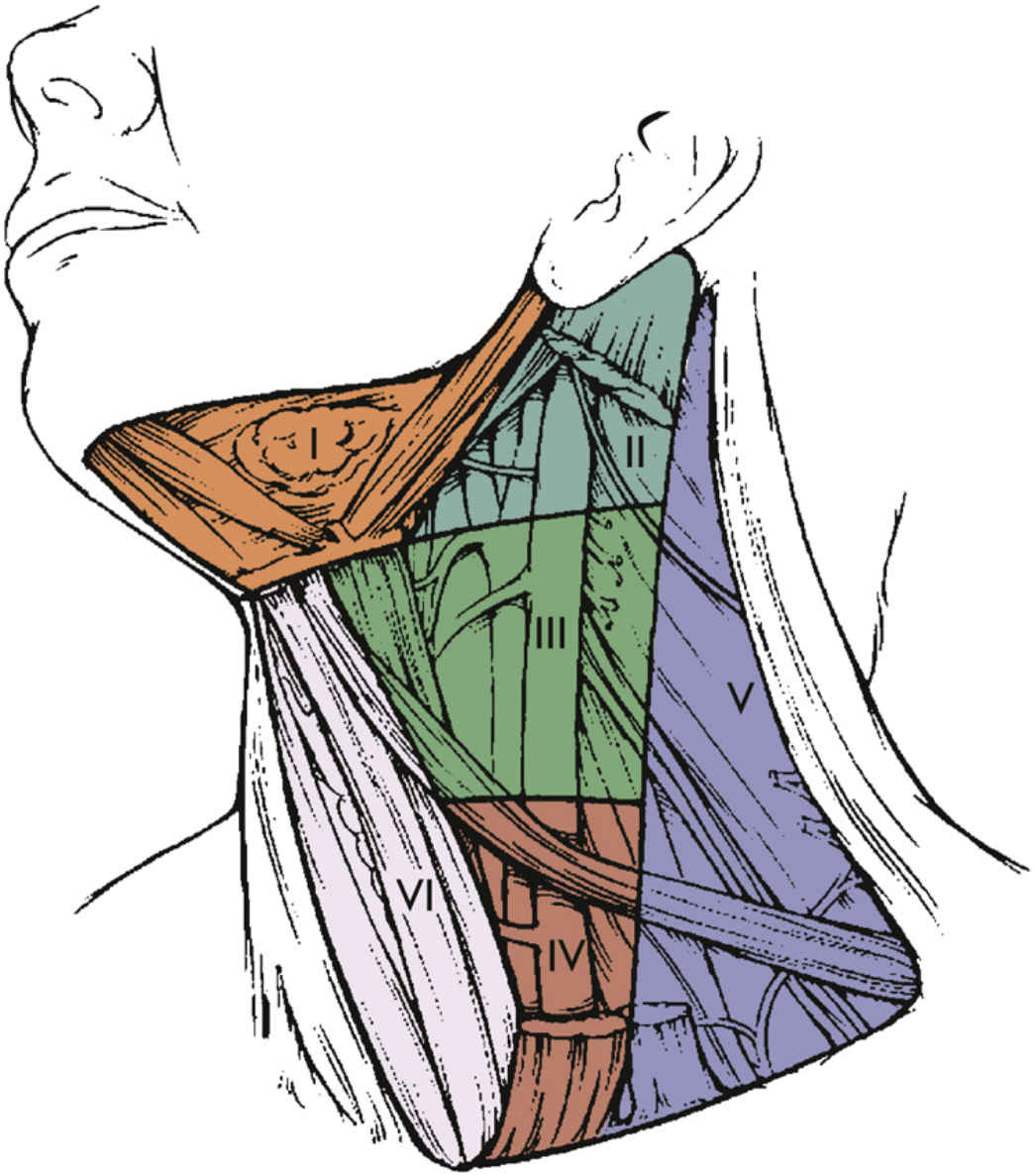

FIGURE 1.2 Diagram of the neck showing levels of lymph nodes.Level I, submandibular; level II, high jugular; level III, midjugular; level IV, low jugular; level V, posterior triangle; level VI, tracheoesophageal; level VII, superior mediastinal, is not shown.(From Robbins KT, Samant S, Ronen O. Neck dissection. In: Flint PW, Haughey BH, Lund VJ, et al, eds. *Cummings Otolaryngology Head and Neck Surgery*. 5th ed. Elsevier; 2010. Reprinted with permission of K. Thomas Robbins, MD.)

PRESENTATION, EVALUATION, DIAGNOSIS, AND STAGING

Signs and symptoms most often include pain and/or mass effects of tumor, involving adjacent structures, nerves, or regional lymph nodes (Table 1.1). This is common for oral cavity cancers. Adult patients with any of these symptoms for more than 2 weeks should be referred to an otolaryngologist. Delay in diagnosis is common due to patient delay, repeated courses of antibiotics for otitis media or sore throat, or lack of follow-up. A persistent lateralized symptom or firm cervical mass is highly suggestive of malignancy and may represent a squamous cell carcinoma (Figure 1.3). For nasopharyngeal and oropharyngeal cancers, a common presenting symptom is a neck mass, often in a node in the jugulodigastric area and/or the posterior triangle. In advanced lesions, cranial nerve abnormalities may be present. Symptoms like hoarseness, hemoptysis, and odynophagia or dysphagia may indicate a laryngeal or hypopharyngeal primary. Distant metastases are uncommon at presentation, but may occur with nasopharyngeal, oropharyngeal, and hypopharyngeal cancers. The most common sites of distant metastases are lung and bone; liver and central nervous system involvement is less common.

TABLE 1.1

Common Presenting Signs and Symptoms of Head and Neck Cancer

Painless neck mass
Odynophagia
Dysphagia
Hoarseness
Hemoptysis
Trismus
Otalgia
Otitis media
Loose teeth
Ill-fitting dentures

Cranial nerve deficits
Nonhealing oral ulcers
Nasal bleeding

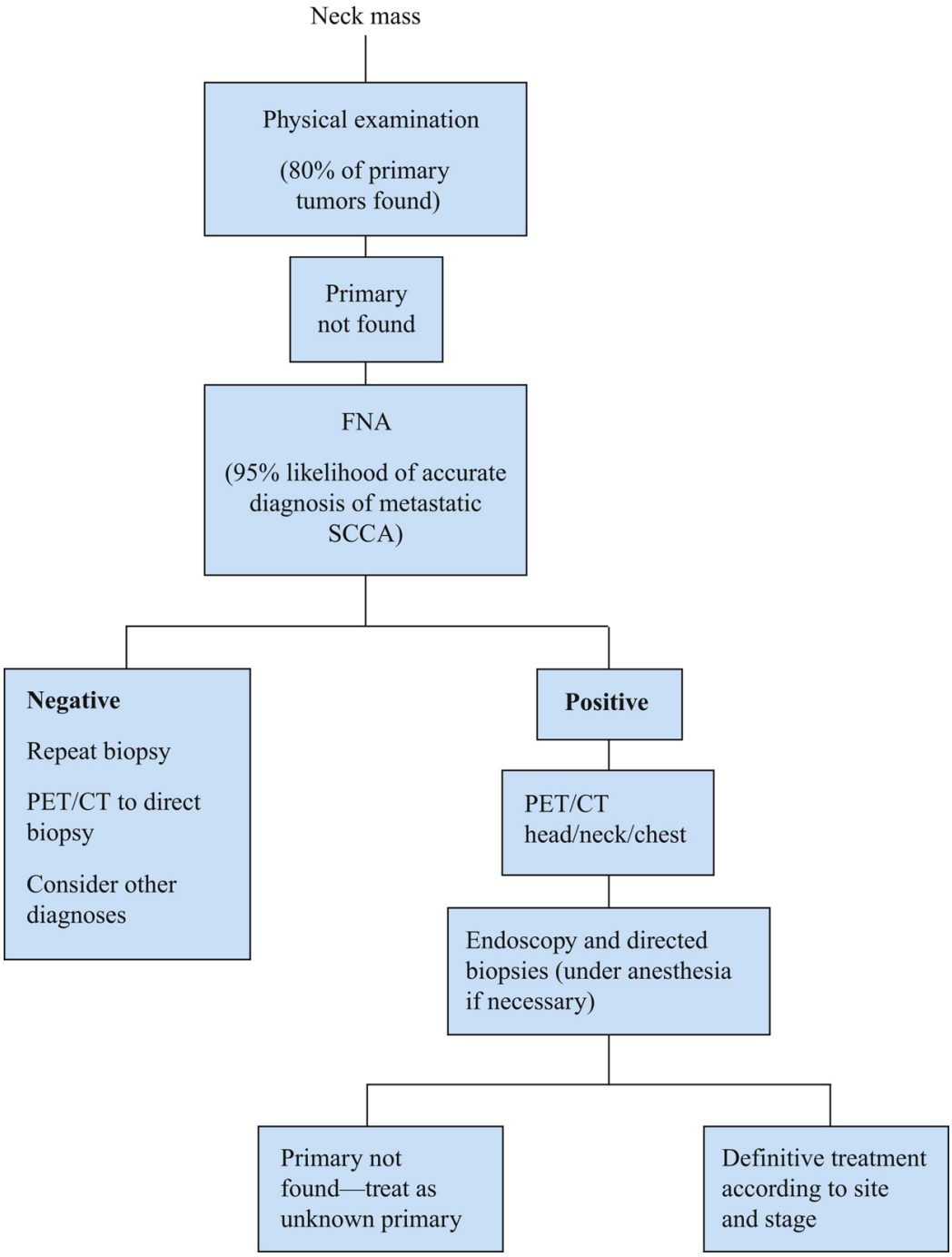

FIGURE 1.3 Evaluation of cervical adenopathy when a primary cancer of the head and neck is suspected.FNA, fine needle aspiration; SCCA, squamous cell carcinoma.

The history should include the following:

1. Signs and symptoms as listed in Table 1.1 and above

2. Tobacco exposure (pack-years; amount chewed; and duration of habit, current or former)
3. Alcohol exposure (number of drinks per day and duration of habit)
4. Other risk factors (chewing betel nut, chronic dental irritation, oral lichen planus, oral submucus fibrosis, leukoplakia, or erythroplakia)
5. Cancer history of patient and family; history of immunosuppression or congenital disorder
6. Thorough review of systems

The head and neck physical examination should include the following:

1. Careful inspection of the scalp, ears, nose, oral cavity, and oropharynx
2. Palpation of the neck including the parotid and thyroid glands and oral cavity, assessment of tongue mobility, determination of restrictions in the ability to open the mouth (trismus), and bimanual palpation of the base of the tongue and floor of the mouth
3. During examination of the nasal passages, nasopharynx, oropharynx, hypopharynx, and larynx, flexible endoscopes or mirrors as appropriate should be strongly considered for symptoms of hoarseness, sore throat, or enlarged lymph nodes not cured by a single course of antibiotics. When a neck mass with occult primary is the first presentation, the primary site can be located by clinical or flexible endoscopic examination in ~80% of cases
4. Special attention should be given to the examination of cranial nerves
5. Dedicated skin exam of the head and neck to evaluate for possible skin cancers

For abnormalities identified by history, physical examination, and/or endoscopy, the following evaluations should be performed.

Superficial cutaneous or oral mucosal lesions, with irregular shape, erythema, induration, ulceration, and/or friability (easy bleeding) of greater than 2-week duration warrant biopsy, as these frequently are early indicators of severe dysplasia, carcinoma in situ, or invasive malignant process. For findings or lesions involving the nose, nasopharynx, oropharynx, hypopharynx and larynx, or neck with unknown primary, computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast should first be performed to identify origin, extent, and potential vascularity of lesions. Surgical biopsy of a neck mass before endoscopy is generally not advisable if a squamous cell carcinoma is suspected. Open biopsy may complicate regional control although an open biopsy may provide additional information to that obtained from fine needle aspiration (FNA) or a core needle biopsy. A direct laryngoscopy is still necessary for staging and treatment planning. Tissue diagnosis obtained by FNA biopsy of the node has a sensitivity and specificity approaching 99%. However, a nondiagnostic FNA or negative flexible endoscopy does not rule out the presence of tumor. Positron emission tomography (PET) scans combined with CT (PET/CT) or MRI can often localize smaller or submucosal primaries of the naso- and oropharynx that present with level II or V cervical adenopathy. Intraoperative endoscopic biopsy is then done with a secure airway under anesthesia. Bilateral tonsillectomy will sometimes reveal the source of an occult cancer, especially for HPV+ cancers. Esophagoscopy and bronchoscopy may be indicated for symptoms such as dysphagia, hoarseness, cough, or to search for occult primary. Transoral robotic surgery (TORS) with removal of base of tongue lymphatic tissue can also be used to diagnose otherwise occult oropharyngeal cancers.

After a diagnosis of cancer is established, the patient should be staged using physical examination, endoscopic studies, and radiologic studies, which usually include CT scan and/or MRI of the primary tumor, neck, and chest. CT scan is considered the primary imaging study for evaluation of bone involvement, regional, mediastinal, and pulmonary metastasis. MRI may complement the

CT scan with greater resolution of soft tissue for primary tumor staging, and evaluation of skull base and intracranial involvement. PET/CT scans are being used more frequently to detect tumors or nodes that are not obvious on other scans and for monitoring disease recurrence in patients with advanced locoregional disease treated with concurrent chemotherapy and radiotherapy. PET/CT scanning is also indicated for staging patients with unknown primaries and for advanced head and neck cancers. Alternatively, a chest CT may also be done for patients with locally advanced disease because of the risk of metastasis or a second lung malignancy.

Specialized tests include tissue p16 immunostaining for oropharyngeal cancers, and tissue Epstein-Barr encoded RNA (EBER) and plasma EBV DNA copy number for nasopharyngeal carcinoma. Laboratory tests typically obtained prior to initiating therapy include complete blood counts, renal and liver function tests, serum calcium and magnesium (if platinum-based chemotherapy will be used), baseline thyroid function tests, and pregnancy testing in females of child-bearing age. Baseline and posttreatment EBV DNA levels are recommended in EBV-related nasopharyngeal cancers.

Dental evaluation should be performed and any necessary extractions should be carried out at least 2 weeks prior to any planned radiation. Baseline speech, swallow, and audiometry evaluation may be indicated depending on the primary site involved and the treatment anticipated. Smoking cessation and counseling should be included as part of a multidisciplinary treatment plan.

Clinical staging is based on physical and endoscopic examinations and imaging tests. The staging systems of the American Joint Committee for Cancer (AJCC) or the Union Internationale Contre le Cancer (UICC) (tumor, node, metastasis [TNM], stages I to IV) are used. The AJCC classification has further subdivided the most advanced disease stages into stage IVA (moderately advanced), stage IVB (very advanced), and stage IVC (distant metastatic).

The staging of primary tumors is different for each site within the head and neck, although some common themes exist. The *AJCC Cancer Staging Manual*, which entered its eighth edition in 2016, has made several significant changes in the previous T, N, and M staging definition.

Below is a summary of the pertinent changes for head and neck cancer staging detailed in the AJCC eighth edition:

1. Oral cavity cancer staging now reflects depth of invasion as an important factor
2. p16-positive and p16-negative oropharyngeal cancers have separate staging systems for their T and N stage
3. The nodal staging for p16-positive oropharyngeal cancer is more akin to nasopharynx nodal staging; the stage grouping is different from other head and neck subsites as well
4. The tumor staging for nasopharyngeal cancer has been revised to more accurately reflect anatomic involvement
5. The nodal staging for nasopharyngeal cancer has been revised to reflect involvement above and below the cricoid cartilage; stage IVC has been eliminated
6. Non–oropharyngeal/nasopharyngeal cancer nodal staging has been revised to reflect the importance of extranodal extension (ENE)—clinical and pathological nodal staging is different on the basis of node size and presence of ENE

Use of the eighth edition of the AJCC staging manual for staging began January 2018. Nevertheless, knowledge of the seventh edition and differences between the two editions is pertinent for treatment especially with respect to HPV-related oropharyngeal cancer.

PRINCIPLES OF DISEASE MANAGEMENT AND GOALS OF THERAPY

Since head and neck cancer involves multiple individual sites of disease, it is useful to think of disease management principles

according to the extent of disease. Certain common themes of management are evident as described below.

Early Disease (Usually Stages I, II, and Selected Stage III)

Early disease is optimally managed with single-modality treatment. This could include surgery or radiation. The objective is to achieve high rates of locoregional control and cure while limiting morbidity of treatment and preserving functional outcomes. Organ conservation is central to management of early cancers. The choice of modality is dependent on how best these goals are achieved along with availability of expertise and patient choice.

Locoregionally Advanced Disease (Usually Stages III, IVA, IVB)

This is a heterogeneous group of patients spanning the spectrum of resectable and unresectable disease. Two or more treatment modalities are often combined to achieve optimal disease control. The primary modality of treatment depends on the site of disease. For example, while primary surgery is considered standard for oral cavity cases, radiation with chemotherapy might be considered for laryngeal cancer cases. Nasopharyngeal cases are treated with definitive chemoradiation in most cases. Trimodality treatment is necessary on occasion. Examples include surgery followed by adjuvant chemoradiation for locally advanced oral cavity cancers or surgical salvage after definitive chemoradiation for oropharyngeal/laryngeal/hypopharyngeal cancers. While organ preservation remains an important goal for laryngeal and hypopharyngeal cancers, disease control is the primary objective. Multimodality therapy including surgical resection is often required to reduce the risk of locoregional recurrence and/or distant metastases and improve survival when organ preservation is not possible.

Recurrent/Metastatic Disease (Stage IVC)

Recurrent and metastatic diseases often have equally poor prognoses. Exceptions may include "oligometastatic" disease, second cancers after a long disease-free interval and metastatic disease from HPV-associated oropharyngeal cancers. These categories may have a long natural history and a comparatively long disease course with therapy. Long-term cures though uncommon are seen, especially with second cancers. This is discussed separately below. The large bulk of recurrent/metastatic cancers are best treated with palliative therapy. Palliative radiation, palliative systemic therapy, or a combination of the two is often used. Occasionally, surgery might be used to debulk the cancer and offer quick relief of symptoms. A tracheostomy may be necessary for airway compromise, and a feeding tube procedure may be required for alimentation. High-dose radiation with stereotactic techniques may be used to achieve durable palliation with lower toxicity rates. Early intervention with hospice care and palliative medicine are often appropriate during the course of disease.

PRINCIPLES OF SURGERY

Surgery plays a central role in the management of head and neck cancers. This includes both diagnosis and management of the primary and the neck in most cases. For the primary cancer, surgical goals include resection of the tumor with an adequate margin (usually 0.5 cm microscopic margin) while preserving function (for early cancers), often with an en-bloc resection. Piece-meal resection is usually not favored. Exceptions include resection of sinus tumors via an endoscopic approach as opposed to an open surgical approach. The extent of primary oncologic cancer surgery depends on the subsite involved and is variably described as such. For example, oral tongue cancer surgery can span the spectrum of wide local excision to hemiglossectomy to total glossectomy depending on the extent of disease. Early oropharyngeal and laryngeal cancers are amenable to transoral robotic resection or transoral microsurgery using laser. These modern procedures are far less morbid than open

procedures like a transcervical approach or mandibular swing done in the past. On occasion however, an open procedure might be necessary and the morbidity of this approach has to be balanced against the alternative of nonoperative therapy. While transoral procedures are becoming more popular, appropriate case selection is crucial to optimize oncologic and functional outcomes.

Management of the neck includes removal of all fibrofatty tissue in the neck levels at risk for disease spread for early disease or removal of all grossly involved nodes along with structures involved by the nodes for locoregionally advanced disease. The extent of neck dissection depends on the amount of neck disease. More comprehensive neck dissections are needed for more extensive neck disease. For example, a selective neck dissection or modified radical neck dissection (type III) is adequate for elective nodal dissection/limited neck disease, but a more extensive neck dissection might be needed if various nonlymphatic structures in the neck are involved by disease (radical, type I). A radical neck dissection might be needed in the salvage setting or if extensive neck disease is present which involves the sternocleidomastoid muscle and/or internal jugular vein. On occasion, multimodality surgical expertise is needed—cardiovascular surgery for reconstructing the carotid and subclavian artery or neurosurgery to assist with skull base resections or intracranial disease.

Surgical resection as described inevitably results in tissue deficits which can significantly affect healing, function, and/or cosmesis or both. This has led to a subspecialty of surgery dedicated to reconstructive surgery. This practice entails the use of various grafts (involving the transfer of skin, soft tissue, and/or bone) to reconstruct or cover tissue defects. This is especially of value for salvage of recurrent disease after initial surgery or definitive radiation/chemoradiation. A detailed discussion is beyond the scope of this chapter but suffice it to say that modern head and neck surgery requires the ability to perform elaborate reconstruction simultaneously with tumor extirpation.

PRINCIPLES OF RADIATION

Radiation, like surgery, also plays an important role in the treatment of HNSCC. It involves the precise delivery of radiation to tumor targets while sparing as much normal tissue as reasonably possible. The intent of radiation therapy may be definitive, adjuvant after surgery (for microscopic disease), or palliative. Definitive doses of radiation (70 Gy equivalent) are generally used to treat gross disease, while lower doses (60-66 Gy equivalent) are used to treat microscopic disease in the postoperative setting. Certain recurrent cases may be treated with definitive reirradiation or with postoperative reirradiation. Reirradiation may be delivered once daily or twice daily as hyperfractionated radiation. Occasionally, neoadjuvant radiation (with or without chemotherapy) may be used. In general, definitive doses of radiation are used for single-modality treatment or when combined with chemotherapy for nonsurgical treatment of locally advanced disease. The dose is usually 70 Gy delivered at 2 Gy per fraction over 7 weeks. This is considered standard fractionation in the United States. However, other definitive dose fractionation schedules have been used around the world. Examples include 60 Gy in 25 fractions over 5 weeks, 64 Gy in 40 fractions over 4 weeks, and 55 Gy in 20 fractions over 4 weeks. Altered fractionation schemes include acceleration (same dose given over shorter periods of time), hyperfractionation (2 or more smaller fractions per day, higher total dose), and hypofractionation (larger doses per fraction with a lower total dose). Hyperfractionation has shown an overall survival benefit and locoregional control benefit compared with standard fractionation. Toxicity profiles are different as well. In general, acute toxicities are worse, but late toxicities are similar with hyperfractionation compared with standard fractionation. Adjuvant radiation after surgery is used to reduce the risk of locoregional recurrence. This is combined with chemotherapy for high-risk disease (positive margins or extracapsular nodal disease) based on a combined analysis of two studies (RTOG 9501 and EORTC 22931). The doses of adjuvant radiation are 60 to 66 Gy in 2 Gy fractions given over 6 to 6.5 weeks. General indications for

adjuvant radiation include T3, T4 disease, close margins (<0.5 cm), positive margins, lymphovascular space invasion, perineural disease, and node-positive disease with or without extracapsular spread.

The technique of radiation delivery has improved dramatically over the years, and intensity-modulated radiation therapy (IMRT) is considered standard for HNSCC. This involves using multiple beams of radiation to target the disease with variable radiation beam intensity in order to optimally spare normal tissue. Many centers have graduated to volumetric modulated arc therapy (VMAT). This is a special form of IMRT using radiation arcs to generate more degrees of freedom and modulate the radiation intensity better. Moreover, this technique is now usually combined with image guidance (IGRT). This involves the use of daily imaging like cone-beam CT scanning while the patient is on the treatment machine to ensure precise and reproducible patient positioning, thereby reducing the amount of normal tissue in the radiation field.

Palliative radiation involves the delivery of a quick and limited volume of radiation often to the gross disease for rapid relief of symptoms. Different fractionation schemes include 20 Gy in 5 fractions, 30 Gy in 10 fractions, 8 Gy in 1 fraction, or 14 Gy in 4 fractions (2 fractions a day 6 hours apart). The response is often short lived but serves the goal of palliation for patients with limited life expectancy. Apart from HPV/EBV-positive disease involving the oropharynx or nasopharynx, HNSCC remains a locoregionally recurrent problem. Recognition of this pattern of recurrence combined with the short-lived response to conventional palliative radiation has led to the development of stereotactic body radiotherapy (SBRT). SBRT is a high-precision radiation delivery technique used to deliver a very high dose of radiation over a few treatments (usually five) in the recurrent/metastatic disease setting. This technique is associated with durable response rates with acceptable morbidity and is favored when life expectancy is more than 6 months.

Proton therapy is a special form of radiation which enables the deposition of dose in the target while sparing the structures beyond the target. It is most often used for pediatric tumors, skull base tumors, and tumors close to optic structures and spinal cord/brainstem, especially in the recurrent setting. There remain several challenges with proton therapy for HNSCC. Some of these are technique specific (range uncertainty, radiobiological effectiveness values near the end of range, need for intensity modulation, lack of image guidance, etc.). Perhaps, the most important challenge remains the cost of proton therapy which is several folds higher than standard photon therapy. More evidence for proton therapy in HNSCC is warranted before considering this therapy as a standard option, especially when compared with techniques like VMAT IGRT using photons. Lastly, all these sophisticated techniques have a long learning curve, and there is evidence of better outcomes for patients treated at high-volume centers.

PRINCIPLES OF SYSTEMIC THERAPY

The use of systemic therapy in head and neck cancer is based on the assumption that squamous cell malignancies of the head and neck share a common sensitivity to chemotherapy. Thus most clinical trials of systemic chemotherapy have included patients with multiple and varied disease subsites. As for most solid tumors, initial exploration of the role of systemic chemotherapy began with the use of these agents as palliation for patients with recurrent or metastatic cancers deemed incurable by other treatment modalities. Despite the fact that these patients were often heavily pretreated with surgery and radiation therapy, and often had a poor or suboptimal performance status, multiple single chemotherapeutic agents were found to have modest activity. Drugs such as methotrexate, bleomycin, fluorouracil, the platins (cisplatin and carboplatin), the taxanes (docetaxel and paclitaxel), and gemcitabine have all demonstrated modest efficacy as single agents, prompting

further study of their use in combination. The best studied of these combinations has been the fluorouracil and cisplatin regimen which has produced consistent responses in approximately one-third of patients with advanced disease. Other drug combinations have been similarly effective. Although these responses can have important palliative benefit, overall survival was not meaningfully impacted by this treatment.

The epidermal growth factor receptor inhibitors, including both the monoclonal antibodies like cetuximab, and the tyrosine kinase inhibitors like gefitinib, erlotinib, and afatinib, have resulted in very marginal response rates in recurrent disease patients progressing after conventional chemotherapy, although temporary disease stability has been frequently possible. When cetuximab was added to the fluorouracil and cisplatin (or carboplatin) combination, however, for the first time, a modest survival improvement was identified in the European EXTREME clinical trial reported in 2008.

Recent success using the immune checkpoint inhibitors in other diseases has led to their study in patients with recurrent head and neck cancer. Phase III data have now been generated demonstrating a survival benefit for the anti-PD-1 monoclonal antibodies when used after failure of first-line platinum-containing therapeutic regimens, and these drugs have now been approved for use in this setting. Pembrolizumab, as monotherapy or in combination with chemotherapy, is also approved in the frontline palliative setting, based on PD-L1 status. Although response rates are quite modest, the responses seen can be durable, and active study of these agents is ongoing in various treatment settings. Table 1.2 depicts selected systemic therapy regimens used for palliation.

TABLE 1.2

Selected Palliative Systemic Therapy Regimens for Metastatic Head and Neck Cancer

Regimens	Common Toxicities

Regimens	Common Toxicities
Cisplatin 100 mg/m^2 IV (or carboplatin AUC 5) on day 1 every 3 wk for 6 cycles plus 5-FU 1000 mg/m^2/d by continuous IV infusion on days 1-4 every 3 wk for 6 cycles plus pembrolizumab 200 mg IV every 3 wk	Nephrotoxicity, ototoxicity, myelosuppression, mucositis, diarrhea, hand-foot syndrome, and various immune-related toxicities
Pembrolizumab 200 mg IV every 3 wk or 400 mg IV every 6 wk	Immune-related toxicities
Nivolumab 240 mg IV every 2 wk or 480 mg IV every 4 wk	Immune-related toxicities
Cisplatin 100 mg/m^2 IV (or carboplatin AUC 5) on day 1 every 3 wk for 6 cycles plus 5-FU 1000 mg/m^2/d by continuous IV infusion on days 1-4 every 3 wk for 6 cycles plus cetuximab 400 mg/m^2 IV loading dose on day 1, then 250 mg/m^2 IV weekly (EXTREME regimen)	Nephrotoxicity, ototoxicity, myelosuppression, mucositis, diarrhea, hand-foot syndrome, allergic reaction, and acneiform rash, black box cardiac warning
Carboplatin AUC 6 IV on day 1 plus paclitaxel 175-200 mg/m^2 IV on day 1 every 3 wk	Neuropathy, myelosuppression, alopecia
Methotrexate 40 mg/m^2 IV weekly	Mucositis, myelosuppression
Docetaxel 30-40 mg/m^2 weekly	Neuropathy, alopecia, diarrhea
Cetuximab 250 mg/m^2 weekly or 500 mg/m^2 every 2 wk	Allergic reaction, electrolyte disturbances, acneiform rash, black box cardiac warning

The activity of systemic chemotherapy in poor performance status patients with advanced disease suggested that there might be better ways to utilize this treatment modality. As for other malignancies, the previously untreated patients given systemic chemotherapy experience a considerably higher response rate than that seen in patients with recurrent tumors. In head and neck cancer, the fluorouracil and cisplatin combination results in only a 30% response rate in the previously treated recurrent disease patient, but has been reported to produce response rates of up to 90% in the previously untreated. When patients continue to receive multiple course of chemotherapy, however, they invariably progress, and single-modality chemotherapy cannot be considered a curative treatment when given alone. The obvious suggestion instead, would be to exploit this biologic activity as part of definitive management, rather than limiting its use to the recurrent and metastatic disease setting. This has led to a number of multimodality treatment schedules.

The first approach considered was the use of induction chemotherapy. This is based on the high response rates in previously untreated patients and the hope that tumor shrinkage induced by chemotherapy might result in more successful definitive locoregional management. Multiple phase II clinical trials of induction chemotherapy were successfully completed, suggesting a high but transient response rate to systemic chemotherapy, with good tolerance of subsequent locoregional definitive management. Phase III trials, however, comparing induction followed by definitive radiation or surgery, to definitive treatment alone, were unsuccessful and failed to produce any meaningful survival improvement. As such, this treatment schedule has not been adopted.

The alternative strategy of adding systemic chemotherapy after definitive surgery and/or radiation has also been tested. Phase III trials of this approach have similarly failed to demonstrate an improvement in overall survival. It should be noted, however, that with both the induction and the adjuvant schedules the use of systemic chemotherapy was successful in reducing the risk of distant metastatic disease. The lack of impact on overall survival likely reflected the limited importance of distant metastases in disease natural history.

It is only when the chemotherapy is given concurrently with radiation that any benefit can be consistently identified. Concurrent treatment appears to be effective due to the ability of chemotherapy to potentiate the impact of radiation, coupled with its demonstrated success in reducing the risk of distant micrometastatic disease. The approach has several potential disadvantages however, including the additive toxicity from the concurrent use of two treatment modalities which then results in a tendency to compromise dose intensity of either radiation or chemotherapy. Nonetheless, phase III trials comparing concurrent chemotherapy and radiation with radiation alone have now reproducibly demonstrated a clear survival benefit for the concomitant regimens. The best studied of these concurrent regimens has employed high-dose single-agent cisplatin given every three weeks in conjunction with the radiation.

Alternative single-agent and multiagent concurrent chemoradiotherapy regimens have also proven successful, but are less well studied. Meta-analysis data from more than 17,000 patients and 93 clinical trials have confirmed the lack of a survival benefit from either induction or adjuvant chemotherapy, compared to a clear improvement in survival when chemotherapy is used concurrently. As a result, this treatment approach has become the standard of care in the definitive nonsurgical management of patients with locoregionally advanced disease. Table 1.3 includes induction and concurrent chemotherapy regimens used most often.

TABLE 1.3

Concurrent and Induction Therapy Systemic Agents in Head and Neck Cancer

Regimens	Common toxicities
Concurrent: Cisplatin 100 mg/m^2 IV every 21 days during radiation or cisplatin 40 mg/m^2 every week	Nephrotoxicity, severe nausea/delayed vomiting, dehydration, mucositis, ototoxicity, neuropathy, myelosuppression
Concurrent: Carboplatin 70 mg/m^2/d IV on days 1-4, 22-25, and 43-46 plus 5-FU 600 mg/m^2/d by continuous IV infusion on days 1-4, 22-25, and 43-46	Thrombocytopenia, mucositis, diarrhea, hand-foot syndrome, neuropathy
Concurrent: Cetuximab loading dose 400 mg/m^2 IV followed by 250 mg/m^2/wk IV	Acneiform rash, mucositis, allergic reaction
Induction: Docetaxel 75 mg/m^2 IV day 1, cisplatin 100 mg/m^2 IV day 1, 5-FU 1000 mg/m^2 per day (continuous 24-h infusion) for 4 days (day 1-4)	Nephrotoxicity, severe nausea/delayed vomiting, dehydration, mucositis, ototoxicity, neuropathy, myelosuppression, diarrhea
Induction: Cisplatin 80-100 mg/m^2 IV day 1, 5-FU 1000 mg/m^2 per day (continuous 24-h infusion) for 4-5 d	Nephrotoxicity, severe nausea/delayed vomiting, dehydration, mucositis, ototoxicity, neuropathy, myelosuppression, diarrhea

The monoclonal anti–epidermal growth factor receptor antibody cetuximab has also been studied in conjunction with radiation and compared to radiation therapy alone. Again, a survival benefit was demonstrated for the combination. This approach has thus become

another potential treatment option for the nonoperative management of locoregionally advanced disease.

The marked improvement in locoregional control achieved with concurrent chemoradiotherapy has, not surprisingly, been accompanied by an increase in the relative frequency of distant metastatic disease. Given the reproducible benefit of induction chemotherapy on the incidence of distant metastases, the suggestion has emerged that the use of induction chemotherapy followed by concurrent chemoradiotherapy, or "sequential treatment," might further improve treatment results. In addition, the incorporation of a taxane into the fluorouracil and cisplatin induction combination has proven successful in increasing the response rates after induction chemotherapy, suggesting additional potential benefit from a three-drug regimen in this sequential schedule. Although a theoretically attractive approach, this treatment paradigm is accompanied by an increase in treatment duration, an increase in treatment toxicity, and a significant increase in expense. To date, three phase III trials comparing concurrent chemoradiotherapy to sequential induction followed by concurrent chemoradiotherapy have been completed. None of these three trials have demonstrated a survival benefit for the sequential treatment, and all have resulted in increased toxicity. Thus the current standard of care for the nonoperative management of locoregionally advanced disease is the use of concurrent chemoradiotherapy, and the sequential treatment schedules have no defined role.

Many patients, however, will first undergo surgical resection, but are then found to have pathologic features suggesting a high risk of disease recurrence. The standard approach for these high-risk patients has been the use of postoperative adjuvant radiation. Two phase III cooperative group clinical trials from the RTOG and the EORTC have explored the role of postoperative radiation and concurrent high-dose cisplatin, compared to radiation alone in patients with high-risk features after surgical resection. These trials both reported a clear improvement in local disease control and disease-free survival in the concurrently treated patients. When an

unplanned subgroup analysis was conducted of pooled data from both trials, it appeared that this benefit was limited to those patients with extracapsular nodal spread or margin positivity. As such, the use of concurrent high-dose cisplatin with radiation was considered standard for this subgroup of postoperative patients. Recent prospective randomized studies comparing postoperative radiation and concurrent high-dose cisplatin with lower weekly cisplatin dosing have been reported. The Tata Memorial group study demonstrated better 2-year locoregional control in the high-dose arm compared with weekly cisplatin (73.1% vs 58.5%, HR 1.76, $P = .014$), though no statistical significance between progression free survival (PFS) and overall survival (OS). However, several limitations may have affected the study results, including use of cisplatin 30 mg/m^2 instead of the 40 mg/m^2 typically used in the United States. A more recent study, JCOG1008, was a multi-institutional study of postoperative chemoradiation therapy (CRT) comparing 3-weekly cisplatin with weekly cisplatin (40 mg/m^2) in high-risk patients. The study demonstrated statistically significant benefit in the weekly arm with respect to 3-year OS, local relapse-free survival rate, and improved toxicity profile over the 3-weekly dosing.

SPECIAL CONSIDERATIONS

Oral Cavity

The oral cavity includes the lip, anterior two-thirds of the tongue, floor of the mouth, buccal mucosa, gingiva, hard palate, and retromolar trigone. The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites are shown in Table 1.4.

TABLE 1.4

Head and Neck Cancer: Oral Cavity

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement
Lip	Risk factors are sun exposure and tobacco; 3600 new cases a year; 10-40 times more common in white men than in black men or women (black or white)	Exophytic mass or ulcerative lesion; more common in lower lip (92%); slow-growing tumors; pain and bleeding	5%-10% Midline tumors spread bilaterally Level I more common (submandibular and submental); upper lip lesions metastasize earlier: level I and also preauricular
Alveolar ridge and retromolar trigone	10% of all oral cancers; M:F, 4:1	Exophytic mass or infiltrating tumor, may invade bone; bleeding, pain exacerbated by chewing, loose teeth, and ill-fitting dentures	30% (70% if T4) Levels I and II more common
Floor of mouth	10%-15% of oral cancers, (occurrence 0.6/100,000); M:F, 3:1; median age, 60 y	Painful infiltrative lesions, may invade bone, muscles of floor of mouth and tongue	T1, 12%; T2, 30%; T3, 47%; and T4, 53% Levels I and II more common
Hard palate	0.4 cases/100,000 (5% of oral cavity); M:F, 8:1; 50% cases squamous, 50% salivary glands	Deeply infiltrating or superficially spreading pain	Less frequently: 6%-29%
Buccal mucosa	8% of oral cavity cancers in the United States; women > men	Exophytic more often, silent presentation; pain, bleeding, difficulty in chewing, trismus	10% at diagnosis

M:F, male-to-female ratio.

Early oral cavity cancers are treated with surgery alone. This usually involves a wide local excision of the primary with surgical management of the neck. Elective nodal dissection was considered standard except for very small, superficial primaries (T1 cancers less than 3-4 mm depth of invasion). Recently, a phase III study demonstrated the oncologic equivalence of sentinel node biopsy and neck dissection for T1-T2 oral cavity and oropharyngeal cancers. The sentinel node biopsy group had lower associated morbidity. Hence,

sentinel node biopsy represents a new alternative standard of care for this patient population. Small primaries of the oral cavity resected with a wide margin, without adverse pathological features and with negative nodes, may be followed without adjuvant management. An alternative approach to manage the primary is with definitive radiation, usually using brachytherapy. This approach remains dependent on local practice patterns and availability of expertise and is generally not a standard of care in the United States.

Locoregionally advanced cases including T2 oral tongue cancers with more than 5 mm depth of invasion are usually treated with wide local excision and neck dissection. Select cases may undergo sentinel node biopsy when/where appropriate. The extent of primary site excision depends on the size of the primary and its extent. For example, an oral tongue resection might range from a wide local excision to a near total or total glossectomy. Similarly, the extent of neck dissection varies by the extent of disease in the neck and the proximity of the tongue cancer to the midline (lesions near/crossing the midline may require bilateral dissection). A phase III trial of elective nodal dissection versus therapeutic nodal dissection at relapse for early stage lateralized oral squamous cell carcinoma has shown a survival advantage to elective nodal dissection. As mentioned previously, sentinel node biopsy has emerged as a new, alternative standard of care for these patients. When indicated, a selective neck dissection (levels I-IV) or modified radical neck dissection is done in most cases for node-negative necks and those with minimal neck disease. Patients with more extensive neck disease and salvage cases may require a more extensive surgery such as a radical neck dissection. Many cases require reconstruction with the help of a surgeon trained in head and neck reconstruction techniques. Definitive radiation or chemoradiation is an inferior alternative to initial surgical management of locally advanced oral cavity cancers and is not favored unless the patient is medically inoperable or unresectable.

Radiation plays an important role in the adjuvant management of locoregionally advanced oral cavity cancers and has been shown to improve locoregional control. Chemotherapy is generally added for positive margin or extracapsular extension of nodal disease. This approach has been shown to provide a locoregional control benefit over radiation alone. Several intermediate risk factors are recognized including close margins (<5 mm), lymphovascular space invasion, perineural invasion, T3/T4 disease, T2 oral cancer with >5 mm thickness of primary (AJCC seventh edition criteria), and node-positive disease without extracapsular extension. Adjuvant radiation with cetuximab is being explored in a phase III trial (RTOG 0920) to improve outcomes for intermediate-risk disease where surgery and radiation remain the current standard but locoregional control still remains far from optimal. Similarly, even with adjuvant chemoradiation after surgery for high-risk disease (extracapsular extension from a node, positive margin), locoregional control and overall survival remain poor. RTOG 0234 was a phase II study exploring the safety and efficacy of docetaxel and cetuximab to further intensify treatment for high-risk disease. Encouraging results from this study have resulted in the ongoing RTOG 1216 study comparing radiation with cisplatin to radiation with docetaxel or radiation with docetaxel and cetuximab for the management of high-risk cancers.

Oropharynx

The oropharynx includes the base of the tongue, vallecula, tonsils, posterior pharyngeal wall, and the soft palate. The epidemiology, natural history, common presenting symptoms, and risk of nodal involvement are shown in Table 1.5.

TABLE 1.5

Head and Neck Cancer: Oropharynx

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement
Base of tongue	4000 new cases annually in the United States; M:F ratio, 3-5:1. May be HPV-associated	Advanced at presentation (silent location, aggressive behavior); pain, dysphagia, weight loss, and otalgia (from cranial nerve involvement); neck mass is a frequent presentation	All stages: 70% (T1) to 80% (T4) Levels II and III more commonly involved
Tonsil, tonsillar pillar, and soft palate	Tobacco and alcohol; HPV common	Tonsillar fossa: more advanced at presentation: 75% stage III or IV, pain, dysphagia, weight loss, and neck mass Soft palate: more indolent, may present as erythroplakia	Tonsillar pillar T2, 38% Tonsillar fossa T2, 68% (55% present with N2 or N3 disease)
Posterior pharyngeal wall		Advanced at diagnosis (silent location); pain, bleeding, and weight loss; neck mass is common initial symptom	Clinically palpable nodes T1, 25% T2, 30% T3, 66% T4, 75% Bilateral involvement is common

Oropharyngeal cancers can be divided into two large prognostic groups by their etiology, namely HPV-induced or HPV-unrelated (usually tobacco/alcohol induced cancers), and the most recent AJCC staging system now recognizes these as two different diseases with separate staging systems. The overwhelming majority of oropharyngeal cancers are HPV positive in the western world. Positive immunohistochemistry for p16 is a surrogate marker for the presence of HPV. A large RTOG experience has validated the prognostic value of HPV and divided oropharyngeal cancers into low-, intermediate-, and high-risk groups. Data from the Princess Margaret Hospital in Canada have further categorized HPV-positive disease into low- and high-risk groups. Age and smoking have stood out as prognostic factors as well. Based on these data, it is clear the

HPV-positive disease has a far better prognosis than HPV-negative tumors. Currently, all oropharyngeal cancers are treated similarly regardless of their etiology. However, various treatment de-escalation and intensification strategies are being investigated based on etiology (HPV-related or HPV-unrelated disease) and risk grouping.

Early stage oropharyngeal cancers are usually managed with single-modality treatment, namely surgery or definitive radiation (T1/T2, N0/N1 AJCC seventh edition). Locoregional control and overall survival remain high for these stages. More locally advanced disease is traditionally managed with definitive chemoradiation or bioradiation (with cetuximab) with surgery reserved for salvage (especially for advanced neck disease). A select subset of patients can be managed with surgery followed by adjuvant treatment. Surgical options include transoral resection (less commonly open surgery) and appropriate neck dissection or sentinel node biopsy. Case selection is often tailored to achieve optimal functional outcomes and avoid multiple modalities of therapy thereby minimizing morbidity. For example, a T2N2bM0 (AJCC seventh edition), tonsil primary amenable to TORS, may undergo this procedure and neck dissection in the absence of overt clinical extracapsular extension of disease in the nodes thereby avoiding the addition of concurrent chemotherapy with adjuvant radiation.

Since the prognosis for HPV-related disease is better than HPV-unrelated disease, various treatment de-escalation approaches have been studied or are under active study. RTOG 1016 was a randomized phase III noninferiority study exploring the combination of radiation and cetuximab to radiation and cisplatin for locally advanced HPV-related oropharyngeal cancer. The radiation and cetuximab arm showed inferior overall survival and PFS compared to the standard arm along with similar toxicity. Similar results were noted in the De-ESCALaTE HPV study for HPV-related low-risk disease underscoring the value of carefully conducted randomized trials for treatment de-escalation. NRG Oncology HN002 was a randomized phase II trial studying a more

favorable HPV-related patient population with ≤10 pack-years of smoking. This study identified 60 Gy of IMRT over 6 weeks with concurrent weekly cisplatin as a favorable de-escalation strategy that met prespecified endpoints of survival and swallowing function. This arm will be tested with the standard of care in a larger phase III study. Similarly, ECOG 3311 is a study exploring the role of TORS and neck dissection to de-escalate adjuvant treatment. While several other treatment de-escalation studies have been conducted or are underway, it must be emphasized that the current treatment of oropharyngeal cancer does not differ by HPV status outside of a clinical trial.

High-risk HPV-positive oropharyngeal cancer (T4, N2c-N3 disease, tobacco use) is still associated with a relatively high locoregional recurrence and distant failure rate. Therefore, this group may not benefit from treatment de-escalation (particularly elimination of systemic therapy), and strategies to improve locoregional and systemic control are warranted. High-risk HPV-negative cancer (T3, T4, N2c-N3 disease) is associated with equally poor distant failure. Locoregional control is also inferior with about 40% failure at 3 years. Fortunately, this group of patients is becoming less common. Aggressive therapy is warranted for these patients and usually takes the form of definitive chemoradiation followed by surgical salvage as needed. Consolidation immunotherapy approaches are also being studied in an effort to improve outcomes for this patient population.

Larynx

Laryngeal cancers can be supraglottic, glottic, and/or subglottic. The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites of the larynx are shown in Table 1.6.

TABLE 1.6

Head and Neck Cancer: Larynx

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement
Supraglottis	35% of laryngeal cancers	Most arise in epiglottis; early lymph node involvement due to extensive lymphatic drainage; two-thirds of patients have nodal metastases at diagnosis	Overall rate: T1, 63%; T2, 70%; T3, 79%; T4, 73% Levels II, III, and IV more common
Glottis	Most common laryngeal cancer	Most favorable prognosis; late lymph node involvement; usually well differentiated, but with infiltrative growth pattern; hoarseness is an early symptom; 70% have localized disease at diagnosis	Sparse lymphatic drainage, early lesions rarely metastasize to lymph nodes. Clinically positive: T1, T2 Levels II, III, and IV more common T3, T4, 20%-25%
Subglottis	Rare, 1%-8% of laryngeal cancers	Poorly differentiated, infiltrative growth pattern unrestricted by tissue barriers; rarely causes hoarseness, may cause dyspnea from airway involvement; two-thirds of patients have metastatic disease at presentation	20%-30% overall Pretracheal and paratracheal nodes more commonly involved

M:F, male-to-female ratio.

Laryngeal cancer mainly comprises cancers of the glottis and supraglottis and less commonly of the subglottis. This distinction is important considering the glottis is devoid of lymphatics while the supraglottis and subglottis are rich in lymphatics.

Early T1 glottic cancers can be managed with voice-conserving transoral laryngeal microsurgery. The local control with this technique is excellent often with superior voice quality. In general, superficial lesions affecting one vocal cord and not extending to the anterior commissure are best treated with this technique. Local recurrences can be managed with further surgery so long as they are superficial. Deeply invasive lesions require more extensive surgery. While these lesions are technically resectable, more extensive

surgery or multiple surgeries can lead to deterioration in the voice quality. Such procedures are best avoided.

Definitive radiation is considered an alternative for early glottic cancers, especially when the lesion is more extensive and not suitable for microsurgical excision. Voice quality is often superior with radiation but depends on the baseline voice quality. Early glottic cancers can be treated with definitive radiation with excellent outcomes. The radiation field is usually a small laryngeal parallel-opposed field. Mild hypofractionation to 2.25 Gy has shown improved local control versus 2 Gy fractions.

T1 cancers of the supraglottis can be treated with transoral or transcervical (open) voice preserving surgery. An open or endoscopic supraglottic laryngectomy is often done, and some form of bilateral neck management is usually advocated given the high risk of lymph node spread. Definitive radiation is an alternative management option and usually includes both necks in the treatment field.

T2 tumors of the glottis and supraglottis can be managed with either surgery or definitive radiation. Various forms of voice preserving laryngectomy procedures are utilized based on the extent of the tumor. Some of these options include a supraglottic laryngectomy (open or endoscopic), supracricoid laryngectomy, and a vertical partial laryngectomy. Bilateral neck dissections are also advised for supraglottic disease. Alternatively, the primary and both necks can be treated with definitive radiation. The dose is usually slightly higher than for T1 tumors. Though not a part of formal AJCC staging, T2 glottic cancers have been divided into T2a and T2b based on true vocal cord mobility restriction. T2b glottic cancers have a worse outcome with standard dose radiation alone. It is believed that these cases represent early paraglottic space involvement, and these may require more intensive treatment. Hyperfractionation and chemoradiation are some strategies utilized to achieve better local control.

The management of T3N0M0 laryngeal cancer is controversial. In certain cases, a voice preserving surgical approach may be warranted. A fixed cord is usually a contraindication for such conservative procedures. If no adverse postoperative pathological factors are identified, the patient may be observed without further adjuvant treatment. Total laryngectomy is usually avoided but remains an oncologically acceptable option. Definitive chemoradiation remains an alternative voice preserving treatment strategy, with similar oncologic outcomes, although salvage surgery may be needed.

The management of locally advanced laryngeal cancer takes into account the baseline function of the larynx, baseline swallowing function, and disease extent. The standard surgical procedure remains a total laryngectomy with bilateral node dissection. This may be followed by adjuvant radiation or chemoradiation based on the pathological risk factors. This surgical management approach is best used for patients with severely compromised laryngeal and/or swallowing function. Select cases might undergo a voice-preserving surgery for the primary with neck dissections followed by adjuvant treatment as indicated. Perioperative speech rehabilitation is critically important for patients with advanced laryngeal cancer who are undergoing total laryngectomy. Phonation options include tracheoesophageal puncture at the time of total laryngectomy, esophageal speech, or a mechanical electrolarynx. Most patients can obtain satisfactory communication through one of these techniques.

Nonetheless, because of the significant resulting functional compromise, a total laryngectomy is not a surgical procedure that is readily embraced by patients. Larynx-preserving, nonoperative approaches have emerged as reasonable options and are most appropriate for patients without significant preexisting laryngeal and/or swallowing dysfunction. The nonoperative management of locally advanced laryngeal cancer with radiation/chemoradiation has evolved in a systematic fashion. The VA larynx study compared induction chemotherapy with cisplatin/5-FU followed by radiation with total laryngectomy followed by radiation for locally advanced

laryngeal cancers. The rate of larynx preservation was 64% and overall survival was not compromised. The RTOG 91-11 study compared induction chemotherapy followed by radiation to either definitive concurrent chemoradiation or to radiation alone. Large-volume T4 lesions (with destruction of larynx or massive extension of supraglottic laryngeal cancer to the base of tongue) were excluded as these are felt to be best treated with a primary surgical approach. The larynx preservation rate at 10 years was 82% for the concurrent chemoradiation arm, and this approach has become a treatment standard in North America. Although the overall survival was statistically similar between all three treatment arms, likely reflecting the success of salvage surgery, a concerning trend toward an inferior survival was noted in the concurrent arm for reasons that are not entirely clear. As a result, induction chemotherapy followed by radiation, or even radiation alone, remains an acceptable treatment standard despite the reduced likelihood of larynx preservation.

Hypopharynx

The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites of the hypopharynx are shown in Table 1.7.

TABLE 1.7

Head and Neck Cancer: Hypopharynx, Nasal Cavity, Paranasal Sinuses, and Nasopharynx

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement
Hypopharynx	2500 new cases yearly in the United States; etiology: tobacco, alcohol, and nutritional abnormalities	Aggressive, diffuse local spread, early lymph node involvement; occult metastases to thyroid and paratracheal node chain; pain, neck stiffness (retropharyngeal nodes), otalgia (cranial nerve X), irritation, and mucus retention 50% present as neck mass; high risk of distant metastases	Abundant lymphatic drainage Up to 60% have clinically positive lymph nodes at diagnosis

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement
Nasal cavity and paranasal sinuses	Rare, 0.75/100,000 occurrence in the United States Nasal cavity and maxillary sinus, four-fifths of all cases M:F, 2:1 Increased risk with exposure to furniture, shoe, textile industries; nickel, chromium, mustard gas, isopropyl alcohol, and radium	Nonhealing ulcer, occasional bleeding, unilateral nasal obstruction, dental pain, loose teeth, ill-fitting dentures, trismus, diplopia, proptosis, epiphora, anosmia, and headache, depending on site of invasion Usually advanced at presentation	10%-20% clinically positive nodes Levels I and II more common
Nasopharynx	Rare (1/100,000) except in North Africa, Southeast Asia, and China, far northern hemisphere Associated with EBV, diet, genetic factors	Most common initial presentation: neck mass Other presentations: otitis media, nasal obstruction, tinnitus, pain, and cranial nerve involvement	Clinically positive: WHO I, 60% WHO II and III, 80%-90%

M:F, male-to-female ratio; EBV, Epstein-Barr virus.

The large majority of hypopharyngeal cancers present at an advanced stage. The hypopharynx has a rich lymphatic network, and nodal metastases are common at presentation. The retropharyngeal nodes may be involved as well. Early stage primary cancers may be addressed with transoral or open voice-conserving procedures with neck dissections as indicated. Adjuvant therapy is administered as indicated by the pathology findings.

The standard surgical approach for locally advanced hypopharyngeal cancer is a total laryngectomy with a partial pharyngectomy and bilateral node dissections. Microvascular free flap reconstruction of the surgical defect is common in the modern era. Adjuvant treatment is based on the adverse factors noted on

pathology and usually includes adjuvant radiation. Similar to the trials conducted in laryngeal cancer, voice-conserving nonoperative treatment has been studied for hypopharygeal cancers as well. The EORTC 24891 study compared induction cisplatin/5-FU followed by radiation versus surgery followed by radiation. Larynx preservation at 5 years was 22% (in surviving patients). Overall survival was similar in both arms. Several recent retrospective institutional series have shown high larynx preservation rates (around 90% at 3 years) with better overall survival (around 50% at 3 years) with modern radiation/chemoradiation techniques. Overall, similar to laryngeal cancer, patients with significant laryngeal/swallowing dysfunction are best treated with initial surgery and adjuvant therapy. Patients with retained laryngeal and swallowing function may be best served by definitive nonoperative chemoradiation. General medical fitness for either approach is of paramount importance since these patients are often medically compromised.

Nasopharynx

The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for nasopharyngeal cancer are shown in Table 1.7.

Nasopharyngeal cancers span a spectrum from more endemic EBV-associated undifferentiated carcinoma (WHO type III) to keratinizing squamous cell carcinoma (WHO type I). A p16-positive, EBV-negative subset has also been identified. The nasopharynx is very rich in lymphatics, and nodal metastases are commonly found with nasopharyngeal cancer. The anatomy of the nasopharynx generally precludes a primary surgical approach especially since both necks are at risk from disease spread. As such, radiation plays a major role in the management of this cancer. Early, node-negative primaries of the nasopharynx are treated with radiation alone. This includes the primary and both necks. Appropriate elective skull base coverage is necessary. Locally advanced nasopharyngeal cancers are often treated with definitive chemoradiation followed by three cycles of adjuvant chemotherapy, based on the INT 0099 study which

demonstrated a large survival benefit with concurrent and adjuvant chemotherapy versus radiation alone. Despite several criticisms to this approach and the demographic differences noted with nasopharyngeal squamous cell cancers in the west versus the east, this approach remains standard in the United States. More recently, two large phase III trials comparing induction chemotherapy followed by concurrent chemoradiation versus chemoradiation alone were reported and demonstrated improvement in outcomes with induction chemotherapy. Cisplatin and fluorouracil followed by concurrent chemoradiation therapy resulted in improved disease free survival and distant metastasis-free survival. Induction chemotherapy with gemcitabine/cisplatin (a combination also approved in the recurrent or metastatic setting) demonstrated improved recurrence-free and overall survival in the induction arm, offering a compelling new standard of care for these patients.

The ongoing NRG HN 001 study is a randomized trial exploring the importance of this adjuvant chemotherapy based on clinical response and plasma EBV DNA levels. Patients with undetectable plasma EBV DNA after concurrent chemoradiation will be randomized to standard adjuvant cisplatin/5-FU versus observation. Patients with detectable plasma EBV DNA after concurrent chemoradiation will be randomized to standard adjuvant cisplatin/5-FU versus an alternative combination of paclitaxel/gemcitabine. Locally recurrent nasopharyngeal cancer that is nonmetastatic can be treated with surgical and nonsurgical approaches. Reirradiation is usually advocated especially when the patient is not a surgical candidate.

De novo metastatic nasopharyngeal cancer has traditionally been treated with palliative systemic therapy and radiation as indicated. Prospective, phase III data demonstrate prolonged PFS with use of gemcitabine/cisplatin over fluorouracil/cisplatin, establishing this combination as standard frontline systemic therapy. A recent phase III randomized trial compared chemotherapy and locoregional radiation versus chemotherapy alone for treatment-naïve metastatic nasopharyngeal cancer patients and demonstrated improved overall

survival in favor of chemotherapy plus radiotherapy. This study also represents a new standard of care for de novo metastatic patients with nasopharyngeal cancer.

Nasal Cavity and Paranasal Sinuses

The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for carcinomas of the nasal cavity and paranasal sinuses are shown in Table 1.7. Nasal cavity and the paranasal sinus tumors comprise a broad variety of tumors. Some of these include squamous cell carcinomas, various types of adenocarcinomas, transitional cell carcinomas, minor salivary gland carcinomas, small cell carcinomas, esthesioneuroblastomas, and sinonasal undifferentiated carcinomas. Rare benign tumors like hemangiomas and angiofibromas may also be seen.

There is no consensus on the management of these tumors. In general, these tumors are resected surgically, optimally using an endoscopic approach, or if necessary a combined open and endoscopic approach. Tumor resection often proceeds in a piecemeal rather than en-bloc fashion, and negative margins are often difficult to obtain. A combined team approach with neurosurgery may be needed especially for tumors involving the skull base. Certain cases where the tumor approaches the orbit might necessitate an orbital exenteration. Exceptions include radiosensitive and chemosensitive tumors like small cell carcinoma (high-grade neuroendocrine carcinoma) which may be treated with definitive chemoradiation. Adjuvant radiation/chemoradiation usually follows surgical management of any high-grade histology. Locally advanced unresectable tumors may be treated with definitive chemoradiation provided the patient has adequate performance status and is medically fit to receive aggressive CRT. The remaining patients are best treated with palliative radiation and chemotherapy.

Salivary Glands

Salivary gland cancers are a rare subset of head and neck cancers. They comprise a variety of histologies and are found in various locations throughout the head and neck region including the major and minor salivary glands. Salivary gland tumors may be both benign and malignant. Benign lesions are more commonly found in major salivary glands while lesions of the minor salivary glands are more likely to be malignant. The fourth edition of the WHO classification of head and neck tumors details various salivary gland histologies. The benign salivary gland tumors are listed in Table 1.8.1 and malignant salivary gland tumors are listed in Table 1.8.2.

TABLE 1.8.1
Salivary Gland Benign Tumors

Pleomorphic adenoma (benign mixed tumor)
Warthin tumor (papillary cystadenoma lymphomatosum)
Monomorphic adenoma
Benign lymphoepithelial lesion
Oncocytoma
Ductal papilloma
Sebaceous lymphadenoma

TABLE 1.8.2
Salivary Gland Malignant Tumors

Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low grade adenocarcinoma
Epithelial-myoepithelial carcinoma
Basal cell adenocarcinoma
Sebaceous carcinoma
Papillary cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma

Squamous cell carcinoma
Small cell carcinoma

The clinical characteristics and prognosis of specific malignant salivary gland tumors are shown in Table 1.8.3.

TABLE 1.8.3

Selected Salivary Gland Malignant Tumors: Clinical Characteristics and Prognosis

Histology	Clinical Characteristics
Mucoepidermoid carcinoma	Most common malignant tumor in major salivary glands; most common in parotid glands (32%) Low grade: local symptoms, long history, cure with aggressive resection; rarely metastasizes t(11;19)(q21;p13) in 50%-70% High grade: locally aggressive, invades nerves and vessels, and metastasizes early
Adenocarcinoma	16% of parotid and 9% of submandibular malignant tumors Grade correlates with survival
Squamous cell carcinoma	Very rare Grade correlates with survival Squamous cell carcinoma of temple, auricular, and facial skin can metastasize to parotid nodes and can be confused with primary parotid tumor
Acinic cell carcinoma	<10% of all salivary gland malignant tumors Low grade with slow growth, infrequent facial nerve involvement, infrequent and late metastases (lungs) Regional metastasis in 5%-10% of patients
Adenoid cystic carcinoma	Most common malignant tumor in submandibular gland (41%), 11% of parotid gland High incidence of nerve invasion, which compromises local control t(6;9)(q22-23;p23-24) in 50% 40% of patients develop metastases; most common site of metastases is the lung. Patients may live many years with lung metastasis, but visceral or bone metastases indicate poor prognosis

While major salivary gland cancers are usually clinically obvious as to site of origin, minor salivary gland tumors are often mistaken for more common mucosal lesions. In either case, pretreatment imaging and tissue diagnosis are important for optimal management. Inadvertent partial excision of a lesion can

compromise further oncological surgical excision. FNA biopsy is usually the first diagnostic step and can help in management, as it is effective at determining benignity versus malignancy. Definitive surgical management is considered the standard initial treatment. In the absence of a clear preoperative diagnosis, major salivary gland lesions are often resected with intraoperative frozen section for diagnosis. An oncological resection, with or without neck dissection, is achieved after establishing the diagnosis. Benign lesions like pleomorphic adenomas are also resected keeping oncological principles in mind (no tumor spillage) since these tumors show preponderance for local recurrence. Obviously malignant lesions (fast preoperative growth, facial nerve paralysis) are resected with a wide margin. Wide negative resection margins are desired but may be difficult to obtain in proximity to the facial nerve. The facial nerve is usually preserved if it is functioning preoperatively and grossly uninvolved intraoperatively, and fortunately, close margins here usually do not affect locoregional control. A paralyzed or grossly involved facial nerve is sacrificed and an attempt is made to obtain negative proximal and distal margins. Meticulous skull base dissection may be required. The facial nerve should be reconstructed (grafted) during the primary surgery, and other adjunct procedures considered for facial reanimation, eg, temporalis tendon transfer. Management of the neck is still controversial. In general, patients with T3/T4, high-grade or node-positive diseases are usually managed with ipsilateral neck dissection.

The adjuvant management of salivary gland cancers is based on retrospective data. Adjuvant radiation appears to play an important role in improving locoregional control. General indications for postoperative radiation include T3/T4 primary lesions, high-grade tumors, lymphovascular space invasion, perineural invasion, close/positive margins, node-positive disease, or recurrent disease. The principles of adjuvant radiation including doses required are similar to those of more common mucosal tumors discussed previously. Adjuvant radiation also plays a role in improving locoregional control for benign tumors like multiply recurrent

pleomorphic adenomas. The role of chemotherapy is controversial and far less established for salivary gland tumors. The RTOG 1008 trial is a phase III trial exploring the role of concurrent cisplatin with radiation for high risk salivary gland tumors. Some histologic subtypes may express potential hormonal or other therapeutic targets, such as HER2 and androgen receptors in salivary duct carcinomas. The role of targeted therapies for these diseases is being explored in various settings. Like other head and neck cancers, single-modality adjuvant chemotherapy currently does not have a defined role in the management of salivary gland cancers. In recurrent/metastatic disease, it is reasonable to consider combination chemotherapy, single-agent chemotherapy, or targeted therapy in the form of tyrosine kinase inhibitors, though response rates are variable and dependent upon histology. Lenvatinib, a multikinase inhibitor, demonstrated clinical benefit in recurrent or metastatic adenoid cystic carcinoma. Next-generation sequencing may be considered to evaluate for molecular aberrations that may be amenable for targeted therapies in salivary gland cancers.

Unknown Primary of the Head and Neck

Unknown primary of the head and neck region comprises about 3% of all head and neck cancers. While squamous cell carcinomas are thought to originate from mucosal sites, other histologies are also seen and may indicate the source of their primary origin. For example, adenocarcinomas might arise from the salivary glands or the thyroid/parathyroid gland. The site of lymph node presentation is often linked to the potential site of the primary, and this knowledge helps in evaluation and management. For example, a level III node might arise from the larynx, hypopharynx, or upper cervical esophagus. A level IA node is likely to arise from an oral cavity primary, while a level IB node might indicate a primary in the oral cavity, maxillary sinus, or nasal cavity. A level II node might indicate a primary in the oropharynx though several sites primarily drain to level II. A level V node raises the possibility of a nasopharynx or skin cancer. A parotid gland node usually indicates

a cutaneous primary squamous cell carcinoma. An isolated supraclavicular node (Virchow node) is very unlikely to indicate a head and neck primary. The primary in this case is almost always below the clavicle (lung, thoracic esophagus, breast, etc). Evaluation follows the usual workup of head and neck cancers. An ultrasound-guided, core needle biopsy of the node is preferred especially to obtain p16 and EBER evaluation which may point to an HPV-related oropharyngeal primary or nasopharyngeal primary, respectively. However, caution is advised while doing so, and the primary drainage pattern of the involved node should be taken into account before interpreting the immunohistochemistry results. For example, an isolated level V node might be p16+ but is more likely to indicate a cutaneous primary/nasopharynx primary rather an oropharyngeal primary. A PET CT should be considered before surgical diagnostic procedures are performed since this information might aid in finding the primary, especially when a contrast-enhanced CT scan is unrevealing. Random biopsies are considered low yield and not recommended. Transoral lingual tonsillectomy (tongue base resection) is being increasingly utilized to detect a tongue base primary, which is usually found in a high number of cases with a level II node presentation, especially when a palatine tonsillectomy is unrevealing.

When no primary is found, management usually follows the purported site of the primary. For example, a level I node is subjected to a neck dissection assuming the oral cavity as the primary site. N1 disease may be resected and in the absence of adverse pathological features, the patient may be observed without further treatment. This is based on the fact that data regarding emergence rates of the primary, although inconsistent in the literature, appear to indicate a low emergence rate. When radiation is used for treatment, however, it is considered standard to prophylactically radiate potential primary sites. For example, a p16+ level II node is treated with definitive neck radiation and prophylactic coverage of the oropharynx. A p16− level II node is treated similarly but prophylactic coverage of the nasopharynx and

hypopharynx may be considered in addition to the oropharynx based on the clinical scenario. An EBV+ node is treated along the lines of nasopharyngeal cancer. In general, the oral cavity, larynx, and hypopharynx are excluded in the prophylactic radiation volume since this approach is considered excessively morbid with low yield. More advanced disease may be treated with surgery followed by radiation with or without chemotherapy based on pathological risk factors. When treating N2/N3 disease nonoperatively, concurrent chemotherapy is usually added to the radiation although the benefit of this is unclear. Salvage surgery may be needed for more advanced neck disease. Patients with distant metastases presenting with a neck node and no primary are treated with palliation (radiation and chemotherapy). The results of treatment usually follow similarly staged head and neck cancers with a known primary site. Therefore, in nonmetastatic cases, a cure is possible despite not knowing where the primary originated. ASCO guidelines for the diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck were recently published.

Recurrent Nonmetastatic Disease

Locoregional recurrence is the most frequent pattern of disease failure in patients with locally advanced head and neck cancer and remains a major challenge. Distant failure, however, is being recognized more frequently, particularly in patients with HPV-related oropharyngeal tumors. These cancers could either be true recurrent disease or may represent second primaries, a distinction that is often difficult, especially if disease is identified within 2 to 3 years of the primary disease. Management is based on the intent of treatment which may be either palliative or definitive. Recurrent cancer within a short time span (usually 6 months), advanced age, poor performance status, and large burden of unresectable disease are factors associated with particularly poor outcomes and are best treated with palliative radiation and/or systemic palliative therapy. SBRT may be an option for some cases with an estimated survival of

more than 6 months. This strategy is employed to quickly deliver reasonably durable palliative treatment with acceptable morbidity.

More favorable disease features include second primaries, or recurrent disease occurring more than 2 years after treatment of the initial tumor, young age, good performance status, low-volume disease, resectable disease, and low morbidity from previous treatment. When possible, these patients should be treated with surgery followed by adjuvant chemoradiation. The GORTEC trial demonstrated a disease-free survival, but not overall survival advantage to adjuvant chemoradiation versus observation after surgery in this group of patients. The volume of radiation is usually minimized to include the recurrent disease bed while maximally sparing normal tissue, thereby sparing morbidity. Case selection is crucial since the morbidity of this approach is not trivial. More modern and technologically advanced radiation delivery may offset the morbidity noted historically.

TOXICITY MANAGEMENT AND FOLLOW-UP

Acute Toxicities of Treatment

Patients treated with radiation therapy or concomitant CRT require frequent clinical assessment and prompt institution of supportive care to avoid severe or fatal consequences during the acute phase of treatment (during treatment and for the first several months after treatment).

Nutrition

Careful assessment of the need for a feeding tube should be performed. In general, reactive feeding tube placement is preferred to prophylactic placement before therapy begins. These devices have been shown to be beneficial for patients who are thin, or have lost significant weight. They are not necessary for all patients, but if not

placed, such patients must be assessed every 1 to 2 weeks for toxicity and weight loss.

Hydration

Radiation and chemoradiation leads to increased fluid loss, especially with severe mucositis, and/or with loss of normal taste or appetite. Patients should be assessed every 1 to 2 weeks for skin turgor, orthostatic blood pressure changes, lightheadedness on standing, or renal dysfunction (especially when platinum-based chemotherapy is used).

Mucositis

A significant number of patients receiving CRT will develop severe mucositis that impairs nutrition and causes severe pain. Candida infection of the affected mucosal surfaces is fairly common. At the first sign of candidiasis, antifungal therapy should be instituted, topically and/or orally. A preparation containing an antifungal, anesthetic, and calcium carbonate suspension is useful. Narcotic pain control should be aggressive and patients should be taught to track pain severity and self-administer their narcotics before the peak of pain occurs. It is useful to use a transdermal administration route, using careful dose calculation based on total use of short-acting narcotic, plus a short-acting (liquid) narcotic to control pain.

Radiation Dermatitis and Rash

Mild radiation dermatitis is managed with a moisturizer during and after radiation. Moist desquamation may be managed with vinegar soaks and saline dressings. These reactions will often heal after radiation is concluded. Superficial infections should be managed with antibiotics.

Cetuximab may cause an acneiform rash in the upper torso and face which may become infected if not treated. Patients should be started prophylactically on moisturizers as topical therapy. Steroid-containing topical creams and doxycycline are also helpful for a

more severe rash (confluent in more than one body area). The rash often improves after the first few weeks and may be present outside the radiation fields.

Allergic Reactions

Severe and life-threatening allergic reactions have occurred with cisplatin, taxanes, carboplatin, and anti–epidermal growth factor receptor antibodies. Infusion of these agents should only be done when appropriate emergency equipment and trained personnel are available.

Late Toxicities of Treatment

Xerostomia

Risk of dry mouth due to incidental radiation to the salivary glands is common but has been lessened by more accurate treatment planning and delivery with IMRT. Initial management typically includes saliva substitutes, oral mucosal lubricants, and frequent sips of water. Systemic cholinergic agonists can be considered for xerostomia that persists for more than 1 year after treatment completion. There is growing evidence supporting a role for acupuncture or acupuncture-like transcutaneous electrical nerve stimulation in palliation of xerostomia as well.

Late Dysphagia

A minority of patients will have swallowing difficulties for several years or permanently, with attendant risk of aspiration and pneumonia. Swallowing therapy and potentially continued enteral nutrition with a percutaneous tube may be necessary for these patients. Serial dilatations of the oropharyngeal inlet and esophagus might be needed to deal with radiation/surgery-related strictures.

Dental Caries

An increased risk of developing dental caries accompanies any change in salivary flow or composition. For this reason, any patient who has had head and neck radiation should have regular, frequent dental evaluations. Long-term, daily use of fluoride trays is often recommended. Meticulous oral hygiene can reduce the likelihood of other late effects, such as osteoradionecrosis (ORN).

Osteoradionecrosis

Bone exposure following radiation may lead to progressive ORN, which occurs in 5% to 7% of patients treated with radiation. To prevent ORN, extractions should be performed in patients with poor dentition and allowed adequate time for healing prior to therapy (at least 2 weeks). If ORN develops, patients with dead sequestra (necrotic bone) should be referred to an oral maxillofacial surgeon for sequestrectomy. Culture may provide sensitivities for IV antibiotic therapy. Sequestrectomy coupled with long-term pentoxifylline has been reported to result in healing in most patients within 1 year. Hyperbaric oxygen has been used for many years, but was not found to be of benefit in a randomized clinical trial. Nonresponsive or advanced ORN requires open surgical resection (eg, segmental mandibulectomy) and reconstruction with vascularized tissue, eg, fibula free flap reconstruction for segmental mandibulectomy.

Mobility Impairment

Both surgery and radiation can cause fibrosis of soft tissues of the neck, impacting cosmesis and/or neck mobility. Treatment often includes physical therapy for neck stretching and strengthening and massage. Greater regression is generally achieved with earlier initiation of therapy.

Hypothyroidism

Up to 75% of patients may have increased thyroid stimulating hormone levels (TSH) after radiation therapy. Following radiation

treatment to the neck, TSH should be monitored regularly and appropriate replacement therapy instituted.

FOLLOW-UP

Curative treatment of patients with head and neck cancer should be followed by a comprehensive head and neck physical examination every 1 to 3 months during the first year after treatment, every 2 to 4 months during the second year, every 3 to 6 months from years 3 to 5, and every 6 to 12 months after year 5. In patients treated nonoperatively, restaging imaging studies should be done approximately 12 weeks after completion of radiation therapy and then as needed for any symptoms or signs suggesting recurrence or second primary cancer. A randomized study established the role of PET CT obtained 12 weeks after definitive chemoradiation for disease surveillance. Neck dissection is warranted for incomplete response and equivocal findings on imaging. This approach resulted in equally good survival and was cost effective compared with planned neck dissections. The highest risk of relapse is during the first 3 years after treatment. After 3 years, a second primary tumor in the lung or head and neck is the most important cause of morbidity or mortality. Because of this risk, annual chest imaging, particularly in smokers, is recommended.

PREVENTION

The most important recommendation for prevention of head and neck cancer is to encourage smoking cessation and to limit alcohol intake. HPV vaccination should be encouraged for eligible populations (males and females, aged 9-45 years), as it has been shown to prevent cervical cancer in woman and is expected to have similar effects on oropharyngeal cancer.

Premalignant lesions occurring in the oral cavity, pharynx, and larynx may manifest as leukoplakia (a white patch that does not

scrape off and that has no other obvious cause) or erythroplakia (friable reddish or speckled lesions). These lesions require biopsy and potentially excision. The risk of leukoplakias without dysplasia progressing to cancer is about 4%. However, up to 40% of severe dysplasias or erythroplasias progress to cancer.

Presently, there is no effective chemoprevention for patients at risk for head and neck squamous cancer, and chemoprevention outside a clinical trial is not recommended.

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2

Non–Small Cell Lung Cancer

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EPIDEMIOLOGY

- Lung cancer, broadly divided into small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), is the leading cause of cancer death in the United States and worldwide.
- As of 2020, an estimated 227,875 new cases of lung and bronchus cancer (116,335 in men and 111,540 in women) were diagnosed in the United States, resulting in 138,225 deaths (73,009 in men, 65,216 in women).
- The 2-year relative survival rate for lung cancer in the general US population was approximately 35% and 44% in 2014, substantially improving from 26% to 35% in male and female from 2001. The improvement in survival was found across all races and ethnic groups. This is probably due to the considerable reduction in smoking and treatment advances, particularly targeted therapies and immunotherapies.
- Stage at diagnosis accounts for the most marked variation in prognosis. Other clinical characteristics associated with poorer prognosis include older age, male gender, performance status (PS), and smoking.
- Although, in the general population, lung cancer is more common in males compared with females, this trend is reversed in the young (age < 50 years), which is not fully explained by differences of smoking behaviors. Majority of young female

lung cancer patients are diagnosed with adenocarcinoma, potentially suggesting a distinct biology in this population.

ETIOLOGY AND RISK FACTORS

- Most of lung cancer deaths are directly attributable to cigarette smoking.
- Tobacco smoke contains a highly complex mixture of carcinogens that have the potential to damage DNA. Polycyclic aromatic hydrocarbons, aromatic amines, and tobacco-specific nitrosamines have been implicated as the major mutagenic carcinogens responsible for DNA adduct formation. The number of DNA adducts formed is directly related to the number of cigarettes consumed; in heavy smokers, they can be responsible for as many as 100 mutations per cell genome.
- Compared to those who have never smoked, smokers have an approximate 20-fold increase in lung cancer risk. The likelihood of developing lung cancer decreases among those who quit smoking compared to those who continue to smoke.
- Estimates indicate that passive smoking accounts for approximately 3000 lung cancer deaths per year in the United States.
- Radon, a radioactive gas produced by the decay of radium 226, is the second leading cause of lung cancer in the United States, accounting for 6000 to 36,000 cases of lung cancer each year. The decay of radium 226 produces substances that emit alpha particles, which may cause cell damage. Residential radon exposure has been associated with an increased risk of developing lung cancer.
- Occupational exposure to carcinogens such as asbestos, arsenic, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, and other agents is estimated to cause approximately 9% to 15% of lung cancers. Asbestos exposure in smokers is associated with a synergistic risk of developing lung cancer. Cigarette smoking impairs bronchial clearance and

thereby prolongs the presence of asbestos in the pulmonary epithelium.

- The contribution of hereditary factors to the development of lung cancer is not well understood. Rarely, EGFR T790M has been identified as a germline variant associated with hereditary lung cancer. A meta-analysis revealed increased lung cancer risk associated with having an affected relative (relative risk 1.8, 95% confidence interval [CI] 1.6-2.0). Proof that the familial occurrence of lung cancer has a genetic basis is complicated by the central role of cigarette smoking in the etiology of lung cancer.
- Large randomized, double-blind, placebo-controlled chemoprevention trials reported in the 1990s provided no evidence that specific dietary constituents confer protection against lung cancer.

PATHOLOGY

- NSCLC can be divided into three major subtypes:
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Large cell carcinoma
- Adenocarcinoma is the most frequently diagnosed form of NSCLC; approximately, 50% of NSCLC in both men and women in the United States. Tumors are classically peripheral and arise from surface epithelium or bronchial mucosal glands. Histologic diagnosis requires evidence of either neoplastic gland formation, pneumocyte marker expression (TTF-1 ± napsin), or intracytoplasmic mucin.
- The histologic characteristics of lung cancer in several developed countries, including the United States, have changed in the past few decades, demonstrating that the frequency of adenocarcinoma has risen while the frequency of squamous cell carcinoma has declined. This is probably due to declining smoking rates.

- Since 2015, WHO classification has eliminated bronchioloalveolar carcinoma (BAC) and instead introduced new categories to better categorize tumors based on the extent of invasiveness.
    - Atypical adenomatous hyperplasia: generally <5 mm
    - Adenocarcinoma in situ: ≤3 cm adenocarcinoma in which growth is restricted to tumor cells growing along alveolar structures (lepidic growth pattern) and lacks any component of invasion
    - Minimally invasive adenocarcinoma: ≤3 cm of lepidic tumor with ≤5 mm of invasion.
    - Invasive adenocarcinoma including lepidic predominant with >5 mm of invasion (formerly nonmucinous BAC) and variants such as invasive mucinous adenocarcinoma (formerly mucinous BAC).
- Squamous cell carcinoma accounts for approximately 25% of NSCLC and has the strongest association with cigarette smoking. This tumor arises most frequently in the central proximal bronchi and can lead to bronchial obstruction, with resultant atelectasis or pneumonia. The diagnosis of squamous cell carcinoma is predicated upon visible keratinization, with prominent desmosomes and intercellular bridges, or by immunohistochemistry consistent with squamous cell carcinoma (ie, expression of p40, p63, CK5, or CK5/6, desmoglein).
- Large cell carcinoma is the least common subtype of lung cancer lacking neither of glandular, squamous, or small cell features, accounting for approximately 10% of all NSCLCs. Large cell carcinoma usually presents as a large peripheral mass with prominent necrosis.
- Sarcomatoid carcinoma contains a component of sarcoma or sarcoma-like elements. This histology is a broad term that represents a heterogeneous group of NSCLC comprising <1% of all NSCLC. Overall sarcomatoid carcinoma histology associates with worse survival.
- Recent updated WHO 2020 classification added several new tumor entities: bronchiolar adenoma (ciliated muconodular papillary tumor); thoracic SMARCA4-deficient undifferentiated tumor; and invasive nonmucinous pulmonary adenocarcinoma.

BIOLOGY

- Lung cancer evolves through a multistep process from normal bronchial epithelium to dysplasia to carcinoma in situ and finally to invasive cancer. These changes include activation of oncogenes, inactivation of tumor suppressor genes, and loss of genomic stability. Changes can be both genetic (via deletions or mutations) or epigenetic (methylation), leading to altered cell proliferation, differentiation, and apoptosis. Mutations in multiple tumor suppressor genes and oncogenes have been associated with the development of NSCLC. A small subset of somatic mutations (driver mutations) are essential for lung carcinogenesis and tumor progression and confer a selective growth advantage to the cancer cell. Cancer cells are often "addicted to" the continued activity of these somatically mutated genes for maintenance of their malignant phenotype.
    - p53 is involved in DNA repair, cell division, apoptosis, and growth regulation. In normal conditions, p53 production increases when DNA damage occurs. Increased amounts of p53 induce cell cycle arrest in the G1 phase, allowing DNA repair. If a p53 deletion or mutation exists, G1 arrest is not achieved and the abnormal cell proceeds to S phase, further dividing and propagating genetic damage. Mutations in p53 are found in 50% of NSCLC.
    - The RB gene also regulates G1 growth arrest. Hypermethylation of the CpG-rich island at the 5′ end of the RB gene is thought to lead to the silencing of the RB gene and tumor progression. RB gene mutations occur in 15% of NSCLC.
    - The human epidermal growth factor receptor (HER) family is a group of four trans-membrane tyrosine kinase receptors: EGFR, ErbB1, or HER1; ErbB2 (HER2/nu or HER2); ErbB3 (HER3); and ErbB4 (HER4). Following binding of a ligand to its extracellular receptor, dimerization occurs, leading to activation of tyrosine kinases and a subsequent increase in downstream signaling pathways, including RAS-RAF and AKT protein kinases. These pathways regulate angiogenesis, cell proliferation, and survival. Point mutations within EGFR exons 18 to 21 which encode a portion of the EGFR tyrosine kinase domain predict tumor sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Common EGFR sensitizing mutations include exon 19 deletions and exon 21 L858R point mutations. These mutations are more frequently found in female patients with adenocarcinoma histology, patients of Asian origin, or never or light smokers. They occur in up to 10% of US or European populations and 30% to 50% of Asian patients with NSCLC and smokers and are less frequent in Asians.
    - KRAS is a member of the RAS family of oncogenes and codes for a 21-kDa guanine-binding protein that mediates signal transduction pathways from cell surface receptors to intracellular molecules. The RAS-RAF pathway produces

signaling downstream of the EGFR transmembrane tyrosine kinase and promotes survival and proliferation. Most frequent mutation in KRAS mutant NSCLC is G12C (42% among the KRAS variants in NSCLC). Mutations in EGFR and KRAS are, in general, mutually exclusive. The RAS oncogene can be activated either by a point mutation or by overexpression. KRAS mutations are found with greater frequency in patients with adenocarcinomas (~15%-30%), Caucasians, and smokers and are less frequent in Asians.

- The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of malignancies. ALK rearrangements occur because of a chromosomal inversion within the short arm of chromosome 2, which results in the formation of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion oncogene. ALK fusion—with its most frequent fusion partner EML4 and less frequently with a variety of other partner genes—results in its dimerization and constitutive kinase activity, which leads to activation of pathways involved in cell growth and proliferation. Approximately, 3% to 7% of NSCLC harbor ALK fusions. ALK fusions are more common in younger patients, never or light-smokers, and patients with adenocarcinoma with signet ring or acinar histology and in most cases are mutually exclusive of EGFR and KRAS mutations. ALK fusions predict sensitivity to ALK/MET TKIs.
- Proto-oncogene tyrosine-protein kinase (ROS1) is a gene coding a receptor tyrosine kinase of the insulin receptor family. Chromosomal rearrangements involving the ROS1 gene lead to constitutive kinase activity and are found in approximately 2% of NSCLC. The clinical profile of ROS1-rearranged NSCLC patients is similar to that of ALK-rearranged NSCLC; younger patients, never-smokers, and those with adenocarcinomas. ROS1 rearrangements predict sensitivity to the several targeted TKIs including entrectinib and crizotinib.
- c-MET is a tyrosine kinase receptor for hepatocyte growth factor. MET exon-14–skipping mutation (found in 3% of NSCLC) and MET gene amplification (in 2%-4% of treatment-naïve NSCLC and 5%-20% of EGFR-mutated tumors that have acquired resistance to EGFR inhibitors) are known to activate MET signaling. The MET exon-14–skipping mutation predicts sensitivity to MET inhibitors including capmatinib and tepotinib.
- The rearranged during transfection (RET) gene encodes a transmembrane tyrosine kinase receptor. Fusions between RET and various upstream gene partners (CCDC6, KIF5B, NCOA4) result in constitutively activation of ligand-independent signaling and oncogenesis. RET fusion has been identified in 1% to 2% of adenocarcinomas and occur more frequently in younger patients and in never-smokers. RET inhibitors (selpercatinib, pralsetinib) show antitumor efficacy in RET fusion-positive NSCLC.
- BRAF is a gene coding B-Raf protein which is a downstream of KRAS signaling that activates mitogen-activated protein kinase (MAPK) pathway. BRAF mutations, especially at V600 position of exon 15, constitutively activates RAF kinase and subsequent MAPK pathways. Activating BRAF mutations have been observed in 1% to 3% of NSCLCs and are usually associated with a history of smoking. V600 BRAF mutations associates with better overall survival (OS) compared with non-V600 BRAF mutations. Dual blockade of BRAF signaling pathway by BRAF and MEK inhibitors (dabrafenib and trametinib) is effective in BRAF V600-mutated NSCLC.

    - Fusions in one of three tropomyosin receptor kinases (NTRK1, NTRK2, NTKR3) occur across many tumor types although the frequency in NSCLC is very rare (<1%). NTRK fusions lead to overexpression of the chimeric protein, resulting in constitutive activation of ligand-independent downstream signaling. NTRK fusions predict sensitivity with NTRK inhibitors (larotrectinib, entrectinib).
- Both cellular (T lymphocyte–mediated) and humoral (antibody-mediated) immune antitumor responses are known to occur in patients with advanced lung cancer. Despite this, spontaneous tumor regressions rarely occur, indicating that the tumor cells can escape an immune response. These include suppression of antigen-presenting machinery (eg, altered human leukocyte antigen expression that prevents antigen presentation and an effective immune response), release of immune inhibitory cytokines (eg, interleukin 10 and transforming growth factor-β), immunosuppressive cells in the tumor microenvironment (eg, regulatory T cells and myeloid-derived suppressor cells), and expression of immune checkpoints. Immune checkpoints are molecules expressed on the surface of T lymphocytes that modulate the immune response to antigens via inhibitory or stimulatory signaling to T cells. Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1) and its ligand (PD-L1) are among the most extensively studied immune checkpoints. Activation of immune checkpoints causes downregulation and inhibition of immune responses.

LUNG CANCER SCREENING

- Randomized trials of screening with chest radiography with or without sputum cytology have shown no reduction in lung-cancer mortality.
- Low-dose computed tomography screening benefits individuals at an increased risk for lung cancer.
    - The United States–based National Lung Screening Trial, a randomized trial compared annual screening by low-dose chest CT (LDCT) with chest x-ray for 3 years in high-risk individuals (age between 55 and 74 years with at least 30 pack-year cigarette smoking and former smokers who had quit within the previous 15 years), enrolling 53,454 individuals. There were 247 deaths from

lung cancer per 100,000 person-years in the LDCT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with LDCT screening of 20.0% (95% CI, 6.8-26.7; *P* = .004). The rate of death from any cause was reduced in the LDCT group, as compared with the radiography group by 6.7% (95% CI, 1.2-13.6; *P* = .02).

- The Dutch–Belgian lung-cancer screening (NELSON) trial showed that volume CT lung-cancer screening resulted in substantially lower lung-cancer mortality than no screening among high-risk persons. At 10 years of follow-up, the incidence of lung cancer was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group; lung-cancer mortality was 2.50 deaths per 1000 person-years and 3.30 deaths per 1000 person-years, respectively.
- The U.S. Preventive Services Task Force recommends annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

CLINICAL PRESENTATION

- A minority of patients present with an asymptomatic lesion discovered incidentally on chest radiograph. No set of signs or symptoms are pathognomonic of lung cancer, so diagnosis is often delayed.
- Clinical signs and symptoms of lung cancer are outlined in Table 2.1.

TABLE 2.1
Clinical Signs and Symptoms of Lung Cancer

Primary disease
Central or endobronchial tumor growth
Cough
Sputum production
Hemoptysis
Dyspnea
Wheeze (usually unilateral)
Stridor

Pneumonitis with fever and productive cough (secondary to obstruction)

Peripheral tumor growth

Pain from pleural or chest wall involvement
Cough
Dyspnea
Pneumonitis

Regional involvement (either direct or metastatic spread)

Hoarseness (recurrent laryngeal nerve paralysis)
Dysphagia (esophageal compression)
Dyspnea (pleural effusion, tracheal/bronchial obstruction, pericardial effusion, phrenic nerve palsy, lymphatic infiltration, superior vena cava obstruction)
Horner syndrome (sympathetic nerve palsy)

Metastatic involvement (common sites)

Bone (pain exacerbated by movement or weight-bearing, often worse at night; fracture)
Liver (right hypochondrial pain, icterus, altered mental status)
Brain (altered mental status, seizures, motor and sensory deficits)

Paraneoplastic syndromes

Hypertrophic pulmonary osteoarthropathy
Hypercalcemia
Dermatomyositis (Eaton-Lambert syndrome)
Hypercoagulable state
Gynecomastia

CLINICAL EVALUATION

Single Pulmonary Nodule

- Definition: solitary mass, often found incidentally, surrounded by lung tissue, well circumscribed, measures <3 cm without mediastinal or hilar adenopathy.
- Benign inflammatory vascular abnormalities or infectious lesions can mimic more sinister lesions. Review of previous chest imaging is a crucial first step. A stable lesion over a 2-year period suggests a benign condition.

- CT of the chest is required to assess for other nodules, adenopathy, or chest wall invasion.
- Invasive carcinomas can present with a spectrum of nodular patterns including ground glass opacities (GGO), mixed GGO/solid nodules, or consolidations.
- Once single pulmonary nodule (SPN) is found, follow-up management will be determined based on the presentation of SPN (purely solid vs contains features of GGO), risk stratification (high-risk: history of smoking or other risk factors including history of lung cancer in a first-degree relative, exposure to asbestos, radon, or uranium; low-risk: minimal or absent history of smoking or known other factors), and the size of the SPN (Figure 2.1).

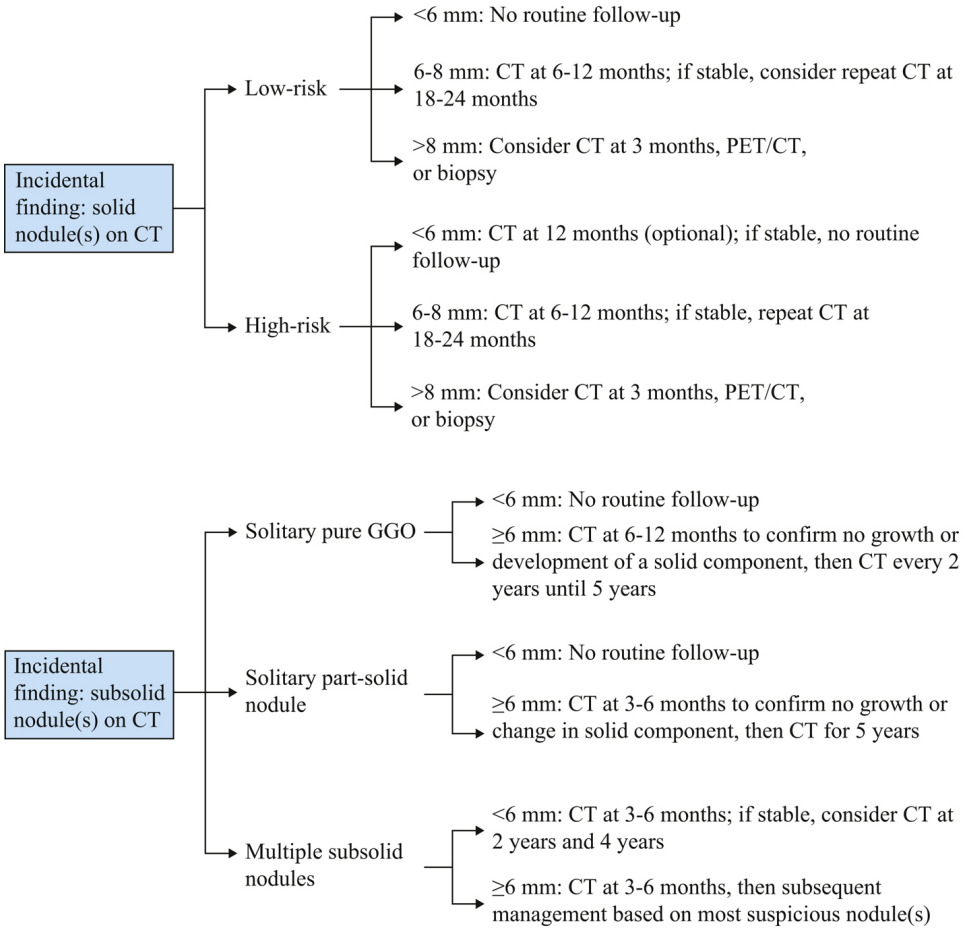

FIGURE 2.1 Follow-up algorithm for single pulmonary nodule (SPN); risk stratification is defined by high-risk: history of smoking or other risk factors including history of lung cancer in a first-degree relative; exposure to asbestos, radon, or uranium; low-risk: minimal or absent history of smoking or known other factors.GGO, ground glass opacities. (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2022. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.)

- ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is used to evaluate SPNs. False-positive PET scans may occur in conditions such as tuberculosis or histoplasmosis. False-negative results have been reported for small lesions (<1 cm) and neoplasms with low-metabolic activity, such as in

some cases of preinvasive or minimally invasive disease. Mean sensitivity of FDG-PET is 96%; mean specificity is 75%. The negative and positive predictive value of PET for pulmonary nodules is approximately 90%.

- A growing SPN needs a pathologic diagnosis. Tissue can be obtained by fine needle aspiration (FNA), transbronchial biopsy, or surgical resection. Flexible fiber optic bronchoscopy is appropriate for central lesions and can lead to a diagnosis in 97% of cases via biopsies, bronchial washings, and brushings.

Suspected Lung Cancer

- Full history and physical examination are recommended, followed by complete blood count and chemistry tests, chest x-ray, and contrast-enhanced CT of the chest and abdomen (including adrenal glands).
- Sputum analysis may be helpful in cases of central lesions.
- Bone scans and plain films of affected areas are warranted where bone pain exists.
- Peripheral lesions may require percutaneous transthoracic FNA, which can be performed under CT or fluoroscopic guidance.
- Mediastinoscopy, a more invasive method, may be needed to obtain a histologic diagnosis in difficult-to-reach primary tumors. Mediastinoscopy can reveal unsuspected tumors in mediastinal lymph nodes—a negative implication for survival. Evaluation of the mediastinum is recommended before surgery in suspected mediastinal disease and intraoperatively prior to any planned resections.
- Given high incidence of brain metastasis in patients with NSCLC, brain MRI needs to be considered when patients have neurological symptoms or disease with advanced disease (pathological stage II to IV).
- An accurate pathologic diagnosis and staging of disease is essential in the management of lung cancer. Stage of disease determines whether surgical resection is warranted. Clinical staging often underestimates the true extent of the disease. The

combination of PET evaluation and mediastinoscopy is routinely used to complete staging.

- Presurgical forced expiratory volume/1 second should be ≥2 L for pneumonectomy, 1 L for lobectomy, or 0.6 L for segmentectomy. Presurgical forced vital capacity should be ≥1.7 L.
- In patients who undergo surgical resection, surgical/pathologic staging should be used to predict recurrence and to evaluate the need for adjuvant therapy.

STAGING

- The tumor-node-metastasis (TNM) staging system bases patient prognoses on tumor size, lymph node involvement, and metastasis. OS rate at 5 years for patients with pathologic stage IA1, IA2, IA3, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, and IVB are 92%, 83%, 77%, 68%, 60%, 53%, 36%, 26%, 13%, 10%, and 0%, respectively.
- The eighth edition of the *TNM Classification of Malignant Tumors* (UICC) was adopted by the American Joint Committee on Cancer in 2018. A summary of the TNM classification, stage grouping, and anatomical drawing can be found at https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq. In stages I and II, disease is limited to one lung and does not involve the mediastinum or more distant sites; Stage IA < 3 cm; Stage IB: 3 to 4 cm; Stage II: >4 cm in the tumor size, respectively. Involvement in stage IIIA is heterogeneous ranging from tumor ≤ 1 cm with metastasis in ipsilateral mediastinal and/or subcarinal lymph node (T1a, N2) to a localized large tumor > 7 cm without any lymph node involvement (T4, N0). Stage IIIB consists with tumors ≤ 5 cm and contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node (T1-2b, N3) or tumor > 7 cm with N2 involvement. Stage IIIC is tumors with >5 cm with N3 involvement. Stage IV includes tumor

involvement in a contralateral lobe, presence of malignant pleural (or pericardial) nodules/effusions, or distant metastases.

TREATMENT

Stages I and II

- Stages I and II NSCLC are considered early-stage disease. These two stages combined account for approximately 30% of all NSCLC patients.
- Five-year survival rates are 68% to 92% for stage I and 53% to 60% for stage II.
- Surgical resection is the recommended treatment for patients with stage I and stage II NSCLC. In patients who are medically fit for surgical resection, lobectomy or greater resection is recommended rather than sublobar resections (wedge resection or segmentectomy) (Figure 2.2).
    - A study of the surveillance, epidemiology, and end results database evaluating wedge resection versus lobectomy found that OS and lung cancer–specific survival (LCSS) favored lobectomy when compared with segmentectomy or wedge resection in patients with tumors ≤ 1 cm and > 1 to 2 cm. With sublobar resection, lower OS and LCSS was demonstrated for NSCLC > 1 to 2 cm after wedge resection, whereas similar survivals were observed for NSCLC ≤ 1 cm.

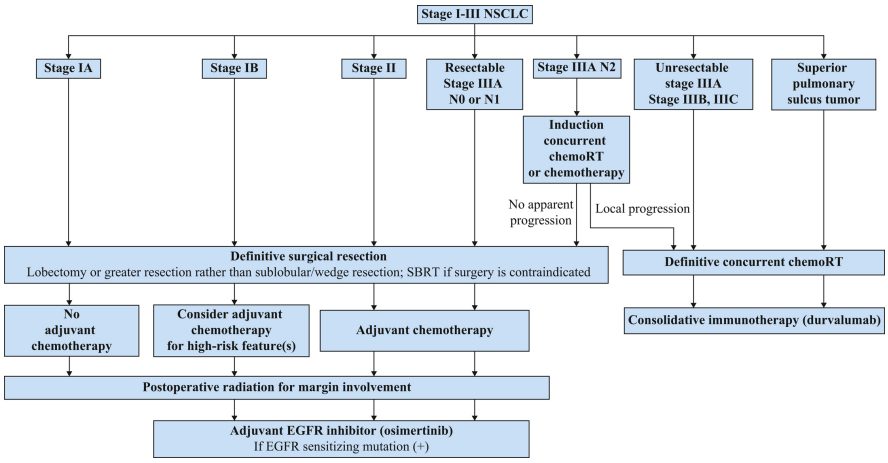

FIGURE 2.2 Definitive treatment algorithm for non–small cell lung cancer (NSCLC) patients with stage I-III; TNM Classification of Malignant Tumors (UICC) eighth edition by American Joint Committee on Cancer (AJCC) is adopted.High-risk features for stage IB NSCLC include poor differentiation, vascular invasion, visceral or pleural involvement, wedge resection, and unknown of lymph node status (Nx). chemoRT, concurrent chemoradiation; SBRT, stereotactic body radiation therapy.

- Video-assisted thoracoscopic surgery or robotic-assisted thoracoscopic surgery are acceptable alternatives to open thoracotomy.
- Intraoperative systematic mediastinal lymph node sampling or dissection is recommended for accurate pathologic staging.
- If surgery is contraindicated in early-stage NSCLC, radiotherapy can be an effective means of local control. Stereotactic body radiation therapy (SBRT) rather than conventional radiotherapy is recommended given a phase III randomized study reporting that SBRT demonstrated significant better local control of the primary disease compared with conventional radiation in stage I NSCLC (hazard ratio, HR [95% CI]: 0.32 [0.13-0.77], P = .0077).
- When both adjuvant chemotherapy and RT are planned, RT should be given after completion of adjuvant chemotherapy since concurrent chemoradiotherapy might compromise the ability to deliver the recommended dose and cycles of chemotherapy based on observational data from the National Cancer Database.
- Even with complete curative treatment, approximately half of the patients eventually experience relapse, with a two- to threefold higher proportion of distant metastases over local

recurrences. Adjuvant chemotherapy plays an important role preventing recurrence.

- In selected patients who undergo complete surgical resection, several large trials have demonstrated a statistically significant survival benefit from cisplatin-based adjuvant chemotherapy.
- The lung adjuvant cisplatin evaluation (LACE) meta-analysis which used individual patient data (n = 4584) from five trials with a median follow-up of 5.2 years found that adjuvant cisplatin-based chemotherapy was associated with a decrease in absolute risk of death of 5.4 % at 5 years compared with no chemotherapy (HR [95% CI]: 0.89 [0.82-0.96]).

- Among completely resected early-stage NSCLC, adjuvant chemotherapy is not recommended for stage IA, is standard for stage II, and may be useful in a subset of patients with stage IB.
    - In the LACE meta-analysis, the OS benefit varied considerably by stage of disease, with potential harm seen in stage IA (HR 1.40; 95% CI, 0.95-2.06), a trend toward benefit in stage IB (HR 0.93; 95% CI, 0.78-1.10), and clear benefit in stage II (HR 0.83; 95% CI, 0.73-0.95) patients.
- Since there is no reliable way to identify which stage IB patients may derive benefit from adjuvant chemotherapy, current guidelines recommend chemotherapy in stage IB high-risk patients, defined by poor differentiation, vascular invasion, visceral or pleural involvement, wedge resection, and unknown of lymph node status (Nx).
- Cisplatin-based doublet is the usual adjuvant chemotherapy of choice. Vinorelbine, docetaxel, or gemcitabine and pemetrexed (the latter for nonsquamous histology) can be combined with cisplatin. These combination chemotherapies are given up to four cycles. Although OS and disease-free survival (DFS) are similar with these combinations, adverse event profiles vary. Cisplatin is preferred over carboplatin in the adjuvant setting unless the patient has comorbidities such as preexisting hearing loss or neuropathy that might be worsened with cisplatin.
- EGFR sensitizing mutations should be evaluated in surgically resected tumors. If targetable EGFR mutations are identified and the patients completed adjuvant chemotherapy, adjuvant osimertinib (80 mg once daily) is recommended until disease recurrence, or unacceptable toxicity, or for up to 3 years.
    - Efficacy was demonstrated in a randomized, double-blind, placebo-controlled trial (ADAURA) in patients with EGFR-mutated (exon 19 deletions or exon 21

L858R) NSCLC who had complete tumor resection (stage IB—IIIA), with or without prior adjuvant chemotherapy. Patients were randomized to receive osimertinib 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy, if given. Osimertinib group showed significantly improved 2-year DFS rates (90 vs 44%, HR [95% CI]: 0.17 [0.11-0.26]). Common toxicities with osimertinib were diarrhea (46%), paronychia/dry skin/pruritus (18%-25%), and stomatitis (18%).

- Patients with microscopic involvement of the resection margin with tumor should consider reresection or postoperative radiotherapy (PORT). National Cancer Database study showed OS benefit with PORT in margin-involved stage II and III NSCLC patients (median OS: 33.5 vs 23.7 months; $P < .001$ with and without PORT, respectively).
- The role of targeted therapies beyond EGFR and immunotherapy in the adjuvant setting are under investigation.

Stage IIIA

- Stage IIIA NSCLC is a therapeutically challenging subset of lung cancer, with a 5-year survival rate of only 36%.
- Randomized trials strongly suggest a combined modality approach in stage IIIA disease. Conflicting data, however, have led to difficulties in proposing specific management guidelines. This, in part, is secondary to the heterogenous nature of stage IIIA disease.
- Clinically N0 or N1 patients (=no mediastinal/subcarinal lymph node involvement) are often taken for upfront surgical resection with cure achievable in 25% to 50% of these patients. However, should incidentally discovered N2 disease be found at surgery, complete tumor resection and mediastinal lymphadenectomy is recommended. With the high rate of recurrence in this patient population adjuvant chemotherapy to address micrometastatic disease is recommended.
    - The International Adjuvant Lung Cancer Trial of 1867 patients with stages IB to IIIA (39% stage IIIA) randomized patients to three to four cycles of postoperative cisplatin-based chemotherapy versus surgery alone, with adjuvant 60 Gy radiotherapy given to both arms of stage IIIA patients (the use of radiotherapy was left to investigator's choice). After a median 56-month follow-up, the OS rate was significantly higher in the chemotherapy group (HR

of 0.86, $P < .03$), with a 5-year OS rate of 44.5% in the chemotherapy group versus 40.4% in the control arm, with the strongest benefit in patients with stage III disease in the subgroup analysis.
    - The ANITA study randomized 840 completely resected patients with stages I to IIIA (35% stage IIIA) to four postoperative cycles of cisplatin and navelbine versus observation (radiotherapy as per preference of participating center). After a median follow-up of >70 months, long-term 5-year OS of stage IIIA patients in the chemotherapy arm was significantly greater at 42% versus 26% in the observation arm ($P = .013$).
- Similar to high-risk stage IB and II, adjuvant osimertinib after completion of adjuvant chemotherapy is recommended for surgically resected stage IIIA EGFR-mutated tumors.
- PORT while reducing local recurrence does not improve survival, may be detrimental, and is not recommended as standard of care unless surgical margin is involved. Advocates of radiotherapy have emphasized that there are several differences between the treatment administered in several trials included in the meta-analysis below and current practices in the United States.
    - The PORT meta-analysis (Meta-Analysis Trialist Group) of 2128 patients treated in nine randomized trials with a median follow-up of 3.9 years found a significant increase in risk of death with PORT (overall risk ratio 1:21; $P = .001$).
- Individuals with clinically apparent (bulky) N2 disease or those found at mediastinoscopy prior to thoracotomy should not undergo upfront surgery based on the poor results of primary resection for bulky stage IIIA disease. Poor survival rates with surgery alone in N2 disease, even with postoperative chemotherapy or radiotherapy, have led to the use of radiotherapy and/or chemotherapy in the neoadjuvant setting, with the aim of making an unresectable tumor resectable and improving long-term survival. Theoretically, advantages include shrinking the tumor to allow for easier resection and nodal clearance, decreased surgical seeding, in vivo chemosensitivity testing of the chemotherapy regimen, and increased patient acceptance and compliance. Disadvantages of neoadjuvant therapy may include delayed tumor resection and increased surgical morbidity and mortality. While high rates of pathologic complete response and negative mediastinal nodes

result from neoadjuvant chemoradiotherapy, it is also associated with substantial toxicity.
    - A meta-analysis evaluating neoadjuvant chemotherapy found a nonstatistically significant trend in favor of neoadjuvant chemotherapy (HR 0.65; 95% CI, 0.41-1.04).
    - Two clinical trials (European Organization for Research and Treatment of Cancer 08,941 and North American Intergroup 0196) showed no significant difference in OS between patients with bulky stage IIIA NSCLC treated with neoadjuvant chemotherapy then surgery versus definitive chemoradiation alone (no surgery).
- The standard dose-fractionation of radiation used in concurrent chemoradiation is 60 Gy given in 2-Gy once-daily fractions over 6 weeks.
- Recommended concurrent chemotherapy regimens are; for nonsquamous NSCLC: cisplatin + pemetrexed, carboplatin + pemetrexed, paclitaxel + pemetrexed, or cisplatin + etoposide; for squamous NSCLC: paclitaxel + carboplatin or cisplatin + etoposide. No randomized phase III trials of concurrent chemoradiotherapy have shown the superiority of one chemotherapy regimen over another.
- If disease progresses locally after induction chemotherapy, concurrent chemoradiation can be considered similar to the treatment for stage IIIB and IIIC (described below). If the disease systemically progress, palliative systemic treatment should be considered as stage IV disease.
- The use of concurrent chemotherapy/radiotherapy versus sequential treatment has been addressed in numerous trials. At present, for patients with bulky N2 or N3 disease treatment with concurrent over sequential chemotherapy/radiotherapy is recommended.
- Concurrent chemotherapy/radiotherapy followed by consolidation chemotherapy is currently not recommended as standard of care.

Stage IIIB, IIIC

- All patients with N3 (metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or

supraclavicular node) involvement or T4 N2 disease are stage IIIB. Patients with T3 or 4 N3 NSCLC are stage IIIC. Anticipated 5-year survival rates for most patients with stage IIIB and IIIC disease is 26% and 13%, respectively.

- Optimal treatment depends on extent of disease, age of patient, comorbidities, PS, and weight loss.
- Stage IIIB and IIIC lung cancers are not amenable to curative surgical resection.
- For patients with stage IIIB or IIIC disease with PS of 0 to 1 and minimal weight loss (<5%), platinum-based combination chemoradiotherapy followed by chemotherapy is recommended.
- Induction chemotherapy followed by concurrent chemoradiotherapy is not superior to initial treatment with concurrent therapy.
- The role of additional cycles of chemotherapy following concurrent chemoradiotherapy is uncertain; however, this is usually administered to manage potential micrometastatic disease, especially if full doses of systemic chemotherapy were not delivered during radiotherapy.
- After completion of chemoradiation for unresectable stage III NSCLC, consolidative treatment with a PD-L1 inhibitor durvalumab is recommended.
    - A randomized phase III PACIFIC trial demonstrated PFS and OS benefit with consolidative durvalumab treatment (10 mg/kg every 2 weeks up to 12 months) compared with placebo after completion of concurrent chemoradiation therapy in patients with unresectable stage III NSCLC (HR [95% CI]: 0.51 [0.41-0.63] and 0.68 [0.54-0.86], respectively).

Superior Pulmonary Sulcus (Pancoast) Tumors

- Superior pulmonary sulcus (Pancoast) tumors are located at the apical pleuropulmonary groove, adjacent to the subclavian vessels, causing shoulder pain, neurological complications involving the upper extremity, and Horner syndrome.
- Superior pulmonary sulcus tumors are typically >5 cm (T3 or T4). In the absence of distant lymph node and organ metastases,

the tumors usually fall into stage IIB (T3 N0), IIIA (T3N1, or T4N0-1), or IIIB (T3-4N2).

- Superior pulmonary sulcus tumors with N0 or N1 involvement should be treated with concurrent chemoradiation. Surgical resection can be considered if the tumor is resectable after chemoradiation. Several studies have shown survival benefit with the concurrent chemoradiation compared with radiotherapy followed by surgery or surgery alone in superior pulmonary sulcus tumors.
- Superior pulmonary sulcus tumors with N2 or N3 involvement are considered unresectable and should be treated with concurrent chemoradiation alone.
- Consolidative durvalumab should follow after completion of chemoradiation, similar to other stage III NSCLC as described above.

Stage IV

- Prognosis for patients with advanced-stage NSCLC is poor. Best supportive care produces median survival rates of 4.5 months and 1-year survival rates of 20%. Addition of chemotherapy improves 1-year survival to 29%.
- Subsets of patients whose intrathoracic disease is not amenable to combined treatment modalities are treated as though they have stage IV disease.
- One exception is M1a disease with contralateral solitary lung nodule. These can be considered as two primary lung tumors if both are curable with surgical resection or other definitive local therapies (radiation including SBRT or image-guided thermal ablation). Similarly, recurrence of limited disease such as solitary brain metastasis can also be treated with definitive local therapy including surgical resection or SBRT. However, only relatively small percentage (15%-25%) of patients will achieve long-term disease-free intervals with local treatment after recurrence.

- Therapy options for patients with advanced or metastatic disease includes targeted therapy, immunotherapy, and/or chemotherapy as these are shown to improve OS and quality of life (QoL) and reduce symptoms from disease burden. However, systemic therapy is only palliative in nature, and not curative, therefore supportive therapy alone may be chosen if the patient is unable to tolerate systemic treatments due to poor PS or other comorbidities. One exception is NSCLC patients with poor PS (Eastern Cooperative Oncology Group [ECOG] PS 3 or 4) and targetable molecular profiles, where the likelihood of response with TKIs is high and can eventually improve their PS and QoL.
- It is important to understand the concepts underlying targeted therapy and immunotherapy and perform molecular testing including immune checkpoint markers (EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, KRAS, PD-L1 expression) before choosing treatment options.

Driver Gene Alterations and Targeted Therapy

- Historically, a lung cancer diagnosis was based on histology but now it incorporates molecular profile of tumors. Identification of specific molecular alterations that drive each tumor have enabled widespread use of targeted therapies.
- Molecular diagnostics should be performed on solid tumor tissues. If it is not feasible, blood-based tests (so-called "liquid" biopsies) can be considered. However, we need to keep in mind a limitation that the blood-based molecular test can be falsely negative compared with traditional tumor biopsies, given possible low amounts of DNA that tumors may shed into circulation.
- If an urgent systemic treatment is required (eg, visceral crisis) before results of genotype testing are available, systemic chemotherapy may be initiated prior before tumor molecular profile is available.
- Although immunotherapy has shown durable efficacy in NSCLC without driver mutations, PD-1 or PD-L1 blockade prior

to or concurrent with targeted therapy for patients with targetable driver mutations is not recommended outside clinical trials. Combination of immunotherapy and TKIs are associated with higher-risk of pulmonary toxicities;

- EGFR mutation
  - Point mutations within EGFR exons 18 to 21, which encode a portion of the EGFR tyrosine kinase domain, predict tumor sensitivity to EGFR TKIs (first generation: erlotinib and gefitinib; second generation: afatinib and dacomitinib; third generation: osimertinib). Generally, first generation TKIs reversibly bind to EGFR, whereas second and third generation agents bind irreversibly and can overcome several resistance-related mutations.
  - First or second generation EGFR TKIs were initially tested and yielded response rates of 55% to 80% and PFS of 9 to 14 months in patients with EGFR-mutated NSCLC. The activity of EGFR-TKIs differs among various types of EGFR mutations with deletion mutations in exon 19 responding more favorably than exon 21 L858R mutations. Diarrhea, cutaneous eruption, nausea, and anorexia reported are the most common adverse effects of EGFR TKIs.
  - The eventual development of acquired resistance generally limits the duration of response to EGFR TKIs. Almost 50% of patients whose disease progress on first or second generation EGFR TKIs develop an EGFR T790M "gatekeeper mutation." Third-generation EGFR TKIs block activating EGFR mutations as well as the T790M resistance mutation and yield responses among patients with EGFR-mutated NSCLC and acquired resistance to initial TKIs. Osimertinib is the current standard first-line treatment of patients with EGFR-mutated NSCLC.
  - Osimertinib yielded an ORR of 61% in patients who had progressed on an EGFR TKI and had confirmed EGFR T790M resistance. The median PFS was 9.6 months in EGFR T790M-positive patients and 2.8 months in EGFR T790M-negative patients.
  - The randomized double-blind phase III study (FLAURA) showed significant PFS and OS benefit with osimertinib compared with first generation EGFR TKIs for patients with previously untreated EGFR exon 19 or L858R–mutated NSCLC (median PFS: 18.9 vs 10.2 months, HR = 0.46; median OS: 38.6 vs 31.8 months, HR = 0.80, respectively).
  - Osimertinib also decreased frequency of CNS progression. Of 116 patients with brain metastases in the FLAURA study, patients in osimertinib arm had significant longer PFS compared with those on the gefitinib or erlotinib arm (median PFS: 15.2 vs 9.6 months, HR = 0.47). Brain metastasis-specific PFS was also longer with osimertinib (not reached vs 13.9 months, HR = 0.48). Moreover, the rate of intracranial disease progression was lower (6% vs 15%) over treatment time course. Among patients with response-evaluable brain metastases, the intracranial ORR was also higher with osimertinib (91% vs 68%).
  - Repeat tumor or liquid biopsy should be considered at progression on EGFR TKIs to elucidate resistance mechanisms. Acquired EGFR TKI resistance mechanisms include additional EGFR resistance mutations (eg, C797S mutation

with osimertinib: observed up to 10%), alternative pathway activation (MET or HER2 amplification, NRAS or PIK3CA mutation, ALK or RET fusion: up to 17%), and histological transformation (epithelial-to-mesenchymal transition, and squamous cell or SCLC transformation: up to 15%). Importantly, the acquired resistance mechanisms remain unknown in approximately 40% of EGFR-mutated NSCLC after progression on TKIs.

- If patients have systemic disease progression on osimertinib, systemic treatment options for NSCLC without any targetable molecular profiles should be considered (discussed below). If patients have systemic disease progression on TKIs other than osimertinib and found to have EGFR T790M mutation, osimertinib is recommended.
- Emerging results of clinical trials suggest that local therapies (eg, surgical resection, SBRT, or ablation) may be effective for patients with EGFR-mutated NSCLC progressing in limited number of areas (<5 lesions, so-called "oligo-disease progression").
- If histological transformation of squamous or SCLC are found, corresponding systemic treatment options for the identified histology should be considered.

- ALK rearrangement
  - Crizotinib is a first-generation oral small molecule inhibitor of the ALK, MET, and ROS tyrosine kinases. It was initially granted FDA approval for first-line therapy of patients with ALK-rearranged nonsquamous NSCLC.
  - Subsequently, next generation ALK inhibitors, alectinib, brigatinib, and lorlatinib were developed and showed OS and/or PFS benefit over crizotinib and are currently recommended to use as first-line treatment for ALK-rearranged NSCLC.
    - In a phase III trial (ALEX), alectinib showed significantly better PFS and OS compared with crizotinib in treatment-naïve advanced ALK-positive NSCLC patients (median PFS: 34.8 vs 10.9 months, HR = 0.43; median OS: not reached vs 57.4 months, HR = 0.67). The time to intracranial progression in the overall population was also improved with alectinib over crizotinib. Alectinib was also less toxic than crizotinib; major toxicities were elevation of liver enzymes and gastrointestinal toxicities (nausea, vomiting, diarrhea).
    - Another phase III study (ALTA 1L) showed that improvement of PFS with brigatinib compared with crizotinib (estimated PFS at 12 months: 67% vs 43%, HR = 0.49). Adverse events that occurred at a higher incidence with brigatinib than crizotinib included an increased creatine kinase level, cough, and hypertension, whereas elevation of liver enzymes and gastrointestinal toxicities were more frequent with crizotinib than brigatinib. Interstitial lung disease/pneumonitis occurred 4% and 2% of patients in brigatinib and crizotinib arms, respectively.
    - A third phase III study (CROWN) demonstrated significantly improved PFS with lorlatinib compared with crizotinib (PFS at 12 months: 78% vs 38%, HR = 0.28). The time to intracranial progression was also improved with lorlatinib compared with crizotinib (intracranial PFS at 12 months: 96% vs 60%, HR = 0.07). Lorlatinib was associated with higher frequency of hypercholesterolemia (at any grade: 70% vs 4%), edema (55% vs 39%), peripheral neuropathy (34% vs 15%), and cognitive effects (21% vs 6%).
  - Another ALK inhibitor ceritinib also demonstrated improvement of PFS compared with combination chemotherapy in a phase III study enrolled patients with previously untreated ALK-mutated NSCLC (ASCEND-4: median PFS: 16.6 vs 8.1 months, HR = 0.55). However, due to lack of clinical evidence comparing ceritinib and crizotinib in the first-line setting, the next-generation ALK inhibitors are preferred in the first-line setting over ceritinib.
  - If patients experience systemic disease progression upon ALK inhibitors and have not received lorlatinib, lorlatinib should be considered.

        - Lorlatinib is known to have activity against ALK inhibitor-resistant mutations including ALK G1202R. In a phase II study (B7461001) that included a subgroup of 139 ALK-positive metastatic NSCLC patients previously treated with second generation ALK TKIs, ORR with lorlatinib was 40%. The ORR and PFS were better in tumors with ALK mutations in addition to the ALK rearrangement than without (ORR: 62% vs 32%; median PFS: 11.0 vs 5.4 months), suggesting that tumor genotyping for ALK mutations after failure of a second-generation ALK inhibitor may identify patients who are more likely to benefit from lorlatinib.
    - If patients experience disease progression with crizotinib, next generation ALK TKIs (alectinib, brigatinib, or ceritinib) can be considered given that several phase II studies have shown better antitumor efficacy with these ALK TKIs over chemotherapy after progression with crizotinib.
- ROS1 rearrangement
    - A ROS1/MET inhibitor crizotinib and ROS1/tropomyosin receptor kinase (NTRK) inhibitor entrectinib have shown antitumor activity in patients with advanced ROS1-rearranged NSCLC and are approved for use in such patients.
        - In an open-label, international phase II trial (PROFILE 1001) of 53 patients with ROS1-rearranged NSCLC, including more than 80% of patients who had been treated with chemotherapy, crizotinib yielded ORR of 72% and median PFS of 19.3 months. Major adverse events included vision disorder (87%), nausea (51%), edema (47%), diarrhea (45%), vomiting (38%), and elevation of liver enzymes (36%).
        - In a pooled analysis of three phase I or II trials including 161 ROS1 fusion-positive patients, entrectinib demonstrated ORR of 67% and PFS of 15.7 months. Entrectinib also showed intracranial activity (intracranial ORR of 79.2%). Major adverse events were similar to those of crizotinib.
    - Ceritinib also showed activity in a relatively small single-arm phase II study ($n = 32$) that showed ORR of 62% and median PFS of 9.3 months.
- If patients have systemic disease progression on crizotinib, lorlatinib should be considered given a phase I/II study showing ORR of 35% in patients with crizotinib-treated NSCLC harboring ROS1-rearrangement.
- MET exon-14 skipping mutation
    - Capmatinib is a MET inhibitor showing antitumor response in NSCLC with MET exon-14 skipping mutation. In a phase II GEOMETRY-mono-1 trial, capmatinib demonstrated ORR of 41% and median PFS of 5.4 months among 97 patients with NSCLC harboring MET exon-14 skipping mutation, including 28 treatment-naïve ones. Capmatinib also showed intracranial activity (intracranial ORR of 54%). Most common adverse events were edema (51%), nausea (45%), vomiting (28%), and increased creatinine (24%).
    - Tepotinib, another MET inhibitor, also showed antitumor activity for NSCLC with MET exon-14 skipping mutation (ORR of 46%). Toxicity profiles were similar to capmatinib.
    - If patients have systemic disease progression on either MET inhibitor, systemic treatment options of NSCLC without any targetable molecular profiles should be considered (discussed below).
- RET rearrangements
    - The RET inhibitor selpercatinib has demonstrated efficacy in patients with RET fusion-positive NSCLC. In the multicohort, open-label phase I/II study (LIBRETTO-001), the ORRs were 85% and 64% in treatment-naïve and platinum-treated patients; 90% and 63% of them lasted the response >6 months, respectively. Most frequent grade 3 or 4 adverse events were hypertension

(14%), elevated liver enzymes (10%), hyponatremia (6%), and lymphopenia (6%). Selpercatinib also showed intracranial activity.
    - Another RET inhibitor pralsetinib showed antitumor activity with ORR of 70% and 57%, with 58% and 80% of these responses lasting >6 months, in treatment-naïve and platinum-treated RET-rearranged NSCLC patients, respectively.
    - If patients have systemic disease progression on either RET inhibitor, systemic treatment options of NSCLC without any targetable molecular profiles should be considered (discussed below).
- BRAF V600E mutation
    - In a phase II study, the combination of BRAF and MET inhibitors dabrafenib and trametinib achieved ORR and median PFS of 63% and 9.7 months in previously treated advanced NSCLC with BRAF V600E mutation. Similar antitumor efficacy was also observed in treatment naive population (ORR and median PFS: 64% and 10.9 months). The side effect profile was consistent with those in melanoma: pyrexia, elevation of liver enzymes, and ejection fraction decrease.
    - Single-agent vemurafenib may be considered if the combination of dabrafenib and trametinib is not tolerated.
    - For NSCLC with non-V600E BRAF mutation, the use of BRAF or MEK inhibitors is not recommended.
    - If patients have systemic disease progression on BRAF and/or MEK inhibitor, systemic treatment options of NSCLC without any targetable molecular profiles should be considered (discussed below).
- KRAS p.G12C mutation
    - Sotorasib, the first targeted agent for patients with KRAS-mutated tumors, has been tested in NSCLC. In a single-group, phase 2 trial, sotorasib 960 mg was administered orally for patients with metastatic NSCLC with KRAS p.G12C mutation and treated with at least one line of systemic therapy. Among 126 enrolled patients, the ORR was 37.1% including four patients with complete response. Median duration of response, PFS, and OS were 11.1 months, 6.8 months, and 12.5 months, respectively. Major ≥ grade 3 treatment-related adverse events were liver function test abnormalities and diarrhea. Based on these data, sotorasib was FDA-approved in this setting.
- NTRK fusion
    - For patients with tumors harboring NTRK1, NTRK2, or NTRK3 gene fusions, larotrectinib or entrectinib should be considered given the tumor agnostic FDA approval of these agents for advanced cancers with NTRK fusion. The frequency of NTRK fusion in NSCLC is very low (<1% prevalence). The ORR of larotrectinib and entrectinib were 79% and 57% in patients with advanced cancers with NTRK fusion in early-phase clinical trials.
- Other oncogene mutations.
    - HER2 mutations are detected in approximately 1% to 3% of NSCLC. Multiple anti-HER2 therapy have been tested in clinical trials but no FDA-approved HER2-directed therapies are currently available for NSCLC.

Immunotherapy and Checkpoint Inhibition

- Immune checkpoint inhibitors harness the adaptive immune system, one of the most important regulators in the elimination of malignant cells from the human body through the formation of cancer-specific T lymphocytes.
- Antitumor immune system has been focused on since discovery of immune checkpoints CTLA-4, PD-1, and its ligand PD-L1 in 1990s, leading the Nobel Prize in Physiology or Medicine in 2018. The adaptive immune system utilizes NK cells, macrophages, and additional inflammatory cells to penetrate the microenvironment as antigen-presenting cells, which subsequently activate T cells leading to the formation of CD4 and CD8 cells. The goal of this pathway is the destruction of cancer cells. However, two normal immune pathways, or immune checkpoints including proteins described above, have been found to suppress this T cell response. Blockade of these immune checkpoints has shown tolerability and durable antitumor efficacy in multiple cancers including NSCLC.
- Immune checkpoint inhibitor monotherapy initially showed significant OS benefit compared with single-agent chemotherapy in previously treated relapsed or recurrent NSCLC (details discussed in the section "Second-Line and Subsequent Therapies"). Subsequently the efficacies of these drugs were demonstrated in the first-line setting (1) in combination with platinum-based chemotherapy, (2) single-agent in tumors with high PD-L1 expression, and (3) combination of dual immune checkpoint blockade (inhibitors of PD-1 and CTLA-4), which demonstrated better OS than platinum-doublet chemotherapy alone (details discussed in the section "First-Line Therapy for Metastatic NSCLC Without Targetable Molecular Profiles").
- PD-L1 expression has been reported as a biomarker to predict likelihood of response with immune checkpoint inhibitors. Different PD-L1 antibodies and evaluation methods are used among different immune checkpoint inhibitor trials. Therefore,

it is recommended to evaluate PD-L1 expression by corresponding methods used in the referring clinical trials (eg, nivolumab and ipilimumab: Dako. PD-L1 IHC 28-8 pharmDx; pembrolizumab and cemiplimab: Dako. PD-L1 IHC 22C3 pharmDx test; atezolizumab: VENTANA SP142 PD-L1 IHC assay).

- Tumor mutational burden (TMB) can surrogate overall tumor neoantigen load. High TMB has been reported as a predictive biomarker for immunotherapy in multiple cancer types including NSCLC. Pembrolizumab received FDA approval in June 2020 for irrespective of cancer types with high TMB (≥10 mutations per megabase). Although there are no specific indications of immunotherapy for NSCLC based on TMB, further studies are warranted.
- Common adverse events with immune checkpoint inhibitors are caused by upregulation of systemic autoimmunity: dermatologic (rash, pruritus), pulmonary (pneumonitis), gastrointestinal (diarrhea, colitis), hepatic (hepatitis), pancreatic (pancreatitis), endocrine (thyroiditis, hypophysitis, adrenal insufficiency, type 1 diabetes), and other less common autoimmune disorders. These can sometimes be serous eventually resulting in death but usually are manageable with immunosuppressants such as steroids or hormone replacement therapy.

First-Line Therapy for Metastatic NSCLC Without Targetable Molecular Profiles

- Several factors must be considered in choice of first-line treatment for metastatic or recurrent NSCLC: age, PS, comorbidities, molecular abnormalities, PD-L1 expression, and histology of the tumor (Figure 2.3).

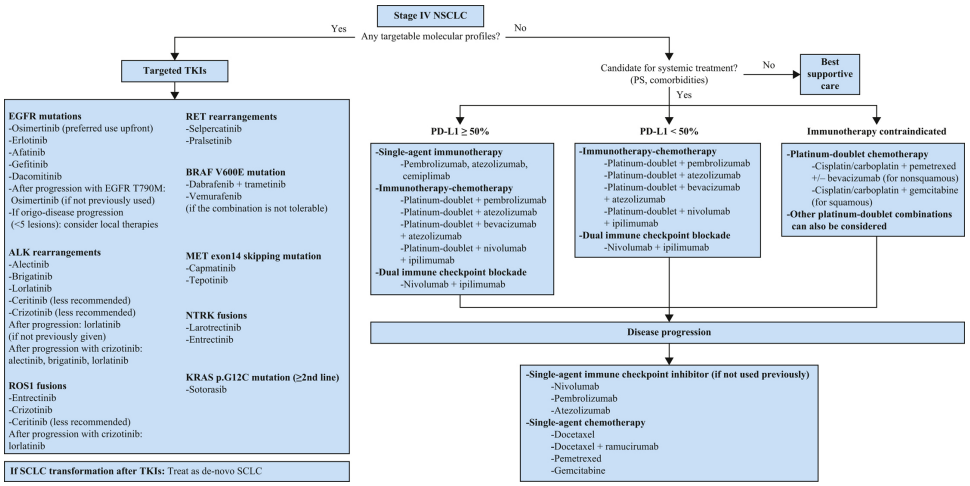

FIGURE 2.3 Palliative treatment algorithm for non–small cell lung cancer (NSCLC) patients with stage IV; targeted tyrosine kinase inhibitors (TKIs) should be considered even if patients have poor performance status (PS) given that the likelihood of response with TKIs in patients with targetable molecular profiles is exceptionally high leading to PS improvement and that TKIs can easily be administered by mouth.Expressions of programmed death-ligand 1 (PD-L1) should be evaluated with the same method used in the corresponding clinical trials of the immune checkpoint inhibitors. Although immunotherapy-involved therapeutic approaches in the first-line setting (single-agent immunotherapy for PD-L1 ≥ 50% tumors, immunotherapy-chemotherapy combination, dual immune checkpoint blockade ± chemotherapy) have separately shown significant better benefit than chemotherapy alone, there are currently no results of head-to-head clinical trials comparing efficacy among them. Therefore, these treatment options need to be addressed case by case considering likelihood of achieving benefit (eg, by PD-L1 expression) versus risk (eg, increasing toxicity by adding platinum-based chemotherapy or CTLA-4 inhibitor to single-agent immune checkpoint inhibitor).

- Patients with tumors harboring targetable molecular profiles should receive corresponding TKIs first. The relevant clinical trial data are discussed above under the section “Driver Gene Alterations and Targeted Therapy.”
- For patients with metastatic NSCLC without targetable molecular profiles and good PS (ECOG PS 0-2), treatment options are determined based on PD-L1 expression. For advanced NSCLC with PD-L1 expression <50% of tumor cells, combination treatment with platinum-doublet chemotherapy

and immunotherapy (± vascular endothelial growth factor [VEGF] inhibitor) is recommended.

- First-line combination of pembrolizumab with platinum-doublet chemotherapy (cisplatin or carboplatin + pemetrexed) was tested in advanced nonsquamous NSCLC without EGFR- or ALK-sensitizing mutations in the phase III KEYNOTE-189 trial. The immunochemotherapy combination demonstrated significant improvement of PFS (median PFS: 8.8 vs 4.9 months, HR = 0.52) and OS (median OS: not-reached vs 11.3 months, HR = 0.49) compared with chemotherapy alone. Twelve-month OS improvements were observed in all PD-L1 expression categories, with the greatest improvement observed in high PD-L1–expressing tumors (OS at 12 months among PD-L1 expression <1% subgroup: 62% vs 52%, HR = 0.59; PD-L1 1%-49%: 72% vs 51%, HR = 0.55; PD-L1 > 50%: 73% vs 48%, HR = 0.42).
- Another phase III study IMpower150 randomly assigned advanced nonsquamous NSCLC patients to platinum-doublet chemotherapy (carboplatin + paclitaxel) + atezolizumab (ACP); chemotherapy + atezolizumab + bevacizumab (ABCP); or chemotherapy + bevacizumab (BCP). Among EGFR or ALK-negative NSCLC patients, ABCP group showed significant better PFS (median PFS: 8.3 vs 6.8 months, HR = 0.62) and OS (19.2 vs 14.7 months, HR = 0.78) compared with BCP. Similarly, randomized phase III studies IMpower130 and IMpower132 demonstrated significant improvement of PFS and OS by adding atezolizumab to carboplatin and nab-paclitaxel or platinum + pemetrexed in nonsquamous advanced NSCLC patients, respectively.
- A phase III study KEYNOTE-407 showed significant benefit of PFS and OS by adding pembrolizumab to carboplatin + paclitaxel or nab-paclitaxel compared with chemotherapy alone (median PFS and OS: 6.4 vs 4.8 months, HR = 0.56; 15.9 vs 11.3 months, HR = 0.64, respectively) in patients with advanced squamous NSCLC.

- For advanced NSCLC with PD-L1 expression ≥ 50% of tumor cells, single-agent immune checkpoint inhibitors can also be considered, sparing patients cytotoxic chemotherapy-related toxicities.
  - In a phase III study (KEYNOTE-024), patients with advanced NSCLC expressing PD-L1 of ≥50% without EGFR- or ALK-sensitizing mutations were randomly assigned to single-agent pembrolizumab or platinum-doublet chemotherapy. Initial analysis showed prolongation of PFS (median PFS: 10.3 vs 6.0 months, HR = 0.50) and subsequent longer follow-up confirmed OS benefit (median OS: 30.0 vs 14.2 months, HR = 0.63). Severe (≥grade 3) treatment-related adverse effects were lower among patients receiving pembrolizumab compared with chemotherapy (27% vs 53%).
  - Atezolizumab also showed significant OS and PFS benefit compared with platinum-based chemotherapy in patients with advanced NSCLC with PD-L1 expression on ≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells (IMpower 110, median PFS and OS: 8.1 vs 5.0 months, HR = 0.63; 20 vs 13 months, HR = 0.59, respectively).

- Another PD-1 inhibitor cemiplimab improved PFS and OS over platinum-doublet chemotherapy in patients with advanced NSCLC expressing PD-L1 of ≥50% without EGFR, ROS1, or ALK genetic aberrations (EMPOWER-Lung 1 trial, median PFS and OS: 8.2 vs 5.7 months, HR = 0.54; not reached vs 14.2 months, HR = 0.57, respectively).

- Even if the tumors express PD-L1 ≥ 50%, chemotherapy-immunotherapy combination is recommended if the patients have rapidly progressing disease or visceral crisis, in whom an early response may be beneficial.
- A potential alternative option for advanced NSCLC expressing PD-L1 ≥ 1% is dual immune checkpoint blockade with PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab ± chemotherapy. However, worse toxicity and recent negative study result of the combination treatment compared with single-agent PD-1 inhibitor, this option should carefully be chosen.
  - In a phase III study CheckMate-227, treatment-naïve NSCLC patients were randomly assigned to either nivolumab + ipilimumab or platinum-based chemotherapy. In the subset of patients with PD-L1 expression ≥ 1%, the median OS was 17.1 versus 14.9 months with HR of 0.79. In patients with PD-L1 expression of 1% to 49%, the median OS was similar between the two treatment arms (median OS: 15.1 vs 15.1 months). Patients with PD-L1 expression of ≥50% showed an OS advantage over chemotherapy (median OS: 21 vs 14 months, HR = 0.70).
  - CheckMate-9LA, a phase III trial, addressed the benefit of adding nivolumab and ipilimumab to standard platinum-doublet chemotherapy in treatment-naïve advanced NSCLC. The dual immunotherapy-chemotherapy combination showed significantly better PFS and OS compared with chemotherapy alone (median PFS and OS: 6.7 vs 5.0 months, HR = 0.68; 15.6 vs 10.9 months, HR = 0.66).
  - However, more patients experience serious (≥grade 3) immune-related adverse events with the combination of ipilimumab and nivolumab compared with single-agent immune checkpoint inhibitor. The frequencies of major organs involved with serious (≥grade 3) adverse events with nivolumab + ipilimumab versus nivolumab alone were: liver (8.2% vs 3.8%); skin (4.2% vs 1.0%); endocrine (4.2% vs 0.5%); lung (3.3% vs 1.5%); and/or gastrointestinal (2.4% vs 1.0%).
  - A recent randomized, double-blinded phase III study (KEYNOTE-598) tested the efficacy of additional ipilimumab (1 mg/kg every 6 weeks for up to 18 doses) to pembrolizumab for previously untreated metastatic NSCLC with PD-L1 tumor proportion score of ≥50%. Median PFS was 8.2 versus 8.4 months in ipilimumab-pembrolizumab versus placebo-pembrolizumab arms (HR 1.08, 95% CI 0.85-1.37, *P* = .74). Similar to trials above, ipilimumab-pembrolizumab combination associated with worse treatment-related toxicities (frequency of

grade 3-5 adverse events: 62.4% of pembrolizumab-ipilimumab recipients vs 50.2% of pembrolizumab-placebo recipients, leading death rate of 13.1% vs 7.5%, respectively).

- Although these immunotherapy-based therapeutic approaches have shown significant benefit compared with chemotherapy alone, there are currently no head-to-head clinical trials comparing these treatment approaches. Therefore, treatment options need to be individualized considering likelihood of achieving benefit (eg, by PD-L1 expression) versus risk (eg, increasing toxicity by adding platinum-based chemotherapy or CTLA-4 inhibitor to single-agent immune checkpoint inhibitor).
- For patients with advanced NSCLC without targetable molecular profiles who have relative or absolute contraindications to immunotherapy (eg, active or previously documented autoimmune disease and/or current use of immunosuppressive agents), especially patients whose tumors do not express PD-L1 (<1%) where the benefit of adding immunotherapy to chemotherapy is relatively small as described above, platinum-doublet chemotherapy without immunotherapy should be a consideration.
- Histology is an important determinant of the choice of chemotherapy agent. A phase III trial comparing pemetrexed/cisplatin to cisplatin/gemcitabine in 1700 advanced/metastatic NSCLC patients in the first-line setting found similar OS between both treatment arms. However, subset analysis based on histology revealed significant differences.
    - In patients with adenocarcinoma histology, combination of pemetrexed with cisplatin demonstrated improved survival and reduced toxicity compared with gemcitabine/cisplatin. OS was 12.6 months in the pemetrexed arm versus 10.9 months in the gemcitabine arm.
    - Conversely, those with squamous histology showed improved survival with cisplatin/gemcitabine (10.8 months) as initial chemotherapy treatment versus pemetrexed/cisplatin (9.4 months).
- Platinum-doublet chemotherapy is usually given up to four to six cycles. Additional cycles of chemotherapy do not improve efficacy but do increase toxicity. After completion of chemotherapy, maintenance treatment is considered based on

efficacy and tolerability with upfront treatment (details discussed in the section "Maintenance Treatment"). Addition of a third chemotherapeutic agent to platinum-based doublet has failed to show benefit.

- Bevacizumab, a recombinant humanized monoclonal antibody that is directed against VEGF, (thereby preventing its interaction with the VEGF receptor) is approved for treatment of nonsquamous advanced/metastatic NSCLC in combination with chemotherapy as first-line treatment.
    - The phase III ECOG 4599 trial randomized patients with nonsquamous NSCLC (n = 878) to chemotherapy (carboplatin/paclitaxel) alone or with bevacizumab and found significant improvements in OS (median 12.3 vs 10.3 months), PFS (median 6.2 vs 4.5 months), and response rates (35% vs 15%) in the bevacizumab arm. The risk of treatment-related deaths was higher in patients who received bevacizumab.
    - The AVAiL trial further evaluated bevacizumab in nonsquamous histology tumors randomizing patients to cisplatin/gemcitabine with or without two different doses of bevacizumab. Although addition of bevacizumab significantly prolonged PFS, the improvement was modest (median 6.7 and 6.5 months, respectively, for bevacizumab 7.5 mg/kg and 15 mg/kg, respectively; 6.1 months for placebo), and there was no OS benefit with addition of bevacizumab. It is unclear if the lack of OS benefit is secondary to differences in chemotherapy between the two trials.
    - The PointBreak trial compared carboplatin and bevacizumab with either pemetrexed or paclitaxel in the first-line setting for nonsquamous NSCLC patients with ECOG PS 0 to 1. After four cycles, patients in the pemetrexed arm received maintenance bevacizumab plus pemetrexed, whereas those in the paclitaxel arm received maintenance with bevacizumab alone. OS was not significantly different between the two arms (12.6 vs 13.4 months).

Maintenance Treatment

- Maintenance therapy is the use of systemic therapy in patients with a response or stable disease after first-line therapy until disease progression or unacceptable toxicity with goals of delaying disease progression and to extend survival, without adversely affecting QoL.
- As described above, treatment paradigms in advanced NSCLC have shifted to use immunotherapy-based treatments upfront. After completion of platinum-based chemotherapy, it is recommended to continue immunotherapy if immunotherapy-

chemotherapy is chosen or dual checkpoint inhibition (nivolumab + ipilimumab) until disease progression or patients cannot be tolerable, as original trials were designed. It is emerging controversy when to stop immunotherapy for patients who achieved durable response (eg, 1 year vs 2 years after completion of chemotherapy). Currently continuation versus discontinuation immunotherapy need to be addressed case by case considering benefit and risk including financial toxicity and need to discuss with individual patients.

- For patients who have completed platinum-doublet chemotherapy, one of the drugs used in first-line therapy (continuation maintenance) or a new agent (switch maintenance) may be used for maintenance.
- Pemetrexed, bevacizumab, gemcitabine, or pemetrexed plus bevacizumab may all be chosen as continuation maintenance options.
    - The PARAMOUNT trial, double-blind, placebo-controlled trial, which investigated continuation pemetrexed maintenance therapy in patients with nonsquamous histology, found that pemetrexed maintenance resulted in a 36% reduction in risk of progression (HR 0.64; 95% CI, 0.51-0.81; *P* = .00025).
    - The phase III, IFCT-GFPC 0502 trial randomized patients to maintenance gemcitabine, erlotinib, or observation after lack of progression on cisplatin/gemcitabine as upfront therapy. A significant improvement in PFS was observed for the gemcitabine maintenance (HR 0.51; 95% CI, 0.39-0.66). Gemcitabine may be used in patients with squamous histology for continuation maintenance.
    - The PointBreak trial discussed previously showed a very small PFS improvement (6 vs 5.6 months) with pemetrexed/bevacizumab maintenance at the expense of increased toxicity in the form of neurotoxicity, neutropenia, and alopecia.
- Pemetrexed (for nonsquamous NSCLC) or docetaxel (for squamous NSCLC) are options for switch maintenance therapy.
    - A phase III study evaluated the use of pemetrexed maintenance following nonprogression with nonpemetrexed-containing platinum-based chemotherapy versus best supportive care. Pemetrexed significantly improved not only PFS (4.3 vs 2.6 months; HR 0.5; 95% CI, 0.42-0.61; *P* < .0001) but also OS (13.4 vs 10.6 months; HR 0.79; 95% CI, 0.65-0.95; *P* = .012) compared to placebo, respectively.
- Maintenance chemotherapy may be ideal in patients where close monitoring for disease progression is not feasible and for whom rapid disease progression after the completion of first-

line treatment may preclude administration of active second-line agents.

Second-Line and Subsequent Therapies

- Most patients who undergo first-line therapy will eventually develop disease progression, and second-line therapy is administered in this setting.
- Second-line therapy has an impact on survival and QoL in advanced NSCLC; therefore, patients with a PS of 0 to 2 should be offered further treatment following progression.
- Immunotherapy is considered as a preferred second-line treatment option if the patient has not received in the first-line setting. Nivolumab, pembrolizumab, or atezolizumab should be considered for patients without a contraindication to this treatment after progression on platinum-doublet ± maintenance therapy.
    - In the CheckMate-017 trial of 272 patients with squamous NSCLC, median OS was 9.2 months with nivolumab versus 6.0 months with docetaxel. HR for death was 0.59 with nivolumab ($P < .001$), and the 1-year OS rate was 42% with nivolumab versus 24% with docetaxel.
    - The CheckMate-057 trial evaluated nivolumab versus docetaxel in patients with advanced nonsquamous NSCLC. Median OS was 12.2 in patients treated with nivolumab versus 9.4 months in patients treated with docetaxel. HR for death was 0.73 with nivolumab ($P = .002$), and 1-year OS rate was 51% with nivolumab versus 39% with docetaxel. Subgroup analysis from this trial showed higher efficacy for all end points in patients with PD-L1–positive tumors.
    - The KEYNOTE-010 trial evaluated the role of pembrolizumab in patients with previously treated advanced NSCLC. Patients enrolled on this trial had at least 1% of tumor cells with PD-L1 expression. With pembrolizumab, median OS was 10.4 months at the 2 mg/kg dose and 12.7 months on 10 mg/kg versus 8.5 months with docetaxel. OS was improved with both the doses of pembrolizumab compared with docetaxel. In patients with at least 50% of tumor cells expressing PD-L1, OS was 14.9 months with pembrolizumab 2 mg/kg and 17.3 months with pembrolizumab 10 mg/kg versus 8.2 months with docetaxel.
    - In the phase III OAK trial enrolling 1225 patients PD-L1 unselected, advanced NSCLC who previously received platinum-doublet chemotherapy, atezolizumab, or docetaxel was administered. Atezolizumab significantly improved OS (median: 13.8 vs 9.6 months, HR = 0.73).

- Generally single-agent immune checkpoint inhibitor is not recommended if patients have already received immune checkpoint inhibitors upfront.
- If no targeted treatment options remain or patients have progressed on or cannot be treated with immunotherapy and continue to have a good PS (0-2), then cytotoxic chemotherapies not previously utilized remain viable options including: docetaxel, docetaxel/ramucirumab, gemcitabine, or pemetrexed.
    - The TAX 317, a phase III trial which randomized patients with advanced NSCLC and prior platinum-based chemotherapy (n = 104) to docetaxel (75 mg/m^2 IV every 21 days) or best supportive care found longer OS with docetaxel (median 7.5 vs 4.6 months).
    - In an open-label randomized phase III trial of patients with advanced NSCLC after failure of one chemotherapy regimen (n = 571), pemetrexed (500 mg/m^2 IV every 21 days) resulted in equivalent efficacy outcomes with docetaxel (median OS 8.3 vs 7.9 months for docetaxel) but with significantly fewer side effects.
    - BR 21, a randomized, double blind, placebo-controlled trial of unselected advanced NSCLC patients after failure of one or two chemotherapy regimens (n = 731), demonstrated improved OS with erlotinib (150 mg PO once daily) (6.7 vs 4.3 months for placebo). The phase III REVEL trial (n = 1253) enrolled patients with squamous or nonsquamous NSCLC who had progressed during or after a first-line platinum-based chemotherapy to receive docetaxel and either ramucirumab or placebo. A slight increase in median OS was seen with the combination versus docetaxel alone (10.5 vs 9.1 months, respectively). This came at the expense of increased rates of gastrointestinal bleeding, perforation, or fistula as well as hypertension in the combination arm.
- If disease progression occurs on subsequent chemotherapy or all therapeutic options are exhausted, it is recommended that patients with a PS of 0 to 2 be enrolled in a clinical trial or treated with best supportive care.

LUNG CANCER AND SARS-COV-2

- At the end of 2019, a novel coronavirus disease COVID-19 was identified as the cause of a cluster of pneumonia cases and rapidly spread throughout the world. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can rapidly become severe and eventually cause death. On January 30, 2020, the WHO

declared the COVID-19 outbreak a public health emergency of international concern. The US Centers for Disease Control and Prevention (CDC) considers that cancer represents an established risk for SARS-CoV-2 given that patients with cancers are considered as immunocompromised due to cancer itself and treatments such as cytotoxic chemotherapy. Therefore, delivering care for patients with cancer during this crisis is challenging due to competing risks of death from cancer versus death or serious complications from SARS-CoV-2.

- Emerging data suggest that patients with cancers, especially lung cancers, have higher risk of COVID-19 infection and worse outcomes with SARS-CoV-2.
    - A largest retrospective case-control study was conducted in United States using electric health records including 73.4 million patients from 360 hospitals and 317,000 clinicians. Among 16,570 patients who were diagnosed with COVID-19, 1200 had a cancer diagnosis and 690 had recent cancer history diagnosed within 1 year before COVID-19 diagnosis. Among them, the risk of COVID-19 infection was significantly higher in lung cancer patients (adjusted odds ratio [95% CI]: 7.66 [7.07-8.29], $P < .001$) following hematologic malignancies such as leukemia and lymphoma. The COVID-19 infection in patients cancers resulted significantly worse outcomes than those without (hospitalization, 47.46% vs 24.26%; death: 14.93% vs 5.26%, both $P < .001$).
- As of August 2021, there is no consensus on lung cancer screening for high-risk patients and those with SPNs in the pandemic era. Guidelines from professional societies suggest discussion with patients and individualized management considering other factors (age, benefit vs risk, etc).
- Definitive therapies with curative intent (surgery, radiation) and neoadjuvant/adjuvant therapy should be administered without any interruptions. It may be reasonable to delay adjuvant chemotherapy for up to 4 months postoperatively.
- Palliative systemic treatments (chemotherapy, targeted TKIs, immunotherapy) and radiation should also proceed without any interruptions for advanced NSCLC patients. Expanding intervals of immunotherapy may be considered given FDA approvals of alternative administration schedules for nivolumab (480 mg every 4 weeks instead of 240 mg every 2 weeks) and

pembrolizumab (400 mg every 6 weeks instead of 200 mg every 3 weeks).

- Pneumonitis or interstitial lung disease caused by TKIs or immunotherapy may overlap clinical symptoms and radiological findings with SARS-CoV-2. Therefore, this possibility should be worked up and managed appropriately (holding drugs, COVID-19 PCR, bronchoscopy/bronchoalveolar lavage, etc).
- Interactions of chemotherapy, immunotherapy, and TKIs with severity of SARS-CoV-2 remains to be evaluated.
- Patients with cancer including NSCLC should receive COVID-19 vaccine as soon as possible. Interaction of the vaccine with systemic treatments remain to be evaluated.
- Updated guidelines from American Society of Clinical Oncology, European Society for Medical Oncology, National Comprehensive Cancer Network, etc should be consulted.

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3

Small Cell Lung Cancer

James P. Stevenson, Logan N. Roof

EPIDEMIOLOGY

Small cell lung cancer (SCLC) accounts for approximately 13% of all new lung cancers and is primarily a disease of the smoking population. SCLC is a biologically aggressive disease but multimodality therapy in early-stage SCLC can result in prolonged survival and potential cure in subsets of patients. SCLC is highly responsive to chemotherapy; however, it often relapses rapidly after an initial response, and therefore generally has a poor prognosis.

PATHOLOGY

SCLC is classified within the WHO grouping of neuroendocrine tumors of the lung. SCLC is often poorly differentiated with a high-mitotic rate and proliferation index. Histologic appearance is characterized by small blue cells with scant cytoplasm and high nuclear-to-cytoplasmic ratio. Immunohistochemical stains consistent with small cell characteristics include keratin, tissue transcription factor-1, and epithelial membrane antigen. Neuroendocrine markers such as chromogranin and synaptophysin are often present on IHC, but the absence of these markers does not rule out small cell histology. Up to 30% of SCLC biopsies may contain NSCLC, thereby leading to the hypothesis that lung carcinoma originates from a pluripotent stem cell. Expert pathologists may have difficulty

differentiating SCLC from NSCLC approximately 5% of the time; therefore, review by multiple pathologists may be necessary. It is also important to distinguish SCLC from other neuroendocrine tumors such as typical and atypical carcinoids due to their distinct prognoses and treatment approaches.

CLINICAL PRESENTATION

SCLC is typically symptomatic at presentation, often due to bulky locoregional disease and/or the presence of distant metastases. SCLC is often centrally located, thereby rendering patients susceptible to pulmonary complications, including dyspnea, cough, and postobstructive infections. Common sites of metastatic disease include the brain, liver, bones, and adrenal glands. SCLC is classically associated with several paraneoplastic syndromes, which typically portend a poor prognosis:

- Lambert-Eaton syndrome
- Syndrome of inappropriate antidiuretic hormone
- Ectopic adrenocorticotropic hormone (ACTH) production (Cushing syndrome)
- Ectopic parathyroid hormone production
- Sensory neuropathy
- Paraneoplastic encephalomyelitis

STAGING

The American Joint Committee on Cancer (AJCC) staging system defines the tumor, nodes, metastasis (TNM) subsets used to stage SCLC.

- This staging system can be helpful in prognostication and selection of patients who may benefit from multimodality treatment approaches, including surgical resection in select cases.

Traditionally, SCLC has been divided into limited-stage (LS) and extensive-stage (ES) disease based on the Veterans Administration Lung Group two-stage system.

- LS SCLC is defined as disease that is encompassed safely into one radiation field, and thus amenable to definitive chemoradiation.
- ES SCLC is defined as tumor burden that extends beyond one radiation field, and thus treatment is primarily systemic chemotherapy with noncurative intent.

This simplified staging approach has practical utility, given that the majority of patients present with bulky lymphadenopathy and/or distant metastasis at the time of diagnosis. However, as the role for surgical resection has increased and become more well-defined, the division of cases as LS or ES has become less useful, and it is important to note that the term LS encompasses multiple AJCC stages (I-III). The AJCC TNM staging system definitions are more precise and allow for more refined evaluation of prognosis by stage and better selection of patients who may be candidates for multimodality treatment.

IMAGING

Routine imaging consists of a computed tomography (CT) scan of the chest and abdomen and brain imaging. Brain imaging is necessary in all patients, but in cases where ES disease has been established, further staging work-up is generally not required.

Ten to fifteen percent of SCLC patients have brain metastases at presentation, and early detection and treatment have been shown to improve both morbidity and mortality. MRI is preferred over CT unless there is a contraindication, as MRI has greater sensitivity in detecting parenchymal brain metastases.

Positron emission tomography (PET) imaging is recommended if LS disease is suspected after initial imaging is completed. Fischer et

al demonstrated that PET/CT has a sensitivity and specificity of 93% and 100%, respectively, compared to 79% and 100% with standard staging. PET/CT is not recommended for the assessment of treatment response. Additional imaging and work-up is only recommended if it will impact treatment approach. In patients who appear to have clinical T1-2N0 disease after initial staging, invasive mediastinal staging should be done if the patient is a surgical candidate.

SURVIVAL

The median overall survival (OS) for patients with LS SCLC who receive treatment is 15 to 20 months and for patients with ES SCLC who receive treatment is 8 to 13 months. If untreated, the median OS for ES SCLC is 6 to 12 weeks. The 2-year survival for LS SCLC is 20% to 40% and for ES SCLC is <5%.

TREATMENT

LS SCLC (Stages I-III)

General Concepts

Multimodal approaches are recommended in early-stage disease. Recent data have suggested that surgical intervention may be beneficial in a subset of patients with clinical T1-2N0 disease (about 5% of patients with SCLC) that has been confirmed by pathologic mediastinal lymph node staging. The optimal adjuvant approach for surgical patients has not been well defined but generally includes chemotherapy or chemoradiation. These patients tend to have a better prognosis overall. From a National Cancer Database analysis of 29,994 patients with clinical stages I to III SCLC, 2089 patients who had surgery were matched to patients who did not undergo surgery. There was an increase in median OS for N0 patients treated with surgery of 38 versus 22 months (Figure 3.1).

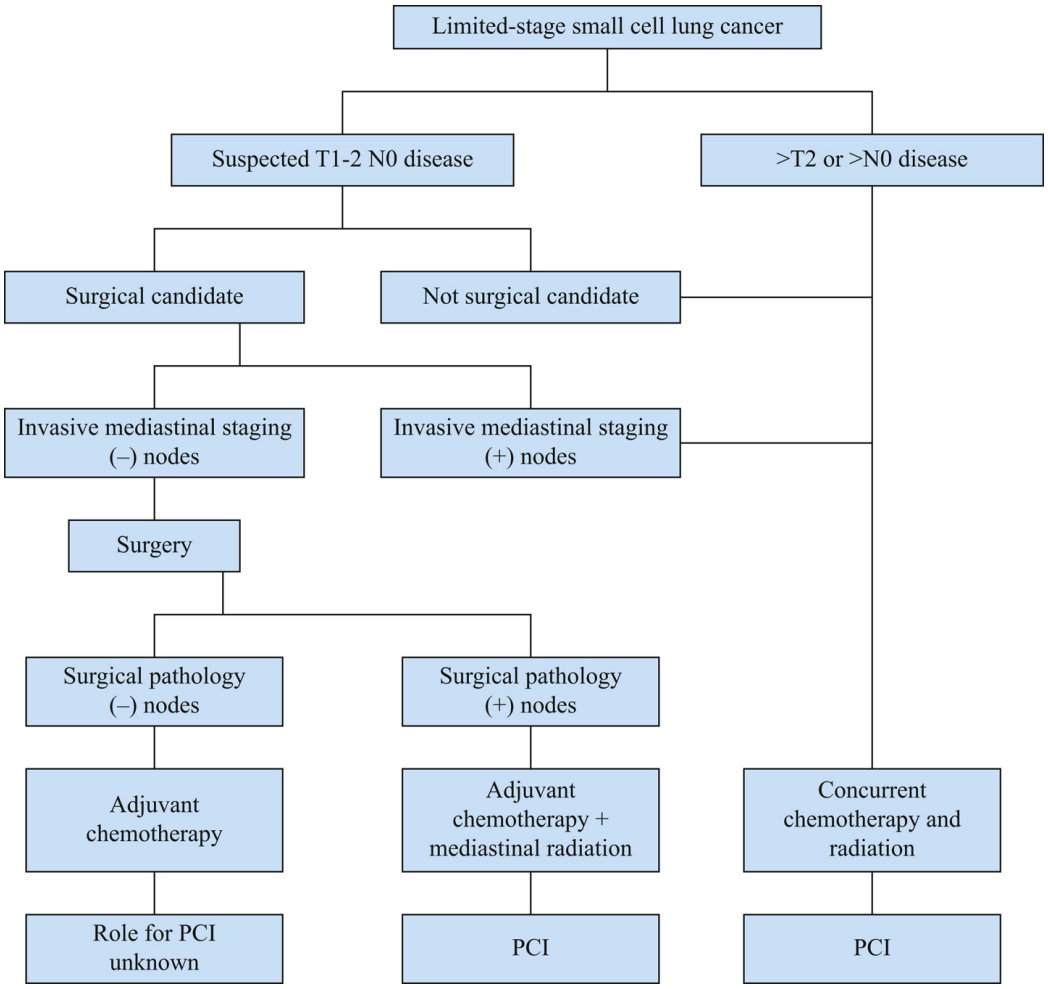

FIGURE 3.1 Recommended treatment algorithm for limited-stage small cell lung cancer.

Stages I to III diseases that are not amenable to surgery (due to nodal involvement or medical contraindications) but can be encompassed within one radiation field should be treated with definitive concurrent chemoradiation. Patients with LS SCLC who are treated with chemotherapy alone have an 80% rate of local recurrence, and the addition of thoracic radiation reduces the rate of local recurrence and improves OS. A meta-analysis of thoracic radiation plus chemotherapy in LS SCLC demonstrated an increase in the rate of local control by 25% to 30%, with a 5% to 7% improvement in 2-year OS when compared to chemotherapy alone.

Chemotherapy in LS SCLC

The most commonly used and preferred chemotherapy regimen in LS SCLC is cisplatin and etoposide. Carboplatin may be substituted in patients who are cisplatin-ineligible (ie, renal insufficiency, substantial hearing loss, neuropathy) or unable to tolerate the volume of fluids needed with cisplatin. Myeloid growth factors are not recommended for use during concurrent chemoradiation. A randomized controlled trial of patients with LS SCLC undergoing chemoradiation with and without granulocyte-macrophage colony-stimulating factors (GM-CSF) found that while the cohort randomized to receive GM-CSF had higher WBC and neutrophil nadirs, there was no significant difference in grade 4 neutropenia or leukopenia. Those randomized to the GM-CSF group were noted to have significantly more life-threatening thrombocytopenia, transfusions, nonhematologic toxicities, days in the hospital, and toxic deaths.

Radiation Therapy in LS SCLC

Concurrent chemoradiation provides superior outcomes when compared to sequential therapy. This approach leads to increased toxicities compared to either modality alone; therefore, candidates for concurrent therapy must be carefully selected. The current standard of care is early thoracic radiation delivered concurrently with cycle 1 or 2 of the standard regimen of cisplatin and etoposide (EP) every 3 weeks and is associated with significantly increased survival rates.

Thoracic radiation may be delivered in single daily fractions over 6 weeks for a total dose of 60 Gy or a hyperfractionated schedule of twice daily fractions over 3 weeks for a total of 45 Gy. The CONVERT trial investigated the efficacy of these treatment schedules and found them to be equivalent; at a median follow-up of 45 months, the median survival in the twice-daily versus once-daily group was 30 versus 25 months, respectively, which was not a statistically significant difference. Prophylactic cranial irradiation (PCI) should be offered to most patients with LS SCLC after

successful completion of combined multimodality therapy and is described in more detail in a subsequent section.

Monitoring Response in LS SCLC

For patients undergoing adjuvant therapy or concurrent chemoradiation, response assessment with imaging should be deferred until completion of the treatment. For patients who are receiving systemic therapy alone or sequential chemotherapy and radiation, surveillance scans after every two cycles and at the completion of therapy is recommended. PET/CT is not recommended to monitor treatment response. In patients who have a complete or partial response, PCI can be considered. For patients with a complete response, partial response, or stable disease, office visits with repeat chest CT scans should be done every 3 months during the first 2 years, every 6 months in years 3 through 5, and then annually. New pulmonary nodules should be worked up as potential second primary malignancies depending on the time frame in which they appear. Patients with LS SCLC who have recurrent disease are candidates for subsequent systemic therapy with noncurative intent.

ES SCLC (Stage IV)

General Concepts

The treatment intent for ES SCLC is noncurative; treatment goals include improved survival and maintenance of good quality of life. Treatment selection should be tailored to achieving these goals (Figure 3.2).

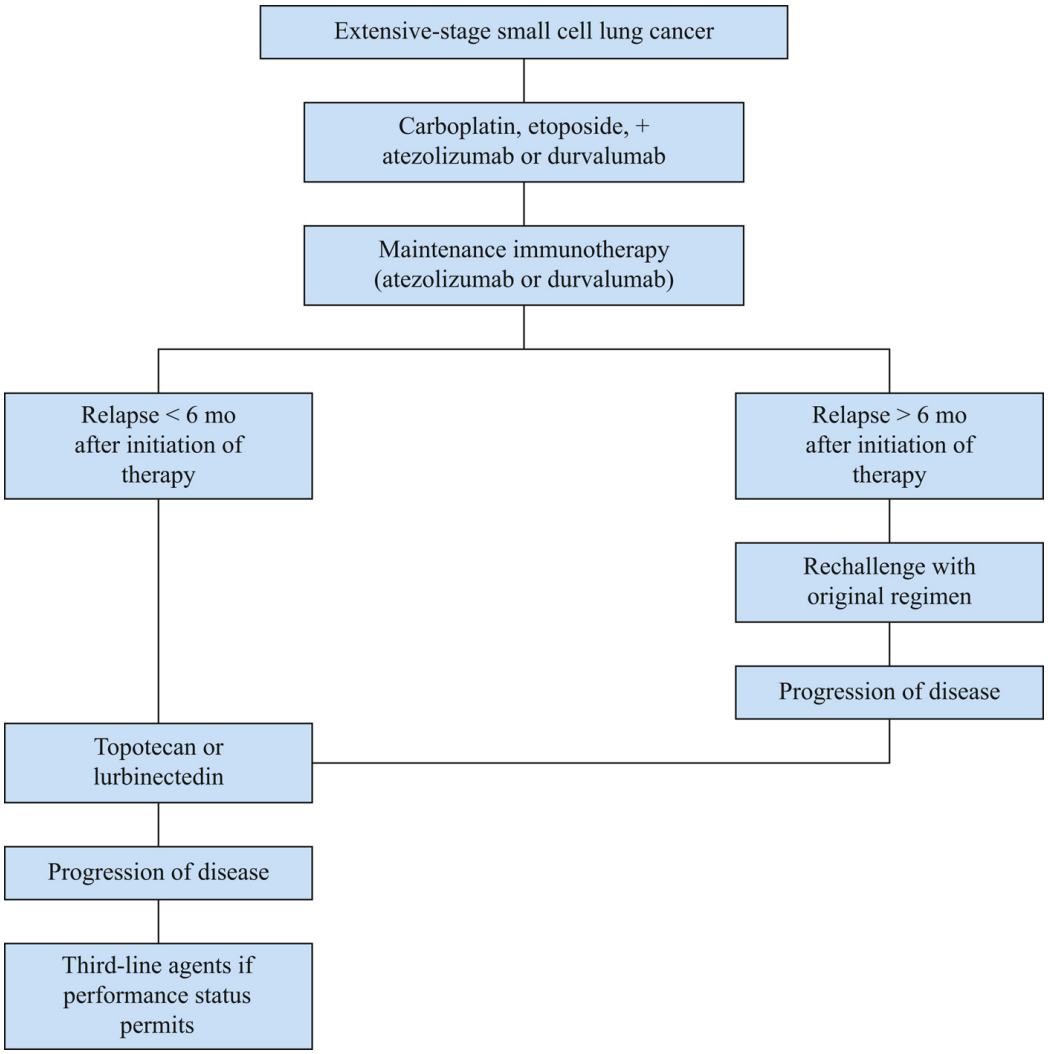

FIGURE 3.2 Recommended treatment algorithm for extensive-stage small cell lung cancer.

Chemotherapy in ES SCLC

There have been significant changes in the treatment of ES SCLC in recent years. Platinum and etoposide regimens remain the standard of care in the frontline setting for ES SCLC. Carboplatin is typically used in ES disease due to its more favorable side effect profile. A meta-analysis of four trials comparing cisplatin and carboplatin in the frontline treatment of SCLC demonstrated similar outcomes; of the 663 patients included in the analysis, 68.3% had ES disease. In these patients, median OS was 9.6 months in the cisplatin group and

9.4 months in the carboplatin group, with a median progression-free survival (PFS) of 5.5 and 5.3 months, respectively. The baseline patient characteristics (ie, gender, age, performance status, stage) and outcomes were not significantly different.

The addition of immunotherapy to standard first-line treatment of ES SCLC has demonstrated efficacy in numerous trials. The first of these was the IMPOWER133 study of the addition of humanized monoclonal antiprogrammed death ligand 1 (PD-L1) antibody atezolizumab to standard carboplatin and etoposide during induction and continued as maintenance in ES SCLC. In this randomized trial, 403 patients were assigned to receive carboplatin and etoposide with either atezolizumab or placebo for four cycles, followed by maintenance atezolizumab or placebo. At a median follow-up of 23 months, the median PFS was 5.2 months in those receiving atezolizumab versus 4.3 months in the placebo group and the median OS was 12.3 months in the atezolizumab group versus 10.3 months in the placebo group; both of these improvements were statistically significant.

Another trial demonstrating benefit was the CASPIAN trial, in which 537 patients with ES SCLC were randomly assigned to receive the anti–PD-L1 antibody durvalumab plus four cycles of platinum-etoposide followed by maintenance durvalumab versus four to six cycles of platinum-etoposide. This study showed improved OS in the durvalumab plus chemotherapy group of 12.9 versus 10.5 months in the chemotherapy group. Updated PFS at 24 months was 11% for durvalumab plus chemotherapy versus 2.9% for chemotherapy. The 2-year response rates with durvalumab plus chemotherapy was shown to be durable at 13.5% versus 3.9% in the chemotherapy group.

Based on these trials, immunotherapy plus platinum-etoposide induction for four to six cycles with immunotherapy maintenance continued until progression or unacceptable toxicity has become the new standard of care in the frontline treatment of ES SCLC. There are multiple ongoing trials of combinations of immunotherapy with

standard chemotherapy in the upfront setting for patients with ES SCLC, with the hope that survival in these patients may be further improved.

Relapsed/Refractory SCLC

Eighty percent of patients with SCLC and nearly all with ES SCLC will have relapsed disease within the first 12 months after first-line therapy. If the cancer relapses within the first 3 months of initial treatment, it is defined as refractory/resistant disease and is associated with a poor prognosis. If patients have disease progression more than 3 months after completion of initial treatment with platinum-based chemotherapy, it is termed sensitive disease. A systematic analysis of 21 trials reported that patients with sensitive SCLC have higher response rates (27.7% vs 14.8%) and longer median OS (7.73 vs 5.45 months) when compared to those with refractory/resistant SCLC. In patients who have refractory disease or relapse within the first 6 months of completion of frontline therapy, topotecan remains a therapy of choice. Oral or IV topotecan may be used, as efficacy and toxicity are similar; both routes of administration lead to OS of approximately 6 months. Topotecan was found to have an improvement in quality of life and survival when compared to best supportive care in a randomized trial.

The original randomized trial of topotecan in relapsed SCLC was published over 20 years ago, underscoring the need to develop more effective systemic agents in this setting. An open-label trial of the alkylating agent lurbinectedin in 105 patients with SCLC and no brain metastases who progressed on platinum-based chemotherapy showed a 35% overall response rate. The median duration of response was 5.1 months, with 25% of the patients who had a response demonstrating a duration of response greater than 6 months. This led to the subsequent FDA approval of lurbinectedin for metastatic SCLC with progression of disease on or after platinum-based chemotherapy.

In 2018, nivolumab was granted accelerated FDA approval for the treatment of SCLC with progression after platinum-based chemotherapy and at least one subsequent line of therapy. This approval was based on Checkmate 032, a phase I/II trial. At a median follow-up of 28.3 months, the objective response rate was 11.9%, with a median duration of response of 17.9 months. Subsequent studies intended to confirm these results did not meet their primary endpoints of OS. Checkmate 451, a phase III trial of nivolumab plus ipilimumab and nivolumab monotherapy as maintenance therapy after first-line chemotherapy in ES SCLC did not show significant prolongation of OS with nivolumab plus ipilimumab versus placebo. Checkmate 331, a phase III trial of nivolumab versus standard chemotherapy (topotecan or amrubicin) in relapsed SCLC did not show improvement in OS with nivolumab versus chemotherapy. This led to the withdrawal of this indication for nivolumab in SCLC.

Patients who relapse greater than 6 months after completion of frontline therapy represent a more favorable prognosis and may be retreated with the original regimen. It is unclear how much benefit the continuation of immunotherapy may have in this population, and there are ongoing studies to help delineate the role for various immunotherapy agents in relapsed ES SCLC. Topotecan and lurbinectedin are the agents to consider in patients who are not candidates for a repeat course of platinum/etoposide.

Radiation Therapy in ES SCLC

Patients with ES SCLC who responded to chemotherapy were randomized to receive thoracic radiation or no thoracic radiation in a phase III randomized controlled trial. All patients in the study received PCI. While the primary endpoint of 1-year survival did not differ between the groups, secondary analysis demonstrated a significant 2-year survival difference of 13% in the radiation group versus 3% in the control. In patients who respond to initial chemotherapy, the addition of thoracic radiation may be considered in select patients, especially those who presented with bulky intrathoracic disease.

Monitoring Response in ES SCLC

During systemic therapy for ES SCLC, CT scans should be obtained after every two to three cycles to assess response. Patients who show a response should continue chemoimmunotherapy for up to six cycles in the frontline setting and should continue immunotherapy until disease progression or unacceptable toxicity. For subsequent lines of therapy, responding patients should continue therapy until disease progression, as tolerated.

Prophylactic Cranial Irradiation

Intracranial metastases occur in more than half of patients with SCLC. These brain metastases represent a significant source of morbidity and mortality in this population. PCI consists of five to ten fractions of whole-brain radiation delivered to prevent the onset of symptomatic brain metastases. Each treatment consists of 1.5 to 2 Gy per fraction. Higher PCI doses (>3 Gy), concurrent chemotherapy, and high total radiation doses have been associated with late neurological toxicity. In LS SCLC, a meta-analysis demonstrated a 25% reduction in the cumulative incidence of brain metastases at 3 years (33% to 58%) and an improvement in 3-year OS (20.7% vs 15.3%) with PCI. There are conflicting data regarding PCI in ES SCLC. An EORTC trial of PCI versus observation alone in patients who showed a partial or complete response to combination chemotherapy demonstrated decreased incidence of brain metastases and improved 1-year OS from 13.3% to 27.1%. However, a subsequent phase III trial of 224 patients demonstrated no survival benefit for patients with ES SCLC with PCI versus observation alone; this trial required brain MRI at baseline and at specified time points in follow-up unlike the EORTC trial.

Therefore, PCI is recommended in patients with LS SCLC who achieve a PR or CR after multimodality therapy. Its use can be considered on an individual basis in patients with ES SCLC but is not generally recommended given the poor OS for these patients and the potential for added toxicity. PCI is not recommended for any

patients with poor ECOG PS (3-4), multiple comorbidities, or impaired cognition. PCI is not given concurrently with chemotherapy due to potentially cumulative neurotoxicity.

New Therapeutic Directions

Many chemotherapeutic combinations have been evaluated against platinum plus etoposide in the frontline setting but none have clearly demonstrated superior outcomes. A phase III trial demonstrated no benefit with the addition of paclitaxel to cisplatin and etoposide in ES SCLC, with an increase in treatment-related mortality in the experimental group (6.5% vs 2.4%). A randomized trial of the addition of the antiangiogenic agent bevacizumab in combination with platinum-based chemotherapy did not show benefit with the addition of bevacizumab compared to chemotherapy alone.

Breakthroughs in immunotherapy have recently changed the standard of care in ES SCLC, with the addition of atezolizumab or durvalumab to standard chemotherapy in the frontline setting. There are many additional ongoing studies of immunotherapy and chemotherapy combinations in both LS and ES SCLC treatment.

Another agent, rovalpituzumab tesirine (Rova-T), targets delta-like protein 3 (DLL-3), which is present on nearly two-thirds of SCLC tumor cells. This is an antibody-drug conjugate, delivering the toxin pyrrolobenzodiazepine to the DLL-3 expressing tumor cell. An open-label single-arm phase II trial enrolled 339 patients with SCLC who had progressed on at least two lines of prior therapy to assess the safety and efficacy of Rova-T. Median OS was 5.6 months in all patients and 5.7 months in DLL3-high patients. Rova-T was the first noted molecular-targeted agent in patients with SCLC; however, results demonstrated modest clinical activity in the third-line and beyond setting and had associated toxicities. Other specific genomic and receptor-based targets will continue to be areas of investigation in SCLC.

Suggested Readings

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4

Esophageal Cancer

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INTRODUCTION

Worldwide, esophageal cancer is the seventh most commonly occurring cancer and the sixth most common cause of cancer-related mortality. Approximately, 50% to 60% of patients present with incurable locally advanced or metastatic disease. Recent years have seen advances in the management of esophageal cancer resulting in meaningful improvements in outcomes.

EPIDEMIOLOGY

United States

Esophageal cancer occurs less frequently in the United States than in other geographic regions. It is estimated that there will be 19,260 cases and 15,530 deaths in 2021, 2.6% of all cancer deaths in the United States. The age-adjusted incidence from 2014 to 2018 was 4.2 per 100,000 per year. The median age at diagnosis is 68 years.

Esophageal cancer is approximately four times more common in men than women. The incidence is higher in lower socioeconomic groups and in urban areas, particularly in black men. Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) account for 93% of all esophageal tumors. The prevalence of esophageal cancer is slightly higher in white people; however, ADC is more common in white people and SCC in Black people. Historically and worldwide, SCC is

the most common type; however, the incidence of ADC has increased significantly, and ADC now accounts for over half of all cases in Western countries. After a steep increase from 1973 to 2001, there has been a plateau in incidence in recent years. In contrast, rates for SCC have been decreasing because of reduced tobacco and alcohol consumption. Five-year relative survival rates were 5% from 1975 to 1977, 10% from 1987 to 1989, and 20% from 2011 to 2017.

Worldwide

About 80% of cases of esophageal cancer occur in less developed regions. The highest incidence occurs in Asia (Northern China, India, and Iran) followed by Southern and Eastern Africa. In the high-risk areas of Asia, 90% of cases are SCC, which may be related to potential environmental and dietary carcinogens, such as low intake of fruits and vegetables and drinking beverages at high temperatures.

ETIOLOGY

Recognized causes of esophageal cancer are described in Table 4.1. Smoking has a synergistic effect with alcohol consumption, and together, they are responsible for 90% of all SCC cases in Western countries. Barrett esophagus is the greatest risk factor for ADC. It increases the risk of ADC 30-fold over the general population.

TABLE 4.1

Causes of Esophageal Adenocarcinoma and Squamous Cell Carcinoma

Adenocarcinoma	Squamous Cell Carcinoma
Barrett esophagus	Tobacco smoking
Induced by chronic GERD	Alcohol
GERD	Achalasia
Obesity	Plummer-Vinson syndrome
Due to risk of GERD	Tylosis
Smoking	Human papillomavirus (HPV)

Adenocarcinoma	Squamous Cell Carcinoma
	Celiac disease
	Esophageal diverticula and webs
	Dietary factors

GERD, gastroesophageal reflux disease

Management recommendations are as follows:

- Nondysplastic Barrett esophagus: endoscopy every 3 to 5 years
- Low-grade dysplasia: endoscopic ablation or surveillance every 6 to 12 months
- High-grade dysplasia: endoscopic eradication therapy (resection of visible irregularities followed by radiofrequency ablation) preferred over esophagectomy or intensive 3-monthly endoscopy

CLINICAL PRESENTATION

Both ADC and SCC have similar presentations. Early symptoms are subtle and nonspecific. Due to vague nonspecific symptoms, unfortunately, the majority of cases present at a locally advanced or metastatic stage. Later symptoms are described in Table 4.2. Physical signs, usually only seen at late presentation, include Horner syndrome, left supraclavicular lymphadenopathy (Virchow node), hepatomegaly, and those related to a pleural effusion.

TABLE 4.2
Clinical Presentation of Esophageal Cancer

Local Tumor Effects	
Dysphagia (solids then liquids)	Odynophagia
Weight loss and anorexia	Regurgitation of undigested food
Iron-deficiency anemia secondary to chronic gastrointestinal blood loss	
Invasion of Surrounding Structures	
Hoarseness secondary to recurrent laryngeal nerve involvement	
Tracheo- or bronchio-esophageal fistula	Hiccups (phrenic nerve invasion)
Distant Metastases	

Cachexia	Pain
Hypercalcemia	Dyspnea/jaundice/ascites (metastatic sites)

DIAGNOSIS

Endoscopy is the gold standard investigation and allows for histological confirmation with biopsy. It has been shown that several biopsies improve diagnostic accuracy and six to eight biopsies are recommended to allow sufficient tissue for histological interpretation and yield a diagnostic accuracy close to 100%.

PATHOLOGY

The common histologic subtypes are ADC and SCC, which account for approximately 93% of esophageal cancers. Rarely, small cell carcinoma, melanoma, sarcoma, lymphoma, or carcinosarcoma may arise in the esophagus. Fifty percent of tumors arise in the lower one-third, 40% in the middle one-third, and 10% in the upper one-third of the esophagus. Most SCCs occur in the upper- and mid-esophagus while ADC generally arises in the distal esophagus and esophagogastric junction (EGJ). Metastases to locoregional lymph nodes occur early because the lymphatics are located in the lamina propria. Involvement of celiac and perihepatic nodes is more common in ADC due to distal tumor location.

STAGING

Adequate staging is required in order to determine the appropriate therapeutic approach. Patients should be assigned a clinical stage according to the American Joint Committee on Cancer tumor-node-metastasis classification, which has distinct SCC and ADC systems. The Siewert classification subclassifies EGJ tumors into three types according to their anatomic location and may be useful for selecting the surgical approach. Type I are distal esophagus tumors, type II are cardia tumors, and type III are subcardia gastric tumors.

Tumors involving the EGJ with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancers, while EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as gastric cancers.

Standard staging includes computed tomography (CT) of thorax, abdomen, and pelvis (TAP) and endoscopic ultrasonography (EUS). CT evaluates for the presence of metastatic disease, with an accuracy of over 90%, and for direct invasion of local structures, which may preclude surgical intervention. EUS allows assessment of the relationship of an esophageal mass to the five-layered esophageal wall and is superior to CT in evaluating the histologic depth of the tumor and determining nodal burden (accuracy of ~80% and 75%, respectively). EUS can facilitate fine-needle aspiration of suspicious lymph nodes to allow confirmation of disease involvement. The accuracy of EUS is operator-dependent, and interobserver variability is significant. Positron emission tomography (PET)/CT is more sensitive than CT for detecting distant disease and guidelines recommend its use in patients who are candidates for definitive local therapy after routine staging. Several studies have suggested a change in management in up to 20% of patients with the use of PET/CT in preoperative assessment. The role of laparoscopy in outruling peritoneal disease is uncertain. Gastroesophageal junction tumors, ≥ stage T3 and/or lymph node–positive disease, have significant risk of occult peritoneal dissemination despite otherwise negative staging scans. Diagnostic laparoscopy may be beneficial in identifying occult peritoneal metastases in these cases and is an optional staging investigation for those with no evidence of distant metastatic disease, warranting multidisciplinary team discussion.

TREATMENT

Due to the borderline location between the esophagus and stomach, clinical trials and studies have historically been heterogenous with varying eligibility criteria, including ADC and SCC and tumors from

the EGJ as well as gastric cancer proper, and this has ultimately led to heterogeneous data and treatment practices.

An overview of management strategies for localized disease is shown in Figure 4.1.

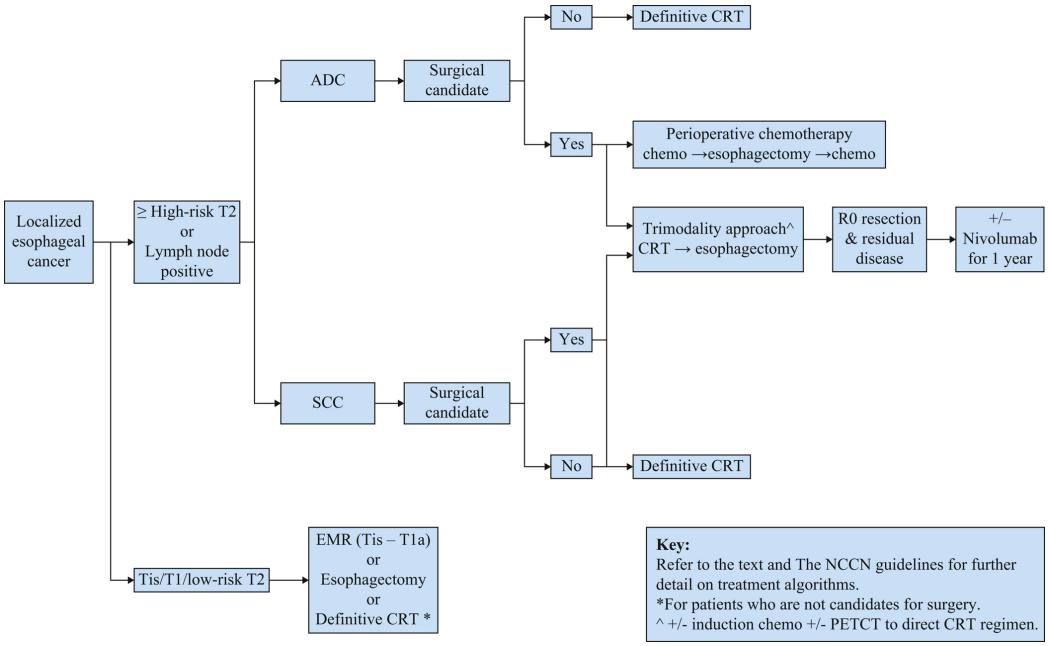

FIGURE 4.1 Algorithm for management of localized esophageal cancers.Refer to the text and The NCCN guidelines for further detail on treatment algorithms.

Surgical Management

- Esophageal cancer (EC) is confined to the esophagus in about 22% and regional nodal disease accounts for a further 30% of cases. Therefore, approximately 50% of patients are potential surgical candidates.
- In recent years, the improved survival seen with combined modality treatment has meant that surgery alone is generally only considered for patients with T1-2N0M0 disease.
- Endoscopic mucosal resection (EMR) is a treatment option for select patients with T1a disease as similar cure rates to

esophagectomy have been reported in specialized centers. EMR is not recommended for T1b cancers as submucosal involvement is associated with a 30% rate of nodal metastases.

- Advances in staging techniques and patient selection have improved surgical morbidity and mortality. Surgical expertise, multidisciplinary management, and management in high-volume centers all contribute to operative mortality rates of less than 5%.
- Surgical principles include a wide resection of the primary tumor and regional lymphadenectomy. Intraoperative frozen section can assess for the presence of residual disease, which may be R1 (microscopic tumor) or R2 (macroscopic tumor). The probability of achieving an R0 resection (no residual tumor) is associated with the depth of tumor infiltration into the esophageal wall.
- The resection status is one of the strongest prognostic factors in esophageal cancer. R0 resection is critical for long-term outcome; results from a retrospective review of 1602 patients demonstrated a 5-year survival of 43.2% for R0-resected patients compared to 11.1% for R1 resection.
- Postesophagectomy cancer-related survival is a function of resection margin and stage, not of surgical approach. The type of resection is dictated by tumor location, conduit choice, surgeon's experience, and patient preference.
- Cervical carcinoma of the esophagus (above the aortic arch) is usually not surgically managed, and definitive chemoradiotherapy (CRT) is the standard of care (SOC).
- The transhiatal (TH), transthoracic (Ivor-Lewis), and tri-incisional esophagectomy procedures are the usual approaches employed in the United States, while esophagectomy with an extended (three-field) lymphadenectomy is commonly utilized in Asia.
- A total thoracic esophagectomy (TTE) is recommended for patients with thoracic esophageal cancer. This involves a cervical esophagogastrostomy, radical two-field lymph node

dissection (mediastinum and upper abdomen nodes), and jejunostomy feeding.

- A tri-incisional approach involving laparotomy, thoracotomy, and a left neck incision for cervical anastomosis is generally advocated over an Ivor-Lewis transthoracic procedure, as tri-incisional surgery allows for more extensive proximal resection margins and a reduced risk of reflux.
- TH esophagectomy is utilized in patients with Siewert II and III EGJ tumors. This involves laparotomy and cervical esophagogastrostomy after resection of the distal esophagus and partial or extended gastrectomy with a two-field lymphadenectomy. TH esophagectomy can also be used for Siewert I EGJ tumors, but a TTE and partial gastrectomy with two-field lymphadenectomy is an option based on a randomized study which showed a nonsignificant improvement in overall survival (OS) for this approach compared to TH esophagectomy.
- Minimally invasive surgical approaches, including laparoscopic, hybrid, and robotic techniques, are increasingly integrated into surgical management of EC, with the aim of reducing complication rates and enhancing recovery times. One randomized trial showed a threefold decrease in postoperative pulmonary infection rate after minimally invasive laparoscopic esophagectomy compared with open transthoracic surgery, this is significant as pulmonary complications are the most frequent complications following esophageal surgery.
- The minimum number of lymph nodes that should be removed has not been established. Some data suggest that a more extensive lymphadenectomy is associated with a better survival. Three-field lymphadenectomy is standard for proximal tumors in Asia, but it is unclear if this approach improves outcomes and it is associated with increased toxicity. In the United States, en bloc resection of the mediastinal and upper abdominal lymph nodes is considered a standard component of transthoracic esophagectomy.

Chemoradiotherapy

Neoadjuvant (Trimodality Approach)

In patients with locally advanced disease (T3-4, N0-3), preoperative therapy is standard. With surgery alone, an R0 resection is not possible in about 30% to 50% and long-term survival rarely exceeds 20%. Preoperative CRT has been shown to result in higher rates of complete resection, better local control, and OS. Several randomized trials have evaluated preoperative CRT versus surgery alone.

Management of patients with clinical T2N0 disease is controversial. These patients were included in three trials including the CROSS trial that showed survival benefit for neoadjuvant CRT but currently there is no clear consensus as to the best approach.

Neoadjuvant CRT is standard for T3 and resectable T4 esophageal cancers based on studies demonstrating a statistically significant OS benefit for CRT. The two most important studies are the CROSS and CALGB 9781 studies:

- CALGB 9781 was a randomized Intergroup trial of trimodality therapy, with cisplatin and 5-FU (CF), versus surgery alone in 56 patients (42 ADC, 14 SCC) with stage I–III esophageal cancer. Five-year OS was 39% versus 16% in favor of trimodality therapy, but this did not reach statistical significance. A pathological complete response (pCR) was achieved in 40% of assessable patients in the trimodality arm, and there was no increase in perioperative mortality.
- The CROSS trial included 363 patients, a majority (75%) had ADC, over 80% had T3/4 tumors, and over 60% were node positive. Preoperative radiation, at a dose of 41.4 Gy, concurrent with carboplatin and paclitaxel weekly for 5 weeks was compared to surgery alone. A significant 5-year OS advantage of 47% versus 33% in favor of the CRT arm was observed, HR 0.67. The benefit appeared significantly greater in patients with SCC. There was also a higher rate of R0 resections (92% vs 69%)

and a 29% complete response rate observed with the use of CRT. Treatment was well tolerated, and there was no increased postoperative mortality associated with the use of CRT.

A meta-analysis in 2011 reported a benefit for trimodality therapy over surgery alone. This included 12 randomized trials of concurrent or sequential neoadjuvant CRT versus surgery alone. The above studies were included. There was an absolute OS benefit of 8.7% at 2 years and benefit was observed across histologic subtypes.

Neoadjuvant CRT has been compared with neoadjuvant chemotherapy in at least four trials, all of which reported similar results, almost exclusively looking at ADC. Of note, two of these trials were underpowered to show a survival advantage. There was no difference in OS between groups but higher rates of pathologic complete response and R0 resections were observed in the CRT groups in all studies.

- The phase III German POET trial evaluated induction chemotherapy alone versus induction chemotherapy followed by low-dose CRT (with cisplatin + etoposide), both followed by surgery. While it was underpowered, secondary to poor accrual, it did show significantly higher pCR (16% vs 2%, $P = .03$) and a nonsignificant trend to improved OS.
- A 2018 network meta-analysis of 31 randomized controlled trials (RCTs) involving 5496 patients demonstrated that neoadjuvant CRT improved OS when compared to neoadjuvant chemotherapy (HR 0.83) and neoadjuvant radiotherapy (HR 0.82).
- The Neo-AEGIS study, reported at ASCO 2021, compared CROSS CRT to perioperative chemotherapy (epirubicin, cisplatin, 5FU [ECF] or equivalent, or FLOT) in esophageal and EGJ ADCs. No difference was seen in 3-year OS (57% vs 56%), but CRT demonstrated increased pCR rates (16% vs 5%) and less toxicity.

There is increased interest in the use of induction chemotherapy prior to CRT and using PETCT to guide post induction CRT regimen as per the phase II CALGB 80803 study. Randomised phase III data are lacking but further studies are on-going to evaluate this. Studies have assessed the addition of biologics, such as trastuzumab and cetuximab, to CRT and have not demonstrated benefit.

Response to previous radiation and/or chemotherapy should be reported as tumor regression grade. Residual primary tumor in resected specimen has prognostic value, as it is associated with OS in both SCC and ADC, and has therapeutic implications, such as the use of adjuvant nivolumab

Definitive CRT in Resectable Disease

Direct comparisons of definitive CRT versus surgery in resectable esophageal cancer are limited. Histological subtypes of SCC and ADC vary in terms of radiosensitivity and role of operative management.

Squamous Cell Carcinoma

Definitive CRT is appropriate in most patients with SCC. The benefit of nonoperative management (avoidance of morbidity and mortality) must be weighed against the lower rates of local control. Two randomized trials have compared CRT alone with CRT followed by surgery and have provided evidence to support a nonsurgical approach in select patients. Despite better local control neither showed improved survival with trimodality therapy.

- A German study evaluated 172 patients with locally advanced resectable SCC. Patients received three cycles of induction 5-FU, leucovorin, etoposide, and cisplatin followed by concurrent CRT (cisplatin/etoposide with 40 Gy radiotherapy) and patients with at least a partial response were randomized to continued CRT (chemotherapy with 20 Gy radiotherapy) or surgery. There was an improvement in local control rates with surgery (64% vs

41% at 2 years), but no difference in OS, and early mortality was less in the CRT arm (12.8% vs 3.5%; *P* = .03).

- FFCD 9102 randomized 444 patients with T3, N0-1, M0 disease to definitive CRT with CF or CRT (lower dose of radiation) and surgery (patients with at least a partial response were randomly assigned to continue CRT or undergo surgery). The majority (89%) had SCC. There was no significant difference in 2-year OS (34% vs 40% for surgery and CRT, respectively) between the groups. Surgically resected patients had lower rates of local recurrence and were less likely to require palliative procedures.

A Cochrane analysis published in 2016 explored this question further, including these two trials, two others comparing CRT alone versus surgery alone and one comparing CRT with surgery and chemotherapy. Again, most patients had SCC. There was no difference in long-term mortality in the CRT group compared with the surgery group (HR 0.88; 95% CI, 0.76-1.03). However, the evidence was considered low-quality and included trials had a high risk of bias.

Adenocarcinoma

Patients with ADC have lower rates of pCR after CRT, and there are limited data on nonsurgical management in this group. Some retrospective studies have reported inferior survival with a nonsurgical approach. MD Anderson published a retrospective analysis of 276 patients, the majority had ADC (78%), who were treated with definitive CRT. Results demonstrated 66.7% of patients relapsed, 14.5% of which were local recurrence only, 15.9% distant relapse only and 36.2% a combination. It is recommended that definitive CRT is reserved for ADC patients with major operative risk.

Experienced multidisciplinary teamwork is required for appropriate use of definitive CRT and decision-making around surgery versus CRT should be taken together with the informed patient.

Definitive CRT in Inoperable Disease

Locally advanced unresectable esophageal cancer is generally incurable but combined modality therapy does offer a small chance of lasting disease control and long-term survival as well as improving quality of life through relief of dysphagia.

The optimal combination, doses and schedule of drugs, that should be used during CRT is not definitively established. Based on the RTOG 85-01 study, CF with radiotherapy can be given for patients with SCC. This study demonstrated an OS advantage (14 vs 9 months median survival and 27% vs 0% 5-year survival) in favor of CRT over radiotherapy alone. The majority of patients had SCC but eligibility for this study did not require surgical unresectability and patients with T4 disease and high nodal burden were not included. Therefore, this cohort likely represents a prognostically more favorable population. A number of randomized trials of CRT versus radiotherapy alone have failed to duplicate these results; however, a Cochrane review has confirmed the superiority of CRT over radiotherapy in patients with a good performance status.

In the PRODIGE-5 study, cisplatin/5-FU was compared to FOLFOX and showed no difference in PFS or toxicity. Weekly carboplatin/paclitaxel has not been directly compared to cisplatin/5-FU with RT in a RCT; however, retrospective analyses suggest equivalence in efficacy. Thus, carboplatin/paclitaxel and FOLFOX are more commonly used in clinical practice due to ease of administration and toxicity profile.

Adjuvant CRT

There are few data available on the use of postoperative CRT in esophageal cancer. It is generally recommended in patients with resected EGJ tumors that are node-positive or T3-4 disease who did not undergo preoperative therapy, based on data extrapolated from gastric cancer studies.

- An influential Intergroup trial (INT-0116) compared postoperative CRT with 5-FU/leucovorin to surgery alone in resected stage ≥ IB esophagogastric (20% of patients) and gastric ADC. The 3-year OS (50% vs 41%) was significantly better with CRT. However, there is criticism of the quality of surgical resections in this trial, as 54% had less than D1 resections. While EGJ tumors are usually treated with neoadjuvant therapy, postoperative CRT remains an option based on these data when required. However, there may be significant toxicity associated with this approach.
- The CALGB 80101 investigated the use of more intensive chemotherapy, ECF, given before and after the INT-0116 protocol regimen but found no improvement in survival compared with the 5-FU regimen used in the Intergroup trial.
- The CRITICS trial compared postoperative epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC or EOC) to postoperative cisplatin-/capecitabine-based CRT in patients with gastric ADCs, 17% of which were EGJ tumors. All patients received three cycles of preoperative ECC or EOC. Postoperative CRT did not improve OS at 5 years.
- Only one-half to two-thirds of patients in INT-0116 and CRITICS studies completed planned postoperative therapy, providing further rationale for the use of preoperative therapy in this patient group.

Chemotherapy

Preoperative and Perioperative Chemotherapy

Several trials have evaluated the benefit of preoperative and perioperative chemotherapy with the rational that hematogenous relapses remain a significant issue and early systemic therapy might eradicate micrometastatic disease. To date, trials have focused on distal esophagus and EGJ tumors and mixed results have been observed:

- A 2015 meta-analysis that included nine randomized comparisons of preoperative chemotherapy versus surgery alone for esophageal or EGJ cancers showed a survival benefit for neoadjuvant chemotherapy with a hazard ratio of 0.88. No significant difference in the rate of R0 resections or risk of distant recurrence was observed.
- INT-0113 randomized 440 patients to preoperative chemotherapy with three cycles of CF or immediate surgery. There was no significant difference in survival in either the overall population or between the SCC and ADC subgroups.
- The Medical Research Council (MRC) OE2 trial of surgery with or without preoperative cisplatin/5-FU demonstrated a survival benefit for this approach.
- The MRC OEO5 study examined the optimal duration of preoperative chemotherapy and compared four cycles of epirubicin, cisplatin, and capecitabine (ECX) to two cycles of cisplatin/5-FU, both followed by surgery, in patients with T3N0-1 lower esophageal and EGJ ADC. There was no significant difference in disease-free survival (DFS) or OS despite use of ECX being associated with higher R0 resection and pCR rates. There was less toxicity associated with cisplatin/5-FU but surgical morbidity was similar between the groups.

Seminal gastric cancer studies which included EGJ tumors and have influenced the SOC in EC include:

- MRC MAGIC trial evaluated perioperative ECF versus surgery alone in gastric and EGJ ADC. Of 503 patients, 15% and 11% had EGJ and lower esophageal tumors, respectively. Patients who received chemotherapy in addition to surgery had better 5-year OS (23% vs 36%). Only 42% of patients completed all planned treatment, again highlighting the difficulty administering postoperative therapy.
- The French FFCD study compared cisplatin/fluorouracil perioperatively to surgery alone and demonstrated a DFS (34%

vs 19%), 5-year OS (38% vs 24%), and R0 resection rate (84% vs 73%) benefit.

- The FLOT trial defined a new SOC in gastric cancer. It compared the combination of docetaxel, oxaliplatin, and fluorouracil to a "MAGIC" regimen, ECF or ECX, 56% of enrolled patients had EGJ ADC tumors. The FLOT regimen improved the median survival significantly from 35 to 50 months (3-year OS of 57% vs 48%), becoming a new SOC in resectable gastric cancer. As seen in other perioperative trials, only 46% of patients completed all eight cycles of chemotherapy. The addition of trastuzumab and ramucirumab to FLOT in ADC is currently under study.

With the above data in mind, perioperative chemotherapy is considered a rational approach in patients unable to tolerate trimodality therapy, particularly ADCs of the EGJ, or in patients deemed to be more gastric than esophageal in terms of location/histology. There are two active phase III studies ongoing comparing perioperative chemotherapy to CRT in EC, the TOPGEAR, and ESOPEC trials. The results will help guide the future optimal neoadjuvant approach to EGJ ADCs.

Adjuvant Chemotherapy

In patients who have not received preoperative chemotherapy or CRT, postoperative chemotherapy may be beneficial, but the data are mostly from Asia in SCC and extrapolated from gastric cancer studies in ADC.

Squamous Cell Carcinoma

Adjuvant chemotherapy is not SOC in SCC. The only RCT evaluating it was the JCOG 9204 study. This Japanese trial compared surgery alone to surgery followed by two cycles of CF in 242 patients with esophageal SCC. The 5-year DFS was significantly better with chemotherapy (55% vs 45%), but there was no significant difference in OS (61% vs 52%). A subsequent JCOG 9907 study showed

superiority of neoadjuvant cisplatin/5-FU over adjuvant cisplatin/5-FU.

Adenocarcinoma

With regard to EGJ ADC, data for the use of adjuvant chemotherapy may be extrapolated from gastric cancer studies, many of which included EGJ tumors, where a benefit has been seen.

- The CLASSIC trial demonstrated a benefit for 6 months of postoperative XELOX in gastric cancer, and a small proportion of EGJ tumors were included (2.3%).
- The ITACA-S Italian study evaluated a more intensive regimen, with four cycles of FOLFIRI, followed by three cycles of docetaxel/cisplatin that was compared to nine cycles of 5FU/leucovorin. There was no benefit for the more intensive chemotherapy arm in DFS or OS and as expected significantly greater toxicity.
- The Japanese Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) study randomized stage II/III gastric cancer patients to surveillance or 1-year of adjuvant S-1, a novel oral fluoropyrimidine, and demonstrated improvements in 5-year relapse-free survival (53% vs 65.4%) and OS (61.1% vs 71.7%).
- The phase III JACCRO GC-07 trial expanded on the ACTS-GC study, to 1 year of adjuvant S-1 with docetaxel, and demonstrated superiority compared to S-1 monotherapy but was associated with more toxicity.

SYSTEMIC THERAPY FOR METASTATIC DISEASE

Up to 50% of patients present with metastatic disease and, despite multimodality therapies, the majority of locally advanced patients will ultimately relapse; therefore, most patients diagnosed with EC will receive palliative systemic therapy at some point. The goals of therapy in the metastatic setting include improvement in disease-

related symptoms and quality of life, as well as prolongation of survival. When deciding on the most appropriate treatment strategy, performance status, histologic subtype, symptom burden, and patient preference should be considered.

Advances in targeted therapy and immunotherapy have changed the landscape of first-line therapy beyond cytotoxic chemotherapy alone. Given these advancing therapeutic options, National Comprehensive Cancer Network (NCCN) recommends considering testing metastatic tumors for microsatellite instability (MSI) status by PCR/NGS or DNA mismatch repair (MMR) deficiency by IHC and PD-L1 expression in both histological subtypes and additionally assessment for HER2 overexpression using immunohistochemical (IHC) or fluorescence in situ hybridization (FISH) analysis in ADCs.

An overview of management strategies for advanced disease is shown in Figure 4.2.

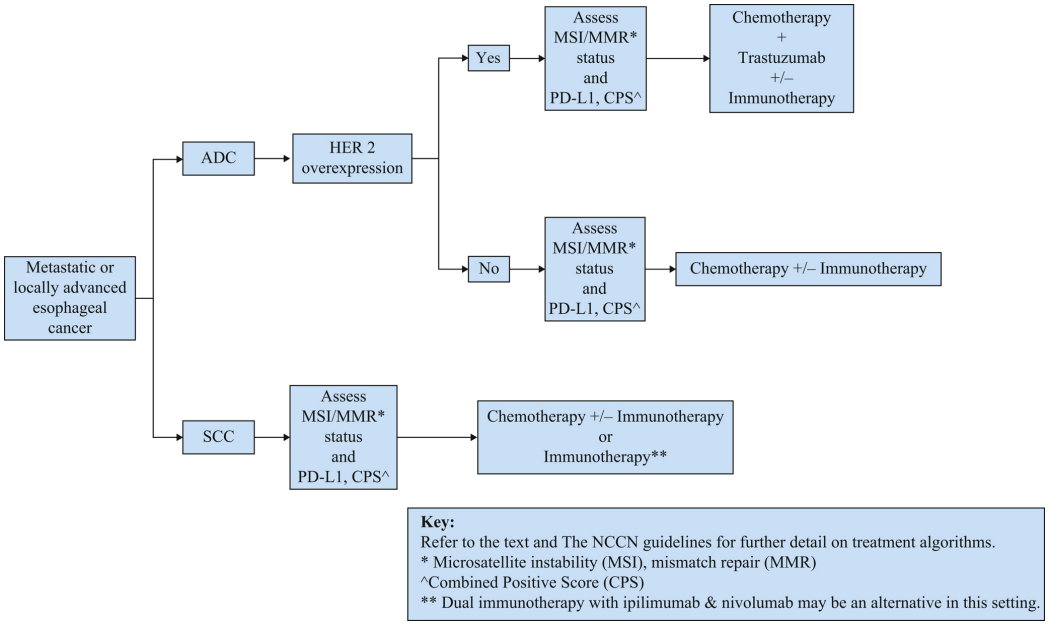

FIGURE 4.2 Algorithm for management of metastatic or locally advanced esophageal cancers.Refer to the text and The NCCN guidelines for further detail on treatment algorithms.

PALLIATIVE CHEMOTHERAPY

There are limited data for chemotherapy in the setting of advanced disease and most evidence is extrapolated from gastric cancer trials that include EGJ tumors. For patients who are fit for aggressive combination therapy, a platinum- and fluoropyrimidine-containing doublet combination regimen is recommended. Combination chemotherapy regimens provide higher response rates, in the range of 25% to 45% versus 15% to 25% for single-agent therapies, but this has been shown to translate into only limited improvements in duration of disease control and survival so must be balanced with increased toxicity. Two-drug regimens are clinically preferred for patients due to lower toxicity, while three-drug regimens should be reserved for medically fit patients with easy access to frequent clinical assessment.

There are a number of first-line chemotherapy options:

- Historically, CF was established as SOC in metastatic EC. Multiple trials were conducted with the aim of improving on this regimen, looking to enhance efficacy and reduce toxicity. For example, docetaxel, cisplatin, and 5-FU (DCF) was compared to CF and demonstrated superiority in overall response rate (ORR) (37% vs 25%) and 2-year OS (18% vs 9%). However, DCF was associated with significant toxicity; 82% grade 3 or 4 neutropenia (vs 57%), and 50% of patients came off study due to toxicity or consent withdrawal.
- The REAL-2 trial published in 2008 was a landmark trial, which evaluated oxaliplatin and capecitabine as alternatives to cisplatin/5-FU. It randomized 1002 patients to ECF, ECX (epirubicin/cisplatin/capecitabine), EOF (epirubicin/oxaliplatin/5-FU), or EOX (epirubicin/oxaliplatin/capecitabine). The median survival was 9.9, 9.9, 9.3, and 11.2 months, respectively. As OS was highest with EOX (P = .02), it subsequently became the SOC in the first-line setting in many institutions.

- Oxaliplatin is generally preferred over cisplatin due to lower toxicity. A 2011 meta-analysis that compared oxaliplatin- versus cisplatin-based regimens showed that oxaliplatin was associated with improved PFS (HR 0.88) and OS (HR for death 0.88), and with less hematological toxicity but with more diarrhea and neuropathy.
- A phase III French trial showed equivalent efficacy between FOLFIRI and ECX, and FOLFIRI was better tolerated.
- Consequently, doublet regimens are preferred over triplet regimens as the latter are not felt to offer a significant advantage and result in more toxicity.
- S-1 represents an alternative fluorouracil in Asia and monotherapy has been shown to be equivalent to both infusional 5FU and capecitabine in Japanese and Korean studies, respectively. S-1 in combination with cisplatin or docetaxel showed superiority compared to S-1 monotherapy in an Asian population. The FLAGS study subsequently looked to assess S-1 in a global population, and it showed equivalence of cisplatin/S-1 to cisplatin/5-FU in the first-line setting. Cisplatin/S-1 was associated with a favorable toxicity profile. S-1 is not commercially available in the United States.
- The FLOT65+ phase II trial randomized elderly patients, 36% EGJ tumors, to FLO or FLOT chemotherapy and demonstrated significantly more toxicity (grade 3/4 AEs 82% vs 39%) and a decline in QoL scores with FLOT. The benefit in ORR and PFS was only seen in the subgroups of locally advanced disease and patients aged 65 to 70 years, further emphasizing the role of doublets in the palliative setting.
- In elderly patients and those with poor performance status, single-agent chemotherapy with 5-FU/leucovorin, capecitabine, weekly taxanes, or irinotecan is appropriate.

SECOND-LINE OR SUBSEQUENT THERAPIES

Patients with good performance statuses routinely receive further lines of therapy. As above, the majority of evidence is extrapolated from gastric cancer trials.

- Docetaxel, paclitaxel, and irinotecan are all associated with a survival benefit over best supportive care (BSC); however, there is no standard regimen and therapy is selected taking into account prior lines of treatment, patient preference, and toxicity profiles.
- Three RCTs have been conducted comparing BSC to docetaxel or irinotecan. A meta-analysis of the patient data from these three trials demonstrated a significant reduction in risk of death by 37% (HR = 0.63, $P < .0001$) with systemic chemotherapy over BSC.
- Two phase III studies have demonstrated equivalence of paclitaxel when compared to irinotecan. The WJOG 4007 Japanese study of 223 patients demonstrated that weekly paclitaxel provided an OS comparable to that achieved with irinotecan in patients refractory to standard first-line treatment (9.5 vs 8.4 months, $P = .38$).
- In the large RAINBOW RCT, second-line paclitaxel in combination with ramucirumab, anti-vascular endothelial growth factor (VEGF) mAb, was compared with paclitaxel monotherapy in 665 patients and showed a prolonged median OS (9.6 vs 7.4 months) and PFS (4.4 vs 2.9 months).
- Trifluridine and tipiracil, an oral fluoropyridine, is approved for third-line or greater, after a trial of 507 heavily pretreated patients demonstrated a median OS benefit (5.7 vs 3.6 months) compared to BSC, and the regimen was well tolerated.

Decision-making around second-line therapy upon progression should also take performance status, patient preference, and histological subtype into account, and clinical trials should be considered where available.

TARGETED THERAPIES

The majority of active research in EC is focused on understanding and exploiting the molecular biology of these tumors, as there is a consensus that the potential for significant advances for patients lies in targeted therapies. Recent advances have led to the standard incorporation of targeted therapies and/or immunotherapy to traditional cytotoxic chemotherapy in the first-line setting (see Figure 4.2).

Immunotherapy

Immune checkpoint inhibitors (ICIs) have shown efficacy in metastatic EC. This is a rapidly developing field with multiple studies ongoing. We outline here the pivotal studies for use of ICIs in EC. Please refer to the chapter on immunotherapy (IO) for discussion on mechanisms of action and the use of biomarkers, such as TMB, MSI-H, dMMR, and PD-L1 expression scores, to predict benefit from immunotherapy, an issue which is in evolution.

Adjuvant Immunotherapy Post Neoadjuvant CRT and Esophagectomy

The CHECKMATE-577 trial was a practice changing addition to the treatment of EC. In this phase 3 global study, 794 patients with resected EC, who had received neoadjuvant CRT and had residual pathological disease, were randomized to a year of adjuvant nivolumab versus placebo. The results demonstrated a doubling of DFS to 22.4 months compared with 11 months and a 31% reduction in the risk of recurrence or death. This benefit was observed across all prespecified subgroups, including age, sex, race, ECOG performance status, disease stage, tumor location, histology, pathologic lymph node status, and PD-L1 expression, and represents the new SOC.

First Line Immunotherapy in Metastatic EC

Immunotherapy in combination with chemotherapy is the new SOC in HER2 negative metastatic/locally advanced EC. However, questions remain regarding optimal biomarker and patient selection for this combination, an issue that is under active research.

Pembrolizumab

- The KEYNOTE-062 trial resulted in the Food and Drug Administration (FDA) approval of pembrolizumab monotherapy in the first-line setting for metastatic ADCs with PD-L1 CPS ≥1. The three arm study compared pembrolizumab monotherapy, combination of chemotherapy with pembrolizumab, and chemotherapy alone. 30% of patients had EGJ tumors. Monotherapy was noninferior in OS (10.6 vs 11.1 months) and less toxic but had a lower objective response rate compared to chemotherapy alone (15% vs 37%). On exploratory analysis in the subgroup of patients with a CPS score ≥ 10 (37%), monotherapy was superior to chemotherapy, median OS 17.4 versus 10.8 months and 2-year OS of 39% compared to 22%. Its use is recommended in a subset of patients with asymptomatic nonbulky disease with high levels of PD-L1 expression because of the lower ORR.
- The KEYNOTE-590 trial evaluated the role of combination therapy in SCC, 74% of patients' included were SCC. Pembrolizumab combined with cisplatin/5FU demonstrated improved ORR (45% vs 29%), median PFS (6.3 vs 5.8 months), and OS (12.3 vs 9.8 months) when compared to chemotherapy alone. The results were driven by the benefit seen in SCC more than ADC, and patients with CPS ≥10 had the greatest benefit but all groups demonstrated statistically significant improvement over SOC chemotherapy.
- The KEYNOTE 811 phase III trial, comparing the triple combination of trastuzumab, chemotherapy (capecitabine, oxaliplatin), and pembrolizumab to the doublet of trastuzumab and chemotherapy, reported the preplanned interim analysis of 264 patients and demonstrated an encouraging ORR of 74% (vs

52%), with 11% obtaining complete response and 65% with ongoing response at 6 months (vs 53%). This led to accelerated FDA approval in the first-line setting.

Nivolumab

- The CHECKMATE-649 phase III global study was practice changing, and it enrolled ADC patients, 30% EC and 70% gastric carcinoma. It compared nivolumab in combination with FOLFOX/XELOX versus chemotherapy alone, with primary endpoints of OS and PFS in patients with PD-L1 CPS ≥ 5. A clear benefit was seen with PFS of 7.7 versus 6.1 months and median OS in patients with CPS ≥ 5 of 16.2 versus 8.8 months. This benefit in OS was more modest but remained significant for the addition of nivolumab in all randomized patients (13.8 vs 11.6 months). However, benefit could not be shown for subgroups with CPS <5 in exploratory analyses. It is FDA-approved irrespective of PD-L1 expression, but the benefits in ADC with no or low PD-L1 expression levels remain uncertain.
- The ATTRACTION-4 study further confirmed the efficacy and safety of IO combined with chemotherapy in the first-line treatment of EGJ/gastric ADC. It compared the combination of nivolumab with SOX/XELOX to chemotherapy alone. It demonstrated a PFS benefit of 10.5 versus 8.3 months (HR 0.68) and better ORR (58% vs 49%). No OS benefit was seen; however, this may be confounded by multiple factors including an Asian study population, the chemotherapy backbone used and subsequent lines of treatment, as 66% of patients received postprogression therapy (vs 39% in CHECKMATE-649) and the median OS was significantly longer, at 17 months in both arms.
- The CHECKMATE-648 study, presented at ASCO 2021, a large trial of 970 SCC patients, compared dual IO (ipilimumab/nivolumab), combination chemotherapy with nivolumab and chemotherapy (CF) alone. In both unselected, and the PD-L1 ≥ 1% population, chemotherapy/nivolumab and dual IO demonstrated superior OS versus chemotherapy alone.

The greatest benefit was seen in the combination of chemotherapy and nivolumab arm, ORR 47% (vs 27%), PFS 5.7 months (vs 3.4), and OS 13.2 months (vs 10.7), in all patients regardless of PD-L1 expression compared to chemotherapy alone. The dual IO arm in PD-L1 ≥ 1% population demonstrated ORR of 35% and median OS of 13.7 months, compared to 53% and 15.4 months in the combination arm; this offers patients a real chemotherapy-free alternative.

Camrelizumab

- The ESCORT-1st phase III trial, presented at ASCO 2021, provided further evidence for first-line combination chemotherapy and immunotherapy, comparing chemotherapy (cisplatin/paclitaxel) with camerlizumab, a humanized anti-PD-1 mAb, versus chemotherapy alone. In 595 Chinese patients with metastatic SCC, they demonstrated an ORR of 72% (vs 62%), a median PFS of 6.9 months (vs 5.6) and a median OS of 15.3 months (vs 12.0 months, HR 0.70).

MSI-H/dMMR Subgroup Analyses

The role of immunotherapy in MSI-H/dMMR patients was first established based on the FDA's 2017 tumor site-agnostic approval of pembrolizumab in the second-line setting for MSI-H/dMMR tumors. Two studies provide data for combination chemotherapy and immunotherapy in MSI-H/dMMR EC patients with PD-L1 overexpression. Subgroup analysis in KEYNOTE-062 of MSI-H/dMMR patients with a CPS > 1 (6.5%, n = 50) suggested superiority of combination therapy over chemotherapy alone, median OS not reached versus 8.5 months. This is further supported by CheckMate-649 subgroup analysis (n = 34), which suggested benefit for combined therapy among patients with both PD-L1 overexpression and dMMR/MSI-H tumors, median OS not reached in combined therapy versus 8.8 months with chemotherapy alone (HR for death 0.33).

Second- and Third-Line Immunotherapy in Metastatic EC

Pembrolizumab

Pembrolizumab is FDA-approved in the second-line setting for SCC tumors with CPS ≥ 10 based on KEYNOTE 181 trial's OS and tolerability benefit when compared to SOC chemotherapy in this subgroup. Additionally, pembrolizumab is FDA-approved in the third-line setting in ADC tumors with CPS ≥1, this approval was based on the results of two single-arm phase II trials which demonstrated doubling of ORR in PD-L1 overexpressing tumors; 15.5% versus 6.4% in gastric and EGJ ADC tumors in KEYNOTE 059 and 14% versus 6% in EC patients (52% SCC, 48% ADC) in KEYNOTE 180. However, this indication is controversial as the evidence is mixed. In the phase III KEYNOTE 061 trial of 592 ADC patients, 37% EGJ, pembrolizumab monotherapy in the second line was not superior to single-agent paclitaxel (OS 9.1 vs 8.3 months) in patients with PD-L1 CPS ≥ 1 though it was better tolerated (Grade 3-5 AEs 14% vs 35%). Ongoing biomarker studies may elucidate the cohort of patients who will derive benefit from immunotherapy.

Nivolumab

Nivolumab is recommended in second line for SCC regardless of PD-L1 expression based on the ATTRACTION-3 study. This phase III trial included 419 patients, >90% male and predominantly Asian study population, demonstrated an ORR of 19% in the nivolumab arm compared with 33% with SOC chemotherapy; however, the median duration of response was 6.9 versus 3.9 months and median OS was 10.9 versus 8.4 months. In addition to the survival benefit, immunotherapy was significantly more tolerable with 18% versus 63% of patients experiencing treatment-related AEs.

Avelumab

There have been two negative studies evaluating the role of avelumab in EC. JAVELIN-100 looked at maintenance avelumab

after 3 months of induction first-line chemotherapy and failed to show improvement in PFS or OS. Additionally, in the third-line setting, avelumab was not superior to chemotherapy.

The treatment of EC is evolving in the era of immunotherapy; however, there are many questions left unanswered, and several ongoing studies are investigating potential biomarkers to aid in improving patient selection to maximize benefit seen with these agents. It is a key player in the continued progress toward improved therapy with less toxicity for patients with EC.

Anti-HER2 Therapy

Seven to 38% of gastroesophageal ADCs have amplification and/or overexpression of HER2. In contrast to breast cancer, the association between HER2 expression/amplification and prognosis in esophagogastric cancer is uncertain.

First-Line

The addition of trastuzumab to combination chemotherapy is recommended in patients with HER2 positive esophageal ADC.

The ToGA trial demonstrated an improvement in response rate (47% vs 35%) and OS (13.8 vs 11.1 months) for patients treated with trastuzumab in combination with cisplatin/5-FU compared with cisplatin/5-FU alone. In a post-hoc subgroup analysis, patients whose tumors were IHC 2+ and FISH-positive or IHC 3+ benefitted substantially from addition of trastuzumab with an OS benefit of 16 versus 11 months, HR 0.65. In contrast, patients whose tumors were IHC 0/1+ and FISH-positive did not demonstrate a significant improvement in OS (10 vs 8.7 months; HR 1.07). NCCN guidelines suggest that trastuzumab can be used with most active first-line regimens except those containing anthracyclines.

Other anti-HER2 agents have also been evaluated; unfortunately and somewhat unexpectedly, the results have not shown benefit. The LOGiC study assessed the addition of lapatinib to first-line chemotherapy (capecitabine/oxaliplatin) and found no benefit, while

the JACOB study evaluating addition of pertuzumab with trastuzumab to first-line chemotherapy (cisplatin/5-FU) also showed no benefit.

Second and Third Line

Anti-HER2 therapy has also been evaluated in the second-line setting. Initial studies were negative; Lapatinib did not show benefit when added to a taxane in the TyTAN study and T-DM1 demonstrated no benefit when compared to a taxane in the GATSBY study. However, the recently reported findings of DESTINY-Gastric01 trial, which included 13% EGJ tumors, looking at antibody-drug-conjugate, Fam-trastuzumab-deruxtecan, showed superior response (51% vs 14%) and a median OS benefit (12.5 vs 8.4 months) versus physician's choice chemotherapy and is now FDA-approved after two or more prior lines of treatment in ADC.

Anti-VEGF Therapy

Therapies against VEGF have been a major focus of research in solid malignancies, especially in the GI tract; however, a reliable biomarker to indicate their use is lacking.

First Line

The benefit of bevacizumab in combination with capecitabine and cisplatin in EGJ ADC in the first-line treatment was evaluated in the phase III AVAGAST trial and found no improvement in OS (12.1 vs 10.1 months) despite improvements in response rates and PFS. Subgroup analysis suggests a potential benefit for patients in the Americas, and while biomarkers may prove useful in identifying patients who might gain from addition of bevacizumab to standard therapy, its role remains poorly defined. The phase III RAINFALL trial looked at the addition of ramucirumab, an anti-VEGFR-2 mAb, to first-line chemotherapy and did not show any PFS or OS benefit.

Second and Third Line

VEGFR-2 was evaluated as a therapeutic target in the second-line setting. REGARD demonstrated a modest but significant OS benefit, 5.2 versus 3.8 months, with the use of single-agent ramucirumab compared to placebo after progression on first-line therapy and RAINBOW reported an improvement in OS, median OS (9.6 vs 7.4 months), and PFS (4.4 vs 2.9 months) with the addition of ramucirumab to weekly paclitaxel.

In the third-line setting, apatinib, an anti-VEGFR-2 tyrosine kinase inhibitor, was shown to modestly improve OS when compared to placebo in a Chinese population and regorafenib, multikinase inhibitor, has demonstrated modest activity in the second- and third-line settings in a randomized phase II study. However, neither of these agents are considered standard currently.

Anti-EGFR Therapy

EGFR is expressed in the majority of esophageal SCC, and 25% to 55% of ADCs but the addition of panitumumab or cetuximab to chemotherapy in the first-line metastatic setting showed no benefit in two phase III trials. Of note, anti-EGFR antibodies have also been studied in the locally advanced setting in combination with CRT in two phase III trials which also demonstrated no benefit.

Other Targeted Therapies

Zolbetuximab is a monoclonal antibody that binds Claudin 18.2, a phase II study in EGJ ADCs showed a PFS and OS benefit with its addition to EOX in CLDN 18.2-positive tumors; this is undergoing further evaluation in ongoing phase III trial SPOTLIGHT.

Based on the impressive results from tumor-agnostic basket studies of patients with NTRK gene fusion–driven cancers, next generation sequencing of EC patient's tumors in later lines of therapy is warranted to assess for targetable mutations, given significant benefit of NTRK inhibitors, entrectinib, or larotrectinib, seen in NTRK gene fusion–driven solid tumors.

Palliative Care

Due to the anatomy and complications from surgery or local disease progression, patients with advanced esophagogastric cancer have a high incidence of malnutrition, and psychologic distress, early referral and initiation of interdisciplinary and palliative care services is an essential component of care, which has been shown to improve QoL as well as OS. Radiotherapy alone may be used in the palliative setting for control of dysphagia. Endoscopic laser or balloon dilatation or stenting are alternative options, and placement of a gastrostomy or jejunostomy may improve a patient's nutritional status.

Surveillance of Patients With Locoregional Disease

The majority of recurrences develop within 1 year and over 90% develop within 2 to 3 years. Isolated local recurrences occur more frequently after definitive CRT, where salvage surgery may have a role and more vigilant surveillance is recommended in the first 2 years.

There are currently no data that demonstrate improved survival from earlier detection of recurrences or to guide the optimal surveillance strategy. NCCN do advocate imaging and endoscopy in selected patients. Multidisciplinary discussion is recommended to tailor surveillance. Current guidelines advise history and physical examination every three to 6 months for one to 3 years, then every 6 months for years 4 and 5, then annually, in combination with CT-TAP every 6 months for the first 2 years and the addition of esophagogastroduodenoscopy 3 to 6 monthly if treated with definitive CRT.

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5

Gastric Cancers

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EPIDEMIOLOGY

Worldwide, gastric carcinoma represents the fourth most common malignancy. The frequency of gastric carcinoma occurrence at different sites within the stomach has changed in the United States over recent decades. Cancer of the distal half of the stomach has been decreasing in the United States since the 1930s. However, over the past 2 decades, the incidence of cancer of the cardia and gastroesophageal junction (GEJ) has been rapidly rising, particularly in patients younger than 40 years. Gastric cancer accounts for 1.5% of all new cancers diagnosed in the United States. There are projected to be 26,560 new cases and 11,180 deaths from gastric cancer in the United States in 2021.

RISK FACTORS

- Average age at diagnosis is 68 years
- Male-to-female ratio is 1.7:1
- African American-to-white ratio is 1.8:1
- Precursor conditions include chronic atrophic gastritis and intestinal metaplasia, pernicious anemia (10%-20% incidence), partial gastrectomy for benign disease, *Helicobacter pylori* infection (especially childhood exposure—three- to fivefold increase), Ménétrier disease, and gastric adenomatous polyps.

These precursor lesions are largely linked to distal (intestinal type) gastric carcinoma

- Family history: first degree (two- to threefold); the family of Napoléon Bonaparte is an example; familial clustering; patients with hereditary nonpolyposis colorectal cancer (Lynch syndrome II) are at increased risk; germline mutations of E-cadherin (*CDH1* gene) have been linked to familial diffuse gastric cancer and associated lobular breast cancer. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal dominant syndrome characterized by fundic gland polyposis and intestinal type adenocarcinoma
- Tobacco use results in a 1.5- to 3-fold increased risk for cancer
- High salt and nitrosamine food content from fermenting and smoking process
- Deficiencies of vitamins A, C, and E; β-carotene; selenium; and fiber
- Blood type A
- Alcohol
- The marked rise in the incidence of gastroesophageal and proximal gastric adenocarcinoma appears to be strongly correlated to the rising incidence of Barrett esophagus

SCREENING

In most countries, screening of the general populations is not practical because of a low incidence of gastric cancer. However, screening is justified in countries where the incidence of gastric cancer is high. Japanese screening guidelines include initial upper endoscopy at the age of 50 years, with follow-up endoscopy for abnormalities. Routine screening is not recommended in the United States.

PATHOPHYSIOLOGY

Most gastric cancers are adenocarcinomas (more than 90%) of two distinct histologic types: intestinal and diffuse. In general, the term "gastric cancer" is commonly used to refer to adenocarcinoma of the stomach. Other cancers of the stomach include non-Hodgkin lymphomas (NHLs), leiomyosarcomas, carcinoids, and gastrointestinal stromal tumors (GIST). Differentiating between adenocarcinoma and lymphoma is critical because the prognosis and treatment for these two entities differ considerably. Although less common, metastases to the stomach include melanoma, breast, and ovarian cancers.

Intestinal Type

The *epidemic* form of cancer is further differentiated by gland formation and is associated with precancerous lesions, gastric atrophy, and intestinal metaplasia. The intestinal form accounts for most distal cancers with a stable or declining incidence. These cancers in particular are associated with *H. pylori* infection. In this carcinogenesis model, the interplay of environmental factors leads to glandular atrophy, relative achlorhydria, and increased gastric pH. The resulting bacterial overgrowth leads to production of nitrites and nitroso compounds causing further gastric atrophy and intestinal metaplasia, thereby increasing the risk of cancer.

The recent decline in gastric carcinoma in the United States is likely the result of a decline in the incidence of intestinal-type lesions but remains a common cause of gastric carcinoma worldwide. Intestinal-type lesions are associated with an increased frequency of overexpression of epidermal growth factor receptor (EGFR) *erbB-2* and *erbB-3*.

Diffuse Type

The *endemic* form of carcinoma is more common in younger patients and exhibits undifferentiated signet-ring histology. There is a predilection for diffuse submucosal spread because of lack of cell cohesion, leading to linitis plastica. Contiguous spread of the

carcinoma to the peritoneum is common. Precancerous lesions have not been identified. Although a carcinogenesis model has not been proposed, it is associated with *H. pylori* infection. Genetic predispositions to endemic forms of carcinoma have been reported, as have associations between carcinoma and individuals with type A blood. These cancers occur in the proximal stomach where increased incidence has been observed worldwide. Stage for stage, these cancers have a worse prognosis than do distal cancers.

Diffuse lesions have been linked to abnormalities of fibroblast growth factor systems, including the *K-sam* oncogene as well as E-cadherin mutations. The latter results in loss of cell-cell adhesions.

Molecular Analysis

- Loss of heterozygosity of chromosome 5q or APC gene (deleted in 34% of gastric cancers), 17p, and 18q (DCC gene).
- Microsatellite instability, related to deficiencies in mismatch repair genes, can either be inherited (ie, Lynch syndrome) or acquired through a sporadic somatic mutation.
- p53 is mutated in approximately 40% to 60% caused by allelic loss and base transition mutations.
- Mutations of E-cadherin expression (*CDH1* gene on 16q), a cell adhesion mediator, is observed in diffuse-type undifferentiated cancers and is associated with an increased incidence of lobular breast cancer.
- EGFR overexpression, specifically *Her2/neu* and *erbB-2/erbB-3*, especially in intestinal forms.
- *Ras* mutations are rarely reported (less than 10%) in contrast to other gastrointestinal (eg, pancreatic and colorectal) cancers.
- Epstein-Barr viral genomes are detected, and in these patients, programmed cell death (PD-1) receptor ligand (PD-L1) expression is found more frequently.

DIAGNOSIS

Gastric carcinoma, when superficial and surgically curable, typically produces no symptoms. Among 18,365 patients analyzed by the American College of Surgeons, patients presented with the following symptoms: weight loss (62%), abdominal pain (52%), nausea (34%), anorexia (32%), dysphagia (26%), melena (20%), early satiety (18%), ulcer-type pain (17%), and lower-extremity edema (6%).

Clinical findings at presentation may include anemia (42%), hypoproteinemia (26%), abnormal liver functions (26%), and fecal occult blood (40%). Medically refractory or persistent peptic ulcer justifies repeat endoscopic evaluation with biopsies.

Gastric carcinomas primarily spread by direct extension, invading adjacent structures with resultant peritoneal carcinomatosis and malignant ascites. The liver, followed by lung, is the most common site of hematogenous dissemination. The disease may also spread as follows:

- To intra-abdominal nodes and left supraclavicular nodes (Virchow node)
- Along peritoneal surfaces, resulting in a periumbilical lymph node (Sister Mary Joseph node, named after the operating room nurse at the Mayo Clinic), which forms as tumor spreads along the falciform ligament to subcutaneous sites
- To a left anterior axillary lymph node resulting from the spread of proximal primary cancer to lower esophageal and intrathoracic lymphatics (Irish node)
- To enlarged ovary (Krukenberg tumor; ovarian metastases)
- To a mass in the cul-de-sac (Blumer shelf), which is palpable on rectal or bimanual examination

Paraneoplastic Syndromes

- Skin syndromes: acanthosis nigricans, dermatomyositis, circinate erythemas, pemphigoid, and acute onset of seborrheic keratoses (Leser-Trélat sign)

- Central nervous system syndromes: dementia and cerebellar ataxia
- Miscellaneous: thrombophlebitis, microangiopathic hemolytic anemia, membranous nephropathy

Tumor Markers

Carcinoembryonic antigen (CEA) is elevated in 40% to 50% of cases. It is useful in follow-up and monitoring response to therapy but not for screening. α-Fetoprotein and CA 19-9 are elevated in 30% of patients with gastric cancer but are of limited clinical use.

STAGING

The American Joint Committee on Cancer (AJCC) has designated staging by tumor, node, metastasis (TNM) classification. In the 2017 AJCC eighth edition, tumors arising at the GEJ or in the cardia of the stomach within 5 cm of the GEJ that extend into the GEJ or esophagus are termed esophageal rather than gastric cancers. Gastric tumors involving muscularis propria (T2), subserosa (T3), and serosa (T4a) are considered resectable, whereas invasion of adjacent structures (T4b) is not. Nodal stage relates to number of involved regional nodes: N1, 1 to 2 involved nodes; N2, 3 to 6 involved nodes; N3a, 7 to 15 involved nodes; N3b, 16 or more involved nodes. The presence of positive peritoneal cytology is considered M1 as are distant metastases. Many of these staging classifiers represent changes from previous AJCC staging system editions but continue to refine prognostic groups based on the best available outcomes data (Table 5.1). Of note, alternative staging systems are used in Japan.

TABLE 5.1

Observed Survival Rates for Surgically Resected Gastric Adenocarcinomas in a Representative Western Population

	Survival Rates		
Stage	5 Year (%)	10 Year (%)	Median (Months)

	Survival Rates		
Stage	**5 Year (%)**	**10 Year (%)**	**Median (Months)**
IA	82	68	ND
IB	69	60	151
IIA	60	43	102
IIB	42	32	48
IIIA	28	18	28
IIIB	28	11	19
IIIC	11	6	12
IV	6	5	9

ND, not determined.

Modified from Reim D, Loos M, Vogl F, et al. Prognostic implications of the seventh edition of the international union against cancer classification for patients with gastric cancer: the Western experience of patients treated in a single-center European institution. *J Clin Oncol*. 2013;31(2):263-271.

- Initial upper gastrointestinal endoscopy and double-contrast barium swallow identify suggestive lesions and have diagnostic accuracy of 95% and 75%, respectively, but add little to staging otherwise.
- Endoscopic ultrasonography assesses the depth of tumor invasion (T staging) and nodal involvement (N staging) with accuracies up to 90% and 75%, respectively.
- Computed tomographic scanning is useful for assessing local extension, lymph node involvement, and presence of metastasis although understaging occurs in most cases.
- Although whole-body 2-[18F]fluoro-2-deoxyglucose (FDG)–positron emission tomography (PET) may be useful in detecting metastasis as part of preoperative staging in some gastric cancer patients, the sensitivity to detect early stage gastric cancer is only about 20% and overall appears less reliable than in esophageal cancer.

PROGNOSIS

Pathologic staging remains the most important determinant of prognosis (see Table 5.1). Other prognostic variables that have been

proposed to be associated with an unfavorable outcome include the following:

- Older age
- Male gender
- Weight loss greater than 10%
- Location of tumor
- Tumor histology: Diffuse versus intestinal (5-year survival after resection, 16% vs 26%, respectively); High-grade or undifferentiated tumors
- Four or more lymph nodes involved
- Aneuploid tumors
- Elevations in EGFR or P-glycoprotein level
- Overexpression of ERCC1 and p53; loss of p21 and p27

MANAGEMENT OF GASTRIC CANCER

Standard of Care

Although surgical resection remains the cornerstone of gastric cancer treatment, the optimal extent of nodal resection remains controversial. The high rate of recurrence and poor survival of patients following surgery provides a rationale for the use of adjuvant or perioperative treatment. Adjuvant radiotherapy (RT) alone does not improve survival following resection. In addition to complete surgical resection, either postoperative adjuvant chemoradiotherapy (chemoRT) or perioperative polychemotherapy appears to confer survival advantages. The results of the Intergroup 0116 study show that the combination of 5-fluorouracil (5-FU)–based chemoRT significantly prolongs disease-free survival (DFS) and overall survival (OS) when compared to no adjuvant treatment. Similarly, the use of polychemotherapy pre- and postoperatively can increase DFS and OS compared to observation.

In advanced gastric cancer, chemotherapy enhances quality of life and prolongs survival when compared with the best supportive care.

Of the commonly used regimens, triple combination chemotherapy with either docetaxel, cisplatin, and 5-FU (DCF) or epirubicin, oxaliplatin, and capecitabine (EOX) probably has the strongest claims to this role for the majority of fit patients, with modified FOLFOX (5-FU, leucovorin, and oxaliplatin) also frequently used in the United States. Human EGFR 2 (HER2), a key driver of tumorigenesis, is overexpressed in 7% to 34% of esophagogastric tumors. The standard of care for HER2 overexpressing advanced or metastatic gastric cancer is trastuzumab in combination with cytotoxic chemotherapy. Immunotherapy checkpoint inhibitor treatments are now also considered standard for some advanced gastric tumors that may or may not overexpress PD-L1. However, there is a pressing need for assessing new agents including cytotoxic, immunotherapeutic, and targeted therapies in the advanced and adjuvant settings, and enrollment in clinical trial is highly encouraged.

Resectable Disease

Surgery

Complete surgical resection of the tumor and adjacent lymph nodes remains the only chance for cure. Unfortunately, only 20% of US patients with gastric cancer have disease at presentation amenable to such therapy. Resection of gastric cancer is indicated in patients with stage I to III disease. Tumor size and location dictate the type of surgical procedure to be used. An exploration to exclude carcinomatosis just prior to the definitive resection is justified in this disease. Current surgical issues include subtotal versus total gastrectomy, extent of lymph node dissection, and palliative surgery.

Subtotal Versus Total Gastrectomy

Subtotal gastrectomy (SG) may be performed for proximal cardia or distal lesions, provided that the fundus or cardioesophageal junction is not involved (Figure 5.1). Total gastrectomy (TG) is more

appropriate if tumor involvement is diffuse and arises in the body of the stomach, with extension to within 6 cm of the cardia. TG is associated with increased postoperative complications, mortality, and quality-of-life decrement, necessitating thorough consideration of complete gastric resection (Figure 5.2).

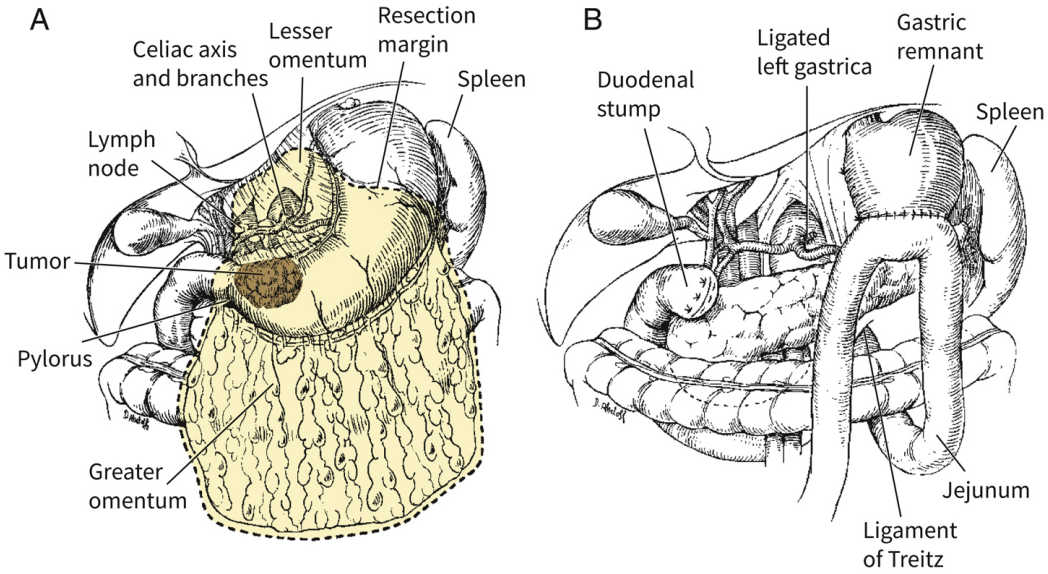

FIGURE 5.1 A and B, Subtotal gastrectomy.

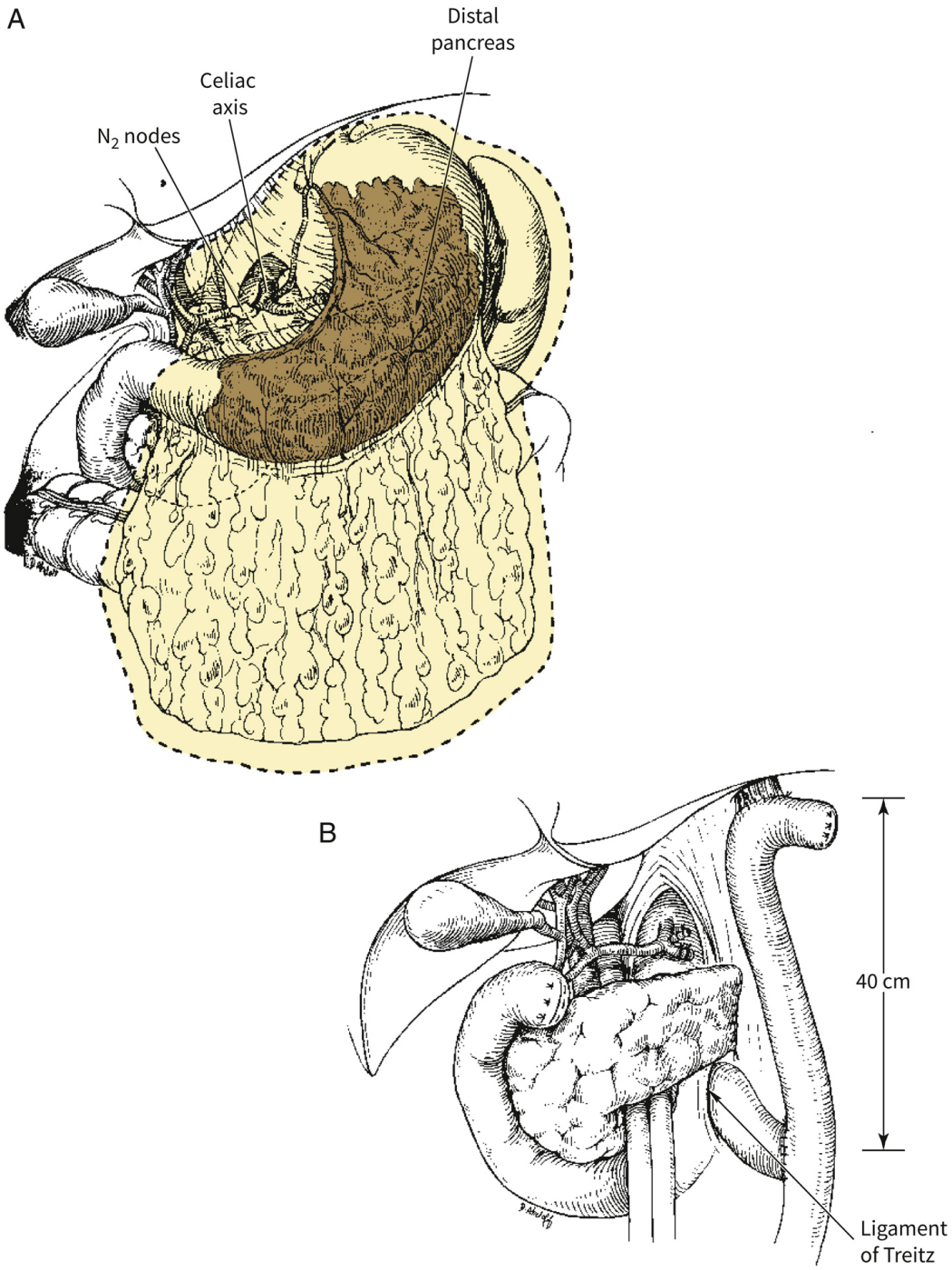

FIGURE 5.2 A and B, Total gastrectomy.

Extent of Lymph Node Dissection

Regional lymph node dissection is important for accurate staging and may have therapeutic benefit as well. The extent of

lymphadenectomy is categorized by the regional nodal groups removed (Table 5.2). At least 16 lymph nodes must be reported for accurate AJCC staging. D2 lymphadenectomy is reported to improve survival in patients with T1, T2, T3, and some serosa-involved (currently T4a) lesions as compared to D1. However, factors such as operative time, hospitalization length, transfusion requirements, and morbidity are all increased. The routine inclusion of splenectomy in D2 resections is no longer advocated given higher postoperative complications. The greatest benefit of more extensive lymph node dissection may occur in early gastric cancer lesions with small tumors and superficial mucosal involvement as up to 20% of such lesions have occult lymph node involvement.

TABLE 5.2

Classification of Regional Lymph Node Dissection

Dissection (D)	Regional Lymph Node Groups Removed
D0	None
D1	Perigastric
D2	D1 plus nodes along hepatic, left gastric, celiac, and splenic arteries; splenic hilar nodes; +/– splenectomy
D3 [a]	D2 plus periaortic and porta hepatis

[a]Periaortic and porta hepatis nodes are typically considered distant metastatic disease.

Radiation Therapy

- For patients with locally advanced or metastatic disease, moderate doses of external-beam radiation can be used to palliate symptoms of pain, obstruction, and bleeding but do not routinely improve survival.
- Local or regional recurrence in the gastric or tumor bed, the anastomosis, or regional lymph nodes occurs in 40% to 65% of patients after gastric resection with curative intent. The high frequency of such relapses has generated interest in perioperative therapy. RT in this setting is limited by the

technical challenges inherent in abdominal irradiation, optimal definition of fields, diminished performance status, and nutritional state of many patients with gastric cancer.

- A prospective randomized trial from the British Stomach Cancer Group failed to demonstrate a survival benefit for postoperative adjuvant radiation alone although locoregional failures had decreased from 27% to 10.6%.
- Attempts to improve the efficacy and minimize toxicity with newer RT techniques have been investigated. Sixty patients who underwent curative resection at the National Cancer Institute were randomized to either receive adjuvant intraoperative radiotherapy (IORT) or conventional RT. IORT failed to afford a benefit over conventional therapy in OS and remains unavailable to many outside of a clinical trial or specialized center.
- In patients with locally unresectable pancreatic and gastric adenocarcinoma, the Gastrointestinal Tumor Study Group has shown that combined-modality therapy is superior to either RT or chemotherapy alone. On the basis of this concept, combined chemoRT (typically in combination with 5-FU) has been evaluated both in the neoadjuvant (preoperative) and the adjuvant (postoperative) settings.

Perioperative Chemoradiotherapy

Aside from GEJ and high gastric cardia tumors, the available data on the role of neoadjuvant chemoRT for gastric cancer are not conclusive. Although neoadjuvant therapy may reduce the tumor mass in many patients, several randomized, controlled trials have shown that, compared with primary resection, a multimodal approach does not result in a survival benefit in patients with potentially resectable tumors. In contrast, for some patients with locally advanced tumors (ie, patients in whom complete tumor removal with upfront surgery seems unlikely), neoadjuvant chemoRT may increase the likelihood of complete tumor resection

on subsequent surgery. However, predicting those likely to benefit from this approach remains an ongoing research question.

Adjuvant chemoRT has been evaluated in the United States. In a phase 3 Intergroup trial (INT-0116), 556 patients with completely resected stage IB to stage IV M0 adenocarcinoma of the stomach and GEJ were randomized to receive best supportive care or adjuvant chemotherapy (5-FU and leucovorin) and concurrent radiation therapy (45 Gy). With >6-year median follow-up, median survival was 35 months for the adjuvant chemoRT group as compared to 27 months for the surgery-alone arm (P = .006). Both 3-year OS (50% vs 41%; P = .006) and relapse-free survival (48% vs 31%; P < .0001) favored adjuvant chemoRT. Although treatment-related mortality was 1% in this study, only 65% of patients completed all therapy as planned and many had inadequate lymph node resections (54% D0). After 10-year median follow-up, persistent benefit in OS (HR 1.32, 95% CI, 1.10-1.60; P = .0046) and relapse-free survival (HR 1.51, 95% CI, 1.25-1.83; P = .001) were observed without excess treatment-related late toxicities. This study established adjuvant chemoRT as a standard of care for gastric cancer in the United States.

Perioperative Chemotherapy

In Japan, patients who underwent complete surgical resection for stage II and III gastric cancer with D2 lymphadenectomy appeared to benefit from adjuvant S-1, a novel oral fluoropyrimidine. In a randomized controlled trial, patients were randomized to 1 year of monotherapy or surveillance only. The study was closed early after interim analysis confirmed a 3-year OS (80% vs 70%; P = .002) and relapse-free survival (72% vs 60%; P = .002) advantage in favor of adjuvant chemotherapy. At 5-year follow-up, the improved OS rate (72% vs 61%) and relapse-free survival rate (65% vs 53%) persisted. S-1 is approved for adjuvant therapy for gastric cancer in Japan and for advanced gastric cancer in Europe, but it is not commercially available in the United States.

In Europe, focus has been on the role of more potent polychemotherapy regimens in the perioperative setting without RT. The UK Medical Research Council conducted a randomized controlled trial (MAGIC trial) comparing three cycles of pre- and postoperative epirubicin, cisplatin, and 5-FU (ECF) to surgery alone in patients with resectable stage II–IV nonmetastatic gastric cancer; 503 patients were stratified according to surgeon, tumor site, and performance status. Perioperative chemotherapy improved 5-year OS (36% vs 23%; $P = .009$) and reduced local and distant recurrence. There appeared to be significant downstaging by chemotherapy treatment, with more patients deemed by the operating surgeon to have had a "curative" resection (79% vs 70%; $P = .03$), had smaller tumors (median 3 vs 5 cm; $P < .001$), had T1/T2 stage tumors (52% vs 37%; $P = .002$), and had N1/N2 stage disease (84% vs 71%; $P = .01$). Toxicity was feasible with postoperative complications comparable; however nearly one-third of patients who began with preoperative chemotherapy did not receive postoperative chemotherapy due to progressive disease, complications, or patient request.

A French multicenter trial also showed a survival benefit for perioperative chemotherapy. Patients with potentially resectable stage II or higher adenocarcinoma of the stomach, GEJ, or distal esophageal (total 224) were randomly assigned to two or three preoperative cycles of cisplatin/5-FU infusion and three or four postoperative cycles of the same regimen versus surgery alone. At a median follow-up of 5.7 years, 5-year OS (38% vs 24%, HR, 0.69; 95% CI, 0.50-0.95; $P = .02$) and DFS (34% vs 19%, HR 0.65; 95% CI, 0.48-0.89; $P = .003$) was improved in the polychemotherapy arm. Curative resection rate was significantly improved with perioperative polychemotherapy (84% vs 73%; $P = .04$) with similar postoperative morbidity in the two groups. In Europe, perioperative polychemotherapy is considered a standard of care.

Postoperative Chemoradiotherapy Versus Perioperative Chemotherapy

There are no randomized controlled trials directly comparing these two standards of care. The ARTIST randomized phase III trial did not show a survival improvement with adjuvant chemoRT compared to adjuvant chemotherapy alone in patients with D2-resected gastric cancer. Patients (n = 458, stage IB-IV M0) were randomly assigned to chemotherapy (capecitabine and cisplatin) or chemoRT (cisplatin/capecitabine followed by capecitabine/radiation [45 Gy] followed by cisplatin/capecitabine). After >4-years follow-up, no significant difference in locoregional recurrences (8.3% in chemo alone vs 4.8% in chemoRT; P = .3533) or distant metastases (24.6% in chemo vs 20.4% in chemoRT; P = .5568) were observed. Treatment completion rate was better than the INT-0116 trial with 75% of patients having completed the planned chemotherapy and 82% the chemoRT. Given that a multivariate analysis showed chemoRT improved 3-year DFS in those with node-positive disease (HR 0.68; 95% CI, 0.47-0.99; P = .047), a subsequent phase III trial (ARTIST-II) study to evaluate the benefit of chemoRT in patients who underwent D2 lymph node dissection with positive lymph nodes is currently enrolling.

CALGB 80,101, a US Intergroup study, compared the INT-0116 adjuvant chemoRT versus postoperative ECF before and after chemoRT. Patients (n = 546) with completely resected gastric or GEJ tumors that were >T2 or node positive were included. Through a preliminary report, patients receiving ECF had lower rates of diarrhea, mucositis, and grade >4 neutropenia. However, the primary endpoint of OS was not significantly better with ECF at 3 years (52% vs 50%). The primary tumor location did not impact treatment outcome.

To assess the role of postoperative intensification of treatment with chemoRT, the phase III CRITICS study recently completed. Patients with stage Ib-IVa gastric cancer (n = 788) were treated with preoperative epirubicin, capecitabine, and a platinum compound (cisplatin or oxaliplatin) followed by surgery. After surgery, patients were randomized to an additional three cycles of the same chemotherapy versus chemoRT (45 Gy with weekly cisplatin and

daily capecitabine). There was no difference in the 5-year survival between two arms. (40.8% vs 40.9%).

Unresectable or Metastatic Disease

Primary goals of therapy should focus on improvement in symptoms, delay of disease progression, pain control, nutritional support, and quality of life. Although a role for palliative surgery and RT exist (see previous sections), chemotherapy remains the primary means of palliative treatment in this setting. The most commonly administered chemotherapeutic agents with objective response rates in advanced gastric cancer include mitomycin, antifolates, anthracyclines, fluoropyrimidines, platinums, taxanes, and topoisomerase inhibitors. Monotherapy with a single agent results in a 10% to 30% response rate with mild toxicities (Table 5.3). 5-FU is the most extensively studied, producing a 20% response rate. Complete responses with single agents are rare and disease control is relatively brief. Combination chemotherapy provides a better response rate with survival advantage over best supportive care in randomized studies. Molecularly targeted therapies against the HER2, vascular endothelial growth factor (VEGF) pathways, and PD-L1 now have an active role in the treatment of metastatic gastric cancer.

TABLE 5.3

Antineoplastic Therapy With Activity in Advanced Gastric Cancer

Class	Examples
Antifolates	Methotrexate
Anthracyclines	Doxorubicin, epirubicin
Fluoropyrimidines	5-FU, capecitabine, S-1, UFT
Platinums	Cisplatin, carboplatin, oxaliplatin
Taxanes	Docetaxel, paclitaxel
Topoisomerase inhibitors	Etoposide, irinotecan

Class	Examples
Targeted therapies Immunotherapy	Trastuzumab, ramucirumab, apatinib, fam-trastuzumab deruxtecan-nxki Pembrolizumab, nivolumab

Palliative Surgery & Stents

This should be considered in patients with obstruction, bleeding, or pain despite operative mortalities of 25% to 50%. Gastrojejunostomy bypass surgery alone may provide a twofold increase in mean survival. The selection of patients most likely to benefit from this or other palliative surgical interventions require further evaluation with prospective studies and multidisciplinary conference discussion.

Plastic and expansile metal stents are associated with successful palliation of obstructive symptoms in more than 85% of patients with tumors in the GEJ and in the cardia.

Palliative Chemotherapy

Various combinations of active agents have been reported to improve the response rate (20%-50%) among patients with advanced gastric carcinoma (Table 5.4). While utilizing 5-FU as a backbone, FAMTX (5-FU, doxorubicin, methotrexate) became an international standard after direct comparison to FAM (5-FU, doxorubicin, mitomycin), supporting a superiority with a survival advantage for FAMTX. The addition of cisplatin into combination regimens was supported by subsequent studies in both Europe and the United States.

TABLE 5.4

Randomized Antineoplastic Combination Therapy Trials in Advanced Gastric Cancer

Treatment Arms	Patients (*n*)	RR (%)	Median Survival (mo)
FAMTX vs FAM	213	41 vs 9 [a]	10.5 vs 7.3 [a]
PELF vs FAM	147	43 vs 15 [a]	8.8 vs 5.8
FAMTX vs EAP	60	33 vs 20	7.3 vs 6.1

Treatment Arms	Patients (*n*)	RR (%)	Median Survival (mo)
ECF vs FAMTX	274	45 vs 21 [a]	8.9 vs 5.7 [a]
DCF vs CF	445	37 vs 25 [a]	9.2 vs 8.6 [a]
EOX vs ECF	488	48 vs 40	11.2 vs 9.9 [a]
Cis/S-1 vs Cis/5-FU	1053	29 vs 32	8.6 vs 7.9
CF + Trastuzumab vs CF	298	47 vs 35	13.8 vs 11.1
TD vs (Irinotecan or Paclitaxel)	187	51 vs 14 [a]	12.5 vs 8.4 [a]
Ram vs BSC	355	8 vs 3	5.2 vs 3.8
PAC + Ram vs PAC	655	28 vs 16	9.6 vs 7.4
Apatinib vs BSC	270	3 vs 0	6.5 vs 3.7
Pembro + chemo vs chemo	749	45 vs 29 [a]	12.4 vs 9.8 [a]
Nivo + chemo vs chemo	1581	60 vs 45 [a]	13.8 vs 11.6 [a]

BSC, best supportive care; CF, cisplatin, 5-FU; chemo, chemotherapy; DCF, docetaxel, cisplatin, 5-FU; EAP, etoposide, doxorubicin, cisplatin; ECF, epirubicin, cisplatin, and 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; FAM, 5-FU, doxorubicin, mitomycin-C; FAMTX, 5-FU, doxorubicin, and methotrexate; Nivo, nivolumab; PAC, paclitaxel; PELF, cisplatin, epidoxorubicin, leucovorin, 5-FU with glutathione and filgrastim; Pembro, pembrolizumab; Ram, ramucirumab; RR, response rate; S-1; oral fluoropyrimidine; TD, trastuzumab deruxtecan.

[a]Difference is statistically significant ($P < .05$).

Historically, the most commonly used combination regimens include FAMTX, FAM, FAP, ECF, ELF, FLAP (5-FU, leucovorin, doxorubicin, cisplatin), PELF (cisplatin, epidoxorubicin, leucovorin, 5-FU with glutathione and filgrastim), and FUP or CF (5-FU, cisplatin). The combination of a fluoropyrimidine and platinum is the most commonly used in the United States.

Cytotoxic Chemotherapy Agents

Chemotherapeutic agents, including irinotecan, docetaxel, paclitaxel, and alternative platinums and fluoropyrimidines, have shown promising activity as single agents and have been actively incorporated into combination therapy (see Tables 5.3 and 5.4). A complete review of all agents is beyond the scope of this chapter.

Docetaxel is FDA approved in combination with cisplatin and 5-FU (DCF) in patients with advanced or metastatic gastric cancer based on the results of a large phase 3 international trial; 445 patients were randomized to receive cisplatin and 5-FU with or without

docetaxel. The addition of docetaxel resulted in an improvement in tumor response (37% vs 25%; $P = .01$), time to progression (5.6 vs 3.7 months; $P < .001$), and median survival (9.2 vs 8.6 months; $P = .02$) with a doubling of 2-year survival (18% vs 9%). These findings were at the cost of anticipated increased toxicity; however, maintenance of quality of life and performance status indices were longer for DCF. In a Japanese study, 20% of patients who showed no response to previous chemotherapy had a partial response to monotherapy with docetaxel.

S-1 is an oral fluoropyrimidine derivative composed of tegafur (5-FU prodrug), 5-chloro-2, 4-dihydroxypyridine (inhibitor of 5-FU degradation), and potassium oxonate (inhibitor of gastrointestinal toxicities). Because of the favorable safety profile of S-1 compared to infusional 5-FU, a multicenter prospective randomized phase III trial was conducted in 24 Western countries including the United States. Previously untreated patients ($n = 1053$) with advanced gastric or GEJ adenocarcinoma were randomized to either cisplatin/S-1 or cisplatin/infusional 5-FU. The median OS (8.6 vs 7.9 months; $P = .20$), overall response rate (29.1% vs 31.9%; $P = .40$), median duration of response (6.5 vs 5.8 months; $P = .08$), and treatment-related deaths (2.5% vs 4.9%; $P < .05$) favored the cisplatin/S-1 arm. The cisplatin/S-1 arm had significant favorable toxicities as well. The lack of survival benefit but improved toxicity profile could have been due to the lower dose of cisplatin used in the cisplatin/S-1 arm.

Capecitabine is another oral fluoropyrimidine that has been substituted for infusional 5-FU in a variety of settings. It was formally evaluated with encouraging results in combination with a platinum alternative.

Oxaliplatin is a third-generation platinum with less nephrotoxicity, nausea, and bone marrow suppression than cisplatin. In a two-by-two designed study in patients with advanced gastric cancer, standard ECF chemotherapy was modified with oxaliplatin substituted for cisplatin and capecitabine substituted for 5-FU; 1002 patients were randomly allocated between the four arms

(ECF, EOF, ECX, and EOX). Capecitabine and oxaliplatin appeared as effective as 5-FU and cisplatin, respectively. Response rates and PFS were nearly identical between the groups, with the EOX regimen showing superiority in OS over ECF (11.2 vs 9.9 months; $P = .02$).

Targeted Agents/Immunotherapy

New biologic therapies aimed to inhibit or modulate targets of aberrant signal transduction in gastric cancer have been actively investigated. Inhibition of angiogenesis, VEGF, and EGFR pathways are undergoing clinical testing and have shown early promising activity. (see Tables 5.3 and 5.4). Immunotherapy targeting PD-1 or PD-L1 alone or in combination with chemotherapy has demonstrated survival benefit in certain treatment settings.

EGFR-2 (HER2)

Overexpression of EGFR-2 (HER2) is seen in approximately 7% to 22% of esophagogastric cancers. The prognostic significance of HER2 overexpression in esophagogastric adenocarcinoma is unclear. Similar to breast cancer, HER2 overexpression is predictive for response to anti-HER2 therapies. HER2 protein expression is assessed by immunohistochemical (IHC) staining and gene amplification by fluorescence in situ hybridization (FISH). HER2 overexpression in esophagogastric cancer is different from that of breast cancer because it tends to spare the digestive luminal membrane. Thus, an esophagogastric cancer with only partially circumferential (ie, "basolateral" or "lateral") membrane staining can still be categorized as 2+ or 3+. In contrast, a breast tumor must demonstrate complete circumferential membrane staining to be designated as 2+ or 3+. Using breast cancer, HER2 interpretation criteria may underestimate expression in esophagogastric cancers. Modified criteria for interpreting HER2 by IHC in esophagogastric cancers were developed and validated with a high-concordance rate of HER2 gene amplification and HER2 protein overexpression for

IHC 0-1+ and 3+ cases. For an equivocal IHC 2+ expression, FISH analysis is recommended for confirmation.

Therapeutic targeting of HER2 overexpressing esophagogastric adenocarcinoma by a monoclonal antibody, trastuzumab, was studied in combination with chemotherapy. Patients (n = 592) with HER2 overexpressed advanced gastric and GEJ adenocarcinoma (ToGA trial) were randomized to standard chemotherapy (cisplatin/5-FU) with or without trastuzumab. The study demonstrated improved median OS (13.8 vs 11.1 months; HR 0.74; 95% CI, 0.60-0.91; P = .0046) in those receiving trastuzumab. The toxicities between the two arms were comparable. Subgroup analysis demonstrated patients with HER2 IHC 3+ scores derived the greatest benefit from targeted therapy (HR 0.66, 95% CI, 0.50-0.87). This trial established a new standard of care for advanced HER2 overexpressing esophagogastric tumors. Lapatinib, an orally active small molecule targeting EGFR1 and EGFR2 (HER2), failed to show a survival benefit when added to chemotherapy with capecitabine and oxaliplatin. Lapatinib also failed to improve OS when combined with paclitaxel in second line therapy but demonstrated a trend toward improvement in median OS (11 vs 8.9 months; P = .1044). It is noteworthy that few patients had received prior trastuzumab (only 7% in lapatinib arm and 15% in combination). Following prior trastuzumab-based treatment, the FDA approved fam-trastuzumab deruxtecan-nxki in 2021 as a HER2 antibody-drug conjugate based on improved response rate, PFS, and OS compared to cytotoxic chemotherapy. Early phase trials have also demonstrated the promising efficacy of novel HER2 targeting strategies including combination therapy with immune checkpoint inhibitors and other novel HER2 antibody-drug conjugates. Thus, testing for and targeting HER2 overexpressing tumors with trastuzumab represents a clinically meaningful treatment option.

Epidermal Growth Factor Receptor

Overexpression of EGFR is seen in 27% to 64% of gastric cancers with some studies suggesting it as a poor prognostic variable.

Cetuximab is a partially humanized murine anti-EGFR monoclonal antibody that has been the most extensive studied in gastric cancer. This agent has minimal activity as a single agent, while in combination with doublet or triplet chemotherapy regimens, it showed variable overall response rates (see Table 5.4). The EXPAND trial randomized 904 patients with metastatic or locally advanced gastric cancer to chemotherapy (cisplatin and capecitabine) with or without cetuximab. The addition of cetuximab provided no benefit in PFS but added toxicity. A fully humanized anti-EGFR monoclonal antibody (panitumumab) in combination with EOC (epirubicin, oxaliplatin, and capecitabine) was investigated in a randomized phase III (REAL-3) study. The addition of panitumumab to chemotherapy significantly reduced survival from 11.3 to 8.8 months. Of note, small molecule tyrosine kinase inhibitors of the EGFR (ie, erlotinib and gefitinib) showed very limited activity in multiple phase II trials. Based upon currently available evidence, anti-EGFR therapy should not be used outside the context of a clinical trial.

Targeting Angiogenesis

A high tumor and circulating serum level of VEGF in gastric cancer is associated with a poor prognosis. Ramucirumab, a recombinant monoclonal antibody of the IgG1 class targeting VEGFR-2, has demonstrated a survival advantage for palliative patients with previously treated gastric cancer. In the phase III REGARD trial, 355 previously treated patients with advanced or metastatic esophagogastric adenocarcinoma were randomly assigned to ramucirumab versus best supportive care. Ramucirumab was associated with significantly improved median PFS (2.1 vs 1.3 months) and OS (5.2 vs 3.8 months; HR 0.78; 95% CI 0.60-0.998; *P* = .047). The phase III RAINBOW trial added ramucirumab or placebo to weekly paclitaxel in 665 patients with metastatic esophagogastric adenocarcinoma who had disease progression on or within 4 months after first-line platinum and fluoropyrimidine-based combination therapy. The combination treatment was also

associated with an improved median PFS (4.4 vs 2.9 months) and OS (9.6 vs 7.4 months; HR 0.807; 95% CI 0.678-0.962; *P* = .017). Ramucirumab, either alone or in combination with paclitaxel, is considered a standard targeted therapy for previously treated patients with metastatic gastric adenocarcinoma. Clinical trials are ongoing to determine any benefit in the first line setting.

Of note, another monoclonal antibody against VEGF, bevacizumab, has already been tested in combination with first-line chemotherapy (cisplatin/capecitabine or 5-FU) in advanced gastric cancer. Although the initial phase II study showed promising OS, the benefit was not sustained in the global, phase III AVAGAST study. This study randomized 774 patients to cisplatin/fluoropyrimidine combination chemotherapy with or without bevacizumab. Response rate (46% vs 37%; *P* = .0315) and PFS (6.7 vs 5.3 months; *P* = .0037) were both improved with bevacizumab; however, there was no improvement in OS (12.2 vs 10.1 months; *P* = .1002). Bevacizumab is currently under investigation in the perioperative setting.

Another orally active VEGFR 2 inhibitor is currently approved for use in China based on a multicenter randomized, double-blind trial in which 270 patients with advanced gastric cancer were randomly assigned in a 2:1 ratio to apatinib (850 mg daily) or placebo. Apatinib was associated with prolonged median PFS (2.6 vs 1.8 months) and OS (6.5 vs 4.7 months; HR 0.709; 95% CI, 0.537-0.937; *P* = .0156).

Programmed Death-1/Programmed Death Ligand-1

Immunotherapy has become essential in the treatment of advanced stage gastric cancer. Namely, anti–PD-1 agents are approved for use in first-, second-, and third-line settings in certain subsets of patients with advanced gastric cancer. In the first-line setting, pembrolizumab (anti–PD-1) plus chemotherapy was approved in 2021 for patients with esophageal carcinoma, which include esophageal adenocarcinoma and GEJ cancer, both of which are considered the same disease entities as gastric cancer. This recent

approval was based on the results of the KEYNOTE-590 trial. Pembrolizumab plus chemotherapy demonstrated an improved OS compared to chemotherapy alone in the overall population (HR 0.73, 0.62-0.86).

Moreover, nivolumab (anti–PD-1) with chemotherapy was also approved in 2021 by the FDA for first-line therapy in patients with advanced gastric cancer, regardless of PD-L1 expression status. The expression of PD-L1 is defined by the combine positive score (CPS), which is defined as the sum of lymphocytes, macrophages, and tumor cells staining positive for PD-L1 divided by the total number of viable tumor cells multiplied by 100. This approval was based on the randomize phase III CheckMate-649 trial. Compared to chemotherapy alone, nivolumab with chemotherapy demonstrated superior OS (HR 0.77, 0.64-0.92).

In the second-line setting, pembrolizumab is approved for gastric cancer patients with mismatch repair deficiency or microsatellite instability. This is the first tumor agnostic approval given to an anticancer agent by the FDA, which was based on the phase II KEYNOTE-158 trial. This trial enrolled 258 patients with 27 tumor types including 24 patients with gastric cancer. All patients had failed on at least one prior line of systemic therapy and had mismatch repair deficiency or microsatellite instability. Objective response rate was 34.3% in the overall population and 45.8% in gastric cancer patients. Median PFS was 11.0 months in gastric cancer patients.

For third-line therapy, pembrolizumab is approved for gastric cancer patients with PD-L1 expressing tumors. This approval was based on the multicohort, phase II KEYNOTE-059 trial. In patients with PD-L1 positive tumors, as defined by a PD-L1 CPS of 1 or higher, the objective response rate was 15.5% with a complete response rate of 2.0%.

Given the assimilation of immunotherapy in the advanced disease setting, it is actively being investigated in the perioperative settings.

TREATMENT OF GASTRIC CANCER ACCORDING TO STAGE

Stage 0 Gastric Cancer

Stage 0 indicates gastric cancer confined to the mucosa. Based on the experience in Japan, where stage 0 is diagnosed more frequently, it has been found that more than 90% of patients treated by gastrectomy with lymphadenectomy will survive beyond 5 years. An American series has confirmed these findings. No additional perioperative therapy is necessary.

Stage I and II Gastric Cancer

1. One of the following surgical procedures is recommended for stage I and II gastric cancer:
    - Distal SG (if the lesion is not in the fundus or at the cardioesophageal junction)
    - Proximal SG or TG, with distal esophagectomy (if the lesion involves the cardia)
    - TG (if the tumor involves the stomach diffusely or arises in the body of the stomach and extends to within 6 cm of the cardia or distal antrum)
    - Regional lymphadenectomy is recommended with all of the previously noted procedures
    - Splenectomy is not routinely performed
2. Postoperative chemoRT is recommended for patients with at least stage IB disease.
3. Perioperative polychemotherapy could also be considered for patients who present with at least a T2 lesion preoperatively.

Stage III Gastric Cancer

1. Radical surgery: Curative resection procedures are confined to patients who do not have extensive nodal involvement at the time of surgical exploration.
2. Postoperative chemoRT or perioperative polychemotherapy is recommended. The latter should be considered particularly for bulky tumors or with significant nodal burden.

Stage IV Gastric Cancer

Patients With Distant Metastases (M1)

All newly diagnosed patients with hematogenous or peritoneal metastases should be considered as candidates for clinical trials. For many patients, chemotherapy may provide substantial palliative benefit and occasional durable remission although the disease remains incurable. Patients with HER2 overexpression should be treated with trastuzumab in combination with chemotherapy. Incorporating immunotherapy into clinical algorithms is another important consideration, given an increasing number of FDA approvals. Balancing the risks to benefits of therapy in any individual patient is critical.

Peritoneal Carcinomatosis

In approximately 50% of patients with advanced gastric cancer, the disease recurs locally or at an intraperitoneal site, and this recurrence has a negative effect on quality of life and survival. intraperitoneal (IP) 5-FU, cisplatin, and/or mitomycin have been used at select centers. IP chemotherapy administration does not routinely alter survival and should be reserved only for clinical trial at an experienced center.

POSTSURGICAL FOLLOW-UP

- Follow-up in patients after complete surgical resection should include routine history and physical, with liver function tests and CEA measurements being performed.
- Evaluation intervals of every 3 to 6 months for the first 3 years, then annually thereafter have been suggested.
- Symptom-directed imaging and laboratory workup is indicated, without routine recommendations otherwise.
- If TG is not performed, annual upper endoscopy is recommended due to a 1% to 2% incidence of second primary

gastric tumors.

- Vitamin B_{12} deficiency develops in most TG patients and 20% of SG patients, typically within 4 to 10 years. Replacement must be administered at 1000 μg subcutaneously or intramuscularly every month indefinitely.

PRIMARY GASTRIC LYMPHOMA

Gastric lymphomas are uncommon malignancies representing 3% of gastric neoplasms and 10% of lymphomas.

Classification and Histopathology

Gastric lymphomas can be generally classified as primary or secondary:

- Primary gastric lymphoma (PGL) is defined as a lymphoma arising in the stomach, typically originating from mucosa-associated lymphoid tissue (MALT). PGL can spread to regional lymph nodes and can become disseminated. Most are of B-cell NHL origin, with occasional cases of T-cell and Hodgkin lymphoma seen. Examples of PGLs include extranodal marginal zone B-cell lymphoma of MALT type previously called low-grade MALT lymphoma, diffuse large B-cell lymphoma (DLBCL) previously called high-grade MALT lymphoma, and Burkitt and Burkitt-like lymphoma. This section will primarily address PGLs.
- Secondary gastric lymphoma indicates involvement of the stomach associated with lymphoma arising elsewhere. The stomach is the most common extranodal site of lymphoma. In an autopsy series, patients who died from disseminated NHL showed involvement of the gastrointestinal tract in 50% to 60% of cases. Examples of secondary gastric lymphoma include several common advanced-stage systemic NHLs, particularly mantle cell lymphoma.

Epidemiology

- The prevalence of PGL has been increasing over the past 20 years without a clear explanation.
- PGL incidence rises with age, with a peak in the sixth to seventh decades with a slight male predominance.
- Risk factors include *H. pylori*–associated chronic gastritis (particularly low-grade MALT lymphoma), autoimmune diseases, and immunodeficiency syndromes including AIDS and chronic immunosuppression.

Diagnosis

Clinical symptoms that are most common at presentation include abdominal pain, weight loss, nausea, vomiting, and early satiety. Frank bleeding is uncommon and patients rarely present with perforation. Findings on upper endoscopy are diverse and may be identical to typical adenocarcinoma.

Since PGL can infiltrate the submucosa without overlying mucosal changes, conventional punch biopsies may miss the diagnosis. Deeper biopsy techniques should be employed. If an ulcer is present, the biopsy should be at multiple sites along the edge of the ulcer crater. Specimens should be pathologically evaluated by both standard techniques to determine histology and *H. pylori* positivity as well as flow cytometry to determine clonality and characteristics of any infiltrating lymphocytes. The latter requires fresh tissue placed in saline, not preservative. In addition, FISH or polymerase chain reaction are used to test for t(11;18). This cytogenetic finding is associated with more advanced disease and relative resistance to *H. pylori* therapy.

Staging

Lugano staging system is commonly used for gastric lymphoma because the Ann Arbor stating system is considered to be inadequate as it does not incorporate depth of tumor invasion, which is known to affect the prognosis. Early (stage IE/IIE) disease includes a single

primary lesion or multiple, noncontiguous lesions confined to the GI tract that may have local or distant nodal involvement. There is no stage III in the Lugano system. Advanced (stage IV) has disseminated nodal involvement or concomitant supradiaphragmatic involvement. Patients present with stage IE and stage IIE PGL with an equal prevalence ranging between 28% and 72%.

Presentation with high-grade and low-grade disease is also equal, with 34% to 65% of disease presenting as high-grade lymphoma and 35% to 65% presenting as low-grade lymphoma. CT scanning of the chest and abdomen is important to determine the lymphoma nodal involvement. FDG-PET scanning and bone marrow biopsy may be useful in high-grade PGL staging.

Treatment

Treatment of PGL is dependent primarily by stage and histologic grade of the lymphoma. However, given the rarity of the disease and lack of clinical trial data, treatment recommendations are based primarily on retrospective studies.

Extranodal marginal zone B-cell lymphoma of MALT type is usually of low-grade histology (40%-50%) and confined to the stomach (70%-80% stage IE). Very good epidemiologic data support *H. pylori*–induced chronic gastritis as a major etiology for this tumor. Eradication of *H. pylori* infection with antibiotics should be the initial standard treatment. Complete histologic regression of the lymphoma has been demonstrated in 50% to 80% of patients treated in this manner with good long-term DFS. RT can provide durable remission for cases that relapse or are *H. pylori*–negative. One-third of PGL is associated with the t(11;18) translocation, which has a low response to *H. pylori* therapy and should warrant consideration of RT as a primary treatment. More advanced stage or aggressive histologies at presentation should be treated like DLBCL.

Previously called high-grade MALT lymphoma, DLBCL is a more aggressive PGL. Eradication of *H. pylori* provides less reliable and

durable disease control. Gastrectomy was the traditional treatment of choice; however, this appears to be no longer necessary. Five hundred eighty-nine patients with stage IE and IIE DLBCL PGL were randomized to receive surgery, surgery plus RT, surgery plus chemotherapy, or chemotherapy alone. Chemotherapy was six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). OS at 10 years were 54%, 53%, 91%, and 96%, respectively. Late toxicity and complications were more frequent and severe in those receiving surgery. Gastric perforation or bleeding as a result of initial chemotherapy was not evident. Organ preservation has been a major advance for this disease with the use of chemotherapy.

Highly aggressive PGLs including Burkitt and Burkitt-like lymphoma have seen dramatic improvement in survival over the past decade as a result of potent chemotherapy combinations for systemic disease as well as better treatment of underlying immunodeficiency states (ie, highly effective antiretroviral therapy for AIDS).

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6

Biliary Tract Cancer

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INTRODUCTION

Carcinomas of the biliary tract include cancers arising in either the gallbladder or the bile duct system—the latter usually referred to as cholangiocarcinomas and further categorized as intra- or extrahepatic. There will be an estimated 11,980 new cases of gallbladder and biliary tract cancers (excluding intrahepatic biliary tract cancer) in 2021 in the United States with 4310 expected deaths. The incidence of intrahepatic cholangiocarcinoma in the United States has risen from 0.44 to 1.18 cases per 100,000 between 1973 and 2012, though some of this increase may be accounted for by reclassification of carcinomas of unknown primary as intrahepatic cholangiocarcinoma. Worldwide, an estimated 219,420 cases and 165,087 deaths were reported in 2018. Gallbladder cancer is the most common biliary tract cancer, occurring nearly twice as often as cholangiocarcinomas. The epidemiology, clinical features, staging, and surgical treatment are distinct for carcinomas arising in the gallbladder and bile duct; therefore, these are described separately. The systemic therapy options are similar and are discussed together later in the chapter.

CARCINOMA OF THE GALLBLADDER

Epidemiology

- Women have a two- to sixfold higher incidence of gallbladder cancer.
- There is a prominent geographic variation in the incidence of gallbladder cancer. Higher rates are seen among Native Americans, in South American countries (particularly Chile), and in countries such as India, Pakistan, Japan, and Korea. These populations share a high prevalence of cholelithiasis, which is a common risk factor.
- The United States is considered a low-incidence area. The age-adjusted incidence of carcinoma of the gallbladder is 1.26 per 100,000 population in the United States.

Etiology

- Cholelithiasis (gallstones): A history of gallstones appears to be one of the strongest risk factors for gallbladder cancer. Most (70%-90%) patients have gallstones. The risk increases with an increase in the size and duration of the stones.
- Porcelain gallbladder: Extensive calcium deposition in the gallbladder wall was associated with cholecystitis in nearly all cases. Previously, the incidence of gallbladder cancer in patients with this condition was thought to range from 12.5% to 60% although more recent data suggest the incidence is closer to 2% to 3%. Stippled, mucosal calcifications appear to be associated with a higher risk than diffuse intramural calcifications.
- Chronic infection: Carriers or those colonized with *Salmonella typhi* and *Helicobacter pylori* may be at increased risk of developing gallbladder cancer.
- Gallbladder polyps: Polyps > 1 cm have the greatest malignant potential and therefore are an indication for cholecystectomy.
- An anomalous pancreatobiliary duct junction may contribute to the development of gallbladder cancer.
- Miscellaneous: Obesity, diabetes, medications (methyldopa, estrogens, isoniazid), and carcinogen exposure (radon, chemicals from the rubber industry, cigarettes) have also been associated with this disease.

Clinical Features

Early-stage disease may be asymptomatic or present with very nonspecific symptoms, including the following:

- Often, it is noted as an incidental finding on cholecystectomy for cholelithiasis or cholecystitis
- Pain
- Weight loss
- Anorexia
- Nausea or vomiting
- Mass in the right upper quadrant
- Jaundice
- Abdominal distension
- Pruritus

Diagnosis

Three clinical scenarios exist in patients presenting with gallbladder cancer: final pathology after a routine laparoscopic cholecystectomy incidentally discovers gallbladder cancer; gallbladder cancer is suspected/diagnosed intraoperatively; or gallbladder cancer is suspected preoperatively.

- An incidental surgical or pathologic finding is the most common clinical scenario. It is estimated that 1% to 2% of patients undergoing exploration for presumed benign disease will be found to have gallbladder cancer.
- Ultrasound is a useful modality in the preoperative workup for gallbladder pathology. In the case of gallbladder cancer, the ultrasonographic findings may include a thickened or calcified wall, a protruding mass, or a loss of gallbladder to liver interface; however, these may not be specific for gallbladder cancer.
- Triple-phase computed tomography (CT) scan (liver protocol), which includes a noncontrast phase, a hepatic arterial phase, and a portal venous phase, allows visualization of the extent of

tumor growth, can aid in determining the nodal status as well as identifying distant metastases, and is particularly useful in determining the relationship of the tumor mass to the major hilar inflow structures, which is an important preoperative determinant. This modality is less helpful in distinguishing benign from malignant polyps.

- Cholangiography: Magnetic resonance cholangiopancreatography (MRCP) can provide further information regarding the extent of disease.
- Laboratory studies are generally not diagnostic. Elevated serum bilirubin or alkaline phosphatase can indicate biliary obstruction. CA19.9, a tumor marker, is often checked but is neither sensitive nor specific for a diagnosis.

Pathology

- Adenocarcinoma accounts for close to 85% of cases. It is further classified into papillary, tubular, mucinous, or signet cell type. Other histologies include anaplastic, squamous cell, small-cell neuroendocrine tumors, sarcoma, and lymphoma.

Staging

There are several staging systems available for gallbladder cancer. The original staging system was developed by Nevin in 1976; the preferred classification scheme in the United States is the tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) (Table 6.1).

TABLE 6.1

AJCC Staging System for Gallbladder Cancer (8th Edition, 2017)

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor invades lamina propria or muscular layer		

Primary Tumor (T)			
T1a	Tumor invades lamina propria		
T1b	Tumor invades muscular layer		
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum), or tumor invades the perimuscular connective tissue on the hepatic side, with no extension in to the liver		
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)		
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension in to the liver		
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts		
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastases to one to three regional lymph nodes		
N2	Metastases to four or more regional lymph nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

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2017:303-309.

- The AJCC TNM staging classification was updated in 2017.
- The updated stage groupings were realigned to better correlate with resectability and prognosis.

Treatment

Surgery

- Surgical resection remains the only potentially curative therapy.
- The lack of a peritoneal lining on the side of the gallbladder that is attached to the liver represents an important anatomic consideration in the surgical management of gallbladder cancer. In a simple cholecystectomy, the surgeon dissects the plane between the muscularis of the gallbladder and the cystic plate, which is a fibrous lining that occupies the space between the gallbladder and the liver. For this reason, simple cholecystectomy is considered inadequate surgical therapy for all but the earliest stages of the disease.
- Factors determining resectability include the stage of the tumor as well as the location. T0-2 tumors are potentially resectable with curative intent. T3 tumors are difficult to resect.
- For incidentally detected gallbladder cancer after simple cholecystectomy, careful clinical, laboratory, radiologic, and pathologic evaluation should be conducted to assess the extent of disease.
- For completely resected (margin-negative) nonperforated T1a tumors with no evidence of nodal or metastatic disease, observation alone is usually sufficient as 5-year overall survival is over 90%.
- Patients with T1b or greater lesions should undergo extended cholecystectomy after metastatic disease has been ruled out. Optimal resection (extended cholecystectomy) includes a cholecystectomy with en bloc hepatic resection and regional lymphadenectomy with or without bile duct excision.

Achievement of R0 resection margins correlates strongly with long-term survival.

- The type of resection that is ultimately required to achieve an R0 resection can at times depend on the location of the tumor within the gallbladder. Tumors of the body and fundus may be manageable with a localized segment IV/V resection while those of the infundibulum may require division of inflow structures and consequently major hepatic resection with or without bile duct resection/reconstruction.
- Contraindications to surgery include distant metastases, extensive involvement of the porta hepatis causing jaundice, significant ascites, and encasement or occlusion of major vessels. Direct involvement of adjacent organs is not an absolute contraindication.
- If cancer is suspected, perforation of the gallbladder (such as during percutaneous biopsy) during surgery should be avoided to prevent seeding of the peritoneal cavity.

Radiation

- A number of reports have documented improvements in survival rates in cases of intraoperative or postoperative adjuvant radiotherapy. No prospective randomized controlled trials have been performed to address this issue. However, one study found that only 15% of patients had locoregional recurrence as their only site of recurrent disease, which highlights the importance of effective, adjuvant systemic strategies.

Systemic Therapy and Palliation

The benefits and options available for systemic therapy and palliation of carcinoma of the gallbladder are the same as those for cholangiocarcinoma, which is discussed in the next section.

Survival

The survival rates for gallbladder cancers according to stage are shown in Table 6.2.

TABLE 6.2

Five-Year Survival of Gallbladder Cancers and Intrahepatic Cholangiocarcinomas According to Stage

TNM Stage	Five-Year Survival
Gallbladder Cancer	
Stage I (T1N0M0)	90%
Stage IIA (T2aN0M0)	75.5%
Stage IIB (T2bN0M0)	48.2%
Stage IIIA (T3N0M0)	38.0%
Stage IIIB (T1-3N1M0)	28.0%
Stage IVA (T4N0-1M0) Stage IVB (Any T, N2M0) (Any T, Any N, M1)	2.0%
Intrahepatic Cholangiocarcinoma	
Stage IA (T1aN0M0)	90.0%
Stage IB (T1bN0M0)	50.6%
Stage II (T2N0M0)	55.1%
Stage IIIA (T3N0M0)	49.7%
Stage IIIB (T4N0M0) (Any T, N1M0)	16.2%
Stage IV (Any T, Any N, M1)	2.0%

CARCINOMA OF THE BILE DUCTS (CHOLANGIOCARCINOMA)

Epidemiology

- Cholangiocarcinomas arise from the epithelial cells of either intrahepatic or extrahepatic bile ducts.
- The reported incidence within the United States is 1 to 2 cases per 100,000 persons.
- Median age at diagnosis is between 50 and 70 years. However, patients with primary sclerosing cholangitis (PSC) and those

with choledochal cysts tend to present at younger ages.

- In contrast to gallbladder cancer, cholangiocarcinomas are more common in males.
- Cholangiocarcinomas are categorized into proximal extrahepatic (perihilar or Klatskin tumor; 50%-60%), distal extrahepatic (20%-25%), intrahepatic (peripheral tumor; 20%-25%), and multifocal (5%) tumors.
- Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas, and perihilar cholangiocarcinoma is the most common type.

Etiology

A number of risk factors have been associated with the disease in some patients; however, no specific predisposing factors have been identified.

- Inflammatory conditions: PSC is associated with an annual risk of 0.6% to 1.5% per year and a 10% to 15% lifetime risk of developing cholangiocarcinoma. Ulcerative colitis and chronic intraductal gallstone disease also increase risk. Nearly, 30% of cholangiocarcinomas are diagnosed in patients with coexistent ulcerative colitis and PSC.
- Bile duct abnormalities: Caroli disease (cystic dilatation of intrahepatic ducts), bile duct adenoma, biliary papillomatosis, and choledochal cysts increase risk. The overall incidence of cholangiocarcinoma in these patients can be as high as 28%.
- Infection: In Southeast Asia, the risk can be increased 25- to 50-fold by parasitic infestation from *Opisthorchis viverrini* and *Clonorchis sinensis.* These parasitic infections are more commonly associated with intrahepatic cholangiocarcinoma. An association with viral hepatitis has also been seen. A higher than expected rate of hepatitis C–associated cirrhosis was noted in patients with cholangiocarcinoma. An association with hepatitis B has also been suggested.

- Genetic: Lynch syndrome II and multiple biliary papillomatosis are associated with an increased risk of developing cholangiocarcinoma. Biliary papillomatosis should be considered a premalignant condition as one study noted that up to 83% will undergo malignant transformation. More recently, certain genetic polymorphisms (NKG2D) have been determined to be possible risk factors for developing cholangiocarcinoma.
- Miscellaneous: Smoking, toxic exposures, such as Thorotrast (a radiologic contrast agent used in the 1960s), asbestos, radon, and nitrosamines are also known to increase the risk. Recently, patients with diabetes or a metabolic syndrome have been noted to have an increased risk of developing a cholangiocarcinoma as well.

Clinical Features

Cholangiocarcinomas usually become symptomatic when the biliary system becomes obstructed.

- Extrahepatic cholangiocarcinoma usually presents with symptoms and signs of cholestasis (icterus, pale stools, dark urine, pruritus, or cholangitis, which includes pain, icterus, and fever). Laboratory studies will typically suggest biliary obstruction with elevated direct bilirubin and alkaline phosphatase.
- Intrahepatic cholangiocarcinoma may present as a mass, be asymptomatic, or produce vague symptoms such as pain, anorexia, weight loss, night sweats, and malaise. These patients are less likely to be jaundiced.

Diagnosis

- A cholestatic picture may be seen as described previously. Liver function tests may be elevated, particularly with intrahepatic cholangiocarcinoma. Tumor markers such as CEA and CA-19-9 by themselves are neither sensitive nor specific enough to make

a diagnosis. Ultrasonography is the first-line investigation for suspected cholangiocarcinoma, usually to confirm biliary duct dilatation, localize the site of obstruction, and rule out cholelithiasis. This technique can often overlook masses and is poor at delineating anatomy.

- CT/MRI is recommended as part of the diagnostic workup of cholangiocarcinoma, intrahepatic tumors in particular. These imaging modalities can help determine tumor resectability by evaluating the tumor and the surrounding structures (major vessels, lymph nodes, presence of metastases).
- Cholangiography: MRCP is noninvasive and can provide excellent imaging of the intrahepatic and extrahepatic bile ducts. This provides valuable information about disease extent and surgical options. Due to their ability to obtain brushings from as well as stent across strictures within the biliary tree, endoscopic retrograde cholangiopancreatography, and/or percutaneous transhepatic cholangiography offer both diagnostic and therapeutic value in the workup and management of biliary obstruction; however, the diagnostic yield on cytology obtained from biliary brushings can be low.
- Endoscopic ultrasound (EUS) may be useful in visualizing the extent of tumor and lymph node involvement of distal bile duct lesions. EUS is also useful for obtaining a fine needle aspiration or core needle biopsies, which have better diagnostic yields compared to cytology obtained from biliary brushings. Its role in proximal bile duct lesions is less clear.

Pathology

- Adenocarcinomas account for 90% to 95% of tumors. The remainder are squamous cell carcinomas. Adenocarcinomas are graded as well, moderately and poorly differentiated, and are further classified as sclerosing, nodular, and papillary subtypes. Patients with papillary tumors present with earlier disease and have the highest resectability and cure rates; however, they are the least common subtype.

Staging

- The AJCC TNM staging system is primarily based on the extent of ductal involvement by the tumor.
- The eighth edition staging system for extrahepatic cholangiocarcinomas separates perihilar and distal bile duct tumors. These changes have improved the prognostic stratification of the TNM staging system. Please refer to the eighth edition AJCC Staging Manual for details.
- Cancers arising in the perihilar region have been also further classified according to their patterns of involvement of the hepatic ducts, the Bismuth-Corlette classification.

Treatment

Surgery

Except in the case of distal common bile duct cancer, cholangiocarcinoma is a disease that, when managed surgically, often requires major hepatic resection (segmentectomy, anatomic lobectomy, and trisegmentectomy) with or without bile duct resection/reconstruction. Therefore, the general principles of such resection(s) should be reviewed.

From the standpoint of major hepatic resection, the surgical principles are simple and revolve primarily around leaving the patient with an adequate volume of a functioning liver remnant to sustain them postoperatively. This requires executing an operation that ensures both adequate inflow to (hepatic artery and portal vein) and outflow from (hepatic vein and bile duct) the remnant liver.

Generally speaking, roughly 75% of a patient's liver volume can safely be resected; however, consideration must be given to the health of the background liver. Such consideration includes underlying chronic liver disease (hepatitis, prior alcohol use, and steatosis/steatohepatitis) as well as any acute insults, which in the case of cholangiocarcinoma often involves cholestasis. The former

issues can limit the extent of resection that can safely be performed, while the latter often necessitates preoperative delays while the cholestatic picture resolves.

If there is any concern about the adequacy of the planned future liver remnant, portal vein embolization on the side of the liver that is anticipated to be resected can be performed in an attempt to allow the contralateral side to hypertrophy preoperatively.

Intrahepatic Cholangiocarcinoma

- Surgery is the only potentially curative therapy for patients with intrahepatic cholangiocarcinoma; however, most patients present with advanced disease and are not surgical candidates.
- Multiple hepatic tumors, regional lymph node involvement, large tumor size, and vascular invasion predict poor recurrence-free survival postresection.
- The extent of surgery is dictated by what is necessary to obtain clear margins. R0 resection with adequate margins is the aim and is ultimately associated with significantly longer survival rates that can range from 30% to 67%.
- If microscopic positive tumor margins (R1) or residual local disease (R2) is noted after resection, patients should be evaluated for possible reresection versus chemoradiation options.
- The role of routine nodal dissection in the management of intrahepatic cholangiocarcinoma is controversial.
- During laparotomy, thorough assessment of the intra-abdominal lymph node basins should be undertaken prior to hepatic resection. Suspicious nodes should be biopsied, and attempts at resection should be aborted if nodal metastases are confirmed intraoperatively.
- The survival rates for intrahepatic cholangiocarcinomas according to stage are shown in Table 6.2

Distal Cholangiocarcinoma

- Primarily treated with a Whipple procedure (pancreaticoduodenectomy).

Perihilar Cholangiocarcinoma

- The main curative therapy for patients with extrahepatic perihilar cholangiocarcinoma is complete surgical resection.
- Surgery for extrahepatic hilar cholangiocarcinomas is based on the stage of disease, and the goal of surgical intervention is to obtain a tumor-free margin (Table 6.3).

TABLE 6.3

Five-Year Survival of Extrahepatic Bile Duct Cancers According to Stage

TNM Stage	Five-Year Survival (%)
Stage 0 (TisN0M0)	100.0
Stage I (T1N0M0)	84.8
Stage II (T2N0M0)	59.0
Stage IIIA (T3N0M0)	45.7
Stage IIIB (T4N0M0)	37.7
Stage IIIC (Any T, N1M0)	25.4
Stage IVA (Any T, N2M0) Stage IVB (Any T, Any N, M1)	10.8

- For patients with hilar cholangiocarcinoma, bile duct resection leads to high local recurrence rates. Hilar resection with lymphadenectomy and en bloc liver resection and biliary reconstruction are recommended for lesions in the extrahepatic biliary tree. Caudate resection is often required to achieve an R0 resection, particularly for tumors involving the left hepatic duct.
- Five-year survival rates range from 20% to 40% in patients treated with surgical resection for hilar cholangiocarcinoma.

Adjuvant Chemotherapy and Chemoradiation

- Adjuvant chemotherapy with capecitabine is the standard of care for resected biliary tract cancers. This is based on results from the BILCAP study, which randomized patients to either

adjuvant capecitabine for 6 months or observation. In the intention-to-treat analysis, which included 223 patients in the capecitabine group and 224 patients in the observation group, the capecitabine group had numerically improved median overall survival (51.1 vs 36.4 months) though this difference did not meet statistical significance (HR 0.81; *P* = .097). In a prespecified, per-protocol analysis with 210 patients in the capecitabine group and 220 in the observation group, median overall survival was 53 months in the capecitabine group and 36 months in the observation group (HR 0.75, *P* = .028). Despite the conflicting statistical analyses, it appears that adjuvant capecitabine has a clinically meaningful benefit in overall survival. Patients with positive lymph nodes, poorly differentiated tumors, and tumors > 5 cm derived the greatest benefit.

- While there is an absence of prospective randomized trial data establishing the benefit of adjuvant chemoradiotherapy, the SWOG 0809 study provides some meaningful evidence for its use. The study included 79 patients who were treated with adjuvant gemcitabine combined with capecitabine followed by concurrent capecitabine and radiotherapy. The results showed very similar outcomes for patients who underwent R0 versus R1 resections (34 vs 35 months). This suggests that improving local control with radiotherapy can meaningfully impact overall survival for patients with residual disease after surgery.

Chemotherapy in Advanced-Stage Disease

- For metastatic biliary tract cancer, the standard of care for first-line therapy is combination chemotherapy with gemcitabine and cisplatin, based on a large randomized controlled trial (ABC-02 study) that showed improved overall survival with the combination, compared with gemcitabine alone (11.7 vs 8.1 months; HR 0.64; 95% CI, 0.52-0.80).
- Oxaliplatin can be considered instead of cisplatin, in combination with gemcitabine, to minimize toxicities from

therapy, based on extrapolation of data from phase II studies.

- The NIFTY and ABC-06 studies have established liposomal irinotecan (nal-IRI) combined with 5-fluorouracil (5-FU) and FOLFOX (5-FU, leucovorin, and oxaliplatin) as two standard of care options for second-line therapy in advanced biliary tract cancers. The NIFTY study compared the combination of nal-IRI and 5-FU with 5-FU alone and showed a significant improvement in median overall survival with the combination (8.6 vs 5.5 months; HR 0.68, *P* = .0349). The ABC-06 study compared FOLFOX with supportive care alone and demonstrated a modest improvement in median overall survival with FOLFOX (6.2 vs 5.3 months; HR 0.69, *P* = .031).

Targeted Therapy

- A number of actionable genomic alterations have been identified in biliary tract cancers in recent years, including fibroblast growth factor receptor 2 (FGFR2), isocitrate dehydrogenase 1 (IDH1), and B-rapidly accelerated fibrosarcoma (BRAF). The frequencies of these genomic alterations based on site of origin along the biliary tract are shown in Table 6.4

TABLE 6.4

Common Genomic Alterations in Biliary Tract Cancers That Are Potentially Actionable

Mutation	Gallbladder Cancer (%)	Extrahepatic Cholangiocarcinoma (%)	Intrahepatic Cholangiocarcinoma (%)
FGFR1-3 fusion	3	0	11-12.5
IDH1/2 substitution	0	3-4	15-23
BRAF mutation	1	3	5
HER2 amplification	16	11	3

Mutation	Gallbladder Cancer (%)	Extrahepatic Cholangiocarcinoma (%)	Intrahepatic Cholangiocarcinoma (%)
KRAS mutation	11-19	42-57	15-22
MET amplification	0	0	4
PIK3CA mutation	14	7	5

- Pemigatinib, a potent inhibitor FGFR1-3, appears to be effective in patients with FGFR2 fusions or gene rearrangements. This is based on FIGHT-202, a single-arm study that included 146 patients with advanced cholangiocarcinoma that had received at least one prior therapy. Among patients with FGFR2 fusions or gene rearrangements, the study demonstrated an objective response rate of 35.5% and median overall survival of 21.1 months. Common important toxicities include hyperphosphatemia, ocular keratitis, stomatitis, and hand-foot rash.
- IDH1 mutations appear to be important in cholangiocarcinoma pathogenesis through their effect on liver progenitor cell differentiation and proliferation. The IDH1 inhibitor ivosidenib has been evaluated in the ClarIDHy trial, a randomized, double-blind, placebo-controlled phase III clinical trial of patients with previously treated, advanced cholangiocarcinoma. Median progression-free survival was modestly improved in the ivosidenib group compared to the placebo group (2.7 vs 1.4 months, HR 0.37, $P < .0001$). The study did not demonstrate a difference in median overall survival between the ivosidenib and placebo groups (10.3 vs 7.5 months, HR 0.79, $P = .093$). Common adverse events include nausea, diarrhea, fatigue, anemia, and ascites. As of August 2021, ivosidenib is under review for the Food and Drug Administration (FDA) approval.
- BRAF V600E mutations, which among the biliary tract cancers are most prevalent in intrahepatic cholangiocarcinoma, have been associated with higher tumor stage, greater likelihood of lymph node involvement, and poorer overall survival. The Rare

Oncology Agnostic Research basket trial assessed the safety and efficacy of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in multiple advanced cancers, including biliary tract cancers. The study demonstrated a 47% objective response rate and median overall survival of 14 months. Common adverse events include pyrexia, nausea, fatigue, and hepatitis. The dabrafenib and trametinib combination is not currently approved in biliary tract cancers.

Palliation

- Patients with unresectable or metastatic disease may benefit from palliative surgery, radiation, chemotherapy, or a combination of these.
- Biliary drainage can be achieved by Roux-en-Y choledojejunostomy, bypass of the site of obstruction to left or right hepatic duct, or endoscopic or percutaneously placed stents (metal-wall stents have a larger diameter and are less prone to occlusion or migration and are preferably used in patients with a life expectancy of greater than 6 months and/or in those who have unresectable disease).
- Celiac plexus blockade may also ameliorate symptoms of pain in the patient with inoperable disease.

Suggested Readings

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Primary Cancers of the Liver

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INTRODUCTION

Hepatocellular carcinoma (HCC) arises from hepatocytes and is the most common type of primary liver cancer, generally occurring in the setting of cirrhosis or chronic hepatitis B virus (HBV) infection. It is a leading cause of global cancer death. Intrahepatic cholangiocarcinoma arises from hepatic biliary epithelium. Secondary or metastatic cancer to the liver is the most common type of malignancy discovered in the liver. This chapter will focus on HCC.

EPIDEMIOLOGY

- HCC is the sixth most common cancer, and second leading cause of death from cancer around the world. In the United States, it is the thirteenth most common cancer but the sixth leading cause of cancer death.
- The highest incidence is in Asia and Africa, correlating with prevalence of HBV infection. China accounts for more than 50% of global cases.
- In the United States, the incidence has risen steadily since early 1980s but started to decline since 2015.
    - Incidence of HCC in the United States between 2014 and 2018 is 13.8 per 100,000 for men and 4.9 per 100,000 for women (http://seer.cancer.gov/statfacts/html/livibd.html).

    - Black, Hispanics, Pacific Islanders, and American Indians have higher incidence rates than White and non-Hispanics.
- Median age at diagnosis is 65 years. Two-thirds of new cases are diagnosed between the ages of 55 and 75.
- In 2021, 42,230 new primary liver cancer cases and 30,230 deaths are expected in the United States.
- The 5-year overall survival for all stages is 20%.

ETIOLOGY

- In high-incidence global regions, chronic HBV infection is the major risk factor for HCC. The risk increases with cirrhosis and higher serum levels of HBV DNA.
    - HBV can lead to HCC through cirrhosis or integration into host DNA.
- In lower incidence regions such as the United States, cirrhosis due to chronic hepatitis C virus (HCV) infection, alcohol abuse, and nonalcoholic fatty liver disease plays a major role in HCC development.
    - HCV infection accounts for up to 50% of HCC cases in the United States.
    - Alcoholic cirrhosis accounts for 15% of HCC cases and commonly coexists with chronic HCV infection.
- Other less common etiologies include hemochromatosis, α1-antitrypsin deficiency, cardiac cirrhosis, and aflatoxin exposure.
- Five-year cumulative risk of developing HCC in cirrhotic patients ranges from 5% to 30% depending on region, cause of cirrhosis, and degree of liver inflammation/cirrhosis.

CLINICAL FEATURES

- HCC is commonly asymptomatic and is either incidentally found or discovered during screening in cirrhotic patients or those with viral hepatitis B or C infection.
- Symptoms are usually a sign of advanced disease (pain, constitutional symptoms), and most accompanying symptoms are due to cirrhosis or coexisting hepatic disease.

- HCC is usually confined to liver, but the risk of metastases increases with larger tumor burden and the presence of vascular involvement.
    - Common metastatic sites are regional lymph nodes, lungs, and bone.
    - There is a very small risk (<3%) of needle track seeding in abdominal wall following percutaneous biopsy.
- Acute pain with large and/or superficial tumors in the liver may indicate tumor rupture.
- Hepatic functional reserve as assessed by the Child-Pugh system and/or Model for End Stage Liver Disease score is essential for care planning.

DIAGNOSIS

- Diagnosis is usually suspected in patients with known cirrhosis with abnormal routine screening ultrasound of the liver and/or alpha-fetoprotein (AFP) serum levels.
- The American Association for the Study of Liver Disease has issued guidelines outlining the diagnosis, staging, and management of HCC.
- **Screening**
    - At-risk population should be screened with liver ultrasound every 6 months.
    - Abnormal liver ultrasound should be followed by dedicated liver multiphase sectional imaging such as computed tomography scan (CT) or magnetic resonance imaging (MRI).
    - AFP use for screening is controversial but is common; AFP has ineffective sensitivity and specificity for screening.
- **Liver imaging**
    - A multiphasic CT scan or MRI is indicated when HCC is suspected (arterial, venous, delayed phases).
    - Organ Procurement and Transplantation Network (OPTN) has devised specific imaging classification system for transplant listing approval.
        - HCC-compatible lesions are referred to as OPTN-5 or LIRADS-5 lesions.
    - Characteristic HCC lesions show arterial phase enhancement and venous or delayed phase washout in at risk population in lesions larger than 2 cm.
        - Lesions less than 1 cm should be followed every 3 months.
        - Lesions between 1 and 2 cm should have a pseudocapsule in addition to meet diagnostic criteria.
    - If first imaging modality was not confirmatory (CT or MRI) and suspicion was high, a diagnosis can be made if the other imaging modality shows characteristic OPTN-5 lesions.

    - The United Network for Organ Sharing allows only biopsy-proven or OPTN-5 lesions for orthotopic liver transplantation (OLT) approval.
- **Liver biopsy**
    - Liver biopsy is indicated for suspicious lesions when diagnosis cannot be confirmed radiologically or if alternative diagnoses are suspected.
    - Percutaneous biopsies should be avoided as much as possible, especially in those who may be candidate for OLT due to risk of needle track seeding and abdominal wall recurrence.
- **AFP**
    - The presence of a liver mass with cirrhosis and an AFP >400 ng/mL is usually indicative of HCC. This is not acceptable for OLT listing. Liver disease and cholangiocarcinoma can also at times elevate AFP.
    - AFP is neither sensitive nor specific for diagnosis.
    - AFP can be normal in up to 40% of cases.

PATHOLOGY

- HCC is the most common primary liver cancer accounting for 80% to 90%, followed by intrahepatic cholangiocarcinoma (10%-20%).
- Other rare primary liver malignancies include fibrolamellar carcinoma (a subtype of HCC), hepatoblastoma, angiosarcoma, hemangiosarcoma, and epithelioid hemangioendothelioma.
- Although not as common in patients with cirrhosis, liver metastases should be suspected when liver lesions do not meet radiological characteristics of HCC.
- HCCs are vascular tumors and are frequently associated with micro- or macrovascular invasion.

STAGING

- Multiple staging systems have been developed for HCC.
- Although the American Joint Committee on Cancer (AJCC) TNM staging system is prognostic, it lacks incorporation of liver function and functional status.
- Other staging systems such as Okuda, Cancer of the Liver Italian Program, and Barcelona Clinic Liver Cancer (BCLC) have

incorporated elements pertaining to liver function.

- The BCLC staging system is the most widely used and incorporates elements of tumor size, number, Child-Pugh score, and performance status with implications in regard to treatment options (Figure 7.1).

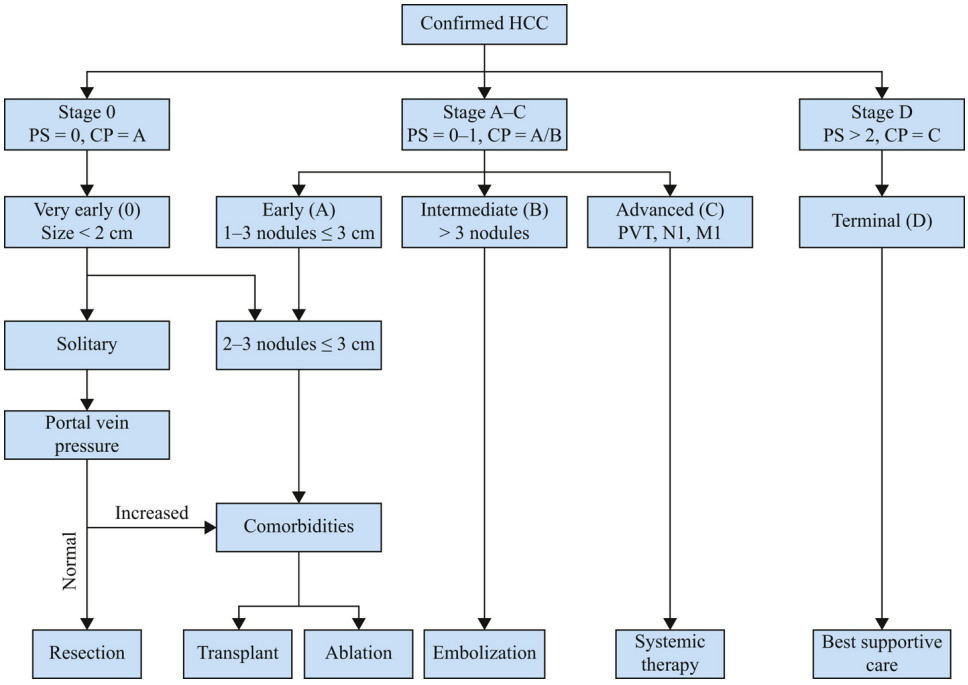

FIGURE 7.1 Barcelona Clinic Liver Cancer (BCLC) hepatocellular carcinoma staging classification.The BCLC algorithm incorporates liver function, tumor characteristics, performance status, and comorbidities in staging and treatment assignment. CP, Child-Pugh; HCC, hepatocellular carcinoma; M1, metastatic disease; N1, positive regional lymph nodes; PS, performance status; PVT, portal vein tumor thrombus.(Adapted from Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022. Copyright © 2011 American Association for the Study of Liver Diseases. Reprinted by permission of John Wiley & Sons, Inc.)

- Child-Pugh scoring system is key in assessment of liver health and determining management options (Table 7.1).
  - One-year survival with Child-Pugh class A, B, and C without HCC is 100%, 80%, and 45%, respectively.

TABLE 7.1
Child-Pugh Classification

Score Attribution	1	2	3
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR (or PT)	<1.7 (<4)	1.7-2.3 (4-6)	>2.3 (>6)
Ascites	None	Mild (or medically suppressed)	Moderate to severe (or refractory)
Encephalopathy grade	None	1-2	3-4

INR, international normalization ratio; PT, prothrombin time.

Class A: score 5-6, class B: score 7-9, class C: score 10-15.

One-and two-year survival rates are 100% and 85% for class A, 81% and 57% for class B, and 45% and 35% for class C, respectively.

TREATMENT

- HCC treatment is best done in a multidisciplinary fashion. Often different interventions are needed, simultaneously or sequentially to achieve best outcome.
- Discussion at a dedicated tumor board allows for better care planning.

Surgery

- Surgery is the main curative option for HCC whether through resection or transplantation.
- Candidacy for surgery is determined by liver function, degree of portal hypertension, tumor burden (see Figure 7.1), and to a certain extent anatomical location of lesions.
- Those who undergo surgery should have liver-confined disease, no macrovascular invasion, and no regional lymph node involvement. Except in highly select situations, metastatic disease is a contraindication to surgery.
- **Hepatic resection**
  - Resection can be curative for those with liver-confined disease without underlying cirrhosis or fibrosis.
  - Cirrhotic patients without portal hypertension may be eligible for resection, but are still at risk of de novo HCC.
  - Five-year survival is 50% to 70%. Factors affecting survival include size and number of lesions.

- Risk of recurrence at 5 years can be as high as 70% (60% intrahepatic metastases, 40% de novo HCC).
- There is no benefit from adjuvant sorafenib after resection (STORM trial). Studies assessing adjuvant immunotherapy are ongoing.

- **Liver transplantation**
  - Liver transplantation is the mainstay of curative management for patients with both HCC and cirrhosis.
  - Candidates for transplantation should meet Milan selection criteria:
    - One lesion ≤5 cm, or up to three lesions each ≤3 cm
    - No macrovascular invasion or portal vein thrombosis
    - No regional lymph node involvement or metastatic disease
  - Liver transplantation is dependent on available cadaveric livers. Living donor transplantation is another viable option.
  - For HCC within Milan criteria, transplantation is associated with 4-year overall survival of 70% and recurrence-free survival of 80%.
  - In the United States, eligible patients should have OPTN-5 lesions, and can only be given exception points for enlisting after a period of 6 months of controlled or stable disease.
  - Locoregional control with hepatic artery embolization techniques is frequently used as "bridging" therapy awaiting transplantation.
  - Listing for OLT is sometime possible if tumor characteristics are within the San Francisco criteria and "down-staged" to Milan criteria with locoregional therapy.
  - Patients with chronic viral hepatitis infections should be treated with goal of sustained viral response prior to transplantation. HCV infections sometimes are treated after transplantation in order to increase donor pool.
  - Living donor transplantation may be possible when a donor is available, and may offer a more timely access to transplantation.
- **Postsurgical surveillance**
  - Imaging of chest, liver, and pelvis every 3 to 6 months for 2 years, then annually.
  - AFP every 3 to 6 months for 2 years, then every 6 months.

Locoregional Treatment

- Locoregional therapies for HCC can be employed with curative (ablation) or palliative intent for local control (embolization). They can also be used to maintain local control awaiting OLT.
- **Ablative therapy**
  - These include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MWA).
  - RFA and MWA can be done percutaneously or laparoscopically.
  - PEI is less commonly used in recent years.
  - RFA or MWA are very effective for local control in lesions < 2 cm.
  - Local recurrence can be as high as 50% to 70%.

- Factors influencing recurrence include larger size, proximity to major vessels, subcapsular lesions, percutaneous approach, and ablation margin < 1 cm.
- Best candidates are those with very early or early BCLC stage who are not candidate for resection.
- Needle tract seeding recurrence can occur in up to 3% after RFA, especially with repeat intervention and treatment of subcapsular lesions.

Hepatic artery embolization

- Transarterial chemoembolization (TACE) and bland embolization are effective means of locoregional control of liver-confined HCC, but are not considered curative interventions.
- At least 80% of HCC vascular supply is derived from hepatic artery branches; in contrast, normal liver parenchyma receives its main vascular supply from the portal vein.
- TACE has been shown to improve survival compared to best supportive care with 2-year survival rate of 63% versus 27%, respectively.
- TACE is commonly done using drug-eluting beads (DEBs) laden with doxorubicin.
    - A randomized trial of conventional TACE compared to DEBs in unresectable HCC showed better local control (44% vs 52% at 6 months, respectively) and lower rate of toxicity in favor of DEB/TACE.
- There is continued controversy in regard to the added benefit of chemotherapy to bead therapy.
- Suitable patients are those with relatively preserved liver function (Child-Pugh class A-B), unresectable disease, portal hypertension, and "bridging" therapy prior to transplantation. Chemoembolization often requires more than one treatment for optimal local control.
- TACE may be used with the intent of "down-staging" to meet Milan criteria.
- There is no role for sorafenib in conjunction with TACE per the SPACE phase II trial. Studies assessing adjuvant immunotherapy are ongoing.

Radioembolization

- HCC is radiosensitive but is also located in a radiosensitive organ. Normal liver can tolerate radiation up to about 20 Gy.
- Radioembolization utilizes yttrium-90 microspheres. Resin and glass microspheres are commercially available.
- A mapping hepatic artery angiogram is an important first step to rule out vascular shunting prior to therapy. Radiation pneumonitis is a major complication in the event of large hepatopulmonary radiation shunting.
- It is generally contraindicated in decompensated hepatic function and if bilirubin is >2 mg/dL.
- Radiation segmentectomy is a method whereby the radiation dose is selectively delivered to one or two segments instead of the whole lobe. This allows higher radiation dose exposure leading to better tumor necrosis and local control.
- There is indication overlap with chemoembolization. Larger lesions, significant lobar involvement, or diffuse disease are more suitable for radioembolization. Deciding the best locoregional therapeutic intervention should be done in a multidisciplinary tumor board setting.

Radiation

- Stereotactic body radiation therapy (SBRT) is a precise and conformal way of delivering external radiation in high dosage to a specific area. In radiosensitive tumors SBRT has a high success rate of achieving local control.
- SBRT for HCC is a plausible option in small (preferably less than 5 cm) lesions not amenable to locoregional therapy or ablation. Anatomically challenging location for ablation such as liver dome can be treated with SBRT.
- Tumor thrombus (especially symptomatic) can also be treated with SBRT in combination with other locoregional treatment.
- In one series, local control rate with or without TACE was 96% with an overall survival rate of 67% at 3 years.

Systemic Therapy

- Systemic therapy for HCC is indicated in advanced disease not amenable to locoregional treatment or metastatic disease. The goal of therapy is palliation with the main benefit being increase in life expectancy.
- Patients with advanced HCC should be considered for clinical trials when possible.
- Conventional chemotherapy has been associated with low rates of partial response in certain series and has not been shown to improve survival.
- **First-line therapy**
  - *Sorafenib*
  - Sorafenib is a multikinase inhibitor with antiangiogenic properties. It targets RAF-1, BRAF, VEGFR 1-3, and PDGFR-β. It was approved by FDA in 2007.
  - In the SHARP trial, patients with advanced HCC and Child-Pugh class A cirrhosis were randomized to placebo or sorafenib at 400 mg twice daily. Survival was significantly improved with placebo (10.7 vs 7.9 months). The Asia-Pacific trial used a similar design in Asian population and a statistically significant improvement in survival was also noted in favor of sorafenib (6.5 vs 4.2 months).
  - Response rates are 2% to 3%; about 70% will have stable disease at follow-up.
  - Side effects of sorafenib include fatigue, diarrhea, hypertension, mouth sores, bone marrow, and hepatic toxicity. Palmar plantar erythrodysesthesia (PPE)

can occur in up to 45% of patients. At least 30% will require dose reduction due to side effects.

- Sorafenib should be used with caution in patients with Child-Pugh class B cirrhosis.
- There is no benefit with adjuvant sorafenib after curative intent resection or ablation. The STORM trial showed no difference in recurrence-free survival between adjuvant sorafenib and placebo given up to 4 years.
- Sorafenib was studied in conjunction with TACE in locally advanced HCC in the phase II SPACE trial. There was no difference in time to progression between sorafenib and placebo.
- *Lenvatinib*
- Lenvatinib is an inhibitor of VEGFR 1-3, FGFR 1-4, PDGFR-α, RET, and KIT.
- It was approved as a first-line treatment in 2018 based on results from the REFLECT study, which showed it was noninferior to sorafenib in overall survival (13.6 vs 12.3 months).
- Response rate to lenvatinib was 24% versus 9%. Median time to progression was 8.9 months and was associated with disease control rate of 73%.
- Lenvatinib is associated with less PPE and alopecia than sorafenib, but more hypertension, proteinuria, dysphonia, and hypothyroidism.
- *Atezolizumab and bevacizumab*
- Atezolizumab is a PD-L1 monoclonal antibody (checkpoint inhibitor) and bevacizumab is a VEGF monoclonal antibody.
- The combination was approved by the FDA in 2020 and was the first therapy to show superiority over sorafenib in the treatment of Child-Pugh class A patients with HCC per the phase III IMBRAVE 150 study.
- Median overall survival for the combination was not reached versus 13.2 months with sorafenib. Disease control rate was 73% with 27.3% response rate.
- Eligible patients should have an upper endoscopy to assess and treat esophageal varices prior to treatment.

Second-line therapy

- *Regorafenib*
- In the RESORCE randomized study of regorafenib versus placebo in patients with Child-Pugh class A patients with progressive HCC on sorafenib, regorafenib was associated with statistically significant improvement in survival (10.6 vs 7.8 months). Response rate was 11% with 65% disease control rate. It was approved by FDA in 2017.
- Common side effects included PPE, diarrhea, fatigue, and hypertension.
- *Cabozantinib*
- Cabozantinib is an inhibitor of VEGF 1-3, MET, and AXL. It was compared to placebo in patients with Child-Pugh class A patients with progressive HCC on sorafenib in the CELESTIAL study. Median overall survival was 11.3 versus 7.2 months. It was FDA-approved in 2019.
- Objective responses were 4% with a 63% disease control rate.
- Dose reduction was needed in 62% and most common side effects included PPE, hypertension, fatigue, and diarrhea.
- *Nivolumab/ipilimumab*

- The addition of ipilimumab to nivolumab was gained FDA approval in 2020 after data from the phase I/II CheckMate 040 study showed 32% response rate and a median overall survival of 22.2 months.
- *Pembrolizumab*
- Pembrolizumab is another PD-1 monoclonal antibody and was studied in the randomized phase III KEYNOTE-240 study. Median overall survival was 13.9 versus 10.6 months but did not reach statistical significance. Response rate was 19.3%. It was approved by FDA in 2018.
- *Ramucirumab*
- Ramucirumab is a monoclonal antibody against VEGFR-2. In the REACH-2 trial patients with class A Child-Pugh cirrhosis and AFP >400 ng/mL, ramucirumab was compared to placebo and was approved by FDA in 2019 based on an improvement in median overall survival of 8.5 versus 7.3 months. Response rate was 5%.

- **Sequencing of systemic therapy**
  - There are no data on the proper sequencing of systemic therapy in advanced HCC.
  - Given survival data, atezolizumab and bevacizumab combination is a preferred first-line option, except when contraindicated and transplant patients.
  - There are no comparative studies to establish choice of agent in the second line and beyond.

Suggested Readings

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8

Gastrointestinal Stromal Tumors

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal (GI) tract. Most GISTs have a mutation in the proto-oncogene *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes. Ideally, these tumors are resected, which is curative for many patients. The development of targeted therapies that inhibit *KIT* and *PDGFRA* has improved cure rates after surgery and outcomes in metastatic disease.

EPIDEMIOLOGY

The age-adjusted annual incidence of GIST in the United States is approximately 7 per 1,000,000 people, leading to 4000 to 6000 new cases. The majority of cases are sporadic with patients having no family history of GIST. The median age at diagnosis is around 63 years. There are no established risk factors for the development of most GIST, although some conditions, including neurofibromatosis type 1, are associated with the development of GIST.

PATHOLOGY

GISTs originate from interstitial cells of Cajal. It is important to differentiate GIST from other subepithelial tumors of the GI tract, including leiomyosarcoma, leiomyoma, and desmoid tumors. GIST

can be identified by the presence of *KIT* overexpression, present in 95% of GIST, or *KIT* mutations that are present in 80% of GISTs. *KIT* overexpression can be detected by immunohistochemistry (IHC) with anti-CD117 antibodies. About 70% of *KIT* mutations are found on exon 11 and 10% on exon 9; mutations in exons 13 and 17 may be identified, but are rare. DOG1 detection by IHC is another sensitive and specific marker for the diagnosis of GIST. GISTs may also have mutations in *PDGFR*A, most of which affect exon 18. *PDGFR*A mutations are homologous to those responsible for *KIT*- and FLT3L-independent kinase activation in other malignancies, including acute myeloid leukemia, mast cell disorders, and seminomas. *KIT* and *PDGFR*A mutations and overexpression are usually mutually exclusive in GIST. Thirty-five percent of *KIT* wild-type GISTs have *PDGFR*A mutations. Mutations in both *KIT* and *PDGFR*A lead to dysregulation of downstream intracellular signaling processes involving protein kinases and transcription factors such as Akt, mitogen-activated protein kinase, and signal transducer and activator of transcription (STAT1 and STAT3), which play a critical role in the development and progression of cancer. GISTs lacking *KIT* and *PDGFR*A mutations usually demonstrate loss of function mutations in *SDH* gene subunits or loss of SDHB protein expression.

Morphologically, GIST are characterized as spindle cell type (70%), epithelioid (20%), or mixed (10%). About 90% of GISTs are seen in the stomach and small intestine, followed by the duodenum, rectum, esophagus, and appendix. About 10% to 20% of patients present with metastatic disease at the time of diagnosis, predominantly with involvement of the liver, omentum, or peritoneum. Lymph node involvement at presentation is rare.

CLINICAL PRESENTATION

Small GISTs may be asymptomatic and are usually found incidentally during imaging or endoscopic studies. Larger tumors may cause symptoms related to their location. These include early satiety, pain, bloating, bleeding, or fatigue related to anemia. Rarely,

patients may present with an acute abdomen secondary to tumor rupture or obstruction.

PROGNOSTIC FACTORS

Factors associated with an increased risk for recurrence of GIST include tumor size, mitotic index, tumor location, and presence of rupture of the tumor (Table 8.1). Based on these tumor characteristics, patients can be stratified into very low, low, intermediate, or high risk of recurrence. Tumors less than 2 cm have very low risk, while tumors greater than 10 cm are associated with high risk. A mitotic index of ≤5 per 50 high-power fields is associated with a very low or low risk for recurrence. A mitotic index of greater than 10 leads to a high risk. Tumor rupture is prognostic for a high risk of recurrence regardless of tumor size or mitotic index. Gastric GISTs are associated with a better outcome than GISTs in other locations.

TABLE 8.1

Modified National Institutes of Health Risk Stratification for Recurrence of Gastrointestinal Stromal Tumor

Risk	Size (cm)	Mitotic Index (per 50 HPFs)	Primary Tumor Site
Very low	<2	≤5	Any
Low	2.1-5	≤5	Any
Intermediate	2.1-5	>5	Gastric
	<5	6-10	Any
	5.1-10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	2.1-5	>5	Any
	2.1-5	>5	Nongastric
	5.1-10	≤5	Nongastric

HPFs, high-power fields.

Adapted from Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol*. 2008;39(10):1411-1419. Copyright © 2008 Elsevier. With permission.

DIAGNOSIS

Computed tomography (CT) scans of the abdomen and pelvis with contrast or MRI are recommended for initial staging to determine the resectability of the tumor and to evaluate for metastatic disease. Endoscopic ultrasound (EUS) may be used to further characterize submucosal GI lesions, and a fine-needle aspiration (FNA) during this procedure may be used to collect tissue for cytology and IHC to establish a diagnosis. An EUS-guided FNA is preferred over a percutaneous biopsy given the risk of tumor hemorrhage and dissemination. These biopsies are not required for patients who have a resectable tumor with a high degree of suspicion for GIST. A biopsy should be obtained in patients with clearly unresectable tumors or with tumors that may become resectable if treated with preoperative tyrosine kinase inhibitors (TKIs). Positron emission tomography scans are not routinely used for the diagnosis or monitoring of patients with GIST.

TREATMENT

Upfront resection is generally the standard for resectable disease in patients with no contraindications to surgery. Preoperative imatinib may impact the assessment of the risk of recurrence and should be reserved for patients in whom a decrease in the size of the tumor will minimize the morbidity of the surgery. Following resection of the tumor, patients with an intermediate or high risk of recurrence (Table 8.1) should start adjuvant therapy with imatinib TKIs for at least 3 years. Patients who received neoadjuvant imatinib followed by a complete resection and patients who have residual disease after surgery should receive postoperative imatinib. Re-resection for microscopically positive margins is generally not indicated. During

treatment, patients should be seen in the clinic with a CT of the abdomen and pelvis with contrast every 3 to 6 months for 3 to 5 years, with surveillance annually afterward. Approximately 50% of patients with resected GIST will be cured with surgery alone. The median time to recurrence after resection of a primary high-risk GIST is about 2 years; however, metastatic disease can develop several years after initial resection of the primary tumor, necessitating long-term clinical follow-up.

Patients with unresectable or metastatic disease at the time of their diagnosis should start treatment with a TKI and have repeat imaging with CT scans after 3 months to assess the treatment response. Mutational testing of the tumor helps with the selection of TKI. Tumors with a *KIT* exon 9 mutation may be more likely to benefit from an increase in the dose of imatinib from 400 mg daily to 800 mg daily. GISTs with a *PDGFRA* D842V mutation or without a mutation in *KIT* have a decreased likelihood of response to imatinib. Patients with the *PDGFRA* D842V mutation should receive avapritinib. Patients with initially unresectable disease who have a response to TKIs should be assessed again for possible resection, although downstaging with neoadjuvant therapy generally requires several months of treatment. Patients who continue to have unresectable tumors or who have metastatic disease with stable disease or a response to therapy should remain on TKIs indefinitely.

Patients with recurrent GIST should be treated with TKIs, if not given previously. Treatment options for patients with recurrence who have received prior TKIs or progression of their GIST while receiving TKIs include resection, embolization, radiofrequency ablation, palliative radiation, escalation of the dose of imatinib, or alternative TKIs.

Patients with GIST tumors in the stomach measuring less than 2 cm without high-risk EUS features, such as irregular borders, cystic spaces, ulceration, foci of echogenicity, and heterogeneity, may be managed by surveillance with endoscopy and may not require surgery.

ADJUVANT THERAPY

Approximately 50% patients will develop recurrence following curative resection only, with a 5-year survival rate of 50%. Adjuvant therapy has shown to improve survival in patients with a high risk for recurrence.

Imatinib is approved as adjuvant therapy for patients with GIST based on the results of the American College of Surgeons Oncology Group Intergroup Adjuvant GIST Study—Z9001 study. In this phase III trial, 713 patients were randomized to 1 year of imatinib 400 mg daily or placebo following complete gross resection of a primary GIST expressing *KIT* measuring at least 3 cm. Upon recurrence, patients were allowed to crossover from placebo to imatinib or increase the dose of imatinib to 800 mg daily. Recurrence-free survival (RFS) at 1 year, the primary end point of the trial, was 98% in the imatinib arm versus 83% in the placebo arm ($P < .0001$). Overall survival (OS) was not statistically significant between the two arms, likely due to the short-term follow-up and the crossover from placebo to imatinib. A subsequent phase III study from Scandinavian Sarcoma Group, SSG XVIII/AIO, demonstrated better 5-year RFS (71.1% vs 52.3%, $P < .001$) and 5-year OS (91.9% vs 85.3%, 0.036) with 3 years of imatinib compared to 1 year in patients with a high risk for recurrence after surgery.

NEOADJUVANT THERAPY

A prospective phase II trial, RTOG 0132/ACRIN 6665, evaluated the safety and efficacy of neoadjuvant treatment with imatinib for 8 to 12 weeks before surgery with continuation of imatinib for at least 2 years after surgery or disease progression. Patients had a resectable *KIT*-positive GIST measuring at least 5 cm. In patients with a primary GIST, there was a partial response in 7% of patients and stable disease in 83%. There was 5% partial response and stable disease in 91% of patients with resectable metastatic disease. With a median follow-up of 5 years, the progression-free survival (PFS) rate

for patients with a primary tumor was 57% and OS rate was 77%. Complications of surgery and toxicity from the imatinib were minimal.

For GISTs that harbor *PDGFR*A exon 18 mutations that are insensitive to imatinib, including the D842V mutation, neoadjuvant use of avapritinib should be considered for patients with unresectable disease.

DRUGS USED FOR TREATING PATIENTS WITH GIST

Imatinib

Imatinib is a TKI of c-KIT and PDGFRA receptors. Imatinib is approved for patients with unresectable or metastatic *KIT* (CD117)–positive GIST or for adjuvant treatment after resection of *KIT*-positive GIST. Two large, randomized phase III trials confirmed the efficacy of imatinib in patients with advanced GIST. In the S0033 trial, patients were randomized to receive either 400 mg of imatinib once daily (with crossover to 800 mg/d with disease progression) or 400 mg twice daily. The median OS was 55 and 51 months for patients receiving 400 and 800 mg imatinib daily, respectively. There were no significant differences in response rates, PFS, or OS between the two groups. In a subgroup analysis of a retrospective analysis, patients with *KIT* exon 9 mutations receiving 800 mg imatinib daily had an improvement in PFS, but not in OS. Approximately 80% of patients eventually develop secondary mutations in *KIT* exons resulting in progressive disease. Patients should start therapy at 400 mg daily or 800 mg daily for patients with an exon 9 *KIT* mutation. Treatment with imatinib is generally well tolerated with nausea, diarrhea, periorbital edema, muscle cramps, fatigue, headache, and dermatitis as the most common toxicities.

Avapritinib

Avapritinib is a TKI that inhibits *PDGFR*A exon 18 mutations, including the D842V mutation that confers resistance to imatinib. Avapritinib is approved for advanced GIST harboring the above mutations in the first-line setting. The approval is based on a phase II trial where patients with *PDGFR*A exon 18 mutations (n = 43) received 300 mg or 400 mg of avapritinib daily. Overall responses were observed in 84% (7% complete responses and 77% partial responses). Toxicities include fatigue, cognitive impairment, change in hair color, diarrhea, edema, nausea, and decreased appetite.

Sunitinib

Sunitinib is an oral inhibitor of several tyrosine kinase receptors approved for the patients with GIST after disease progression on or intolerance to imatinib. In a double-blind, placebo-controlled, multicenter, randomized phase III trial, patients with GIST with disease progression on or intolerance to imatinib were randomized to receive sunitinib 50 mg daily for 4 weeks, with 2 weeks off (n = 207) or placebo (n = 105). Objective response rates in the sunitinib and placebo arms were 8% and 0%, respectively, and the median time to progression was significantly longer in the sunitinib arm (6.3 vs 1.5 months). A lower dose of sunitinib given continuously (37.5 mg daily) in a phase II trial has demonstrated a clinical benefit rate of 53% (13% partial response and 40% stable disease) and a median time to progression of 7.5 months. The most common toxicities include fatigue, diarrhea, hand-foot syndrome, hypertension, bleeding events, and nausea.

Regorafenib

Regorafenib, an inhibitor of multiple tyrosine kinases including KIT and PDGFRA, is approved for patients who have progressed after imatinib and sunitinib. In a randomized phase III trial, the median PFS was 4.8 months for patients receiving regorafenib and 0.9 months for patients receiving placebo (hazard ratio [HR] 0.27, P < .0001). Regorafenib should be preferred over sunitinib in the second line if an exon 17 mutation in *KIT* is observed after the use of

imatinib. This resistance mutation confers resistance to both imatinib and sunitinib. The most common toxicities include fatigue, diarrhea, hand-foot skin reactions, hypertension, nausea, and hyperbilirubinemia.

Ripretinib

Ripretinib is a TKI that inhibits KIT and PDGFRA including wild-type, primary, and secondary mutations. It is approved for patients with advanced GIST who have received three or more TKIs including imatinib. In a randomized phase III placebo controlled trial, ripretinib improved the PFS from 1.0 to 6.3 months (HR 0.15, $P < .001$). The most common toxicities include alopecia, fatigue, nausea, palmar-plantar erythrodysesthesia, diarrhea, abdominal pain, constipation, and vomiting.

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9

Colorectal Cancer

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EPIDEMIOLOGY

- Colorectal cancer (CRC) is the second leading cause of cancer deaths among men and women combined in the United States and is the third most common cause of cancer, separately, in men and in women.
- An estimated 104,270 new cases of colon cancer and 45,230 new cases of rectal cancer will be diagnosed in 2021 and over one-third will die as a result of the disease.
- The lifetime risk of developing CRC for both men is 4.3% and women is 4.0%.
- Surgery will cure almost 50% of all diagnosed patients; however, 40% to 50% of newly diagnosed CRC cases will eventually develop metastatic colorectal cancer (mCRC) disease.
- The incidence of colon cancer is higher in the more economically developed regions, such as the United States or Western Europe, than in Asia, Africa, or South America.
- US incidence and mortality rates from CRC continue to decline among patients 55 years of age or older (3.6% decrease per year).
- Incidence rates have increased among patients younger than the age of 50 years (2% increase per year from 2012 to 2016). This increase is mostly for rectal cancer diagnoses. The reason for this increase in younger adults is unclear.

RISK FACTORS

Although certain conditions predispose patients to develop colon cancer, up to 70% of patients have no identifiable risk factors:

- Age: Approximately 90% of colon cancers occur in patients older than 50 years.
- Gender: The incidence of colon cancer is similar in men and women, but rectal cancer is more prominent in men.
- Ethnicity: The occurrence of CRC is 20% more common in African Americans than in whites, and mortality is nearly 40% higher in African Americans compared to whites.
- Personal history of CRC or adenomatous polyps:
  - Tubular adenomas (lowest risk)
  - Tubulovillous adenomas (intermediate risk)
  - Villous adenomas (highest risk)
- Tobacco use is associated with increased incidence and mortality from CRC compared to never smokers. The association is stronger for rectal cancers.
- Obesity: People who are obese have a 30% increase in rates of CRC
- Dietary factors: High-fiber, low caloric intake, and low animal fat diets may reduce the risk of cancer.
- Calcium deficiency: Daily intake of 1.25 to 2.0 g of calcium was associated with a reduced risk of recurrent adenomas in a randomized placebo-controlled trial. Oral bisphosphonate therapy for at least 1 year's duration may also reduce CRC risk.
- Vitamin D: There is no prospective evidence that vitamin D supplementation reduces risk of colorectal adenomas or cancer although a meta-analysis of five studies showed that patients with CRC and higher levels of vitamin D had improved overall survival and disease-specific mortality.
- Micronutrient deficiency: Selenium and vitamins E and D deficiency may increase the risk of cancer. The role of folate remains unclear.
- Inflammatory bowel disease (IBD): IBD is associated with a 2.9-fold increase risk of CRC. The risk of CRC is associated with

duration of IBD.

- Nonsteroidal anti-inflammatory drugs: An American Cancer Society study reported 40% lower mortality in regular aspirin users, and similar reductions in mortality were seen in prolonged nonsteroidal anti-inflammatory drug use in patients with rheumatologic disorders. The cyclooxygenase-2 (COX-2) inhibitor celecoxib is approved by the US Food and Drug Administration (FDA) for adjunctive treatment of patients with familial adenomatous polyposis (FAP). Chemoprevention with selective COX-2 inhibitors must be balanced against increased cardiovascular risks.
- Family history: 80% of colon cancer cases are diagnosed in the absence of a positive family history. In the general population, if one first-degree relative develops CRC, it increases the relative risk for other family members to 1.72, and if two relatives are affected, the relative risk increases to 2.75. Increased risk is also observed when a first-degree relative develops an adenomatous polyp before the age of 60 years. True hereditary forms of cancer account for only 6% of CRCs.

FAMILIAL CANCER SYNDROMES

Familial Adenomatous Polyposis

FAP is an autosomal-dominant inherited syndrome with more than 90% penetrance, manifested by hundreds of polyps developing by late adolescence. The risk of developing invasive cancer over time is virtually 100%. Germline mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21 have been identified. The loss of the APC gene results in altered signal transduction with increased transcriptional activity of β-catenin. Several FAP variants with extraintestinal manifestations also exist:

- Attenuated FAP: This variant generates flat adenomas that arise at an older age. Mutations tend to occur in the proximal and

distal portions of the APC gene.

- Gardner syndrome: Associated with desmoid tumors, osteomas, lipomas, and fibromas of the mesentery or abdominal wall.
- Turcot syndrome: Involves tumors (esp. medulloblastoma) of the central nervous system.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder in which there is a propensity to develop non-neoplastic hamartomatous polyps at young ages throughout the gastrointestinal tract and perioral melanin pigmentation. This is characterized by a mutation in the STK11/LKB1 gene.

Juvenile Polyposis

Juvenile polyposis is an autosomal dominant disorder characterized by benign polyps in the colon, small bowel, and stomach which start at the age of 20 years. Mutations in the *BMPR1A* and *SMAD4* genes are responsible for this disease.

Hereditary Nonpolyposis CRC (Lynch Syndrome)

The Lynch syndromes, named after Henry T. Lynch, include Lynch I or the colonic syndrome, which is an autosomal-dominant trait characterized by distinct clinical features, including proximal colon involvement, mucinous or poorly differentiated histology, pseudodiploidy, and the presence of synchronous or metachronous tumors. Patients develop colon cancer before 50 years, with a lifetime risk of cancer approximating 75%. In Lynch II or the extracolonic syndrome, individuals are susceptible to malignancies in the endometrium, ovary, stomach, hepatobiliary tract, small intestine, and genitourinary tract.

The Amsterdam criteria (3-2-1 rule) were established to identify potential kindreds and include the following:

- Histologically verified CRC in at least three family members, one being a first-degree relative of the other two members
- CRC involving at least two successive generations
- At least one family member being diagnosed by 50 years

Inclusion of extracolonic tumors and clinicopathologic and age modifications was introduced by the Bethesda criteria in 1997 and subsequently revised to account for microsatellite instability (MSI). Lynch syndrome is characterized by germline defects in DNA mismatch–repair genes (eg, *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*). These defects result in alterations to the length of microsatellites, segments of DNA with repeating nucleotide sequences, thus making them unstable and detectable in diagnostic assays. This MSI can be identified in virtually all Lynch syndrome kindred and in approximately 15% of sporadic CRCs the latter almost always due to hypermethylation of the *MLH1* promoter.

SCREENING

Several professional societies have developed screening guidelines for the early detection of colon cancer. There are a number of early detection tests for colon cancer in average-risk asymptomatic patients. The US Preventative Service Task Force (USPSTF) has recently lowered the colorectal screening age to begin at 45 years. This is a B recommendation. Screening initiation at age 50 to 75 years remains an A recommendation. USPSTF screening guidelines (Table 9.1) are the most widely cited at this time. The USPSTF does not endorse one test over the other, only that some form of recommended screening be done. Any positive or abnormal screening test should be followed up with colonoscopy. Individuals with a family or personal history of colon cancer or polyps, or a history of chronic IBD, should be tested earlier and possibly more frequently.

TABLE 9.1

Recommended Colorectal Cancer Screening Guidelines for Asymptomatic Average-Risk Individuals Beginning at the Age of 45 years, All Patients at Average Risk of Colorectal Cancer Should Have *One* of the Screening Options Listed Below [a]

Test	Frequency
Guaiac-based fecal occult blood test (gFOBT) or fecal immunochemical test (FIT)	Every year
Multitarget stool DNA	Every 1-3 y
Colonoscopy [b]	Every 10 y
Flexible sigmoidoscopy	Every 5 y
Flexible sigmoidoscopy with FIT	Flex sigmoidoscopy every 10 y, FIT every year
Computed tomography (CT) colonography (virtual colonoscopy)	Every 5 y

[a]2021 USPSTF Recommendations did not specify which screening approach is preferred.

[b]Colonoscopy should be done if the fecal blood test shows blood in the stool or if sigmoidoscopy shows a polyp. This colonoscopy is considered a screening completion colonoscopy.

PATHOPHYSIOLOGY

More than 90% of CRCs are adenocarcinomas, the focus of this chapter. Other primary cancers of the colon and rectum include Kaposi sarcoma, non-Hodgkin lymphomas, small cell carcinoma, and carcinoid tumors. Metastases to the large bowel can rarely occur with melanoma, ovarian, and gastric cancer.

Colon carcinogenesis involves progression from hyperproliferative mucosa to polyp formation, with dysplasia, and transformation to noninvasive lesions and subsequent tumor cells, with invasive and metastatic capabilities. CRC is a unique model of multistep carcinogenesis resulting from the accumulation of multiple genetic alterations. Stage-by-stage molecular analysis has revealed that this progression involves several types of genetic instability, including loss of heterozygosity, with chromosomes 8p, 17p, and 18q representing the most common chromosomal losses.

The 17p deletion accounts for loss of p53 function, and 18q contains the tumor-suppressor genes deleted in colon cancer (ie, DCC) and the gene deleted in pancreatic 4 (ie, DPC4).

Colon carcinogenesis also occurs as a consequence of defects in the DNA mismatch–repair (dMMR) system. The loss of *hMLH1* and *hMSH2*, predominantly, in sporadic cancers leads to accelerated accumulation of additions or deletions in DNA. This contributes to the loss of growth inhibition mediated by transforming growth factor-β due to a mutation in the type II receptor. Mutations in the APC gene on chromosome 5q21 are responsible for FAP and are involved in cell signaling and in cellular adhesion, with binding of β-catenin. Alterations in the APC gene occur early in tumor progression. Mutations in the proto-oncogene *ras* family, including K-*ras* and N-*ras*, are important for transformation and also are common in early tumor development.

DIAGNOSIS

Signs and Symptoms

The presentation of CRC can include abdominal pain, which is typically intermittent and vague, weight loss, early satiety, and/or fatigue. Bowel changes may be noted for left-sided colon and rectal cancers, including constipation, decreased stool caliber (pencil stools), and tenesmus. Bowel obstruction or perforation is less common. Unusual presentations include deep venous thrombosis, nephrotic-range proteinuria, and *Streptococcus bovis* bacteremia with or without endocarditis. The clinical finding of iron deficiency in the absence of an overt source of anemia should prompt a diagnostic endoscopic workup.

Diagnostic Evaluation

- Endoscopic studies provide histologic information, potential therapeutic intervention, and overall greater sensitivity and

specificity.

- Carcinoembryonic antigen (CEA) elevations occur in non–cancer-related conditions, reducing the specificity of CEA measurements alone in the initial detection of colon cancer.
- Basic laboratory studies including complete blood count, electrolytes, liver and renal function tests, and computed tomography (CT) scan of the chest, abdomen, and pelvis with IV contrast are useful in initial cancer diagnosis and staging.
- In colon cancers, CT scan sensitivity for detecting distant metastasis is higher (75%-87%) than for detecting nodal involvement (45%-73%) or the extent of local invasion (~50%).
- *Fluorodeoxyglucose* (FDG)-positron emission tomography (PET) scanning adds little over conventional imaging in the initial staging and diagnosis of CRC in the absence of abnormalities seen on CT scan.
- Contrast-enhanced magnetic resonance imaging (MRI) can help determine the status of suspicious lesions in the liver as well as the characteristics (not just size) of rectal cancers.
- For rectal cancers, endoscopic rectal ultrasound (ERUS) is a valuable tool in the preoperative evaluation, with high accuracy of determining the extent of the primary tumor (sensitivity 63%-95%) and perirectal nodal status (sensitivity 63%-82%). However, as compared to ERUS, MRI can better visualize proximal tumors and allow for noninvasive evaluation of circumferential (ie, obstructing) tumors. Additionally, MRI can better characterize the perirectal lymph nodes and approximate the tumor to the pelvic side wall.

STAGING

The eighth edition of the American Joint Committee on Cancer Staging for CRC uses the tumor, nodes, and metastases (TNM) classification system. The Dukes or MAC staging systems are only of historic interest. The tumor designation, or T stage, defines the extent of bowel wall penetration including invasion into the

submucosa (T1), muscularis propria (T2), pericolic tissue (T3), visceral peritoneal surface (T4a), or an adjacent organ or other structure (T4b). At least 12 lymph nodes must be sampled for accurate staging and represents an important quality control metric. The number of regional nodes involved varies from 1 to 3 (N1a/b) to 4 or more (N2a/b). N1c includes direct tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis. Metastases confined to one organ or site (M1a) have a better prognosis than metastases confined to the peritoneum or multiple sites (M1b).

PROGNOSIS

Pathologic stage remains the most important determinant of prognosis (Table 9.2) with similar outcomes for both colon and rectal cancers in the modern era. Other prognostic variables proposed to be associated with an unfavorable outcome include advanced age of the patient, high tumor grade, perineural or lymphovascular invasion, high serum CEA level, bowel obstruction or perforation at the time of presentation, and persistence of circulating tumor DNA following complete surgical resection.

TABLE 9.2

Prognosis by Stage for Colorectal Cancers

Stage	5-Y Observed Survival Rate (%)
I	74
IIA	65
IIB	58
IIC	37
IIIA	73
IIIB	45
IIIC	28
IV	6

Adapted from Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol*. 2010;28(2):264-271.

- Biochemical and molecular markers such as elevated thymidylate synthase, p53 mutations, loss of heterozygosity of chromosome 18q (DCC gene), and lack of CDX2 expression are also proposed as prognostic. The latter appears to portend for a worse 5-year disease-free survival (DFS) in patients with stage II and III colon cancers, yet adjuvant chemotherapy was associated with a significant DFS improvement upon retrospective analysis. However, a defective dMMR system (eg, altered *MLH1*, *MSH2*; associated with Lynch syndrome) is associated with an improved outcome for patients with early stage, node-negative disease. Regardless of stage, the presence of a B-*raf* (V600E) mutation has been associated with a worse prognosis. The presence of a somatic B-*raf* mutation in the setting of *MLH1* absence precludes the germline diagnosis of Lynch syndrome. There are multiple commercially available multigene assays that have been developed to help define the risk of recurrence and prognosis for stage II CRC (see "Adjuvant Chemotherapy Regimens for Colon Cancer").

MANAGEMENT ALGORITHM

Surgery

- For colon cancers, the primary curative intervention requires en bloc resection of the involved bowel segment and mesentery, with pericolic and intermediate lymphadenectomy for both staging and therapeutic intent. Negative proximal, distal, and lateral surgical margins are of paramount importance. Laparoscopic techniques adhering to these surgical principles are an acceptable option.
- For rectal cancers, en bloc resection of the primary tumor with negative proximal, distal, and radial margins is critical as well as a sharp dissection of the mesorectum (total mesorectal excision [TME]) to optimally reduce local recurrence. The

location of the tumor in relation to the anal sphincter is the primary determinant in a low anterior resection versus an abdominoperineal resection. The latter generates a permanent colostomy. For highly selected early-stage rectal cancer cases, transanal endoscopic microsurgery may be considered.
- Surgical intervention is indicated if polypectomy pathology reveals muscularis mucosa involvement or penetration.
- Surgical palliation may include colostomy or even resection of metastatic disease for symptoms of acute obstruction or persistent bleeding.

Radiation Therapy

- Routine administration of abdominal radiotherapy (RT) is limited by bowel-segment mobility, adjacent small bowel toxicity, previous surgery with adhesion formation, and other medical comorbidities.
- Local control and improved DFS have been reported in retrospective series of patients with T4 lesions or perforations, nodal disease, and subtotal resections, who have been treated with 5000 to 5400 cGy directed at the primary tumor bed and draining lymph nodes. However, there are no randomized data to support the routine use of RT in the management of colon cancer.
- RT can be valuable in select palliative settings for pain relieve from hepatic capsule stretch associated with mCRC.
- In contrast, RT is routinely utilized in rectal cancers to reduce local recurrence and improve resectability. RT can also be useful for palliation of pain and bleeding in rectal cancer.

Pivotal Adjuvant Chemotherapy Studies for Colon Cancer

Establishing Benefit and Duration of Adjuvant Fluoropyrimidine Therapy

The Intergroup 0035 trial is of historic importance because it demonstrated that the use of 5-fluorouracil (5-FU) and levamisole (Lev) reduced the relapse rate by 41% and overall cancer mortality by 33%. This study resulted in the National Institutes of Health consensus panel recommending that 5-FU–based adjuvant therapy be administered to all patients with resected stage III colon cancer.

The subsequent Intergroup 0089 trial randomized 3759 patients with stage II or III disease to one of four therapeutic arms. The results demonstrated that the 5-FU- and leucovorin (LV)-containing schedules (Mayo Clinic and Roswell Park regimens) were equivalent without the need for Lev. A 6-month schedule of the 5-FU and LV was similar to a protracted 12 months of therapy.

Utilization of an oral fluoropyrimidine (capecitabine) was evaluated in patients with stage III disease. Capecitabine (1250 mg/m^2 b.i.d. for 14 days, every 3 weeks) was compared with the Mayo Clinic bolus of 5-FU and LV. The study was designed to demonstrate equivalency, with a primary endpoint of 3-year DFS. The capecitabine (cape) arm was noninferior and demonstrated a trend toward DFS superiority (64% vs 60%; HR 0.87; 95% CI, 0.75-1.00; P = .0526). Toxicity was improved in cape arm in all categories except hand-foot syndrome (HFS). A 3-year DFS endpoint was chosen because a retrospective analysis of more than 20,000 patients treated with 5-FU demonstrated equivalency to the conventional 5-year OS benchmark, thus allowing DFS to serve as a valid short-term surrogate for long-term survival.

Intensifying Adjuvant Chemotherapy with Oxaliplatin

With adjuvant fluoropyrimidine monotherapy well-established, studies began testing the potential benefit of polyagent chemotherapy. In Europe, 2246 patients with stage II (40%) and III disease were treated with infusional 5-FU with LV modulation versus the same combination with oxaliplatin (FOLFOX4) every 2 weeks for 6 months, demonstrated a 3-year DFS benefit favoring the FOLFOX4 combination over standard 5-FU with LV (78.2% vs 72.9%; HR 0.77; 95% CI, 0.65-0.92; P = .002). With a median 6-year

follow-up, the OS advantage was confirmed in the patients with stage III disease (72.9% vs 68.7%; HR 0.80; 95% CI, 0.65-0.97; *P* = .023). No difference in OS was seen in the stage II population. Treatment with FOLFOX4 was well tolerated, with 41% patients having grade 3 and 4 neutropenia, only 0.7% being associated with fever. Anticipated grade 3 peripheral neuropathy or paresthesias were observed (12%), which almost entirely resolved 2 years later (persisted in only 0.7% of patients).

The addition of oxaliplatin to three cycles of adjuvant Roswell Park 5-FU with LV (FLOX) was evaluated in 2407 stage II (30%) and III patients. The combination improved 3-year DFS (76.1% vs 71.8%; HR 0.80; 95% CI, 0.69-0.93; *P* = .003). Grade 3 diarrhea (38%) and peripheral neuropathy (8%) were significantly worse with FLOX without any difference in treatment-related mortality. MOSAIC and the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 established doublet adjuvant chemotherapy with fluoropyrimidine and oxaliplatin for 6 months as a standard of care.

Adjuvant Irinotecan

Unlike oxaliplatin, at least three studies failed to confirm a benefit for the use of adjuvant irinotecan. CALGB 89,803 was a study of irinotecan with bolus 5-FU and LV (IFL) versus weekly 5-FU in patients with stage III disease. Increased grade 3 and 4 neutropenia and early deaths were observed in the experimental arm, and a higher number of patients withdrew from the study. Overall, IFL was not better than the 5-FU and LV arm. The two European studies (PETACC-3 and ACCORD) together randomized over 3500 patients to infusional 5-FU with or without irinotecan. Both studies failed to reach their primary endpoint of 3-year DFS although toxicities were less than in the IFL study. The use of irinotecan is thus not recommended in the adjuvant setting outside of a clinical trial.

Adjuvant Biologics

Both cetuximab (cmab) and bevacizumab (bev) are biologic-targeted agents (see the mCRC section) that have been shown to improve outcomes when combined with chemotherapy in mCRC and have each been definitively tested in the adjuvant setting.

Intergroup 0147 tested whether the addition of cmab to standard mFOLFOX6 adjuvant chemotherapy for resected stage III colon cancer improved outcomes. The protocol was amended to allow only patients with wild-type K-*ras* tumors to be eligible. The study terminated early after a second interim analysis demonstrated no benefit when adding cmab. Three-year DFS for patients with wild-type K-*ras* was 71.5% with mFOLFOX plus cmab and 74.6% with mFOLFOX alone (HR 1.21; 95% CI, 0.98-1.49; *P* = .08), suggesting a trend toward harm. There were no subgroups that benefitted from cmab, with increased toxicity and greater detrimental differences in all outcomes in patients aged older than 70 years.

The addition of bev to mFOLFOX6 was tested in NSABP C-08. This randomized phase III trial assessed DFS in stage II (25%) and III patients. Bev was administered for 6 months concurrently with chemotherapy and then continued for an additional 6 months beyond (total of 1 year of biologic therapy). mFOLFOX6 plus bev did not significantly improve 3-year DFS compared to mFOLFOX6 (77.4% vs 75.5%; HR 0.89; 95% CI, 0.76-1.04; *P* = .15). However, survival curve analysis suggested a time-dependent improvement in DFS with maximal separation of the curves occurring at 15 months, which correlated with 1 year of bev treatment followed by 3 months off drug. This benefit disappeared with time. No OS benefit, unexpected toxicity, or difference in patterns of relapse was seen.

The AVANT trial also tested bev in a three-arm study that randomized 3451 patients with high-risk stage II (17%) or stage III colon cancer to either FOLFOX4, FOLFOX4 plus bev, or CAPOX plus bev. The 3-year DFS was not significantly different between the groups with 5-year OS hazard ratio for FOLFOX 4 plus bev versus FOLFOX4 (HR 1.27; 95% CI, 1.03-1.57; *P* = .02) and CAPOX plus bev

versus FOLFOX4 (HR 1.15; 95% CI 0.93-1.42; *P* = .21), suggesting a potential detriment.

Adjuvant Chemotherapy Regimens for Stage III Colon Cancer

Based on these studies, 6 months of adjuvant chemotherapy has historically been recommended for all patients with stage III colon cancer with several acceptable options (Table 9.3). Combination regimens offer increased efficacy and toxicity. The international IDEA Study recently assessed the noninferiority of 3 versus 6 months of FOLFOX or CAPOX (capecitabine and oxaliplatin) chemotherapy in completely resected stage III patients. Noninferiority was seen for 3 months of CAPOX (hazard ratio, 0.95; 95% CI, 0.85-1.06) but not for 3 months of FOLFOX (hazard ratio, 1.16; 95% CI, 1.06-1.26). Additional analyses showed that patients with a high risk of recurrence (T4 and/or N2) should be offered 6 months of adjuvant chemotherapy and patients with low-risk disease (T1-T3 and/or N1) can be offered 3 months of CAPOX or 6 months of FOLFOX chemotherapy. The use of irinotecan or biologic-targeted therapies in the adjuvant setting is not recommended outside of a clinical trial. Adjuvant chemotherapy should be started within 8 weeks of surgery with data supporting that a delay beyond 2 months may compromise the effectiveness of adjuvant treatment.

TABLE 9.3

Acceptable Adjuvant Chemotherapy Regimens for Stage III Colon Cancer

Name	Regimen and Dose	Repeated (d)	Total Cycles
Mayo Clinic	LV 20 mg/m^2/d IV followed by	28	6
	5-FU 425 mg/m^2/d IV days 1-5		
Roswell Park	LV 500 mg/m^2 IV followed by	8 wk	3-4
	5-FU 500 mg/m^2 IV weekly × 6		
Capecitabine	1250 mg/m^2 PO twice daily × 14 d	21	8

Name	Regimen and Dose	Repeated (d)	Total Cycles
FOLFOX4	Oxaliplatin 85 mg/m^2 IV on day 1 followed by	14	12
	LV 200 mg/m^2/d IV on days 1 and 2 followed by		
	5-FU 400 mg/m^2/d IV on days 1 and 2 followed by		
	5-FU 600 mg/m^2/d CIVI for 22 h on days 1 and 2		
FOLFOX6	Oxaliplatin 85-100 mg/m^2 IV on day 1 followed by	14	12
	LV 400 mg/m^2/d IV on day 1 followed by		
	5-FU 400 mg/m^2/d IV on day 1 followed by		
	5-FU 2400 mg/m^2 CIVI for 46 h		
FLOX	LV 500 mg/m^2 IV followed by	8 wk	3
	5-FU 500 mg/m^2 IV on days 1, 8, 15, 22, 29, 36 and		
	Oxaliplatin 85 mg/m^2 IV on days 1, 15, and 29		
CAPOX	Oxaliplatin 100-130 mg/m^2 IV on day 1	21	8
	Capecitabine 1000 mg/m^2 PO twice daily on days 1-14		

5-FU, 5-fluorouracil; CIVI, continuous intravenous infusion; LV, leucovorin; IV, intravenous.

There is no role for biologic-targeted therapy or irinotecan-containing regimens in the adjuvant setting outside of a clinical trial.

Adjuvant Chemotherapy for Stage II Colon Cancer

Despite the 75% 5-year survival with surgery alone, some patients with stage II disease have a higher risk of relapse, with outcomes being similar to those of node-positive patients. Adjuvant chemotherapy provides up to 33% relative risk reduction in mortality, resulting in an absolute treatment benefit of approximately 5%.

Several analyses have reported varying outcomes in patients with stage II disease who received adjuvant treatment:

- NSABP summary of protocols (C-01 to C-04) of 1565 patients with stage II disease reported a 32% relative reduction in mortality (cumulative odds, 0.68; 95% CI, 0.50-0.92; *P* = .01). This

reduction in mortality translated into an absolute survival advantage of 5%.

- A meta-analysis by Erlichman et al detected a nonsignificant 2% benefit (82% vs 80%; *P* = .217) in 1020 patients with high-risk T3 and T4 cancer treated with 5-FU and LV for 5 consecutive days.
- Schrag et al reviewed Medicare claims for chemotherapy within the surveillance, epidemiology, and end results database and identified 3700 patients with resected stage II disease among whom 31% received adjuvant treatment. No survival benefit was detected with 5-FU compared to surgery alone (74% vs 72%) even with patients considered to be at high risk because of obstruction, perforation, or T4 lesions.
- The Quasar Collaborative Group study reported an OS benefit of 3.6% in 3239 patients (91% Dukes B colon cancer) prospectively randomized to chemotherapy versus surgery alone. With a median follow-up of 5.5 years, the risk of recurrence (HR 0.78; 95% CI, 0.67-0.91; *P* = .001) and death (HR 0.82; 95% CI, 0.70-0.95; *P* = .008) favored 5-FU and LV chemotherapy.
- In the MOSAIC study, FOLFOX4 chemotherapy showed nonsignificant benefits in DFS over 5-FU and LV in patients with stage II disease (86.6% vs 83.9%; HR 0.82; 95% CI, 0.57-1.17).
- The American Society of Clinical Oncology Panel concluded that the routine use of adjuvant chemotherapy for patients with stage II disease could not be recommended. A review of 37 randomized controlled trials and 11 meta-analyses found no evidence of a statistically significant survival benefit with postoperative treatment of stage II patients. However, treatment should be considered for specific subsets of patients (eg, T4 lesions, perforation, poorly differentiated histology, or inadequately sampled nodes), and patient input is critical.
- For stage II patients without high-risk features, molecular analysis can provide improved recurrence risk determination.
- MSI is a surrogate marker for functional defects in the dMMR system. When these occur at a high-frequency microsatellite instability high (MSI-H) in node-negative colon cancer, it

portends a very favorable prognosis. There is controversy as to whether MSI-H tumors benefit from adjuvant fluoropyrimidine chemotherapy. Given the more favorable outcome and questionable response to adjuvant chemotherapy, it is recommended to test this molecular marker in all stage II patients to aid in personalized treatment decisions.

- Commercially available microarray gene expression profile assays may aid in determining the risk of recurrence of stage II CRC. An example is Oncotype Dx (Genomic Health, Inc), which uses a 12-gene signature and excludes patients with MSI-H tumors. A recurrence score can be generated for an individual patient with stage II disease that classifies them as low-, intermediate-, or high-risk. Circulating tumor DNA assays are similarly gaining clinical interest. However, given that these tests only offer prognostic and not predictive value, the National Comprehensive Cancer Network states there is insufficient evidence to recommend use of these assays to determine adjuvant therapy.

Treatment for Rectal Cancer

In contrast to colon cancer, local treatment failures after potentially curative resections represent a major clinical problem. Combined-modality chemotherapy with RT (chemoRT) is the standard therapy for patients with stage II and III rectal cancer (T3, T4, and nodal involvement).

Establishing Combined Modality Neoadjuvant Therapy As Standard of Care

A four-arm study of 1695 postoperative patients compared 5-FU alone, 5-FU and LV combination, 5-FU and Lev combination, and 5-FU and LV and Lev combination. Two cycles of chemotherapy were administered before and after chemoRT using 5040 cGy of external beam RT (4500 cGy with 540 cGy boost). The chemotherapy during the RT was given as a bolus with or without LV. The DFS and OS were similar in all treatment arms, leading to the conclusion that 5-

FU alone was as effective as other combinations. Subsequent studies sponsored by the North Central Cancer Treatment Group (NCCTG) demonstrated improvements in both DFS and OS when continuous infusion of 5-FU was provided during RT compared with those receiving bolus 5-FU. This survival benefit has led to continuous infusion of 5-FU during RT being considered as a standard.

The benefit of delivering chemoRT in a preoperative (neoadjuvant) fashion was evaluated by the German Rectal Study Group in 421 patients compared to 401 similar patients randomized to receive postoperative chemoRT. In both groups, 5-FU was administered in a continuous fashion during the first and fifth weeks of RT. All patients received an additional four cycles of adjuvant 5-FU after chemoRT and surgery. Results of neoadjuvant treatment provided improvement in local recurrence (6% vs 13%; P = .006) but no difference in 5-year OS. Both acute toxic effects (27% vs 40%; P = .001) and long-term toxicities (14% vs 24%; P = .01) were less common with neoadjuvant treatment. Preoperative chemoRT followed by surgical resection with postoperative 5-FU–based chemotherapy represents a standard for patients with stage II and III rectal cancer.

Modifications to ChemoRT

NSABP R-04 was a phase III, 2 × 2 noninferiority trial, which evaluated the substitution of oral capecitabine (cape) for infusional 5-FU (CVI 5-FU) as well as the intensification of radiosensitization by adding oxaliplatin in stage II and III rectal carcinoma. Over 1500 patients were randomized into one of four neoadjuvant chemoRT arms. The primary endpoint for this study was local regional tumor control. The 3-year local regional tumor event rates were similar in both the cape and CVI 5-FU arms, 11.2% versus 11.8%, respectively. There was also equivalence for cape and CVI 5-FU in terms of rates of pathologic complete response (pCR) and surgical downstaging. Rates of grade 3 diarrhea were equal in both arms (11.7%). However, the addition of oxaliplatin failed to improve DFS, OS, pCR rates, surgical downstaging, or sphincter-sparing surgery. The addition of

oxaliplatin did increase (16.5% vs 6.9%) grade 3 and 4 diarrhea. This and other studies confirmed that cape is an acceptable replacement for CVI 5-FU and that adding oxaliplatin to chemoRT offers no benefit in the neoadjuvant treatment of rectal cancer. Other attempts to intensify or modulate the efficacy of RT through the use of novel radiosensitizers are an area of active investigation.

Traditional chemoRT long-course radiotherapy involves delivery of 45 to 50 Gy over a period of 5 to 6 weeks concurrent with a fluoropyrimidine. However, short-course radiotherapy is an established treatment option in many parts of the world, delivering 25 Gy over 1 week without any supplemental radiosensitization. Randomized controlled trials have demonstrated similar local control rates between the two approaches when followed by comprehensive surgical resection.

Total Neoadjuvant Therapy, Sequencing of Therapy, and Future Directions

Most patients with rectal cancer who recur succumb to metastatic disease, yet contemporary randomized controlled trials show that 25% to 70% of the patients never receive or complete their intended adjuvant systemic chemotherapy. Thus, a "total neoadjuvant therapy" (TNT) approach to care has been developed, which provides both systemic chemotherapy and local (chemo)RT preoperatively. The randomized phase II platform TNT study (NRG GI002; ClinicalTrials.gov #NCT02921256) helped to establish TNT as a standard option in the United States for locally advanced rectal cancer. The study utilized induction chemotherapy (FOLFOX) followed by chemoRT (with or without experimental agents tested in a series of parallel treatment arms) followed by surgical resection. Results from all interventions demonstrated consistent pCR rates of 20% to 30% while establishing safety, feasibility, and a new benchmark for future studies. The TNT approach also has the benefit of determining therapeutic response, which can guide potential delay or elimination of certain portions of traditional treatment in an attempt to reduce morbidity. For example, a multicenter randomized

phase II trial (OPRA; ClinicalTrials.gov identifier: NCT02008656) is examining the approach, whereby patients undergo TNT and those who achieve a clinical complete response (cCR) or near-complete clinical response can be managed nonoperatively. This trial is based, in part, on a Brazilian cohort of patients with resectable rectal cancers who were treated with TNT and those with a cCR were observed while all others were taken to surgery. A provocative 57% of patients maintained a cCR at 1 year and were spared from TME. Prospective validation of this approach is needed particularly to confirm the efficacy of salvage operations for those with persistent disease.

Another important ongoing phase II/III trial (PROSPECT; ClinicalTrials.gov #NCT01515787) is randomizing low-risk patients with stage II and III rectal cancer to standard of care neoadjuvant chemoRT versus induction chemotherapy (FOLFOX for 12 weeks) followed by MRI and/or ERUS. If the tumor decreases by >20% with neoadjuvant chemotherapy alone, patients proceed to surgery without chemoRT. Postop chemoRT is allowable should pathology support that need, but avoidance of pelvic RT for those patients with highly chemosensitive disease is the goal of the study design.

Combined-Modality Options for Rectal Cancer

1. Neoadjuvant therapy (chemoRT):
    - Continuous infusion 5-FU (1000 mg/m^2/day) given daily for 5 days during the first and fifth week of radiation therapy OR 225 mg/m^2/day given Monday through Friday continuously throughout RT.
    - Oral capecitabine 825 mg/m^2 twice daily given Monday through Friday on days of RT.
    - Either of these concurrent with external beam RT given in 180 cGy fractions to a total dose of 5040 cGy.
2. Complete surgical resection adhering to TME standards.
3. Systemic therapy for 4 months (before or after surgery):
    - Given the previously discussed data for adjuvant chemotherapy regimens in colon cancer, several different regimens (see Table 9.3) may be considered as components of the systemic chemotherapy phase of therapy in rectal cancer (eg, fluoropyrimidine and oxaliplatin).

FOLLOW-UP AFTER CURATIVE TREATMENT

Eighty percent of recurrences are seen within 2 years of initial therapy. The American Cancer Society recommends total colonic evaluation with either colonoscopy or double-contrast barium enema within 1 year of resection, followed every 3 to 5 years if findings remain normal. Synchronous cancers must be excluded during initial surgical resection, and metachronous malignancies in the form of polyps must be detected and excised before more malignant behavior develops.

History and physical evaluations with serum CEA measurements should be performed every 3 to 6 months for the first few years after therapy. These evaluations can be further reduced during subsequent years. Surveillance imaging should be reserved for those individuals who would be considered operable candidates if localized metastases were to be identified. Elevations of CEA postoperatively may suggest residual tumor or early metastasis. Patients with initially negative levels of CEA can subsequently exhibit positive levels; therefore, serial CEA measurements after completion of treatment may identify patients who are eligible for a curative surgery; in particular, patients with oligometastatic liver or lung recurrence.

TREATMENT FOR ADVANCED CRC

Unprecedented improvements in OS have been recognized during the past decade with systemic chemotherapy in advanced or metastatic disease. Median survival has improved from 6 months with best supportive care to over 30 months with incorporation of all active agents. Based upon clinical practice and supported by total cancer genomic analyses, there are no differences in the molecular characteristics or systemic management of metastatic colon or rectal cancers. Data also support proceeding with systemic therapy without surgical intervention on the primary tumor, as long as the intact primary tumor is asymptomatic. Treatment for advanced

disease can be separated into those therapies that do or do not depend upon specific molecular tumor features. Therefore, determination of molecular profiling of the tumor to include RAS, B*raf* V600E, NTRK gene fusion, tumor mutation burden, and MMR/MSI status at the time of diagnosis is now a critical requirement for personalized treatment selection and outcome optimization.

Fluoropyrimidine-Based Chemotherapy

5-FU inhibits thymidylate synthase, an enzyme critical in thymidine generation. LV potentiates this inhibition. 5-FU and LV chemotherapy regimens in advanced CRC have objective response rates of 15% to 20%, with median survival of 8 to 12 months. Toxicity is predictable and manageable. The activity of continuous infusion of 5-FU may be equivalent to or slightly better than that of bolus 5-FU and LV and is generally well tolerated despite the inconvenience of a prolonged intravenous ambulatory infusion apparatus. Toxicities include mucositis and palmar-plantar erythrodysesthesia (HFS); however, myelosuppression is less common. Continuous infusions of 5-FU may have activity in patients who have progressed with bolus 5-FU.

Capecitabine, an oral fluoropyrimidine prodrug, undergoes a series of three enzymatic steps in its conversion to 5-FU. The final enzymatic step is catalyzed by thymidine phosphorylase, which is overexpressed in tumor tissues and upregulated by RT. Two phase III studies have compared single-agent capecitabine to the Mayo Clinic 5-FU and LV regimen and demonstrated higher response rates for the former but equivalent time to progression and median survival. Capecitabine was associated with decreased gastrointestinal and hematologic toxicities and fewer hospitalizations but with an increased frequency of HFS and hyperbilirubinemia.

Trifluridine and tipiracil is an FDA-approved oral therapy for the treatment of metastatic CRC who have been previously treated with

all other standard therapies. Trifluridine is a thymidine-based nucleoside analog while tipiracil is a thymidine phosphorylase inhibitor and in effect increases trifluridine activity. Once trifluridine is taken up in the cancer cell, it is incorporated into the DNA and inhibits cell proliferation and interferes with DNA synthesis. The phase III, randomized placebo-controlled registration trial (RECOURSE) studied trifluridine and tipiracil in patients with previously treated (at least two prior lines) metastatic CRC. Results showed an improvement in median PFS (2 vs 1.7 months; $P < .001$) and OS (7.1 vs 5.3 months; $P < .001$) for trifluridine/tipiracil versus placebo, respectively. The main side effects of trifluridine/tipiracil were grade 3 to 4 asthenia/fatigue (7%), grade 3 anemia (18%), grade 3 to 4 neutropenia (38%), and grade 3 to 4 thrombocytopenia (5%).

Oxaliplatin

Oxaliplatin is an agent that differs structurally from other platinums in its 1,2-diaminocyclohexane moiety but acts similarly by generating DNA adducts. Oxaliplatin exhibits synergy with 5-FU with response rates as high as 66% even in patients who are refractory to 5-FU. Despite its unique toxicities (ie, peripheral neuropathy, laryngopharyngeal dysesthesias, and cold hypersensitivities), oxaliplatin lacks the significant emetogenic and nephrogenic toxicities of cisplatin.

Oxaliplatin has no clinical activity as monotherapy in CRC and must be combined with another agent (typically a fluoropyrimidine). Such combination regimens (eg, FOLFOX or CAPOX) constitute some of the most common therapies used in several different CRC settings.

Irinotecan

Irinotecan is a topoisomerase I inhibitor, with activity in advanced CRC deemed refractory to 5-FU. As a single agent, response rates as high as 20% are observed, and an additional 45% of patients achieve disease stabilization. Significant survival advantages have been

shown for irinotecan as second-line therapy after 5-FU compared with supportive care or with continuous-infusion 5-FU regimens. Several schedules are typically administered with and without 5-FU; however, the cumulative data now suggest that irinotecan should not be utilized with bolus 5-FU (ie, IFL) due to excessive treatment-related mortality. Irinotecan obtained initial FDA approval based on a study comparing IFL to the 5-FU bolus Mayo Clinic regimen. A higher response rate (39% vs 21%; P = .0001) and OS (14.8 vs 12.6 months; P = .042) were observed favoring IFL. The most common combinations of irinotecan are with infusional 5FU (eg, FOLFIRI) or with anti-EGFR therapies (see below).

Delayed-onset diarrhea is common and requires close monitoring and aggressive management (high-dose loperamide, 4 mg initially and then 2 mg every 2 hours until diarrhea stops for at least 12 hours). Neutropenia, mild nausea, and vomiting are common. This combination of toxicities can be severe and life-threatening, which was evident in NCCTG 9741 (see previous oxaliplatin section). A higher 60-day mortality was observed (4.5% vs 1.8%), and the dose of irinotecan required reduction.

NCCTG-9741 conducted a trial comparing first-line FOLFOX versus IFL versus IROX (irinotecan in combination with oxaliplatin). Higher 60-day mortality was detected in the IFL arm, resulting in a dose reduction in the protocol. The response rate, time to progression, and OS were significantly better in the FOLFOX arm than in the modified IFL arm. However, imbalances in the second-line chemotherapy administered to patients in this study may confound the survival differences. Approximately, 60% of the oxaliplatin failures were treated with irinotecan, whereas only 24% of patients who were refractory to irinotecan received oxaliplatin. In addition, the study was not designed to address the effect of infusional 5-FU. The observed toxicities in the study were reflective of the specific drug combinations and included grade 3 or higher paresthesias (18%) in the FOLFOX arm and a 28% incidence of diarrhea in the IFL arm. Despite a higher degree of neutropenia (60% in FOLFOX vs 40% in IFL) with FOLFOX, febrile neutropenia was

significantly greater in the IFL arm. IROX also exhibited significant toxicities. Oxaliplatin was approved by the FDA for use in the first-line treatment of patients with metastatic CRC largely based on this study.

Although FOLFOX is clearly a superior regimen compared to IFL, the use of infusional 5-FU with irinotecan (FOLFIRI) may produce results similar to those seen using FOLFOX. Tournigand et al reported an equivalent median survival of 21.5 months with FOLFIRI followed by FOLFOX and a median survival of 20.6 months with the opposite sequence (P = .99). Similar survival is observed in patients receiving either sequence and both are acceptable first-line therapies for advanced disease.

Anti-VEGF Therapies

Bevacizumab (bev) is a recombinant humanized monoclonal antibody targeting the VEGF, which blocks VEGF-induced angiogenesis by preventing it from binding to VEGF receptors. When added to IFL, bev increased the response rate (45% vs 35%; P = .004) and had a longer median survival (20.3 vs 15.6 months; P < .001). When added to FOLFOX in the second-line setting, response rates are again increased (23% vs 9%; P < .001) along with an improvement in OS (12.9 vs 10.8 months; P = .0011). Bev has been approved by the FDA for the treatment of patients with advanced CRC in combination with any intravenous 5-FU–based regimen. Two trials (ML18147, BRiTE) looked at bev beyond progression following first-line chemotherapy. Both studies showed PFS and OS advantage with continuation of bev with second-line chemotherapy. This approach was further explored as a maintenance strategy. The CAIRO-3 study enrolled 558 patients to receive "induction" chemotherapy with CAPOX plus bev for six cycles. Patients were then randomized to observation versus maintenance treatment with cape and bev. Upon progression (PFS1), patients on either observation or cape and bev were restarted on CAPOX plus bev, and the next progression (PFS2) was the primary endpoint. The maintenance group had a significantly improved PFS2 compared to

observation, 11.7 versus 8.5 months, respectively (HR 0.67; 95% CI 0.56-0.81; $P < .0001$).

Ziv-aflibercept is a fully humanized recombinant fusion protein that blocks angiogenesis by binding to VEGF-A, VEGF-B, and placental growth factor and preventing their interaction with endogenous receptors. It is FDA approved for use in combination with FOLFIRI for second-line treatment in metastatic CRC based on results from the VELOUR study. This phase III, placebo-controlled trial randomized 1226 metastatic patients with CRC after an oxaliplatin-based regimen to second-line therapy with FOLFIRI plus ziv-aflibercept or placebo. Median OS of FOLFIRI plus ziv-aflibercept was statistically superior to FOLFIRI (13.5 vs 12 months; HR 0.87; 95% CI 0.713-0.937; $P = .0032$) as was PFS (6.9 vs 4.7 months; $P < .0001$).

Ramucirumab is another humanized monoclonal antibody that blocks activation of VEGF receptor 2, effectively blocking the binding of VEGF-A, VEGF-C, and VEGF-D. It is FDA approved for use in combination with FOLFIRI for second-line treatment in metastatic CRC based on results from the RAISE study. This phase III, placebo-controlled trial randomized 1072 patients with previously oxaliplatin-treated metastatic CRC to FOLFIRI plus ramucirumab or placebo. The addition of ramucirumab demonstrated a median PFS improvement of 1.2 months (5.7 vs 4.5 months; $P < .001$) and median OS improvement of 1.6 months (13.3 vs 11.7 months; $P = .023$).

The first and currently only approved oral multikinase inhibitor for metastatic CRC is regorafenib. This agent blocks several kinases involved in angiogenic and oncogenic survival pathways including VEGFR1, VEGFR2, VEGFR3, TIE2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR. The CORRECT trial randomized heavily pretreated metastatic CRC patients who progressed within 3 months after treatment with all currently available standard therapies to oral regorafenib versus placebo. Median OS was found to be improved with regorafenib compared to placebo (6.4 vs 5 months; HR 0.77;

P = .0052). Studies which incorporate this treatment in earlier lines of therapy are ongoing.

There are no biomarkers or tumor features that can reliably predict benefit or resistance to anti-VEGF therapies. The use of anti-VEGF therapies in the perioperative or peritoneal carcinomatosis settings should be done with caution given risks of poor wound healing and visceral perforation, respectively.

Anti-Epidermal Growth Factor Therapies

The epidermal growth factor receptor (EGFR) and pathway represent another targeted approach in advanced CRC therapy. Two monoclonal antibodies are FDA approved for use in patients with mCRC. Importantly, tumor EGFR positivity by IHC staining does not correlate with treatment response; however, K-*ras*, N-*ras*, and B-*raf* mutational status does. Both intracellular signal transduction proteins exist in either a wild-type (normal functional) or mutated (via activating mutation resulting in continuous overactivity) state. Mutations in K- and N-*ras* (~50% together) and B-*raf* (5%-10%) have high concordance between primary and mCRC tumors (in excess of 90%), with recommendations for testing these at the time of metastatic diagnosis.

Cetuximab (cmab) is a chimerized IgG1 antibody that prevents ligand binding to the EGFR and its heterodimers through competitive displacement. Panitumumab (pmab) is a fully humanized IgG2 antibody also targeting EGFR in a similar manner. These agents both block receptor dimerization, tyrosine kinase phosphorylation, and subsequent downstream signal transduction. Both can cause a skin rash, diarrhea, hypomagnesemia, and infusion reactions but to a less degree with pmab for the latter two toxicities. A correlation between the intensity of the skin rash and improved survival has been consistently noted with agents in this class.

Cmab was initially FDA-approved based on a study in irinotecan-refractory advanced disease. Patients were randomized to the combination of cmab and irinotecan versus cmab alone with

improvements in the response rate (22.9% vs 10.8%; *P* = .0074) and time to progression (4.1 vs 1.5 months; *P* < .0001) favoring the combination. Despite manageable toxicity, no improvements in survival outcomes were observed but tumor resensitization to irinotecan was clearly demonstrated. Cmab is also approved for use as first-line metastatic treatment for patients with wild-type K-*ras* tumors. The CRYSTAL phase III trial randomized 1217 patients to FOLFIRI with or without cmab. FOLFIRI plus cmab demonstrated a 15% relative reduction in the risk of recurrence (HR 0.85; 95% CI 0.72-0.99; *P* = .048) with an improvement in the median PFS (8.9 vs 8 months). The addition of cmab produced significantly more skin reactions, diarrhea, and infusional reactions. Median progression-free survival directly correlated with increased grade of skin rash. K-*ras* status was available on a subgroup analysis of 540 tissue samples. Patients with wild-type K-*ras* had a favorable outcome on response rate, OS, and PFS (HR 0.68). However, mutated K-*ras* tumors were associated with a decrease in OS and response rates, particularly with cmab addition, confirming that *ras* mutations are a negative predictor of response to EGFR inhibition.

Panitumumab is FDA-approved as monotherapy given improvement in progression-free survival over best supportive care in heavily pretreated patients (HR 0.54; 95% CI 0.44-0.66; *P* < .0001) although no OS advantage was noted. This agent also has data supporting improvements in PFS when combined with FOLFIRI in the second-line treatment.

BRAF Inhibition

B-*raf* V600E mutations are typically mutually exclusive with RAS mutations and are associated with a much worse prognosis including a PFS of 4 to 6 months and OS of 9 to 14 months. Attempts to directly target this pathway with the BRAF inhibitors failed given unanticipated feedback through EGFR accessory pathways. A dual pathway targeted approach has been shown to be effective. Encorafenib in combination with cmab was FDA-approved in the second-line setting for B-*raf* V600E and RAS- WT CRC after

encouraging results from the BEACON trial. An OS of 9.3 months was observed and ORR of 20% observed. Testing for extended *ras* and *raf* mutations is recommended and widely available.

TRK Inhibition

Less than 1% of CRC have NTRK gene fusions; however, the FDA has approved larotrectinib and entrectinib for metastatic or unresectable solid tumors who have no other treatment alternatives. In a pooled analysis of three studies collectively with four CRC patients, an ORR of 20% was observed. In the NAVIGATE study, eight colon cancer patients were treated with larotrectenib with 50% of patients achieving a partial response and 50% achieving stable disease.

Immunotherapy

Programmed cell death protein 1 (PD-1) is expressed on activated T-cells and is a negative regulator of T-cell activity when it interacts with its ligand PD-L1. As a mechanism of immune evasion, tumor cells overexpress PD-L1. Antibodies to block this interaction have been developed with varying success in a multitude of malignancies. In CRC, anti−PD-1 therapy has only demonstrated clinical activity in tumors harboring mismatch-repair deficiency (dMMR) or MSI-H. This represents about 5% of patients with metastatic CRC.

The PD-1 checkpoint inhibitor, pembrolizumab, received accelerated approval for dMMR or MSI-H mCRC who have progressed on fluoropyrimidine, oxaliplatin, or irinotecan based upon results of KEYNOTE-164. Aggregate data from 90 patients with CRC with dMMR/MSI-H status had an ORR of 33% with median duration of response not reached and median PFS of 4.1 months. Pembrolizumab has also been recently approved for first-line treatment of dMMR or MSI-H mCRC based upon results of the KEYNOTE-177. In this clinical trial, the ORR was 43.8% versus 33.1% in the chemotherapy arm (investigator's choice of therapy). The median PFS was 16.5 versus 8.2 months.

Nivolumab with or without ipilimumab (an anti–CTLA-4 antibody) are also FDA approved for use in mCRC after progression with a fluoropyrimidine, oxaliplatin, and irinotecan based upon the Checkmate-142 trial. This study randomized patients with treatment resistant dMMR/MSI-H mCRC to nivolumab or nivolumab and ipilimumab. In the 74 patients who received single-agent nivolumab, the ORR was 31%, PFS 50%, OS: 73% at 1 year. Those who received the combination had an ORR of 55%, PFS 71, OS 85% at 1 year. After a follow up of 29 months, the ORR was 69% and complete response was 13%.

In a pan-cancer approval, the FDA has also approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) solid tumors after progression on prior treatment and without alternative treatment options. In mCRC, this biomarker can be sometimes found independent of the dMMR/MSI-H tumor status.

CHEMOTHERAPY REGIMENS FOR METASTATIC CRC

See Tables 9.3 and 9.4 and Figure 9.1. Investigations into the optimal timing and sequence of treatment combinations both with and without EGFR and VEGF inhibition continue.

TABLE 9.4

Select Chemotherapy Regimens for Advanced Colorectal Cancer [a]

Name	Regimen and Dose	Repeated (d)
CAPOX	Oxaliplatin 100-130 mg/m^2 IV on day 1	21
	Capecitabine 850-1000 mg/m^2 PO twice daily on days 1-14	
Irinotecan	300-350 mg/m^2 IV	21

Name	Regimen and Dose	Repeated (d)
Irinotecan	125 mg/m^2 IV on days 1, 8, 15, and 22	6 wk
FOLFIRI	Irinotecan 180 mg/m^2 IV on day 1 followed by	14
	LV 400 mg/m^2/d IV on day 1 followed by	
	5-FU 400 mg/m^2/d IV on day 1 followed by	
	5-FU 2400 mg/m^2 CIVI for 46 h	
Bevacizumab [b]	5 mg/kg IV	14
Ziv-aflibercept	4 mg/kg IV	14
Ramucirumab	8 mg/kg IV	14
Cetuximab [c]	400 mg/m^2 IV on day 1 followed by	Weekly
	250 mg/m^2 IV weekly thereafter	
Cetuximab [c]	500 mg/m^2 IV	14
Panitumumab [c]	6 mg/kg IV	14
Regorafenib	160 mg PO once daily for 21 d	28
Trifluridine and tipiracil	35 mg/m^2/dose PO twice daily on days 1-5 and 8-12	28
Pembrolizumab [d]	200 mg IV	21
Pembrolizumab [d]	400 mg IV	6 wk
Nivolumab [d]	240 mg IV	14
Nivolumab [d]	480 mg IV	28
Encorafenib and Cetuximab [e]	Encorafenib 300 mg PO daily	
	Cetixumab 400 mg/m^2 followed by 250 mg/m^2 weekly	
Entrectinib [f]	600 mg PO once daily	
Larotrectinib [f]	100 mg PO twice daily	

5-FU, 5-fluorouracil; CIVI, continuous intravenous infusion; IV, intravenous; LV, leucovorin.

[a]These are in addition to those presented in Table 9.3.

[b]In combination with any 5-FU–containing regimen.

[c]Only indicated for patients with *RAS* wild-type tumors.

[d]Only indicated for patients with dMMR or MSI-H tumors.

[e]Only indicated for patients with B-*raf* V600E mutant tumors.

[f]Only indicated for patients with NTRK gene fusion positive tumors.

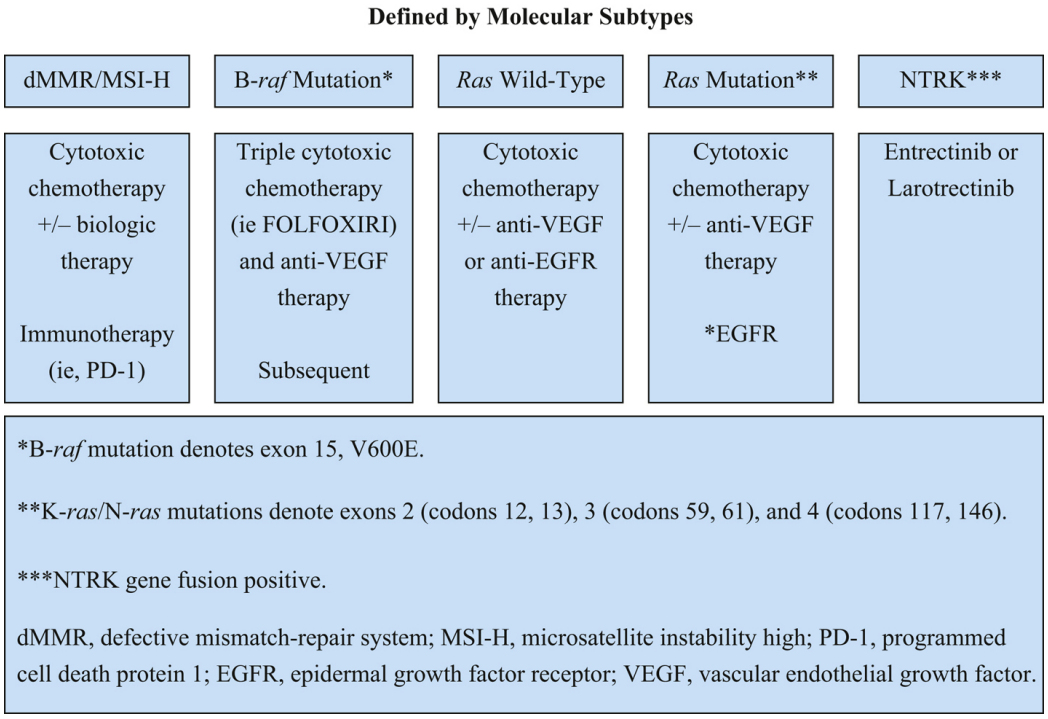

FIGURE 9.1 Palliative treatment considerations for metastatic colorectal cancer as defined by molecular subtypes.*Note*: *Consideration of clinical trial enrollment for each patient in these categories for each line of therapy is prudent*.

Optimal Therapy Selection and Sequencing

The choice of systemic therapy should be based upon several factors including the patient's burden of disease, performance status, and results of molecular tumor profiling. CALGB 80,405 was an important international phase III trial, which tested the optimal first-line treatment in 1137 patients with metastatic K-*ras* wild-type (WT) CRC. Patients were treated with FOLFOX (or FOLFIRI at provider discretion) and randomized to the addition of either cmab or bev. Median OS (the primary endpoint) was essentially the same (32 vs 31.2 months; P = .40) between treatment with chemo and cmab versus bev, respectively. PFS was also similar between the arms. Retrospective analysis identified that left-sided tumors were associated with a longer median overall survival compared to those from the right colon (OS 33.3 vs 19.4 months; P < .0001). Results

suggested that bev may also benefit right-sided tumors more than cmab-based chemotherapy (OS 24.2 vs 16.7 months; $P < .0001$). The opposite was true for left-sided cancers suggesting cmab was more effective than bev-based chemotherapy (OS 36 vs 31.4 months; $P < .0001$). This suggests distinct molecular variability of colon cancers depending on their "sidedness."

The FIRE-3 study was the European equivalent of the CALGB 80,405 study. It enrolled 592 similar patients and randomized them to FOLFIRI plus either bev or cmab. In contrast to the prior study, the median OS favored treatment with cmab (33.1 vs 25.6 months; $P = .011$). Importantly, there was no difference in PFS between the groups suggesting subsequent therapy may have accounted for the improvement in OS. It should be noted that neither trial prospectively tested for N-*ras* or B-*raf* mutations, as either predictive or prognostic biomarkers.

OLIGOMETASTATIC DISEASE

The liver is the most common site for metastasis, with one-third of cases involving only the liver. Approximately 25% of liver metastases are resectable, with certain patient subsets showing 30% to 40% 5-year survival after resection and 3% to 5% operative morbidity and mortality. Nonoperative ablative techniques (ie, cryoablation, radiofrequency ablation, stereotactic RT, and hepatic artery embolization with or without chemotherapy) have not shown consistent durable prospective survival benefits. Intraoperative ultrasound is the most sensitive test for initial detection, followed by CT scan or MRI. PET scanning can help identify occult extrahepatic disease in select patients being considered for resection.

Patients with unresectable disease limited to the liver can be treated with locoregional hepatic artery infusion (HAI) or systemic chemotherapy. Kemeny et al reported a 4-year DFS and hepatic disease-free benefit in patients with resected liver metastases who had received intra-arterial floxuridine with systemic 5-FU compared

to those who did not receive any postoperative therapy although there was no statistically significant difference in OS (62% vs 53%; P = .06). Such an approach has typically been reserved for select centers and its utility has been challenged by the advent of more effective systemic chemotherapy.

The feasibility of converting initially unresectable disease to a potentially curative disease has been investigated by Bismuth and colleagues. Resection was possible in 99 patients with either downstaged or stable disease and the 3-year survival was encouraging (58% for responders, 45% for patients with stable disease). Similar observations have been reported by Alberts using preoperative FOLFOX4 on 41% of patients undergoing resection with an observed median survival of 31.4 months (95% CI 20.4-34.8) for the entire cohort. Given objective response rates of 60% to 70% in RAS WT tumors treated initially with cmab-based chemotherapy, this could provide rationale for personalizing treatment selection to optimize response and improve chances of conversion of borderline or unresectable disease. Alternatively, for those with RAS mutations where anti-EGFR therapies are contraindicated, FOLFOXIRI (5-FU/LV, irinotecan, oxaliplatin) with bev demonstrated a 65% objective response rate; however, the rate of hepatic R0 surgical resections was not improved over FOLFIRI with bev.

Indeed, current management of resectable liver disease typically includes appropriate patient selection, adequate imaging to confirm isolated and limited disease burden, multidisciplinary clinical collaboration, and consideration of perioperative systemic chemotherapy. The latter recommendation is based, in part, on the results of a European study showing a progression-free survival advantage to the use of 3 months of FOLFOX chemotherapy pre- and post-resection compared to surgery alone. However, attention must be paid to the potential hepatotoxicity and surgical complications from prolonged perioperative chemotherapy. The maximum radiographic response from chemotherapy is typically seen at 12 weeks. Importantly, systemic chemotherapy fails to sterilize hepatic metastases, even if radiographic complete response

is noted. Patients with B-*raf* mutations appear to have limited benefit from oligometastatic management given the aggressive and refractory nature of metastatic disease.

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10

Pancreatic Cancer

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INTRODUCTION

The majority of pancreatic neoplasms arise from the exocrine pancreas and are of the pancreatic ductal adenocarcinoma (PDAC) subtype. PDAC comprises 90% of all primary pancreatic neoplasms. Other subtypes of exocrine pancreatic cancer such as acinar cell carcinoma are rare. The pancreatic neuroendocrine tumors that arise from the endocrine islet cells form a small minority of primary pancreatic neoplasms. The focus of this chapter is PDAC, which will hereafter be treated as synonymous with the term pancreatic cancer.

EPIDEMIOLOGY

In 2021, there will be an estimated 60,430 cases of newly diagnosed pancreatic cancer and 48,220 deaths from pancreatic cancer in the United States. Over 85% of patients are diagnosed after the age of 55 years, and the median age of diagnosis is 70 years. Males have a slightly increased incidence compared with females. Despite comprising only 3% of new cancer diagnoses, pancreatic cancer has the lowest survival rate (10%) and is the fourth leading cause of cancer-related deaths.

Risk Factors

The primary risk factors for development of pancreatic cancer are smoking, family history and hereditary syndromes, chronic pancreatitis, and alcohol use. Twenty-five percent of pancreatic cancer is attributable to smoking. There is clear association of family history with lifetime risk of pancreatic cancer—6% of patients have one affected first-degree relative (FDR) and 40% of patients have at least three affected FDRs. Table 10.1 summarizes inherited syndromes associated with pancreatic cancer.

TABLE 10.1
Inherited Syndromes Associated With Pancreatic Cancer

	Affected Gene	Relative Risk	Comments
Hereditary pancreatitis	*PRSS1* (cationic trypsinogen)	20-75	Present in youth with recurrent acute pancreatitis leading to chronic pancreatitis. Pancreatic cancer occurs 2-3 decades after onset of chronic pancreatitis.
Peutz-Jeghers syndrome	*STK11/LKB1* (serine threonine kinase 11)	132	Tumor suppressor gene. Presents with benign gastrointestinal (GI) polyps, melanosis of mouth/hands/feet. Also associated with breast, lung, endometrial, gonadal cancers.
Familial atypical multiple mole melanoma (FAMMM)	*CDKN2A* (p16)	13-22	Tumor suppressor gene. Also associated with melanoma, breast, endometrial, lung cancers.
Hereditary breast/ovarian cancers (HBOC)	*BRCA1, BRCA2, PALB2*	2.3-3.6 3-10 Unknown	Tumor suppressor genes. BRCA2 is the most common hereditary risk factor for pancreatic cancer.
Familial adenomatous polyposis (FAP)	*APC*	5	Tumor suppressor gene. Associated with numerous colon polyps beginning in adolescence and colon cancer in young adulthood.

	Affected Gene	Relative Risk	Comments
Hereditary nonpolyposis colon cancer (HNPCC)	*MSH2, MLH1*	Unknown	Mismatch repair proteins. Less frequently from *MSH6*, *PMS1*, and *PMS2* mutations. Associated with cancers of colon (especially right-sided), endometrium, ovary, stomach, small intestine, biliary tract, upper genitourinary (GU) tract, brain, skin.

Other risk factors that are less well-defined include dietary habits (with some studies supporting an association between processed and red meat intake and pancreatic cancer), chronic infections such as *Helicobacter pylori*, and ABO blood type (non-O blood groups have a higher risk).

PATHOPHYSIOLOGY

The pancreas is anatomically divided into the *head* which lies within the duodenal curvature, the *neck*, the *body* which crosses the midline posterior to the stomach pylorus, and finally tapers into the *tail* which terminates near the splenic hilum. About 70% of pancreatic cancer arises from the pancreatic head. The pancreas abuts major vascular structures including the aorta, celiac artery, gastroduodenal artery, splenic artery/vein, superior mesenteric artery/vein (SMA/SMV), and inferior vena cava. The pancreatic duct courses from the tail to the head and joins the common bile duct to exit in union at the ampulla into the second part of the duodenum. PDAC arises from the pancreatic ductal epithelium.

About 95% of invasive PDAC is preceded by pancreatic intraepithelial neoplasia (PanIN), a flat or papillary duct cell proliferation that is <0.5 cm in size. Other preinvasive changes such as intraductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasia are less common. IPMN lesions are frequently found on imaging, occurring in 2% of adults, and have a 25% chance of becoming invasive cancer.

Several driver gene mutations are implicated in PDAC—*KRAS*, *CDKN2A*, *SMAD4*, *TP53*. Activation of the *KRAS* oncogene and telomere shortening is observed in early PanIN lesions and is followed by inactivation of the tumor suppressor genes *CDKN2A*, *TP53*, and *SMAD4* as they progress toward a more invasive phenotype. When pancreatic cancer metastasizes, it typically involves the liver, peritoneum, or lung. *SMAD4* loss has been shown to correlate with presence of widely metastatic disease.

CLINICAL PRESENTATION

The most common symptoms of pancreatic cancer are fatigue, weight loss, anorexia, abdominal pain, and obstructive jaundice. Loss of exocrine tissue or pancreatic duct obstruction leads to malabsorption and steatorrhea, which can necessitate the use of pancreatic enzyme supplementation. Development of diabetes can also be the presenting symptom due to loss of functioning islet cells. Abdominal and back pain occur from involvement of celiac and mesenteric nerve plexi.

SCREENING AND DIAGNOSIS

There is no role for screening of the general population for pancreatic cancer. Per the most recent Cancer of the Pancreas Screening consortium consensus guidelines, diabetes screening and imaging with endoscopic ultrasound (EUS) or MRI of select individuals at higher risk (FDRs of patients with pancreatic cancer from a familial kindred with ≥2 affected FDRs; patients with Peutz-Jeghers syndrome; and carriers of p16, BRCA2, HNPCC mutations with ≥1 affected FDR) are recommended.

Initial diagnostic evaluation in patients with suspected pancreatic cancer includes laboratory studies and abdominal imaging. The primary tumor marker associated with PDAC is carbohydrate antigen 19-9 (CA 19-9) but is of limited clinical utility. The imaging

study of choice is a "pancreatic protocol" computed tomography (CT) scan, which involves triple-phase contrast enhancement on multidetector CT. The late arterial phase helps to distinguish the hypoattenuating tumor from normal parenchyma, and the portal phase allows visualization of interface between the tumor and adjacent venous structures and detection of liver metastases. Abdominal ultrasound can identify pancreatic cancer as a solid, hypoechoic mass and show associated biliary ductal dilatation from tumor obstruction. However, it is subject to variability based on operator skill, may miss tumors <3 cm, and incompletely evaluates the pancreas when overlying bowel gas is present.

Endoscopic retrograde cholangiopancreatography (ERCP) is of limited diagnostic utility as the sensitivity of ERCP biopsy or brushing for cytology is low and the classically described finding of the "double duct sign" (pancreatic and biliary duct dilatation) is not specific to pancreatic tumors. EUS with fine-needle aspiration has a sensitivity of 92% and specificity of 96% in diagnosing pancreatic cancer and is the preferred method of obtaining a histopathologic diagnosis. Percutaneous biopsy is avoided due to a theoretical concern for seeding of tumor in the biopsy needle tract or peritoneal cavity.

STAGING

The technical staging of pancreatic cancer is based upon the tumor, node, and metastasis system of the American Joint Committee on Cancer. Practically, however, the disease is staged as resectable, borderline resectable, unresectable, or metastatic, depending on the anatomic extent of the cancer, and these categories determine treatment approaches.

TREATMENT

Patients are best evaluated by multidisciplinary teams at high-volume centers. Efforts should always be made to offer clinical trial enrollment to eligible patients. Pancreatic cancer portends a high burden of morbidity and mortality, so palliative care should be implemented early.

Resectable Disease

Approximately 15% of patients present with resectable disease, which means there is no arterial tumor contact and no SMV or portal vein contact (or ≤180° contact without vein contour irregularity). Treatment involves surgical resection followed by 6 months of adjuvant chemotherapy with FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin). There is no proven role for chemoradiotherapy (CRT) in improving survival.

Surgical Resection. Resection offers a potentially curative treatment, but recurrences are common even with R0 resections. Patients must have good functional status to tolerate a major abdominal surgery. Pancreatic head tumors undergo conventional or pylorus-preserving pancreaticoduodenectomy (Whipple procedure), whereas pancreatic body/tail tumors undergo a distal pancreatectomy, often with splenectomy. Total pancreatectomy can be required if the entire gland is involved by tumor but has a high morbidity. Extended pancreatectomy and extended lymphadenectomy do not improve survival.

Adjuvant Chemotherapy. All patients who have undergone resection should receive 6 months of adjuvant chemotherapy. Chemotherapy should be initiated within 12 weeks after resection—the sooner the better. The current standard of care is driven by a recent trial demonstrating FOLFIRINOX as a very effective regimen. This study, however, enrolled a highly select group of patients, and results in routine practice may not achieve the stated benefits. Historical clinical trials involving adjuvant chemotherapy are summarized below:

- **ESPAC-1** used a 2 × 2 factorial design to randomize 289 patients after resection into four treatment arms: (1) CRT alone; (2) chemotherapy alone; (3) both CRT and chemotherapy; and (4) observation. Five-year overall survival (OS) was 21% in those who received chemotherapy versus 8% in those who did not (P = .009).
- **CONKO-001** randomized 368 patients after resection to 6 months of adjuvant chemotherapy with gemcitabine versus observation. Median disease-free survival (DFS) was 13.4 and 6.7 months in the gemcitabine and observation groups, respectively, with HR 0.55 (P < .001). Five-year OS was 20.7% and 10.4% with gemcitabine and observation, respectively, with HR 0.76 (P = .01).
- **ESPAC-3 (v2)** randomized 1088 patients after resection to 6 months of adjuvant chemotherapy with gemcitabine versus 5-fluorouracil/folinic acid (5FU/FA). There was no significant difference with median survival of about 23 months in each group. More adverse events were noted with 5FU/FA.
- **RTOG 9704** randomized 451 patients with gross resection to receive chemotherapy with either gemcitabine or 5FU/FA at 3 weeks prior and 12 weeks after planned CRT. No significant difference in OS was noted. The subset with pancreatic head tumors trended toward improved median survival and 5-year OS but did not reach statistical significance.
- **ESPAC-4** randomized 732 patients to gemcitabine alone (N = 366) or gemcitabine plus capecitabine (N = 364). Enrolled patients received six cycles of either 1000 mg/m^2 gemcitabine alone administered once a week for 3 of every 4 weeks (one cycle) or with 1660 mg/m^2 oral capecitabine administered for 21 days followed by 7 days' rest (one cycle). The median OS was 28.0 months in the gemcitabine plus capecitabine group and 25.5 months in the gemcitabine monotherapy group (HR 0.82; 95% CI, 0.68-0.98; P = .032). There was increased incidence of grade 3 to 4 toxicities in the combination arm.
- **PRODIGE 24/CCTG PA 6** randomized 493 patients after R0 or R1 resection to modified FOLFIRINOX or gemcitabine for

24 weeks. Both median OS and DFS were significantly improved in the mFOLFIRINOX group versus the gemcitabine group (DFS: 21.6 vs 12.8 months, OS: 54.4 vs 35.0 months). However, patients in the mFOLFIRINOX arm experienced more adverse events though toxicity was manageable. This trial established mFOLFIRINOX as an effective adjuvant chemotherapy regimen compared to gemcitabine.

- **APACT** randomized 866 patients to adjuvant *nab*-paclitaxel plus gemcitabine versus gemcitabine alone. Independent-reviewer DFS was not significantly different between the two arms.

Adjuvant CRT. There is no recommendation for CRT in the adjuvant setting. Multiple clinical trials, with the key ones listed above, have shown no survival benefit from adjuvant CRT.

Neoadjuvant Therapy. Theoretical advantages of neoadjuvant therapy in potentially resectable disease include upfront treatment of micrometastases, higher likelihood of negative resection margins, and ability to administer systemic treatment before postresection complications. Although there are no reliable data from randomized studies in this setting yet, neoadjuvant therapy is gaining more support at major centers, especially for patients with borderline resectable disease.

Borderline Resectable Disease

Approximately 25% of patients present with borderline resectable disease, which typically means that tumor focally involves the visceral arteries (≤180°) or has short-segment encasement or occlusion of major veins. Treatment involves use of chemotherapy for 2 to 3 months to downstage the tumor before attempted resection. Multiagent chemotherapy is typically given (eg, FOLFIRINOX or gemcitabine/nab-paclitaxel). Many completed and ongoing studies are helping define the role of neoadjuvant therapy in this setting.

Locally Advanced, Unresectable Disease

About 20% of patients present with locally advanced, unresectable disease. Typically, it is treated with multiagent chemotherapy (gemcitabine/nab-paclitaxel or FOLFIRINOX based on extrapolation of data in the metastatic setting) for at least 3 months. CRT offers no survival advantage but may help in palliation of symptoms such as pain. Relevant clinical trials are summarized below:

- **ECOG 4201** compared CRT followed by gemcitabine versus gemcitabine alone with median OS of 11.1 and 9.2 months, respectively (one-sided P = .017). However, grade 4 or higher toxicity was more in CRT arm (41% vs 9%). It was limited by poor accrual (only 74 patients).
- **FFCD-SFRO** enrolled 119 patients and compared CRT followed by gemcitabine versus gemcitabine alone. OS was shorter in the CRT group than in the gemcitabine-alone group (8.6 vs 13 months; P = .03) and more grade 3 to 4 toxicity was seen in the CRT arm.
- **LAP 07** studied CRT versus gemcitabine maintenance in patients who had already received induction chemotherapy for 4 months without progression. No difference in median OS was noted at 16.5 versus 15.3 months (HR 1.03; P = .83). However, CRT was associated with decreased local progression. There was no increased grade 3 to 4 toxicity in the CRT group except for nausea.

Metastatic Disease

Around 40% of patients present with metastatic disease. The first-line treatment of metastatic disease remains combination cytotoxic chemotherapy, with FOLFIRINOX and gemcitabine/nab-paclitaxel being the two main first-line regimens. Single-agent chemotherapy is recommended in those with poor performance status. Clinical trials should be encouraged in eligible patients.

- **PRODIGE4/ACCORD11** randomized 342 patients to receive FOLFIRINOX or gemcitabine and showed superiority of FOLFIRINOX with HR for death of 0.57 (P < .01) and median

survival improved by 4.3 months. Quality of life was preserved for a longer period despite more grade 3 to 4 toxicities in the FOLFIRINOX group.

- **MPACT** randomized 861 patients to receive gemcitabine/nab-paclitaxel versus gemcitabine alone with median OS of 8.5 versus 6.7 months (HR 0.72; $P < .01$).

Second-line therapy involves use of gemcitabine-containing chemotherapy in those initially treated with 5FU/FA-containing regimen, and vice-versa. Recent data suggest benefit with the addition of nanoliposomal irinotecan.

- **NAPOLI-1** evaluated the use of nanoliposomal irinotecan with 5-FU/FA versus each agent alone in patients previously treated with gemcitabine. Median survival improved in the combined treatment group compared to 5-FU/FA alone (6.1 vs 4.2 months; HR 0.6; $P = .012$).

Immunotherapies and targeted therapies have been tested in many trials in pancreatic cancer but have not achieved any meaningful clinical benefit so far.

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11

Anal Cancer

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INTRODUCTION

Anal cancer is an uncommon cancer, and in the United States, approximately 9100 new cases are diagnosed on an annual basis, accounting for approximately 2.5% of all gastrointestinal malignancies. The incidence of anal cancer has been rising steadily over the past several decades both in the United States and worldwide. The most important consideration for the treatment of anal cancer is preservation of organ function. Over the past many decades, significant progress has been made in the treatment of both localized and metastatic anal cancer.

EPIDEMIOLOGY

Although anal cancer is an uncommon malignancy, the incidence of anal cancer has been rising steadily over the past several decades. The median age of diagnosis is 61 and the risk of developing anal cancer increases with increasing age. Between 2001 and 2015, the incidence of anal squamous cell cancer increased at a rate of 2.7% per year with the risk being more pronounced in older women and young black men. Furthermore, there has been a tripling of distant-stage disease and a doubling of regional (nodal)-stage disease during the same time frame. The incidence of anal cancer in certain populations such as men who have sex with other men (MSM) and HIV-infected patients has been estimated to be as high as 37 per

100,000, similar to the incidence of cervical cancer prior to the initiation of wide spread screening.

ETIOLOGY AND RISK FACTORS

Several important risk factors have been identified that are associated with the development of anal cancer:

- Human papillomavirus (HPV): HPV infection is one of the most important sexually transmitted diseases (STDs) and has been significantly associated with development of premalignant and malignant lesions of the anus. Epidemiologic studies have shown that >90% of anal squamous cell carcinomas (SCCs) are associated with HPV infection. Although a variety of HPV strains have been found in the anogenital tract, HPV 16 and 18 are the most common strains associated with the development of anal cancer. Early results from HPV-vaccination trials suggest a significant utility in preventing HPV infection as well as reduction in the development of premalignant HPV-associated lesions. Furthermore, history of cervical cancer (which is also associated with HPV infection) is also associated with the development of anal cancer.
- Sexual activity: Sexual activity is an important risk factor not only for the development of anal cancer but also for the development of HIV and HPV infections, both of which are also associated with the development of anal cancer. History of STDs (gonorrhea, syphilis, herpes simplex 2, or chlamydia), 10 or more sexual partners, receptive anal intercourse, and MSM have been associated with the development of anal cancer.
- HIV infection: It is unclear whether HIV infection has a direct effect on the development of anal cancer or if it is mediated through concurrent HPV infection. In a recent report, the incidence of anal cancer per 100,000 person-years was 131 for HIV-infected MSM, 46 for other HIV-infected men, and 2 for HIV-uninfected men. Furthermore, the risk of developing

premalignant and malignant anal lesions is higher in HIV-infected patients regardless of sexual orientation.

- Chronic immunosuppression (not HIV-related): Chronic immunosuppression such as after organ transplantation is also associated with development of premalignant and malignant anal lesions.
- Cigarette smoking: Risk of anal cancer development is elevated in smokers, especially in current smokers.

ANATOMY AND PATHOLOGY

The anal canal is approximately 2.5 to 3.5 cm in length. It begins at the puborectalis muscle at the apex of the anal sphincter complex and ends at the anal verge where the squamous mucosa blends with the perianal skin. The dentate line divides the anal canal and demarcates the transition from the proximal glandular (or columnar) mucosa to the distal squamous mucosa. The anal margin is commonly defined as an area within 5 cm of the anal verge.

The lymphatic drainage of the anal cancer is dependent upon the location with respect to the dentate line. Anal tumors arising above the dentate line drain primarily to the mesorectal and internal iliac nodes. Tumors arising below the dentate line may also spread to the superficial inguinal and external iliac nodes.

Several histologic types of epithelial malignancies arise within the anal canal including SCC, adenocarcinoma, and neuroendocrine carcinoma. Other much more rare histologies include Bowen disease, extramammary Paget, and melanoma which are more common at the anal margin.

SCCs are characterized into keratinizing and nonkeratinizing. SCCs that develop below the dentate line are keratinizing and those that develop above the dentate line are nonkeratinizing. The fourth edition of the WHO classification system does not utilize modifiers such as keratinizing, nonkeratinizing, or basaloid; instead all

subtypes are included under SCC. Cancers arising from the columnar mucosa typically develop into adenocarcinomas.

CLINICAL PRESENTATION

The most common presenting symptom is rectal bleeding (45%). Anorectal pain or mass-like sensation may also occur (30%). Other symptoms include anorectal pruritus, discharge, and changes in bowel habits. Frequently, rectal bleeding and pruritus may be attributed to hemorrhoids and can delay diagnosis of anal cancer. Up to 20% of patients may not have any symptoms at all.

MEDICAL WORKUP

Pretreatment staging includes physical examination, digital rectal examination (DRE) to palpate the tumor, anoscopy and biopsy of the primary tumor, computed tomography (CT) scan of the chest, CT or magnetic resonance imaging (MRI) of the abdomen and pelvis, and positron emission tomography (PET) scan. For women, a gynecologic examination is also highly recommended to screen for cervical cancer or premalignant lesions.

PROGNOSTIC FACTORS

- The size of the primary lesion has been shown to be one of the most significant factors in predicting local control and survival for lesions confined to the pelvis. The 5-year survival rate based on T stage is as follows: T1—86%, T2—86%, T3—60%, T4—45%.
- The presence or absence of lymph nodes also has been shown to impact survival. The 5-year survival in node-positive versus node-negative patients is 54% versus 76%.
- The most significant prognostic risk factor for overall survival is the presence or absence of extrapelvic metastases.

- High viral load HIV and low $CD4^+$ count in some series have predicted for survival and local control.

TREATMENT

Stage I

Per the AJCC eighth edition, stage I anal cancer is defined as T1N0M0. Treatment options for these patients include local excision or definitive chemoradiation (as for stage II-IIIB, below). If local excision is to be pursued, careful patient selection is paramount. Patients with very favorable (well-differentiated, not involving the sphincter), small (<1-2 cm) superficially invasive tumors, with ≤3 mm basement membrane invasion and ≤7 mm horizontal spread, are good candidates for local excision. Retrospective studies have shown good local control and survival with this approach and definitive chemoradiation can be reserved for salvage treatment, if necessary. If local excision is pursued, close surveillance is crucial to detect recurrences early.

Stage II-IIIB

Prior to publication of Nigro et al in 1974, abdominoperineal resection (APR) was the standard of care for anal canal cancer. Local control with APR for node-negative patients was approximately 70% and survival was approximately 50%. Inguinal nodal involvement led to a significant decrement in survival (10%-20%). Given that three patients achieved a complete remission (CR) on the Nigro et al study despite the low radiation doses utilized, chemoradiotherapy become the standard of care in order to preserve the sphincter. Hence, APR is generally reserved as salvage for locoregional recurrence.

Radiation modalities for anal cancer include external beam radiotherapy (three-dimensional conformal radiotherapy, intensity-modulated radiotherapy [IMRT]), and brachytherapy. Over the past

several decades, radiation therapy techniques have evolved significantly, especially with respect to incorporation of IMRT for definitive chemoradiation, which has become the new standard of care. IMRT is a technically complex treatment modality and requires experience and expertise on the part of the treating radiation oncologist. RTOG 0529 was a phase II trial evaluating the role of IMRT in patients with anal cancer and showed a reduction in grade 2+ hematologic, grade 3+ dermatologic, and gastrointestinal toxicities. Importantly, it showed there was a high rate of pretreatment planning revisions echoing the complexity in IMRT treatment planning. Several consensus contouring guidelines are available to aid treating physicians so that all areas at risk for harboring microscopic disease are adequately treated.

The Wayne State/Nigro regimen of concurrent chemotherapy (5-FU/mitomycin C-C) with moderate-dose radiotherapy (30 Gy in 15 treatments) was developed as a presurgery strategy to reduce the risk for local recurrence. Given that three patients developed CR, definitive chemoradiation has been adopted as an organ-preservation strategy and reserving APR for salvage. Current treatment strategy for locally advanced anal canal cancer includes concurrent chemotherapy (preferred regimen: 5-FU [1000 mg/m^2 days 1-4, 29-32] and mitomycin C-C [10-15 mg/m^2 day 1]) and radiation (50-58 Gy in 25-29 treatments). No prospective evidence has shown improvement in local control with dose escalation beyond 58 Gy. Several prospective trials have shown good local control and survival in patients with locally advanced anal cancer. Different trials with their outcomes are shown in Table 11.1.

TABLE 11.1

Summary of Trial Outcomes for Anal Cancer

Trial	Eligibility	Treatment Arms	% CR	% DFS	% LC	% OS
EORTC	T3/4 or N+	RT alone: 45 Gy + response-based boost (15-20 Gy)	54		55	64

Trial	Eligibility	Treatment Arms	% CR	% DFS	% LC	% OS
		RT with concurrent chemotherapy (5-FU/MMC)	80		66	69
RTOG 87-04	T1-4, N0-3	RT (45 Gy) with concurrent 5-FU	85	51	59	67
		RT (45 Gy) with concurrent chemotherapy (5-FU/MMC)	92	73	84	76
RTOG 98-11	T2-4, N0-3	RT (45 Gy + 10-14 Gy boost) with concurrent chemotherapy (5-FU/MMC)		68	80	78
		Induction chemotherapy (5-FU/cisplatin) + RT with concurrent 5-FU/cisplatin		58	74	71
ACT I	T1-4, N0-3	RT alone: 45 Gy + response-based boost (15-25 Gy)	30	24	41	36
		RT with concurrent chemotherapy (5-FU/MMC)	39	36	66	42
ACT II	T1-4, N0-3	RT (50.4 Gy) with concurrent chemotherapy (5-FU/MMC)	91	69		79
		RT (50.4 Gy) with concurrent chemotherapy (5-FU/cisplatin)	90			
		RT (50.4 Gy) with concurrent chemotherapy (5-FU/MMC) + maintenance 5-FU/cisplatin	91	70		76
		RT (50.4 Gy) with concurrent chemotherapy (5-FU/cisplatin) + maintenance 5-FU/cisplatin	90			
ACCORD-03	Tumor >4 cm or N+	RT (15 Gy boost) with concurrent chemotherapy (5-FU/cisplatin)		77	84	
		RT (20-25 Gy boost) with concurrent chemotherapy (5-FU/cisplatin)		73	78	
		Induction chemotherapy followed by RT (15 Gy boost) with concurrent chemotherapy (5-FU/cisplatin)		70	72	
		Induction chemotherapy followed by RT (20-25 Gy boost) with concurrent chemotherapy (5-FU/cisplatin)		82	88	

Adapted from Martin D, Balermpas P, Winkelmann R, et al. Anal squamous cell carcinoma – State of the art management and future perspectives. *Cancer Treat Rev*. 2018;65:11-21.

Chemoradiotherapy Versus Radiation Therapy Alone

Two trials so far have examined the role of radiotherapy with and without chemotherapy in the nonoperative setting:

One major trial was conducted by the Anal Cancer Trial Working Party of the United Kingdom Coordination Committee on Cancer Research, where 585 patients with SCC of anal canal (T1-T4) were randomized to receive either radiation or radiation combined with 5-fluorouracil (1000 mg/m^2 for 4 days or 750 mg/m^2 for 5 days) during the initial and final weeks of radiation along with mitomycin C (12 mg/m^2) on day 1 of the first course. The same regimen of radiotherapy was given to both groups: 45 Gy in 20 to 25 fractions over 4 to 5 weeks. The clinical response was assessed 6 weeks after initial treatment. Chemoradiotherapy was associated with significant decrease in local failure (59% vs 36%) after 42 months follow-up. The combined modality was associated with more morbidity in the acute setting compared to radiation alone. The rate of morbidity in the late setting was comparable, however. Overall survival was interestingly similar in the two groups.

The second major trial that compared radiation to combined modality therapy was conducted by the European Organization for the Research and Treatment of Cancer, which randomly assigned 110 patients with locally advanced anal cancer (T3-T4 or N1-N3) to either radiotherapy alone or combination of radiotherapy and concurrent chemotherapy from 1987 to 1994. Chemotherapy consisted of infusional 5-fluorouracil (750 mg/m^2/d on days 1-5 and 29-33) plus mitomycin C (15 mg/m^2) on day 1 only. Radiotherapy consisted of 45 Gy in 5 weeks with a daily dose of 1.8 Gy. In case of partial or complete response after 6 weeks of rest, a boost of 20 or 15 Gy was given, respectively. Chemoradiotherapy was associated with a significantly higher number of pathologically complete responses (80% vs 54%). The locoregional control rate improved by 18% at 5-year interval and the colostomy-free rate also increased by 32% with the combined modality therapy. Severe side effects were very similar with the exception of anal ulcers that were more frequent in the combined modality treatment arm.

The Role of Mitomycin C

In a joint trial from the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group, 310 patients with anal cancer were randomly assigned to combined modality therapy with or without mitomycin C per the Wayne State regimen from 1988 to 1991. Patients who received mitomycin C were shown to have significantly higher 4-year colostomy-free survival (71% vs 59%) and disease-free survival (DFS) (73% vs 51%). Therefore, although mitomycin C is not known to have very high antitumor activity against SCCs and can cause debilitating side effects in the kidney, lungs, or bone marrow, its use in a definitive regimen is considered justified. It should be noted however that overall survival was not statistically significantly different in the two groups.

Mitomycin C Versus Cisplatin

The RTOG 98-11 was a phase III randomized controlled trial that compared treatment of anal cancer using 5-fluorouracil plus mitomycin C and radiation versus 5-fluorouracil plus cisplatin and radiation. Six hundred eighty-two subjects were enrolled between 1998 and 2005. The participants assigned to the mitomycin C–based group received 1000 mg/m^2 of 5-fluorouracil on days 1 through 4 and 29 through 32 plus 10 mg/m^2 of mitomycin C on days 1 and 29 plus 45 to 59 Gy of radiation. The participants assigned to the cisplatin-based group received 1000 mg/m^2 5-fluorouracil on days 1 through 4, 29 through 32, 57 through 60, and 85 through 88 plus 75 mg/m^2 cisplatin on days 1, 29, 57, and 85 plus 45 to 59 Gy of radiation starting on day 57. The patients were followed up for a median of 2.5 years. The 5-year DFS rate was 60% in the mitomycin C–based group versus 54% in the cisplatin-based group (P = .17). The 5-year overall survival rate was 75% in the mitomycin C–based group and 70% in the cisplatin-based group (P = .10). The 5-year rate of locoregional recurrence and distal metastasis were 25% and 15%, respectively, in the mitomycin C–based group and 33% and 19%, respectively, in the cisplatin-based group. It is worth mentioning that the rate of colostomy-free survival was significantly higher for

mitomycin C–based group compared to cisplatin-based group (P = .02). In addition, the mitomycin C–based group endured more severe hematologic toxicity (P < .001). Overall, the cisplatin-based regimen failed to show improvement in DFS, but it did result in a significantly higher colostomy rate.

The long-term update of this trial suggested that concurrent chemoradiation with 5-fluorouracil and mitomycin C had a statistically better DFS and overall survival compared to 5-fluorouracil and cisplatin plus radiation (5-year DFS 67.8% vs 57.8% P = .006, 5-year overall survival 78.3% vs 70.7% P = .026). Therefore, based on the result of the trial, mitomycin C–based regimen remains the preferred standard of care.

The ACT II trial, a randomized phase III open-label trial, enrolled 940 subjects with SCC of the anus without metastatic disease and randomly assigned them to one of four groups to receive either 12 mg/m^2 mitomycin C on day 1 or 60 mg/m^2 cisplatin on days 1 and 29 with 1000 mg/m^2 5-fluorouracil per day on days 1 through 4 and 29 through 32 plus 28 daily fractions of radiation for a total of 50.4 Gy with or without two courses of maintenance chemotherapy (5-fluorouracil and cisplatin on weeks 11 and 14). Median follow-up was 5.1 years. In the mitomycin C–based group, 90.5% of subjects had a complete response at 26 weeks versus 89.6% in the cisplatin-based group. Toxic effects were similar in all groups. These data suggest that mitomycin C–based regimen should remain the standard of care, but cisplatin-based therapy could also be a reasonable alternative.

Capecitabine in Place of 5-Fluorouracil

EXTRA trial is a phase II study, where 31 patients were enrolled and were given 12 mg/m^2 mitomycin C on day 1 and capecitabine on each radiation treatment day (825 mg/m^2 twice daily). Four weeks after completion of chemoradiation, 77% of patients had a complete clinical response and 16% had partial response. There were no

treatment-related deaths. After a median follow-up of 14 months, locoregional relapse of cancer occurred in only three subjects.

A retrospective study of 105 patients with nonmetastatic squamous cell anal carcinoma investigated the effectiveness of capecitabine compared to 5-fluorouracil. Forty-seven patients were given 750 mg/m^2 of continuous 5-fluorouracil on days 1 to 5 and 29 to 33, 10 mg/m^2 mitomycin C on day 1, and radiation. Fifty-eight patients were given 825 mg/m^2 capecitabine twice daily on weekdays, 10 mg/m^2 mitomycin C on day 1, and radiation. In the fluorouracil-treated group, 89.1% of subjects achieved complete response. In the capecitabine-treated group, 89.7% achieved complete clinical response. The 3-year overall survival was 78% in the 5-fluorouracil group and 86% in the capecitabine-treated group. Although this was not a head-to-head trial, this retrospective analysis showed that capecitabine could be just as effective as 5-fluorouracil in treatment of nonmetastatic squamous cell anal cancer.

Treatment of Anal SCC in HIV Patients

Another retrospective study compared the compliance, toxicity, and clinical outcome of chemoradiation for anal cancer in HIV-positive individuals treated with antiretrovirals and HIV-negative individuals between 1997 and 2008. Patients received standard of care 5-fluorouracil and mitomycin C along with radiation. Acute grade 3/4 toxicities were not statistically different. In addition, complete response, 5-year local control rate, and overall survival rate were also not significantly different between the two groups.

In general, patients with HIV are treated similarly to non–HIV-positive patients. A large retrospective study collected treatment data on 42 HIV-positive patients and compared it to the outcome in 100 HIV-negative patients with anal cancer who were treated between 1997 and 2015 in a single-center experience. These patients received standard chemoradiation with concurrent 5-fluorouracil and mitomycin C with 5-fluorouracil scheduled for the first and fifth weeks of radiation. The difference in complete response, 5-year local

failure rate, and 5-year distant failure rate as well as 5-year overall survival were not statistically significant in the two groups. However, HIV-positive subjects had a lower 5-year cancer-specific survival than the HIV-negative group in the univariate analysis (80.5% vs 93.8%, $P = .029$). It should be noted however that this is not a randomized clinical trial. It was concluded by the authors of the study that tolerance and clinical outcome were comparable between HIV-positive and HIV-negative subjects after standard chemoradiotherapy.

PERSISTENT OR RECURRENT SCC

For patients with anal SCC who underwent definitive chemoradiation and had either locally recurrent or residual disease, APR is the treatment of choice. In a retrospective study, 185 patients with anal SCC who were treated with either radiation or chemoradiotherapy definitively, 42 patients developed local failure and required some form of salvage therapy. Twenty-three patients underwent APR and three patients underwent local excision of the residual tumor. The 5-year overall survival and the locoregional control rates were 45% and 43%, respectively.

TREATMENT OF OTHER HISTOLOGIES/SUBTYPES OF ANAL CANCER

Patients with anal adenocarcinomas should be treated according to the rectal cancer protocol as outlined in colorectal cancer chapter.

Small cell carcinomas or poorly differentiated neuroendocrine tumors are rare entities with no standard treatment. If localized, chemoradiation can be pursued. Radical resection does not always prove helpful as these tumors are fast-growing and have significant rate of distant recurrence. If surgical treatment is used as an option,

adjuvant systemic therapy is highly recommended due to high risk of relapse. There are no randomized clinical trials due to rarity of these cancer types. Our approach is based on extrapolation of data from small cell lung cancer studies. For those with advanced disease, chemotherapy as first-line based on small cell lung cancer studies and immunotherapy as second-line can be used. Chemotherapy typically includes a platinum-based agent plus etoposide.

Tumors arising in the perianal skin are typically SCCs and treatment of these tumors is controversial. Most clinicians treat these tumors similar to anal cancer (chemoradiation). However, when there is a clear separation between the anal verge and the anal margin cancer, treatment akin to treatment of skin cancer is reasonable (local therapy alone).

Stage IV Anal SCC

First-Line Chemotherapy

For patients with advanced/metastatic anal SCC, the recommended first line of therapy is paclitaxel plus carboplatin rather than cisplatin plus 5-FU. In the InterAACT trial, patients with previously untreated advanced anal SCC were assigned to either AUC 5 of carboplatin on day 1 of the cycle plus weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15) every 28 days or 60 mg/m^2 of cisplatin on day 1 of each cycle plus 1000 mg/m^2 of 5-FU on days 1 through 4 in a 21 day cycle. The carboplatin/paclitaxel group had similar response rate to cisplatin/5-FU group (59% vs 57%). However, the carboplatin/paclitaxel group had a higher median overall survival (20 vs 12.3 months) and a much better toxicity profile with reduced serious adverse events (36% vs 62%).

Role of Immunotherapy in Treatment of Anal SCC

In a prospective phase II trial, nivolumab was administered at a dose of 3 mg/kg intravenously every 14 days to patients with anal SCC, regardless of the programmed cell death ligand 1 (PD-L1)

expression. Overall, 39 subjects were enrolled. Nine subjects demonstrated objective responses to immunotherapy, 2 had complete response, and 17 had stable disease. It should be noted that the median number of cycles delivered was six for this population. Median PFS was noted to be 4.1 months and median overall survival was 11.5 months.

As part of another trial, KEYNOTE-028, pembrolizumab was administered intravenously at a dose of 10 mg/kg every 14 days for up to 2 years in 25 patients with PDL-1–positive anal cancer. Four subjects among the 25 patients had confirmed partial responses and 10 subjects had stable disease.

Role of Radiation in Metastatic Anal SCC

Radiotherapy plays an important role for patients with metastatic anal cancer. For patients who have oligometastatic (≤5 metastatic lesions) anal cancer, consideration should be placed on treating these patients with curative intent: definitive chemoradiation with metastasis directed local therapy (surgical resection or stereotactic body radiotherapy). Emerging data suggest that control of all foci of metastatic disease can lead to favorable survival outcomes. For patients who have widely metastatic anal cancer, treatment of pelvic tumor and metastatic deposits should be undertaken with palliative intent (30 Gy in 10 treatments, 20-25 Gy in 5 treatments).

Toxicity

Management of acute and late toxicities during and after definitive chemoradiotherapy is crucial to optimize treatment outcomes.

Acute Toxicity

Toxicities during and soon after completion of chemoradiation are due to both chemotherapy and radiotherapy and require multidisciplinary management. These toxicities include hematologic (neutropenia, thrombocytopenia, anemia), dermatologic (dermatitis), gastrointestinal (nausea/vomiting, abdominal pain, proctitis,

increased stool frequency/urgency), and genitourinary (urinary frequency, urinary urgency, vaginitis). Majority of these toxicities can be managed on an outpatient basis; however, some including neutropenic fever and severe radiation dermatitis may require hospitalization. It is important to continue radiotherapy and minimize treatment breaks whenever possible (even if chemotherapy needs to be held). Acute toxicity-related deaths with modern treatment and supportive care is low (<5%).

Late Toxicity

Late toxicities have not been well characterized in the literature. Important toxicities to consider include dermatitis, proctitis, rectal bleeding, fecal incontinence, fistula formation, urinary frequency/urgency, hematuria, vaginal stenosis in women and erectile dysfunction in men, cytopenias, and secondary malignancies (myelodysplastic syndrome, bladder cancer, soft tissue sarcoma, etc). Majority of late toxicities are grade 1 or 2, and grade 3+ toxicities are uncommon (<15%). With advanced radiation treatment planning, the risk of requiring an APR due to late toxicity is <10%.

Follow-Up

Strict surveillance and follow-up after completion of definitive anal cancer treatment is crucial in order to identify not only the patients who do not achieve complete regression but also to identify recurrences as early as possible. After completion of initial therapy, patients must be evaluated at 8 to 12 weeks with DRE and high-resolution anoscopy. MRI rectum is optional but highly recommended. Patients with persistent disease should be reevaluated in 4 weeks to see if further regression occurs. In the ACT II trial, 72% of patients who did not show a CR at 11 weeks achieved a complete response by 26 weeks. If CR is achieved, patients should undergo DRE, high-resolution anoscopy, and inguinal lymph node palpation every 3 to 6 months for 5 years. For patients with stage II/III disease, annual CT chest/abdomen/pelvis with contrast is recommended for 3 years. Should a concern for recurrence arise

during follow-up, a biopsy is necessary, and if recurrence is histologically confirmed, restaging scans including MRI rectum and PET/CT should be done. Salvage APR should be considered in patients with biopsy-confirmed recurrence.

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12

Breast Cancer

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INTRODUCTION

Breast cancer is now the most commonly diagnosed cancer worldwide, and it accounts for 25% of all cancers diagnosed among women. It is second only to lung cancer as the leading cause of death from cancer in women in North America. When diagnosed early, breast cancer can be treated primarily using surgery, radiation, and systemic therapy. In Western countries, at the time of diagnosis more than 90% of patients will have only localized disease. But in many other parts of the world, about 60% of patients will have locally advanced or metastatic disease at the time of diagnosis.

EPIDEMIOLOGY

- In the United States, as per the American Cancer Society (ACS), in 2021, an estimated 281,550 women and 2650 men will be diagnosed with breast cancer.
- In addition, about 49,290 new cases of noninvasive (in situ) breast cancer will be diagnosed in 2021.
- In 2021, 43,600 women and 530 men are expected to die of breast cancer in the United States.
- As per the International Agency for Research on Cancer, about 2.3 million women had a diagnosis of breast cancer worldwide

in 2020 and more than half a million died globally from breast cancer.
- A US woman's lifetime risk of developing breast cancer is one in eight or about 13%.
- There are more than 3.8 million breast cancer survivors in the United States in 2021.

RISK FACTORS

The risk factors for developing breast cancer in women are listed in Table 12.1. The etiologies of most breast cancers are unknown and sporadic. About 5% to 10% of breast cancers are familial or hereditary.

TABLE 12.1

Risk Factors for Breast Cancer in Women

Increasing age
Family history of breast cancer at a young age
Genetic mutations such as BRCA1 or BRCA2 mutations
Increased mammographic breast density
Early menarche
Late menopause
Nulliparity
Older age at first child birth
Increased body mass index
History of atypical lobular hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ, or flat epithelial atypia
Prior breast biopsies
Long-term postmenopausal estrogen and progesterone replacement
Prior thoracic radiation therapy younger than 30 y

Genetics (For More Details Refer to Chapter 44 on Genetics)

- About 5% to 10% of all women with breast cancer may have a specific mutation in a single gene that is responsible for the

breast cancer, with the most common mutations occurring in the BRCA1 or BRCA2 genes. Other genes implicated with breast cancer are PTEN (associated with Cowden syndrome), TP53 (associated with Li-Fraumeni syndrome), CDH1 (associated with hereditary diffuse gastric cancer syndrome), STK11 (associated with Peutz-Jeghers syndrome), PALB2, CHEK2, and ATM.

- Individuals with these hereditary syndromes may develop cancers early in life or multiple cancers, including bilateral breast cancer.
- Mutations of BRCA1 (chromosome 17q21) and BRCA2 (chromosome 13q12-13q13) are responsible for 85% of hereditary breast cancer. These genes are involved in DNA repair.
- Specific mutations of BRCA1 and BRCA2 are more common in women of Ashkenazi Jewish ancestry.
- Overall prevalence of disease-related mutation in BRCA1 has been estimated at 1 in 300, while BRCA2 at 1 in 800.
- The cumulative risk estimates for developing breast cancer by age 80 years were 72% for *BRCA1* carriers and 69% for *BRCA2* carriers.
- The cumulative risk of a contralateral breast cancer within 20 years after a first breast cancer was 41% for *BRCA1* mutation carriers and 21% for *BRCA2* mutation carriers.
- BRCA-related breast cancer is more likely to be triple negative particularly in the setting of BRCA1 mutations.
- The cumulative risk estimates for developing ovarian cancer by age 80 years were 44% for *BRCA1* mutation carriers and 17% for *BRCA2* mutation carriers.

Indications for Genetic Testing

All patients should have a basic assessment for risk of a hereditary breast/ovarian cancer syndrome including documentation of personal and family history (both paternal and maternal sides) of malignancy. All patients with high risk for a hereditary syndrome

based on personal/family history and age at diagnosis should undergo genetic counseling before undergoing the genetic test. The genetic counseling visit is an important step in addressing the patient's goals of testing and is an opportunity to address misconceptions/limitations of genetic testing. There are three possible outcomes of genetic testing for the BRCA mutations: positive, variant of uncertain significance, or negative. A negative result indicates no increased risk of breast cancer due to a germline mutation. A variant of uncertain significance (indeterminate) test result indicates that no conclusive evidence exists to indicate that the mutation does or does not carry an increased risk of the development of breast cancer due to an inherited genetic mutation. A positive result indicates that there exists a mutation in the patient's genes that has been associated with an inherited risk of developing breast cancer. In general, patients with a history suggestive of a single inherited cancer syndrome should have testing sent for that specific syndrome.

Multigene testing may be cost effective and efficient if multiple different inherited cancer syndromes could be considered based on the history or if single gene testing is negative in a patient with a compelling personal or family history suggestive of an inherited cancer syndrome. One concern with the multigene testing approach is the increased likelihood of detecting a variant of uncertain significance. This also increases the importance of appropriate genetic counseling in conjunction with genetic testing such that results are interpreted in the appropriate manner.

As per NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic (Accessed January 2022), the following are examples of patient with a personal history of breast cancer who should be recommended to undergo further genetic risk evaluation/testing. Full details can be found at NCCN.org.

- Personal diagnosis of early onset breast cancer (age ≤45)
- Personal diagnosis of breast cancer from age 46 to 50 AND

    - unknown or limited family history
    - multiple primary breast cancers
    - at least one relative* with a history of breast, ovarian, pancreatic or prostate cancer
- Diagnosed at any age with:
    - ≥1 close blood relative with breast cancer diagnosed at age ≤50 years or ovarian, pancreatic, metastatic, intraductal/cribriform histology or high/very high risk group prostate cancer at any age
    - ≥3 total diagnoses of breast cancer in a patient and/or close blood relatives
- Personal history of triple negative (ER-, PR-, HER2-) breast cancer
- Personal history of male breast cancer OR family history of male breast cancer in at least one relative*
- Personal history of lobular breast cancer and known personal or family history of diffuse gastric cancer
- History of Ashkenazi Jewish ancestry

*Should be a first, second or third degree blood relative

Management of Patients With Positive BRCA Test

Management recommendations for patients with a known genetic mutation are highly individualized and should be made by an expert. General recommendations include the following as per National Comprehensive Cancer Network (NCCN) Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic (Accessed January 2022):

- Breast awareness starting age 18 years.
- Clinical breast examination every 6 to 12 months, starting at age 25 years.
- Breast magnetic resonance imaging (MRI) with contrast starting at age 25 years or earlier based on family history or mammogram with consideration of tomosynthesis if breast MRI is not available.
- Annual mammogram with consideration of tomosynthesis and annual breast MRI with contrast from age 30 to 75 years.
- Discuss option of bilateral prophylactic mastectomy on a case-by-case basis, since it could prevent breast cancer in >90% of

patients with known BRCA1 or BRCA2 mutation.

- Recommend risk-reducing bilateral salpingo-oophorectomy (RRBSO) ideally between the ages of 35 and 40 years or after completion of childbearing. BSO alone will reduce breast cancer risk by about 50%, but it may vary depending upon the specific genes and prevents ovarian cancer by about 95%.
- Patients who defer RRBSO may consider concurrent transvaginal ultrasound and blood test such as CA-125, although it is not sufficiently sensitive or specific. This can be done at the discretion of the clinician, starting from the age of 30 and 35 years or 5 to 10 years prior to the earliest age of ovarian cancer in family history.

CHEMOPREVENTION

Risk Assessment

There are many risk models available to assess a woman's risk for sporadic breast cancer, which accounts for 90% of the breast cancer. One of the most commonly used models is the modified Gail risk model (https://www.cancer.gov/bcrisktool). It is a statistical model that calculates a woman's absolute risk of developing breast cancer in the next 5 years and during their lifetime by using the following criteria:

1. Age
2. Race/ethnicity
3. Age at menarche
4. Age at first live birth
5. Number of previous biopsies
6. History of atypical ductal hyperplasia (ADH)
7. Number of first-degree relatives with breast cancer

The original Gail model was revised to incorporate race as a risk factor to allow for more accurate assessment in women of non-

Caucasian ethnicity. This model is not intended to be used in patients with age ≤35 years or in patients with an existing history of invasive cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS). It underestimates the risk of breast cancer in a person with hereditary breast cancer.

The Tyrer-Cuzick model is another widely used model. It takes into account personal risk factors such as body mass index, hormonal exposure, breast density, and benign breast disease in conjunction with a comprehensive family history including second- and third-degree relatives, their age at diagnosis, ovarian cancer, male breast cancer, family members without cancer, and genetic testing information. It provides a predicted 10-year and lifetime risk of developing invasive breast cancer. However, it has been found to overestimate the risk in women with atypia. Other risk models include the Claus, BOADICEA, and BRCAPRO models.

Prevention Studies

The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1)

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study showed a 49% reduction in the incidence of invasive breast cancer in high-risk subjects (based upon the Gail risk model) who took tamoxifen at a dose of 20 mg daily for 5 years. Women eligible for this trial were at least 35 years of age and were assessed to have an absolute risk of at least 1.66% over the period of 5 years using the Gail model or a pathologic diagnosis of LCIS. Notable adverse events associated with tamoxifen therapy in this study include increased risk of endometrial cancer (particularly in women aged 50 years or older), cataracts, and venous thromboembolism (VTE) (both deep venous thrombosis and pulmonary embolism). An update of results with 7 years of follow-up was published in 2005, showing a continued statistically significant improvement in the rate of invasive breast cancer (risk ratio 0.57) and noninvasive breast cancer (risk ratio 0.63) with tamoxifen compared to placebo.

The use of tamoxifen for breast cancer risk reduction should be considered after weighing the risk-benefit ratio for each patient. Women with a life expectancy of ≥10 years and no diagnosis/history of breast cancer who are considered at increased risk of breast cancer should receive individualized counseling to decrease breast cancer risk.

NSABP P-2: Study of Tamoxifen and Raloxifene

In the NSABP P-2 study, tamoxifen 20 mg daily was compared with raloxifene 60 mg daily in postmenopausal women with high risk of developing breast cancer (Gail risk model estimate of 5-year breast cancer risk of at least 1.66%). The results of the study revealed that raloxifene was equivalent to tamoxifen in preventing invasive breast cancer (about a 50% reduction). Raloxifene has a better side effect profile, which resulted in a lower incidence of uterine hyperplasia, hysterectomy, and cataracts and a lower rate of thromboembolic events. A 2010 update of the NSABP P-2 study after a median follow-up of nearly 7 years confirmed no statistical difference between invasive breast cancer events in the tamoxifen- and raloxifene-treated patients. In addition, significant reductions in risk of endometrial cancer/hyperplasia as well as thromboembolic events were reported with raloxifene compared to tamoxifen.

Aromatase Inhibitors for Risk Reduction

Aromatase inhibitors (AIs) are known to decrease the incidence of contralateral breast cancer when used in the adjuvant setting. These data led to the investigation of AI as chemoprevention for women at high risk for developing breast cancer.

The MAP.3 trial evaluated the role of exemestane in a risk reduction setting, randomizing women at increased risk for breast cancer (based on age 60 years or older, Gail 5-year risk score of at least 1.66%, prior ADH/lobular hyperplasia, or LCIS or DCIS status postmastectomy) to either exemestane or placebo. At a median follow-up of 3 years, it was found that exemestane reduced the

relative incidence of breast cancers by 65% when compared to placebo. Exemestane was not associated with any significant serious side effects, although hot flashes and arthritis were very common in both the exemestane and placebo groups.

In the randomized phase III IBIS-II trial, postmenopausal women with increased risk of breast cancer (defined as significant family history, history of atypical hyperplasia, or LCIS, nulliparity, or age at first birth of ≥30 years) were randomized to receive anastrozole or placebo for 5 years. Results showed a reduction in the risk of developing breast cancer (both invasive and noninvasive) of more than 50% (hazard ratio of 0.47) with the use of anastrozole compared to placebo. Musculoskeletal events and vasomotor symptoms were significantly more common in patients receiving anastrozole rather than placebo. In a 2020 update after a median follow-up of 131 months, anastrozole showed continued benefit (hazard ratio = 0.51; $P < .0001$) with no evidence of new late side effects.

Summary

In premenopausal women with increased risk of breast cancer, it is reasonable to recommend tamoxifen 20 mg daily for 5 years. In postmenopausal women, raloxifene and tamoxifen are equally effective, but raloxifene has been shown to have less side effects. AIs can also be considered, given the data from the MAP.3 and IBIS-II trials; however, the Food and Drug Administration (FDA) has not approved AIs in this setting. Any risk reduction approach should be carefully decided after a detailed risk versus benefit discussion with the patient.

BREAST CANCER SCREENING

Screening Mammograms

- Screening mammography has been shown to decrease breast cancer mortality in women between the ages of 40 and 70 years

with an absolute mortality benefit of 1% for women screened annually for 10 years.

- Potential harms associated with screening mammography include overdiagnosis and treatment of cancers that would otherwise have been clinically insignificant in a woman's lifetime as well as the unnecessary anxiety and additional testing that is associated with false-positive screening examination.
- Screening recommendations are highly variable among the different societies. The ACS recommends that women aged 40 to 44 years should have the choice to start annual mammography screening and women aged 45 to 54 years should receive annual mammograms. At age 55 years, the ACS suggests that women may switch to having mammograms every other year for breast cancer screening although annual screening may be continued if the patient desires.
- Women who are at higher than average risk of breast cancer (women with a family history of breast cancer, women with either the BRCA1 or the BRCA2 gene, women with a history of chest irradiation between the ages of 10 and 30 years, or women with a lifetime risk of breast cancer ≥20%) are recommended to initiate screening mammograms at age 25 to 30 or 10 years earlier than the age of the affected first-degree relative at diagnosis (whichever is later) or 8 years after radiation therapy, as per the American College of Radiology guidelines.
- Mammograms should be continued regardless of a woman's age, as long as she is in good health with an expected life expectancy of at least 10 years. Age alone should not be the reason to stop having regular mammograms. Women with serious health problems or short life expectancies should discuss with their doctors whether to continue having mammograms.

Digital Mammography

The diagnostic superiority of digital mammography was demonstrated in the Digital Mammographic Imaging Screening Trial published in 2005. This study concluded that the overall accuracy of digital and film mammography was similar; however, in pre- or perimenopausal women younger than 50 years or women at any age with dense breasts, digital mammography more accurately detected breast cancer.

Tomosynthesis

Digital breast tomosynthesis (DBT), commonly referred to as three-dimensional (3D) mammography, is an x-ray technique that uses a finite number of low-dose projections to reconstruct a series of thin-section images of the breast. Multiple studies have shown improved sensitivity and specificity when DBT is combined with conventional two-dimensional (2D) mammography. DBT reduces tissue overlap, thereby increasing lesion conspicuity, which in turn improves the detection of invasive breast cancer while also reducing false-positive screening recalls.

While DBT has been shown to be beneficial in all women, the degree of that benefit is dependent on breast tissue density. The greatest benefit of DBT appears to be achieved by women with heterogeneous dense breast tissue. Women with less dense breasts, predominately fatty or scattered fibroglandular tissue, have also been shown to benefit from the addition of DBT. However, in women with extremely dense breast tissue, DBT has shown limited benefit.

The addition of DBT to conventional 2D mammography increases the overall radiation dose for the screening examination by approximately twofold, however, is still within Mammography Quality Standards Act guidelines. Recently, in effort to reduce radiation from the screening examination, the FDA has approved reconstructed or “synthetic” 2D-like images to replace conventional 2D mammography. Early clinical data have shown that synthetic 2D

mammography with DBT is noninferior to conventional 2D mammography with DBT.

Magnetic Resonance Imaging

Breast MRI has a higher sensitivity but lower specificity than screening mammography. As a result, screening breast MRI has been shown to lead to more benign biopsy findings and short-interval follow-up recommendations. However, when screening breast MRI is combined with screening mammography in high-risk women, the highest sensitivity for detecting breast cancer is achieved (92.7%).

The ACS recognizes that breast MRI can be used as an adjunct to screening mammography in high-risk women, specifically women with BRCA gene mutations (along with their untested first-degree relatives), women with a lifetime risk of breast cancer exceeding 20%, women who received chest radiation between the ages of 10 and 30 years, and women with genetic predisposition for developing breast cancer such as Li-Fraumeni syndrome and Cowden and Bannayan-Riley-Ruvalcaba syndromes.

Supplemental Screening

Two additional supplemental screening techniques are gaining attention, although application is limited due to availability, insurance coverage, and utility.

Whole-breast screening ultrasound is often used for supplemental screening in women with dense breasts. However, whole-breast ultrasound has been associated with high false-positive and short-interval follow-up rates. In a high-risk population, the combined sensitivity of ultrasound with mammography is 52%, less than MRI with mammography (92.7%). Therefore, if supplemental screening is indicated, breast MRI is the better test.

Abbreviated breast MRI, also commonly referred to as fast MRI, is a supplemental screening technique available to women who do not have risk factors to qualify for full breast MRI. The abbreviated

breast MRI protocol has fewer sequences and faster acquisition and interpretation times than the full breast MRI protocols. Studies are currently being conducted to evaluate the efficacy of abbreviated breast MRI and the impact on clinical outcomes.

CLINICAL FEATURES OF BREAST CANCER

Clinical features may include a breast lump, skin thickening, dimpling of the skin, (peau d'orange), nipple inversion, retraction or changes (Paget disease), unilateral nipple discharge (clear or bloody), and new onset of breast pain. They also may have an enlarged or palpable lymph node in the axilla or supraclavicular region.

DIAGNOSIS

1. History and physical examination
2. Bilateral mammogram
3. Ultrasound for symptoms of palpable mass in breast or axilla, skin or nipple changes, or pain
4. Biopsy: Any distinct mass should be considered for a biopsy, even if the mammograms are negative
5. The standard method of diagnosis for palpable lesions is:
    - Core-needle biopsy
    - The options in nonpalpable breast lesions are:
    - Ultrasound-guided core-needle biopsy if mass identified on ultrasound
    - Stereotactic core-needle biopsy under mammographic localization for an asymmetry or calcifications only seen on mammogram
    - MRI-guided biopsy
6. Laboratory studies
    - Complete blood count, liver function tests, and alkaline phosphatase level can be considered depending upon the history and physical.
    - Routine use of breast cancer markers such as CA 27-29 and CA 15-3 is not recommended.
7. Pathology and special studies
    - Histology and diagnosis (invasive vs in situ)
    - Pathologic grade of the tumor

- Tumor involvement of the margin
- Tumor size
- Lymphovascular invasion

8. ER/PR status should be tested in all invasive tumors and biopsies of metastatic or recurrent (patients those who relapsed) lesions. As per the updated American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (2020):
    - ER/PR is considered as positive if ≥1% of tumor cell nuclei are immunoreactive.
    - For ER, if 1% to 10% of tumor cell nuclei are immunoreactive, it should be reported as ER-low positive with a recommended comment acknowledging limited data on endocrine responsiveness and the status of internal controls.
    - Testing of DCIS for ER is recommended to determine potential benefit of endocrine therapies for chemoprevention, while testing for PR is optional.
9. HER2 testing (as per updated ASCO/CAP Guidelines 2018) (Figures 12.1 and 12.2):
    - Positive for HER2 is immunohistochemistry (IHC) 3+ (defined as circumferential membrane staining that is complete, intense, and in >10% of tumor cells).

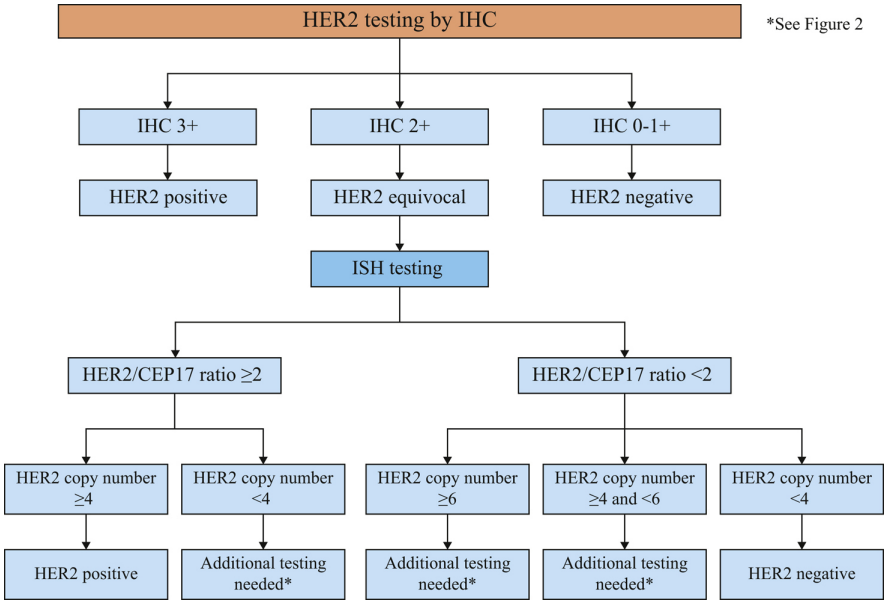

FIGURE 12.1 Usual HER2 testing algorithm.IHC, immunohistochemistry; ISH, in situ hybridization.

FIGURE 12.2 Uncommon HER2 testing scenarios.IHC, immunohistochemistry. (Adapted with permission from Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018;36(20):2105-2122. Copyright © 2018 by American Society of Clinical Oncology and College of American Pathologists.)

- Negative for HER2 is defined as IHC 0 (defined as incomplete membrane staining that is faint/barely perceptible in >10% of tumor cells) or IHC 1+ (defined as weak to moderate complete membrane staining in >10% of tumor cells).
- Equivocal for HER2 is defined as IHC 2+ (defined as weak to moderate complete membrane staining in >10% of tumor cells). For these cases, reflex HER2 testing of the invasive component by validated single-probe ISH assay should be ordered on the same specimen or on a new test with a new specimen if available, using IHC or ISH.
- The test is considered HER2-positive in cases with HER2/CEP17 ratio ≥2.0 and average HER2 copy number ≥4.0 signals per cell (ISH group 1).
- Conversely, the test is considered HER2-negative with HER2/CEP17 ratio <2.0 and average HER2 copy number <4.0 signals per cell (ISH group 5).
- Less common clinical scenarios described as ISH group 2 (HER2/CEP17 ratio ≥2.0; average HER2 copy number <4.0 signals per cell), ISH group 3 (HER2/CEP17 ratio <2.0; average HER2 copy number ≥6.0 signals per cell), and ISH group 4 (HER2/CEP17 ratio <2.0; average HER2 copy number ≥4.0 and <6.0 signals per cell) require concomitant IHC review in order to arrive at the most accurate HER2 status designation as either positive or negative. These algorithms are illustrated in Figure 12.2.

10. Indices of proliferation (eg, mitotic index, Ki-67, or S phase) can be helpful. Ki-67 can be helpful in distinguishing luminal A versus B in ER/PR-positive lesions. Lack of standardization of Ki-67 testing limits its wide utilization in clinical practice.

11. Radiographic studies are performed on the basis of the findings of the history and physical examination, diagnostic breast imaging, and blood tests. Appropriate imaging studies such as CT scan, ultrasound, MRI, or computed tomography (CT)/positron emission tomography (PET) scan can be considered as per the clinical indications. They are not routinely recommended for all patients.
    - As per the ASCO "choosing wisely" guidelines, it is not recommended that patients with DCIS or clinical stage I/II disease receive staging PET, CT, or radionucleotide bone scan as there is no clear evidence indicating benefit, and unnecessary imaging can lead to unnecessary invasive procedures/radiation exposure, overtreatment, or misdiagnosis.
    - The NCCN Guidelines® recommend that systemic imaging be considered in patients with locally advanced (stage III) patients and in those with signs or symptoms suggestive of metastatic disease.
12. Breast MRI may be helpful in determining the extent of disease and to facilitate surgical planning in the following patients (as per NCCN Guidelines®):
    - Those with heterogeneous and extremely dense mammographic tissue
    - Those with newly diagnosed invasive lobular carcinoma
    - Those with axillary nodal metastasis with unknown primary
    - Those who are candidates for neoadjuvant chemotherapy and as part of monitoring response to neoadjuvant therapy
    - Evaluating the extent of disease in known cancer patients
    - Those with multifocal and multicentric disease
    - Tumor patients with pectoralis and chest wall involvement
    - Post lumpectomy patients to evaluate residual disease (close or positive margins)
    - Those with suspected recurrence of breast cancer
    - Those with inconclusive mammographic/clinical findings
    - Those undergoing reconstruction with tissue flaps or implants
    - Those with inconclusive findings on mammogram, ultrasound, and physical examination
    - Those with pathologic nipple discharge with normal mammogram and retroareolar ultrasound (unilateral, spontaneous, from a single duct, clear or bloody color)

PATHOLOGY

Infiltrating or invasive ductal cancer is the most common breast cancer histologic type and comprises 70% to 80% of all cases.

Invasive lobular carcinoma is the second most common histologic type and comprises 15% of all cases (Table 12.2).

TABLE 12.2
Pathologic Classification of Breast Cancer

Ductal
Intraductal (in situ)
Invasive with predominant intraductal component
Invasive, NOS
Comedo
Inflammatory
Medullary with lymphocytic infiltrate
Mucinous (colloid)
Papillary
Scirrhous
Tubular
Other
Other
Undifferentiated
Lobular
In situ
Invasive with predominant in situ component
Invasive
Nipple
Paget disease, NOS
Paget disease with intraductal carcinoma
Paget disease with invasive ductal carcinoma
Other Types (not typical breast cancer)
Phyllodes tumor
Angiosarcoma
Primary lymphoma

NOS, not otherwise specified.

STAGING OF BREAST CANCER

For staging of breast cancer, the American Joint Committee on Cancer (AJCC) manual eighth edition should be followed and is the standard for cancer registries in the United States. This edition

includes separate anatomic and prognostic staging group systems for breast cancer, reflecting the importance of biomarkers in breast cancer prognosis and treatment decisions. These biomarkers provide a sense of tumor biology. The traditional anatomic stage groups (including only the "TNM" or tumor size, nodal status, and metastasis categories) should now only be used in regions of the world where biomarker tests are not routinely available. The prognostic staging system is based on populations of breast cancer patients who have been treated with standard of care therapy and hence is valid only in such patients.

This prognostic group staging system includes the TNM categories in addition to the following:

1. Histologic grade
2. HER2 status
3. ER status
4. PR status
5. Oncotype DX recurrence score (RS) (only for patients with T1-2 [<5 cm], node-negative, nonmetastatic, hormone receptor (HR)–positive, and HER2-negative cancers).

Prognostic Factors

Anatomic features such as tumor size and lymph node status are important prognostic features; however, biologic features of the tumor are equally important or possibly even more important than anatomic features.

1. Number of positive axillary lymph nodes
    - This is an important prognostic indicator. Prognosis is worse with increasing number of lymph nodes.
    - Axillary lymph node metastases ≤2 mm in size (micrometastasis) is associated with a more favorable prognosis than metastases >2 mm (macrometastasis).
    - Axillary lymph node involvement with isolated tumor cells (≤0.2 mm or < 200 cells) has prognosis similar to node-negative disease. Consequently, many guidelines recommend against using IHC to detect these cells.
2. Tumor size

- In general, tumors smaller than 1 cm have a good prognosis in patients without lymph node involvement.

3. Histologic or nuclear grade

- Patients with poorly differentiated histology and high nuclear grade have a worse prognosis than others.
- Scarff-Bloom-Richardson grading system and Fisher nuclear grade are commonly used systems. The modified Scarff-Bloom-Richardson grading system assigns a score (1-3 points) for features such as size, mitosis, and tubule formation. These scores are added and tumors are labeled low grade (3-5 points), intermediate grade (6-7 points), or high grade (8-9 points).

4. ER/PR status

- ER- and/or PR-positive tumors have better prognosis, and these patients are eligible to receive endocrine therapy.

5. Histologic tumor type

- Prognoses of infiltrating ductal and lobular carcinoma are similar.
- Mucinous (colloid) and tubular histologies have better prognosis.

6. HER2 expression

- HER2 overexpression is a poor prognostic marker, and patients with HER2 overexpression are candidates for HER2-targeted therapies. Availability of effective HER2-targeted therapies has revolutionized the treatment and outcome of HER2-positive breast cancer. Because of targeted therapies, for all practical purposes, HER2 positivity can be considered as a good prognostic feature now.

7. Gene expression profiles

- Oncotype DX is a diagnostic genomic assay based on reverse transcription polymerase chain reaction on paraffin-embedded tissue. This assay was initially developed to quantify the likelihood of cancer recurrence in women with newly diagnosed, stage I or II, node-negative, ER-positive breast cancer. The RS ranges from 0 to 100, and patients are divided into low-risk (≤15), intermediate-risk (16-25), and high-risk (≥26) groups on the basis of the expression of a panel of 21 genes. The RS determined by this assay is found to be a better predictor of outcome than standard measures such as age, tumor size, and tumor grade (Figure 12.3).

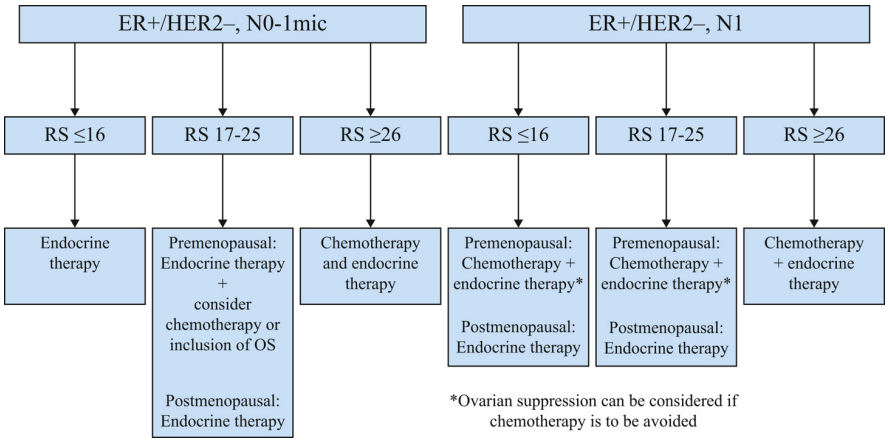

FIGURE 12.3 Oncotype DX testing algorithm.ER, estrogen receptor; RS, recurrence score.

- The Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study enrolled women who were aged 18 to 75 years with HR-positive, HER2-negative, axillary node–negative breast cancer with a tumor size of 1.1 to 5.0 cm (or 5 mm-1.0 cm plus unfavorable histological features such as high grade).
- TAILORx demonstrated excellent overall survival (OS), freedom from recurrence, and invasive disease-free survival (iDFS) at 5 years in "low-risk" patients defined as those with a RS of 0 to 10, all of whom received endocrine therapy only. Further, when patients with mid-range RS of 11 to 25 were randomly assigned to receive chemotherapy plus endocrine therapy or endocrine therapy alone, endocrine therapy was found to be noninferior to chemoendocrine therapy in terms of iDFS, freedom from disease recurrence, and OS. The study concluded that adjuvant chemotherapy was not beneficial in these patients, although some benefit of chemotherapy was found in women aged 50 years or younger with a RS of 16 to 25.
- Based on these data, a focused update to the ASCO clinical guidelines recommends that for patients with HR-positive, axillary node–negative breast cancer whose tumors have Oncotype DX RS of less than 26, there is little to no benefit from chemotherapy, especially for patients older than age 50 years. Clinicians may recommend endocrine therapy alone for women older than age 50 years. For patients aged 50 years or younger with RS of 16 to 25, clinicians may offer chemoendocrine therapy. Patients with RS greater than or equal to 26 should be considered candidates for chemoendocrine therapy.
- The RxPONDER trial investigated the role of Oncotype DX testing in women with HR-positive, HER2-negative breast cancer with one to three lymph nodes positive (Figure 12.3). Results demonstrated that postmenopausal women with these tumor characteristics and an Oncotype DX RS of ≤25 derived no benefit from chemotherapy added to endocrine therapy and can safely avoid chemotherapy treatment. However, premenopausal women with the same characteristics experienced a 45% relative risk reduction in iDFS events with the addition of chemotherapy and thus are routinely offered chemotherapy at present time. Ongoing trials will answer the question of the role of chemotherapy versus ovarian suppression and endocrine therapy in premenopausal patients with RS less than ≤25.

- Oncotype DX testing has also been studied in DCIS, where the resulting "DCIS score" quantifies the ipsilateral breast event risk for both invasive and noninvasive disease after surgical excision. This testing is largely used to assist in determining need for radiation.
- MammaPrint is a DNA microarray assay of 70 genes designed to predict the risk of recurrence of early-stage breast cancer. This testing classifies patients as low risk or high risk. There is no "intermediate" group as there is with the Oncotype. The MINDACT (Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) study was done to prospectively assess the clinical utility of the MammaPrint in selecting early-stage patients with up to three axillary lymph nodes involved for adjuvant chemotherapy. The patients in this study had both genomic and clinical risk defined, and those with discordant results (meaning low genomic risk/high clinical risk or high genomic risk/low clinical risk) were randomized to either receive chemotherapy or not. The primary endpoint of the study was survival without distant metastases in patients with high-risk clinical features and low-risk genomic features. Its long-term results approaching 9-year follow-up were published in 2021 and found that 5-year metastasis-free survival in these patients with low genomic risk was similar whether or not chemotherapy was given (absolute difference 2.6%).
- Other genomic assays available for decision-making in early breast cancer include the Breast Cancer Index (BCI), EndoPredict, PAM50 risk of recurrence score, Mammostrat, urokinase plasminogen activator, and plasminogen activator inhibitor type 1. Each of these tests is intended to help clinicians identify patients with HR-positive, HER2-negative early-stage breast cancer who have a low risk of distant recurrence. This information can then be used to aid in making decisions regarding adjuvant systemic therapy.
- As per the 2019 ASCO clinical practice guideline on "use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer," there is intermediate quality evidence for use of EndoPredict and BCI in ER/PR-positive, HER2-negative patients with node-negative breast cancer to guide decisions on adjuvant systemic therapy. For the PAM50 risk of recurrence score, the evidence is considered high quality, and recommendation for use in the above setting is strong.

Genomic Subtypes of Breast Cancer

Several distinct types of breast cancer are identified by gene expression studies. They differ markedly in prognosis and in the therapeutic targets they express (Table 12.3). The five main subtypes, known as the "intrinsic subtypes of breast cancer," are described here:

TABLE 12.3

Systemic Treatment Recommendations Based Upon Subtypes

Luminal A	Endocrine therapy alone
Luminal B (HER2 negative)	Endocrine ± chemo
Luminal B (HER2 positive)	Chemo + anti-HER2 drug endocrine therapy
HER2 positive (nonluminal)	Chemo + anti-HER2 drugs
Triple negative	Chemotherapy
Special Biologic Subtypes	
Endocrine responsive (cribriform, tubular, and mucinous)	Endocrine therapy
Endocrine nonresponsive (medullary, adenoid, and metaplastic)	Chemotherapy

- **Luminal A and B subtypes:** These subtypes express genes associated with luminal epithelial cells of normal breast tissue and overlap with ER-positive breast cancers defined by clinical assays. The luminal A subtype amounts to about 40% to 50% of cancers and has the best prognosis. These tumors are generally ER/PR positive and HER2 negative. Approximately 20% of breast cancers are of luminal B subtype, and they have worse prognosis compared to luminal A. The luminal B subtype tends to include tumors that are ER or PR positive and HER2 negative as well as those that are ER, PR, and HER2 positive. Luminal B cancers also tend to be higher grade tumors compared to luminal A cancers. Luminal A cancers are generally responsive to endocrine therapy, while luminal B tumors may benefit from a combined approach including chemotherapy and endocrine therapy.
- **HER2–enriched subtype:** This subtype comprises the majority of clinically HER2-positive breast cancers. It accounts for 10% to 15% of breast cancers. Not all HER2-positive tumors are HER2 enriched. About half of clinical HER2-positive breast cancers are HER2 enriched; the other half can include any molecular subtype including HER2-positive luminal subtypes. Those tumors that are ER/PR negative and grade 3 tend to fall into the HER2-enriched subtype.

- **Basal-like subtype:** These tumors are usually ER negative and characterized by low expression of HR-related genes. Up to 90% of triple-negative breast cancers (those that are ER negative, PR negative, and HER2 negative) are classified in the basal-like subtype. They have a more aggressive clinical course with higher risk of relapse and derive benefit from chemotherapy.
- **Normal-like subtype:** This subtype is represented in a minority of breast cancers and is similar in biomarker profile to luminal A tumors but with a gene profile more consistent with normal breast tissue rather than a luminal A tumor.

MANAGEMENT

High-Risk Lesions

Atypical Ductal Hyperplasia

- There is a four- to fivefold increase in the risk of developing breast cancer in patients with ADH.
- There is wide variation in the criteria used in the diagnosis of ADH.
- If diagnosis is made with core-needle biopsy, the presence of invasive cancer may be missed due to sampling error. As a result, surgical excision of the site of ADH is recommended.
- About 15% to 30% of cases may be "upgraded" to diagnosis of invasive cancer.
- Clinical breast examination and mammogram are the preferred screening methods; the role of MRI is under investigation and can be considered in patients with a risk calculation of >20% lifetime risk of developing breast cancer.

Lobular Carcinoma In Situ

- LCIS is not considered a form of cancer, but rather a lesion that indicates an increased lifetime risk of developing invasive breast

cancer in either breast. In the eighth edition of the *AJCC Cancer Staging Manual*, Tis (LCIS) has been eliminated, reflecting the nonmalignant nature of these lesions.

There is about 20% chance of developing breast cancer in patients within 10 years of developing LCIS.

- Classical LCIS can have surgical excision performed to ensure there is no cancer associated with the area of concern initially targeted for core biopsy.
- Pleomorphic LCIS should be excised with negative margins.
- Patients with classical LCIS can be followed up by clinical breast examination every 4 to 12 months and annual mammogram. MRI can be considered for high-risk follow-up.

Medical Management of High-Risk Lesions

Patients with high-risk lesions may be eligible for breast cancer prevention studies. Tamoxifen and raloxifene are two FDA-approved drugs for breast cancer prevention in high-risk settings. As per the MAP.3 study, exemestane was found to be effective in breast cancer prevention; however, the drug is not FDA approved for this indication. For breast cancer prevention, in premenopausal patients, tamoxifen is the drug of choice, but in postmenopausal patients, raloxifene or AIs can be used.

In the TAM-01 study, a lower dose of tamoxifen (5 mg/d) for a shorter duration of treatment (3 years) halved the risk of new breast neoplastic events in women with ADH, DCIS, or LCIS compared to placebo with limited toxicity. However, the current formulation of tamoxifen on the market is 10- or 20-mg tablets, whereas the 5-mg tablet is not available. Until a new formulation is available, cutting the tablet into two or using 10 mg on alternate days may be reasonable for chemoprevention in women with breast intraepithelial neoplasia.

Noninvasive Breast Cancer

Ductal Carcinoma In Situ

- The extensive use of mammograms has led to the increasing diagnosis of DCIS.
- Microcalcification or soft-tissue abnormality is seen in the mammogram of DCIS.
- DCIS is considered a precursor lesion for invasive breast cancer.
- Comedonecrosis and high nuclear grade have been associated with shorter time to recurrence but do not predict higher overall recurrence rates.

Treatment of DCIS

In patients with ER-positive DCIS, lumpectomy followed by radiation treatment followed by endocrine therapy for 5 years can be considered as the standard treatment approach.

- Based upon the NSABP B-24 study, in premenopausal women with ER-positive DCIS treated with lumpectomy, tamoxifen 20 mg daily for 5 years reduced the risk of breast cancer recurrence (ipsilateral and contralateral). As highlighted earlier, a lower dose of tamoxifen (5 mg/d) for a shorter duration of treatment (3 years) may also be an option based on the TAM-01 study.
- Based upon the NSABP B-35 study, in postmenopausal women with ER-positive DCIS, anastrozole 1 mg daily resulted in improvement in breast cancer–free interval for women younger than 60 years. Based on these data, AIs can be used in postmenopausal patients with ER-positive DCIS after lumpectomy.
- Mastectomy with or without lymph node evaluation can also be considered as a treatment option. In patients who undergo mastectomy, the role of endocrine therapy is limited. In selected patients, endocrine therapy can be considered for contralateral breast cancer prevention.

- Axillary lymph node evaluation is not recommended in pure DCIS without evidence of invasive cancer. In patients with DCIS on biopsy who are treated with mastectomy, a sentinel lymph node (SLN) evaluation can be considered at the time of initial surgery.
- Routine testing of HER2 is not recommended for DCIS. In the NSABP B-43 study, over 2000 women with HER2-positive DCIS were randomly assigned to receive either whole-breast radiotherapy (RT) alone or RT with two doses of trastuzumab following lumpectomy. The addition of trastuzumab to RT did not reach the protocol objective of a 36% reduction in the ipsilateral breast tumor recurrence rate. However, the trial did find a statistically nonsignificant, modest (19%) reduction in the rate of recurrence among women who received trastuzumab.

Invasive Breast Cancer

A multidisciplinary team should manage breast cancer, with the input from a radiologist, pathologist, breast surgeon, reconstructive surgeon, medical oncologist, and radiation oncologist. Other key members of the multidisciplinary team should include genetic counselors, psychologists, social workers, nurses, and care navigators.

After the diagnosis of breast cancer with a core-needle biopsy or fine-needle aspiration cytology, it is important to confirm the histology, prognostic markers, and receptors. Various treatment options should then be discussed with the patient before the treatment plan is finalized.

Surgery

There are two components to surgical management of breast cancer: removal of the breast cancer and evaluation of lymph nodes.

Patients with DCIS or invasive cancer have two options for removing breast cancer, either a mastectomy or lumpectomy. As per NSABP B-06 and European Organization for Research and

Treatment of Cancer 10801, 20-year local recurrence for mastectomy is 5%, for lumpectomy alone is 39%, and lumpectomy with radiation is 14%. Despite these differences in local recurrence, there is no survival difference seen in patients who are treated with mastectomy versus lumpectomy and radiation therapy (breast conservation therapy [BCT]) and therefore both are offered as treatment options. In some cases, despite a desire for BCT, a mastectomy may be recommended. These include a contraindication to receiving radiation, such as multicentric disease, inflammatory breast cancer, or a large tumor in a small breast where resection would leave a cosmetically unpleasing result.

As per NCCN Guidelines®, contraindications for breast-conserving therapy include the following:

- Radiation therapy during pregnancy
- Widespread disease or calcifications that cannot be incorporated by breast conservation that achieves negative margins with a satisfactory cosmetic result
- Persistent positive pathologic margin (no ink on tumor for invasive cancer, 2 mm margin for DCIS)
- Homozygous (biallelic inactivation) for ATM mutation

Women with a known genetic predisposition to breast cancer such as BRCA1 or BRCA2 have an increased risk of contralateral breast cancer or new primary ipsilateral breast cancer with breast-conserving therapy. Prophylactic bilateral mastectomy for risk reduction in these patients may be considered.

Sentinel Node Biopsy

The goal of sentinel lymph node biopsy (SLNB) is to provide prognostic information regarding the accurate pathologic staging of breast cancer. This information is used to guide additional management decisions. The SLN is defined as the main lymph node(s) that receives drainage directly from the primary tumor. SLN

mapping and resection is the preferred method for staging the clinically negative axilla as per NCCN Guidelines®.

SLNB is performed by injection of technetium-labeled sulfur colloid, blue dye, or both around the tumor, or the subareolar area. The dyes are taken up into the breast lymphatic system with a predominant pattern into the axilla. Nodes that contain dye or technetium are identified as the SLN. Identification rates of 92% to 98% of patients are the standard, especially when both techniques are used. If breast cancer were to spread, typically it would spread to the SLN first before moving to the other lymph nodes. This selective biopsy of potentially positive SLN, and sparing removal of negative lymph nodes, decreases pain, sensation loss, and lymphedema compared to traditional axillary lymph node dissection (ALND).

The ACOSOG Z0011 clinical trial showed that in patients with T1-T2 invasive breast cancer with clinically negative lymph nodes, found to have one to two positive lymph nodes on SLNB, there is no benefit in disease-free survival (DFS) or OS in performing a complete axillary node dissection. For patients who meet these criteria, a complete ALND can be potentially avoided.

Axillary Lymph Node Dissection

- ALND is complete surgical removal of level I and II axillary lymph nodes. The goal of ALND is to remove axillary burden of the disease.
- A complete axillary node dissection is associated with approximately 10% to 25% risk of lymphedema, which can be mild to severe.
- Indications:
    - Patients who present with more than 2 clinically positive lymph node(s) who undergo surgery as first line of treatment.
    - Patients with a persistent positive SLN after neoadjuvant chemotherapy.
    - Patients with N2 or N3 disease.
    - Patients with an axillary recurrence.

Reconstruction

Reconstructive surgery may be used for patients who opt for a mastectomy. It may be done at the time of the mastectomy (immediate reconstruction) or at a later time (delayed reconstruction). Patients diagnosed with early-stage breast cancer and electing to undergo a mastectomy should be offered immediate reconstruction as long as their comorbid conditions do not preclude this intervention. For patients with locally advanced or inflammatory breast cancer, undergoing mastectomy with delayed reconstruction may be the more appropriate management option.

Reconstruction can be done in one of two ways: implant based (silicone or saline implants) or an autologous tissue graft. Examples of autologous tissue grafts include transverse rectus abdominis myocutaneous flaps, the latissimus dorsi flap, and the deep inferior epigastric perforator flap.

Radiotherapy

- RT is an integral part of breast-conserving treatment (lumpectomy). It is associated with a large reduction in local recurrence and a positive impact on survival.
- Standard radiation is 45 to 50.4 Gy at 1.8 to 2 Gy per fraction to the whole breast. RT boost to the tumor bed cavity is recommended in patients at higher risk for local failure (based on age, pathology, and margin status). The boost dose is 10 to 16 Gy at 2 Gy per fraction. An alternative hypofractionation schedule is 40 to 42.5 Gy at 2.66 Gy per fraction to the whole breast. This treatment method has been demonstrated to provide comparable cosmetic and oncologic results following breast-conserving surgery in patients with clear surgical margins and negative lymph nodes. Patients with early-stage, favorable biology disease may be considered for a partial breast RT technique. 3D planning, inverse planning for intensity modulation, respiratory control, prone positioning, and proton therapy are techniques employed to minimize cardiac risks for patients with left-sided breast cancer.

- RT is usually done after chemotherapy when systemic chemotherapy is indicated.
- Postmastectomy radiation treatment to the chest wall, axillary, supraclavicular, and internal mammary lymph node regions decreases the risk of locoregional recurrence and improves survival in patients with multiple positive lymph nodes and patients with T3 or T4 tumors.
- Two randomized trials showed improvement in OS for postmastectomy radiation in patients with one to three positive lymph nodes, and this is being evaluated in more clinical trials. In selected patients, this should be discussed.
- Other indications that may place patients at risk for local-regional failure and drive the decision for postmastectomy radiation include positive margins, extranodal extension and high-grade disease, young age and high-risk biology (eg, triple-negative disease), and omission of axillary dissection after positive SLNB if sufficient information is present without needing to know if additional axillary lymph nodes are involved. ASCO, ASTRO (American Society for Radiation Oncology), and SSO (Society of Surgical Oncology) updated guidelines for postmastectomy radiation therapy in 2016.
- Patients receiving neoadjuvant chemotherapy, those who present with clinically node-positive, cT3, or cT4 disease, will typically be recommended for postmastectomy radiation regardless of pathologic response outside of a clinical trial. Biopsy is recommended to confirm clinical suspicion of lymph node involvement prior to the initiation of chemotherapy. Results from the NSABP B-51 study will help determine the benefit of adjuvant radiation therapy for patients with biopsy-proven lymph node metastasis with ypN0 after neoadjuvant chemotherapy.

Accelerated Partial Breast Irradiation

The primary goal of accelerated partial breast irradiation (APBI) is to shorten the duration of radiation therapy while maintaining

adequate local control by targeting the lumpectomy cavity and adjacent at-risk tissue while sparing normal tissues. There are several APBI techniques currently in use and under study, including external beam radiation techniques, intraoperative radiation therapy (IORT), and brachytherapy; however, brachytherapy is the most widely used technique. Patients who are clinically felt to be at a lower risk recurrence outside of the lumpectomy site should be selected according to published criteria since the whole breast is not treated. ASTRO and SSO have published guidelines to aid in patient selection, for example, older patients with Tis or T1 disease, screen-detected, low-intermediate grade, <2.5 cm with margins negative by at least 3 mm. The standard dose for balloon catheter brachytherapy is 34 Gy in 10 fractions delivered twice daily. Phase III data support the use of intensity-modulated external beam radiation therapy delivering 30 Gy in five fractions for select patients.

Intraoperative Radiation Therapy

IORT delivers a concentrated dose of radiation to the tumor bed immediately after the tumor is removed. Two large studies evaluated the role of IORT in women with early-stage breast cancer. In the TARGIT-A study, women aged 45 years or older were randomized to receive IORT or whole-breast external beam radiation (WBRT) after lumpectomy. Survival rates were similar in both groups, but local recurrence was more common in the IORT group. These findings are supported by the ELIOT trial results. In this study, women aged 48 to 75 years with tumors ≤2.5 cm were randomized to IORT or WBRT, and survival rates were similar in both groups but local recurrence was more common in the IORT group.

Per the 2017 ASTRO/SSO APBI consensus statement update, IORT should be restricted to patients who are also suitable to partial breast radiation, and patients should be counseled that the risk of ipsilateral breast cancer might be higher with IORT.

Adjuvant Systemic Therapy

Adjuvant therapy decisions are made after carefully considering patient- and tumor-related factors. Patient-related factors include age, comorbid conditions, performance status, patient preference, risk-benefit discussion, and life expectancy. Tumor-related factors are tumor size, lymph node status (stage), ER/PR status, HER2, grade of the tumor, and genomic expression profile (eg, Oncotype DX, MammaPrint) (Figure 12.4).

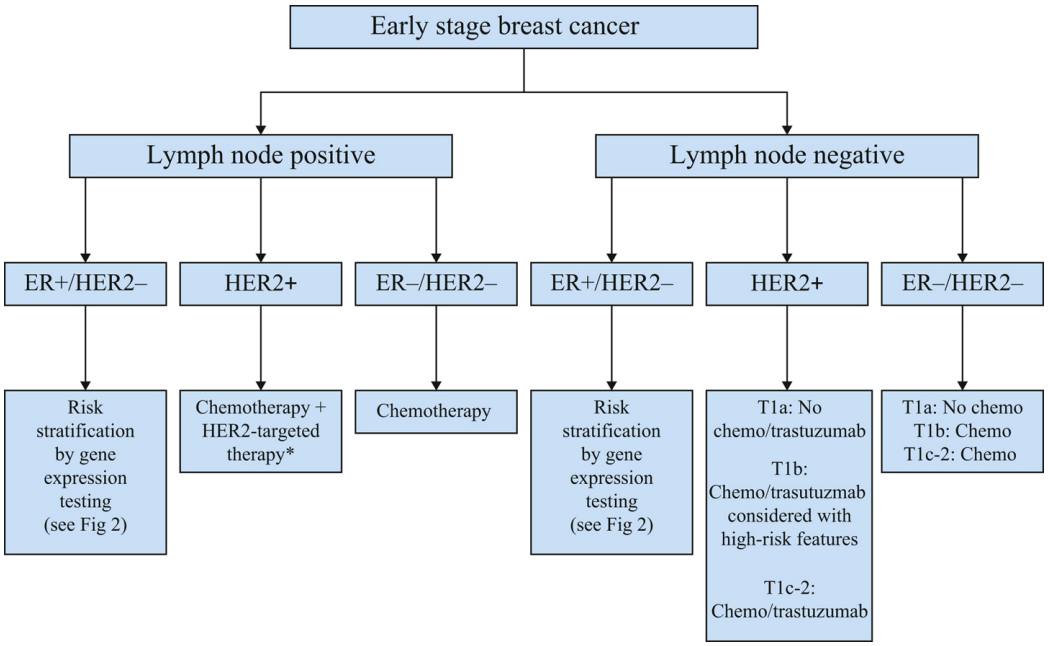

FIGURE 12.4 Algorithm for use of chemotherapy in early-stage breast cancer.ER, estrogen receptor.

General Principles of Adjuvant Therapy

1. All patients with breast cancer should be screened for potential clinical trials.
2. ER/PR-positive patients should be recommended to receive antiestrogen therapy.
3. HER2-positive patients should be recommended to receive HER2-targeted therapy.
4. Chemotherapy should be considered for the following patients:

a. ER/PR-negative, HER2-negative ("triple-negative") patients
b. HER2-positive patients
c. Node-positive patients
d. High-risk patients based upon Oncotype DX, MammaPrint, or other gene expression profiles

Adjuvant Therapy in HER2-Negative Patients

A variety of adjuvant regimens have been used across the world. Depending upon the biology of the tumor, stage of the disease, patient's health status, comorbid conditions, and chance of recurrence, an optimal regimen can be chosen (Table 12.4).

TABLE 12.4
Non–Trastuzumab-Containing Combinations

Commonly Used Regimens
Dose-dense AC followed by dose-dense paclitaxel chemotherapy Doxorubicin 60 mg/m^2 IV on day 1 Cyclophosphamide 600 mg/m^2 IV on day 1 Cycled every 14 d for four cycles (all cycles are with filgrastim support) Followed by: Paclitaxel 175 mg/m^2 by 3 h IV infusion on day 1 Cycled every 14 d for four cycles (all cycles are with filgrastim support)
Dose-dense AC followed by weekly paclitaxel chemotherapy Doxorubicin 60 mg/m^2 IV on day 1 Cyclophosphamide 600 mg/m^2 IV on day 1 Cycled every 14 d for four cycles (all cycles are with filgrastim support) Followed by: Paclitaxel 80 mg/m^2 by IV infusion weekly for 12 wk
Paclitaxel/carboplatin with pembrolizumab followed by AC or EC with pembrolizumab (for preoperative triple-negative breast cancer only) Paclitaxel 80 mg/m^2 IV once weekly × 12 wk Carboplatin AUC 1.5 IV once weekly × 12 wk OR carboplatin AUC 5 IV once every 3 wk (for total 12 wk)

Pembrolizumab 200 mg IV once every 3 wk

Followed by:

Doxorubicin 60 mg/m^2 IV on day 1 OR epirubicin 90 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1
Pembrolizumab 200 mg IV on day 1

Cycled every 21 d for four cycles (all cycles with filgrastim support)
Followed by:

Pembrolizumab 200 mg IV on day 1 every 21 d for nine cycles

Capecitabine
1000-1250 mg/m^2 PO twice a day on days 1-14
Cycled every 21 d for six to eight cycles

Olaparib
300 mg PO twice a day
Cycled every 28 d for 1 y

Other Regimens

TC chemotherapy

Docetaxel 75 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 21 d for four to six cycles

AC chemotherapy

Doxorubicin 60 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 21 d for four cycles

TAC chemotherapy

Docetaxel 75 mg/m^2 IV on day 1
Doxorubicin 50 mg/m^2 IV on day 1
Cyclophosphamide 500 mg/m^2 IV on day 1

Cycled every 21 d for six cycles (all cycles are with filgrastim support)

FAC chemotherapy

5-Fluorouracil 500 mg/m^2 IV on days 1 and 8 or days 1 and 4
Doxorubicin 50 mg/m^2 IV on day 1 (or by 72 h continuous infusion)
Cyclophosphamide 500 mg/m^2 IV on day 1

Cycled every 21 d for six cycles

CAF chemotherapy

Cyclophosphamide 100 mg/m^2 PO on days 1-14

Doxorubicin 30 mg/m^2 IV on days 1 and 8
5-Fluorouracil 500 mg/m^2 IV on days 1 and 8

Cycled every 28 d for six cycles

CEF chemotherapy

Cyclophosphamide 75 mg/m^2 PO on days 1-14
Epirubicin 60 mg/m^2 IV on days 1 and 8
5-Fluorouracil 500 mg/m^2 IV on days 1 and 8

Cycled every 28 d for six cycles
With cotrimoxazole support

CMF chemotherapy

Cyclophosphamide 100 mg/m^2 PO on days 1-14
Methotrexate 40 mg/m^2 IV on days 1 and 8
5-Fluorouracil 600 mg/m^2 IV on days 1 and 8

Cycled every 28 d for six cycles

AC followed by docetaxel chemotherapy

Doxorubicin 60 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 21 d for four cycles
Followed by:

Docetaxel 100 mg/m^2 IV on day 1

Cycled every 21 d for four cycles

EC chemotherapy

Epirubicin 100 mg/m^2 IV on day 1
Cyclophosphamide 830 mg/m^2 IV on day 1

Cycled every 21 d for eight cycles

FEC followed by docetaxel

5-Fluorouracil 500 mg/m^2 IV on day 1
Epirubicin 100 mg/m^2 IV on day 1
Cyclophosphamide 500 mg/m^2 IV on day 1

Cycled every 21 d for three cycles
Followed by:

Docetaxel 100 mg/m^2 IV on day 1

Cycled every 21 d for three cycles

FEC followed by weekly paclitaxel

5-Fluorouracil 600 mg/m^2 IV on day 1 Epirubicin 90 mg/m^2 IV on day 1 Cyclophosphamide 600 mg/m^2 IV on day 1 Cycled every 21 d for four cycles Followed by: Paclitaxel 100 mg/m^2 IV weekly for 8 wk
FAC followed by weekly paclitaxel 5-Fluorouracil 500 mg/m^2 IV on days 1 and 8 or days 1 and 4 Doxorubicin 50 mg/m^2 IV on day 1 (or by 72 h continuous infusion) Cyclophosphamide 500 mg/m^2 IV on day 1 Cycled every 21 d for four cycles Followed by: Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 wk

ER+, HER2− Patients

A non–anthracycline-containing regimen such as docetaxel and cyclophosphamide (TC) for four to six cycles can be used in ER-positive patients who require systemic chemotherapy. The benefit of anthracycline-containing regimens in receptor-positive patients is limited. This was illustrated in the ABC (anthracyclines in early breast cancer) trials (combined analysis of USOR 06-090, NSABP B-46, and NSABP B-49) where women with early-stage breast cancer were randomized to TC for six cycles versus standard anthracycline/taxane/cyclophosphamide-based chemotherapy. This trial showed the anthracycline-based chemotherapy improved iDFS compared to TC for six cycles overall; however, in subgroup analysis, it was found that the benefit of anthracyclines for ER/PR-positive patients was most substantial for those with four or more lymph nodes involved. In high-risk (such as more than four nodes),

ER/PR-positive patients, an anthracycline-containing regimen such as dose-dense AC followed by dose-dense paclitaxel or TAC regimen should be considered.

ER− and PR− (HR−), HER2− Patients

These patients are often treated with anthracycline-based chemotherapy in the adjuvant setting; however, the ABC trials showed that the greatest benefit of anthracycline-containing chemotherapy for ER/PR-negative patients occurred when patients had one or more lymph nodes involved. For patients with lymph node–negative or small tumors (less than 2 cm), TC chemotherapy for four to six cycles can be considered. In high-risk, triple-negative patients, anthracycline-containing regimens, such as dose-dense AC followed by dose-dense paclitaxel or a TAC regimen should be considered. The role of carboplatin in adjuvant triple-negative breast cancer is being evaluated in NRG-BR003 clinical trial.

Adjuvant Therapy in HER2-Positive (HER2+) Patients

Incorporation of trastuzumab into adjuvant therapy has changed the natural history of HER2-positive breast cancer. The clinical trials that initially showed benefit for the addition of trastuzumab to standard chemotherapy in treatment of HER2+ breast cancer (NSABP B-31 and NCCTG N9831) have published 10-year follow-up, showing 40% improvement in DFS and 37% improvement in OS. Many trastuzumab-containing regimens have been tested and all are equally effective (Table 12.5). The major difference between the regimens is in the risk of cardiac toxicity. Non–anthracycline-containing regimens (such as TCH from the BCIRG 006 trial) and the HERA trial regimens (the majority of which were anthracycline based but used sequential rather than concurrent trastuzumab) had less cardiac toxicity compared to other anthracycline-containing regimens with excellent long-term outcomes. In the adjuvant setting, trastuzumab has only been tested in combination with chemotherapy.

TABLE 12.5
Trastuzumab-Containing Combinations

Commonly Used Regimens
Paclitaxel chemotherapy and trastuzumab Paclitaxel 80 mg/m^2 IV weekly for 12 wk With: Trastuzumab 4 mg/kg IV with first dose of paclitaxel Followed by: Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment (alternative: trastuzumab 6 mg/kg IV every 21 d to complete 1 y of treatment)
TCH chemotherapy followed by trastuzumab Docetaxel 75 mg/m^2 IV on day 1 Carboplatin AUC 6 IV on day 1 Cycled every 21 d for six cycles With: Trastuzumab 8 mg/kg IV on day 1 Followed by: Trastuzumab 6 mg/kg IV every 3 wk to complete 1 y of trastuzumab therapy
TCHP chemotherapy followed by trastuzumab (± pertuzumab) Docetaxel 75 mg/m^2 IV on day 1 Carboplatin AUC 6 IV on day 1 Cycled every 21 d for six cycles With: Trastuzumab 8 mg/kg IV on day 1 Pertuzumab 840 mg IV on day 1 Followed by: Trastuzumab 6 mg/kg IV every 3 wk to complete 1 y of trastuzumab therapy Pertuzumab 420 mg IV every 3 wk for six cycles (can be continued to complete 1 y of dual HER2 blockade, if indicated)
Other Regimens
Dose-dense AC followed by dose-dense paclitaxel chemotherapy with trastuzumab

Doxorubicin 60 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 14 d for four cycles
Followed by:

Paclitaxel 175 mg/m^2 by 3 h IV infusion on day 1

Cycled every 14 d for four cycles (all cycles are with filgrastim support)
With:

Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:

Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment (alternative: trastuzumab 6 mg/kg IV every 21 d to complete 1 y of treatment)

(Cardiac monitoring is recommended before and during treatment)

AC followed by paclitaxel chemotherapy with trastuzumab

Doxorubicin 60 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 21 d for four cycles
Followed by:

Paclitaxel 80 mg/m^2 by 1 h IV weekly for 12 wk

With:

Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:
Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment (alternative: trastuzumab 6 mg/kg IV every 21 d to complete 1 y of treatment)

AC or dose-dense AC followed by paclitaxel chemotherapy with trastuzumab + pertuzumab

Doxorubicin 60 mg/m^2 IV on day 1
Cyclophosphamide 600 mg/m^2 IV on day 1

Cycled every 21 d for four cycles
Or For dose-dense: Cycled every 14 d for four cycles
Followed by:

Paclitaxel 80 mg/m^2 IV days 1, 8, and 15

Cycled every 21 d for four cycles
With:

Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV Pertuzumab 840 mg IV day 1 followed by 420 mg IV Followed by: Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment (alternative: trastuzumab 6 mg/kg IV every 21 d to complete 1 y of treatment) Pertuzumab 420 mg IV every 21 d to complete 1 y of treatment
Docetaxel/cyclophosphamide chemotherapy with trastuzumab Docetaxel 75 mg/m^2 IV day 1 Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 21 d for four cycles With: Trastuzumab 4 mg/kg IV wk 1 Followed by: Trastuzumab 2 mg/kg IV weekly for 11 wk Followed by: Trastuzumab 6 mg/kg IV Cycled every 21 d to complete 1 y of treatment ORTrastuzumab 8 mg/kg IV wk 1 Followed by: Trastuzumab 6 mg/kg IV Cycled every 21 d to complete 1 y of treatment
Neratinib 120 mg PO daily on days 1-7, followed by: 160 mg PO daily on days 8-14, followed by: 240 mg PO daily on days 15-28 Cycled every 28 d × 1 cycle Followed by: 240 mg PO daily on days 1-28 Cycled every 28 d × 12 cycles beginning with cycle 2
Ado-trastuzumab emtansine (T-DM1) 3.6 mg/kg IV day 1 Cycled every 21 d for 17 cycles

The addition of adjuvant pertuzumab to a standard trastuzumab-containing regimen for HER2+ breast cancer resulted in a statistically significant but modest 2.8% improvement in iDFS with benefit

predominantly in the lymph node–positive patients regardless of the HR status according to the 6-year follow-up of the APHINITY study. Addition of pertuzumab was associated with a greater incidence of diarrhea. Given these results, the use of adjuvant pertuzumab for 1 year in addition to trastuzumab can be considered in select high-risk patients such as those with positive lymph nodes.

In low-risk patients, especially ER-positive patients, up to 3 cm tumor with negative lymph nodes, weekly trastuzumab/paclitaxel for 12 cycles is a very reasonable option as per the APT (adjuvant paclitaxel and trastuzumab in node-negative, HER2-positive breast cancer) study. The 7-year DFS in this single-arm study was 93% and OS was 95%. Only 4 distant recurrences were observed in the 410 patients enrolled in this study.

Extended HER2-targeted therapy has also been investigated and is of value for certain high-risk patients. The ExteNET study tested the irreversible pan-HER inhibitor neratinib 240 mg PO daily for 12 months in patients who completed standard trastuzumab-based adjuvant therapy and found a 2.3% benefit in 2-year iDFS for patients who received neratinib compared to placebo. Interestingly, prespecified subgroup analysis showed greater benefit in HR-positive patients compared to HR-negative patients. Based on these results, the FDA approved neratinib for extended adjuvant treatment of early-stage HER2-positive breast cancer following adjuvant trastuzumab-based therapy in July 2017. Results from the final analysis published in 2020 demonstrated that at 8 years of follow-up, there were fewer deaths with neratinib than placebo in the intent-to-treat population, but the results did not reach statistical significance. In analyses of the HR+/≤ 1-year population, the absolute iDFS benefit of neratinib versus placebo at 5 years was 5.1%, and the absolute OS benefit at 8 years was 2.1%. Greater benefits were apparent in patients with residual disease after neoadjuvant therapy (5-year iDFS, 7.4%; 8-year OS, 9.1%). In addition, patients who received neratinib consistently experienced fewer central nervous system (CNS) events compared with placebo.

The primary side effect of neratinib is diarrhea, which is very common and can be quite severe. In ExteNET, grade 3 diarrhea was noted in 40% of patients and 17% of patients discontinued use of neratinib due to diarrhea. The diarrhea tends to occur in the first 2 months of treatment initiation. The CONTROL trial sought to identify the optimal method to control diarrhea during neratinib use. This trial compared five groups, including loperamide alone (L), budesonide + mandatory loperamide (BL), colestipol + mandatory loperamide (CL), colestipol + as-needed (PRN) loperamide (CL-PRN), and neratinib dose escalation (DE). Except loperamide alone, all of these methods were effective at reducing the incidence of grade 3 diarrhea when compared to the ExteNET trial. The percentage of patients who discontinued neratinib due to diarrhea was 20% with L, 8% with BL, 4% with CL, 8% with CL-PRN, and 3% with DE. Therefore, in patients who are starting neratinib, it is a common practice to consider dose escalation as well as antidiarrheal prophylaxis to optimally control symptoms and reduce the likelihood of treatment discontinuation due to diarrhea.

Neoadjuvant or Preoperative Chemotherapy

Neoadjuvant or preoperative chemotherapy can be considered for patients with locally advanced breast cancer (IIB, IIIA, IIIB, IIIC) and is the standard of care for inflammatory breast cancer. Response to neoadjuvant chemotherapy is highest in triple-negative and HER2-positive patients. In these patients, giving neoadjuvant therapy may allow clinicians to optimize the adjuvant therapy based on preoperative response.

- Preoperative evaluation of the breast mass by mammogram and ultrasound is recommended. MRI is often helpful in determining extent of disease for surgical planning.
- Systemic staging using CT scans/bone scan or CT/PET scan should be considered for these patients before starting chemotherapy.

- Neoadjuvant chemotherapy can potentially reduce the size of the primary tumor so breast-conserving surgery can be performed. It may also help downstage lymph nodes so full ALND may be avoided.
- Complete pathologic response (pCR) is associated with better outcome compared with residual disease at the time of surgery as demonstrated in the NSABP B-18 and NSABP B-27 trials. These trials showed no difference in DFS or OS between the groups treated with neoadjuvant and adjuvant therapy.
- Patients who have residual invasive breast cancer after the receipt of neoadjuvant chemotherapy for triple-negative and HER2-positive cases have a shorter event-free survival (EFS) and OS.
- For HR-positive, HER2-negative patients:
    - Usually, a preoperative regimen contains an anthracycline and a taxane. Any adjuvant regimen can be used in a neoadjuvant setting.
    - In a meta-analysis combining data from 37,298 women enrolled in 26 trials, the Early Breast Cancer Trialists' Collaborative Group compared trials of every-2-week versus standard every-3-week schedules and sequential full-dose versus concurrent lower dose regimens of anthracycline and taxane chemotherapy. Increased dose intensity was associated with a reduced risk of breast cancer recurrence and mortality; hence, these dose-dense schedules (with treatment every 2 weeks) are preferred. Growth factor support (granulocyte colony-stimulating factor [G-CSF]) is needed to maintain the every-2-week schedule.
- For triple-negative patients:
    - Preoperative regimens have historically been anthracycline and taxane based; however, newer data involve incorporation of platinum chemotherapy and immunotherapy as detailed below.
    - In the CALGB 40603 trial, the addition of carboplatin to an anthracycline-based neoadjuvant regimen in patients with triple-negative breast cancer was associated with improvement in pCR rates (41% vs 54%). The GeparSixto trial also showed higher pCR rates with carboplatin in the neoadjuvant setting. In selected high-risk, triple-negative patients, it is reasonable to consider adding carboplatin, especially if the tumor is not responding to standard anthracycline and taxane regimens. If platinum is included in a neoadjuvant regimen, weekly administration along with taxane is most tolerable.
    - The KEYNOTE-522 trial evaluated the efficacy and safety of neoadjuvant pembrolizumab-chemotherapy (anthracycline, taxane, and platinum) as compared with neoadjuvant placebo-chemotherapy, followed by adjuvant pembrolizumab or placebo in patients with early triple-negative breast cancer. A significantly higher percentage of patients in the pembrolizumab-chemotherapy group had a pCR at the time of definitive surgery (64.8% vs 51.2%) and the benefit was generally consistent across subgroups regardless of

PD-L1 status. In July 2021, 3-year EFS data from this study were presented, showing improvement with pembrolizumab-containing therapy compared to standard chemotherapy (84.5% vs 76.8%). The most common EFS event was distant recurrence (7.7% in pembrolizumab/chemotherapy arm, 13.1% with chemotherapy alone). A benefit was observed for those with pCR (94.4% vs 92%); however, it was larger for those without pCR (67.4% vs 56.8%). A concern about this regimen is that of long-term toxicity as 19% of patients treated with pembrolizumab had an unresolved immune-mediated adverse event at last assessment. Shortly after presentation of the EFS data, the FDA approved pembrolizumab in combination with chemotherapy (with continuation of pembrolizumab adjuvant × nine cycles) for preoperative treatment of triple-negative breast cancer patients with 1 cm or greater disease in the breast or positive lymph nodes. PD-L1 positivity is not required for use.

- IMpassion031 study compared efficacy and safety of atezolizumab versus placebo combined with nab-paclitaxel followed by doxorubicin plus cyclophosphamide as neoadjuvant treatment for early-stage, triple-negative breast cancer patients. The regimen significantly improved pCR rate (58% vs 41%) with an acceptable safety profile, and the benefit was observed across subgroups, regardless of PD-L1 status, stage II versus III disease, or lymph node–positive versus lymph node–negative disease. Survival data are awaited and this combination is not yet approved.
- Patients who do not have a pCR after the receipt of neoadjuvant taxane and anthracycline chemotherapy have a 20% to 30% risk of relapse.
- The CREATE-X study evaluated the addition of adjuvant capecitabine after standard neoadjuvant chemotherapy in patients with HER2-negative residual invasive breast cancer and found that DFS and OS were longer in the capecitabine group than in the control group. This effect was limited to patients with ER−/HER2− disease. Side effects were as expected with use of capecitabine in the metastatic setting. In ER−/HER2− patients with residual invasive disease after neoadjuvant chemotherapy, adjuvant therapy with capecitabine for six to eight cycles is recommended.
- Poly(ADP-ribose) polymerase (PARP) inhibitors induce a synthetic lethality effect in cancer cells harboring BRCA1/2 mutations. Olaparib is an oral PARP inhibitor that has shown activity in ovarian and breast tumors with known BRCA mutations. OlympiA, a randomized double-blinded phase III trial, compared 1 year of adjuvant olaparib (300 mg PO twice daily) versus placebo in patients with high-risk early-stage HER2-negative, germline BRCA1/2-positive breast cancer following local treatment and adjuvant or neoadjuvant chemotherapy. With a 2.5-year median follow-up, adjuvant olaparib reduced the risk of iDFS event by 42% and achieved a 43% reduction in distant DFS event compared with placebo. OS showed a trend toward improvement with olaparib, but results were not statistically significant. The side effects were consistent with the safety profile of olaparib in the metastatic setting. Importantly, there was no increased risk of AML/MDS observed compared to placebo.

- For HER2+ patients:

- Several clinical trials have shown an advantage for dual HER2 blockade in the neoadjuvant setting. Pertuzumab in combination with trastuzumab and docetaxel in the neoadjuvant setting was approved in 2013 based on the results of the phase II NeoSphere and TRYPHAENA trials. Lapatinib in combination with trastuzumab and paclitaxel in the neoadjuvant setting was studied in the NeoALTTO trial and was shown to be associated with higher rates of pCR than either anti-HER2 drug alone.
- Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy with HER2-targeted therapy/chemotherapy have a worse prognosis than those who have no residual cancer. Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative, and microtubule inhibitor. The KATHERINE study randomized patients with HER2-positive early breast cancer who were found to have residual invasive disease in the breast or axilla at surgery after receiving neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab to receive adjuvant T-DM1 or trastuzumab for 14 cycles. The interim analysis found that the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. Subgroup analyses showed a consistent benefit, irrespective of HR status, the extent of residual disease at surgery, single or dual HER2-targeted therapy in the neoadjuvant regimen, and baseline characteristics of the patients. This is now the standard of care for HER2-positive patients who have residual disease following neoadjuvant therapy.

Adjuvant Endocrine Therapy

Unless there is a contraindication, endocrine therapy should be considered for all patients with ER-positive and/or PR-positive tumors (Figure 12.5; Table 12.6).

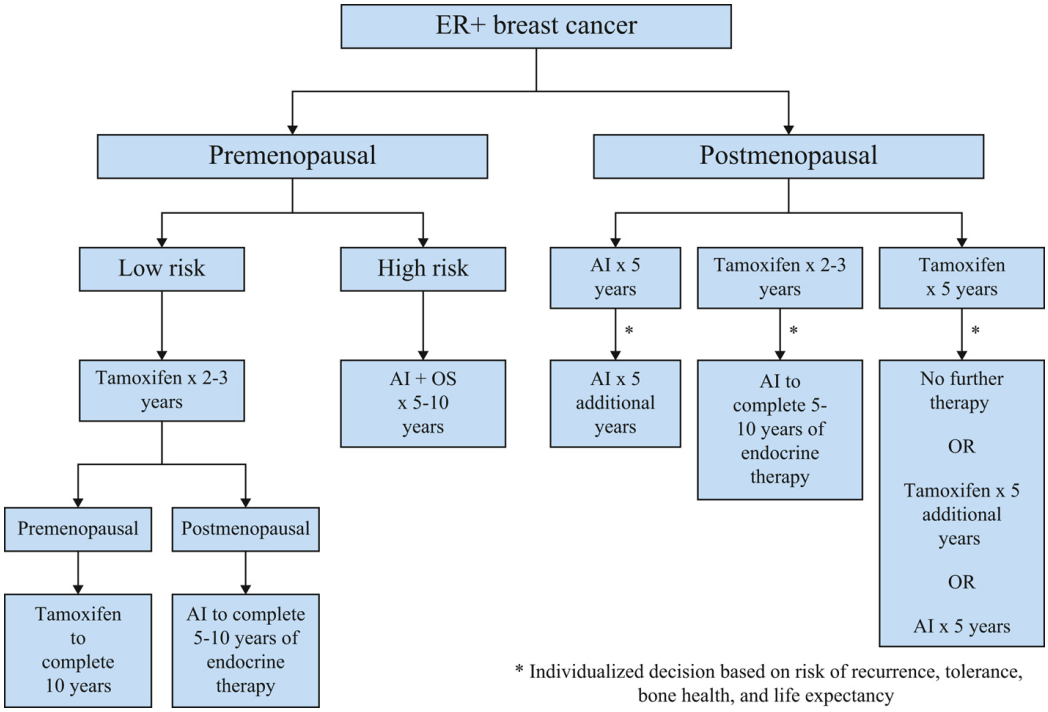

FIGURE 12.5 Algorithm for adjuvant endocrine therapy in early-stage HR+ breast cancer.AI, aromatase inhibitor; HR, hormone receptor; OS, ovarian suppression.

TABLE 12.6
Endocrine Agents Used in Treatment of Breast Cancer

Selective Estrogen Receptor Modifier With Combined Estrogen Agonist and Estrogen Antagonist Activity
Tamoxifen (Nolvadex), 20 mg daily PO
Estrogen Receptor Downregulator
Fulvestrant 500 mg IM on days 1, 15, and 28 and then once every 4 wk
Aromatase Inhibitors
Anastrozole (Arimidex), 1 mg daily PO
Letrozole (Femara), 2.5 mg daily PO
Exemestane (Aromasin), 25 mg daily PO
LHRH Agonist Analog in Premenopausal Women
Leuprolide (Lupron Depot), 3.75 or 7.5 mg/dose IM monthly, or
Leuprolide (Lupron Depot), 11.25 or 22.5 mg/dose IM every 3 mo
GnRH Agonist Analog
Goserelin (Zoladex), 3.6 mg/dose s.c. implant into the abdominal wall every 28 d, or
Goserelin (Zoladex), 10.8 mg/dose s.c. implant into the abdominal wall every 12 wk

GnRH, gonadotropin-releasing hormone; IM, intramuscular; LHRH, luteinizing hormone–releasing hormone; s.c., subcutaneous.

Postmenopausal Women

Several large randomized studies have shown superiority of AI over tamoxifen in the adjuvant setting. If the patient has no contraindication, AIs are the preferred agents in postmenopausal patients. Anastrozole, letrozole, and exemestane are all approved by the FDA for adjuvant use. The major side effects include arthralgia, vasomotor effects, and loss of bone density.

Anastrozole

One of the largest adjuvant breast cancer trials (ATAC) compared tamoxifen with anastrozole and combination of both anastrozole and tamoxifen. It was shown that anastrozole is superior to tamoxifen in improving DFS and reducing the incidence of contralateral breast cancer with a more favorable side effect profile. For postmenopausal patients, the recommended dose of anastrozole is 1 mg PO daily for 5 years; however, there has been much interest in extending adjuvant therapy to a duration of 10 years as described in the following "Extended Adjuvant Endocrine Therapy" section.

Letrozole

BIG 1-98 showed a similar magnitude of improvement as seen with anastrozole in the ATAC trial. Both DFS and a reduction of distant metastasis were observed with use of letrozole over tamoxifen. For postmenopausal patients, the recommended dose of letrozole is 2.5 mg PO daily for 5 years. Studies of extended adjuvant therapy with letrozole have been completed and are summarized below.

Switching From Tamoxifen to an AI

In the IES study, exemestane therapy after 2 to 3 years of tamoxifen therapy significantly improved DFS and reduced the incidence of contralateral breast cancer as compared with the standard 5 years of tamoxifen therapy. The FDA has approved exemestane 25 mg daily

after 2 to 3 years of tamoxifen in postmenopausal patients (total of 5 years of endocrine therapy).

Endocrine Therapy: Premenopausal Patients

HR-positive, premenopausal patients are generally treated with tamoxifen if low risk and ovarian suppression/AI if high risk.

Tamoxifen

Tamoxifen is a selective ER modulator with both estrogen agonist and antagonist potential. In premenopausal patients, tamoxifen 20 mg daily is the treatment of choice unless the patient has any contraindications such as history of thromboembolic disease, stroke, or endometrial cancer. Major adverse effects include vasomotor effects, mood changes, and metabolic changes as well as higher incidence of cerebrovascular accidents, VTE, and endometrial hyperplasia/malignancy.

In general, tamoxifen is recommended for 5 years; however, multiple studies support a longer duration of treatment. In the ATLAS study, women who took tamoxifen for a total of 10 years rather than 5 years had lower recurrence rate and increased OS. Extended adjuvant use of tamoxifen had little effect on recurrence or mortality rates from 5 to 9 years after diagnosis, but in the second decade following diagnosis, women who had continued tamoxifen treatment beyond 5 years had a 25% lower recurrence rate and a 29% lower breast cancer mortality rate. The results of the aTTom trial also demonstrated improved survival with 10 years of tamoxifen. Prolonged use of tamoxifen is associated with increased side effects (particularly endometrial carcinoma and VTE); therefore, the decision to use tamoxifen for 10 years needs to be individualized, depending on the risk of recurrence and potential adverse effects.

Ovarian Ablation or Ovarian Suppression

The Oxford overview and several other studies have found that premenopausal patients who stopped having menses after

completion of chemotherapy have better survival than those who continued to have menses. Ovarian ablation can be achieved by surgery, by radiation, or with luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide or goserelin.

The TEXT and SOFT trials, published in 2014, addressed the use of ovarian suppression as adjuvant therapy in premenopausal women with ER-positive breast cancer. In the TEXT trial, women were randomized to receive 5 years of tamoxifen with ovarian suppression or exemestane with ovarian suppression. In the SOFT trial, women were randomized to 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. DFS was higher in the exemestane plus ovarian suppression group comparing to the tamoxifen plus ovarian suppression group in both trials. In a subgroup analysis of the TEXT trial, younger women (younger than 35 years) with high-risk disease warranting chemotherapy had higher DFS with exemestane and ovarian suppression compared to tamoxifen alone or tamoxifen with ovarian suppression. The updated analysis after a median follow-up of 8 years concluded that among premenopausal women with breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of both disease-free and OS than tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group. Based on these results, it is reasonable to consider exemestane with ovarian suppression for premenopausal women with high-risk disease, particularly those younger than 35 years.

In general, we recommend use of monthly LHRH agonists such as leuprolide, gonadotropin-releasing hormone (GnRH) analogs such as goserelin, or surgical removal of ovaries for those patients who would benefit from ovarian suppression. In patients who are treated with GnRH analogs or LHRH agonists, it is important to make sure that they achieve a complete ovarian suppression by checking the serum estradiol, luteinizing hormone, and follicle-stimulating

hormone, although optimal frequency of this monitoring is unknown. Before a young woman decides to undergo bilateral oophorectomy, it is important to make sure that she understands the risks and benefits including its impact on quality of life. In this situation, it may be advisable to use medical ovarian suppression for a period of time so that potential side effects can be reversed with discontinuation of the medication, if needed, prior to considering oophorectomy.

Adjuvant Endocrine Therapy With Cyclin-Dependent Kinase 4/6 Inhibitors

Cyclin-dependent kinases (CDKs) play a key role in cell cycle progression from G1 to S phase, and CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib interfere with cell cycle progression, induce cell senescence, and might promote cancer cell disruption by a cytotoxic T cell–mediated effect.

The phase III PALLAS trial was designed to investigate whether the addition of palbociclib to adjuvant endocrine therapy improves outcomes compared with endocrine therapy alone in patients with HR+, HER2− early breast cancer. At the planned second interim analysis, addition of 2 years of adjuvant palbociclib to adjuvant endocrine therapy did not improve iDFS compared with adjuvant endocrine therapy alone. On the basis of these findings, this regimen cannot be recommended in the adjuvant setting. Long-term follow-up and correlative studies are ongoing.

The PENELOPE-B trial evaluated the addition of 1 year of palbociclib to standard adjuvant endocrine therapy in high-risk HR+, HER2− breast cancer. Despite initial promising results, the combination failed to meet the primary endpoint on longer follow-up and is also not recommended for clinical use.

The monarchE trial compared 2 years of abemaciclib plus adjuvant AI therapy with endocrine therapy alone in patients with high-risk early-stage HR+, HER2− breast cancer. The interim analysis found that the addition of abemaciclib to endocrine therapy reduced the

risk of invasive disease by 28.7%. In the ASCO 2021 update, the 2-year iDFS rate for the combination arm versus endocrine therapy alone arm was 87.2% versus 80.6%, respectively, while the 2-year DRFS was 89.5% versus 82.8%, respectively. Abemaciclib is the first CDK4/6 inhibitor to demonstrate a significant improvement in iDFS, but OS data are currently immature and this combination is not yet FDA approved.

Extended Adjuvant Endocrine Therapy

Multiple studies have shown a benefit for extended adjuvant endocrine therapy, defined as >5 years of treatment. The MA-17 study showed approximately 43% reduction in recurrence in postmenopausal patients receiving 2.5 mg of letrozole after completing 5 years of tamoxifen. Similar results were seen with ABCSG-6 (anastrozole) and NSABP B-33 (exemestane) as well. The MA.17R trial (an extension of the MA.17 trial) evaluated the role of 10 years of adjuvant letrozole in postmenopausal women compared to 5 years of treatment. The five additional years of letrozole increased the 5-year DFS by 4% but only decreased the rate of distant recurrence by 1.1%. The 10-year update of the NSABP B-42 randomized phase III trial showed a statistically significant improvement in DFS and an absolute improvement of 3.3% with 5 additional years of adjuvant letrozole. There was also a large benefit seen in reduction of contralateral primary breast cancers. The IDEAL trial found no statistically significant benefit in DFS and OS for 5 years of extended letrozole treatment in comparison to an extended 2.5 years of AI treatment. Similar results were seen with DATA (anastrozole) trial as well.

A recent meta-analysis concluded that extended adjuvant endocrine therapy with AI reduced the occurrence of secondary breast tumors with smaller impact on distant metastasis-free survival. No OS benefit has yet been established. The benefit in distant disease recurrence is primarily seen in patients at high risk for recurrence (node positive and/or large tumors), and ASCO guidelines recommend extended adjuvant therapy only for high-risk

patients with ER-positive disease as longer time on therapy is associated with greater risk of osteoporosis and skeletal-related events.

The BCI can be used to aid in selecting patients who will benefit from extended adjuvant therapy. The BCI HOXB13/IL17BR ratio (BCI-H/I) combines a five-gene molecular grade index that reports predicted benefit to extended endocrine therapy independent of risk of late recurrence. While this test can be helpful in selecting patients who may benefit from extended therapy, the decision largely remains a clinical one based on pretreatment risk of recurrence, tolerance of therapy, and concern about long-term side effects. For patients with intact contralateral breast tissue, the extended therapy can be meaningful to reduce new breast cancer events.

Role of Adjuvant Bisphosphonate Therapy in Early Breast Cancer

In an Oxford overview analysis including data from nearly 19,000 patients treated with adjuvant bisphosphonate therapy, significant reductions in distant breast cancer recurrence (particularly bone recurrence) and breast cancer mortality were found. These effects were limited to women who were postmenopausal when treatment was started. Definition of menopause in this guideline includes both natural menopause and that induced by ovarian suppression or ablation. Based on these data, ASCO clinical practice guidelines now recommend that postmenopausal women (whether naturally occurring or induced with ovarian suppression/oophorectomy) with breast cancer be considered for treatment with either zoledronic acid (4 mg IV every 6 months) or clodronate (1600 mg PO daily). Optimal dosing duration and intervals are not known although up to 5 years of treatment can be considered.

BREAST CANCER IN PREGNANCY

- Breast cancer during pregnancy was initially thought to be more aggressive biologically; however, the overall poor outcome associated with breast cancer in pregnancy is likely related to more advanced stage at the time of diagnosis.
- Breast biopsy is safe in all stages of pregnancy and should be done for any mass concerning for cancer.

Treatment

- Lumpectomy and axillary node dissection can be performed in the third trimester and radiation therapy can be safely delayed until after delivery.
- Modified radical mastectomy is the treatment of choice in the first and second trimesters because radiation treatment is contraindicated during pregnancy.

Chemotherapy

- Chemotherapy should not be administered during the first trimester.
- An anthracycline combined with cyclophosphamide (eg, AC given every 3 weeks for four cycles) has been used safely in the adjuvant or neoadjuvant setting during the second or third trimesters.
- Chemotherapy should be scheduled to avoid neutropenia and thrombocytopenia at the time of delivery.
- Paclitaxel is generally avoided during pregnancy due to reports of teratogenicity.
- Growth factors such as filgrastim and pegfilgrastim have been used in pregnancy when necessary; however, data regarding safety of use are limited to case reports and small retrospective series. The FDA considers these drugs as Category C so use is generally avoided.
- HER2–targeted agents such as trastuzumab have been reported to cause oligo/anhydramnios and fetal renal failure so should be avoided during pregnancy.

- Tamoxifen is teratogenic and should not be used in pregnant women.
- Therapeutic abortion does not change the survival rate for the woman affected by breast cancer.

MALE BREAST CANCER

- Male breast cancer is uncommon, accounts for 1% of all breast cancer diagnoses.
- Risk factors include family history, germline mutation, especially BRCA2, Klinefelter syndrome, and radiation to the chest wall.
- It often presents as a palpable mass.
- The mean age of occurrence is 60 to 70 years.
- Eighty percent of male breast cancer is HR positive.

Treatment

- Modified radical mastectomy is the usual standard of care.
- Lumpectomy is rarely done because it does not offer any cosmetic benefit.
- Bilateral mastectomy is not recommended for male BRCA carriers as contralateral risk is low.
- Systemic treatment with chemotherapy should follow the general guidelines for female patients.
- Tamoxifen 20 mg daily is the preferred endocrine therapy agent in male breast cancer.

Phyllodes Tumor

- A phyllodes tumor is clinically suspected when the tumor is growing rapidly and clinical and radiologic features suggestive of fibroadenoma.
- Phyllodes tumor is classified as benign, borderline, or malignant.

- It is treated with wide excision without an axillary node dissection.
- In patients who have recurrent phyllodes tumor, radiation therapy can be considered after wide excision.
- Role of chemotherapy in phyllodes tumor is limited.
- Patients with Li-Fraumeni syndrome have an increased risk for phyllodes tumors.

Paget Disease of the Nipple

- Paget disease may present as bleeding, ulceration, or eczema-like changes of the nipple.
- Patients should be evaluated for any evidence of invasive or noninvasive breast cancer by appropriate imaging and biopsy as Paget's disease has been reported to occur with cancer elsewhere in the breast in up to 90% of cases.
- If the patient has only Paget disease of the nipple areolar complex (NAC), the patient can be treated with wide excision of the NAC and axillary node evaluation followed by whole-breast radiation.
- Patients with invasive or noninvasive breast cancer should be managed accordingly.

Survivorship

Studies have suggested that up to 50% of cancer survivors experience late effects of cancer treatment. In breast cancer survivors, providers must consider the potential long-term impacts of chemotherapy, surgery, radiation, and endocrine therapy on the patient including risks of cardiac dysfunction, cognitive changes, depression, persistent fatigue, pain, neuropathy, lymphedema, premature menopause, sexual dysfunction, deterioration in bone health, and secondary malignancies.

As per the 2016 Commission on Cancer accreditation standards, a survivorship care plan should be provided to all patients at the completion of curative intent treatment with information including a

personalized treatment summary with associated providers identified, guidance of signs of recurrence, information of long-term effects of treatment, guidelines for follow-up care, and identification of support services available to the patient. Given the growing body of evidence supporting the importance of a healthy lifestyle, including maintaining an appropriate body weight and incorporating regular physical activity, in decreasing risk of cancer, oncologists should be mindful to ask questions regarding healthy lifestyle behaviors during routine follow-up.

Pregnancy After Breast Cancer

Many patients and oncologists harbor reservations about pregnancy following a breast cancer diagnosis for a variety of reasons. Two of the biggest concerns, particularly for HR-positive breast cancer survivors, are that pregnancy produces higher levels of estrogen, which could result in breast cancer cell growth and that pregnancy necessitates a gap in adjuvant endocrine treatment.

A large retrospective study presented at the ASCO 2017 meeting challenged these concerns by demonstrating that DFS 10 years following diagnosis was no different in survivors who became pregnant compared to those who did not become pregnant. Importantly, this held true when the ER-positive cohort was analyzed individually. In secondary analyses, the timing of pregnancy (<2 years after diagnosis or >2 years after diagnosis) and breastfeeding did not affect DFS. An additional meta-analysis presented at the San Antonio Breast Cancer Symposium in 2020 demonstrated that pregnancy was not associated with poor patient outcomes. In fact, this study found a 44% reduced risk of death and 27% reduced risk of breast cancer recurrence in women who had a pregnancy after breast cancer compared to those who did not. The ongoing Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer study will provide additional insight into the impact of interrupting adjuvant endocrine therapy during pregnancy for survivors of ER-positive breast cancer. This trial has accrued premenopausal women aged 18

to 42 years old who have received adjuvant endocrine therapy for HR-positive stage I-III breast cancer to investigate if temporary interruption of endocrine therapy, with the goal to permit pregnancy, is associated with a higher risk of breast cancer recurrence.

FOLLOW-UP FOR PATIENTS WITH OPERABLE BREAST CANCER (BASED ON ASCO GUIDELINES, DECEMBER 2015)

1. History and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and annually thereafter.
2. Physicians should counsel patients regarding symptoms of recurrence including new breast lumps, bone pain, chest pain, dyspnea, abdominal pain, and persistent headaches or vision changes.
3. All women should be counseled to do monthly breast self-examination.
4. Annual mammogram of the contralateral and ipsilateral (in the remaining breast after lumpectomy) breast.
5. Regular gynecologic follow-up (annual) is recommended for all patients. Those who receive tamoxifen should be advised to report any unusual vaginal bleeding to their doctors.
6. Coordination of care: The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for patients with breast cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts.
7. Follow-up by a primary care physician seems to lead to the same health outcomes as specialist follow-up with good patient satisfaction.

8. Routine blood tests including a complete blood count, liver function tests, and alkaline phosphatase levels are not recommended. Serum tumor markers (CA 27-29 and CA 15-3) are not recommended.
9. Chest X-ray, ultrasound of the liver, breast MRI, bone scan, and CT scans of the chest, abdomen, pelvis, and brain or PET scans are not recommended routinely, but they are done if symptoms or lab abnormalities are present.
10. Second primary cancer screening should proceed as is appropriate for patient age group in the general population.
11. Assessment should regularly include evaluation for physical and psychosocial impacts of cancer diagnosis and treatment. This includes assessment of body image concerns, lymphedema, mood disorder, fatigue, cognitive impairment, sexual dysfunction, bone health, pain/neuropathy, and menopausal symptoms.

LOCALLY RECURRENT BREAST CANCER

After Mastectomy

- Eighty percent of local recurrences occur within 5 years.
- Treatment of choice is surgical excision and radiation therapy.
- Systemic therapy may be considered based upon ER/PR and HER2 status. As per the CALOR study, a survival advantage was seen for patients who received systemic therapy after local recurrence but maximum benefit with chemotherapy was in triple-negative patients.

After Lumpectomy

- Mastectomy is the treatment of choice for patients who have only isolated breast cancer recurrence.

METASTATIC BREAST CANCER

See Figure 12.6.

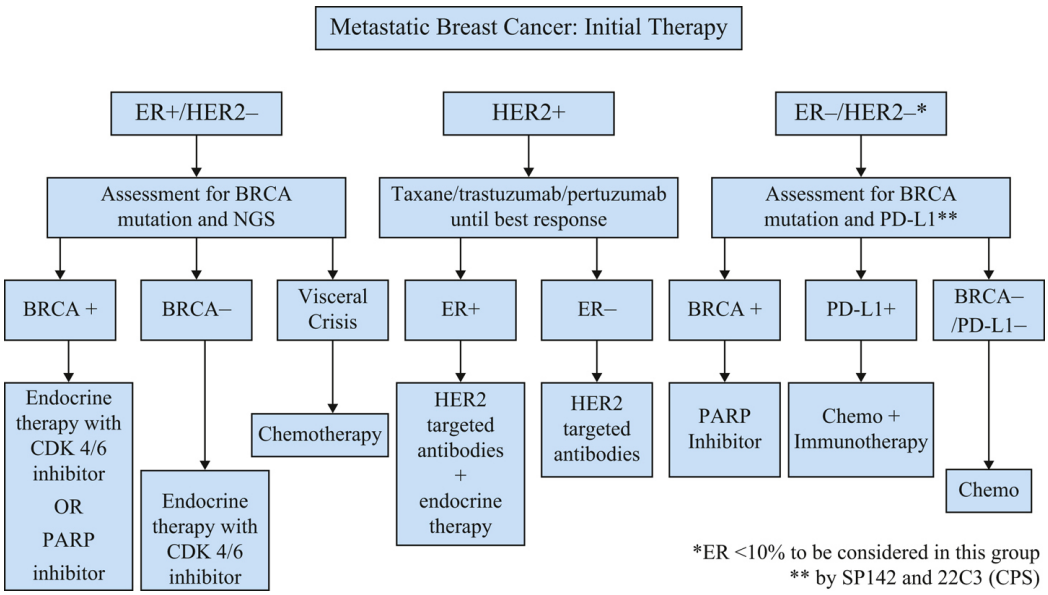

FIGURE 12.6 Algorithm for the initial management of metastatic breast cancer.ER, estrogen receptor; NGS, next-generation sequencing.

Principles of Treatment

1. Repeat biopsy to confirm the diagnosis of recurrent/metastatic breast cancer.
2. Strongly recommend repeating all biomarkers including ER/PR and HER2.
3. All patients should be considered for clinical trials.
4. Genomic profiling using next-generation sequencing (NGS) is now the standard of care to assess whether genomic-based clinical trials or targeted therapy options are available.
5. MSI (microsatellite instability), dMMR (mismatch repair deficient), and TMB (tumor mutational burden) testing should be obtained in all patients given recent approvals for immunotherapy for those who met criteria.

6. Germline BRCA-positive patients should be considered for treatment with PARP inhibitors.
7. HER2-positive patients should be treated with HER2-targeted agents such as trastuzumab, pertuzumab, antibody-drug conjugates, or tyrosine kinase inhibitors (TKIs).
8. All ER/PR-positive, HER2-negative patients should be considered for antiestrogen therapy with or without an additional targeted agent such as a CDK4/6 inhibitor, PIK3CA inhibitor, or a mammalian target of rapamycin (mTOR) inhibitor.
9. Premenopausal patients with ER-positive disease should be considered for ovarian suppression and endocrine therapy with or without targeted therapy.
10. In ER-positive patients, use of chemotherapy should be limited to those with visceral crisis (defined as severe organ dysfunction as evidenced by clinical symptoms or lab abnormalities) or those who have progressed through various endocrine agents, CDK4/6 inhibitors, or mTOR inhibitor.
11. Since combination chemotherapy regimens have not shown DFS or OS benefit, most patients should be treated with single agents in a sequential manner. Doublet chemotherapy can be considered with visceral crisis as time to response may be faster.
12. All patients with metastatic disease involving the bone should be considered for bone-modifying agents such as bisphosphonates (zoledronic acid/pamidronate) or denosumab (receptor activator of nuclear factor-κB [RANK] ligand inhibitor).
13. Before starting treatment, a detailed assessment of comorbid conditions, performance status, and patient preferences should be conducted. Additionally, toxicities of the treatment should be explained and a risk versus benefit discussion should be had with each patient.
14. Goals of treatment should be discussed in detail since treatment is palliative for the majority of patients.

ER-Positive Metastatic Breast Cancer

See Table 12.7.

TABLE 12.7

Agents Used in Combination With Endocrine Therapy for Metastatic Breast Cancer

CDK4/6 Inhibitors
Palbociclib 125 mg daily PO on days 1-21 every 28 d in combination with fulvestrant or AI
Ribociclib 600 mg daily PO on days 1-21 every 28 d in combination with fulvestrant or AI
Abemaciclib • 150 mg twice a day (continuous dosing) in combination with fulvestrant or AI • 200 mg twice a day as single agent
PIK3CA Inhibitor
Alpelisib 300 mg daily PO in combination with fulvestrant
mTOR Inhibitor
Everolimus 10 mg PO daily in combination with exemestane or tamoxifen

- Endocrine therapy is the mainstay of treatment.
- Introduction of CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib has revolutionized the treatment of ER-positive metastatic breast cancer.
- Selection of endocrine therapy will depend upon the adjuvant or previous endocrine therapy, menopausal status, and the interval between completion of adjuvant therapy and development of metastatic disease.
- Premenopausal patients should be treated with ovarian suppression and an AI in combination with a CDK4/6 inhibitor in the first-line setting. Data are strongest for ribociclib in this space as per the MONALEESA-7 trial. If patient was on an AI at time of metastatic diagnosis, fulvestrant in combination with a CDK4/6 inhibitor is the appropriate treatment.
- In postmenopausal patients, an AI combined with a CDK4/6 inhibitor should be considered as standard first-line treatment. If metastatic disease is diagnosed while the patient was taking an AI or within 1 year of completion of AI, one can use

fulvestrant in combination with a CDK4/6 inhibitor in these settings.

- Second-line options include a PARP inhibitor for women who have BRCA mutations (somatic or germline). PARP inhibitors can also be considered for patients with PALB2 mutations. Alpelisib (in combination with fulvestrant) should be considered for women who have a PIK3CA mutation. For women whose tumors lack a targetable mutation and who have progressed on an AI, consider fulvestrant as a single agent or in combination with a CDK4/6 inhibitor, exemestane with everolimus, or tamoxifen. At this time, it is unclear whether there is a benefit to treating with a different CDK4/6 inhibitor after progression on initial CDK4/6 inhibitor.
- Abemaciclib can be used as single-agent treatment for patients who have had disease progression on prior endocrine therapy and chemotherapy for metastatic disease.

HER2-Positive Metastatic Breast Cancer

- Based upon the CLEOPATRA study, dual HER2 blockade with trastuzumab and pertuzumab in combination with a taxane (THP) is considered standard treatment in first-line metastatic setting. This regimen is associated with a nearly 17-month improvement in median OS, and 35% of patients treated remained alive at 8 year follow-up. The most commonly used regimen is docetaxel with trastuzumab and every 3 weeks with growth factor support. Weekly paclitaxel can be used rather than docetaxel in this setting.
- In the second-line setting, T-DM1 is recommended based upon the EMILIA trial, which demonstrated an OS benefit compared to capecitabine/lapatinib.
- Second-line approval has also been granted to the combination of tucatinib, trastuzumab, and capecitabine as per the HER2CLIMB study.
- Trastuzumab deruxtecan, an antibody-drug conjugate with a topoisomerase I inhibitor as the cytotoxic payload, has been

approved for third-line treatment and beyond based on the results of the DESTINY-Breast01 trial showing encouraging progression-free survival (PFS, 16.4 months) and response rate (RR, 60.9%).

- Margetuximab, an Fc-engineered, ERBB2-targeted antibody, was FDA approved based on the SOPHIA trial, which demonstrated efficacy in patients who have received at least two prior anti-HER2–directed regimens with at least one being in the metastatic setting.
- Other treatment options include capecitabine with a HER2-targeted TKI (neratinib or lapatinib) or trastuzumab-containing chemotherapy regimens such as navelbine and trastuzumab or gemcitabine and trastuzumab.

Targeted Therapy Used for Treatment of Metastatic Breast Cancer

HER2-Targeted Agents

See Table 12.8.

TABLE 12.8

HER2-Targeted Agents

HER2-Targeted Monoclonal Antibodies
Trastuzumab • 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly OR • 8 mg/kg IV loading dose followed by 6 mg/kg IV every 3 wk
Pertuzumab 840 mg IV loading dose followed by 420 mg IV every 3 wk
Trastuzumab/pertuzumab/hyaluronidase (Phesgo) Loading dose: • 15 mL subcutaneously administered over approximately 8 min • 600 mg trastuzumab, 1200 mg pertuzumab, 30,000 U hyaluronidase per 15 mL Maintenance dose: • 10 mL subcutaneously administered over approximately 5 min every 3 wk

• 600 mg trastuzumab, 600 mg pertuzumab, 20,000 U hyaluronidase per 10 mL
Margetuximab 15 mg/kg IV every 3 wk
Trastuzumab Biosimilar Antibodies—all IV every 3 wk
Herzuma (trastuzumab-pkrb) Kanjinti (trastuzumab-anns) Ogivri (trastuzumab-dkst) Ontruzant (trastuzumab-dttb) Trazimera (trastuzumab-qyyp)
HER2-Targeted Antibody-Drug Conjugates
Ado-trastuzumab emtansine 3.6 mg/kg IV every 3 wk
Fam-trastuzumab deruxtecan 5.4 mg/kg IV every 3 wk
HER2-Targeted Tyrosine Kinase Inhibitors
Lapatinib 1250 mg PO daily (continuous) in combination with capecitabine 1000 mg/m^2 PO twice daily on days 1-14 of a 21-day cycle
Neratinib • Early-stage breast cancer: 240 mg PO daily × 1 y Dose escalation can be considered for improved tolerance as follows: 120 mg PO daily × 1 wk, 160 mg PO daily × 1 wk, 240 mg PO daily for weeks 3-52 • Metastatic breast cancer: 240 mg PO daily (continuous) in combination with capecitabine 750 mg/m^2 PO twice daily on days 1-14 of a 21-day cycle
Tucatinib 300 mg PO twice daily (continuous) in combination with trastuzumab IV every 3 wk and capecitabine 1000 mg/m^2 PO twice daily on days 1-14 of a 21-day cycle

HER2-Targeted Monoclonal Antibodies

Trastuzumab (Herceptin)

Trastuzumab is a monoclonal antibody directed against HER2/neu, which has been found to be highly effective in the neoadjuvant, adjuvant, and metastatic breast cancer settings. The dose is 4 mg/kg as a loading dose followed by 2 mg/kg weekly. An every-3-week regimen with a loading dose of 8 mg/kg followed by 6 mg/kg is the most commonly used regimen. Addition of 1 year of adjuvant trastuzumab improves DFS and OS among women with HER2-positive breast cancer. In general, trastuzumab is given in combination with chemotherapy in neoadjuvant, adjuvant, and metastatic settings.

Trastuzumab is well tolerated, although, rarely, it can cause infusion reactions and pulmonary toxicity. The major side effect from trastuzumab is cardiac toxicity, particularly when it is used with or after anthracyclines. With anthracycline-containing regimens, the congestive heart failure rate is about 2% to 4%. Nonanthracycline-based regimens such as TCH did not show increased cardiac toxicity. It is important to monitor cardiac function with an echocardiogram or multigated acquisition scan at baseline and every 3 months while patients are receiving trastuzumab.

Pertuzumab (Perjeta)

Pertuzumab is a humanized monoclonal antibody that binds HER2 at a different epitope of the HER2 extracellular domain than that of trastuzumab. It prevents HER2 from dimerizing with HER3. Similar to trastuzumab, pertuzumab causes antibody-dependent, cell-mediated cytotoxicity. Since pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action, when pertuzumab is combined with trastuzumab, it provides a more comprehensive blockade of HER2 signaling and results in greater antitumor activity in clinical trials. In the CLEOPATRA study, when pertuzumab was given with trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, in first-line treatment for HER2-positive metastatic breast cancer, it significantly prolonged PFS and OS. No additional cardiac toxicity was seen. The FDA-approved dose of pertuzumab is 840 mg, followed by 420 mg every 3 weeks.

Pertuzumab/Trastuzumab/Hyaluronidase-zzxf (Phesgo)

This is a fixed-dose, subcutaneous form of dual HER2-targeted therapy that is FDA approved for every-3-week administration. The loading dose is pertuzumab 1200 mg/trastuzumab 600 mg/hyaluronidase 30,000 U. Maintenance dosing is pertuzumab 600 mg/trastuzumab 600 mg/hyaluronidase 20,000 U once every 3 weeks. The risk for cardiotoxicity with this drug is similar to other HER2–directed therapies.

Margetuximab (Margenza)

Margetuximab is a monoclonal antibody that shares specificity and antiproliferative effects with trastuzumab; however, it was engineered with an Fc region that increases immune activation. In the SOPHIA trial, when combined with single-agent chemotherapy (either capecitabine, eribulin, gemcitabine, or vinorelbine), margetuximab demonstrated a 1 month improvement in PFS (5.8 months vs with 4.9 months; hazard ratio 0.76; P = .033) compared to trastuzumab/chemotherapy. Common adverse events included infusion-related reactions. Serious toxicities include left ventricular dysfunction (2%) and embryo-fetal toxicity. The dose of margetuximab is 15 mg/kg once every 3 weeks.

Trastuzumab Biosimilars

Recently, a number trastuzumab biosimilars have come to clinical practice. These drugs have noninferior clinical efficacy and similar toxicity to standard trastuzumab. Currently, Herzuma (trastuzumab-pkrb), Kanjinti (trastuzumab-anns), Ogivri (trastuzumab-dkst), Ontruzant (trastuzumab-dttb), and Trazimera (trastuzumab-qyyp) are FDA approved and can be used in all situations in which standard trastuzumab would be used. Cardiac monitoring should occur as would typically be recommended.

HER2-Targeted Antibody-Drug Conjugates

Ado-Trastuzumab Emtansine (Kadcyla)

T-DM1 is an antibody-drug conjugate composed of trastuzumab linked to a highly potent cytotoxic derivative of maytansine (DM1) by a stable linker. DM1 is a microtubule inhibitor. Trastuzumab targets the conjugate to HER2 receptors, and the stable linker releases the cytotoxic agent only when the compound is internalized through receptor endocytosis. T-DM1 has been found to be active in trastuzumab- and lapatinib-resistant metastatic breast cancer, as well as in trastuzumab-naïve tumors.

Results of the phase III EMILIA trial that compared trastuzumab emtansine with capecitabine plus lapatinib in advanced HER2-positive breast cancer showed an improvement in PFS and OS with the conjugate, leading to FDA approval of T-DM1 in 2013. Final OS results of the EMILA trial published in 2017 continued to demonstrate an OS advantage of T-DM1 compared to capecitabine plus lapatinib, despite crossover that was allowed from the control group to T-DM1 following initial result reporting.

In the TH3RESA trial, patients with progressive disease after two or more anti-HER therapies were randomized to T-DM1 or treatment of physician's choice (TPC). The median PFS was significantly longer with T-DM1. In an update of OS results published in 2017, a 7 month OS benefit of T-DM1 was found (22.7 vs 15.8 months) despite nearly 50% of patients crossing over from TPC to T-DM1.

The dose of T-DM1 is 3.6 mg/kg IV every 3 weeks. Side effects include thrombocytopenia, liver function abnormalities, and peripheral neuropathy. No significant increase in cardiomyopathy was seen; however, routine EF monitoring is recommended.

Fam-Trastuzumab Deruxtecan (Enhertu)

Trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. Trastuzumab deruxtecan has a higher drug-to-antibody ratio compared to T-DM1 (8 vs 3-4), and the released payload more easily crosses the cell membrane giving the potential for a cytotoxic effect on nearby cells, a so-called bystander effect. In the DESTINY-Breast01 trial, the confirmed RR was 60.9% and the median response duration was 20.7 months despite these patients being heavily pretreated (the median number of prior therapies was 6). Common toxicities include gastrointestinal issues and bone marrow suppression. A unique and important toxicity with this drug is interstitial lung disease (ILD). About 13.6% of patients had any grade ILD including four treatment-related deaths. This toxicity is more common in patients with Japanese ancestry (OR

3.6; 95% confidence interval [CI] 2.1-6.1; $P < .001$). Renal impairment also increases the risk. Early cessation of the drug and initiation of steroids is crucial when ILD is suspected. The FDA-approved dose is 5.4 mg/kg once every 3 weeks. Interestingly, in the DESTINY-Breast01 trial, 43 patients had lower expression of HER2 (a score of 1+ or 2+ on IHC, and no amplification of fluorescent in situ hybridization [FISH]), yet 44% had a response to treatment. Trastuzumab deruxtecan is currently under additional investigation in this HER2-low population of patients.

HER2-Targeted TKIs

The TKIs have proven to be an effective class of drugs in the treatment of HER2–positive breast cancers. These drugs are small molecules and bind to the intracellular aspect of their respective HER receptor, inhibiting the downstream signaling of the epidermal growth factor receptor (EGFR). It is suspected that it is due to the small, intracellular nature of the drug that allows it to penetrate the blood-brain barrier more effectively than some of the other therapies, and thus potentially more useful in the setting of CNS metastasis. The various TKIs differ in their specificity for the HER receptor. For example, lapatinib is a potent, small molecule inhibitor of the HER1 and HER2 tyrosine kinases, as well as EGFR-1. The inhibitory effects, though reversible, result in blockade of receptor-mediated activation and propagation of downstream signaling involved in regulation of cell proliferation and cell survival. Neratinib, by comparison, is an irreversible small molecule inhibitor of HER1, HER2, and HER4. Finally, tucatinib is a TKI that is highly selective for the kinase domain of HER2, and only minimally inhibits EGFR.

Lapatinib (Tykerb)

Lapatinib is approved for use in combination with capecitabine. It was compared to capecitabine alone in women with metastatic HER2–positive breast cancers who had progressed on previously lines of therapy, including an anthracycline, a taxane, and

trastuzumab. In the lapatinib plus capecitabine arm, the time to progression was increased at 8.4 months when compared to the capecitabine alone arm at 4.4 months (hazard ratio 0.49; 95% CI 0.34-0.71; $P < .001$). The study was not powered to detect significant differences in OS. FDA-approved dose of lapatinib is 1250 mg daily PO. The common side effects include diarrhea and rash. Historically, this has been used as third-line therapy after T-DM1; however, the use has waned with other more effective agents/combinations being approved.

Neratinib (Nerlynx)

Neratinib was approved by the FDA in 2017 for the extended adjuvant treatment of patients with early-stage HER2-amplified breast cancer, following adjuvant trastuzumab-based therapy based on the results of the phase III ExteNET as discussed in the adjuvant treatment section of this chapter. Neratinib has also been studied in the metastatic setting. The NALA trial compared neratinib/capecitabine with lapatinib/capecitabine after prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine. The neratinib-containing arm was found to have improved overall response rate (ORR) (32.8 vs 26.7; $P = .1201$) and median duration of response (8.5 vs 5.6 months), and fewer patients required intervention for CNS metastases. There was also a nonsignificant trend toward improved survival with the neratinib combination. Diarrhea was more severe in the neratinib arm, where antidiarrheal medication was mandated for the duration of cycle 1, compared to the lapatinib plus capecitabine arm, where antidiarrheal medication was optional.

Tucatinib (Tukysa)

Tucatinib is an oral TKI that is highly selective for the kinase domain of HER2 and only minimally inhibits EGFR.

In the phase III, double-blinded, placebo-controlled HER2CLIMB study, tucatinib was studied in combination with capecitabine and trastuzumab. Patients in this trial were previously treated with

trastuzumab, pertuzumab, and trastuzumab emtansine. This trial is unique in that it allowed patients with active, untreated brain metastases as well as those with treated brain metastases to enroll. Leptomeningeal disease was excluded. PFS at 1 year was 33.1% in the tucatinib-containing arm and 12.3% in the standard of care arm. The survival data for patients with brain metastases at 1 year are particularly encouraging. At 1 year, patients with CNS disease who received tucatinib-combination had a 24.9% survival rate, compared to 0.0 in the placebo-combination group (hazard ratio 0.48; 95% CI 0.34-0.69; $P < .001$). In this same population of patients with brain metastases, the tucatinib-combination group had a median duration of PFS of 7.6 months, compared to 5.4 months in the placebo-combination group. The most common adverse events in the tucatinib-combination group were diarrhea, plantar erythrodysesthesia syndrome, elevation of liver enzymes, and fatigue. Tucatinib is administered as 300 mg orally twice daily continuously, with capecitabine 1000 mg/m^2 administered twice daily on days 1 to 14 of a 21-day cycle and trastuzumab given IV every 3 weeks.

CDK4/6 Inhibitors for Metastatic Breast Cancer

Introduction of the novel class of drugs known as CDK4/6 inhibitors was a major advancement in the treatment of HR-positive breast cancer. Palbociclib, ribociclib, and abemaciclib are the FDA-approved CKD 4/6 inhibitors for the treatment of HR-positive metastatic breast cancer. There are evolving data on the role of palbociclib, ribociclib, and abemaciclib in early breast cancer also. Overall, CDK4/6 inhibitors are well tolerated. Leukopenia is the most common class-related side effect, but the incidence of febrile neutropenia is less than 2%. Abemaciclib causes more diarrhea, and ribociclib requires monitoring for QT prolongation. Importantly, postmarketing surveillance has demonstrated a measurable risk of potentially severe lung inflammation. Patients should be monitored for pulmonary signs such as hypoxia, cough, dyspnea, or radiographic changes. Those with grade 2 ILD should be considered

for dose interruption. Patients with grade 3 or 4 ILD should have the drug class discontinued.

Palbociclib (Ibrance)

Palbociclib is a CDK4/6 inhibitor that has been used in the treatment of hormone-positive metastatic breast cancer in combination with endocrine therapy. In the phase II trial, PALOMA-1, patients treated with letrozole and palbociclib had longer PFS compared to letrozole alone (20.2 vs 10.2 months). These results led to FDA approval of palbociclib with letrozole in the first-line metastatic setting in February 2015. The phase III study (PALOMA-2) confirmed this benefit, showing a median PFS of 27.6 months with letrozole plus palbociclib versus 14.5 months with letrozole alone (hazard ratio 0.563; $P < .0001$). In the PALOMA-3 study, patients with hormone-positive, HER2–negative breast cancer who had progressed during prior endocrine therapy were randomized to receive fulvestrant alone or fulvestrant with palbociclib. The median PFS was 9.5 months in the combination group and 4.6 months in the fulvestrant group. In February 2016, the FDA approved palbociclib in combination with fulvestrant for patients with advanced or metastatic hormone-sensitive breast cancer with progression on prior endocrine therapy. The most notable side effect of palbociclib is neutropenia, which occurs in the vast majority of patients, although the neutropenic fever incidence in these studies was less than 2%. FDA-approved dose of palbociclib is 125 mg daily for 3 weeks and 1 week off, repeating every 4 weeks.

Ribociclib (Kisqali)

Ribociclib was approved for use in combination with an AI as the initial endocrine treatment of metastatic HR-positive breast cancer based on the results of the MONALEESA-2 trial. In this trial, postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer were treated with letrozole/ribociclib or letrozole/placebo as first-line therapy. It was found that the primary endpoint of PFS was significantly longer in the ribociclib-containing

arm of 25.3 months when compared to the placebo-containing arm at 16.0 months. OS results remain immature at time of this writing. The MONALEESA-7 trial included 672 pre- or perimenopausal women who were randomized to first-line treatment with ribociclib or placebo with goserelin plus either a nonsteroidal AI or tamoxifen. There was an improvement if PFS was seen in the experimental arm (median PFS 24 vs 13 months; hazard ratio 0.55). At 3.5 years, OS was improved in the ribociclib arm (70% vs 46%; hazard ratio 0.71; P = .0097). The MONALEESA-3 trial comprised 726 patients with advanced HR-positive breast cancer and found that fulvestrant + ribociclib improved PFS when compared to fulvestrant alone (21 vs 13 months; hazard ratio 0.59), and an OS benefit at 42 months of 57.8% in the experimental group versus 45.9% in the placebo group.

The FDA-approved dose of ribociclib is 600 mg daily by mouth 3 weeks on followed by 1 week off treatment (with continuous AI therapy or usual schedule of fulvestrant). Notable side effects of this drug include neutropenia, QT interval prolongation, diarrhea, LFT elevation, and ILD. Electrocardiogram monitoring is recommended during the first cycle of treatment to assess for QT interval prolongation. Because of the increased risk for QT prolongation, ribociclib is not approved for use concurrent with tamoxifen. The NATALEE trial is evaluating the use of ribociclib in combination with endocrine therapy as adjuvant treatment for women and men of any menopausal status with early HR-positive, HER2-negative breast cancer. This trial is yet ongoing.

Abemaciclib (Verzenio)

Abemaciclib is the third CDK4/6 inhibitor that is approved for use in advanced breast cancer. It can be used in combination with AI or fulvestrant at a dose of 150 mg twice daily or as a single agent at a dose of 200 mg twice daily for disease progression following prior endocrine therapy and chemotherapy in the metastatic setting. It is unique in its greater specificity for CDK4 inhibition, which may

translate into a different side effect profile than the other drugs in this class.

The phase II MONARCH 1 study, which used abemaciclib 200 mg PO twice a day as a single agent in previously treated HR-positive metastatic breast cancer, was initially presented at the 2016 ASCO meeting and subsequently published. In this study, a 20% objective RR was found with over 40% of patients experiencing clinical benefit (including stable disease). In terms of side effects, abemaciclib is associated with less myelosuppression than the other medications in this class but is associated with more diarrhea, nausea, and vomiting.

Subsequently, the phase III MONARCH 2 study, which investigated abemaciclib 150 mg PO twice a day (continuous dosing) plus fulvestrant in HR-positive metastatic breast cancer patients previously treated with endocrine therapy, was published showing a significant improvement in OS with the addition of abemaciclib to fulvestrant (46.7 vs 37.3 months, $P < .001$) when compared to fulvestrant plus placebo. A more pronounced effect was seen in patients with visceral disease. The RR was also improved with the addition of abemaciclib. The MONARCH 3 study investigated abemaciclib plus a nonsteroidal AI as initial treatment of HR-positive metastatic breast cancer compared to AI alone. Median PFS was prolonged in the abemaciclib containing arm compared to AI alone (hazard ratio 0.54; 95% CI 0.41-0.72; $P = .000021$.) As seen in the MONARCH 1 study, common adverse events that occurred with abemaciclib in these studies included diarrhea, nausea, fatigue, and neutropenia.

PARP Inhibitors for Metastatic Breast Cancer

The PARP enzymes function to help repair DNA. Inhibition of the PARP enzymes results in double-stranded DNA breaks in dividing cells. In most cells, DNA double-strand breaks are able to be repaired through homologous recombination; however, in BRCA1/2-deficient cells, this mechanism is absent. Such cells rely on PARP

enzymes for DNA repair and when these enzymes are inhibited, the cells will die. This concept is the foundation for use of PARP inhibitors in germline or somatic BRCA1/2 mutation–positive breast cancer patients. Other breast cancers may also be susceptible to PARP inhibition, particularly triple-negative breast cancer where homologous recombination defects may also be present. Based upon supporting data, olaparib and talazoparib are category 1 options for those with germline BRCA1/2 mutations.

Olaparib (Lynparza)

Olaparib has been studied in a variety of breast cancer settings, including the phase III OlympiAD metastatic breast cancer trial. In this study, metastatic breast cancer patients with germline BRCA mutations were randomized to receive either olaparib 300 mg twice daily or chemotherapy of physician's choice (capecitabine, eribulin, or vinorelbine). The study showed a statistically significant 3-month improvement in PFS and 42% decrease in risk of disease progression with olaparib compared to standard chemotherapy. The RR was higher in the olaparib-treated patients (60% vs 29%), and grade 3 or higher adverse events occurred less frequently (37% vs 50%). Olaparib has also demonstrated efficacy in patients with somatic BRCA mutations, as supported by the TBCRC 048 trial. Results noted an ORR of 33% (90% CI 19%-51%) in the 54 patients with somatic BRCA mutations. Responses were also seen in patients with germline PALB2 mutations. For these patients, there was an 82% objective RR (90% CI 53%-96%) and the clinical benefit rate was 100% (90% CI 74%-100%). Median PFS for patients with a germline PALB2 mutation was 13.3 months. No responses were observed for somatic PALB2 mutations. No responses were observed for ATM or CHEK2 mutations.

Talazoparib (Talzenna)

Talazoparib is a PARP inhibitor that has demonstrated efficacy in patients who are deficient in the repair mechanism for double-stranded DNA breaks. Talazoparib works by two mechanisms:

catalytic inhibition of the PARP enzyme, which is responsible for repair of single-strand breaks. It also works by trapping PARP at the site of DNA damage. Prior data have suggested that the addition of PARP trapping provides a more effective method of cell death. Talazoparib has been tested in the phase III EMBRACA trial. In the trial, patients with a germline BRCA mutation were randomized to talazoparib or to physician's choice of single-agent chemotherapy. The median PFS among the 287 patients who received talazoparib was 8.6 versus 5.6 months (hazard ratio 0.54; $P < .001$).

Other PARP Inhibitors

Rucaparib, veliparib, and niraparib are other PARP inhibitors that are currently being studied in breast cancer but are not FDA approved for use.

Other Agents Used for Treatment of Metastatic Breast Cancer

Fulvestrant (Faslodex)

Fulvestrant is an ER antagonist (ER downregulator), and it is indicated in the treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly on days 1, 15, and 29 and once monthly thereafter. Side effects are mainly related to pain and injection site reaction.

Alpelisib (Piqray)

Alpelisib is an α-specific PI3K inhibitor that was shown to improve PFS for patients with ER+/HER2−, PIK3-mutated advanced breast cancer when used in combination with fulvestrant as per the SOLAR-1 study. The PFS difference was 11.0 versus 5.7 months (hazard ratio 0.65; $P < .001$). Importantly, there was no difference in PFS noted for the patients without PIK3CA mutation. The use of

alpelisib is associated with risk of hyperglycemia, rash, and diarrhea. Prophylactic antihistamine use is recommended for prevention of rash, and metformin is the medication of choice for management of hyperglycemia.

Everolimus (Afinitor)

Everolimus is FDA approved for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole. A randomized phase III study (BOLERO-2) showed everolimus 10 mg per day plus exemestane 25 mg/d improved PFS compared to placebo plus exemestane 25 mg/d. The most common adverse reactions in patients receiving everolimus and exemestane were stomatitis, infections, rash, fatigue, diarrhea, hyperglycemia, and pneumonitis.

Neurotrophic Tropomyosin Receptor Kinase–Targeted Medications

The neurotrophic tropomyosin receptor kinase (NTRK) pathway has been identified as a driver of malignancies in a number of cancers. Overall, NTRK gene mutations are rare. Breast cancers in general have a low incidence of an NTRK fusion gene mutation (<5%), but in a rare type of breast cancer, such as secretory carcinoma of the breast, the frequency of NTRK gene fusions can be much higher (>90%). NTRK gene fusions can be identified by various methods, including PCR, FISH, and NGS. The FDA has granted NTRK inhibitor tumor-agnostic approval, meaning that the drug can be used in any solid tumor type with the particular genomic alteration and no known acquired resistance, and there is no satisfactory alternative for treatment.

Larotrectinib (Vitrakvi)

Larotrectinib is a highly selective inhibitor of tropomyosin receptor kinases. In a trial assessing 55 adults and children with NTRK fusion–positive cancers as detected by molecular profiling, patients

treated with larotrectinib had an ORR of 75% according to independent review. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression free. Adverse events were usually grade 1 and included anemia, an increase in alanine aminotransferase or aspartate aminotransferase level, weight increase, and a decrease in the neutrophil count.

Entrectinib (Rozlytrek)

Entrectinib is a potent oral inhibitor of the tyrosine kinases TRKA/B/C, ROS1, and ALK. In the trial leading to FDA approval, patients were included if they had a metastatic solid cancer, with or without CNS disease, harbored of NTRK1/2/3, ROS1, or ALK gene fusions, and were naïve to prior TKI treatment. Entrectinib demonstrated antitumor activity in patients with rearrangements in the NTRK, ROS1, or ALK genes; 3 of 54 patients had a complete response. In patients with CNS disease, response was noted in 63% of patients. Some adverse events such as altered taste, neuropathy, cognitive changes, and weight gain are thought to be on-target toxicities of entrectinib mediated by TRK receptor inhibition.

Selected Chemotherapy Agents Used for Metastatic Breast Cancer

Capecitabine (Xeloda)

Capecitabine (Xeloda) is a fluoropyrimidine carbamate, and it is an orally administered systemic prodrug of 5′-deoxy-5-fluorouridine (5′-DFUR), which is converted to 5-fluorouracil. It is indicated as monotherapy for metastatic breast cancer and is used in combination with certain targeted agents. The FDA-approved dose is 1250 mg/m^2 twice a day given for 2 weeks on and 1 week off, repeating every 21 days. For practical purposes, most clinicians use 1000 mg/m^2 twice a day 2 weeks on, 1 week off. A 7 days on, 7 days off schedule can also be considered. The most common side effects are hand-foot syndrome and diarrhea. Patients should be educated about management of the hand-foot syndrome.

Eribulin (Halaven)

Eribulin mesylate is a nontaxane, tubulin, and microtubule-targeting chemotherapeutic agent that binds directly with tubulin-disrupting mitotic spindles and inhibits microtubule polymerization. A phase III study compared eribulin to TPC in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane. This study showed improvement in PFS and OS with eribulin. The most common side effects were neutropenia and peripheral neuropathy. Eribulin is the only chemotherapy agent that has shown a survival advantage in late lines of therapy for breast cancer. The FDA-approved dose of eribulin is 1.4 mg/m^2 administered on days 1 and 8 of a 21-day schedule.

Sacituzumab (Trodelvy)

Sacituzumab is an antibody-drug conjugate composed of an anti-trop-2 antibody coupled to the active metabolite of irinotecan. It has been approved for patients with metastatic triple-negative breast cancer who have progressed on at least two lines of prior therapies based upon the ASCENT trial. In this trial, 529 patients were randomized to either sacituzumab or single-agent chemotherapy (capecitabine, eribulin, vinorelbine, or gemcitabine). Results demonstrated improved median PFS (5.6 vs 1.7 months; hazard ratio 0.41; $P < .0001$) and median OS (12.1 vs 6.7 months; hazard ratio 0.48; $P < .0001$). The recommended dose is 10 mg/kg IV on days 1 and 8 cycled every 3 weeks. There are some data to support use in patients with metastatic HR-positive, HER2–negative breast cancer. The phase I/II IMMU-132-01 trial administered the drug to 54 patients who had received at least two prior therapies. At 11.5 months, the ORR was 31.5% (95% CI 19.5%-45.6%; 17 partial responses). Further trials in this space are ongoing. Common toxicities were neutropenia (including febrile neutropenia), diarrhea, and anemia. The use of G-CSF with this medication can be considered for neutropenic fever prevention.

Nab-Paclitaxel (Abraxane)

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a novel paclitaxel formulation that does not require cremophor or polysorbate 80 for solubilization, thus reducing solvent-related toxicity and micelle formation. The FDA-approved dose of nab-paclitaxel is 260 mg/m^2 every 3 weeks for the treatment of metastatic breast cancer. The side effects include neutropenia, peripheral neuropathy, nausea, etc. Due to lack of cremophor, nab-paclitaxel does not require premedication with steroids.

Ixabepilone (Ixempra)

This drug belongs to a novel class of drugs called epothilones. Epothilones are nontaxane microtubule–stabilizing agents. The tubulin-polymerizing activity of ixabepilone is stronger than paclitaxel. It has proven efficacy in taxane-resistant settings. Ixabepilone has low susceptibility to tumor resistance mechanisms such as P-glycoprotein (P-gp) and multidrug-resistance protein-1. The FDA approved ixabepilone in combination with capecitabine in patients with metastatic or locally advanced breast cancer, who are resistant to or refractory to a taxane and anthracycline. Ixabepilone is also approved as monotherapy in patients who are resistant or refractory to taxane, anthracycline, and capecitabine. The dose is 40 mg/m^2 administered over 3 hours every 3 weeks. Patients should be premedicated with diphenhydramine and cimetidine an hour prior to the infusion with ixabepilone.

Use of Immunotherapy in Metastatic Breast Cancer

It is known that PD-L1 is expressed in 20% to 30% of breast cancers with more frequent expression in HER2+ and triple-negative disease compared to hormone-sensitive disease. As of this writing, two PD-L1 inhibitors have been approved for use in metastatic triple-negative breast cancer: pembrolizumab and atezolizumab. Additionally, in May 2017, the FDA approved pembrolizumab for patients with unresectable or metastatic, MSI high, dMMR, or TMB high solid tumors who have progressed on prior treatment and have no satisfactory treatment options.

Pembrolizumab (Keytruda)

In the KEYNOTE-355 trial, patients with untreated metastatic triple-negative breast cancer were assigned to receive pembrolizumab every 3 weeks plus chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin) or placebo plus chemotherapy. The participants were evaluated for a Combined Positive Score (CPS) via IHC 22C3. The CPS is a ratio of the PD-L1–expressing cells, which could include tumor cells, lymphocytes, and macrophages, to the number of all tumor cells. Among patients with CPS of 10 or more, median PFS was 9.7 months with pembrolizumab-chemotherapy and 5.6 months with placebo-chemotherapy (hazard ratio for progression or death 0·65; P = .0012). Grade 3 to 5 treatment-related adverse event rates were 68% in the pembrolizumab-chemotherapy group and 67% in the placebo-chemotherapy group.

Atezolizumab (Tecentriq)

The combination of atezolizumab plus nab-paclitaxel was approved for treatment of first-line, PD-L1–positive metastatic triple-negative breast cancer based on results of the IMPASSION 130 study. In this trial, 902 patients with triple-negative breast cancer who had not received treatment in the metastatic setting were randomized to atezolizumab/nab-paclitaxel versus placebo/nab-paclitaxel. Patients who had tumors that expressed PD-L1 of at least 1% had improvement in PFS (7.5 vs 5.0 months; hazard ratio 0.62; $P < .001$) and OS (25 vs 15.5 months; hazard ratio 0.62) with the immunotherapy-containing treatment. It is important to note that in this trial, in comparison to some other trials, the PD-L1 testing was on tumor immune cells, not tumor cells. Additionally, the cells were tested via SP142 and not 22C3, as in the CPS (see above "Pembrolizumab").

Role of NGS for Metastatic Breast Cancer

NGS has become widely available with the advent of many commercial assays. In the metastatic breast cancer setting, NGS may help to identify targets for treatments that are FDA approved or

accessible via clinical trial participation or by use of an FDA-approved medication in an off-label manner. These tests are currently standard of care and should be carried out on all patients with metastatic breast cancer. NGS can test for BRCA1/2 mutations, PIK3CA mutations, NTRK fusions, microsatellite stability status, and TMB. Each of the aforementioned abnormalities has a potential targeted therapy.

Supportive Care Agents

Bisphosphonates

- Bisphosphonates should be used in patients with bony metastatic disease because they prevent progression of lytic lesions, delay skeletal-related events, and decrease pain. However, the optimal frequencies of administration and duration of therapy are not known.
- Zoledronic acid (4 mg by 15-minute infusion) and pamidronate (90 mg by 2-hour infusion) are two available bisphosphonates approved for bony metastatic disease.
- In the OPTIMIZE-2 trial, metastatic breast cancer patients with bone metastasis were randomized to receive zoledronic acid 4 mg IV once every 4 weeks or once every 12 weeks for 1 year. The incidence of skeletal-related events and safety profile was similar for both groups. Based on these results, 12-week interval of dosing for zoledronic acid can be considered noninferior to 4-week interval of dosing.
- Osteonecrosis of the jaw (ONJ) is a very rare but a potential complication of long-term treatment with intravenous bisphosphonates.

RANK Ligand Inhibitor

The RANK, the RANK ligand, and osteoprotegerin, a decoy receptor for RANK, regulate osteoclastogenesis and may play a key role in bone metastasis. Denosumab (Xgeva), a fully human monoclonal

antibody that binds to and neutralizes RANK ligand, inhibits osteoclast function, prevents generalized bone resorption and local bone destruction, and has become a therapeutic option for preventing or delaying first on-study skeletal-related events in various malignancies.

It is approved for patients with bone metastasis from breast cancer, prostate cancer, and other solid tumors. The dose is 120 mg subcutaneous every 4 weeks. It can cause significant hypocalcemia. So patients should take appropriate calcium replacement. The incidence of ONJ is about 2.2% with denosumab. It does not have to be adjusted for renal impairment.

CNS Metastasis

CNS metastasis may consist of either parenchymal or leptomeningeal metastasis. The control of systemic disease is crucial to improving the survival of patients with resectable brain metastasis. Symptomatic brain metastases and patients with moderate to severe edema on MRI or CT should be treated with dexamethasone. The standard treatment for multiple brain lesions remains local therapy with either whole-brain radiation therapy or stereotactic radiosurgery (SRS) for symptom control. Therapy for a single-brain metastasis includes either surgery or SRS. The superiority of intrathecal versus systemic chemotherapy in leptomeningeal metastasis is controversial.

Up to 50% of HER2-positive patients will develop brain metastases. In patients with HER2–positive disease and brain metastases, the NALA trial supports the use of neratinib with capecitabine. In this trial, there were fewer interventions needed for CNS disease in patients who were on neratinib plus capecitabine versus lapatinib plus capecitabine (cumulative incidence 22.8% vs 29.2%; P = .043). Additionally, the HER2CLIMB trial provides evidence supporting the use of tucatinib with trastuzumab and capecitabine for patients with metastatic HER2-positive breast cancer with CNS disease. Among the patients with brain metastases,

PFS at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group (hazard ratio 0.48; $P < .001$).

In patients with ER+ metastasis to the brain or with leptomeningeal disease, a recent study provided evidence supporting the use of abemaciclib in these patients. In the trial, abemaciclib was found to have achieved therapeutic concentrations in brain metastases tissue, far exceeding those necessary for CDK4 and CDK6 inhibition, though further studies are warranted. Additionally there are ongoing trials testing efficacy of sacituzumab in patients with HER2-negative metastatic breast cancer brain metastases.

Suggested Readings

1. Adams S, Robinson Diamond J, Hamilton EP, et al. *Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC)*. Abstract presented at: ASCO Annual Meeting; 2016; Chicago, IL. Abstract 1009.
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Renal Cell Cancer

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INTRODUCTION

Renal cell cancer (RCC) comprises several histologically, biologically, and clinically distinct entities that arise from the kidney. Historically, surgical resection for localized disease and cytokine-based immunotherapy for metastatic disease were the mainstays of therapy for RCC until 2005. Currently, advances in our understanding of the molecular mechanisms underlying individual subtypes of the disease have led to the development of newer, more effective, targeted approaches as well as immune checkpoint inhibitor (ICI)–based strategies for managing localized and metastatic RCC.

EPIDEMIOLOGY

- An estimated 76,080 new cases of cancer arising in the kidney and renal pelvis were expected in the United States in 2021, leading to approximately 13,780 deaths.
- Incidence is higher in men, with a male:female ratio of 1.8:1. It is also more common in African Americans and American Indian/Alaska Natives.
- Incidence from 2004 to 2008 increased by 4.1% per year in men and 3.3% per year in women, largely due to an increase in diagnosis of early stage disease. Mortality decreased during the same period by 0.4% per year in men and 0.6% in women. Both incidence and mortality have remained relatively stable from 2013 to 2017.
- Largely a disease of adulthood, with a peak incidence after the fifth decade of life, RCC may also occur in younger adults and children.

ETIOLOGY AND RISK FACTORS

Nonhereditary Risk Factors

- Tobacco use: Up to one-third of cases in men and one-fourth of cases in women may be linked to smoking
- Hypertension
- Occupational exposure to trichloroethylene, cadmium, asbestos, and petroleum products
- Obesity
- Chronic kidney disease and acquired cystic disease of the kidney associated with long-term dialysis

Genetic Predisposition/Familial Syndromes

Several familial kidney cancer syndromes have been identified. Although they represent a minority of RCC patients, individuals affected by these heritable disorders have a predisposition for developing kidney cancer, which is often bilateral and multifocal. Systematic evaluation of at-risk families has helped elucidate the molecular mechanisms underlying the origins of several types of kidney cancer. Several forms of sporadic kidney cancer have histologically similar familial counterparts with which they share aberrant oncogenic pathways. The following familial kidney cancer syndromes have been described:

- ***Von Hippel-Lindau (VHL) disease***
  - VHL is inherited in an autosomal dominant pattern.
  - Affected individuals have a predilection for developing a variety of tumors, including bilateral, multifocal renal tumors (clear cell RCC [ccRCC]); pancreatic neuroendocrine tumors; renal and pancreatic cysts; central nervous system (CNS) hemangioblastomas; retinal angiomas; pheochromocytomas; endolymphatic sac tumors; and epididymal/broad ligament cystadenomas.
  - Genetic linkage analysis led to the identification of the *VHL* tumor suppressor gene located on chromosome 3p25. Affected individuals have a mutated/deleted allele of the *VHL* gene in their germline. Acquisition of a somatic "second hit" that inactivates the normal copy of *VHL* leads to tumor formation in the affected organ(s).
- ***Hereditary papillary renal carcinoma (HPRC)***
  - Affected individuals have bilateral, multifocal type 1 papillary RCC. There are no known extrarenal manifestations of this disease.
  - The underlying genetic alteration is an activating germline mutation in the *MET* proto-oncogene, located on the long arm of chromosome 7, accompanied by a nonrandom duplication of the aberrant chromosome 7 (resulting in trisomy or polysomy 7).
  - Patients usually present with renal tumors in or beyond the fifth decade of life, although an early-onset form that presents in the second or third decades has also been described.
- ***Birt-Hogg-Dubé (BHD) syndrome***
  - Affected individuals are at increased risk of developing cutaneous fibrofolliculomas, pulmonary cysts predisposing to the development of spontaneous pneumothorax, and renal tumors.

- Several histologic types of renal tumors have been described in BHD, including chromophobe (34%), hybrid chromophobe oncocytomas (50%), clear cell, papillary, and oncocytomas.
- The BHD gene, localized to chromosome 17p11, encodes a protein known as folliculin. Identification of somatic "second hit" mutations in *BHD/folliculin* indicates that this gene functions as a tumor suppressor.

- ***Hereditary leiomyomatosis and RCC (HLRCC)***
  - Affected individuals have a predisposition to developing multiple cutaneous and uterine leiomyomas, as well as papillary RCC.
  - Renal tumors are often solitary, but bilateral, multifocal disease has also been described.
  - Histologically, these tumors have a distinct appearance and may be mistaken for collecting duct RCC. The distinctive histopathologic hallmark of these tumors is the presence of a large nucleus with a prominent orangiophilic nucleolus surrounded by a halo.
  - Tumors tend to metastasize early and have a characteristically aggressive clinical course.
  - The underlying defect is a germline mutation in the gene encoding the Krebs cycle enzyme fumarate hydratase (FH), located on chromosome 1. Loss of FH and the accompanying alteration in Krebs cycle function result in a metabolic switch characterized by a reliance on aerobic glycolysis for cellular energy needs (Warburg effect). Other critical cellular events associated with loss of FH include dysregulated hypoxia-inducible factor 1-alpha (HIF1-α) expression and downregulation of AMP-activated protein kinase (AMPK), a key cellular energy sensor, and impaired mitochondrial function leading to loss of oxidative phosphorylation.
- ***Succinate dehydrogenase–associated RCC (SDH-RCC)***
  - Succinate dehydrogenase is a multiunit mitochondrial enzymatic complex that catalyzes the conversion of succinate to fumarate in the Krebs cycle.
  - Germline mutations in the genes encoding SDHA, SDHB, SDHC, and SDHD have been identified in patients with hereditary forms of kidney cancer. Patients with germline *SDH* mutations are also at risk for developing pheochromocytomas and paragangliomas as well as gastrointestinal stromal tumors.
  - Loss of SDH activity leads to impaired Krebs cycle function and may result in metabolic and biochemical alterations similar to those seen with *FH* inactivation, although these changes are not as well understood as those occurring in FH-deficient RCC.
  - The precise histologic variants associated with SDH-RCC remain to be determined and may vary depending on the SDH subunit affected. RCC is seen more frequently in patients with SDHB alteration than with alterations in the other subunits. SDH-RCC is characterized by loss of SDH staining by immunohistochemistry.
- ***Other genes associated with hereditary kidney cancer***
  - Mutations in multiple genes involving the liver kinase B1/tuberous sclerosis complex (TSC)/mammalian target of rapamycin (mTOR) are associated with familial forms of RCC.
  - Mutations in the genes responsible for TSC1/2 have been associated with kidney cancer. While the majority of renal tumors resulting from TSC mutations are benign (angiomyolipomas), clear cell, papillary, and other subtypes of RCC have also been described.
  - More recently, familial kidney cancer associated with mutations in the BAP1 gene has been recognized.

PATHOLOGIC CLASSIFICATION

Based on histopathologic features, the vast majority of RCC can be classified into the following subtypes:

- ccRCC: The most common variety, comprising 75% to 85% of all kidney cancers. Composed predominantly of cells with a clear cytoplasm.

- Papillary RCC: Further divided into type 1 and type 2 based on morphologic appearance. Represents approximately 10% to 15% of all kidney cancers.
- Chromophobe RCC: Represents approximately 5% of all malignant renal neoplasms. Characterized histologically by the presence of sheets of cells with pale or eosinophilic granular cytoplasm.
- RCC associated with HLRCC: Characterized by the presence of a large nucleus with a prominent orangiophilic nucleolus surrounded by a halo.
- Microphthalmia-associated transcription factor translocation renal cell carcinoma (MiTF-tRCC): More commonly seen in children and young adults but can occur at any age. Characterized by translocations involving one of the four MiT family genes—TFE3, TFEB, TFEC, or MiTF.
- Collecting duct RCC: Rare (<1%) variant believed to originate in the collecting system.
- Medullary RCC: Has some features suggestive of collecting duct RCC, is seen almost exclusively in patients with sickle cell trait, and is characterized by an aggressive clinical course.
- Unclassified RCC: Represents approximately 3% to 5% of renal tumors. Lacks distinct features of a particular subtype or variant.
- Renal tumors with sarcomatoid features do not comprise a separate entity. Instead, they represent sarcomatoid differentiation of one of the subtypes of RCC. Generally associated with poor prognosis.

MOLECULAR MECHANISMS

The identification of familial forms of kidney cancer was an important step in unraveling the complex aberrant pathways leading to the development of several types of both hereditary and sporadic RCCs. This has enabled the development of therapeutic agents that target pathways critical to the development and growth of these tumors.

Clear Cell RCC

- The vast majority of patients with sporadic ccRCC show evidence of *VHL* inactivation in tumor tissue (somatic alteration) resulting from either mutation or promoter hypermethylation. The absence of functionally active VHL protein has several consequences, the best understood of which is the accumulation of a group of transcription factors called hypoxia-inducible factors (HIF1 and HIF2).

- Increased intracellular HIF leads to transcriptional upregulation of several pro-angiogenic growth and survival factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-α), and the glucose transporter 1. This sequence of events, particularly upregulation of HIF2, appears to be important in the genesis and propagation of ccRCC.
- More recently, mutations in several genes associated with chromatin remodeling, including *PBRM1*, and *SETD2* and in the *BAP1* gene, which encodes a deubiquitinase, have been identified in some kidney tumors. The biologic significance of these alterations is under investigation.
- A recent effort at molecular characterization of ccRCC by The Cancer Genome Atlas (TCGA) reiterated the association of both *VHL* mutations and alterations in chromatin remodeling genes with ccRCC. In addition, high-grade tumors and those with a poor prognosis demonstrated changes consistent with a glycolytic shift. Several components of these pathways are potential targets for novel therapeutic agents.

Type 1 Papillary RCC

- MET is a cell surface receptor normally activated on binding its ligand, hepatocyte growth factor (HGF). The HGF/MET axis mediates a variety of biologic functions including cell growth, proliferation, and motility. Activating germline mutations in the *MET* proto-oncogene (which render the receptor constitutionally active) are responsible for the bilateral, multifocal, type 1 papillary renal tumors seen in patients with the inherited kidney cancer predisposition noted in HPRC.
- Activating somatic mutations in the tyrosine kinase domain of *MET* have also been identified in ~15% of patients with sporadic papillary RCC. Duplication of chromosome 7, where genes for both MET and HGF are located, is seen more frequently than *MET* mutations in sporadic papillary tumors (~70% in one series) and has been suggested as an alternative mechanism for activation of the HGF/MET pathway. Gain of chromosome 17 has also been identified as a frequent event in type 1 papillary RCC.
- Agents targeting the MET pathway are currently being evaluated in patients with papillary RCC.

Type 2 Papillary RCC

- This includes a heterogeneous group of tumors with papillary architecture but with features inconsistent with type 1 papillary tumors.

- Kidney cancer associated with HLRCC is generally characterized by a papillary architecture and was previously described as a type 2 papillary RCC variant.
- The underlying molecular defect in HLRCC-related tumors is the inactivation of the Krebs cycle enzyme FH, leading to accumulation of its substrate fumarate. Fumarate interferes with HIF degradation and leads to its accumulation and consequent transcriptional activation of its target genes (VEGF, PDGF, TGF-α, etc). Fumarate accumulation also leads to mitochondrial dysfunction and impaired oxidative phosphorylation, with consequent dependence of these cells on aerobic glycolysis as the primary source of ATP production (Warburg effect). While no sporadic counterpart for this tumor has been described, it is speculated that some sporadic type 2 papillary tumors may be associated with impaired Krebs cycle activity.
- A comprehensive molecular characterization of papillary renal tumors undertaken by TCGA has also identified changes involving CDKN2A, the NRF2 oxidative stress pathway, and chromatin remodeling genes, particularly *SETD2* in type 2 papillary RCC.

Chromophobe RCC

- The precise biochemical aberrations underlying chromophobe RCC are being investigated; however, patients with BHD syndrome often present with chromophobe renal tumors, and understanding the molecular alterations in BHD-associated tumors may provide some insight into those underlying sporadic chromophobe RCC.
- The gene for BHD (*folliculin*) appears to interact with the mTOR and AMPK pathways, which may be important in chromophobe tumors and, potentially, other histologic RCC subtypes seen in BHD.
- Molecular characterization of sporadic chromophobe RCC under the aegis of TCGA revealed loss of most or all of chromosomes 1, 2, 6, 10, 13, and 17. In addition, *TP53* was mutated in 32% of cases, and mTOR pathway changes occurred in 23% of cases. Mitochondrial DNA alterations as well as mutations in the TERT promoter were additional recurrent changes seen in these tumors.

Other Subtypes

- Other histologic subtypes of RCC include (1) medullary RCC, seen almost exclusively in association with sickle cell trait, which is characterized by loss of SMARCB1 and evidence of DNA replication stress, and (2)

collecting duct RCC, which shares similarities with upper urinary tract tumors.
- MiTF-tRCCs or translocation RCCs are so named because of the presence in these tumors of characteristic translocations involving members of the microphthalmia transcription factor/transcription factor E (MiTF/TFE). In its most common form, tumors exhibit translocations involving TFE3. These tumors are more common in children and young adults and can exhibit aggressive clinical behavior with a propensity for early metastasis.

CLINICAL PRESENTATION

- Many renal masses are found incidentally during evaluation for unrelated medical issues or metastatic foci.
- Only 10% of patients present with the classic triad of hematuria, pain, and flank mass.
- Initial presentation may be a paraneoplastic syndrome or laboratory abnormality, such as elevated erythrocyte sedimentation rate, weight loss/cachexia, hypertension, anemia, hypercalcemia (ectopic release of parathyroid hormone–like substance), elevated alkaline phosphatase, polycythemia (increased erythropoietin), and Stauffer syndrome (reversible, hepatic dysfunction not related to hepatic metastasis, which usually resolves once the primary tumor is removed).
- Approximately 50% of RCC patients present with localized disease, 25% with locally advanced disease, and 25% to 30% with metastatic disease. Of those without evidence of metastatic disease at presentation, approximately 30% will go on to develop metastases subsequently.
- Common sites of metastatic spread include the lung (70%-75%), lymph nodes (30%-40%), bone (20%-25%), liver (20%-25%), and CNS.

DIAGNOSIS AND EVALUATION

- Initial workup for a patient with a renal mass includes a history and physical examination, complete blood count with differential, full chemistry panel, and prothrombin time/partial thromboplastin time.
- Computed tomography (CT) scan of the abdomen and pelvis, with and without contrast, is the standard for evaluating the renal mass and regional lymph nodes. If the CT scan suggests renal vein and/or inferior vena cava involvement, a magnetic resonance image (MRI) of the abdomen and chest imaging is warranted.

- Chest x-ray is also recommended. Chest CT is indicated in the presence of an abnormal x-ray, a large primary tumor, or symptoms suggestive of pulmonary or mediastinal involvement such as cough, hemoptysis, or chest pain.
- Bone scan is indicated in patients with elevated alkaline phosphatase, hypercalcemia, pathologic fracture, or bone pain.
- MRI of the brain is usually reserved for patients with clinical features suggesting brain metastases, but is increasingly performed in some centers as part of initial staging in asymptomatic patients with known metastatic disease.

STAGING

The most commonly used system for staging RCC is the tumor–lymph node–metastasis staging system outlined by the American Joint Committee on Cancer (AJCC). Stage I disease encompasses any tumor not greater than 7 cm in greatest dimension and is limited to the kidney. Stage II includes any tumor greater than 7 cm in greatest dimension but is limited to the kidney. Stage III disease is present if there is metastasis to regional lymph nodes or if the tumor extends into the major veins or perinephric tissues but not the ipsilateral adrenal gland or Gerota fascia. Stage IV disease includes any distant metastasis or tumor invading beyond Gerota fascia or contiguous extension into the ipsilateral adrenal gland.

PROGNOSTIC FACTORS

- Several tumor and patient characteristics appear to influence outcome for patients with localized kidney cancer. Nomograms based on factors such as tumor stage and nuclear grade, tumor histology, mode of presentation, and performance status are used to predict the risk of disease recurrence following nephrectomy. Several such nomograms are currently available and have gained acceptance in both clinical practice and clinical trial design as an effective means of risk stratification.
- In patients with metastatic disease, clinical characteristics (performance status, prior nephrectomy, number of metastatic sites, etc.) as well as laboratory parameters (serum lactate dehydrogenase, serum calcium, hemoglobin, etc.) are predictive of survival. A widely used prognostic model based on patients treated with either cytokines or chemotherapeutic

agents (Memorial Sloan-Kettering Cancer Center [MSKCC] prognostic criteria) implicates the following features with poor outcome:
    - Poor performance status (Karnofsky Performance Score < 80)
    - Elevated lactate dehydrogenase (>1.5 × upper limit of normal)
    - Elevated corrected calcium (>10 mg/dL)
    - Low hemoglobin (<lower limit of normal)
    - Time for diagnosis to systemic therapy < 1 year
- The presence or absence of one or more of these prognostic features allows stratification of patients into the following prognostic categories:
    - Favorable: no risk factors, median survival 19.9 months
    - Intermediate: one or two risk factors, median survival 10.3 months
    - Poor: three to five risk factors, median survival 3.9 months
- With the advent of VEGF pathway antagonists, the role of the above prognostic criteria and risk stratification have been reexamined. Based on retrospective analyses, time from diagnosis to therapy, elevated calcium, decreased hemoglobin, and poor performance status remain important predictors of poor outcome; additionally, elevated neutrophil count and platelet count also portend poor prognosis in these models (IMDC [International Metastatic RCC Database Consortium] model for risk stratification, now the most widely used system for prognostication)

TREATMENT OF LOCALIZED RCC

Surgery

- For patients with early stage localized RCC, surgical resection is often curative; for small renal masses (<4 cm), a partial nephrectomy/nephron-sparing surgery is typically performed using an open, laparoscopic, or robotic-assisted approach.
- For tumors > 4 cm, radical nephrectomy (open or laparoscopic procedure) as well as nephron-sparing procedures may be considered. The size of the primary tumor, tumor stage, age, medical comorbidities, renal function, and metastatic potential are some of the factors that guide the choice of radical nephrectomy versus nephron-sparing surgery.
- Active surveillance of small renal masses is also an alternative option in selected patients including the elderly and those with significant competing health risks and comorbidities.
- Less invasive techniques such as radiofrequency ablation and cryotherapy are being evaluated and may be effective in eradicating smaller renal tumors; however, studies demonstrate an increased risk of local recurrence when compared to surgery, and long-term outcome data are lacking.

Adjuvant Therapy

Studies of Adjuvant Therapy Evaluating VEGF Receptor or mTOR Targeted Agents

- Following the demonstration that VEGF receptor (VEGFR) and mTOR inhibitors were active in patients with advanced ccRCC, a variety of studies evaluated the efficacy of these agents in improving recurrence-free outcomes in high-risk patients following resection of the primary tumor.
- These studies largely failed to demonstrate a significant benefit to adjuvant therapy, although one study showed an improvement in disease-free survival (DFS); two of the earliest studies are highlighted below.

Adjuvant Sorafenib or Sunitinib (ECOG-ACRIN E2805) (Table 13.1)

TABLE 13.1

Results From Key Studies of Adjuvant Targeted Agents in Renal Cell Carcinoma

Agent(s)	Phase	Study Population	# Of Patients	DFS[a]	5 Year OS (%) [a]
Sunitinib vs placebo (S-TRAC) [b]	Phase 3	Clear cell RCC	615	Median **6.8 vs 5.6**	Data not mature
Sunitinib vs sorafenib vs placebo (ECOG-ACRIN E2805) [c]	Phase 3	Clear and non–clear cell RCC	1943	Median 5.8 vs 6.1 vs 6.6	77.9 vs 80.5 vs 80.3
Pembrolizumab vs placebo [d]	Phase 3	Clear cell RCC	994	**24 months DFS 77.3 vs 68.1 months**	Data not mature

[a]Statistically significant differences indicated in boldface type.

[b]Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375(23):2246-2254.

[c]Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG- ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387:2008-2016.

[d]Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*. 2021;385(8):683-694.

- E2805: This is the first phase 3 trial investigating the role of VEGFR inhibitors in the adjuvant setting in high-risk patients.
- A total of 1943 treatment-naïve patients with high-risk, nonmetastatic RCC were randomized to 54 weeks of sunitinib 50 mg/d (4 out of 6 week cycles),

sorafenib 400 mg twice/d continuously, or matched (sunitinib or sorafenib) placebo. A study amendment permitted reducing initial doses to sunitinib 37.5 mg/d (or matched placebo) or sorafenib 400 mg/d (or matched placebo) due to toxicity and high rate of treatment discontinuation.

- The study included heterogeneous histologies (*clear cell and non–clear cell*) and staging groups: 9% of sunitinib and sorafenib patients were stage I (AJCC). There was an equal proportion of intermediate-high versus very high risk (UCLA [University of California, Los Angeles] Integrated Staging System [UISS] risk stratification) in all treatment and placebo groups.
- Primary end point was DFS in the intention to treat patient population. Secondary end points were overall survival (OS), DFS (clear cell), and adverse events (AEs) classified by National Cancer Institute Common Terminology Criteria for Adverse Events such as tyrosine kinase inhibitor (TKI)–related hypertension, hand-foot syndrome, and rash.
- After a median follow-up of 5.8 years, median DFS was not significantly different among sunitinib, sorafenib, or placebo groups (70.0 vs 73.4 vs 79.6 months, respectively). No benefit was demonstrated in a subgroup analysis in patients with clear cell histology in either treatment arm. Five-year OS was comparable between the groups (sunitinib 77.9%; sorafenib 80.5%; placebo 80.3%).
- There were many dose reductions due to AEs. In patients starting on full doses, the overall treatment discontinuation rates were high (44% for sunitinib and 45% for sorafenib).
- Common AEs for sunitinib and sorafenib included hand-foot syndrome (15% and 33%, respectively), hypertension (17% and 16%), fatigue (18% and 7%), and rash (2% and 15%). Overall, there was a high proportion of grade 3 or greater AEs in the two treatment arms (sunitinib 63%; sorafenib 72%). Despite starting dose reductions, more than half of patients in each group experienced grade 3 or greater AEs.
- Subgroup analyses demonstrated no difference in DFS with patients who received full starting dose versus reduced, starting dose sunitinib or sorafenib (with trend favoring placebo at reduced doses), total dose received, or treatment duration.
- These data failed to provide data supporting the use of adjuvant sunitinib or sorafenib in high-risk RCC.

Adjuvant Sunitinib (S-TRAC Trial)

- Sunitinib is approved as a first-line treatment option for metastatic RCC. The E2805 (see above) demonstrated no benefit with adjuvant sunitinib or sorafenib in locally advanced RCC.

- However, a phase 3 trial (S-TRAC: sunitinib as adjuvant treatment for patients at high risk of recurrence of RCC following nephrectomy) highlighted the role of sunitinib in the adjuvant setting for nonmetastatic (locoregional) RCC with a high risk for relapse post nephrectomy.
- A total of 615 treatment-naïve patients with nonmetastatic (locoregional), high-risk ccRCC were prospectively randomized to sunitinib 50 mg/d or placebo post nephrectomy. Treatment was administered for 4 weeks on followed by 2 weeks off for 1 year. Patients were randomized in a stratified fashion based on the UISS high-risk group.
- Primary end point was DFS. Secondary end points were OS (did not reach maturity), safety, and health-related quality of life (HRQOL).
- After a median follow-up of 5.4 years in the sunitinib arm, the median DFS was significantly improved over placebo (6.8 vs 5.6 years; hazard ratio [HR] 0.76). About 36.6% of patient receiving sunitinib had a recurrence, second malignancy, or death compared to 47.1% in the placebo arm.
- Slightly more than half (54.2%) continued the initial dose of sunitinib 50 mg/d, with 55.6% completing the actual treatment. The majority of discontinuations were due to AEs.
- A higher percentage of patients in the sunitinib arm encountered AEs than those in placebo group (99.7% vs 88.5%). Most common AEs were diarrhea, palmar-plantar erythrodysesthesia (PPE), hypertension, fatigue, nausea, dysgeusia, and mucosal inflammation. More grade 3 or greater AEs were reported in the sunitinib versus placebo arm (63.4% vs 21.7%). There were 34.3% sunitinib dose reductions, 46.4% interrupted doses, and 28.1% treatment discontinuations. No treatment-related deaths were reported, and there were equivalent rates of *serious* AEs between the two arms.
- Adjuvant sunitinib improved median DFS in patients with locoregional ccRCC with a high risk for relapse post nephrectomy as compared to placebo. Based on these data, the Food and Drug Administration (FDA) recently approved the use of sunitinib in patients with RCC at high risk of recurrence. However, the lack of long-term/OS data and the toxicity profile has limited its use in the nonmetastatic setting.

Other Targeted Agents Evaluated in the Adjuvant Setting

- Several studies evaluating a variety of targeted agents including axitinib and pazopanib, or longer duration of therapy (1 vs 3 years), failed to demonstrate a significant clinical benefit.
- Adjuvant therapy with VEGFR- or mTOR-targeted agents is seldom, if ever, used in clinical practice, given the lack of benefit and associated

toxicity in multiple studies.

Adjuvant Therapy With ICIs

- Pembrolizumab is approved in combination with axitinib or lenvatinib for the treatment of previously untreated advanced ccRCC.
- Data from the international phase 3 KEYNOTE-564 study examined the utility of pembrolizumab in patients with high-risk ccRCC after complete resection of disease.
- Nine hundred ninety-four patients with high-risk ccRCC who were ≤12 weeks post nephrectomy +/− metastatectomy were randomized (1:1) to receive adjuvant pembrolizumab (200 mg every 3 weeks up to 17 cycles) or placebo.
- Primary end point was DFS. Secondary end points included OS and safety/tolerability.
- At a median follow-up of 24 months, median DFS was not met in either arm. Pembrolizumab reduced the risk of recurrence or death by 32% compared to placebo (HR 0.68, P = .001). DFS at 12 months was 85.7% versus 76.2% for the pembrolizumab and placebo groups, respectively. Estimated DFS rate at 24 months was 77.3% for pembrolizumab versus 68.1% for placebo. OS data were not mature at the time of this analysis.
- Grade 3-5 all-cause AEs were seen in 32.4% of the pembrolizumab group and 17.7% of the placebo group. Additionally, there were no deaths related to pembrolizumab.
- A supplemental biologics license application for adjuvant pembrolizumab is currently undergoing priority review by the FDA based on these findings.
- Several studies evaluating a variety of ICI-based strategies in the adjuvant setting are currently ongoing.

TREATMENT OF METASTATIC RCC

- Metastatic RCC is generally incurable, with most patients dying from their disease.
- The development of targeted therapeutic approaches directed against downstream consequences of VHL/HIF dysregulation and ICIs over the last 2 decades has resulted in significant improvements in the outcome of patients with advanced ccRCC. However, few patients enjoy durable remission, and the 5-year survival rates for patients with distant metastases is <15%.

- Most patients will require systemic therapy at some point in their clinical course, although some patients may benefit from surgical resection with curative intent or active surveillance.
- Surgical resection, radiation, or focal ablative therapy may be appropriate palliative options in some patients.

Surgery

Metastatectomy

- There are no randomized studies evaluating the utility of metastatectomy.
- In selected patients with isolated metastases, surgical resection may be associated with extended disease-free intervals. Five-year survival rates of 30% to 50% have been reported in retrospective analyses using this approach.
- Tumor burden, number and location of metastatic sites, tumor kinetics, and the ability to completely resect metastatic disease are some of the key factors associated with the outcome.
- Metastatectomy may be appropriate in well-selected patients with oligometastatic disease and favorable risk features amenable to complete resection.

Cytoreductive Nephrectomy

- Removal or debulking of the primary tumor in the presence of metastatic disease has been the subject of considerable debate since the observation in the 1980s that this approach was associated with improved outcomes.
- Cytoreductive nephrectomy (CN) preceding systemic cytokine therapy demonstrated a survival advantage in at least two randomized phase 3 trials of patients receiving interferon alpha (IFN-α) following nephrectomy versus patients receiving IFN-α alone. Based on these data, CN was offered to well-selected patients with metastatic ccRCC receiving cytokine therapy.
- However, a change in the standard of care from cytokines to antiangiogenic therapies in the mid-2000s necessitated reevaluation of this strategy. Several retrospective series suggested that there was some benefit from CN as a prelude to antiangiogenic targeted therapies.
- A randomized phase 3 trial of CN followed by sunitinib versus sunitinib alone in patients with metastatic ccRCC (CARMENA) was undertaken to address the role of CN in patients receiving antiangiogenic therapy.

- A total of 576 patients with intermediate- and poor-risk RCC were randomized to the two treatment arms with risk stratification based on the MSKCC prognostic model. The primary objective was to assess the noninferiority of sunitinib alone with OS as the primary end point. With a median follow-up of 50.9 months, the OS in the nephrectomy arm was 13.9 months (95% confidence interval [CI] 11.8-18.3) versus 18.4 months in the sunitinib arm (95% CI 14.7-23.0) (HR 0.89, 95% CI 0.76-1.10), suggesting that sunitinib alone was noninferior to CN followed by sunitinib in patients with intermediate- or poor-risk disease.
- A subsequent subgroup analysis based on risk stratification using IMDC criteria suggested that CN followed by sunitinib may provide benefit for IMDC intermediate-risk patients with one risk factor.
- The study was hampered by slow accrual, and the outcome may have been influenced by the inclusion of a large number of patients with poor risk features unlikely to benefit from this approach. However, based on these data, CN is not offered to most patients with intermediate- or poor-risk features.
- Carefully selected patients with limited metastatic burden, favorable tumor kinetics, and good performance status are likely to benefit from CN and might be considered in this patient population.
- CN can also be performed for palliation of intractable hematuria and pain associated with RCC.

Systemic Therapy

Historical Perspective and Overview

- Conventional cytotoxic chemotherapy is ineffective in the vast majority of patients with metastatic RCC (~5%-6% overall response rate with single agent) and is not part of the standard approach to this disease. However, some patients with sarcomatoid variants of RCC are responsive to gemcitabine-based regimens.
- The development of cytokines (high-dose interleukin 2 [IL-2] and IFN-α) beginning in the late 1980s led to the FDA approval of the first agent (high-dose IL-2) for patients with advanced ccRCC in 1992.
- Response rates with cytokines were modest (overall risk reduction [ORR] 15%-20%); however, a proportion of patients receiving high-dose IL-2 (7%-9%) achieved durable complete responses. The significant toxicity associated with this agent limited its widespread use, with only a few centers worldwide able to administer the agent safely.

- The development of targeted therapeutic approaches directed against downstream consequences of VHL inactivation in the mid-2000s led to a paradigm shift in the approach to patients with advanced ccRCC. Targeted agents directed against the VEGF/PDGF and mTOR pathways were successfully evaluated in patients with metastatic RCC and had largely supplanted cytokines as standard first-line agents in the management of ccRCC. Both sunitinib and pazopanib were evaluated in the front-line setting and found to be superior to the prevalent standard of care, with response rates of 30% to 40% and median progression-free survival (PFS) approaching a year. A number of VEGFR-targeted TKIs such as axitinib, the mTOR inhibitor everolimus, and less selective TKIs such as cabozantinib were evaluated and found to be active in patients who had progressed on front-line agents (Table 13.2).

TABLE 13.2

Key Studies of Targeted Agents in Metastatic Renal Cell Carcinoma

Agent(s)	Phase	Study Population	# Of Patients	Overall Response Rate (RECIST) [a]	Median PFS (mo) [a]	Median OS (mo) [a]
First-line therapy						
Sunitinib vs IFN-α	Randomized phase 3	Clear cell	750	**47% vs 12%**	**11 vs 5**	**26.4 vs 21.08**
Tem vs IFN-α vs tem + IFN-α	Randomized phase 3	Poor prognosis, all subtypes	626	8.6% vs 4.8% vs 8.1%	5.5 vs 3.1 vs 4.7	**10.9 vs 7.3** vs 8.4
Bev + IFN-α vs IFN-α	Randomized phase 3	Clear cell	649	**31% vs 13%**	**10.2 vs 5.4**	23.3 vs 21.3
Bev + IFN-α vs IFN-α	Randomized phase 3	Clear cell	732	**26% vs 13%**	**8.5 vs 5.2**	18.3 vs 17.4
Pazopanib vs placebo	Randomized phase 3	Clear cell	233	**32% vs 4%**	**11.1 vs 2.8**	
Cabozantinib vs sunitinib	Randomized phase 2	Clear cell	157	**33% vs 12%**	**8.2 vs 5.6**	30.3 vs 21.8
Second-line and subsequent therapy						
Sunitinib	Single-arm phase 2	Clear cell, prior cytokines	63	40%	8.7	NA
Sunitinib	Single-arm phase 2	Clear cell, prior cytokines	106	44%	8.1	NA
Sorafenib vs placebo	Randomized phase 3	Clear cell, prior cytokines	903	10% vs 2%	**5.5 vs 2.8**	17.8 vs 15.2

Agent(s)	Phase	Study Population	# Of Patients	Overall Response Rate (RECIST) [a]	Median PFS (mo) [a]	Median OS (mo) [a]
Bev (10 mg/kg) vs bev (3 mg/kg) vs placebo	Randomized phase 2	Clear cell, prior cytokines	116	10% vs 0% vs 0%	**4.8** vs 3.0 **vs 2.5**	NA
Pazopanib vs placebo	Randomized phase 3	Clear cell, prior cytokines	202	**29% vs 3%**	**7.2 vs 4.2**	
Everolimus vs placebo	Randomized phase 3	Clear cell RCC, prior VEGF-targeted therapy	410	1% vs 0%	**4.0 vs 1.9**	NR vs 8.8
Axitinib vs sorafenib	Randomized phase 3	Clear cell, prior VEGF, mTOR, or cytokine	723	**19% vs 9%**	**6.7 vs 4.7**	NA
Nivolumab vs everolimus	Randomized phase 3	Clear cell, prior VEGF-targeted therapy	821	**25% vs 5%**	4.6 vs 4.4	**25 vs 19.6**
Lenvatinib + everolimus vs everolimus	Randomized Phase 2	Clear cell	153	**17% vs 3%**	**14.6 vs 5.5**	25.5 vs 17.5
Cabozantinib vs everolimus	Randomized phase 3	Clear cell, prior VEGF-targeted therapy	658		**7.4 vs 3.9**	**21.4 vs 16.5**

Bev, bevacizumab; IFN-α, interferon alpha; mTOR, mammalian target of rapamycin; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; tem, temsirolimus; VEGF, vascular endothelial growth factor.

[a]Statistically significant differences indicated in boldface type.

- The development of ICIs targeting the PD-1/PD-L1 axis and CTLA-4 over the last few years was followed by the evaluation of these agents in the front-line setting and in patients who had progressed on antiangiogenic therapy.
- Based on data from a number of well-designed phase 3 studies, ICI-based strategies (anti PD-1 antibody in combination with either a VEGFR TKI or a CTLA-4 antibody) are now considered the standard initial approach for most patients with metastatic ccRCC.
- There is a paucity of data in patients who have progressed on ICI-based treatment, and most treatment choices are based on data from studies in patients who had progressed on antiangiogenic therapy. A number of

novel approaches, including small molecules targeting HIF2, are currently under evaluation in this setting.

- The management of patients with advanced non–clear cell variants remains challenging, although several interesting mechanism-based approaches are beginning to show promise in individual subtypes.
- This section will focus on currently relevant management approaches to patients with advanced kidney cancer.

Management of Treatment-Naïve Patients With Advanced ccRCC

- A number of studies have demonstrated the superiority of ICI-based combinations over sunitinib, an erstwhile standard for the initial treatment of patients with advanced ccRCC (Table 13.3).

TABLE 13.3

Immune Checkpoint Inhibitor–Based Combination Trials in the Initial Treatment of Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

Agents	Phase	Study Population	# Of Patients	Overall Survival	Median Progression-Free Survival (mo)
Nivolumab + ipilimumab vs sunitinib	Phase 3	Previously untreated clear cell renal cell carcinoma (RCC)	1096	75% vs 60% (at 18 mo)	11.6 vs 8.4
Pembrolizumab + axitinib vs sunitinib	Phase 3	Previously untreated clear cell RCC	861	89.9% vs 78.3% (at 12 mo)	15.1 vs 11.1
Avelumab + axitinib vs sunitinib	Phase 3	Previously untreated advanced RCC with a clear cell component	886	55.2% vs 25.5%	13.8 vs 8.4
Nivolumab + cabozantinib vs sunitinib	Phase 3	Previously untreated advanced RCC with a clear cell component	651	85.7% vs 75.6% (at 12 mo)	16.6 vs 8.3

Agents	Phase	Study Population	# Of Patients	Overall Survival	Median Progression-Free Survival (mo)
Lenvatinib + pembrolizumab or everolimus versus sunitinib	Phase 3	Advanced RCC	1069	79.2% vs 66.1% vs 70.4% (at 24 mo)	23.9 vs 14.7 vs 9.2

- It is unclear which, if any, of these combinations is superior to others since there have been no studies directly comparing the various regimens. Individual patient/clinical considerations generally guide the choice of regimen in clinical practice.
- Cabozantinib has also been shown to be superior to sunitinib in patients with intermediate- and poor-risk ccRCC in a randomized phase 2 study.
- VEGFR TKIs such as cabozantinib, sunitinib, and pazopanib may still be appropriate choices in patients with contraindications to immunotherapy.
- Some of the key studies are detailed below.

Combination of Anti-PD-1/PD-L1 Antibodies and TKIs

Axitinib Plus Pembrolizumab

- In an international, randomized, open-label phase 3 study (KEYNOTE-426), 681 treatment-naïve metastatic ccRCC patients were assigned to receive either pembrolizumab (a monoclonal antibody against human PD-1) (200 mg every 3 weeks for up to 35 cycles) plus axitinib (a relatively selective VEGFR-targeted TKI) (5 mg twice daily) or sunitinib (50 mg once daily for 4 weeks per 6-week cycle).
- Primary end points included OS and PFS. OS favored pembrolizumab and axitinib versus sunitinib monotherapy with the median OS not reached for the combination and 35.7 months for sunitinib (95% CI 33.3—not reached; HR 0.68, 95% CI 0.55-0.85). PFS followed a similar pattern with a median of 15.4 months for pembrolizumab and axitinib compared to 11.1 months for sunitinib (HR 0.71, 95% CI 0.60-0.84, $P < .0001$).
- Data from this study formed the basis for approval of this combination as a first-line treatment option for patients with metastatic RCC.

Axitinib Plus Avelumab

- Avelumab is a humanized monoclonal IgG1 antibody (PD-L1).
- The phase 3 JAVELIN Renal 101 trial randomized previously untreated patients with metastatic RCC to axitinib (5 mg twice daily) plus avelumab (10 mg/kg every 2 weeks) or sunitinib (50 mg once daily for 4 weeks per 6-week cycle). Primary end points were PFS and OS for patients with PD-L1–positive tumors. Secondary end points include PFS in the overall population, objective response, and safety.
- Median PFS in the PD-L1–positive tumors was 13.8 months with avelumab and axitinib versus 7.0 months with sunitinib (HR 0.62, 95% CI 0.490-0.777, $P < .0001$). The benefit extended to the overall population as well with a median PFS of 13.3 months compared to 8.0 months for avelumab plus axitinib and sunitinib, respectively (HR 0.69, 95% CI 0.574-0.825, $P < .0001$).
- ORR was 52.5% in the avelumab plus axitinib group and 27.3% for the sunitinib group.
- Grade 3 or higher AEs were seen in 71.2% of the combination patients and 71.5% of the sunitinib patients.
- Axitinib plus avelumab is FDA-approved for first-line treatment in metastatic RCC.

Cabozantinib Plus Nivolumab

- In a randomized, open-label phase 3 trial, patients with untreated metastatic ccRCC were treated with nivolumab (240 mg every 2 weeks) and cabozantinib (40 mg once daily) or sunitinib (50 mg once daily for 4 weeks of each 6-week cycle).
- The median PFS in patients treated with nivolumab plus cabozantinib was 16.6 months compared to 8.3 months for sunitinib (HR 0.51, 95% CI 0.41-0.64, $P < .001$). Objective response, a secondary end point, also favored the combination arm (ORR 55.7% vs 27.1%, $P < .001$).
- Grade 3 or higher AEs occurred in 75.3% of the nivolumab plus cabozantinib group versus 70.6% in the sunitinib group. Notably, 19.7% of patients in the combination group stopped at least one of the trial drugs due to AEs and 5.6% stopped both. Still, patients reported a higher HRQOL with nivolumab plus cabozantinib compared to sunitinib.
- Cabozantinib plus nivolumab is approved as a first-line treatment for patients with metastatic RCC.

Lenvatinib Plus Pembrolizumab

- The combination of lenvatinib (multitargeted TKI with activity against VEGFR and fibroblast growth factor receptor [FGFR]) (20 mg/d) plus pembrolizumab (200 mg IV q 3 weeks) was evaluated in a phase 3 study in

patients with previously untreated metastatic ccRCC. A total of 1069 patients were randomized (1:1:1) to receive either this combination, a combination of lenvatinib (18 mg/d) plus everolimus (5 mg/d), or sunitinib (50 mg once daily for 4 weeks of each 6-week cycle).

- Lenvatinib plus pembrolizumab was associated with better PFS (median 23.9 vs 9.2 months, HR for disease progression or death 0.39, 95% CI 0.32-0.49, $P < .001$) and OS (HR for death 0.66, 95% CI 0.49-0.88, $P = .005$) compared to sunitinib. The combination of lenvatinib plus everolimus was associated with a significantly longer PFS than sunitinib (median 14.7 vs 9.2 months, HR 0.65, 95% CI 0.53-0.80, $P < .001$) but OS was comparable.
- The incidence of grade 3 or greater AEs was similar in the two combination arms (82.4% with lenvatinib plus pembrolizumab, 83.1% with lenvatinib plus everolimus), while 71.8% of patients who received sunitinib encountered a ≥grade 3 AE.
- The combination of lenvatinib and pembrolizumab is approved by the FDA for treatment of patients with previously untreated metastatic ccRCC.

Dual Checkpoint Inhibitor Combination

Ipilimumab Plus Nivolumab

- The combination of ipilimumab (human monoclonal IgG1 antibody against CTLA-4) (1 mg/kg) and nivolumab (monoclonal antibody against PD-1) (3 mg/kg) was evaluated in a phase 3 randomized study that included patients with untreated clear cell advanced RCC and assigned them to either the combination treatment or sunitinib (50 mg once daily for 4 weeks in a 6-week cycle). Patients were stratified by IMDC risk.
- Coprimary end points were OS, ORR, and PFS in patients with intermediate- and poor-risk groups. Median OS was not reached for nivolumab plus ipilimumab and was 26.0 months with sunitinib (HR 0.63, $P < .001$). ORR was 42% compared to 27% ($P < .001$) for each group, respectively. Median PFS was 11.6 months for the combination therapy versus 8.4 months for sunitinib monotherapy (HR 0.82, $P = .03$, not significant per prespecified 0.009 threshold). The survival benefit associated with the combination did not appear to extend to patients in the IMDC favorable risk category.
- Grade 3 or 4 treatment-related AEs (TRAEs) were seen in 46% of the patients treated with combination therapy and in 63% of the sunitinib group. TRAEs led to discontinuation in 22% and 12% of patients, respectively.

- The combination of ipilimumab and nivolumab is FDA approved in intermediate- or poor-risk, treatment-naïve metastatic RCC.

Management of Patients Who Have Progressed on Front-Line Therapy

- There are no data currently available from randomized phase 3 studies in patients who have progressed on ICI-based combination therapy.
- Both single-agent checkpoint inhibitors and a variety of targeted agents have been evaluated in patients who have progressed following front-line therapy with antiangiogenic agents. Data from these studies as well as smaller phase 2 studies are used to guide therapeutic choices in patients who have progressed on ICI-based regimens and/or TKIs.
- Post front-line choices in these patients typically consist of a targeted agent not previously used in a given patient +/− ICI or dual checkpoint combinations in those who have not received this combination.
- A number of clinical trials are currently evaluating novel treatment options including small molecule inhibitors of HIF2 in this patient population.
- Some key studies in the post front-line setting are highlighted below.

METEOR Study (Cabozantinib Versus Everolimus)

- Cabozantinib is an oral multi-TKI (MET, VEGFR, AXL).
- The phase 3 METEOR trial evaluated the efficacy of cabozantinib (60 mg/d) compared with everolimus (mTOR inhibitor) (10 mg/d) in 658 patients with advanced/metastatic ccRCC, who had progressed on prior VEGFR TKI.
- The trial demonstrated improved OS, PFS, and objective response with cabozantinib; OS was significantly increased with cabozantinib compared to everolimus (21.4 vs 16.5 months). More patients on the cabozantinib arm were alive at 6, 12, 18, and 24 months than the everolimus arm. Median PFS in all randomized patients was also considerably greater with cabozantinib versus everolimus (7.4 vs 3.9 months). Finally, 17% of cabozantinib-treated patients and only 3% of everolimus-treated patients experienced an objective response.
- More grade 3 to 4 AEs were reported with cabozantinib than everolimus (71% vs 60%). Common AEs included hypertension, diarrhea, fatigue, PPE, anemia, hyperglycemia, and hypomagnesemia. Cabozantinib was also associated with serious AEs such as abdominal pain (3%), pleural effusion (2%), pneumonia (2%), pulmonary embolism (2%), anemia (2%), and dyspnea (1%).

- Based on these data, the agent was approved for use in metastatic RCC following progression on front-line VEGF pathway–directed therapy.
- Cabozantinib has also been evaluated in the front-line setting in a randomized phase 2 study compared to sunitinib (CABOSUN). In this study, 157 patients with intermediate- or poor-risk (IMDC) metastatic ccRCC with no prior therapy were randomized to cabozantinib (60 mg/d) or sunitinib 50 mg/d (4 weeks on, then 2 weeks break). Median PFS was significantly prolonged for cabozantinib versus sunitinib, with PFS of 8.6 versus 5.3 months, respectively, and ORR was 20% versus 9%, respectively. Median OS was 26.6 months with cabozantinib and 21.2 months with sunitinib.

CheckMate 025: Nivolumab Versus Everolimus

- Nivolumab is a humanized IgG4 (PD-1) ICI.
- It is evaluated in a phase 3 study in 821 patients with advanced/metastatic ccRCC who had received prior antiangiogenic therapies. Patients were randomized to nivolumab (3 mg/kg IV) every 2 weeks or everolimus 10 mg/d.
- The primary end point of OS clearly demonstrated the superiority of nivolumab over everolimus (medial OS 25 vs 19.6 months, HR for mortality 0.73).
- Objective response rates (25% vs 5%) were also higher with the nivolumab group, while median PFS was comparable in the two groups (4.6 vs 4.4 months).
- Common AEs with nivolumab were fatigue, nausea, and pruritus. A variety of autoimmune AEs including pneumonitis, colitis, and hypophysitis were also associated with nivolumab but were generally amenable to medical management.

Lenvatinib Plus Everolimus

- Lenvatinib is an oral multi-TKI (VEGFR, FGFR, PDGFRα, RET, KIT).
- A phase 2 randomized study evaluated the efficacy of lenvatinib, together with everolimus, or each agent alone in 153 patients with advanced/metastatic ccRCC who progressed on prior anti-VEGF. Patients were randomized to lenvatinib 18 mg/d plus everolimus 5 mg/d, single-agent lenvatinib 24 mg/d, or standard dose everolimus 10 mg/d alone. The primary end point was PFS.
- PFS in the combination (lenvatinib + everolimus) was better than with single-agent everolimus (14.6 vs 5.5 months, HR 0.4, P = .0005). ORR with

combination therapy was 43% compared to 6% in the everolimus arm (rate ratio 7.2, $P < .0001$). Furthermore, the combination group demonstrated greater OS benefit compared to everolimus alone (median 25.5 vs 15.4 months, HR 0.51).

- There were more grade 3 or 4 AEs in the lenvatinib-containing arm versus single-agent everolimus (71% combination vs 50% everolimus). Most common grade 3 AEs in the lenvatinib-everolimus arm were diarrhea, fatigue, or hypertension, and anemia, dyspnea, hypertriglyceridemia, and hyperglycemia with everolimus alone.
- The combination of lenvatinib and everolimus has been approved by the US FDA for use in the second-line setting following progression on VEGF-pathway targeted therapy.

Lenvatinib Plus Pembrolizumab

- Pembrolizumab is a humanized monoclonal IgG4 antibody (PD-1).
- A multicenter, open-label phase 1b/2 trial of lenvatinib (20 mg/d) plus pembrolizumab (200 mg/3wk) in metastatic solid tumors examined patients who progressed on approved therapies and had no standard treatment options available. There was no preselection based on biomarkers. The phase 2 primary end point was ORR at 24 weeks.
- At data cutoff, the overall ORR for the RCC cohort was 70% (95% CI 50.6%-85.3%). The median duration of response (DOR) was 20.0 months (95% CI 9.0-22.9 months), and the median PFS was 19.8 months (95% CI 9.9-24.1 months).
- The most common grade 3-4 TRAEs for all patients on the trial were hypertension, fatigue, diarrhea, proteinuria, and increased lipase levels.
- This regimen may be an acceptable alternative in patients who have progressed on a different ICI-based combination.

Non-ccRCC

- There are currently no standard systemic options of proven benefit for the treatment of many patients with advanced RCC of non–clear cell histology.
- VEFGR- and mTOR-targeted therapy has modest activity at best in these subtypes.
- MET-directed therapy has been associated with some activity in patients with papillary RCC, while ICIs and bevacizumab-based regimens are associated with activity in some subtypes of non-ccRCC.
- A better understanding of the molecular changes driving individual subtypes of non–clear cell tumors is likely to lead to the development of

mechanism-based treatment strategies for each histological/molecular variant. Enrollment on well-designed clinical trials is still the preferred approach for most patients with advanced non-ccRCC.
- Some key studies are highlighted below.

Anti-PD-1/PD-L1 Therapy

- The activity of pembrolizumab (200 mg every 3 weeks for 24 months) monotherapy in treatment-naïve patients with advanced non–clear cell was evaluated in a phase 2 study. The majority histology of patients included had papillary RCC (71.5%), but patients with unclassified (15.8%), sarcomatoid, and chromophobe (12.7%) subtypes were also included. Most patients were intermediate or poor risk (67.9%) as per IMDC criteria. PD-L1 combined positive score (CPS) ≥1 was seen in 61.8% of tumors.
- ORR was 26.7% for all patients with a median DOR of 29.0 months. A larger portion of patients with CPS ≥ 1 had ORR (35.3%) compared to patients with CPS < 1 (12.1%). ORR in individual histologic subgroups was as follows: 30.8% for unclassified, 28.8% for papillary, and 9.5% for chromophobe.
- Median PFS was 4.2 months with a 24-month rate of 18.6%. Median OS was 28.9 months and OS at 24 months was 58.4%.
- TRAEs were seen in 69.7% of all patients, with the most frequent being pruritus (20.0%) and hypothyroidism (14.5%).
- This trial suggests antitumor activity of PD-1 inhibitors in non-ccRCC, particularly in tumors with CPS ≥ 1.
- ICI-based combinations including the combination of savolitinib (MET inhibitor) and durvalumab (PD-L1 inhibitor) as well as the combination of atezolizumab and bevacizumab are also active in patients with non-ccRCC with ORRs in the 25% to 35% range.

MET Inhibitors

- In a large phase 2 trial, foretinib, a novel inhibitor of MET and VEGFR2, was associated with activity in patients with papillary RCC, with an overall response rate of 13.5% and a median PFS of 9.3 months. Efficacy was most pronounced in patients with papillary type 1 RCC carrying a germline mutation in *MET* (overall response rate 50%), although patients without this alteration also appeared to benefit to some extent.
- A randomized phase 2 study in metastatic papillary RCC compared monotherapy with the MET kinase inhibitors cabozantinib, crizotinib, or

savolitinib, with sunitinib. Prespecified futility analysis resulted in the early closure of the crizotinib and savolitinib groups. However, cabozantinib was superior to sunitinib with a longer PFS (9.0 vs 5.6 months, HR 0.60, P = .019). Grade 3 or 4 AEs occurred in a similar percentage of cabozantinib (74%) and sunitinib (69%) patients. Cabozantinib is a reasonable option in patients with advanced papillary RCC.

Bevacizumab Plus Erlotinib

- The combination of bevacizumab and erlotinib was evaluated in patients with advanced papillary RCC with or without prior therapy.
- Patients were enrolled into two parallel, independent cohorts evaluating the efficacy of this regimen in FH-deficient RCC and sporadic RCC.
- The ORR in FH-deficient RCC was 72% with a median PFS of 21 months; ORR in the sporadic papillary RCC cohort was 35% with a median PFS of 8.8 months.
- This combination is generally considered the preferred option in patients with advanced FH-deficient RCC but is also a reasonable option in patients with sporadic papillary RCC.

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14

Prostate Cancer

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EPIDEMIOLOGY

- Prostate cancer (CaP) is the most common noncutaneous malignancy and the second most frequent cause of cancer-related mortality in men in the United States; in 2021, there will be an estimated 248,530 men diagnosed with CaP and 34,130 deaths from the disease. A greater than 30% decline in incidence in recent years is likely due to decreased screening with increased incidence of metastatic disease at diagnosis. The long-term implications of this remain unknown.
- The frequency of clinically aggressive disease varies geographically, but the frequency of occult tumors does not, suggesting the influence of environmental factors in the etiology of CaP.

RISK FACTORS

- Age: Risk increases progressively with age, with about 70% of cases in men over the age of 65 years.
- Family history: Risk increases twofold with a first-degree relative diagnosed with CaP, fivefold with two first-degree relatives.
- Race: In the United States, incidence is highest among African-Americans, followed by whites, then Asians. African-American

men are more likely to be diagnosed with advanced disease and have a greater than twofold risk of death from the disease.

- Geography: Risk is lowest in Asia, high in Scandinavia and the United States.
- Diet: Consumption of red meat and animal fat has been associated with CaP, while eating cruciferous vegetables, soy products, and lycopene-containing tomato products may be protective.
- Genetics: Per guidelines, family and personal history of cancer and family history for known germline variants at the time of initial diagnosis of disease is necessary. Germline genetic testing is recommended in CaP patients and any of the following:
    - High-risk, very-high-risk, regional, or metastatic CaP
    - Ashkenazi Jewish ancestry
    - Family history of high-risk germline mutations (eg, *BRCA 1/2*, Lynch syndrome)
    - A positive family history for cancer including a brother or father or multiple family members diagnosed with CaP at <60 years of age or who died from CaP or ≥3 cancers on the same side of the family, especially diagnosed at ≤50 years of age
- Family history for known germline variants and genetic testing for germline variants should include *MLH1, MSH2, MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1, BRCA2, ATM, PALB2*, and *CHEK2.*
- Genetic counseling resources are critical.

CHEMOPREVENTION TRIALS

5-α Reductase Inhibitors

- Two clinical trials have evaluated the ability of 5-α reductase inhibitors to prevent CaP in asymptomatic men older than 50 years although neither is approved for this purpose.
- The US Food and Drug Administration (FDA) does not endorse either finasteride or dutasteride for the prevention of CaP.

SCREENING

- Screening for CaP involves testing for levels of prostate-specific antigen (PSA) and/or digital rectal examination (DRE). Screening of asymptomatic men is controversial. Debate centers on whether biologically and clinically significant cancers are being detected early enough to reduce mortality or, conversely, whether cancers detected by screening would cause clinically significant disease if left undetected and untreated. Autopsy series have shown that more men die with, rather than from, CaP, and the rate of occult CaP in men in their 80s is approximately 75%.
- The prostate, lung, colon, and ovary (PLCO) screening trial and the European Study on Screening for Prostate Cancer are evaluating clinical outcomes based on screening versus no screening. Data from the PLCO trial reveal that the rate of death from CaP was very low and did not differ significantly between subjects assigned to screening (n = 38,340) or no screening (n = 38,343), with nearly 15 years of follow-up. Despite these two large studies, the evidence does not clearly support uniform population-based screening practices using PSA.
- Data from the European study suggest that PSA screening was associated with a reduction in the rate of death from CaP by 21% after a median follow-up of 13 years. These data indicate 781 men would need to be screened and 27 additional cases of CaP would need to be treated to prevent one death from CaP. Contamination from PSA screening outside the trial was less likely in Europe and could explain the differences with this study and the PLCO study. Of note, racial and ethnic minorities are underrepresented in these studies.
- Controversy surrounds screening recommendations for CaP in the United States. As of 2018, the US Prevention Services Task force (USPSTF) recommends men aged 55 to 69 years old should discuss the potential harms and benefits of screening with their health care provider and emphasizes the decision to undergo

PSA screening is an individual one. African-American men and men with a family history of CaP have additional clinical considerations for making informed decisions regarding screening. The USPSTF recommends against PSA-based screening in men 70 years of age and older.

- The American Cancer Society suggests patients make an informed decision about PSA screening after a discussion with their health care provider. Such decisions should be at the age of 50 years for men who are healthy and expect to live 10 more years, at the age of 45 years for men who are at high risk (African-American or those with a first-degree relative having CaP at an age below 65 years) or 40 years for the high-risk patients (multiple first-degree relatives having CaP at an early age).
    - Most advocates of screening acknowledge the limited benefits in men who are over 75 years of age or men with less than 10 years of projected survival due to other comorbidities. It is likely that most men who fall in this category will not have their lifespan limited by CaP, and thus screening may be unnecessary.
- CaP screening is evolving to recognize genetically susceptible populations, including men with known germline or likely pathogenic variants in genes such as *BRCA2.*

SIGNS AND SYMPTOMS

- Even with declines in PSA screening in the United States, most men are asymptomatic at diagnosis.
- Patients with local or regional disease may be asymptomatic or have lower urinary tract symptoms similar to those of benign prostatic hypertrophy or occasionally hematuria.
- Symptoms of metastatic disease include bone pain, changes in urination patterns, and weight loss; spinal cord compression is a rare but serious complication of metastatic disease and may be a presenting symptom.

WORKUP AND STAGING

Biopsy

- Abnormal PSA and/or DRE is followed by transrectal ultrasound with core biopsy. Historically, a PSA of >4 ng/mL was the threshold for biopsy, but current data suggest that cancers can be seen with lower PSA levels. In recent years, a greater emphasis has also been placed on rate of PSA rise as a trigger for biopsy. A negative biopsy should prompt reassessment in 6 months with repeat biopsy as needed.
- There is an evolving role for combining multiparametric magnetic resonance imaging (mpMRI) and ultrasound-guided prostate biopsy in the diagnosis of CaP. As opposed to random biopsies of the prostate, data from mpMRI imaging of the prostate is used to identify anatomic regions in the prostate that likely contain tumor. These regions can be deliberately oversampled during the biopsy procedure (informed biopsy) or using software that creates a fusion of the MRI image with real-time ultrasound, a targeted biopsy of the intraprostatic tumor can be done.

Pathology

- Ninety-five percent of CaPs are adenocarcinomas. Adenocarcinoma arises in the peripheral zone of the prostate in approximately 70% of patients.
- Small cell variants of prostate cancer are rare and characterized by aggressive tumors with increased likelihood to have soft tissue metastasis, especially to the liver. These tumors may be more susceptible to DNA damaging agents (poly [adenosine diphosphate (ADP)-ribose] polymerase [PARP]-inhibitors or platinum agents) although randomized data in this population is lacking. It is important to note that adenocarcinoma with

"neuroendocrine features" is more common than small cell variants and should be treated primarily as adenocarcinoma.
- Sarcoma, lymphoma, small cell carcinoma, and transitional carcinoma of the prostate are rare.
- Primary and secondary Gleason grades are determined by the histologic architecture of biopsy tissue. The primary grade denotes the dominant histologic pattern; the secondary grade represents the bulk of the nondominant pattern or a focal high-grade area. Primary and secondary grades range from 1 (well differentiated) to 5 (poorly differentiated). The combined grades comprise the Gleason Score (GS) (range 2-10). Gleason 6 or less are considered low risk, Gleason 7 is considered intermediate risk, and Gleason 8 to 10 is considered high risk.
- A new grading system has been proposed and is being increasingly incorporated into pathologic review of prostate tumors. This system is designed to subdivide Gleason 7 based on morphology and dominant pathology.
    - There is no role in reevaluating GS once treatment has begun.
- At diagnosis, because of sampling bias, GS may change following radical prostatectomy (RP) (20% of scores are upgraded and up to 10% are downgraded).
- Prostatic intraepithelial neoplasia, and perhaps proliferative inflammatory atrophy, are considered precursor lesions.

Baseline Evaluation

- In candidates for local treatment, a bone scan is indicated for patients with bone pain, T3 or T4 lesions, GS > 7, or PSA > 10 ng/mL. There is no clinical evidence that a baseline bone scan improves survival in populations with better prognostic factors.
- In candidates for surgery, computed tomography (CT) or MRI of the abdomen and pelvis is obtained for T3 and T4 lesions, PSA > 20 ng/mL, or GS > 7 to detect enlarged lymph nodes. Endorectal MRI may help in determining the presence of

extraprostatic extension. CT scans aid in treatment planning for radiation therapy (RT).
- Baseline laboratory tests include complete blood count, creatinine level, PSA (if not yet done), testosterone, and alkaline phosphatase level.

PROGNOSTIC FACTORS

- Stage at diagnosis
- Gleason Score
- PSA level
- Number of cores and percentage of each core involved
- Age at diagnosis
- Inherited genetic abnormalities

TREATMENT OF LOCALIZED DISEASE

Active Surveillance

For men aged 60 to 75 years with a >10-year life expectancy or low-grade (GS ≤ 6), T1c-T2a tumors, active surveillance is a reasonable alternative to immediate local therapy. In addition, men aged 50 to 60 years with those same features and low-volume (<3 cores, <50% of any one core involved) tumor may also be candidates for active surveillance. For patients with a <10-year life expectancy, CaP-specific mortality is very low and local definitive therapy may not be appropriate.

Surgery

Radical Prostatectomy

- Approaches include retropubic radical prostatectomy (RRP), Radical perineal prostatectomy (RPP), or laparoscopic, with the

latter often done with robotic assisted *laparoscopic prostatectomy* (RALP). Typical hospital stays are 1 to 2 days, with 7 to 14 days of urethral catheterization. Surgeries are somewhat longer with RALP, but hospital stays are usually shorter.

- Pelvic lymph node dissection may be performed at the time of RP in patients at high risk of developing positive lymph nodes but may not be necessary in patients with T1c disease, PSA < 10 ng/mL, and GS < 7.
- Nerve-sparing RP may conserve potency in men with disease not adjacent to the neurovascular bundles that travel posterior-lateral to the prostate. The bilateral nerve-sparing technique is associated with 60% to 90% of patients recovering spontaneous erections versus only 10% to 50% with the unilateral technique. Both groups, however, may respond to oral therapy for erectile dysfunction.
- There is no role for neoadjuvant androgen-deprivation therapy (ADT) prior to RP, although ongoing studies in high-risk patients are evaluating ADT with modern antiandrogens (enzalutamide and abiraterone) to determine the potential to decrease or eliminate tumor prior to RP.
- Patients with microscopic lymph node metastasis diagnosed following RP may have a longer overall survival (OS) if given ADT rather than at time of clinical recurrence/metastatic disease.
- Salvage RP following RT may be done in select cases where local disease is organ confined. However, salvage RP is more technically demanding and is associated with higher morbidity.

Surgical Complications

- Immediate morbidity or mortality: less than 10%.
- Impotence: 20% to 60%, varying with age and extent of disease.
- Urinary incontinence: improves with time, generally less than 10% to 15% 2 years after surgery.
- Urinary structure: approximately 10%, most can be managed with simple dilatation.

- Inguinal hernia: approximately 10% but substantially less with minimally invasive surgery.
- The Prostate Cancer Outcomes Study found statistically significant differences in outcomes following RP or RT. For patients with normal baseline function, RP was associated with inferior urinary function, better bowel function, and similar sexual dysfunction compared with RT.

Radiation Therapy

RT as Definitive Therapy

- External beam radiation therapy (EBRT) targets the whole prostate, frequently including a margin of extraprostatic tissue, seminal vesicles, and pelvic lymph nodes.
- Higher doses given over approximately 8 weeks are associated with higher PSA control rates, but shorter courses of therapy are also under investigation.
- Three-dimensional (3D) conformal RT allows for maximal doses conforming to the treatment field, while sparing normal tissue.
- Intensity-modulated RT is a type of 3D conformal RT that is designed to conform even more precisely to the target.
- Proton beam irradiation focuses virtually greater energy within a very small area, thus theoretically minimizing damage to normal tissue but further studies are needed in prostate cancer.
- Stereotactic body radiotherapy (SBRT) may allow for higher doses of radiation to be given in less fractions.
- There is incomplete data comparing EBRT, proton, and SBRT at this time, and so patients should have discussions about the relative benefits of these options with their radiation oncologists.

RT With Adjuvant ADT

At least three randomized controlled trials have shown that combining ADT with RT in patients at high risk for recurrent disease

(Table 14.1) improves OS. ADT is usually given during RT and for 2 to 3 years thereafter. It may also be used for 2 months prior to RT to help decrease tumor size and thus the target volume of RT. For patients with intermediate risk disease, 6 months of ADT has demonstrated improved outcomes as well.

TABLE 14.1

Risk Categories for Posttherapy Prostate-Specific Antigen Failure

	Low [a]	Intermediate [b]	High [b]
Stage	T1c, T2a	T2b	T2c
PSA	<10	10-20	>20
Gleason score	≤6	7	≥8

[a]All parameters required.

[b]Only one parameter required.

Adapted from D'Amico AV, Whittington R, Malkowicz SB, et al. Optimizing patient selection for dose escalation techniques using the prostate-specific antigen level, biopsy Gleason score, and clinical T-stage. *Int J Radiat Oncol Biol Phys*. 1999;45(5):1227-1233. Copyright © 1999 Elsevier. With permission.

RT With Adjuvant ADT and Chemotherapy

A randomized phase III trial suggested that in high-risk patients, six infusions of docetaxel 75 mg/m^2 administered in 21-day cycles with prednisone starting 28 days after RT improved 4-year OS (93% vs 86%; HR 0.49 using a one-sided 0.05 type I error and 90% power). One key limitation of this study was the use of a one-sided type I error, raising concerns about the robustness of the data. It remains unclear how widely adopted this approach is but longer follow-up will certainly be of interest.

Brachytherapy

Interstitial brachytherapy with radioactive palladium or iodine seeds that delivers a much higher dose of radiation to the prostate is used in CaP patients with low-risk tumors and some intermediate-risk

patients. Better definitions of tumor volume and radiation dosimetry have made this outpatient technique more accurate. CT and/or transrectal ultrasound are used to guide seed placement.

Combined EBRT and Brachytherapy

EBRT followed by brachytherapy boost is an increasingly used strategy. Preliminary clinical data support the safety and efficacy of this approach in a selected population of patients but long-term follow-up and head to head comparisons is lacking. Nonetheless, many radiation oncologists are using this treatment combination in patients with high-risk disease.

Adjuvant RT

- General indications for the use of adjuvant RT after RP include positive surgical margins, seminal vesicle involvement, and evidence of extracapsular extension. Nonetheless, the potential for cure with adjuvant RT will vary significantly from patient to patient and thus the risks and benefits of adjuvant RT should be evaluated in each case individually. Some studies have indicated that lower PSA and Gleason score have been associated with better disease-free survival.

Salvage RT

For select patients with rising PSA after RP and a high likelihood of organ-confined local recurrence (eg, PSA < 1.0 and slowly rising), salvage RT may be considered. However, there are limited data on which to make recommendations.

Complications of RT

Acute (Typically Resolve Within 4 Weeks)

- Cystitis
- Proctitis/enteritis

- Fatigue

Long Term

- Impotence (30%-45%)
- Incontinence (3%)
- Frequent bowel movements (10% more than with RP)
- Urethral stricture (RT delayed 4 weeks after transurethral resection of the prostate).

Focal Therapy for Disease Confined to a Region of the Prostate

Focal therapy for newly diagnosed CaP confined to a limited area of the prostate remains investigational. This strategy is different from other therapies for localized disease; in that, only a focal region of the prostate, as opposed to the entire glad, is targeted with hopes of limiting side effects. Cryosurgery destroys CaP cells through probes that subject prostate tissue to freezing followed by thawing. This procedure is associated with the high rates of erectile dysfunction due to freezing of the neurovascular bundle. Additional focal therapy strategies include thermal ablation via laser or high-intensity focused ultrasound among other techniques. There are limited data in highly selected populations on long-term outcomes for focal therapy. Thus, at most centers, prostate focal therapies are largely reserved for consideration as salvage procedures.

COMPARISON OF PRIMARY TREATMENT MODALITIES

Comparing treatment modalities in terms of overall and disease-free survival is difficult because of the differences in study design, patient selection, and treatment techniques. Randomized trials are difficult to accrue to as patient choice for radiation or surgery can often not be overcome. Historical comparisons are flawed because

patients with more comorbidities or advanced age often get radiation.

- While there are no satisfactory randomized trials comparing RT with RP, these approaches appear to have similar PSA-free survival (also called biochemical relapse-free survival) in appropriately matched patients at 5 years but differ in type and frequency of side effects.
- In recent years, high-risk patients who previously were treated predominantly with radiation and adjuvant ADT are increasingly having surgery. To some degree, this is related to the emergence of MRI imaging where discrete lesions and possible extracapsular extension is better defined. Longer follow-up is required to determine the impact of surgery in this population.

FOLLOW-UP AFTER DEFINITIVE TREATMENT

- Patients treated with curative intent should have PSA levels checked at least every 6 months for 5 years, then annually. Annual DRE is appropriate for detecting recurrence.
- After RP, a detectable PSA suggests a relapse. PSA failure after RT is defined as 2 ng/mL over the nadir, whether or not the patient had ADT with RT.

TREATMENT FOR MEN WITH RISING PSA AFTER LOCAL THERAPY

- Treatment for patients who have rising PSA (biochemical failure) after local therapy has not been standardized and clinical trial data is incomplete.

- Salvage RT, salvage RP, or salvage focal therapy (as previously described) may be offered to select patients with local recurrence.
- Men may live more than a decade after biochemical failure, thus a more conservative approach (eg, surveillance, treating when symptomatic, or based on PSA velocity) is a reasonable option for many men.
- Using PSA doubling time (ie, less than 3-6 months) as a trigger to initiate ADT is frequently done in clinical practice; however, no randomized trials have prospectively evaluated this approach. Retrospective data suggests that a PSA doubling time of less than 3 to 6 months may be associated with development of metastatic disease visible on conventional imaging.
- ADT effectively lowers PSA; however, there are no definitive data indicating better survival with ADT than with no ADT in biochemical recurrent prostate cancer.
- Randomized data from over 1300 subjects demonstrated that ADT given intermittently (in 8-month cycles) was noninferior to continuous ADT in terms of OS. Intermittent ADT was predictably associated with better quality of life outcomes.
- Emerging imaging platforms that are more sensitive at detecting (micro) metastatic disease may alter how this stage of disease is managed in the future. The FDA approved the first PSMA-targeted PET imaging drug, Ga 68 PSMA-11, in December 2020, In May 2021, a second PSMA-targeted positron emission tomography (PET) imaging drug, Pylarify (piflufolastat F18) was approved for men with newly diagnosed or biochemically recurrent CaP.

TREATMENT OF SYSTEMIC DISEASE EVOLUTION OF RESPONSE CRITERIA IN METASTATIC DISEASE

The Prostate Cancer Working Group 3 and the Implications for Clinical Practice

- As the understanding of CaP has evolved in the past decade, in the context of new available therapies and greater experience with older therapies, a consensus was generated by Prostate Cancer Working Group 3 (PCWG3) on determining response in clinical trials.
- Perhaps, most importantly, PSA should not be used as the sole criteria to discontinue a therapy. Furthermore, the PCWG3 recommends that early changes in PSA and modest increases in pain, which could represent a tumor flare phenomenon, should not result in the discontinuation of therapy. This is especially important because PSA was not solely used to evaluate response of some of the latest therapies, thus discontinuing based on PSA alone could diminish the expected benefits of some therapies.
- For patients with metastatic CaP, objective changes on imaging studies (CT and bone scan) should be the primary criteria used to assess progression of disease in the absence of clear clinical progression of symptoms.
- To assess imaging, lymph nodes must be greater than 2 cm at baseline. In addition, physician discretion can be used for baseline lymph nodes less than 1.0 cm that grow to larger than 1.5 cm.
- Two new bone lesions on bone scan are required to document progressive disease, with one important exception. New lesions on the first bone scan should trigger another bone scan 6 or more weeks later, as these new lesions may have been present on the first scan but missed on initial imaging or they may represent the "tumor flare phenomenon." If the second (and subsequent) bone scans show less than two new lesions and the patient is otherwise clinically stable, he should be considered to have stable disease.
- For the treatment of patients outside of clinical trials, the implications of the PCWG3 are as follows:

- Radiographic response criteria should be used to determine disease progression in metastatic CaP as opposed to PSA alone.
- Initial changes on bone scan are not sufficient to remove patients from a treatment; patients could continue therapy if subsequent bone scans show less than two new lesions.
- Changes in lymph nodes less than 2 cm in diameter should be interpreted with caution.
- PSA should still be followed but interpreted with caution and not be used as a singular criteria to determine when to discontinue a therapy.

THERAPEUTIC STRATEGIES FOR METASTATIC DISEASE: ADT

- ADT is the mainstay of treatment for metastatic CaP (Table 14.2), in addition to its potential role with localized disease and in neoadjuvant and adjuvant setting with RT.

TABLE 14.2

Systemic Therapies for Prostate Cancer

Treatment	Dose	Most Common Side Effects
Bilateral orchiectomy	N/a	Impotence, loss of libido, gynecomastia, hot flashes, and osteoporosis
GnRH agonists (most common formulations)		
Goserelin acetate (Zoladex)	3.6 mg SC every month or 10.8 mg SC every 3 mo	Potential for tumor flare due to transient initial increase in testosterone, loss of libido, gynecomastia, hot flashes, and osteoporosis
Leuprolide acetate (Lupron)	7.5 mg SC every month or 22.5 mg i.m. every 3 mo, or 30 mg SC every 4 mo	Potential for tumor flare due to transient initial increase in testosterone, loss of libido, gynecomastia, hot flashes, and osteoporosis
GnRH agonist		
Degarelix (Firmagon)	240 mg SC initial dose followed by 80 mg SC every 28 d	Hot flashes, weight gain, erectile dysfunction, loss of libido, hypertension, hepatotoxicity, gynecomastia, and osteoporosis

Treatment	Dose	Most Common Side Effects
Androgen biosynthesis inhibitors		
Abiraterone (Zytiga)	1000 mg PO daily (on an empty stomach) Taken with prednisone 5 mg PO twice a day	Peripheral edema, hypertension, fatigue, hypokalemia, hypernatremia, increased triglycerides, hepatotoxicity, and hot flashes. (Abiraterone is a potent inhibitor of CYP3A4, and thus multiple drug interactions are possible, so review of medications is important.)
Androgen receptor inhibitor		
Enzalutamide	160 mg PO once daily	Fatigue, hot flashes, diarrhea, peripheral edema, fatigue, arthralgia, and musculoskeletal pain. Limited risk of seizures (< 1%) but care should be taken in patients with seizure history or those who are on medications that may lower the seizure threshold
Immunotherapy		
Sipuleucel-T (Provenge)	Infusion of ≥50 million autologous CD54+ cells after ex vivo cellular processing given every 2 wk for three total doses	Fatigue, fever, chills, headache, nausea, emesis, myalgias, and infusion reaction symptoms
Chemotherapy regimens		
Docetaxel (Taxotere)	75 mg mg/m^2 IV every 21 d with prednisone 5 mg PO twice daily	Granulocytopenia, infection, anemia, fatigue, anemia, neutropenia, fluid retention, sensory neuropathy, nausea, fatigue, myalgia, and alopecia
Cabazitaxel (Jevtana)	25 mg mg/m^2 IV every 21 d with prednisone 5 mg PO twice daily	Myelosuppression, infection, fatigue/weakness, fever, diarrhea, nausea, emesis, peripheral neuropathy, arthralgias, peripheral edema, alopecia, and dyspepsia
Mitoxantrone (Novantrone)	12-14 mg mg/m^2 IV every 21 d with prednisone 5 mg PO twice daily	Edema, myelosuppression, cardiac toxicity, fever, fatigue, alopecia, nausea, diarrhea, infection, and hepatotoxicity

Treatment	Dose	Most Common Side Effects
Docetaxel (Taxotere) + carboplatin (Paraplatin)	Docetaxel at 60 mg/m^2 with carboplatin AUC 4 every 21 d with daily prednisone 5 mg PO twice daily	Myelosuppression, infection, hyperglycemia, hypoglycemia, pain, renal failure, and thrombosis. (These were seen in limited experience with 34 patients.)
Radiopharmaceuticals		
Radium 223	6 monthly infusions at 55 kBq (1.49 µCi) per kg IV	Myelosuppression, nausea, diarrhea, emesis, peripheral edema
PARP inhibitors		
Olaparib (Lynparza)	300 mg PO twice daily	Nausea, vomiting, loss of appetite, constipation, myelosuppression, fatigue
Rucaparib (Rubraca)	600 mg PO twice daily	Nausea, vomiting, fatigue, myelosuppression, constipation, diarrhea, decreased appetite

- Bilateral surgical castration and depot injections of gonadotropin-releasing hormone (GnRH) agonists (eg, leuprolide, goserelin, and buserelin) and a GnRH antagonist (degarelix) provide equally effective testosterone suppression. Combined androgen blockade can be achieved by adding an oral androgen receptor antagonist (ARA; eg, nilutamide, flutamide, and bicalutamide). However, this may provide little if any definitive survival benefit.
- GnRH agonists initially increase gonadotropin, causing a transient (~14 day) increase in testosterone that can lead to tumor flare. Tumor flare can be prevented by the use of an ARA, which binds to the androgen receptor (AR), effectively stopping the ability of the AR to activate cell growth. An ARA is often given for 1 to 2 weeks prior to GnRH agonist in patients at risk for complications (pain, obstruction, and cord compression) associated with tumor flare. The ARA can then be discontinued. For high-risk patients, bilateral orchiectomy can decrease testosterone more quickly.

- The use of the GnRH antagonist (degarelix) obviates the concern for tumor flare as it leads to more rapid reduction in testosterone without an initial increase in serum testosterone levels. For this reason, it may be preferred in the setting of initial treatment for men diagnosed with symptomatic metastatic disease.
    - CaP cells generally respond to ADT, producing durable remissions and significant palliation. Duration of response (DOR) ranges from 12 to 18 months, with a limited number of patients having a complete biochemical response for several years. Ultimately, for most patients, resistant cells emerge, castration-resistance develops, and lead to disease progression.
- Continuing testosterone suppression after patients develop castration-resistant prostate cancer (CRPC) is also considered the standard of care for both nonmetastatic and metastatic disease. Androgens still play a very important role in driving the growth of CRPC, as evidenced by the benefits seen with new antiandrogen therapy (enzalutamide and abiraterone) in metastatic CRPC (mCRPC). Levels of AR and intracellular androgens within the tumor cells are significantly elevated in these patients and thus continuing ADT indefinitely in CRPC is recommended.

TREATMENT FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

- This population of patients develop metastatic disease with normal levels of testosterone (ie, while not on therapy with ADT). The population includes men who have metastatic disease at their primary diagnosis or those who develop it while in the follow-up after definitive therapy but are not receiving ADT.
- A randomized study (n = 790) established that six infusions of docetaxel (75 mg/m^2 every 3 weeks) substantially improved OS in this population 57.6 versus 44.0 months (HR 0.61) (daily

prednisone was not required) in metastatic castrate-sensitive prostate cancer (mCSPC).

- Docetaxel was required to be initiated within 120 days of starting ADT in this population.
- A subgroup analysis with longer follow-up has suggested that patients with low-volume disease (less than four bone lesions, no visceral disease or no disease beyond the spine or pelvis) did not benefit from the addition of docetaxel to ADT, perhaps calling into question the benefits in the "low-volume" population.
- ADT plus abiraterone acetate continued until disease progression is also considered a standard of care option for patients with mCSPC based on the two large clinical trials. In a Phase 3 trial of men with high-risk metastatic CaP that had not been previously treated with ADT, patients were randomized to receive standard ADT with placebos versus ADT plus abiraterone and prednisone. After a median follow-up of 30.4 months at a planned interim analysis, the median OS was significantly longer in the abiraterone group than in the placebo group (53.3 vs 36.5 months). In a multistage, multigroup trial, ADT plus abiraterone and prednisone was associated with significantly higher rates of overall and failure-free survival than ADT alone in mCPSC with an OS benefit of 38% and improvement in all secondary endpoints with abiraterone and prednisone.
- Enzalutamide, a potent AR antagonist, combined with ADT is a treatment option based on two large trials. In a randomized, phase 3 trial, patients were assigned to testosterone suppression plus either enzalutamide or a nonsteroidal antiandrogen. Enzalutamide was associated with longer progression-free survival (PFS) and OS than standard care in mCSPC. In another double-blind phase 3 trial, men with mCSPC were assigned to enzalutamide or placebo plus ADT stratified by disease volume and prior docetaxel. Enzalutamide significantly reduced the risk of metastatic progression or death over-time versus placebo

plus ADT including those with low-volume disease and/or prior docetaxel.

- Apalutamide is an AR inhibitor that has shown PFS and OS benefit in mCSPC. A total of 525 patients were randomly assigned to receive apalutamide plus ADT and 527 patients to placebo plus ADT; 62.7% had high-volume disease and 37.4% had low-volume disease. Radiographic PFS and OS at 24 months was greater with apalutamide than with placebo (82.4% in the apalutamide group vs 73.5% in the placebo group; HR 0.48; 95% CI 0.39-0.60; $P < .001$).
- There is no clear evidence at this time as to which treatment, abiraterone, enzalutamide, apalutamide, or docetaxel is superior with ADT in this population. Daily treatments with the oral antiandrogen therapies produces longer PFS (as would be expected with continuous treatment compared with six cycles of docetaxel) but the impact of the delay in PFS remains unclear with STAMPEDE data, thus far suggesting equivalency between the docetaxel and abiraterone arms of the multiphase trial.

TREATMENT OF NMCRPC AND THE USE OF SECOND-LINE ARAS

- Through the development of resistance mechanisms such as upregulation of the AR or intratumoral production of androgens, patients may develop progressive disease despite castration levels of testosterone (CRPC).
- For patients with a rising PSA but no evidence of metastatic disease, ARAs can be added to ADT to provide a combined androgen blockade, which may delay disease progression or the development of metastasis.
- Upon progression of disease with ARA and ADT, it is important to note that up to 20% of patients treated with combined androgen blockade have a PSA decline of ≥50% upon discontinuation of oral ARA (range, 15%-33%) although these

declines generally last only 3 to 5 months. This proportion may be lower with short-term ARA use. This ARA withdrawal response occurs within 4 to 6 weeks, depending on the ARA's half-life.

- Some patients with rising PSA (and still no evidence of metastasis) after ARA withdrawal may benefit from switching to other ARAs or initiating treatment with ketoconazole. A proportion of patients (35%-50%) will have PSA declines with second-line and even third-line antiandrogen therapy.
- In 2018, apalutamide was approved for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC). In a phase 3 study of apalutamide with ADT versus placebo with ADT in patients with nmCRPC and a PSA doubling time (PSADT) of ≤10 months, apalutamide was associated with a 25% reduction in risk of death compared with placebo (HR 0.75; 95% CI 0.59-0.96; *P* = .0197).
- Based on a phase 3 trial of enzalutamide and ADT versus placebo with ADT, median metastasis-free survival was 36.6 months with enzalutamide and 14.7 months with placebo in men with high-risk nmCPRC defined by a PSADT ≤10 months. Enzalutamide reduced the risk of radiographic progression or death by 71% compared with placebo (HR 0.29; 95% CI 0.24-0.35; *P* < .001). Enzalutamide was also associated with prolonged median OS compared with placebo (67 vs 56.3 months).
- Darolutamide is a second-generation AR inhibitor that is approved for treatment of nmCRPC based on a phase 3 trial of darolutamide plus versus placebo plus ADT in nmCPRC patients with a PSADT ≤10 months. Darolutamide was associated with a significant OS benefit compared with placebo. Darolutamide reduced the risk of death by 31% versus placebo (HR 0.69; 95% CI 0.53-0.88; *P* = .003).

TREATMENT FOR MCRPC

Multiple treatment options are now available for the treatment of mCRPC as opposed to prior to 2010 when only docetaxel had demonstrated the ability to extend survival in this population. Given multiple forms of therapy including immunotherapy, chemotherapy, radiopharmaceuticals, modern antiandrogen therapy, and PARP inhibitors, symptoms, pace of disease, and mutational status will likely dictate which treatments are most appropriate for each individual patient. At this time, no standard sequence of therapy has been demonstrated as most effective (Figure 14.1).

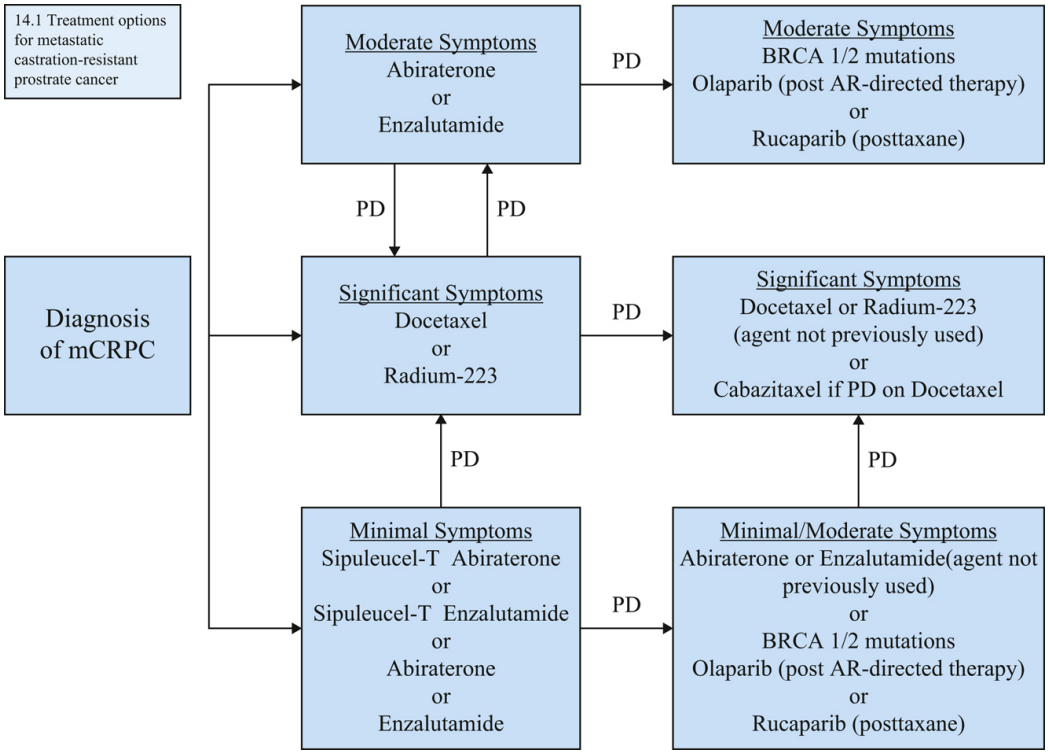

FIGURE 14.1 Suggested treatment approach for patients with metastatic castration-resistant prostate cancer.At this time, there is no clear data on the optimal sequence in mCRPC. One strategy is to base treatment of mCRPC on presenting symptoms of the patient, selecting therapies that are less toxic for patients with minimal symptoms. Pace of disease should also be factored in, as rapidly progressing disease may require earlier chemotherapy, even before the onset of significant symptoms. Also, a brief previous response to androgen-deprivation therapy (ADT) should temper the expectations for subsequent abiraterone or enzalutamide, as these particular disease manifestations may not be as dependent on the androgen receptor pathway for growth.

Immunotherapy

- Sipuleucel-T (Provenge)—is an activated cellular therapy that is derived from a patient's own immune cells, which are collected via leukapheresis. Once removed from circulation, the peripheral immune cells are sent to a central processing facility where they are exposed to a fusion peptide of PAP-GMCSF for 48 hours. The goal is to activate immune cells via ex vivo

processing so that when they are reinfused into the patient, they generate an immune-mediated antitumor response.

- Although sipuleucel-T has been shown to improve survival versus placebo (25.8 vs 21.7 months; HR 0.77; *P* = .02), it does not change short-term disease progression or cause decreases in PSA in most patients. For this reason, sipuleucel-T should ideally be followed by another therapy to provide short-term control and allow for the potential long-term effects, which can potentially improve survival. Patients whose disease on scans, PSA, and symptoms all remain stable after sipuleucel-T could be followed up closely until one of those parameters dictates the initiation of a subsequent therapy.
- Sipuleucel-T is indicated in patients with minimal symptoms related to their CaP. Although sipuleucel-T can be given 3 months after chemotherapy, given its delayed effects, it would seem most appropriate to give this treatment prior to chemotherapy.

Androgen Biosynthesis Inhibitor

- Abiraterone is a selective and irreversible CYP17 inhibitor and significantly reduces secondary androgen production (including testosterone precursors dehydroepiandrosterone and androstenedione) from the adrenal glands and likely within CaP cells.
- Abiraterone has demonstrated improved OS in mCRPC patients relative to placebo regardless of previous chemotherapy.
- Abiraterone can be used in mCRPC patients who are chemotherapy-naïve and who have mild pain from their metastatic disease. It has been shown to delay the need for narcotics in this population.
- Abiraterone has also been shown to improve pain and quality of life in patients who have already received chemotherapy.
- Abiraterone requires coadministration of prednisone (10 mg daily) to limit treatment-related toxicity.

AR Inhibitor

- Enzalutamide is a modern version of the ARAs previously discussed although this agent has broader anti-AR properties beyond binding to the AR with greater binding affinity. It also significantly reduces AR translocation to the nucleus and limits DNA binding and inhibits coactivator recruitment and receptor-mediated DNA transcription. In addition, enzalutamide has not demonstrated any agonist properties unlike previous ARAs.
- Like abiraterone, enzalutamide has demonstrated efficacy compared to placebo in men with mCRPC regardless of previous chemotherapy and can improve moderate levels of pain.
- Unlike abiraterone, enzalutamide does not require daily prednisone.
- Enzalutamide should not be used in patients with a seizure history or medications that may substantially lower the seizure threshold.

CHEMOTHERAPY FOR MCRPC

In spite of the advent of new antiandrogen therapies for mCRPC, chemotherapy is still important in treating symptomatic disease.

- Docetaxel
  - Improved median OS from 16.5 months (mitoxantrone/prednisone) to 18.9 months (P = .0005) and improved quality of life (functional assessment of cancer therapy-prostate, 22% vs 13%; P = .009). Although the absolute magnitude of the difference between the two arms was less than 3 months, it is important to note that the study did employ a cross-over, meaning that patients not randomized to docetaxel initially may have received docetaxel when they had progressive disease.
  - Docetaxel is perhaps most appropriate for patients with mCRPC who have intermediate or significant levels of symptoms.
  - Docetaxel would also be a reasonable option for patients with rapidly progressing disease as determined by objective changes on imaging.
  - Cabazitaxel: This treatment became the second chemotherapy approved for CaP. A phase III study trial compared this taxane with mitoxantrone in patients who already received docetaxel. (Prednisone 5 mg twice daily was also given in

both groups.) Cabazitaxel not only improved time to progression 2.8 versus 1.4 months ($P < .0001$) but also met the primary endpoint of the trial by extending survival 15.1 versus 12.7 months ($P < .0001$).
    - It is important to note that there was an 8% incidence of febrile neutropenia and 2% of patients died from neutropenia-related infections. Thus, serious consideration should be given for the use of growth factor support in appropriate patients.
    - A study comparing docetaxel and cabazitaxel as frontline chemotherapy for mCRPC did not find that cabazitaxel was superior.
- Mitoxantrone (Novantrone) + prednisone
    - Shown to improve quality of life, but not disease-free survival or OS, in two earlier randomized controlled trials versus steroids alone.
    - Mitoxantrone is stopped at a cumulative dose of 140 mg/m^2. Prochlorperazine is used as an antiemetic.
    - Mitoxantrone may be appropriate for symptomatic patients who have either progressed on or who are not candidates for taxane-based chemotherapy regimens.
- Docetaxel (Taxotere) + carboplatin
    - A single-arm phase II trial of patients ($n = 34$) who progressed on docetaxel-based chemotherapy evaluated this combination and showed a partial response rate of 14% with a median PFS of 3 months and an OS of 12.4 months.
    - This combination may be most appropriate in patients who have a small cell variant of CaP (~2% of patients).

RADIOPHARMACEUTICALS FOR METASTATIC PROSTATE CANCER

- The radioisotopes strontium-89 (Metastron) and samarium-153 lexidronam (Quadramet) have previously demonstrated palliative benefits in mCRPC patients with bone disease but were frequently associated with substantial myelosuppression.
- The alpha-emitting radium-223 (Xofigo) has demonstrated the ability to have palliative benefits and, unlike its predecessors, the ability to extend OS in mCRPC. This benefit was seen in symptomatic patients regardless of previous chemotherapy.
- Radium-223 has less impact on the bone marrow because alpha particles have a limited destruction radius, but anemia, thrombocytopenia, and leukopenia can still be encountered.

- Ultimately, radium-223 is commonly reserved for late stage, symptomatic patients because of the historic role of radioisotopes in mCRPC but earlier use may be warranted. Safety data has suggested radium-223 can be safely given with abiraterone and enzalutamide, but it remains unclear if either combination is more beneficial than sequential use.
- Emerging data from a phase 3 trial in men who have already been treated chemotherapy suggested the clinical benefit after treatment of 177Lu-PSMA-617. This will likely become a new option for men with advanced mCRPC.

PARP-Inhibitors

- As described above, increasing data is suggesting that both germline defects and mutations in the DNA repair pathway are present in a subset of men with prostate cancer.
- Early phase II data has suggested that prostate cancer patients with germline or somatic mutations overwhelming response rates to PARP-inhibitors.
- The FDA initially granted breakthrough therapy status to olaparib. More recently, a randomized phase 3 trial evaluated olaparib in men with mCRPC who had disease progression while receiving enzalutamide or abiraterone. Men had a qualifying alteration in prespecified genes involved in homologous recombination (Cohort A: 245 patients with a least one alteration in *BRCA1, BRCA2*, or *ATM*; Cohort B: 142 patients with alterations in any of 12 other prespecified genes). Patients were randomized in a 2:1 ratio to receive olaparib or physician's choice of enzalutamide or abiraterone. Imaging-based PFS was significantly longer in the olaparib group than in the control group (median, 7.4 vs 3.6 months; HR, 0.34; 95% CI, 0.25-0.47; $P < .001$). Median OS in Cohort A was 18.5 months in the olaparib group and 15.1 months in the control group.
- In 2020, the FDA accelerated approval was given to rucaparib for treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated mCRPC who had been

treated with an AR targeted therapy and a taxane. The phase 2 trial enrolled patients with deleterious mutations in *BRCA* 1/2, *ATM*, or other DNA damage repair (DDR) genes. Cohort A enrolled patients with either a *BRCA* or *ATM* mutation. Cohort B enrolled patients with a DDR mutation other than *BRCA* or *ATM*. Objective response rate (ORR) and DOR were assessed in 62 patients with measurable disease. The ORR was 44% (95% CI: 31, 57).

SUPPORTIVE MEASURES

- Hot flashes from hormonal therapy are most commonly treated with low-dose venlafaxine or gabapentin with variable success. The potential side effects of these medicines also have to be taken into account when using them to treat hot flashes.
- Testosterone-lowering therapy causes a decrease in estradiol, needed to maintain bone density, which may lead to osteoporosis. Many specialists recommend that patients receiving ADT should be given daily vitamin D and calcium supplements unless contraindicated. Obtain baseline bone mineral density before starting long-term ADT.
- Treatment with bisphosphonates or a rank-ligand inhibitor should be considered in patients with low-bone mineral density.

MANAGEMENT OF BONE METASTASES

- While narcotics can be used to alleviate bone pain, the anti-inflammatory effects of NSAIDs should not be overlooked in patients with bone metastasis as a first-line measure.
- RT directed to painful spinal cord metastases provides palliation in approximately 80% of patients. Side effects generally are limited to fatigue and anemia that are usually reversible. Generally, the painful vertebral lesion and the two vertebrae superior to and inferior to the lesion are treated with

30 Gy. The spinal cord can tolerate radiation up to approximately 50 Gy, so retreatment of some lesions may be considered.

- Bisphosphonates inhibit osteoclastic bone resorption and can decrease skeletal-related events in patients with advanced mCRPC. Zoledronic acid 4 mg IV every 3 to 4 weeks has been approved for this indication. Side effects include infusion-related myalgias, renal dysfunction, and osteonecrosis of the jaw. Dose should be adjusted for renal insufficiency.
- Denosumab (Xgeva) is a fully humanized antibody that binds to RANK-ligand that is crucial in the function of osteoclasts, which play a vital role in bone resorption. Even though it is mechanistically different from bisphosphonates, there is a similar incidence of osteonecrosis of the jaw.
- In light of the potential toxicity and the benefits, treatment with bisphosphonates or RANK-ligand inhibitor could be considered for mCRPC patients with disease in the spine and other weight-bearing bones of the pelvis and lower extremities. There is no data to support their use in mCSPC to delay metastasis or skeletal-related events.

SPINAL CORD COMPRESSION

- Vertebral column metastases impinging on the spinal cord can cause spinal cord compression, an oncologic emergency common in patients with CaP who have widespread bone metastases.
- Pain is an early sign of spinal cord compression in more than 90% of patients. Muscle weakness or neurologic abnormalities are other indicators of spinal cord compression, along with weakness and/or sensory loss corresponding to the level of spinal cord compression, which often indicate irreversible damage. Genitourinary, gastrointestinal, and autonomic dysfunction are late signs; spinal cord compression usually progresses rapidly at this point.

- Diagnosis requires a thorough history and physical, with special attention to musculoskeletal and neurologic examinations. The standard for diagnosing and localizing spinal cord compression is MRI, usually with gadolinium. A myelogram may be used in patients with contraindications to MRI such as a pacemaker.
- High-dose steroids should be started (eg, dexamethasone ≥ 24 mg IV followed by 4 mg IV or PO every 6 hours) as soon as history or neurologic examination suggests spinal cord compression.
- Neurologic/orthopedic surgeons and/or radiation oncologists should be consulted soon after diagnosis.

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15

Bladder Cancer

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EPIDEMIOLOGY

It is estimated that 83,730 people in the United States will be diagnosed with bladder cancer in 2021 and that 17,200 will die from the disease. The lifetime risk of developing bladder cancer is 3.9% for men and 1.2% for women. Worldwide, more than 573,278 people are diagnosed with bladder cancer each year. The male to female ratio is 3:1, with a peak occurrence in the seventh decade of life, making bladder cancer the fourth most commonly diagnosed cancer in men.

ETIOLOGY

- Smoking: Cigarette smoking is the most common cause of bladder cancer. In fact, for current smokers, the risk of developing bladder cancer is four to five times the risk for those who have never smoked and two times the risk for former smokers. Smoking explains a similar proportion of bladder cancer in both sexes (50% in men and 52% in women). The histology of both urothelial and squamous cell cancer (SCC) of the bladder reveals an association with the duration and amount of cigarette smoking.
- Occupational exposures: Chemical carcinogens are associated with an increased risk of bladder cancer. Workers exposed to arylamines in the dye, paint, rubber, textile, dry cleaning, and leather industries are at increased risk.
- Analgesics: Abuse of the analgesic phenacetin (banned by the U.S. Food and Drug Administration [FDA] in 1983) is associated with an increased risk of urothelial cancers, especially in the renal pelvis.
- Radiation: Prior treatment with pelvic radiation and cyclophosphamide increases the risk of urothelial cancers. Radiotherapy to the prostate confers an increased risk of bladder cancer (hazard ratio [HR]: 1.6).
- Chronic infections or inflammation: In endemic areas such as Africa and the Middle East, chronic infection with *Schistosoma haematobium* or S*chistosoma mansoni* predisposes patients to develop SCC of the bladder (due to squamous metaplasia) as well as urothelial carcinoma. Individuals with an ongoing source of inflammation (ie, a chronic indwelling catheter) also have a higher incidence of bladder cancer, especially SCC, than the general population. Progressive inflammation of the renal parenchyma also occurs in patients with Balkan nephropathy, predisposing patients to low-grade cancers of the upper urinary tract.
- Genetics: Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is associated with an autosomal-dominant germline alteration in one of four mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or *EpCAM.* Alterations in *MSH2* are associated with higher rates of urothelial carcinoma. HNPCC increases the lifetime risk of urothelial carcinoma of the ureter and renal pelvis. Individuals with HNPCC can develop upper urinary tract tumors at a younger age and an almost equal gender ratio compared to the general population.
- Thiazolidinediones: Pioglitazone and rosiglitazone used as second-line treatment of type 2 diabetes mellitus may be associated with an increased risk of bladder cancer. In June 2011, the FDA warned that use of pioglitazone (marketed as Actos) for more than 1 year may be associated with an increased risk of bladder cancer. Longer follow-up studies have shown that this association may be weaker than originally noted.

- Arsenic-contaminated drinking water: Epidemiological studies provide solid evidence of the association of arsenic-contaminated drinking water and bladder cancer.
- Aristolochic acid: Chinese herbal remedies such as *Aristolochia fangchi* and *Aristolochia clematitis,* plants endemic to the Balkan region, are associated with the development of end-stage renal disease and upper tract urothelial carcinoma.

PATHOLOGY

- Most urothelial carcinomas originate in the bladder but may also occur in the urethra or upper urinary tract, including the renal pelvis and ureter. These tumors are less common, accounting for 5% to 10% of all urothelial carcinomas.
- Urothelial carcinoma, previously called transitional cell carcinoma, accounts for around 95% of all bladder tumors in the United States. Other bladder cancer histologies include SCC (1%-2%), adenocarcinomas (including urachal) (1%), and small-cell tumors (approximately 1%). Urothelial tumors often have divergent histologies, including urothelial carcinoma and squamous, sarcomatoid, adenocarcinoma, and/or nested micropapillary subtypes.
- Carcinomas in situ (CIS) are flat tumors that usually present as diffuse urothelial involvement in patients with non–muscle-invasive bladder cancer (NMIBC). CIS increases the risk of subsequent invasive disease and recurrence, alone or in association with NMIBC.
- Papillary tumors have a fibrovascular core and are typically raised on a stalk that can invaginate into the surface layer, lamina propria, or muscularis propria. They can be either low or high grade and have a risk of recurrence and progression over time.
- Patients with upper-tract urothelial tumors have a 20% to 50% incidence of synchronous or metachronous bladder cancer. Patients with bladder cancer have about a 1% to 7% incidence of synchronous or metachronous upper-tract tumor.

CLINICAL FEATURES

- Approximately 85% of patients have painless gross or microscopic hematuria; 20% of patients have symptoms of bladder irritability.
- Patients presenting with gross hematuria have an approximately 16.5% chance of having bladder cancer; those presenting with microscopic hematuria have a 4% chance.
- Patients with invasive disease may present with flank pain due to ureteral obstruction leading to hydronephrosis.
- Patients with advanced disease may present with constitutional symptoms such as weight loss, abdominal pain, or bone pain.

SCREENING

Microscopic or gross hematuria is the most common presenting symptom in patients with bladder cancer. However, because hematuria per se is nonspecific, patients who test positive for hematuria need to undergo further tests to determine its etiology. Other noninvasive screening methods include urine cytology, fluorescence in situ hybridization, or urine-based markers. Markers such as nuclear matrix protein 22, bladder tumor-associated antigen, cytokeratins, somatic gene alteration, expression testing of shed urothelial cells, and many others have widely variable sensitivity and specificity. Assessment of these diagnostic tests demonstrated sensitivity of 0.57 to 0.95 and specificity of 0.68 to 0.93. However, these markers will miss a considerable portion of patients with bladder cancer and thus cannot replace cystoscopy for evaluation of the bladder. Given the approximately 10% false-positive rate of urinary cytology and minimal added benefit in initial evaluation of microscopic hematuria, the American Urologic Association (AUA) has now recommended against cytology testing in the initial evaluation of

patients with asymptomatic microscopic hematuria. Therefore, definitive diagnosis is best established by cystoscopy and biopsy.

DIAGNOSIS AND STAGING WORKUP

- Diagnostic workup of a patient with suspected bladder cancer is a risk-adapted strategy and should begin with an office cystoscopy and upper tract imaging ± urine cytology. The AUA has recently updated their guidelines on screening protocols for patients with microscopic hematuria due to its high incidence in adults and screening's low probability of detecting a malignancy.
- If a bladder mass is detected, the patient should undergo transurethral resection of the bladder tumor (TURBT) for full primary tumor staging. A complete TURBT has prognostic and diagnostic implications and should be attempted whenever technically feasible. The TURBT specimen should include muscle to accurately assess the depth of tumor invasion. A repeat TURBT within 6 weeks is recommended in the case of T1 high-grade disease, even if muscle is present in the specimen, as T1 tumors can be understaged by TURBT, and a repeat TURBT has prognostic value in predicting response to intravesical therapy.
- TURBT is an examination under anesthesia (EUA). EUA is important in clinical staging as it can detect locally advanced bladder cancer by assessing for invasion into adjacent organs, extravesical extension, and abdominal or pelvic sidewall extension. A bladder fixed on EUA suggests that it may be surgically unresectable.
- The upper tracts should also be evaluated by computed tomography (CT) urography (preferred), magnetic resonance (MR) urogram, or a combination of retrograde pyelogram and noncontrast cross-sectional imaging or renal ultrasound.
- In patients with a negative cystoscopy but a positive cytology, clinicians should consider prostatic urethral biopsy, enhanced cystoscopy (blue light [preferred] or narrow-band imaging), and upper-tract imaging. Ureteroscopy and random bladder biopsies are also appropriate.
- It is especially important to fully investigate the upper tracts and biopsy the prostatic urethra of patients with a positive cytology and normal cystoscopy. When CIS is detected, multiple random biopsies should be obtained and blue light cystoscopy, if available, should be offered to assess the extent of involvement.
- In patients with high-grade and/or invasive tumors, radiologic assessment should be performed with a high-resolution CT of the chest, abdomen, and pelvis with IV contrast, or MR of the abdomen and pelvis with gadolinium, and CT of the chest without IV contrast (if the patient has renal insufficiency) to assess for local lymph node involvement, upper-tract disease, and distant metastases.
- Multiparametric magnetic resonance imaging (MRI) of the bladder is currently under investigation in preoperative staging. It shows a promising ability to distinguish between NMIBC and muscle-invasive bladder cancer (MIBC). The Vesical Imaging-Reporting and Data System standardizes reporting and acquisition of images.
- The value of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT for initial staging is still under investigation but appears to be a useful supplementary imaging modality in patients with abnormal findings on CT/MRI and can be helpful in guiding a biopsy in select patients. It is not a substitute for cross-sectional imaging.
- A ^{99m}Tc bone scan, MRI, or FDG-PET/CT are recommended for patients who have elevated blood alkaline phosphatase, bone pain, or high-risk MIBC. Sodium fluoride (NaF)-PET/CT to assess bone disease in bladder cancer is also under investigation.

TUMOR STAGING AND GRADING

- Bladder cancer staging (Table 15.1) is the most important independent prognostic variable for progression and overall survival (OS). Bladder cancers are classified as non–muscle-invasive, muscle-invasive, and metastatic (Figure 15.1).

TABLE 15.1

Stage Grouping of Carcinoma of the Bladder by TNM Involvement (AJCC Eighth Edition)

	T1	T2	T3	T4a	T4b
N0	**Stage I**	**Stage II**	**Stage III**		**Stage IV**
N1-3	**Stage III**				**Stage IV**
M1	**Stage IV**				

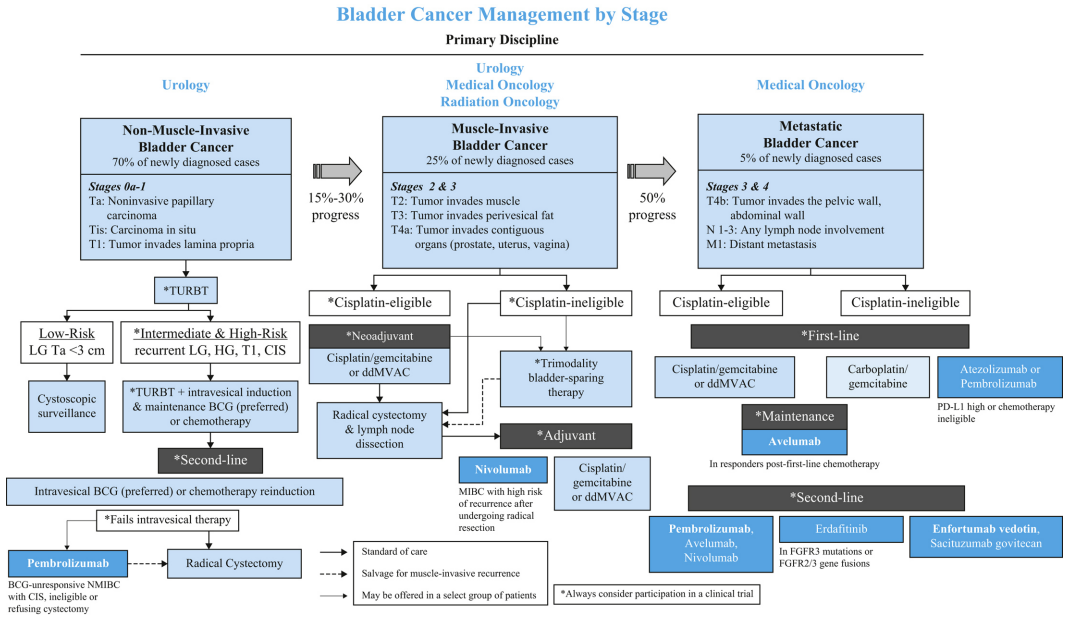

FIGURE 15.1 Management of bladder cancer differs significantly depending on stage.This algorithm depicts the treatment of non-muscle-invasive, muscle-invasive, and metastatic bladder cancer. *T4b, if tumor responds to systemic chemotherapy, consolidation with radical cystectomy may be considered.

- NMIBCs account for approximately 70% of all bladder cancers. They involve only the mucosa (Ta; ~60%) or submucosa (T1; ~30%) and flat CIS (Tis; ~10%). Most NMIBCs recur within 6 to 12 months at the same stage, but 10% to 15% of patients may develop invasive or metastatic disease. Recurrence and progression are highly dependent on grade and stage, with an approximate progression-free survival (PFS) of 95% in low-grade Ta tumors, 60% in high-grade Ta tumors, and 45% in high-grade T1 tumors.
- The grading of bladder cancer has prognostic significance for recurrence and progression of NMIBC. In 1973, the World Health Organization (WHO) graded tumors as papillomas and grade 1 to 3 urothelial tumors. In a 2004 revision of this system, the WHO classified papillomas as papillary urothelial neoplasms of low-malignant potential. Grading of actual urothelial tumors was simplified to low-grade (WHO 1973 grade 1 or 2) or high-grade (WHO 1973 grade 2 or 3).
- Risk factors for recurrence and progression in NMIBC include high-grade disease, multifocal disease, tumors >3 cm, CIS tumors, a recurrence rate of >1 per year, and T1 tumors.
- MIBCs invade the muscularis propria (T2), perivesical tissues (T3), or adjacent structures (T4a). Patients with muscle-invasive disease have a 50% likelihood of occult distant metastases at diagnosis. Note: the term "invasive" can refer to invasion of the lamina propria and can include T1 tumors. The term "muscle-invasive" specifically refers to ≥T2 tumors.
- Tumors that invade the abdominal wall or pelvic sidewall and are fixed or immobile during EUA are staged as T4b tumors and are categorized as unresectable stage IVa advanced disease. Node-positive disease is categorized as stage ≥3 bladder cancer (Figure 15.1).
- The usual sites of metastases (in order of incidence) are pelvic and retroperitoneal lymph nodes, bone, lung, and liver.

PROGNOSIS

- Major prognostic factors are tumor stage at diagnosis and degree of tumor differentiation.
- Five-year cancer-specific survival rates for patients with NMIBC, MIBC, and metastatic bladder cancer are 90%, 50%, and 10%, respectively. Median OS for NMIBC is 10 years, with a natural history characterized by recurrence of non–muscle-invasive tumor or progression to muscle-invasive disease. Non–muscle-invasive tumors recur in 60% to 70% of cases, about one-third of which progress to a higher stage or grade. OS varies significantly in patients with metastatic urothelial cancer undergoing first-line treatment with chemotherapy. To better predict OS in these patients, multiple nomograms were developed to predict survival outcomes in the first-line and salvage settings. In the treatment-naïve setting, Apolo et al identified four pretreatment variables that can predict OS: visceral metastases, albumin, performance status, and hemoglobin. Galsky et al identified similar risk factors: white blood cell count, number of sites of visceral metastasis, site of primary tumor, performance status, and lymph node metastasis.

TREATMENT

Figure 15.1 shows an algorithm for the treatment of bladder cancer.

Non–Muscle-Invasive Bladder Cancer

- TURBT is the cornerstone of treatment for NMIBC (Ta, T1, and Tis bladder cancers). A second TURBT should be considered for high-grade tumors. A complete TURBT with detrusor muscle in the specimen should be performed unless not feasible. A single postoperative dose of intravesical chemotherapy should be administered within 24 hours to reduce recurrence rates. Beyond observation after TURBT, intravesical therapy may be indicated. Close follow-up is recommended for high-risk tumors (recurrent high-grade Ta, CIS, and high-grade T1), with urine cytology and cystoscopy every 3 to 6 months for the first 2 years and longer subsequent follow-up intervals after 2 years, as appropriate.
- Intravesical therapy is primarily an adjunct or prophylaxis following TURBT, employed to lower the incidence of disease recurrence and/or progression. Only a single postoperative dose of intravesical chemotherapy is indicated for low-risk disease (low-grade solitary Ta ≤3 cm). Multiple meta-analyses and a recent phase III randomized clinical trial demonstrated that a single postoperative dose of chemotherapy led to an absolute risk reduction of recurrence of 10% to 20%. Intermediate-risk patients, however, should be offered induction and maintenance intravesical chemotherapy or bacillus Calmette-Guerin (BCG), and high-risk patients should receive induction and maintenance intravesical BCG. Chemotherapeutic agents instilled intravesically include gemcitabine, thiotepa, doxorubicin, epirubicin, and, most commonly, mitomycin C. Data suggest that currently available intravesical chemotherapeutic agents are equally effective but differ in toxicity. Although no standardized dosing or scheduling has been established for intravesical chemotherapy, a standard approach has been to administer a full dose monthly for 6 to 12 months. Immunotherapy with BCG has statistically significant clinical benefits, including complete response in CIS (70%-75%) and reduced recurrence in high-grade Ta or T1 (20%-57%). However, it has not shown consistent reduction in tumor progression unless combined with maintenance BCG administered as per the Southwest Oncology Group (SWOG) protocol described by Lamm et al. Unlike intravesical chemotherapy, BCG has been shown to reduce rates of progression, with one meta-analysis of 24 trials demonstrating a 27% decrease in rate of progression. BCG has also proven superior to intravesical chemotherapy in reducing rates of recurrence and progression but does so at the cost of increased local side effects.
- Recurrent or persistent high-grade tumors may require a second induction course of BCG. Tumors that do not respond to two induction courses of BCG or one induction course of BCG and one maintenance course of BCG are considered BCG-unresponsive, and radical cystectomy is advised. Heterogeneity in how studies define patients who are refractory to therapy with BCG has

precluded the generalizing of results and highlighted the need to standardize definitions. Adequate BCG therapy is defined as the patient receiving at least five of six doses of an initial induction course plus at least two of three doses of maintenance or at least two of six doses of a second induction course. BCG-unresponsive disease is defined as either (1) persistent or recurrent CIS ± Ta/T1 disease within 12 months of adequate BCG therapy, (2) recurrent high-grade Ta/T1 disease within 6 months of adequate BCG therapy, or (3) high-grade T1 disease at first evaluation following an induction BCG course.

- Two FDA-approved agents, intravesical valrubicin and intravenous pembrolizumab, are approved for BCG-unresponsive CIS in patients who are unfit for or refuse cystectomy. Valrubicin is approved for BCG-unresponsive CIS, and pembrolizumab is approved for BCG-unresponsive CIS ± Ta/T1 disease. Some treatments currently being studied in this population are gemcitabine plus docetaxel, nadofaragene firadenovec, Vicineum (oportuzumab monatox-qqrs), hyperthermic chemotherapy, chemoradiation (RTOG-0926), and immunotherapeutics.
- Early radical cystectomy is indicated for BCG-unresponsive patients and can be offered to high-risk patients with persistent high-grade T1 lesions after TURBT or high-grade T1 lesions associated with CIS, variant histologies, or lymphovascular invasion due to the high rates of upstaging to MIBC (~50%) or non–organ-confined disease (~33%) at the time of cystectomy. Patients with NMIBC who progress to muscle invasion have worse outcomes than patients who present with de novo MIBC. High-grade T1 and CIS lesions have a propensity to progress and to metastasize.
- Neoadjuvant therapy is not indicated prior to cystectomy in NMIBC.

Muscle-Invasive Bladder Cancer

- Radical cystectomy with bilateral lymph node dissection is the standard therapy for MIBC. In men, the surgery involves radical cystoprostatectomy. Men who have cancer noted at the margin of the apical urethra should undergo a concomitant or delayed urethrectomy. In women, radical cystectomy involves wide excision of the bladder, urethra, uterus, adnexa, and anterior vaginal wall.
- Preserving the bladder with definitive chemoradiotherapy, or trimodality therapy, is an alternative to radical cystectomy. The two most common approaches include either a continuous or split course protocol. In both protocols, patients undergo complete, maximal TURBT. The split course protocol is followed by an induction dose of chemoradiotherapy and an assessment for response after 40 to 45 Gy is administered. Patients who achieve a complete response then undergo consolidative chemoradiotherapy for bladder preservation (total 55-65 Gy); patients who do not achieve a complete response are referred for salvage radical cystectomy with curative intent. In the continuous course protocol, patients receive a full dose of chemoradiotherapy up front and then are evaluated for therapeutic response. Patients who do not achieve a complete response undergo a salvage radical cystectomy. Cisplatin is the most common radiosensitizer used in trimodal therapy; however, many patients are cisplatin-ineligible due to impaired renal function or poor performance status. For these patients, a combination of 5-fluorouracil and mitomycin or single-agent gemcitabine is an alternative treatment. Patients with multifocal disease, CIS, hydronephrosis, or poorly functioning bladders are not ideal candidates for definitive trimodal therapy. Pooled data from six Radiation Therapy Oncology Group protocols have demonstrated a 5-year disease-free survival (DFS) of 71%, 5-year bladder-intact DFS of 56%, and a 5-year OS of 57%. Though these results are from a group of well-selected patients, trimodality therapy offers promising outcomes to appropriate patients.
- Despite undergoing radical cystectomy for definitive treatment, 50% of patients in the pre-neoadjuvant chemotherapy (NAC) era with MIBC progressed to metastatic disease and eventually died from bladder cancer. Neoadjuvant cisplatin-based chemotherapy prior to definitive therapy improves survival in patients with T2 to T4a MIBC. A trial by the Medical Research Council and the European Organization for Research and Treatment of Cancer tested neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) prior to definitive cystectomy or radiotherapy. Mature results from this trial showed an absolute survival benefit of 6% (30%-36%) and a relative reduction in the risk of death from bladder cancer of 16% at 10 years in 976 randomized patients with MIBC. A

similar survival benefit was seen in a United States Intergroup randomized trial (SWOG-8710) of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) prior to cystectomy or cystectomy alone. An improvement in 5-year OS (43%-57%) and median survival (46-77 months) was noted in the NAC arm; however, the differences were not statistically significant. The number of patients who were able to be downstaged to pT0 increased in the NAC arm (15% vs 38%), and this was strongly associated with long-term OS, with a 5-year OS of 85% in pT0 patients. A meta-analysis of >2600 MIBC patients who received cisplatin-based NAC also showed a 5-year absolute survival benefit of 5% and a relative reduction in mortality of 13%, indicating that cisplatin-eligible patients should receive NAC prior to definitive therapy. Two phase II trials have assessed and supported the use of a dose-dense (dd) schedule for MVAC (ddMVAC) with pegfilgrastim support. In the United States, gemcitabine and cisplatin (GC) or ddMVAC are frequently used in the neoadjuvant setting instead of standard-schedule MVAC or CMV. The ongoing phase III VESPER trial is assessing perioperative ddMVAC versus GC. Secondary outcomes have been reported; no differences were noted in the pT0 rates (42% vs 36%; $P = .2$); however, an improved organ-confined disease rate (<ypT3pN0) was noted in the ddMVAC arm (77% vs 63%; $P = .001$). The primary outcome of 3-year PFS has not been reported yet. Perioperative therapies for cisplatin-ineligible patients are still under investigation. There are no data supporting the administration of non–cisplatin-based NACs, such as carboplatin combinations. The role of checkpoint inhibitors in the neoadjuvant setting is currently under study, and a phase II study of neoadjuvant pembrolizumab has shown promise with a pT0 rate of 42% and <pT2 rate of 54%.

- Data for adjuvant cisplatin-based chemotherapy are less compelling, and trials are plagued by early termination due to poor accrual; thus, adjuvant regimens should not replace NAC. However, patients benefit from cisplatin-based adjuvant chemotherapy if they did not receive NAC and have extensive disease discovered on radical cystectomy. Unfortunately, bladder cancer patients are usually elderly and tend to have multiple comorbidities, making adjuvant chemotherapy after radical cystectomy a challenge. Furthermore, patients may not be able to tolerate chemotherapy after surgery due to delayed healing and/or postsurgical complications.
- In August 2021, the FDA approved nivolumab for the adjuvant treatment of patients with MIBC or muscle-invasive upper-tract urothelial carcinoma at high risk of recurrence after undergoing radical resection. Nivolumab was investigated in CHECKMATE-274 (NCT02632409), a randomized, double-blind, placebo-controlled trial in patients who were within 120 days of radical resection of urothelial carcinoma of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. Patients were randomized 1:1 to receive nivolumab 240 mg or placebo by IV infusion every 2 weeks until recurrence or until unacceptable toxicity for a maximum treatment duration of 1 year. The primary efficacy endpoint was investigator-assessed DFS in the intent-to-treat (ITT) population and in patients with tumors expressing PD-L1 ≥1%. DFS was defined as time to first recurrence (local urothelial tract, local nonurothelial tract, or distant metastasis) or death. At a prespecified interim analysis, a statistically significant improvement in DFS was demonstrated in patients on the nivolumab arm versus placebo for both primary endpoints. In the ITT analysis, the median DFS was 20.8 months (95% CI: 16.5, 27.6) in patients who received nivolumab compared with 10.8 months (95% CI: 8.3, 13.9) in patients who received placebo (HR 0.70; 95% CI: 0.57, 0.86; $P = .0008$). For patients with tumors expressing PD-L1 ≥1%, median DFS was not reached (95% CI: 21.2, not estimable) in those who received nivolumab versus 8.4 months (95% CI: 5.6, 21.2) for patients who received placebo (HR 0.55; 95% CI: 0.39, 0.77; $P = .0005$).

Metastatic Bladder Cancer

First-Line Therapy (Tables 15.2 and 15.3)

TABLE 15.2

Randomized Phase III Studies of Cisplatin-Based Chemotherapy in Metastatic Bladder Cancer

First Author, Year	Regimen	No. of Patients	Objective Response Rate (%)	Median Survival (mo)	*P* Value
Bamias, 2012	ddMVAC vs ddGC	66 64	60 65	19 18	.98
Bellmunt, 2012	GC vs gemcitabine/cisplatin/paclitaxel	314 312	44 56	12.7 15.8	.075
Dreicer, 2004	MVAC vs paclitaxel/carboplatin	44 41	40 28	14.2 13.8	.41
Bamias, 2004	MVAC vs docetaxel/cisplatin	109 111	54 37	14.2 9.3	.025
Sternberg, 2001	MVAC vs ddMVAC	129 134	50 62	14.1 15.5	.122
von der Maase, 2000	MVAC vs GC	202 203	46 49	14.8 13.8	.750
Loehrer, 1992	MVAC vs cisplatin	120 126	39 12	12.5 8.2	<.0002
Logothetis, 1990	MVAC vs CISCA	55 55	65 46	12.6 10	<.05

CISCA, cyclophosphamide, cisplatin, doxorubicin; dd, dose-dense; GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine sulfate, doxorubicin hydrochloride (Adriamycin), and cisplatin.

TABLE 15.3
Common Systemic Regimens for Urothelial Carcinoma

Regimen	Dosing	Duration (days)	Setting
Chemotherapy			
Gemcitabine + cisplatin	Gemcitabine, 1000 mg/m^2 IV on days 1 and 8 Cisplatin, 70 mg/m^2 IV on day 1	21	Neoadjuvant and first-line
MVAC	Methotrexate, 30 mg/m^2 IV on days 1, 15, and 22	28	Neoadjuvant and first-line
	Vinblastine, 3 mg/m^2 IV on days 2, 15, and 22		
	Doxorubicin, 30 mg/m^2 IV on day 2		
	Cisplatin, 70 mg/m^2 IV on day 2		
ddMVAC	Methotrexate, 30 mg/m^2 IV on day 1	14	Neoadjuvant and first-line
	Vinblastine, 3 mg/m^2 IV on day 1		
	Doxorubicin, 30 mg/m^2 IV on day 1		
	Cisplatin, 70 mg/m^2 IV on day 1		
	Pegfilgrastim on day 2		
Gemcitabine + carboplatin	Gemcitabine, 1000 mg/m^2 IV on days 1 and 8	21	Cisplatin-ineligible First-line
	Carboplatin AUC of 5 mg/mL/min IV on day 1 after gemcitabine		
ITP	Ifosfamide, 1500 mg/m^2/d IV on days 1-3	21	Nonurothelial carcinoma histology First-line
	Mesna, 300 mg/m^2 IV 30 min before ifosfamide, then 300 mg/m^2 IV on 4 and 8 h after ifosfamide; 600 mg/m^2 PO 4 and 8 h after ifosfamide		
	Paclitaxel, 200 mg/m^2 IV infusion over 3 h on day 1		
	Cisplatin, 70 mg/m^2 IV on day 1		
	Pegfilgrastim on day 2		
Checkpoint Inhibitors			
Pembrolizumab	Pembrolizumab 200 mg; administer IV over 30 min in a volume of 0.9% sodium chloride injection (0.9% NS) or 5% dextrose injection (D5W) sufficient to produce a pembrolizumab concentration within the range 1-10 mg/mL every 3 wk for up to 24 mo (total dosage/cycle = 200 mg)	21	First- or second-line NMIBC (BCG unresponsive NMIBC with CIS, ineligible or refusing cystectomy)

Regimen	Dosing	Duration (days)	Setting
Nivolumab	Nivolumab 240 mg; administer IV over 30 min in a volume of 0.9% sodium chloride injection (0.9% NS) or 5% dextrose injection (D5W), not to exceed 160 mL and sufficient to produce a nivolumab concentration within the range 1-10 mg/mL, every 2 wk until disease progression (total dosage/cycle = 240 mg)	14	Second-line
	Nivolumab 480 mg; administer IV over 30 min in a volume of 0.9% NS or D5W not to exceed 160 mL and sufficient to produce a nivolumab concentration within the range 1-10 mg/mL, every 4 wk until disease progression (total dosage/cycle = 480 mg)	28	Second-line
Avelumab	Avelumab 10 mg/kg; administer intravenously over 60 min in 250 mL 0.9% sodium chloride injection or 0.45% sodium chloride injection, every 2 wk (total dosage/cycle = 10 mg/kg)	14	Maintenance or second-line
Atezolizumab	Atezolizumab 1200 mg; administer IV in 250 mL 0.9% sodium chloride injection over 60 min every 3 wk (total dosage/cycle = 1200 mg)	21	First- or second-line
FGFR-3 Tyrosine Kinase Inhibitor			
Erdafitinib	Erdafitinib 8 mg/dose; administer PO once daily, without regard to food, continually on days 1-28, every 28 d, until disease progression (total dosage/28-day cycle = 224 mg)	Daily continuously 28	Second-line
Antibody-Drug Conjugate			
Enfortumab vedotin-	Enfortumab vedotin 1.25 mg/kg IV on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity	28	Second-line
Sacituzumab govitecan	Sacituzumab govitecan 10 mg/kg IV once weekly on days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity	21	Second-line

AUC, area under the curve; dd, dose-dense; ITP, ifosfamide, paclitaxel, cisplatin; IV, intravenously; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; PO, per os (by mouth).

- ddMVAC and GC are standard first-line chemotherapy regimens for metastatic urothelial carcinoma. ddMVAC is the most active regimen, with response rates of 40% to 72%.
- A randomized study of standard MVAC (4-week cycles) versus ddMVAC (2-week cycles with growth factor support) showed that treatment could be completed faster, with less toxicity, better objective response rate (ORR) (72% vs 58%), and improved 5-year OS (21.8% vs 13.5%) by eliminating day 15 and 22 of methotrexate and vinblastine. ddMVAC is used almost exclusively in clinical practice.
- GC has been shown to be equivalent to standard MVAC in OS, time to treatment failure, and response rates, with less toxicity. ddMVAC has not been compared to GC in a randomized study. GC is more commonly used, given its favorable toxicity profile.
- A randomized, controlled study of ddMVAC versus ddGC showed that the regimens were comparable in OS and PFS but that ddGC had a better toxicity profile. However, this study halted randomization early due to poor accrual.
- Triplet chemotherapy combination regimens such as paclitaxel, gemcitabine, and cisplatin (PCG) have shown increased response in some patients, but their impact on survival is unclear (Table 15.2). In one study, the PCG arm reported more febrile neutropenia than the GC arm (13.2% vs 4.3%; $P < .001$). There are no data showing that carboplatin can be effectively substituted for cisplatin. Before it closed prematurely due to poor accrual, an Eastern Cooperative Oncology Group (ECOG) phase III study of MVAC versus carboplatin and paclitaxel demonstrated a nonstatistically significant difference in median OS of 15.4 months for the MVAC arm versus 13.8 months for the carboplatin-paclitaxel arm ($P = .65$), with toxicity favoring the carboplatin-paclitaxel arm. Therefore, carboplatin should be substituted for cisplatin only in patients deemed cisplatin-ineligible.
- Phase III data have shown that for patients who have not progressed on first-line GC, the addition of avelumab maintenance therapy compared to best supportive care improved 1-year OS (71% vs 58%), median OS (21.4 vs 14.3 months), and median PFS (3.7 vs 2.0 months). Patients who have not received checkpoint inhibitors in the front-line setting and who have not had progressive disease should receive maintenance avelumab.

Cisplatin-Ineligible Patients

- Patients are considered cisplatin-ineligible if they have poor performance status (ECOG PS ≥ 2), renal insufficiency, hearing loss (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥2), neuropathy (CTCAE grade ≥2), or class III heart failure.

- Current preferred regimens in cisplatin-ineligible patients are gemcitabine and carboplatin with avelumab maintenance in patients who did not progress, atezolizumab, and pembrolizumab. Other acceptable regimens include single-agent gemcitabine or gemcitabine and paclitaxel.
- A randomized phase II/III study in cisplatin-ineligible patients examined gemcitabine and carboplatin versus methotrexate, carboplatin, and vinblastine (M-CAVI). Median OS was 9.3 months in the gemcitabine and carboplatin arm versus 8.1 months in the M-CAVI arm (P = .64). Severe toxicity was seen in 9.3% of patients in the gemcitabine and carboplatin arm versus 21.2% of patients in the M-CAVI arm. These results demonstrated no difference between the two carboplatin-based regimens relative to survival; however, more severe toxicity was associated with the M-CAVI regimen.
- Immunotherapy with checkpoint inhibition of the programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) pathway has demonstrated rapid, durable responses in metastatic urothelial carcinoma. Two checkpoint inhibitors, atezolizumab and pembrolizumab, are FDA-approved for first-line treatment of metastatic urothelial carcinoma in cisplatin-ineligible patients (Table 15.4). The FDA later restricted the use of these two medications in the first-line setting in patients with low–PD-L1 expression based on an ongoing survival analysis.

TABLE 15.4

Reported Trials of PD-1/PD-L1 Inhibitors Leading to FDA Approval in Urothelial Carcinoma

	Pembrolizumab	Atezolizumab*	Nivolumab	Durvalumab*	Avelumab	Atezolizumab	Pembrolizu
NCT number	NCT02256436	NCT02108652	NCT02387996	NCT01693562	NCT01772004	NCT02108652	NCT023354
Authors	Bellmunt et al	Rosenberg et al	Galsky et al	Hahn et al	Apolo et al	Balar et al	Balar et al
FDA approval	May 2017	May 2016	February 2017	May 2017	May 2017	April 2017	May 2017
Phase	III	II	II	I/II	I	II	II
Dose and schedule	200 mg q3w	1200 mg q3w	3 mg/kg q2w	10 mg/kg q2w	10 mg/kg q2w	1200 mg q3w	200 mg q3w
N	542	310	265	182	161	119	370
ORR (%)	Pembro: 21.1 Chemo: 11.4	15	19.6	17.6	17.4	23	24
ORR PD-L1 $^{+}$ (%)	Pembro: 21.6 Chemo: 6.7	26	28.4	27.4	25.4	28	39
PR (%)	Pembro: 14.1 Chemo: 8.1	10	17.4	14.3	11.2	13	19
CR (%)	Pembro: 7 Chemo: 3.3	5	2.3	3.3	6.2	9	5
PD-L1 $^{+}$ assay and cutoff for positivity	Dako 22C3: TC and IC ≥ 10%	Ventana SP142: IC0 (<1%) IC1 (≥1%/<5%) IC2/3 (≥5%)	Dako 28-8: TC ≥ 5%	Ventana SP263 TC and IC ≥ 25%	Dako 73-10: TC ≥ 5%	Ventana SP142: IC0 (<1%) IC1 (≥1%/<5%) IC2/3 (≥5%)	Dako 22C3: TC IC ≥ 10%
PD-L1 $^{+}$ prevalence (%)	Pembro: 27.4 Chemo: 33.1	32.2 (IC2/3)	30.5	52	32.9	27	22
PFS (mo)	Pembro: 2.1 Chemo: 3.3	2.1	2.0	1.5 [a]	1.7	2.7	2
OS (mo)	Pembro: 10.3 Chemo: 7.4	11.4	8.7	18.2 [a]	7.4	15.9	NR
Grade 3/4 AEs (%)	Pembro: 15 Chemo: 49.4	16	17.8	13.6 [a]	8.4 [b]	16	16

[a]Based on cohort of 191 patients (9 chemotherapy-naïve) treated with durvalumab.

[b]Based on cohort of 249 patients (88 with <6 months follow-up) treated with avelumab.

*Voluntary withdrawal of second-line indication by pharmaceutical company.

AEs, adverse events; CR, complete response; FDA, US Food and Drug Administration; NR, not reported; ORR, objective response rate; OS, overall survival; PD-L1^{+}, programmed death-ligand 1-positive; PFS, progression-free survival; PR, partial response; q, qua (every); w, weeks.

- Atezolizumab is a humanized IgG1 monoclonal antibody (mAb) targeting PD-L1. Cohort 1 of the IMvigor 210 trial enrolled 123 treatment-naïve patients. Of these, 119 were cisplatin-ineligible and received atezolizumab as first-line treatment. The ORR was 23% and median OS was 15.9 months, with no enrichment of clinical activity by PD-L1 immunohistochemistry (IHC) expression. Incidence of treatment-related adverse events of any grade was 66%. Fatigue, diarrhea, and pruritus occurred in ≥10% of patients, and grade 3/4 adverse events, most commonly fatigue and elevated ALT and AST (3% each), occurred in 16% of patients.
- Pembrolizumab is a humanized IgG4 mAb targeting PD-1. The phase II KEYNOTE-052 study assessed pembrolizumab as first-line therapy in 370 cisplatin-ineligible patients with metastatic urothelial carcinoma. The ORR was 24%, with high-level PD-L1 IHC expression predicting patients most likely to respond to treatment. Treatment-related adverse events of any grade were seen in 62% of patients; 16% had grade ≥3 adverse events.

Second-Line Systemic Therapy

- Patients who have not received maintenance avelumab may receive a second-line PD-1/PD-L1 immune checkpoint inhibitor. Five immune checkpoint inhibitors (atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab) demonstrated clinical efficacy in the second-line setting in patients with metastatic urothelial carcinoma, with comparable ORRs of 15% to 20% (Table 15.4). Atezolizumab, nivolumab, durvalumab, and avelumab originally received accelerated FDA approval, while pembrolizumab gained regular approval for the treatment of advanced metastatic urothelial carcinoma or metastatic progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy. However, follow-up studies for durvalumab and atezolizumab failed to meet endpoints and FDA approval in the postplatinum setting was voluntarily withdrawn by their respective pharmaceutical developers.
- **Nivolumab.** The phase II CheckMate 275 study investigated the safety and efficacy of nivolumab, mAb to PD-1, in 265 patients with metastatic urothelial carcinoma who had received prior treatment. The ORR was 20% in all patients (7 complete responses and 46 partial responses) and 16% and 24% in patients with negative (≤1%) and positive (>1%) PD-L1 IHC expression on tumor cells, respectively. Median OS was 8.7 months overall and 6.0 and 11.30 months in PD-L1$^-$ and PD-L1$^+$ patients, respectively. Grade ≥3 adverse events occurred in 18% of patients, with fatigue and diarrhea each in 2% of patients.
- **Pembrolizumab.** The phase III KEYNOTE-045 trial compared single-agent pembrolizumab versus the physician's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with metastatic urothelial carcinoma post–platinum-based chemotherapy. The ORR was 21% versus 11% (P = .0011) and median OS was 10.3 versus 7.4 months (HR 0.73; P = .0022), respectively. Patients with a PD-L1 combined positive score of ≥10% demonstrated greater median OS (8.0 vs 5.2 months). There was a lower incidence of adverse events of any grade (61% with pembrolizumab vs 90% with chemotherapy), including grade ≥3 adverse events (15% and 49% for pembrolizumab and chemotherapy, respectively).
- **Avelumab**, an anti–PD-L1 mAb, has been shown to induce antibody-dependent cell-mediated cytotoxicity of tumor cells in preclinical studies. The JAVELIN Solid Tumor phase Ib trial investigated the safety and clinical activity of avelumab in patients with metastatic urothelial carcinoma post–platinum-based chemotherapy. An initial cohort (n = 44) showed encouraging antitumor responses and a manageable safety profile, leading to the addition of an efficacy cohort of 205 patients. A pooled analysis of the initial and efficacy cohorts showed an ORR of 17%. The ORR in patients with or without baseline visceral metastases was 14% and 38%, respectively. Median OS in all postplatinum avelumab-treated patients was 7 months and median duration of response (DOR) was 20.5 months. Adverse events of any grade occurred in 67% of patients and included infusion-related reactions, fatigue, and rash (≥10%); 7% of patients had grade ≥3 treatment-related adverse events, including fatigue (≥1%).
- **Erdafitinib**, a tyrosine kinase inhibitor for FGFR1-4, was evaluated in a phase II study of 99 patients with prespecified somatic FGFR alterations who were cisplatin-ineligible or had progressed on prior first-line chemotherapy. ORR was 40% in the whole population and 59% among patients who

had received prior immunotherapy. Median OS was 13.8 months and median duration of PFS was 5.5 months. Grade ≥3 treatment-related adverse events were noted in 46% of patients, most commonly hyponatremia (11%), stomatitis (10%), and asthenia (7%). Thirteen patients (13%) discontinued treatment due to adverse events. Erdafitinib is FDA-approved for patients with susceptible somatic FGFR2 or FGFR3 genetic alterations and who have progressed after one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

- **Enfortumab vedotin** (EV) is an antibody/drug conjugate directed against Nectin-4. It currently has accelerated FDA approval for patients who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. EV was assessed in a phase II study of 125 patients who underwent prior platinum-containing chemotherapy and PD-1/PD-L1 inhibitor therapy. ORR was 44%, with a 12% rate of complete response. Median OS, PFS, and DOR was 11.7, 5.8, and 7.6 months, respectively.
- EV-301 is a global, open-label, phase III trial that evaluated EV versus chemotherapy in patients with advanced/metastatic urothelial carcinoma previously treated with a platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor. Patients receiving EV had an increased OS of 12.88 versus 8.97 months and PFS of 5.55 versus 3.71 months. The incidence of grade ≥3 treatment-related adverse events was similar in both groups. Notable side effects of EV included peripheral sensory neuropathy, skin toxicity, fatigue, decreased appetite, neutropenia, anemia, and fatigue. In a postmarketing analysis, severe cutaneous adverse reactions, including fatal cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, were discovered.
- **Sacituzumab govitecan** received accelerated FDA approval for patients with locally advanced or metastatic urothelial carcinoma previously treated with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor. Efficacy and safety were evaluated in TROPHY (IMMU-132-06; NCT03547973), a single-arm, multicenter trial that enrolled 112 patients with locally advanced or metastatic urothelial carcinoma who received prior treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor. Patients received sacituzumab govitecan 10 mg/kg IV on days 1 and 8 of a 21-day treatment cycle. The main efficacy endpoints were ORR and DOR, evaluated by independent review using RECIST 1.1. The confirmed ORR was 27.7% (95% CI: 19.6, 36.9) with 5.4% complete responses and 22.3% partial responses. The median DOR was 7.2 months (n = 31; 95% CI: 4.7, 8.6; range 1.4+ to 13.7). Most common adverse reactions (incidence >25%) in patients receiving sacituzumab govitecan are neutropenia, nausea, diarrhea, fatigue, alopecia, anemia, vomiting, constipation, decreased appetite, rash, and abdominal pain. The recommended sacituzumab govitecan dose is 10 mg/kg once weekly on days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity.
- Response rates to second-line chemotherapy are low (5%-20%). Common treatment involves single-agent taxanes or pemetrexed.

Suggested Readings

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16

Testicular Carcinoma

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INTRODUCTION

Testicular cancer represents only 1% of all malignancies in males; however, it is the most common malignancy in men between the ages of 15 and 35 years. The most common type is germ cell tumor (GCT)—up to 95%, followed by gonadal stromal tumors (Leydig cell and Sertoli cell tumors), which comprise most of the remainder. Testicular GCT is further divided into seminoma and nonseminomatous GCTs (NSGCTs) based on distinct biology and different treatment options. Testis can also be a site of metastatic disease, with lymphoma as the most common secondary cancer. Testicular lymphoma is more frequent in men >50 than primary testicular tumors. Due to the availability of effective treatment since the 1970s, the cure rate is now excellent and has reached approximately 95% of all patients.

CLINICAL FEATURES

Epidemiology

- The American Cancer Society estimates that in 2021 in the United States, there would be 9470 new cases of testicular carcinoma and 440 deaths.
- The incidence rate has been increasing in the United States and other countries, mostly seminomas.

- NSGCT peaks in the third decade while seminoma peaks in the fourth decade.
- The incidence varies significantly by ethnicity: highest is among non-Hispanic whites (6.57 per 100,000), followed by Hispanics (3.88), American Indians/Alaska Natives (2.88), Asians/Pacific Islanders (A/PIs; 1.60), and least common among non-Hispanic blacks (1.20)

Risk Factors

- Cryptorchidism (undescended testicle): Cryptorchid testis is associated with a four- to sixfold increase in the risk of testicular cancer, with intra-abdominal testes having an increased risk; therefore, orchiopexy (a surgical procedure to move testicle into the scrotum) is usually performed before puberty to decrease the risk.
- Personal history: Synchronous or metachronous testicular carcinoma may rarely occur; 1% to 5% of patients will have bilateral disease at initial presentation. Patients should be counseled that they have an approximately 2% chance of developing contralateral testicular cancer over time.
- Family history: There is a strong familial component (no definite gene has been identified). A son of an affected father has a 4- to 6-fold increased risk, while for a brother of an affected sibling, the risk increases to 8- to 12-fold. The risk is >70-fold in monozygotic twins.
- Intratubular germ cell neoplasia (ITGCN): It is a premalignant condition seen in 90% of testicular carcinomas (not typically seen with spermatocytic seminoma and is associated with 50% chance of development of GCT at 5 years [70% at 7 years]).
- Chromosomal abnormalities: The most common karyotype abnormality is isochromosome 12p. Klinefelter syndrome has been shown to be associated with increased risk of primary mediastinal GCTs. Some studies have also suggested the possibility of an increased risk with Down syndrome. Additionally, disorders of sexual differentiation are associated

with a variable increased risk of developing testicular cancer when a Y-chromosome is present (gonadoblastoma). For this reason, prophylactic gonadectomy is recommended before puberty for abnormal or streak gonads.

- Viral infections: HIV is associated with a significant higher risk of testicular cancer; however, effective antiretroviral therapy may attenuate the risk. Possible associations between Epstein-Barr virus, cytomegalovirus, and human papilloma virus and testicular cancer have been reported although these associations are modest or inconclusive.

Presentation

- Self-detected asymptomatic/painless testicular nodule or swelling is the most common presentation
- Testicular heaviness, dull ache, and/or hardness (up to 40%)
- Acute testicular pain (up to 10%)
- Disease at extragonadal site (10% of patients; symptoms vary with site):
  - Dyspnea, cough, or hemoptysis (pulmonary metastases)
  - Weight loss, nausea, abdominal, or back pain (retroperitoneal adenopathy)
  - Swelling in neck (left-sided supraclavicular lymphadenopathy)
  - Superior vena cava syndrome due to mediastinal disease
- Rare symptoms:
  - Urinary obstruction
  - Bone pain (bone metastases)
  - Paraneoplastic hyperthyroidism (TSH and hCG have a considerable homology)
  - Gynecomastia due to elevated β-HCG
  - Neurologic symptoms (brain metastases or Anti-Ma2-associated paraneoplastic limbic encephalitis)

DIFFERENTIAL DIAGNOSIS

- Epididymitis (initial diagnosis in 18%-33% of testicular cancer patients)
- Trauma
- Orchitis, hydrocele, varicocele, or spermatocele

- Paratesticular neoplasm (can be benign or malignant)
- Testicular torsion
- Metastases (lymphoma, leukemia, melanoma, or lung cancer)
- Infectious diseases (tuberculosis and tertiary syphilis)

DIAGNOSIS

A solid mass within the testis should be considered testicular cancer until proven otherwise. The initial evaluation of a suspicious testicular mass should include:

- Testicular ultrasound
- Serum tumor markers: alpha-fetoprotein (AFP), β-HCG, and serum lactate dehydrogenase (LDH)

Subsequently, if findings support a testicular tumor, a radical inguinal orchiectomy should be performed. Prior to orchiectomy, sperm banking should be discussed, and if future paternity is desired, opportunity and resources should be provided. There is no role for transscrotal orchiectomy, biopsy, or fine-needle aspiration due to potential scrotal contamination and inadequate local control of the spermatic cord.

Postoperatively, if GCT is confirmed, a chest x-ray (CXR) and computed tomography (CT) of the abdomen/pelvis should be performed, and serum tumor markers should be repeated. Chest CT should be performed for abnormalities on preoperative chest film, pulmonary symptoms, or if retroperitoneal/abdominal disease is noted on staging CT of the abdomen/pelvis. Brain imaging is indicated for symptomatic patients or for poor risk disease with markedly elevated serum tumor markers (especially in patients with choriocarcinoma).

Tumor Markers

Serum AFP

- A glycoprotein with a half-life of approximately 4 to 6 days.
- The upper limit of normal for serum is less than 10 to 15 μg/L.
- Commonly produced by liver, gastrointestinal tract, and the fetal yolk sac.
- Can be elevated in the setting of liver disease and/or malignancy (yolk sac tumor, embryonal cell carcinoma, and hepatocellular carcinoma).
- If levels are mildly elevated, alcohol intake should be determined and the liver should be evaluated.
- Elevated serum AFP levels indicate a nonseminomatous component. Thus, patients with AFP elevation should be managed as NSGCT even when pathology showed pure seminoma.

Serum β-HCG

- Secreted by syncytiotrophoblasts; half-life of 0.5 to 1.5 days.
- Most commonly elevated tumor marker in testicular cancer.
- The normal value in men is less than 5 to 10 IU/L.
- Present in choriocarcinomas and embryonal carcinoma; may be modestly elevated in 15% of pure seminomas (reflects higher disease burden, not necessarily a more aggressive disease).
- High levels may lead to gynecomastia (could be the first sign of testicular cancer).
- False positives may be seen in patients with:
    a. Hypogonadism due to cross reactivity of luteinizing hormone with the β-HCG assay. Thus, if β-HCG is elevated after orchiectomy, serum testosterone should be analyzed, and if low, testosterone should be replaced and β-HCG rechecked
    b. Tumor lysis (after the first dose of chemotherapy)
    c. Marijuana use

Serum LDH

- Nonspecific tumor marker in testicular cancer (reflects overall tumor burden and growth rate)
- Half-life 24 hours
- Elevated in 80% of metastatic seminomas and 60% of advanced nonseminomatous tumors
- May be the only tumor marker in seminoma

Imaging

- Testicular ultrasound: evaluates testicular parenchyma.
- CXR: Posterior-anterior and lateral film evaluation for pulmonary metastases and mediastinal adenopathy.
- CT: CT scans of chest, abdomen, and pelvis are the most effective and commonly used. However, CXR can replace CT chest in stage I disease to minimize radiation exposure.
- Magnetic resonance imaging (MRI): Testicular MRI may provide additional information if ultrasound is indeterminate (rarely needed). MRI of the brain is necessary only when there are neurological symptoms.
- Positron emission tomography (PET) scan: PET scans are not indicated in the initial staging but have a role in characterizing posttreatment residual masses in seminoma (see below). The routine use of PET scans has not been shown to improve the outcome in NSGCT and therefore is not recommended.

Pathology

Patients with testicular masses should undergo complete removal of the testis and spermatic cord up to the internal inguinal ring. Transscrotal orchiectomy or testicular biopsy is not recommended due to incomplete removal of the spermatic cord as well as the possible risk of scrotal seeding of tumor cells.

- GCTs can be composed of pure histologies or combinations of five main histologic subtypes (Table 16.1):
  - Seminoma

TABLE 16.1
Histopathologic Characteristics of Testicular Tumors

Tumor Type	Percentage	Pathologic Feature(s)	Percentage
Germ cell tumors	95	Seminomas	40-50
Single cell–type tumors	60	Primordial germ cell	
Mixed cell–type tumors	40	Nonseminomas	50-60
		Embryonal cell tumors	
		Yolk sac tumors	
		Teratomas	
		Choriocarcinomas	
Tumors of gonadal stroma	1-2	Leydig cell	
		Sertoli cell	
		Granulosa cell	
		Primitive gonadal structures	
Gonadoblastoma	1	Germ cell + stromal cell	

  - Embryonal cell carcinoma
  - Yolk sac tumor
  - Choriocarcinoma
  - Teratoma
- Several genes (either deleted or amplified) located on isochromosome 12p have been implicated in the malignant transformation of primordial germ cells. Among patients with familial testicular GCTs compatible with X-linked inheritance, evidence suggests the presence of a susceptibility gene on chromosome Xq27.

STAGING

Testicular cancer is staged using the American Joint Committee on Cancer tumor/node/metastasis (TNM) criteria (eighth edition, 2017).

- **T classification** is based on pathological findings after radical orchiectomy (pT).
- pT0 = no evidence of disease.
- pTis = ITGCN or carcinoma in situ.
- pT1 = disease limited to the testis and epididymis without lymphovascular invasion (LVI) although it may invade the tunica albuginea but the tunica vaginalis.
- pT2 = similar to pT1 but with LVI or the involvement of the tunica vaginalis.
- pT3 = invasion of the spermatic cord with or without LVI.

- pT4 = involvement of the scrotum with or without LVI.
- pTx is used when the primary tumor cannot be assessed.
- **N classification** is based on lymph node involvement and may be pathologic (pN) or clinical (cN).
- N0 = no regional lymph node involvement.
- N1 = metastasis with a lymph node mass of 2 cm or less in greatest dimension.
- N2 = single or multiple lymph node metastasis with any one mass >2 cm but not more than 5 cm in greatest dimension.
- N3 = Lymph node metastasis greater than 5 cm.
- Nx = Regional lymph nodes cannot be assessed.
- **M classification** is based on the extent of distant metastasis.
- M0 = no distant metastasis.
- M1a = nonregional nodal or pulmonary metastasis.
- M1b = indicates distant metastasis other than nonregional lymph nodes and lung.
- **Serum tumor markers** (unique for testicular GCT staging).
- S0 = normal serum levels of tumor markers.
- S1 = LDH is <1.5 times the upper limit of normal, β-HCG is <5000 mIU/mL, and AFP is <1000 ng/mL.
- S2 = LDH is between 1.5 and 10 times the upper limit of normal, or β-HCG is between 5000 and 50,000 mIU/mL, or AFP 1000 to 10,000 ng/mL.
- S3 = LDH >10 times the upper limit of normal, or β-HCG >50,000 mIU/mL or AFP >10,000 ng/mL.
- Sx refers to tumor markers not available or not performed.
- The TNM classification is then used in the anatomic stage grouping as follows:
    - Stage I: pT1-4, N0, M0, Sx/S0
        - Stage Ia: pT1, N0, M0, Sx/0
        - Stage Ib: pT2-4, N0, M0, Sx/0
        - Stage IS: Any p T/Tx, N0, M0, S1-3
    - Stage II: Any pT/Tx, N1-3, M0, Sx/S0-1
        - Stage IIa: Any pT/Tx, N1, M0, S0-1
        - Stage IIb, Any pT/Tx, N2, M0, S0-1
        - Stage IIc, Any pT/Tx, N3, S0-1
    - Stage III: Any pT/Tx, Any N, M1, Sx/S0-3
        - Stage IIIa: Any pT/Tx, Any N, M1a, S0-1
        - Stage IIIb: Any pT/Tx, AND N0-3, M1a, S2 OR N1-3, M0, S2
        - Stage IIIc: Any pT/Tx, N0-3, M1b, Any S OR M1a, S3 OR N1-3, Any M and S3

PROGNOSIS

- The prognosis for patients with metastatic disease GCT can be estimated by utilizing the International Germ Cell Cancer Collaborative Group (IGCCCG) and published in 1997. This system utilizes postorchiectomy levels of tumor markers, site of primary tumor (for NSGCT), and the site of metastasis (pulmonary vs nonpulmonary visceral metastases) to predict the progression-free survival (PFS) and overall survival (OS) (Table 16.2).

TABLE 16.2

International Consensus Risk Classification for Germ Cell Tumors (Postorchiectomy)

Prognosis	Nonseminoma	Seminoma
Good	Testis/retroperitoneal primary. No nonpulmonary visceral metastases. AFP <1000 mg/mL; HCG <5000 IU/L (1000 mg/mL); LDH <1.5 × ULN (56% of all nonseminomas)	Any primary site. No nonpulmonary visceral metastases. Normal AFP; any concentration of HCG and LDH (90% of all seminomas)
Intermediate	Testis/retroperitoneal primary. No nonpulmonary visceral metastases. AFP ≥1000 and ≤10,000 ng/mL or HCG ≥5000 and ≤ 50,000 IU/L or LDH = 1.5 × NL and ≥10 × NL (28% of all nonseminomas)	Any primary site. No nonpulmonary visceral metastases. Normal AFP; any concentration of HCG; any concentration of LDH (10% of all seminomas)
Poor	Mediastinal primary or nonpulmonary visceral metastases or AFP >10,000 ng/mL or HCG >50,000 IU/L (10,000 ng/mL) or LDH >10 × ULN (16% of all nonseminomas)	No poor prognosis seminoma

AFP, α-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NL, normal limit; ULN, upper limit of normal.

- Patients with clinical stage I have a 99% to 100% survival.
- The 5-year PFS and 5-year OS for metastatic seminomatous and NSGCTs are given in Table 16.3. However, it should be noted

that many patients included in development and validation of the IGCCCG model were treated in the early cisplatin-era. Thus, survival is probably underestimated in this model. For example, a more contemporary review of 273 poor risk patients treated at a referral center revealed IGCCCG poor risk patients to demonstrate a 73% 5-year OS and 58% 5-year PFS.

TABLE 16.3

Expected Survival for Disseminated Disease

	5-y Progression-Free Survival (%)			5-y Overall Survival (%)
Prognosis	**Seminoma**	**Nonseminoma**	**Seminoma**	**Nonseminoma**
Good	82	89	86	92
Intermediate	67	75	72	80
Poor [a]	—	41	—	48

[a]There is no poor prognosis category for seminoma.

TREATMENT MODALITIES

Radical inguinal orchiectomy is the standard surgical diagnostic and therapeutic procedure for all patients with a testicular mass. Adjuvant therapy, which may include chemotherapy, radiotherapy, or further surgery, is tailored to the disease stage and histology.

Pure Seminoma

Adjuvant treatment options for seminoma are outlined in Figure 16.1.

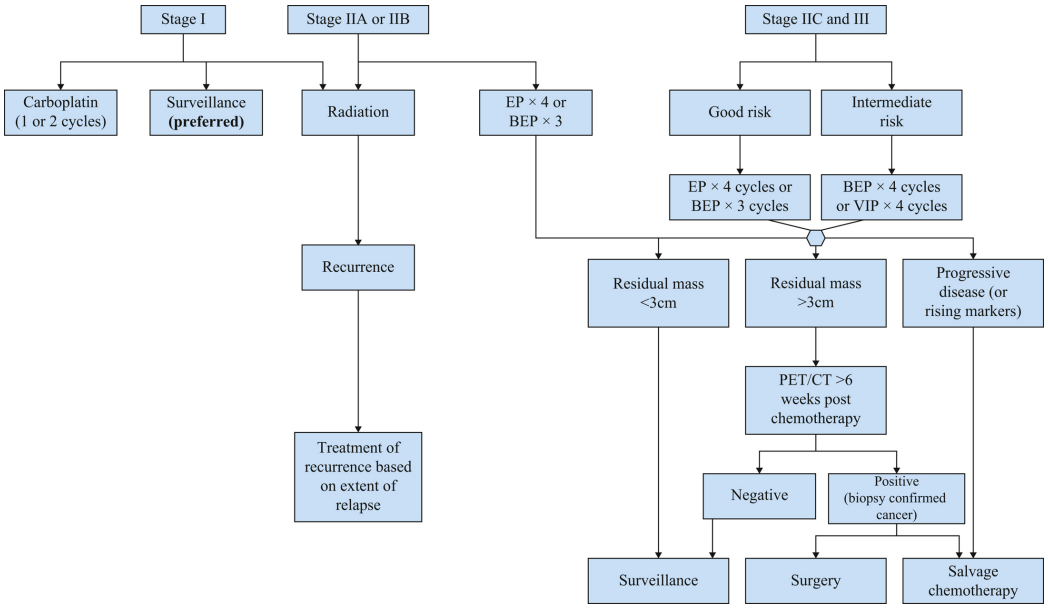

FIGURE 16.1 Adjuvant treatment options for seminoma.Radiation*, radiation therapy to para-aortic lymph nodes; BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; PET, positron emission tomography; VIP, etoposide, ifosfamide, and cisplatin.(Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Testicular Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed [October 25, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.)

Stage I

- Orchiectomy alone is curative in 80% to 85% of patients with stage I seminoma.
- Risk factors for recurrence are primary tumor size of >4 cm and rete testis invasion (recurrence rate increases to approximately 30%).
- Postorchiectomy management options include (1) surveillance (preferred), (2) radiotherapy (20 Gy), and (3) single-agent carboplatin (AUC × 7) one to two cycles.

- Due to excellent cure rate (OS = 99%-100% regardless of postorchiectomy management strategy), active surveillance is the preferred option.
- Despite concerns about possible noncompliance, there is no evidence that noncompliance impacts survival outcomes in stage I disease.
- Disease relapse typically occurs in the retroperitoneal lymph nodes and nearly all patients are successfully cured with radiation or chemotherapy.
- Adjuvant treatment with radiotherapy to the para-aortic lymph nodes or single-agent carboplatin both increase recurrence-free survival (RFS) to approximately 94%.

Stage IIA–B

- For stage IIA–B seminoma, postorchiectomy-managed options include external beam radiation or induction cisplatin-based chemotherapy (IGCCCG good risk). Both radiation therapy (30 Gy for stage IIA; 36 Gy for stage IIB) to ipsilateral iliac and retroperitoneal lymph nodes ("modified dog-leg") and cisplatin-based chemotherapy are associated with a 90% RFS.
- In general, radiation therapy is preferred for stage IIA patients. However, in select stage IIA cases where radiation is contraindicated (ie, horseshoe kidney, inflammatory bowel disease, or history of abdominal/retroperitoneal radiation) or when the patient's preference is to avoid radiation, IGCCCG good risk cisplatin-based chemotherapy is appropriate.
- Chemotherapy is preferred option for stage IIB seminoma.
- Stage II seminoma may be treated with IGCCCG good-risk chemotherapy regimens: three cycles of bleomycin, etoposide, and cisplatin (BEP × 3) or four cycles of etoposide and cisplatin (EP × 4).

Stage IIC–III

Stages IIC and III seminoma are curable in most cases. Intermediate-risk pure seminoma is associated with a >70% 5-year cancer-specific survival. Patients with IGCCCG good-risk disease may be treated with BEP × 3 or four cycles of EP × 4; intermediate risk patients (nonpulmonary visceral metastases) should be treated with BEP × 4 or four cycles of etoposide, ifosfamide, and cisplatin (VIP) if bleomycin is contraindicated.

Management of residual retroperitoneal masses after radiation and/or chemotherapy:

- In most cases, a residual mass after treatment does not indicate active disease as it tends to be a manifestation of the dense desmoplastic reaction to treatment.
- The likelihood of persistent seminoma seems to correlate with the size of the residual mass.
  - For residual masses <3 cm in greatest dimension, observation is recommended.
  - For residual masses >3 cm, a PET scan should be performed at least 6 weeks from completion of treatment. If PET negative, observation is recommended. If positive, treatment options include salvage chemotherapy (standard or high dose) or RPLND (retroperitoneal lymph node dissection) in select cases where disease appears easily resectable.

Nonseminoma

Adjuvant treatment options for stages I, II, and III nonseminoma are outlined in Figures 16.2 and 16.3.

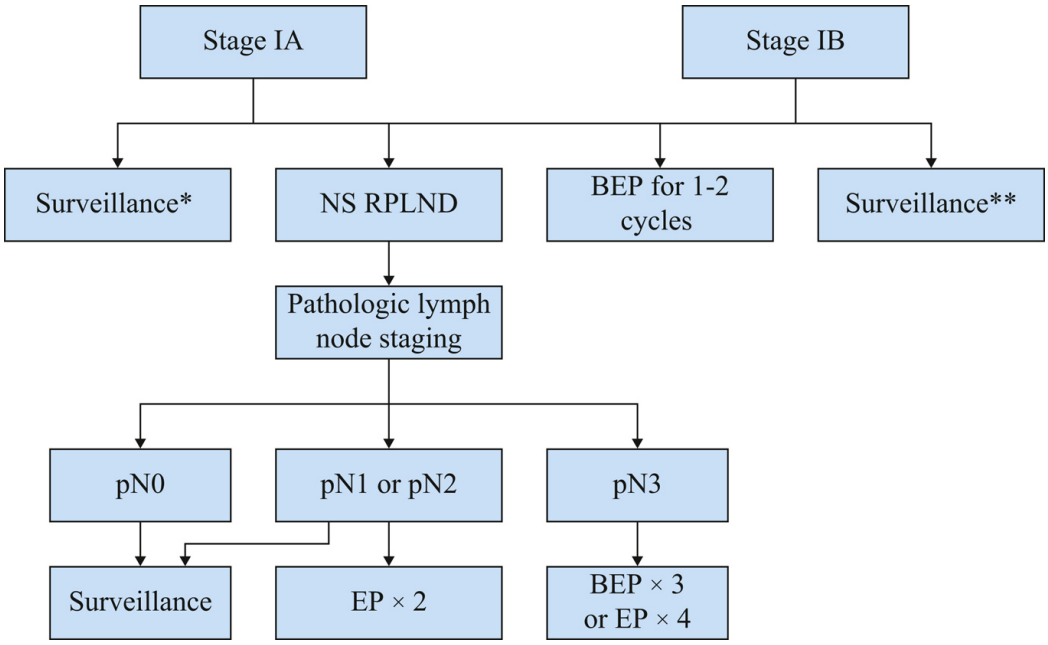

FIGURE 16.2 Adjuvant treatment options for stage I nonseminoma.BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; NS-RPLND, nerve-sparing retroperitoneal lymph node dissection. * Preferred in stage I without risk factors (lymphovascular invasion or invasion of spermatic cord or scrotum). ** For T2 lesions only.(Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Testicular Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed [October 25, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.)

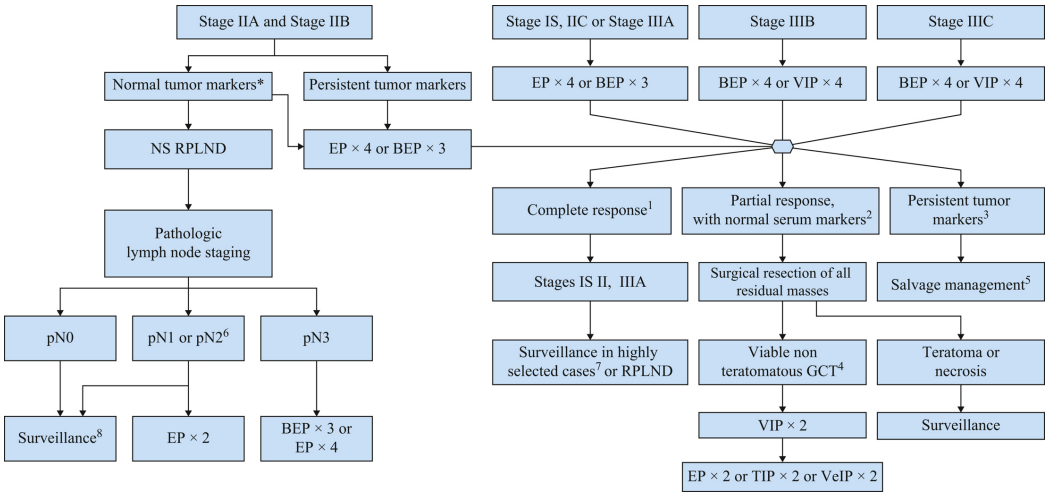

FIGURE 16.3 Adjuvant treatment options for stage II and III nonseminoma.BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; GCT, germ cell tumor; NS-RPLND, nerve-sparing retroperitoneal lymph node dissection; TIP, paclitaxel, ifosfamide, cisplatin; VeIP, vinblastine, ifosfamide, cisplatin; VIP, etoposide, ifosfamide and cisplatin. **1.** Complete response, negative markers. **2.** Partial response residual masses, normal tumor markers. **3.** Partial response, residual mass, abnormal tumor markers. **4.** Viable nonteratomatous germ cell tumor includes yolk sac, embryonal, choriocarcinoma, or seminoma. **5.** Depends on prognosis, treatment options include clinical trial, salvage chemotherapy, or salvage resection. A) elevated, rising tumor markers => second line chemotherapy. B) elevated, stable tumor markers => surveillance. C) elevated, normalizing tumor markers => resection of all residual masses. **6.** Surveillance preferred for pN1; chemotherapy preferred for pN2. **7.** Preferred for Stage IS. **8.** cor pure teratoma pN2.*Chemotherapy preferred if multifocal disease and Stage IIB.(Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Testicular Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed [October 25, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.)

Stage IA–B

- Stage I NSGCT has a 99% to 100% survival regardless of postorchiectomy management option. Chance of recurrence is approximately 25% to 30%. Patients that have LVI and/or embryonal predominance have a >50%, while those with neither risk factor have an approximately 15% chance of recurrence.
- Management options include (1) surveillance, (2) primary RPLND, and (3) adjuvant chemotherapy.
- Surveillance has become the preferred option for patients without the risk factors (LVI and/or embryonal predominance) and also a reasonable option for patients with risk factors for recurrence; since primary RPLND and adjuvant chemotherapy can improve RFS, they have no effect on OS.
- Generally, the main advantage of primary RPLND is avoidance of chemotherapy. In the absence of adjuvant RPLND, patients with pN0 disease have a 10% chance of recurrence (usually pulmonary); those with pN1-2 disease have a 30% to 50% chance of recurrence.
- Two cycles of cisplatin-based chemotherapy (BEP or EP) is offered to patients with pN1-2 disease after primary RPLND. However, adjuvant chemotherapy after primary RPLND has no effect on cancer-specific survival, which is almost 100%.
- Adjuvant chemotherapy is an option but is generally not recommended for pN1 disease postprimary RPLND. Use of adjuvant chemotherapy for pN2 disease varies from center to center. Patients found to have pN3 disease at primary RPLND should have full induction chemotherapy (BEP × 3 or EP × 4).
- Adjuvant chemotherapy: BEP × 1 or BEP × 2 has been recommended for stage I patients with LVI or embryonal predominance given the 50% chance of disease recurrence.

Stage IS

- Patients with elevated postorchiectomy serum tumor markers but no radiographically measurable disease.
- Management is full induction chemotherapy per IGCCCG risk group.

- RPLND should not be performed in those patients due to unacceptably high relapse rate outside of the retroperitoneum.

Stage II

- Management options include primary RPLND or induction cisplatin-based chemotherapy per IGCCCG risk group.
- Stage IIA–B disease with normal tumor markers and lymph node mass ≤3 cm may be treated with RPLND or full induction chemotherapy after orchiectomy (both options are associated with an approximately 65% chance of complete clinical remission).
- Patients with pN1 disease at RPLND for stage CS II disease have an approximately 30% chance of relapse while those with pN2 disease have an approximately 50% chance of relapse. However, 99% to 100% of patients will be cured regardless of whether they receive chemotherapy in the adjuvant or relapsed setting.
- Patients with stage II NSGCT and elevated serum tumor markers or stage IIB/C tumors and nodal disease >3 cm should receive induction cisplatin-based chemotherapy per IGCCCG risk category. Those with a residual postchemotherapy mass of ≥1 cm should undergo consolidative RPLND.

Stage III

- The majority of stage III NSGCT remains curable and should be treated per IGCCCG risk group.
- Management of postchemotherapy masses in NSGCT:
- Patients with residual postchemotherapy masses >1 cm in greatest dimension should undergo full bilateral template RPLND with resection of all residual masses. Tumorectomy alone should be avoided.
- Management of patients with complete clinical response (no residual masses >1 cm in greatest dimension) to induction chemotherapy is somewhat controversial. Although most experts agree that observation of these patients is safe citing a

97% 15-year CSS in one large study, some experts advocate for consolidative PC-RPLND in all patients who had a retroperitoneal mass prior to chemotherapy.

- Patients with brain metastases at diagnosis should receive an IGCCCG poor risk chemotherapy regimen (BEP × 4 in most patients). While multimodality treatment is often necessary, treatment should be individualized based primarily on response to chemotherapy but also on the location and surgical resectability of residual lesions. Utilization of stereotactic radiation therapy has been described, but the specific role is unclear. The survival benefit of whole brain radiotherapy has not been clear.

Histology at RPLND

- In general, histology of residual masses is fibrosis 40% to 45%, teratoma in 40% to 45%, and viable nonteratomatous GCT 10% to 15%.
- Patients found to have fibrosis or teratoma without viable GCT at PC-RPLND demonstrate a >95% 5-year cancer-specific survival. Those with viable GCT have a 60% to 70% 5-year CSS.
- Adjuvant EP × 2 can be delivered to minimize chance of relapse in patients with viable nonteratomatous GCT. However, it may not provide benefit in patients with complete resection of all gross disease, viable malignancy involving <10% of the specimen, and history of IGCCCG good risk disease at presentation as those patients demonstrate a 90% 5-year RFS.

Chemotherapy Regimens

Commonly used chemotherapy regimens (Table 16.4) include BEP and EP, while VIP and VeIP are used less frequently.

TABLE 16.4

Most Commonly Used Chemotherapeutic Agents and Regimens

Agent	Dose	Schedule
BEP	Bleomycin, 30 U IV weekly on day 1, 8, and 15 (can also be given on days 2, 9, and 16)	Two to four cycles administered every 21 d
	Etoposide, 100 mg/m^2 IV daily × 5 d	
	Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	
EP	Etoposide, 100 mg/m^2 IV daily × 5 d Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	Four cycles administered every 21 d
VIP [a]	VePesid (etoposide), 75 mg/m^2 IV daily × 5 d	Four cycles administered every 21 d
	Ifosfamide, 1.2 g/m^2 IV daily × 5 d	
	Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	
	Mesna, 400 mg IV bolus prior to first ifosfamide dose, then 1.2 g/m^2 IV infused continuously daily for 5 d	
VeIP [b]	Velban (vinblastine), 0.11 mg/kg on days 1 and 2	Three to four cycles administered every 21 d
	Ifosfamide, 1.2 g/m^2 IV daily × 5 d	
	Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	
	Mesna, 400 mg IV bolus prior to first ifosfamide dose, then 1.2 g/m^2 IV infused continuously daily for 5 d	
TIP [b]	Taxol (paclitaxel), 175 mg/m^2 IV on day 1	Four cycles administered every 21 d
	Ifosfamide, 1 g/m^2 daily × 5 d	
	Platinol (cisplatin), 20 mg/m^2 daily × 5 d	
	Mesna, 400 mg IV bolus prior to first ifosfamide dose, then 1.2 g/m^2 IV infused continuously daily for 5 d	

d, days; IV, intravenous.

[a]May be used in patients with contraindications to bleomycin.

[b]Generally reserved for tumors that recur after prior chemotherapy.

Follow-Up

Appropriate surveillance of patients with testicular cancer is essential and should be determined by the tumor's histology, stage, and treatment (Tables 16.5 and 16.6).

TABLE 16.5

Surveillance Schedule for Seminoma

Year	H&P, Markers (Interval in Months)	ABD/Pelvic CT (Interval in Months)	CXR (Interval in Months)
Stage I (active surveillance)			
1	3-6	4-6, 12	As clinically indicated
2	6	6	
3	6-12	6-12	
4-5	12	12-24	
Stage IA, IB, IS (postradiation) [a]			
1-2	6-12	12	As clinically indicated
3-5	12	12 (up to year 3)	
Stage IIA, nonbulky IIB (postradiation or chemotherapy)			
1	3	3, 9-12	6
2-3	6	12	6 up to year 2
4-5	6	As clinically indicated	
Stage bulky IIB, IIC, III (postradiation or chemotherapy)			
1	2	4	2
2	3	6	3
3-5	6 (every 12 months in year 5)	Annually (up to year 4)	Annually

ABD, abdomen; CT, computed tomography; CXR, chest x-ray; H&P, history and physical.

[a]Surveillance schedule for stages IA and IB (postchemotherapy) is similar.

TABLE 16.6

Surveillance Schedule for Nonseminoma

Year	H&P, Markers (Interval in Months)	ABD/Pelvic CT (Interval in Months)	CXR (Interval in Months)
Stage I without risk factors			
1	2	4-6	At 4 and 12 mo
2	3	6	12
3	4-6	12	12
4	6	As clinically indicated	12
5	12	As clinically indicated	As clinically indicated
Stage I with risk factors			
1	2	4	4

Year	H&P, Markers (Interval in Months)	ABD/Pelvic CT (Interval in Months)	CXR (Interval in Months)
2	3	4-6	4-6
3	4-6	6	6
4	6	12	12
5	12	As clinically indicated	As clinically indicated
Stage IA/B treated with chemotherapy or RPLND			
1	3	12	6-12
2	3	12	12
3-4	6	–	–
5	12	–	–
Stage II-III nonseminoma with complete response to chemotherapy, with or without postchemotherapy RPLND			
1	2	6	6
2	3	6-12	6
3-4	6	Every 12 months (year 3) and as clinically indicated (year 4)	12
5	6	As clinically indicated	—
Stage IIA-B nonseminoma, after primary RPLND and treatment with adjuvant chemotherapy			
1	6	4 mo after RPLND	6
2	6	As clinically indicated	12
3-5	12	As clinically indicated	12
Stage IIA-B nonseminoma, after primary RPLND and NOT treated with adjuvant chemotherapy			
1	2	3-4	2-4
2	3	12	3-6
3	4	As clinically indicated	12
4	6	As clinically indicated	12
5	12	As clinically indicated	12

ABD, abdomen; CT, computed tomography; CXR, chest x-ray; H&P, history and physical.

Salvage Therapy

- Relapsed disease is diagnosed by increase in tumor markers or by imaging/physical examination. If atypical, biopsy

confirmation may be needed.

- Such patients may also be considered for a clinical trial, especially if they have poor prognostic features.
- The three most commonly used standard second-line regimes are VIP (etoposide, ifosfamide, and cisplatin), VeIP (vinblastine, ifosfamide, cisplatin), and TIP (paclitaxel, Ifosfamide, cisplatin).
- High-dose chemotherapy with autologous bone marrow or peripheral stem cell has demonstrated superior oncologic outcomes to standard-dose salvage therapy particularly when used as second-line treatment. Thus, it has replaced standard dose treatment in a significant number of patients—particularly with cisplatin-refractory or cisplatin-resistant disease as treatment-related mortality has been <5%, and long-term DFS is between 40% and 70%.
- Agents currently under investigation include gemcitabine, paclitaxel, epirubicin, and oxaliplatin.

High-Dose Chemotherapy With Autologous Hematopoietic Stem Cell Rescue

- The benefit of high-dose chemotherapy with hematopoietic stem cell rescue (HDT) as first-line salvage therapy has been shown in nonrandomized trials but not in randomized phase III studies (Table 16.7).

TABLE 16.7

Commonly Used High-Dose Regimens

Agent/Dose	Schedule
IU regimen	
Carboplatin 700 mg/m^2 IV on days 1, 2, and 3	Two cycles given at 14-days interval. Autologous peripheral stem cell infusion on day 6 of each cycle
Etoposide 750 mg/m^2 IV on days 1, 2, and 3	
MSKCC regimen	
Paclitaxel 200 mg/m^2 over 24 h on day 1	Two cycles given at 14-d interval. Leukapheresis on days 11-13

Agent/Dose	Schedule
Ifosfamide 2000 mg/m^2 over 4 h daily on days 2-4 with mesna	
Followed by	
Carboplatin AUC 7-8 IV daily on days 1-3	Three cycles given at 14-d to 21-d interval. Autologous peripheral stem cell infusion on day 5 of each cycle
Etoposide 400 mg/m^2 IV daily on days 1-3	

IU, Indiana University; MSKCC, Memorial Sloan-Kettering Cancer Center.

- Cisplatin refractory GCTs are less likely to have durable response to HDT.
- HDT should be considered in patients with GCTs that are refractory to primary chemotherapy or those that failed first-line conventional salvage chemotherapy.

Late Relapse

- Defined as recurrent disease >24 months after complete remission to primary therapy.
- Has poor prognosis with reported 5-year cancer-free survival of 60% to 70%.
- Chemorefractory in patients treated with prior cisplatin-based chemotherapy. Thus, initially management should be surgical in resectable patients. Chemotherapy can be utilized to cytoreduce unresectable masses where possible.
- Most common histologies are yolk sac tumor although 10% to 20% are nonmalignant teratomas.
- AFP is often elevated (reflecting high prevalence of yolk sac tumor).
- Disproportionally high rate of GCT with somatic-type malignancy (ie, sarcoma, primitive neuroectodermal tumor, adenocarcinoma).

Extragonadal GCTs

- Can arise anywhere along the path of migration of the primordial germ cells from the pineal gland, down through the midline to the gonads.
- The most common locations are the anterior mediastinum and retroperitoneum.
- Up to 70% of primary retroperitoneal GCTs are considered to represent the metastatic burned out testicular GCT.
- Primary mediastinal GCTs should be distinguished from benign or malignant tumors. About 80% of mediastinal GCTs are benign.
- While the prognosis of seminoma is not thought to be affected by site of disease, primary mediastinal NSGCT carries a distinctly poorer prognosis than testicular primaries.
- These tumors are often refractory to cisplatin-based chemotherapy, particularly in the salvage setting. In fact, the futility of high-dose chemotherapy in most of these patients has led some experts to recommend against its utilization in this setting given its toxicity.

Therapy-Related Toxicity

Complications of RPLND

- Complication rates range from 10% to 20% with major complication rates of <10%, more common with postchemotherapy-RPLND than primary RPLND.
- Mortality rate for primary RPLND is 0% and <1% for PC-RPLND.
- Most common complications include wound infections and pulmonary complications, which occur in <5% of patients.
- Chylous ascites, symptomatic lymphocele, or postoperative small bowel obstruction occurs in <3% of patients.
- Utilization of modified unilateral templates as well as sparing of the L1-4 postganglionic sympathetic fibers preserves postoperative antegrade ejaculation in nearly all patients. However, nerve-sparing and/or modified template dissections

are not always possible or appropriate in the postchemotherapy setting.

Fertility

Although 70% to 80% of patients treated with chemotherapy may recover sperm production, sperm banking should be discussed with all patients, prior to initiation of chemotherapy.

- Approximately, 45% of patients have oligospermia or altered FSH levels due in part to the association with cryptorchidism or testicular atrophy at the time of diagnosis.
- Orchiectomy may further impair spermatogenesis.
- Almost all patients become azospermic or oligospermic during chemotherapy.
- Children of treated patients do not appear to have an increased risk of congenital abnormalities.

Pulmonary Toxicity

Pulmonary toxicity occurs in approximately 10% of patients treated with bleomycin.

In approximately 1% of patients, the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis and death. Although this is age and dose related, the toxicity is unpredictable being more common in patients over 70 years of age and in those receiving over 400 U total dose.

- More frequently, asymptomatic decreases in pulmonary function resolve after completion of bleomycin therapy.
- It is recommended that the DLCO be monitored monthly and the drug should be discontinued when the DLCO falls below 30% to 35% of the pretreatment value.
- To monitor the onset of pulmonary toxicity, CXR should be taken every 1 to 2 weeks.
- Corticosteroids may be used to reduce lung inflammation if pulmonary toxicity occurs.

- Smokers should be particularly discouraged from tobacco use and alternatives regimens should be considered (ie, EP × 4 in good-risk patients and VIP × 4 in intermediate- and poor- risk patients).
- Retrospective studies have suggested that low fraction of inspired oxygen (Fio_2 25%) and conservative intravascular volume management during PC-RPLND may reduce the incidence of postoperative bleomycin-induced pulmonary toxicity.

Nephrotoxicity

- Cisplatin-based chemotherapy may result in decreased glomerular filtration rate, which can be permanent in 20% to 30% of patients.
- Electrolyte abnormalities such as hypokalemia and hypomagnesemia are also frequent manifestations of altered kidney function in these patients.

Neurologic Toxicity

- Cisplatin-based chemotherapy may result in persistent peripheral neuropathy in 20% to 30% of patients.
- Cisplatin-induced neuropathy is sensory and distal. Peripheral digital dysesthesias and paresthesias are the most common manifestations.
- Polymorphism in the glutathione S-transferase gene may increase the susceptibility to cisplatin-induced neurotoxicity.
- Ototoxicity in the form of tinnitus or high-frequency hearing loss, usually outside the frequency of spoken language, may be seen in up to 20% of the patients. The risk increases with increasing number of treatment cycles.

Cardiovascular Toxicity

- Bleomycin, cisplatin, and radiation alone or in combination can increase the risk of cardiovascular disease.
- Angina, myocardial infarction, and sudden cardiac death are increased by up to twofold.
- The risk of hypertension, hypercholesterolemia, and insulin resistance is increased in testicular cancer patients treated with chemotherapy.
- Patients are also at increased risk of thromboembolism and Raynaud phenomenon.

Secondary Malignancies

- Secondary malignancies are associated with the use of cisplatin, etoposide, and radiation. (1.7-fold increase which may persist for up to 35 years after the completion of treatment).
- Alkylating agents (cisplatin) may lead to a myelodysplastic syndrome within 5 to 7 years that can eventually progress to leukemia.
- Topoisomerase inhibitors (etoposide) may cause secondary leukemias within 3 years.
- There is an increased incidence of solid tumors in previous radiation fields, including the bladder, stomach, pancreas, and kidney.

Suggested Readings

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17

Ovarian Cancer

Jung-min Lee, Elise C. Kohn

BACKGROUND AND EPIDEMIOLOGY

- Ovarian cancer is the most common cause of gynecologic cancer death and fifth leading cause of cancer death in women in the United States.
- In 2021, an estimated 21,410 new cases of ovarian cancer will occur in the United States, with approximately 13,770 deaths, a pattern that has not changed remarkably over 2 decades.
- The median age at diagnosis is 63 years, with ~70% of new diagnoses at or beyond the age of 55 years.
- Lifetime risk of developing an epithelial ovarian cancer (EOC) is approximately 1 in 70 (1.4%). It can be as high as 60% and 30% for patients with germline deleterious *BRCA1* and *BRCA2* mutation (g*BRCA*m), respectively.
- The majority of EOCs (~75%) are diagnosed at advanced stage (III/IV) (Figure 17.1).

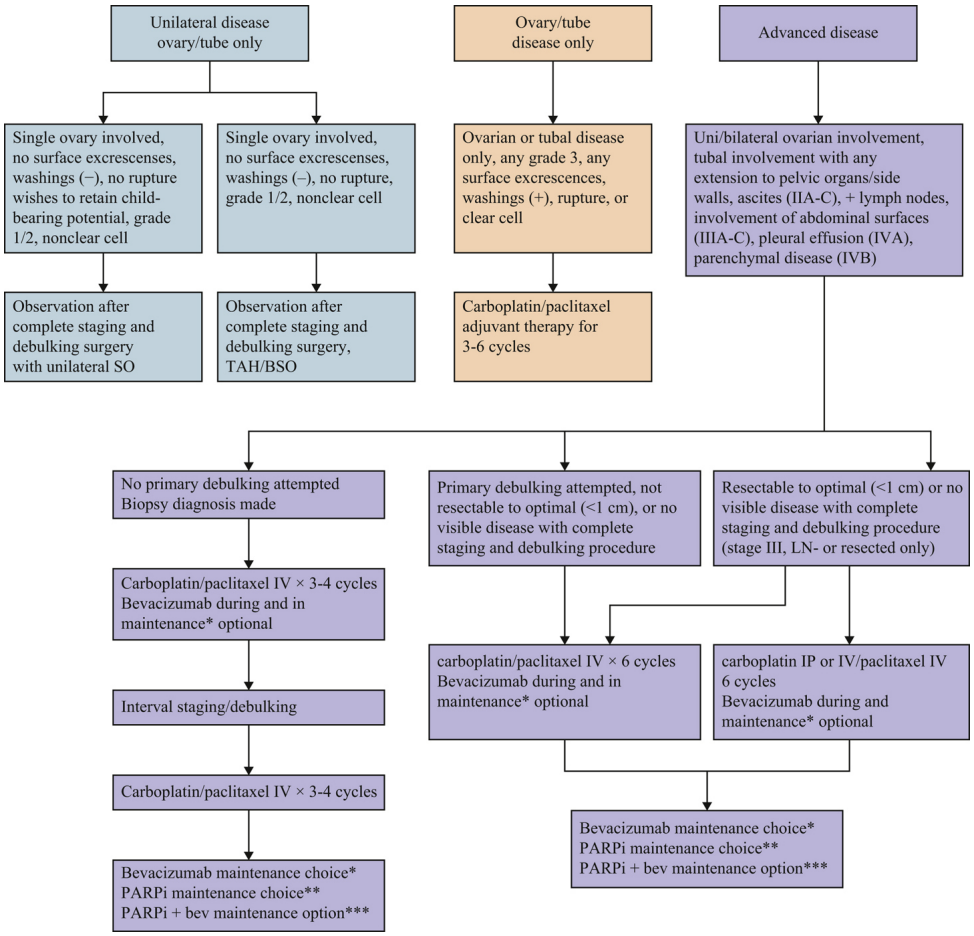

FIGURE 17.1 A flow chart for ovarian cancer FIGO staging.Patients are staged at diagnosis based on the extent of spread of the ovarian cancer. Correct staging is critical as it impacts treatment decisions. Bev, bevacizumab; PARPi, PARP inhibitor; SO, salpingo-oophorectomy; TAH/BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; *bevacizumab can be considered for maintenance after its concomitant use during chemotherapy; **PARPi maintenance may be considered for anyone achieving a PR/CR from primary platinum-based therapy; ***PARPi + bev maintenance may be considered for anyone achieving a PR/CR from primary platinum-based therapy, who had initial inclusion of bevacizumab during chemotherapy, and who has g*BRCA*m or HRD disease.

- The EOC overall 5-year survival is 45%, with >75% of early-stage (stage I) patients alive at 5 years.

MOLECULAR AND CELLULAR PATHOLOGY

- Epithelial histology accounts for 90% of all ovarian cancers.
- EOCs are graded using a two-type grade classification system of low grade, high grade, and ungraded clear cell.
- EOCs consist of several moleculopathologic entities:
    - Low-malignant potential (LMP; borderline) neoplasms account for approximately 15% of EOCs. They are defined by limited layers of stratified epithelial proliferation, without ovarian stromal invasion. They can progress to invasive low-grade malignancies.
    - Low-grade serous ovarian cancer (LGSOC) may be found concomitant and/or in continuity with serous LMP cancers. *BRAF V600E* and *KRAS* mutations can be found in up to 70% of serous LMP tumors with the frequency dropping to ~40% in invasive low-grade cancers.
    - Clear cell and low-grade endometrioid cancers may be contiguous and progress from ovarian endometriosis. They share approximately 40% frequency in somatic mutation in *ARID1A* and may be found as a mixed subtype. Clear cell cancers are more aggressive and have a worse outcome in early stage than other non–high-grade serous EOC.
    - Primary mucinous and transitional cell carcinomas are extremely rare. True mucinous carcinoma of the ovary must be separated anatomically and histopathologically from mucinous cancers of other origins, especially appendiceal malignancies. Advanced stage disease requires a search for a gastrointestinal primary, as primary presentation of advanced stage mucinous ovarian cancer is a rule-out. Nearly 80% of mucinous ovarian cancers have *KRAS* mutation.
    - High-grade serous or high-grade endometrioid ovarian cancers (HGS/EOC; HGSOC for simplicity) are now shown to originate from the serous epithelium of the fallopian tube.
        - Dysregulating mutations in *TP53* is a ubiquitous and, in some cases, defining, event and may be either gain-of-function or loss-of-function.
        - HGSOC is more aggressive and disseminate early within the abdominal cavity upon presentation although parenchymal organ invasion is often a late event.
        - HGSOC, fallopian tube, and primary peritoneal carcinomas are now considered a single clinical entity ("EOC" or "HGSOC").
        - Approximately, 17% of women with HGSOC will be found to have germline deleterious mutations in *BRCA1* or *BRCA2* (g*BRCA*m) upon diagnosis. A further ~8% may have somatic (tumor) mutations in *BRCA1* or *BRCA2* (s*BRCA*m).
        - Mixed Mullerian malignant tumor or carcinosarcoma is a variant of EOC with sarcomatous-appearing histology and molecular changes of carcinoma. It appears to be an aggressive variant of HGSOC.
- The remaining 10% of ovarian cancers consist of sex-cord stromal or germ cell histology.
    - Sex-cord stromal tumors are mesenchymal and include granulosa cell and Sertoli-Leydig cell tumors. They are most often benign and can begin at and post puberty. Granulosa cell tumors account for 70% of sex-cord stromal tumors and may produce estrogen. Sertoli-Leydig cell tumors may produce testosterone.
    - Germ cell neoplasms include dysgerminoma, teratoma, and yolk sac (endodermal sinus) tumors. Malignant germ cell tumors are treated similarly to testicular cancer.

RISK FACTORS

- Table 17.1 lists risk factors for ovarian cancer.

TABLE 17.1

Risk Factors for Ovarian Cancer

Increased Risk
Increasing age • Personal history of breast cancer Genetic factors • Family history of ovarian cancer • Deleterious germline mutations in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, *BARD1*, *MSH2*, *MSH6*, *MLH1*, and/or *PMS2* • Hereditary nonpolyposis colorectal cancer (Lynch syndrome) Reproductive factors • Nulligravity • Early menarche • Late menopause • Primary and secondary infertility • No pregnancy (may be electively nonfertile) • Endometriosis Environmental factors • Obesity and high-fat diet (weak evidence)
Decreased Risk
Reproductive factors • Use of oral contraceptives • Pregnancy/multiparity • Breastfeeding Gynecologic surgery • Salpingoophorectomy • Tubal ligation

- g*BRCA*m women have a high lifetime risk for development of EOC, up to 60% for *BRCA1* and 30% for *BRCA2*, respectively. Germline mutations in *RAD51C* and *RAD51D* and *PALB2* also confer increased risk of HGSOC. Most EOCs with these mutations are HGSOC.
- Germline mutations in Lynch syndrome genes can be found in 3% to 5% of EOCs and are predominantly found in ovarian clear cell and low-grade endometrioid cancers.
- Women with a strong family history without an identified deleterious germline mutation also have a high lifetime risk for development of EOC.

PREVENTION

- The use of oral contraceptives is protective against EOC for the general population. Increasing duration of use is associated with larger reductions in EOC risk.
- Risk-reduction salpingoophorectomy (RRSO) has been shown to reduce the lifetime risk of ovarian/tubal/peritoneal cancer to less than 5% in high-risk women. RRSO is recommended for high-risk women defined as those with familial ovarian cancer syndromes and/or g*BRCA*m. Surgery is recommended after completion of childbearing and should be done where feasible, approximately 10 years earlier than the age of diagnosis of the youngest affected family member or by the ages of 40 and 45 years, for g*BRCA1*m and g*BRCA2*m, respectively.
- The use of salpingectomy without oophorectomy remains controversial and untested. If used, it should be considered in women of childbearing potential who wish to have children after which oophorectomy should be done. This is not expected to occur with salpingectomy without oophorectomy due to continued production of estrogen and progesterone.
- RRSO has been shown to decrease the risk of breast cancer up to 50% in g*BRCA*m carriers.
- Neither RRSO nor opportunistic salpingectomy is recommended for women at average risk.

SCREENING

- On September 7, 2016, the Food and Drug administration (FDA) released a formal recommendation *against* using any screening tests for ovarian cancer.
- The 2012 Reaffirmation Recommendation Statement of the U.S. Preventive Services Task Force reiterated its recommendation against screening for EOC in women who are asymptomatic and without known genetic mutations that increase its risk.

- Women with a family history of breast/ovarian cancer should be offered genetic counseling and genetic testing.
- Familial ovarian cancer syndrome patients and known g*BRCA*m carriers who have not undergone RRSO or salpingectomy may be offered screening consisting of a pelvic examination, yearly transvaginal ultrasound, and a CA-125 blood test every 6 months, beginning between the ages of 30 to 35 years or 5 to 10 years earlier than the earliest age of the first EOC diagnosis in the family. There are no data demonstrating a survival benefit of screening for high-risk patients nor the ability to identify an earlier stage of disease.
- Women with high-risk families in whom deleterious *BRCA* mutations were not found can be referred for panel testing for lower frequency deleterious germline mutations. Absent testing and confirmation of a genetic risk, such women are treated similarly to those in whom genetic risk is identified. RRSO is recommended; absent RRSO, screening as for high-risk women is reasonable.

SERUM BIOMARKERS

- CA-125 is a high–molecular-weight glycoprotein and marker of epithelial tissue turnover produced by ovarian, endocervical, endometrial, peritoneal, pleural, colonic, and breast epithelia.
    - CA-125 is increased in ~50% of early-stage and >90% of advanced stage serous and endometrioid EOC. Production is lower and less reliable in other ovarian cancer types.
    - Specificity of CA-125 for ovarian cancer is poor. It can be increased in many benign conditions, such as endometriosis, first trimester pregnancy, pelvic inflammatory disease, uterine fibroids, benign breast disease, cirrhosis, and in response to pleural or peritoneal effusions of any cause, and other epithelial malignancies.
    - CA-125 is FDA-approved for use as a biomarker for monitoring EOC response to chemotherapy and to identify disease recurrence. It is neither approved nor recommended for screening.
    - The reliability of following CA-125 concentrations during molecularly targeted therapy or immunotherapy is unknown.

- Human epididymis protein 4 (HE4) is a glycoprotein also expressed in some EOC. It is increased in >50% of tumors that do not also express CA-125. HE4 testing is FDA-approved as a biomarker for monitoring recurrence and response to chemotherapy. It is neither approved nor recommended for screening, nor is its behavior during other than chemotherapy known.

DIAGNOSIS AND EVALUATION

- EOC is not a silent disease. Symptoms are present though often nonspecific.
- Several studies suggest usefulness of a symptom index tool to identify women who may have EOC: new (within 1 y) and persistent (more than 12 times/mo) pelvic/abdominal pain, increased abdominal size/bloating, difficulty eating/feeling full, and/or urinary urgency/frequency should trigger evaluation by a gynecologic oncologist.
- Stromal tumors can produce hormones resulting in virilization, precocious puberty, amenorrhea, and/or postmenopausal bleeding, depending on patient age, and type and amount of ectopic hormone produced.
- Early referral to a gynecologic oncologist is strongly recommended.
- The preoperative workup of a patient with a suspected ovarian malignancy is summarized in Table 17.2.

TABLE 17.2

Workup for Patient With a Pelvic Mass and/or Suspected EOC

History of present illness, attention to issues related to symptom index tool
Family history
Gynecologic history
Physical examination, including cervical scraping for PAP smear
Laboratory work: full panels with added: • Consider CA-125 (not diagnostic) • β-HCG (should be used to rule out pregnancy in women of childbearing potential; if the germ cell tumor is considered depending upon age and presentation)

• AFP (germ cell consideration; depending upon age and presentation)
Imaging [a] • Transvaginal/abdominal ultrasound (may skip to CT if high index of suspicion, ascites, etc) • CT abdomen/pelvis with oral and IV contrast • Chest x-ray (chest CT is not done)

[a]Value of PET and MRI uncertain; PET/CT interpretability may be compromised by lack of IV and oral contrast.

- Diagnosis can be made by laparoscopy, or biopsy, especially in situations where R0 surgical extirpation may not be considered feasible and neoadjuvant chemotherapy (NACT) is being considered. The extent and quality of surgical debulking has prognostic value.

TREATMENT

Surgery

- Proper EOC diagnosis and staging require tissue. Diagnosis cannot be made by examination, CA-125, or imaging alone.
- Standards of care are now either primary debulking and adjuvant chemotherapy or tissue sampling for diagnosis, followed by NACT with interim surgical debulking.
    - Primary debulking surgery includes laparotomy with en bloc total abdominal hysterectomy and bilateral salpingo-oophorectomy tumor removal, abdominal fluid sampling, tumor debulking, and pathologic assessment of the abdomen, including diaphragms, paracolic gutters, and serosal surfaces. Unilateral salpingoophorectomy can be considered in women with stage I grade 1/2 tumors who wish to preserve fertility. Completion of salpingoophorectomy is recommended upon completion of child-bearing.
    - Debate remains whether primary debulking surgery should be done in women for whom an R0 or R1 debulking cannot be attained.
    - Interval debulking uses the same complete extent of surgery and occurs after three to four cycles of neoadjuvant therapy.
    - The goal of surgery, whether primary or interval, is “R0” or no visible disease. Optimal debulking remains no lesion greater than 1 cm residual in largest diameter. Data indicate better outcome for women undergoing surgical debulking by a gynecologic oncologist.
    - Lymph node dissection is recommended where stage will be altered, such as early stage disease. Lymphadenectomy may be omitted in non-R0 resections or be done selectively based upon identification of bulky nodal disease at surgery (AGO LION study).

- Stage I disease with favorable prognostic features (grade 1/2, stage IA/B, non–clear cell histology) can be treated by surgery alone.

Adjuvant and NACT

- NACT and adjuvant chemotherapy regimens are summarized in Table 17.3.

TABLE 17.3

Adjuvant Chemotherapy and Therapy for Recurrent Disease

	Neoadjuvant or Adjuvant Primary Chemotherapy	
Indication	*Treatment*	*Supporting Data*
Neoadjuvant chemotherapy (NACT), Stage III/IV	IV carboplatin (AUC5 or 6) and paclitaxel at 175 mg/m^2 every 21 d	NACT followed by interval debulking surgery was not inferior to PDS → adjuvant chemotherapy Patients who cannot tolerate IP therapy or bulky stage IIIC/IV EOC: OS HR = 0.98 (90% confidence interval [CI] 0.84-1.13; *P* = .01), PFS HR = 1.01 (90% CI 0.89-1.15) CHORUS (*Lancet*, 2015): stage III/IV, noninferiority study: OS HR = 0.87 (90% CI 0.72-1.05): median OS 24.1 (NACT) vs 22.6 mo (PDS)
Optimally debulked advanced stage III	IV paclitaxel at 135 mg/m^2 over 24 h on day 1; IP cisplatin at 100 mg/m^2 on day 2; and IP paclitaxel at 60 mg/m^2 on day 8	GOG172: median PFS 18.3 (IV) vs 23.8 mo (IV/IP; *P* = .05); median OS 49.7 (IV) vs 65.6 mo (IV/IP; *P* = .03) 10-y follow-up (GOG114 and 172) median OS 51.4 mo (IV) vs 61.8 (IV/IP; adjusted HR = 0.77; 95% CI, 0.65-0.90; *P* = .002)
Maintenance therapy	Bevacizumab during adjuvant carboplatin/paclitaxel and for maintenance therapy; doses: GOG 218 (15 mg/kg) ICON 7 (7.5 mg/kg)	GOG218 and ICON7: bevacizumab prolongs PFS but does not improve OS. It is not approved for maintenance in the United States. Approved by the EMA for high-risk EOC.

	Neoadjuvant or Adjuvant Primary Chemotherapy	
Maintenance therapy	For patients with response to platinum-based primary therapy: Olaparib 300 mg every 12 h up to 2 y for g*BRCA*m Niraparib 200 or 300 mg every 12 h for up to 3 y	See also JCO ovarian cancer PARPi guidelines 2020. SOLO1 showing unmaintained continued response after 2 y of olaparib. PRIMA showing differential benefit for g*BRCA*m being greatest, HR deficient with benefit, limited benefit for HR proficient.
	For patients with response to platinum/bevacizumab-based primary therapy Bevacizumab 15 mg/m^2 every 3 wk for up to 15 mo + olaparib 300 mg every 12 h for up to 2 y	See also JCO ovarian cancer PARPi ASCO guidelines 2020. PAOLA demonstrating greatest benefit for g*BRCA*m and some benefit for HR-deficient disease.
	Recurrent or Persistent Disease	
Indication	*Treatment*	*Supporting Data*
Platinum-sensitive disease	Platinum-based combination therapy (with pegylated liposomal doxorubicin, gemcitabine, or taxane) ± bevacizumab	ICON-4, AGO-OVAR-2.2, OCEANS GCIG, CALYPSO: 70% of patients >2 y from initial treatment will respond to retreatment. Carboplatin/paclitaxel or carboplatin/gemcitabine is better than carboplatin alone; carboplatin/doxil is better tolerated and equivalent otherwise to carboplatin/paclitaxel
	Platinum-based chemotherapy + PARPi switch maintenance	Additional studies ongoing; PARPi maintenance SOLO2: olaparib vs single-agent chemotherapy in gBRCAm carriers, ARIEL (rucaparib) and NRG-GY004 (olaparib + cediranib vs platinum-based chemotherapy)

	Neoadjuvant or Adjuvant Primary Chemotherapy	
Platinum-resistant/refractory disease	Single-agent chemotherapy: pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, taxotere, oral etoposide, weekly paclitaxel, hexamethylmelamine, and/or consideration of hormone ablation with letrozole/anastrazole or tamoxifen; experimental therapy	
	Bevacizumab + chemotherapy (PLD, topotecan, or weekly paclitaxel) for platinum-resistant recurrent EOC patients who had no more than two prior chemotherapies	AURELIA: PFS benefit; 6.7 (bevacizumab + chemotherapy) vs 3.4 mo (chemotherapy alone; HR = 0.48; 95% CI: 0.38-0.60; *P* = .001)
Maintenance in platinum-sensitive recurrent disease	Olaparib 400 mg capsules BID as the first therapy for the maintenance treatment in *gBRCAm* carriers with HGSOC, fallopian tube, or primary peritoneal cancer. *Olaparib is licensed in the United States* only *for gBRCAm carriers with EOC who had more than three chemotherapy treatments and* not *for maintenance use*	Study 19: PFS benefit after platinum-based chemotherapy; 11.2 (olaparib maintenance) vs 4.3 mo (placebo; HR = 0.18; 95% CI 0.10-0.31; *P* < .0001)
	Bevacizumab (15 mg/kg on day 1 every 3 wk), concurrent with carboplatin/gemcitabine for 10 cycles maximum, followed by bevacizumab alone until disease progression	OCEANS: PFS only benefit for carbo/gemcitabine with maintenance bevacizumab (HR = 0.48; median PFS = 12.4 vs 8.4 mo; *P* < .0001). No OS benefit 33.6 vs 32.9 HR = 0.95, *P* = .65 GOG 213: PFS benefit for carbo/paclitaxel with maintenance bevacizumab (HR = 0.61; median PFS 13.8 vs 10.4 mo; *P* < .0001) surgical randomization still ongoing

BID, twice daily; EOC, epithelial ovarian cancer; HR, hazard ratio; IP, intraperitoneal; IV, intravenous; mo, months; OS, overall survival; PDS, primary debulking surgery; PFS,

progression-free survival; PLD, pegylated liposomal doxorubicin; q, every; wk, weeks; y, years.

- Adjuvant chemotherapy is the current international consensus standard of care for all patients with stage IC and stages II-IV. This chemotherapy should include a platinum and a taxane and should be administered for six cycles, with fewer cycles considered acceptable for IC (GOG-157).
- NACT can be administered with interval debulking for advanced staged patients. The total chemotherapy exposure should be six to eight cycles. NACT with interval debulking has been shown to be noninferior to primary debulking surgery and adjuvant chemotherapy.
- Adjuvant chemotherapy remains the recommendation for all histologic types of ovarian cancer. There are no prospective data to date for use of hormonal therapy initially in LGSOC.
- Intraperitoneal therapy (IP) has resulted in improved overall survival (OS). It is not clear if these results are caused by location of dose administration (IP vs IV), or administered dose intensity or both (GOG-0172). No additional benefit of IP was observed when bevacizumab was included although dose and schedule did not recapitulate that of the original positive trial (GOG-0252).
- Dose-dense paclitaxel/carboplatin therapy is not superior to every 3-week paclitaxel therapy (GOG0262/ICON8A) and can no longer be recommended.
- Paclitaxel and docetaxel have been shown to yield similar outcomes in adjuvant therapy (SCOTROC1).
- Carboplatin dosing should be based on the Calvert formula for calculating AUC (http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf) dosing of carboplatin (AUC × [GFR + 25]), where GFR is the calculated glomerular filtration rate. If a patient's GFR is estimated based on serum creatinine measurements by the isotope-dilution mass spectrometry method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing.

- Patients can demonstrate hypersensitivity to paclitaxel with the initial treatment and subsequent doses due to an anaphylactoid reaction to either the paclitaxel and/or its vehicle. Treatment can be changed to docetaxel, which has a different vehicle if premedication with steroids, H1, and H2 blockers and/or slower infusion is not sufficiently protective.
- Platinum hypersensitivity is an anaphylactic, true atopic, reaction and presents in later cycles (usually >6-10 exposures).
    - Cisplatin and carboplatin can be cross-substituted, depending on the severity of the reaction. The two agents can have cross-sensitivity because the bioactive moiety is the same.
    - Women having a history of platinum allergy may be retreated using slow infusion and premedication with steroids and H1/H2 blockers.
- Phase 3 studies suggest that bevacizumab given during adjuvant carboplatin/paclitaxel and in maintenance prolongs progression-free survival (PFS) in selected subpopulations and does not improve OS (GOG218 and ICON7).
- Maintenance with PARP inhibition (PARPi) has been shown to prolong PFS in women with g/s*BRCA*m or with homologous recombination deficiency (HRD) by FDA-approved test(s). Two years of olaparib maintenance therapy in g/s*BRCA*m patients provides unmaintained remission median PFS of over 5 years. Some benefit was seen with 3 years of niraparib in homologous recombination-proficient patients. Long-term data for niraparib maintenance are pending; OS data are not yet mature.
- PFS benefit was observed with the combination of olaparib and bevacizumab for women with g/s*BRCA*m and HRD (PAOLA). OS data are not yet mature.
- Consideration should be given as to the best time in the life cycle of an individual's EOC in which to use PARPi; repeating PARPi therapy in the treatment of EOC is not recommended at this time (ASCO Guidelines 2020).
- There are no data that adding immune checkpoint inhibitor improves clinical outcome in the first line treatment or maintenance therapy.

Recurrent or Persistent Disease

- Recurrence occurs in >80% of stage III/IV patients; recurrent EOC is not curable although subsequent complete remissions may occur.
- No OS benefit was observed in an RCT comparing early treatment of relapse (based upon increased CA-125 alone) versus observation until symptoms or physical examination trigger disease assessment (MRC OV05/EORTC 55955).
- Secondary cytoreduction surgery can be considered for women with recurrence-free intervals of ≥12 months. However, data indicate that there is a benefit (PFS/OS) only in highly selected patients (DESKTOP3), whereas no OS superiority was observed, and there was indication of possible harm with secondary surgery in patients where limited selection criteria were used (GOG-0213).
- There are no data that immune checkpoint inhibitor monotherapy or combinations improve clinical outcome in treatment or maintenance therapy for recurrent ovarian cancer.
- Patients with a progression-free interval of ≥6 months have platinum-sensitive disease although this is a continuum. Second-line platinum-based therapy, single agent or combination, improves survival in women with platinum-sensitive EOC (Table 17.3).
    - Doublets may include carboplatin with paclitaxel, gemcitabine, or pegylated liposomal doxorubicin.
    - Bevacizumab with chemotherapy and in maintenance enhances PFS for women with recurrent ovarian cancer (OCEANS, GOG-0213) and improved OS (GOG-0213).
    - Prior exposure to bevacizumab during and after chemotherapy has been shown not to prevent a second response to bevacizumab exposure in one recent trial.
    - Maintenance therapy with PARPi has been shown to prolong PFS in women who attained at least stable disease after at least four cycles of platinum-based chemotherapy. An OS benefit trend (P = .054) was observed with olaparib use in women with g/s*BRCA*m (ASCO Guidelines 2020).
    - Treatment with single-agent PARPi may be considered for women with platinum-sensitive recurrent ovarian cancer.
    - There are no data that using a PARPi as treatment in women who have had prior PARPi maintenance therapy provides the same or any treatment benefit as was seen in PARPi-naïve treatment studies.
- Recurrence within 6 months of or progression on initial platinum-based chemotherapy is defined as platinum-resistant or

platinum-refractory disease, respectively.

- Sequential single-agent chemotherapy is preferred for platinum-resistant/refractory patients due to increased toxicity without sufficient evidence of increased benefit of combinations (see Table 17.3).
- Topotecan, pegylated liposomal doxorubicin, or weekly paclitaxel with bevacizumab have been shown to yield superior PFS to single agent alone (AURELIA).
- PARPi is not recommended for treatment or maintenance of benefit for women with platinum-resistant or platinum-refractory disease (ASCO Guidelines 2020).

Nonepithelial Ovarian Cancer

- Most patients with ovarian germ cell tumors are diagnosed with early-stage disease. Lymph node metastases are rare. Unilateral salpingoophorectomy, if contralateral ovary is uninvolved, is possible in women who wish to preserve fertility.
- BEP chemotherapy (bleomycin/etoposide/cisplatin) should be considered after surgery for germ cell tumors: nondysgerminoma, all but stage I grade 1 disease, and ≥stage II dysgerminoma.
- Most ovarian sex-cord stromal tumors are low-grade, early stage at presentation and have excellent survival. Radiation to gross residual tumors and hormonal therapy with progestin for granulosa cell tumors are considered after surgical resection.
- Many malignant stromal tumors including granulosa cell tumors produce estrogen; hence, evaluation of the endometrium for malignant change is needed.

Radiation

Radiation therapy (RT) plays a limited role in the treatment of EOC in the United States. Tumors of ovarian and tubal origin are sensitive to RT. RT should be considered for solitary metastases with functional consequences (brain metastases, bleeding).

Experimental Therapy/Immunotherapy

- Patients with ovarian cancer of all stages, at diagnosis and at recurrence, should be encouraged to participate in clinical trials

(www.clinicaltrials.gov).

- There are no data that immune checkpoint inhibitor monotherapy or combinations improve clinical outcome in treatment or maintenance therapy for ovarian cancer.

SUPPORTIVE CARE

Common Treatment Toxicities

- Myelosuppression: Carboplatin-related bone marrow suppression is a cumulative toxicity (**see** Chapter 34).
- Nausea/vomiting: Carboplatin is less emetogenic than cisplatin. Both acute and delayed nausea/vomiting should be monitored and addressed therapeutically (**see** Chapter 38).
- Renal dysfunction
  - Great care should be taken in patients with borderline or abnormal renal function.
  - Serum creatinine-based calculations of GFR underestimate renal dysfunction in patients who have received platinums.
- Neurotoxicity
  - Both platinums and taxanes cause neuropathy. Platinums cause demyelinating injury and can leave long-lasting neuroresiduals. Taxanes and other chemotherapies cause axonal degeneration, which is recoverable.
  - Grade 3 to 4 neuropathy can have long-term effects and may require substitution or discontinuation of the offending agent(s). Dose modification of drugs with grade 2 neuropathy may be needed to avoid grade 3 to 4 neuropathy.
- Perforation
  - Bevacizumab causes a 5% to 11% risk of gastrointestinal perforation in EOC patients.
  - Possible risk factors for perforation include previous irradiation, tumor involving bowel, and early tumor response.
- Obstruction
  - Patients can present with both bowel and urinary tract obstruction. Presenting symptoms include nausea, vomiting, abdominal pain, abdominal distention, abdominal and/or back pain, and infrequent bowel movements or urination.
  - Initial treatment for bowel obstruction may be conservative, with bowel rest and nasogastric suction, but many patients will require bypass surgery.
  - The aggressiveness of intervention should be balanced with the patient's prognosis, health status, and goals of care. Management with analgesics, antiemetics, anticholinergics, etc and/or endoscopic placement of drainage tubes are options for poor surgical candidates.

- Urinary obstruction may be relieved with ureteral stents or nephrostomy, depending on the location, length, and severity of the obstruction.

SUMMARY

- EOC is the most common cause of death among women with gynecologic malignancies and the leading cause of gynecologic cancer death in women in the United States.
- Adjuvant paclitaxel/carboplatin is recommended for limited disease with high-risk features and advanced disease. The latter may be neoadjuvant or adjuvant treatment.
- PARPi maintenance therapy for the first-line treatment or platinum-sensitive recurrence may be considered. To date, only one of the two is recommended absent data for second PARPi exposure responses.
- Selection of therapy for women who experience a recurrence is based upon response to initial platinum-based treatment.

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Suggested Readings

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18

Endometrial Cancer

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EPIDEMIOLOGY

- Endometrial cancer is the most commonly diagnosed gynecologic malignancy in developed countries. It is the fourth most common cancer in women in the United States, comprising 7% of all new cancer cases.
- Approximately 66,570 new cases of uterine cancer will be diagnosed in 2021 in the United States, and 1 in 33 women will be diagnosed with endometrial cancer during her lifetime.
- This cancer is slightly more common in white women who have a 2.8% lifetime risk of developing uterine cancer compared with a 2.5% lifetime risk for black women.
- The incidence is 28.3 per 100,000 white women per year, compared to 27.9 per 100,000 black women per year.
- Although the incidence is slightly higher in white women than in black women, the 5-year survival rate is lower in black women (62% vs 83%).
- An estimated 12,940 deaths are expected in 2021 due to this malignancy, accounting for 4.5% of all cancer deaths in women.
- Since 2009, deaths from uterine cancer have increased by approximately 1% to 2% each year, largely attributed to a lack of major treatment advances for patients with recurrent and metastatic disease.
- Peak incidence is in the sixth and seventh decades of life, with a median age at diagnosis of 63 years.

RISK FACTORS

- Prolonged and unopposed stimulation of the endometrium by estrogen, either endogenous or exogenous, is one of the primary risk factors for endometrial cancer development.
- Causes of unopposed endogenous estrogen excess:
  - Chronic anovulation (eg, polycystic ovary syndrome [PCOS], perimenopause).
  - Estrogen-producing tumors (eg, granulosa cell tumor of the ovary).
  - Obesity: Peripheral conversion of androstenedione to estrone and the aromatization of androgens to estradiol in the adipose tissue result in high levels of endogenous estrogen in obese patients. Additionally, lower circulating levels of sex hormone–binding globulin lead to an increase in steroid hormone activity. Each 5 kg/m^2 increase in BMI is associated with a 30% to 60% increased risk of endometrial cancer.
  - Advanced liver disease.
  - Early menarche and late menopause: Risk is related to duration of estrogen exposure. Menopause occurring in women older than 52 years increases risk by 2.4-fold.
  - Infertility and nulliparity: While not considered independent risk factors, infertility and nulliparity are likely associated with endometrial cancer development due to chronic anovulatory menstrual cycles. Nulliparous women have twice the risk of developing uterine cancer compared to women with one child and thrice the risk compared to women who give birth to five or more children.
- Unopposed exogenous estrogen sources:
  - Systemic unopposed estrogen therapy: For women with an intact uterus, the use of systemic estrogen from any route (oral, transdermal patch, or vaginal ring) without the concomitant administration of progestin increases the risk of developing endometrial cancer. This risk is directly correlated to the dose of estrogen and duration of use, with risk increasing up to 20-fold in some cases.
  - Tamoxifen (TAM): Depending upon the target organ and circulating endogenous levels of estrogen, TAM exhibits both agonist and antagonist properties. For premenopausal women with high endogenous levels of estrogen, TAM acts as an antagonist in the endometrial tissue, while for postmenopausal women the converse is true. Subsequently, for women 50 years and older taking TAM, there is a 4.01 relative risk of endometrial cancer development as compared to women younger than 50 years. The risk of endometrial cancer development is also dose and duration dependent. Women taking TAM should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas, and any abnormal uterine bleeding should be evaluated.
- Type 2 diabetes mellitus (DM), possibly related to the effects of hyperinsulinemia.
- Hypertension.

- Hereditary factors:
  - Personal history of breast, ovarian, or colorectal cancer.
  - Personal or family history of hereditary nonpolyposis colorectal cancer (HNPCC or Lynch II syndrome) accounts for 2% to 5% of all endometrial cancers. For a woman with Lynch syndrome, the lifetime risk of endometrial cancer ranges from 17% to 71% depending upon the genotype.
  - History of endometrial cancer in a first-degree relative increases the risk by threefold.
  - History of colorectal cancer in a first-degree relative increases risk of endometrial cancer by twofold.

PROTECTIVE FACTORS

- Hormonal contraceptives:
  - The use of estrogen-progestin contraceptives (both oral and nonoral) has been shown to decrease the risk of endometrial cancer by 30% to 40% when used for at least 12 months. The longer the contraceptive use, the greater the risk reduction.
  - Progestin-only contraceptives (eg, depot medroxyprogesterone acetate, progestin implants, and progestin-releasing intrauterine devices [IUDs]) have been found to provide even greater protection.
  - Protection lasts for years after discontinuation of the contraceptive.
  - Similar protection has been observed with long-term use (≥10 years) of hormone replacement therapy that includes daily progestin.
- Physical activity:
  - Lack of sufficient activity (20 minutes or more of vigorous physical activity at least three times per week) has been associated with a 30% to 40% increased risk of endometrial cancer.
  - It is estimated that if women exercised vigorously five or more times per week and sat for 4 or fewer hours per day, then 34% of endometrial cancers could be avoided.
- Cigarette smoking:
  - This appears to have a modest protective role in postmenopausal women likely due to enhanced hepatic metabolism of estrogens. However, this protection is strongly outweighed by the significantly increased risk of lung cancer and other diseases.

DIAGNOSIS AND SCREENING

- There are no cost-effective screening techniques for early detection of endometrial cancer in asymptomatic women. The

diagnosis is typically made during the evaluation of symptomatic patients.

- Women with HNPCC have a significantly greater lifetime risk of developing endometrial cancer, and the disease often occurs 10 to 20 years earlier than nonhereditary cancers. The American Cancer Society therefore recommends that women with HNPCC be offered annual screening with endometrial biopsy and/or transvaginal ultrasound starting at age 35 years. Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) should also be considered as a risk-reducing treatment option for women with Lynch syndrome who have completed childbearing and no later than 40 to 45 years of age.
- Women taking TAM should have a gynecologic evaluation according to the same guidelines for women not taking TAM. Routine endometrial surveillance has not been proved to be effective in increasing the early detection of endometrial cancer and is not recommended.

Signs and Symptoms

- Abnormal uterine bleeding is the most common symptom of endometrial cancer, seen in approximately 75% to 90% of patients.
- Premenopausal women with prolonged/heavy menses or intermenstrual spotting, particularly those who have failed medical management of these symptoms or with risk factors for endometrial cancer (eg, obesity, PCOS), should undergo endometrial biopsy.
- Ten percent of cases present with profuse serous or serosanguinous discharge.
- All postmenopausal women with uterine bleeding should be evaluated for endometrial cancer, as 10% of these patients will ultimately be diagnosed with the malignancy.
- Biopsy is also recommended for women taking estrogen therapy for menopausal symptoms who have withdrawal bleeding.

- Asymptomatic patients with abnormal glandular tissue on Pap smear should be evaluated for endometrial cancer.
- All postmenopausal women with endometrial cells on Pap smear should be evaluated for malignancy.
- Approximately 10% of uterine cancer cases are detected by Pap smear. Pap smear alone, however, is not an adequate tool for detecting endometrial malignancy.
- A palpable, locally advanced tumor detected on pelvic examination is suggestive of endometrial cancer. Common distant sites of metastases include the lung, inguinal, and supraclavicular lymph nodes (LNs); liver; bones; brain; and vagina. Signs and symptoms of advanced disease, manifested in <10% of cases, may include bowel obstruction, jaundice, ascites, and pain.

Procedures

- Endometrial sampling via an in-office endometrial biopsy is the preferred diagnostic test for symptomatic patients with abnormal uterine bleeding. Endometrial biopsy is generally a well-tolerated outpatient procedure and has a diagnostic accuracy of 93% to 98% when compared with subsequent findings of hysterectomy or dilation and curettage (D&C).
- Women with postmenopausal bleeding may be initially assessed with either an endometrial biopsy or transvaginal ultrasound. When ultrasound measurement of endometrial thickness is less than or equal to 4 mm, endometrial sampling is not required because the incidence of malignancy is rare in these cases. However, if postmenopausal bleeding persists, endometrial sampling should be performed.
- Postmenopausal patients taking TAM should undergo evaluation for any uterine bleeding. Endometrial biopsy is typically the preferred method of evaluation, as women taking TAM often have a thickened endometrium on imaging due to TAM-induced subepithelial stromal hypertrophy. Persistent

bleeding should be evaluated further using hysteroscopy for direct visualization with D&C for tissue sampling.

HISTOLOGY

Subtypes

- Subtypes of endometrial cancer include endometrioid (75%-80%), uterine papillary serous (5%-7%), clear cell (1%-5%), mucinous (5%), squamous (<1%), undifferentiated, and mixed. Endometrial carcinoma is also divided into pathogenetic types 1 and 2.
    - Type 1 tumors: These are more common pathogenetic subtype, are of endometrioid histology, occur more often in younger or perimenopausal women, and have a better overall prognosis. Most are estrogen dependent and well-differentiated, with many having positive estrogen and progesterone receptors. These tumors are also more frequently diagnosed in women with DM and obesity. The majority of patients will present symptomatically and undergo diagnostic evaluation resulting in lower stage disease at presentation. Genetic aberrations include mutations in K-ras, β-catenin, PI3K, PTEN, and ARID1A; microsatellite instability (MSI); and DNA mismatch repair (MMR) defects.
    - Type 2 tumors: These are of papillary serous, clear cell, or poorly differentiated endometrioid histology (grade 3, aneuploid). These tumors tend to occur in older, thin, postmenopausal women with no source of excess estrogen, arising in the background of atrophic endometrium. Type 2 tumors are associated with a poorer prognosis than type 1 tumors. These are commonly associated with p53 mutations (serous), chromatin remodeling and ubiquitin ligase complex genes (CHD4, FBXW7, and SPOP), and HER2/neu overexpression.
        - Black women with endometrial carcinoma have a poorer prognosis because they develop a disproportionately higher percentage of type 2 carcinomas.
- While providing a conceptual framework for understanding endometrial cancer, this classification scheme fails to accurately classify some subsets of patients with features that do not fit into either of these two categories (eg, those with mucinous, squamous, or mixed histologies). Pathologic features such as histology and grade have also been found to have poor interobserver reproducibility. As a result, a molecular classification system that offers both predictive and prognostic information as well as highly reproducible assignments has

emerged. This classification system is frequently used in research and clinical trials but has not yet been fully integrated into clinical practice.

MOLECULAR CLASSIFICATION

- Using genomic, transcriptomic, and proteomic analyses to characterize almost 400 endometrial cancer specimens, The Cancer Genome Atlas was able to identify four molecular subtypes of endometrial cancer based on tumor cell genomic architecture. These subtypes are:
    - *POLE* ("ultramutated"): These are copy number–stable cancers that have recurrent mutations in the exonuclease domain of *POLE*, a gene involved in DNA replication and repair. These tumors have a very high somatic mutational frequency, often exceeding 100 mutations per megabase. Most often of endometrioid histology, these cancers have prominent tumor-infiltrating lymphocytes (TIL). While often presenting with aggressive histologic findings (high-grade features and lymphovascular space invasion [LVSI]), this subtype has a highly favorable prognosis (>96% 5-year survival). Given the prominence of TIL, checkpoint inhibition may be an option in rare cases of advanced or recurrent disease.
    - MSI ("hypermutated"): Secondary to dysfunctional MMR proteins (MLH1, MSH2, MSH6, and PMS2), these cancers have a very high mutational burden and high TIL. The majority of these tumors are the result of epigenetic silencing of MLH1, but also include other somatic and germline mutations (eg, Lynch syndrome) in the MMR genes. This subtype is also associated with a high somatic mutational frequency, with 10 to 100 mutations per megabase. MMR-deficient cancers have been found to have an increased sensitivity to radiation therapy (RT), resulting in more favorable outcomes even in patients with advanced stage disease. Immune checkpoint inhibitors are Food and Drug Administration (FDA) approved for use in metastatic or recurrent MSI endometrial cancer.
    - Copy number low: This is a genomically stable subtype that is MMR proficient and p53 wild type, with a low mutational burden (<10 mutations per megabase). These tumors are predominantly of endometrioid histology with estrogen and progesterone positivity and a high response rate to hormonal therapy.
    - Copy number high: This subtype has high somatic copy number alterations and mutational profiles, with the vast majority (~92%) having p53 mutations. HER2 amplification is also seen in approximately 20% of cases, while homologous recombination deficiency is seen in over 40% of cases. These tumors are of serous, mixed, low-grade endometrioid, and high-grade endometrioid histology and are associated with poor clinical outcomes (~50%

5-year survival). Given the high rate of p53 mutations, superior outcomes have been found when patients are treated with chemotherapy in addition to radiation. Studies combining standard of care chemotherapy with agents targeting HER2 amplification (eg, trastuzumab) have shown promising improvements in both progression-free survival (PFS) and overall survival (OS).

PRETREATMENT EVALUATION

- A thorough history, physical examination, and endometrial sampling should be performed to establish the diagnosis and prior to initiating treatment.
- Medical and surgical history may identify comorbidities that can impact surgical planning and/or adjuvant therapy, while family history may reveal hereditary cancer syndromes.
- Physical examination should focus on the size and mobility of the uterus and the presence of extrauterine masses or ascites.
- Pretreatment laboratory tests should include a complete blood count, chemistry panel, and liver function tests. Cancer antigen 125 (CA-125) is typically reserved for those with type 2 endometrial cancers or grade 3 endometrioid cancers to allow for posttreatment surveillance.
- Chest x-ray can be performed to rule out pulmonary metastases. Additional pelvic or abdominal imaging should only be performed for those with suspected advanced stage disease or type 2 cancers or for clinical staging in patients in whom surgery is not planned (eg, fertility-sparing or poor surgical candidates). Contrast-enhanced magnetic resonance imaging appears superior for clinical staging, as it allows for assessment of myometrial invasion, cervical involvement, and LN metastases.
- Routine age-appropriate health maintenance should be completed. If HNPCC is suspected, colonoscopy should be performed before planning treatment.
- Specific symptoms or physical examination findings should be evaluated as indicated.

STAGING

- Endometrial carcinoma is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics/tumor-node-metastasis classification system.
- Staging for endometrial carcinoma is based on information from hysterectomy, BSO, and pelvic and para-aortic lymphadenectomy. Pelvic washings are no longer required for surgical staging; however, the presence of cancer cells in peritoneal washings is a poor prognostic factor.
- Endometrial cancer distribution by stage:
  - Stage I: 70% to 75%
    - IA: Tumor confined to the uterus, no or <50% myometrial invasion
    - IB: Tumor confined to the uterus, >50% myometrial invasion
  - Stage II: 10% to 15%
    - II: Cervical stromal invasion, but not beyond uterus
  - Stage III: 5% to 10%
    - IIIA: Tumor invades serosa or adnexa
    - IIIB: Vaginal and/or parametrial involvement
    - IIIC1: Pelvic LN involvement
    - IIIC2: Para-aortic LN involvement, with or without pelvic node involvement
  - Stage IV: <5%
    - IVA: Tumor invasion of bladder mucosa and/or bowel mucosa
    - IVB: Distant metastases including abdominal metastases and/or inguinal LNs

PROGNOSTIC FACTORS

Uterine

- The prognosis of endometrial carcinoma is determined primarily by disease stage and histology (including both grade and histologic subtype). Most women have a favorable prognosis, as the majority present with early-stage disease and endometrioid histology.
- Five-year survival (%) distribution by stage:
  - Stage I: 81% to 91%
  - Stage II: 71% to 79%
  - Stage III: 30% to 60%
  - Stage IV: 14% to 25%

- Histology: Serous and clear cell have a worse prognosis. Squamous and undifferentiated behave aggressively.
- Tumor hormone receptor status: The presence and levels of estrogen and progesterone receptors are inversely proportional to histologic grade and associated with longer survival.
- Tumor size: Tumors > 2 cm have worse prognosis.
- LVSI: Rate of distant disease recurrence is approximately 25%.

Extrauterine

- Positive peritoneal cytology: Associated with a worse prognosis, regardless of stage. Rate of disease recurrence is approximately 15%.
- LN metastasis:
  - Involvement of pelvic LN or peritoneal metastases: Approximately 25% risk of recurrence.
  - Metastasis to para-aortic LN: Risk increases to 40%.
  - Adnexal metastasis: Approximately 15% risk of recurrence.
- Myometrial invasion and lower uterine segment involvement: Often an indicator of LN metastases.
- Older age: Associated with higher rates of clinical failure and worse prognosis.

CATEGORIZING A PATIENT'S RISK BASED ON HISTOLOGY AND STAGE

- Patients with endometrial cancer are stratified into low, intermediate, or high risk based upon the risk for disease recurrence.
  - Low risk: Stage IA, grade 1 or 2, with endometrioid histology and negative LVSI.
  - Intermediate risk: Stage IA, IB, or II disease of endometrioid histology. Within this subgroup, there are additional adverse prognostic factors used to further stratify women into high- and low-intermediate risk. The number of risk factors needed to classify the disease as high-intermediate risk are based on age and include deep myometrial invasion, grade 2 or 3 histology, and the presence of LVSI.

    - High risk: Stage III or higher endometrial cancer regardless of histology or grade. Women with serous or clear cell histology are categorized as high-risk regardless of stage.
- Additional prognostic considerations that influence decision of adjuvant therapy include lower uterine segment involvement, positive peritoneal cytology, older age, black race, and molecular prognostic factors.

MANAGEMENT

- Treatment of endometrial cancer is multimodal and may include surgery, radiation, hormonal, chemotherapy, and/or immunotherapy depending on the stage of disease, molecular findings, and biomarkers present.
- Surgery is the cornerstone of staging and therapy for most patients with endometrial cancer. Treatment is stratified based on the risk of disease recurrence, which is determined using the stage of disease, histology of the tumor, and other pathologic factors.
- Total extrafascial hysterectomy with BSO and pelvic and para-aortic lymphadenectomy is the standard staging procedure for endometrial carcinoma. Sentinel lymph node (SLN) mapping can be considered as an alternative to lymphadenectomy for apparent uterine-confined disease.
- One of the most important prognostic factors for endometrial carcinoma is the presence of extrauterine disease, particularly pelvic and para-aortic LN metastases.
- The rate of nodal spread varies with tumor stage and grade. The risk is 3% to 5% in patients with well-differentiated superficially invasive tumors, but as high as 20% in poorly differentiated deeply invasive disease.
- The presence of any of the following factors indicates a high-risk of nodal disease and favors performance of lymphadenectomy over SLN mapping:
    - Serous, clear cell, or high-grade histology
    - Myometrial invasion >50%

    - Large tumors (>2 cm in diameter or filling the endometrial cavity)
- Decisions about adjuvant therapy are based upon clinicopathologic factors (eg, grade, tumor size, and patient's age). Other factors may also impact adjuvant therapy decisions (eg, lower uterine segment involvement, positive peritoneal cytology).

TREATMENT GUIDELINES

- Endometrial hyperplasia with atypia: Total hysterectomy with or without BSO (dependent on postmenopausal status) is the treatment of choice for patients who are not planning future pregnancy.
- Endometrial carcinoma: Therapy should be individualized based on histology and stage. The following guidelines may be generally employed:
    - Low risk: Surgical staging to include complete hysterectomy, BSO, LN assessment, and peritoneal cytology without adjuvant treatment (unless patients are interested in and are candidates for fertility-sparing options). A minimally invasive surgical approach is favored when feasible, given its lower rates of peri- and postoperative complications as compared to laparotomy, without negative impacts on oncologic outcomes. SLN mapping and ultrastaging may be considered as an alternative to pelvic lymphadenectomy, given its high sensitivity and specificity for cancer detection and lower risk for lymphedema.
    - Intermediate risk: Surgical staging via a minimally invasive approach as above for uterine-confined disease with the addition of adjuvant RT for those at high risk for recurrence ("high-intermediate risk"). For stage II disease (cervical stromal invasion) extrafascial or radical hysterectomy may be appropriate based on the preoperative evaluation and with the goal of achieving negative margins.
    - High risk: Those with advanced stage disease or high-risk histologies should undergo surgical staging via laparotomy with the addition of adjuvant therapy. Pelvic lymphadenectomy should be performed for all advanced stage disease, and para-aortic LNs should be assessed with any suspicious or enlarged nodes removed. Omental biopsy is performed in those with serous, clear cell, or carcinosarcoma histologies. Adjuvant chemotherapy has been shown to provide a survival advantage, while the benefits of adjuvant RT remain unclear and may be considered to decrease the risk for locoregional recurrence.

Adjuvant Therapies

Chemotherapy

- Adjuvant chemotherapy is recommended for women with advanced stage disease or serous, clear cell, or carcinosarcoma histologies of any stage, as it improves both PFS and OS. The regimen of choice is paclitaxel 175 mg/m^2 and carboplatin AUC 6 for six cycles, with response rates ranging from 47% to 87%.
- Previously TAP (doxorubicin 45 mg/m^2, cisplatin 50 mg/m^2 on day 1; paclitaxel 160 mg/m^2 on day 2) for six cycles with granulocyte colony-stimulating factor support was the regimen of choice, but Gynecologic Oncology Group (GOG) 209 demonstrated noninferiority of paclitaxel plus carboplatin to TAP (equivalent overall response rate [ORR], similar PFS, but with less toxicity when compared to TAP).

Radiation Therapy

- The benefit of RT in women with endometrial cancer is greatly debated, with the majority of studies showing no improvement in OS but a reduction in locoregional recurrence with the addition of RT. The optimal treatment approach remains poorly defined due to the heterogeneity in patient selection criteria, inadequate power, low recurrence rates in early-stage endometrial cancer, and competing risk of death from other causes.
- Current American Society for Radiation Oncology guidelines recommend the use of radiotherapy in the following scenarios:
    - Vaginal cuff brachytherapy for patients with high-intermediate risk cancer (PORTEC-2 trial showed that vaginal cuff brachytherapy was as effective as pelvic RT at preventing vaginal recurrence with less toxicity in these patients).
    - Patients with grade 3, deeply invasive cancer or cervical stromal involvement may benefit from external beam radiotherapy (EBRT) to reduce the risk of pelvic recurrence.
    - Multimodal treatment should be considered for patients with positive nodes, high-risk histologies, or stage III or IV disease.
- There are various strategies for radiation delivery to include:

- Whole pelvic RT: 45 to 50 Gy EBRT along with vaginal irradiation with vaginal cylinder or colpostats to bring the vaginal surface dose to 80 to 90 Gy (5-year disease-free survival of 80% and locoregional control of 90%).
- Vaginal brachytherapy: May be administered alone if the patient has undergone complete surgical staging to confirm that disease is confined to the uterus.
- Whole abdominal irradiation: Reserved for more aggressive, nonendometrioid histologies.
- Preoperative intracavitary radiation plus EBRT: This method is a combination of preoperative intracavitary radiation (consisting of uterine tandem and vaginal colpostat insertions with a standard Fletcher applicator delivering 20-25 Gy to a point A) and EBRT (40-45 Gy with standard fractionation delivered to multiple fields). In patients with extensive cervical involvement precluding initial hysterectomy, EBRT should be followed in 4 to 6 weeks by hysterectomy and BSO with LN sampling. This approach can provide 5-year disease-free survival of 70% to 80%.

Combined Chemotherapy and RT

- The benefit of multimodal therapy remains unclear given the conflicting results from GOG 258 and PORTEC-3 trials. The aim of both of these phase III studies was to elucidate the benefit, if any, of combination therapy for high-risk patients as compared to EBRT alone (PORTEC-3) or chemotherapy alone (GOG 258). Important differences in patient selection, primary end points, and post hoc analyses should be noted and make direct comparisons between the two studies difficult.
    - GOG 258: Women with stage III or IVA endometrial cancer were randomly assigned to chemoradiotherapy versus chemotherapy alone after surgical staging. No residual disease >2 cm was authorized prior to study entry. Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma. This study was not powered to assess differences in OS.
    - PORTEC-3: Women with stage I, high-grade endometrioid with deep myometrial invasion or LVSI, stage II or III endometrioid, or stage I to III serous or clear cell endometrial cancer were randomized to chemoradiotherapy versus radiotherapy alone. The initial published results showed an improvement in failure-free survival (FFS) with the combination therapy compared to RT alone with no improvement in OS. A post hoc survival analysis, however, showed improved 5-year OS and FFS with chemoradiotherapy compared with RT alone, with the greatest absolute benefit seen in women with stage III disease, serous cancers, or both.
- Various methods of combined therapy have been employed, to include administration of radiation after completion of six

cycles of chemotherapy, "sandwiched" in between three cycles of chemotherapy, or given concurrently with chemotherapy.

Biomarker-Directed Systemic Therapy in the Upfront Setting (Trastuzumab)

- While uterine serous carcinoma is rare, accounting for <10% of all endometrial cancers, it accounts for a disproportionate number of endometrial cancer–related deaths and has a much poorer overall 5-year survival rate (45% vs 91% for those with endometrioid histology).
- Treatment for this aggressive histology previously included surgical staging followed by platinum plus taxane combination chemotherapy, but with poor initial response rates (as low as 20%-60%).
- Approximately 30% of these cancers overexpress HER2, a receptor tyrosine kinase essential for cancer signaling, growth, survival, and proliferation. HER2 overexpression and amplification is a poor prognostic factor for serous cancers and can be targeted by the monoclonal antibody trastuzumab.
- Results from NCT01367002, a randomized phase II study in women with advanced, stage III or IV, or recurrent uterine serous carcinomas that overexpress HER2, showed that the addition of trastuzumab in the upfront setting to carboplatin plus paclitaxel and then continued until disease progression improved both PFS and OS in women with advanced and recurrent HER2 serous carcinoma, with the greatest benefit for those with stage III or IV disease.

Special Considerations

- Low-risk, low-grade patients who still desire fertility can be managed with progestational agents such as levonorgestrel-releasing intrauterine system (eg, Mirena IUD), with appropriate follow-up to ensure a response to therapy.

- Low-risk patients who are not surgical candidates can be treated with RT alone; however, this may achieve a lower cure rate than surgery.
- Combined surgery and EBRT has a higher complication rate than either treatment alone (eg, bowel complications, 4%). Therefore, special attention should be given to appropriate patient selection and choice of surgical techniques. Fewer complications are seen with retroperitoneal approach and with LN sampling versus LN dissection.
- Pelvic surgery has an increased risk of thrombophlebitis in the pelvis and lower extremities; hence, low-dose heparin or compression stockings should be used.
- The subgroup of women with isolated ovarian metastasis has a relatively better prognosis. However, some believe that this represents double primary tumors rather than true metastasis from primary endometrial cancer. Five-year disease-free survival ranges between 60% and 82%, depending on histologic grade and depth of myometrial invasion. Pelvic radiation doses of 45 to 50 Gy are given in standard fractionation, with vaginal boost with cylinder or colpostats adding 30 to 35 Gy to the vaginal surface.
- If tumor extends to the pelvic wall, patients should be considered inoperable and treated with RT.
- When parametrial extension is present, preoperative RT (external and intracavitary) is applied.
- Patients who are not candidates for either surgery or RT are treated with progestational agents (see below).

Stage IVB and Recurrent Disease

- Therapy recommendations depend on sites of metastasis or recurrent disease and disease-related symptoms. All patients should be considered for clinical trials.

Local Recurrence

- Pelvic exenteration: This method can be considered for patients with disease extending only to the bladder or rectum or for isolated central recurrence after radiation. Occasional long-term survival has been reported.
- RT: Palliative radiation is applied for localized recurrences, for example, pelvic LN (EBRT together with brachytherapy boost), para-aortic LN, or distant metastases. For isolated vaginal recurrence, radiation may be curative if not previously administered.

Distant Metastasis

- Most women with metastatic disease are presenting in the setting of distant relapse or progression. Only a small subset will present with de novo metastatic disease.
- A biopsy should be performed for pathologic confirmation of the diagnosis with tissue sent for genomic analysis. Useful assessments include estrogen receptor (ER)/progesterone receptor status, HER2 testing, MMR or MSI testing, and next-generation sequencing. Insights into the molecular features can help inform prognosis, guide treatment decisions, and allow for clinical trial enrollment.
- For newly diagnosed metastatic endometrial cancer, surgical cytoreduction followed by systemic treatment is generally recommended. The decision to perform surgery should be guided by the ability to optimally cytoreduce and the performance status of the patient.
- Patients who are not surgical candidates should be offered medical therapy. These patients have a very poor prognosis with 5-year relative survival of <20% and should be counseled that treatment is palliative rather than curative.
- Patients with metastatic endometrial cancer should receive systemic therapy. This may be as primary therapy or following surgical cytoreduction.

Chemotherapy

- There are no FDA-approved chemotherapy agents for the treatment of recurrent and metastatic endometrial cancer. However, the following regimens are typically used:
  - Single-agent therapy
    - Options include doxorubicin, paclitaxel, pegylated liposomal doxorubicin, topotecan, bevacizumab, and temsirolimus.
    - Response rates range from 17% to 28%; partial responses are of short duration (<6 months); OS is 9 to 12 months.
  - Combination chemotherapy
    - Multiagent chemotherapy regiments are preferred, if tolerated.
    - Response rates 36% to 67%; partial responses are short duration (4-8 months).
    - OS not improved over single-agent therapy.
    - Combinations may include carboplatin/paclitaxel (preferred), cisplatin/doxorubicin, cisplatin/doxorubicin/paclitaxel, carboplatin/paclitaxel, and ifosfamide/paclitaxel.
    - Paclitaxel-containing regimens may improve response and progression-free intervals; OS advantages may be seen in time. Such regimens may include TAP (doxorubicin 45 mg/m^2, cisplatin 50 mg/m^2 on day 1; paclitaxel 160 mg/m^2 on day 2) or TC (paclitaxel at 175 mg/m^2 followed by carboplatin AUC of 5-7, every 4 weeks).

Endocrine Therapy

- Endocrine therapy is typically reserved for those with ER receptor positive disease or those with minimally symptomatic or indolent disease. It is an acceptable first- or second-line therapy for those who wish to avoid the toxicity of chemotherapy and is typically continued until progression or unacceptable toxicity.
- It may also be used for those with ER receptor positive disease who have progressed on chemotherapy or immunotherapy.
- Response rates vary from 15% to 30%, with responses lasting for 1 year on average.
- Options include the following:
  - Megestrol acetate (Megace), 160 to 320 mg daily, is the preferred initial regimen.
  - Medroxyprogesterone acetate (Depo-Provera) 400 to 1000 mg IM weekly for 6 weeks and then monthly is preferred.
  - Oral medroxyprogesterone (Provera), 200 mg PO daily, works equally well as 1000 mg per day.
  - TAM, 20 mg PO BID, may be given as second line with or without a progestin (medroxyprogesterone acetate 200 mg per day). Addition of progestin may improve response rate when used with TAM 40 mg per day PO.
  - Aromatase inhibitors (eg, anastrozole, letrozole) are currently being evaluated and to date have response rates of 10%.
- There is currently no role for adjuvant endocrine therapy to treat early-stage disease.

Immune Checkpoint Inhibition

- For women who have progressed on platinum-based chemotherapy, biomarker-directed therapy should be considered. Pembrolizumab, an anti-programmed cell death protein 1 antibody, should be considered for tumors with a high mutational burden (≥10 mutations/megabase), mismatch repair deficiency (dMMR), or MSI-H.
- Treatment should continue until disease progression or unacceptable toxicity.
- For patients with endometrial cancer that is not MSI-H or dMMR, has progressed on prior systemic therapy, and is not amenable to curative surgery or radiation, the combination of pembrolizumab plus lenvatinib (a vascular endothelial growth factor receptor inhibitor) is FDA-approved.
    - A randomized trial evaluating pembrolizumab plus lenvatinib versus physician's choice (single-agent doxorubicin or paclitaxel) for the treatment of advanced endometrial cancer progressive after prior platinum-based chemotherapy showed that combination therapy resulted in improvements in median PFS, OS, and ORR. Similar improvements were seen in those with MMR-proficient tumors. Of note, grade 3 or higher adverse events (AEs) occurred in 89% of patients receiving pembrolizumab plus lenvatinib (most common AEs were hypertension, hypothyroidism, diarrhea, and nausea).

Estrogen Replacement Therapy

- Estrogen replacement therapy for patients with endometrial cancer remains controversial.

Posttherapy Surveillance

- Most recurrences are seen in the first 3 years after primary therapy (>50% of recurrences occur within 2 years and approximately 75% within 3 years of initial treatment).
- National Comprehensive Cancer Network guidelines for posttherapy surveillance of endometrial cancer include the following:

- History and physical examination, every 3 to 6 months for 2 to 3 years, then every 6 months for up to 5 years, and then annually. Up to 70% of patients with recurrent disease will report symptoms of vaginal bleeding, pain, cough, or weight loss.
- CA-125 monitoring is useful if initially elevated.
- Imaging as clinically indicated.
- Genetic counseling or testing is advised in patients younger than 50 years with a significant family history and/or pathologic features suggestive of Lynch syndrome.

Suggested Readings

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Cervical Cancer

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EPIDEMIOLOGY

- Uterine cervix cancer represents the fourth most common cancer in women, and the seventh overall, representing an estimated 604,127 new cancer cases from around the world in 2020.
- There were an estimated 341,127 deaths from uterine cervix cancer worldwide in 2020, making it the fourth most common lethal cancer in women and ninth overall.
- Cervical cancer remains more common in low resource health care settings and remains the most common cause of cancer in women in 23 countries.
- Among American women, uterine cervix cancer is the third most common cancer of the genital system, with an estimated 14,480 new cases and 4290 deaths estimated in 2021.
- Papanicolaou (Pap) smear screening has lowered the incidence and mortality of invasive uterine cervix cancer by almost 75% over the past 50 years; however, nearly 85% of cases occur in less developed regions where Pap screening may not be available.
- Uterine cervix cancer incidence among American women continues to decline but remains disproportionately high among subpopulation (American Blacks, Hispanics of any race, Asian/Pacific Islander Americans, American Indian/Alaskan Natives).

Given the substantial global burden of cervical cancer and the increasing inequity, the WHO called for global action toward the elimination of cervical cancer through the following intervention strategy: (1) vaccinating 90% of all girls by the age of 15 years, (2) screening 70% of women twice in the age range of 35 to 45 years, and (3) treating at least 90% of all precancerous lesions detected during screening.

RISK FACTORS

Human Papillomavirus

- Human papillomavirus (HPV) infection is the most important factor in disease progression to uterine cervix cancer. Up to 90% of uterine cervix cancers retain HPV DNA in the malignant cell phenotype.
- Over 170 HPV subtypes are known, and about 40 subtypes infect the genital system.
- HPV virus subtypes associated with high risk for uterine cervix cancer include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. A 9-valent HPV vaccine includes HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 virus-like particles.
- HPV types 16 and 18 account for 70% of uterine cervix cancer incidence.
- In the United States, up to 50% of sexually active young women will be HPV (+) within 36 months of sexual activity; however, most women clear the infection within 8 to 24 months.
- HPV prevalence in regions with a high incidence of uterine cervix cancer is 10% to 20%, while in regions with a lower incidence of uterine cervix cancer, HPV prevalence is 5% to 10%.
- The HPV oncogenic phenotype involves HPV E6 protein, which inactivates p53, and HPV E7 protein, which inactivates pRb. Resulting loss of a G1/S cell cycle checkpoint leads to unregulated DNA replication, favorable for viral DNA

duplication and implicated in malignant transformation of uterine cervix cells.
- It is not known whether HPV subtyping of invasive uterine cervix cancer impacts clinical outcome or cancer care provider management. For women with high-grade squamous intraepithelial lesions (HSIL), the presence of high-risk HPV (hrHPV) subtypes elevates the hazard for invasive uterine cervix cancer.

At-Risk Populations

- Risk of invasive uterine cervix cancer is largely influenced by HPV exposure, vaccination, and screening as well as immune response to HPV infection.
- Populations at elevated risk for the development of cervical cancer include persons historically underrepresented in medicine (elevated among Hispanics of any race, American blacks, and American Indian/Alaskan Natives), low socioeconomic status (reflective of poverty and poor education status), and immigration from high-HPV prevalence or low-screening worldwide regions.
- Personal risk factors include early onset of coitus (relative risk [RR] is twofold for younger than 18 years compared to 21 years or older), multiple sexual partners (RR is threefold with six or more partners compared to one partner), a partner with multiple sexual partners, and a history of sexually transmitted infections.
- A "current smoker" status raises the RR of squamous cell uterine cervix cancer fourfold and has been shown to accelerate progression of dysplasia to invasive carcinoma twofold.
- Immunosuppression, including renal transplantation (RR = 5.7) and human immunodeficiency virus (HIV) infection (RR = 2.5), increases the risk of uterine cervix cancer.

SCREENING

- Current screening recommendations in the United States include all three screening modalities (cytology, cotesting, and HPV alone).
  - The American College of Obstetricians and Gynecologists and the U.S. Preventive Services Task Force currently recommend screening every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the screening recommendation is for every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology.
  - The American Cancer Society has recommended primary HPV screening beginning at the age of 25 years.
  - Uterine cervix cancer screening of women in the general population should begin no sooner than the age of 21 years.
  - Women aged 21 to 29 should be screened with cervical cytology alone every 3 years.
  - In women aged 30 to 65 years, cotesting with cervical cytology and HPV testing every 5 years is preferred. Continued screening with cervical cytology every 3 years is acceptable.
  - For screening to end at the age of 65 years, women must have had adequate negative prior screening and no history of HSIL within the last 25 years.
  - Screening can end in women who have had a (total) hysterectomy with removal of the cervix and no prior history of HSIL.
- HPV testing has much higher sensitivity for cervical precancer and a much longer lead-time compared with cytology.
  - An additional benefit to HPV testing is that, unlike cytology, it can be successfully performed on self-collected specimens, obviating the need for an in-person pelvic examination and therefore potentially extending access to screening in underscreened/unscreened communities.
- Cytologic test results are divided into nonmalignant findings and epithelial cell abnormalities including squamous and glandular abnormalities.
- HPV infections are more prevalent and persistent in HIV-infected women.
  - Among HIV-infected women, rates of oncogenic HPV and HSIL increase with diminished CD4 counts and higher circulating HIV RNA levels.
  - For women with newly diagnosed HIV-infection, the first cervical cancer screening is recommended to start at the time of HIV diagnosis with repeat in 6 or 12 months.
- Adenocarcinoma incidence has been increasing over past 3 decades because Pap screening is often inadequate for

detecting endocervical lesions; however, HPV screening and vaccine may decrease both squamous and adenocarcinoma rates.

PRECURSOR LESIONS

- High-grade or persistent screening abnormalities will need to be verified with a diagnostic test. Colposcopy or excisional biopsy most commonly results in the diagnosis of a premalignant lesion.
- Low-grade squamous intraepithelial lesions (LSIL) (CIN 1) is more likely to regress than progress than HSIL (CIN 2/3). Nevertheless, the rate of progression of LSIL to HSIL is 1% per year; the rate of progression of moderate dysplasia to severe dysplasia is 16% within 2 years and 25% within 5 years. Untreated CIN 3 has a 30% probability of progression to invasive cancer over a 30-year observation period.
    - In 2019, the American Society of Colposcopy and Cervical Pathology guidelines changed from primarily test results–based algorithms to primarily "risk-based" guidelines. Colposcopy or expedited treatment is recommended for patients with a risk of CIN 3+ or 4%, whereas those at lower risk can defer colposcopy, undergo close surveillance.

SIGNS AND SYMPTOMS OF CERVICAL CANCER

- Early uterine cervix cancers are often asymptomatic.
- In symptomatic patients, abnormal vaginal bleeding (ie, postcoital, intermenstrual, or menorrhagia) is the most common symptom and may lead to anemia-related fatigue.
- Vaginal discharge (serosanguinous or yellowish, sometimes foul smelling) may represent a more advanced lesion.
- Pain in the lumbosacral or gluteal area may suggest hydronephrosis caused by tumor or tumor extension to lumbar

nerve roots.
- Bladder or rectum symptoms (hematuria, rectal bleeding, etc.) may indicate organ invasion.
- Persistent, unilateral, or bilateral leg edema may indicate lymphatic and venous blockage caused by extensive pelvic sidewall nodal or tissue disease.
- Leg pain, edema, and hydronephrosis are characteristic of advanced-stage disease (IIIB).

DIAGNOSTIC WORKUP

- History and physical examination should include bimanual pelvic and rectovaginal septum examinations. These are usually normal with stage IA disease (microscopic invasion only).
- The most frequent examination abnormalities include visible cervical lesions or abnormalities on bimanual pelvic examination.
- About 15% of adenocarcinomas have no visible lesion because the carcinoma is within the endocervical canal.

Standard Diagnostic Procedures

- Cervical cytology for routine screening and in the absence of a gross lesion
- Cervical biopsy of any gross lesion (perhaps by colposcopy)
- Excisional procedure (eg, conization) for subclinical tumor or after negative biopsy when malignancy is suspected
- Conization for microinvasive cancer to assist in primary treatment triage
- Endocervical curettage for suspected endocervical lesions
- Cystoscopy and proctoscopy for symptoms worrisome for bladder or rectal tumor extension

Radiologic Studies

- Because of the limits of low-resource regions, the International Federation of Gynecology and Obstetrics (FIGO) clinical staging had historically limited radiographic imaging for staging purposes to chest x-ray, intravenous pyelography, and barium enema. Although imaging is not mandated, the use of imaging, lymph node biopsy, or surgical assessment of the extent of tumor is based upon the availability or adequacy of access to extensive imaging services.
- Tumor size can be determined by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement.
- If available for treatment planning purposes, computed tomography (CT), positron emission tomography (PET), PET/CT, or magnetic resonance imaging (MRI) are informative.
- MRI is the best for delineating soft-tissue or parametrial tissue invasion.
- CT or PET/CT is useful to evaluate initial pelvic or para-aortic lymph node involvement.

Laboratory Studies

- Complete blood count to evaluate for anemia
- Blood chemistries to evaluate for renal function
- Liver function tests to evaluate synthetic and metabolic factors

HISTOLOGY

- Cervical carcinoma often originates at a squamous-columnar cell junction of the uterine cervix, by name, the transformation zone.
- Seventy-five percent to 80% of uterine cervix cancers are of squamous cell histology; the remaining 20% to 25% are mostly adenocarcinomas or adenosquamous carcinomas.

STAGING

- Because the global burden of uterine cervix cancer occurs in low-resource regions where access to imaging and abilities to surgically stage are often limited, uterine cervix cancer remains primarily clinically staged. The 2018 FIGO definitions and staging system are accepted uniformly. This system has been endorsed by the American Joint Committee on Cancer (AJCC).
- Laparoscopy, lymphangiography, CT, CT/PET, and/or MRI can be used to assign stage; however, they are not obligatory.

PROGNOSTIC FACTORS

- Major prognostic factors include clinical stage, lymph node involvement, tumor volume (or >4 cm in unidimensional measurement), depth of cervical stroma invasion, lymphovascular space invasion (LVSI), and to a lesser extent, histologic type and grade.
- Stage is the most important prognostic factor, followed by lymph node involvement.
- Five-year survival based on the extent of tumor at diagnosis:
  - Uterine cervix confined: 92%
  - Pelvis-contained: 56%
  - Extrapelvic metastatic disease: 16.5%
  - Unstaged at diagnosis: 60%

MODE OF SPREAD

- Disease spread is orderly occurring first along lymphovascular planes to involve parametrial tissues. Disease may extend to the vaginal mucosa or the uterine corpus. Disease spread to adjacent organs is typically by direct extension.
- Ovarian involvement by direct extension of uterine cervix cancer is rare (0.5% of squamous cell carcinomas [SCCs], 1.7%

adenocarcinomas).

- Lymphatic dissemination most commonly involves pelvic lymph nodes first and then para-aortic lymph nodes. Skip para-aortic nodal lesions occur.
- Vascular spread is late in the disease process and metastases occur in lung, liver, and bone.
- Risk of pelvic lymph node metastases increases with increasing depth of tumor invasion, tumor bulk, and presence of LVSI.

TREATMENT

High-Grade Intraepithelial Lesions/Carcinoma In Situ

- AJCC includes stage 0 for in situ disease (Tis), while FIGO no longer includes stage 0 (Tis).
- Noninvasive lesions can be treated with excisional procedures or hysterectomy.
  - A loop electrosurgical excision procedure (LEEP), which allows excision of the entire transformation zone of the cervix with a low-voltage diathermy loop in the outpatient setting.
  - A cold-knife conization (CKC) excises the transformation zone with a scalpel, avoiding cautery artifact on the surgical margins.
- When margin status will dictate the need for, and type of, additional therapy, as in cases of adenocarcinoma in situ or microinvasive SCC, a CKC is preferred.
- Extrafascial (ie, simple or total) hysterectomy is preferred for management of adenocarcinoma in situ in women who have completed childbearing. If preservation of fertility is desired, conization with negative margins followed by surveillance is reasonable.

Invasive Uterine Cervix Cancer

- Treatment for each clinical stage varies depending on the size of the tumor (Figure 19.1). Smaller tumors may be treated surgically or with radiation. Larger tumors are usually only

treated with radiochemotherapy (or, radiation alone in special circumstances).

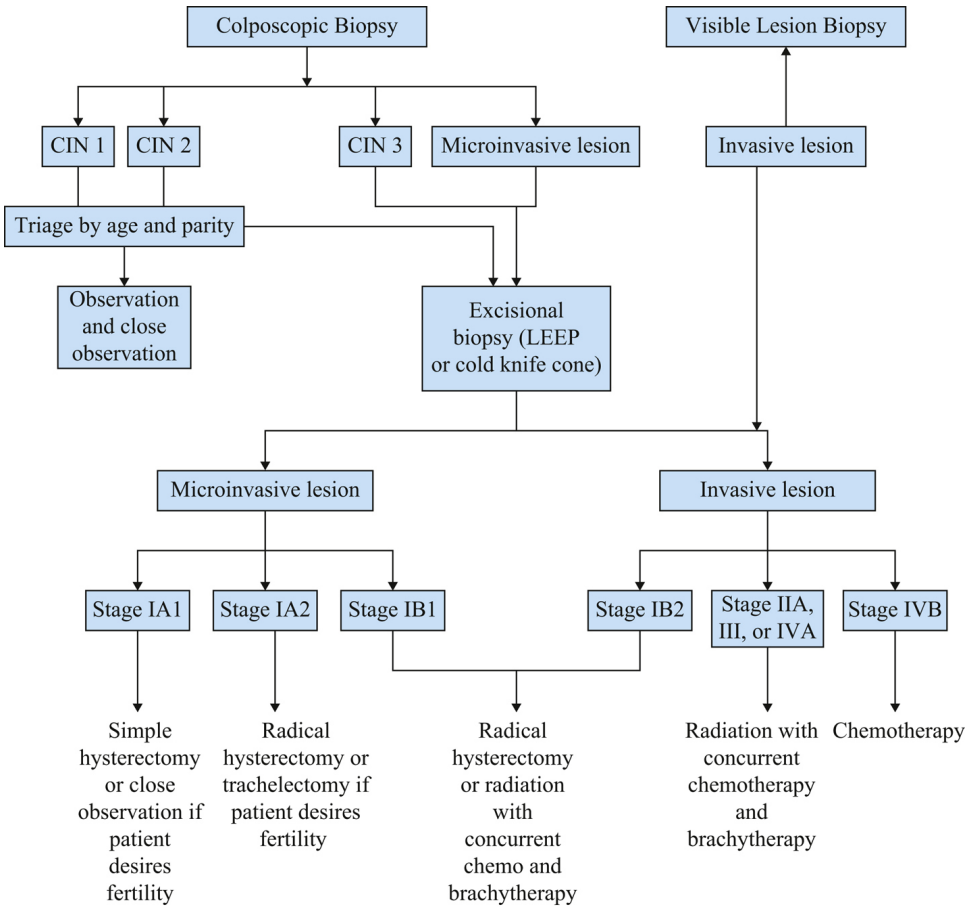

FIGURE 19.1 Overview of the management of preinvasive and invasive lesions of the cervix.

- Results from five randomized phase III trials demonstrated an overall survival (OS) advantage for cisplatin-based chemotherapy coadministered with radiotherapy when compared to radiation-only therapy for patients with locally advanced disease. These trials demonstrated a 30% to 50% risk reduction overall for death in women with FIGO stages IB3 to IVA tumors or in women with FIGO stages I to IIA tumors with poor prognostic factors (ie, pelvic lymph node involvement, parametrial disease, and positive surgical margins).

- Based on these data, the National Cancer Institute issued a clinical alert in 1999 informing cancer care providers that a strong consideration should be given to adding cisplatin-based chemotherapy to radiotherapy in the treatment of invasive uterine cervix cancer.
- The most common regimen for concurrent radiochemotherapy is once-weekly cisplatin, 40 mg/m^2 IV (maximum 70 mg) for six weekly cycles during daily radiation therapy.
- Alternatively, cisplatin with 5-FU given every 3 to 4 weeks during radiation is acceptable.

Stage IA1

- Prior to initial therapy, the most important factors confounding cancer care include (1) a woman's fertility desires, (2) medical operability, and (3) presence of LVSI at biopsy.
- For women with no LVSI and negative histopathological margins on their LEEP or CKC specimen, and who have completed childbearing, a simple hysterectomy is indicated.
- For those with LVSI or positive margins, a modified radical hysterectomy with pelvic lymph node dissection is indicated.
- For those who wish to preserve fertility, a conization with negative margins, followed by observation is adequate therapy. However, if margins are positive, options include radical trachelectomy or repeat cone biopsy.
- Para-aortic lymph node dissection is reserved for patients with known or suspected nodal disease.

Stages IA2, IB1, IB2, IIA1 (Early-Stage Disease)

- General options for early-stage disease include the following:
  - Fertility sparing—radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node dissection
  - Modified radical hysterectomy and pelvic lymph node dissection with para-aortic lymph node dissection for known or suspected nodal disease
  - Definitive radiochemotherapy

- All options are equally effective but differ in associated morbidity and complications.
- For early-stage uterine cervix cancers, primary surgery is often recommended.
- Optimal therapy selection depends on patient's age and childbearing plans, disease stage, current comorbidities, and the presence of histologic characteristics associated with the increased risk of recurrence.

Stage IB3 or IIA2 (Bulky Disease)

- General options for bulky disease include the following:
  - Definitive radiochemotherapy (whole pelvic radiation and brachytherapy), or
  - Radical hysterectomy plus pelvic lymph node dissection with para-aortic lymph node dissection for known or suspected nodal disease
- Radiologic imaging (including PET/CT) is recommended for assessing bulky disease.
- Radiochemotherapy has been shown to improve patient survival.

Surgery

- Outside of special circumstances, a minimally invasive approach to radical hysterectomy for cervical cancer is not recommended. Although laparoscopic and robotic approaches had been associated with shortened recovery time, decreased hospital stay, and less blood loss, results of a prospective trial or minimally invasive radical hysterectomy published in 2018 demonstrated lower rates of disease-free survival and OS compared to open abdominal radical hysterectomy among women with early-stage cervical cancer. Epidemiologic evidence also associates minimally invasive radical hysterectomy with shorter OS compared to open surgery.
- Adjuvant hysterectomy after primary radiochemotherapy appears to improve pelvic control but not OS and has increased morbidity. Adjuvant surgery (ie, after pelvic radiotherapy) is

not routinely performed but may be considered in patients with residual tumor confined to the cervix or in patients with suboptimal brachytherapy because of vaginal anatomy.

- Radical trachelectomy is a fertility-preserving surgery, which may be an option for small-volume, early-stage disease (IA1–IB1).
- Para-aortic lymph node sampling may be indicated in patients with positive pelvic nodes, clinically enlarged nodes, or patients with large-volume disease.
- For select patients desiring future fertility, conservative surgery can be considered. A cone biopsy with or without pelvic lymph node assessment can be considered for patients with stage IA or IB1 disease.

Indications for Adjuvant Therapy

- High risk for recurrent disease:
  - Positive or close margins
  - Positive lymph nodes
  - Positive parametrial involvement
- Intermediate risk for recurrent disease:
  - LVSI
  - Deep stromal invasion (greater than one-third)
  - Large tumor size (greater than 4 cm)

Adjuvant Therapy

- Women who undergo initial surgical treatment should receive adjuvant radiochemotherapy treatment in the presence of risk factors (listed above).
  - For women with intermediate risk factors, a randomized trial demonstrated that adjuvant RT improved progression-free survival (PFS), with a trend toward improved OS.
  - For women with high-risk factors, a randomized trial demonstrated that adjuvant radiochemotherapy was associated with an improved PFS and OS.
- If definitive radiotherapy is used as primary treatment, concurrent cisplatin-based chemotherapy should be administered.

- Following definitive radiotherapy, adjuvant chemotherapy is not recommended as the OUTBACK study (GOG274, NCT01414608) which randomized patients to an additional four cycles of paclitaxel and carboplatin following completion of radiotherapy demonstrated no survival benefit, but an increase in toxicity.

Stages IIB, III, IV

- Patients with stage IIB to IVA disease (commonly referred to as locally advanced-stage disease) should be treated with tumor volume–directed radiotherapy and concurrent cisplatin-based chemotherapy.
- Radiologic imaging (PET/CT) and potentially surgical staging (ie, extraperitoneal or laparoscopic lymph node dissection) are recommended to assess lymph node involvement and serve as a guide to radiation therapy portal design.
- Patients with stage IVA disease (bowel or bladder mucosa invasion), who are poor candidates for radiochemotherapy (ie, acute or chronic pelvic inflammatory disease, coexistent pelvic mass), may be candidates for pelvic exenteration surgery.
- Patients who have distant metastasis (IVB disease) should receive systemic and/or biologic agent chemotherapy with (most often) or without (less often) pelvis-directed radiation therapy.

Radiation Therapy

- For definitive treatment, pelvic external beam radiation therapy (EBRT) with intracavitary brachytherapy is used routinely.
- High (>8000 cGy) radiation dose may be delivered to central primary tumors through use of EBRT and intracavitary brachytherapy. EBRT alone often cannot achieve these doses due to intervening normal tissues (eg, small bowel, large bowel, and bladder).
- In select cases of very early disease (stage IA2), brachytherapy alone may be an option.

- Pelvic inflammatory disease, inflammatory bowel disease, and pelvic kidney are relative contraindications to conventional pelvic radiation but may not impede intensity-modulated radiation therapy (IMRT).
- CT-based treatment planning is considered standard-of-care for EBRT.
- EBRT should encompass gross disease (vaginal margin 3 cm from tumor), parametrial tissues, uterosacral ligaments, and presacral, external/internal iliac, and obturator lymph nodes. For patients at high risk for lymph nodes involvement, the radiation field should also cover common iliac lymph nodes. If common iliac or para-aortic lymph node involvement is clinically suspected, extended-field radiation that raises the superior radiation portal boundary up at least to the level of renal vessels is recommended.
- Both high-dose brachytherapy (isotope ^{192}Iridium; rate 200-300 cGy/h) and low-dose brachytherapy (isotope ^{137}Cesium; rate 40-70 cGy/h) are used. Either brachytherapy source or technique is acceptable.
- Determining maximum effective dose to the primary tumor, as well as to the bladder and rectum, is of primary importance. A typical regimen of EBRT is 4000 to 5000 cGy plus 3000 to 4000 cGy point A brachytherapy, for a total dose of 8000 to 9000 cGy to point A.
- Point A is located 2 cm cephalad and 2 cm lateral to the cervical os. Anatomically, it correlates with the boundary between the lateral uterine cervix and the medial edge of parametrial tissue, an anatomic point where the ureter and uterine artery cross.
- A parametrial boost (900-1440 Gy) by EBRT may be applied to point B (defined as 5 cm lateral to patient midline and corresponding to the pelvic sidewall lymph nodes).
- Radiation treatment is equivalent to surgery for stages IB and IIA, with identical 5-year OS and disease-free survival. Expected cure rate is 75% to 80% (85%-90% in small-volume disease).
- A study by the Radiation Therapy Oncology Group (RTOG 79-20) showed an 11% 10-year survival advantage for patients with

IB2, IIA, and IIB disease treated with prophylactic para-aortic nodal (extended field RT) and total pelvic irradiation compared to those treated with pelvic irradiation alone.

- Multivariate analyses have shown that a total dose of >8500 cGy intracavitary radiation to point A (locally advanced stage only), radiosensitizers like cisplatin, and overall treatment time of <8 weeks are associated with improved pelvic tumor control and survival in women with uterine cervix cancer. Treatment times beyond 8 weeks (56 days) result in an up to 1% decline, per extended treatment day, in recurrence-free survival.

Palliative Chemotherapy

- Combination platinum-based chemotherapy has demonstrated improved response rates in randomized trials compared to single-agent therapy.
  - Cisplatin/paclitaxel demonstrated higher response rate and improved PFS compared to single-agent cisplatin in Gynecologic Oncology Group (GOG) 169. Preliminary data from a Japanese randomized trial demonstrate equivalency of carboplatin/paclitaxel with cisplatin/paclitaxel.
  - Cisplatin/topotecan demonstrated superior response rate, PFS, and median survival compared to single-agent cisplatin in GOG 179.
  - A comparison trial of cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine compared to a control arm of cisplatin/paclitaxel was halted when the experimental arms were not superior to the control. Cisplatin/paclitaxel had the best response rate, 29.1%.
- The addition of bevacizumab to chemotherapy improves OS by 4 months and leads to a 12% higher response rate.
  - Toxicity related to bevacizumab can be substantial (including hypertension, renal dysfunction, and fistula), so patient comorbities and goals of care should be considered.
- Pembrolizumab can be considered as second-line treatment following platinum-based chemotherapy for patients whose tumors express PD-L1.
  - The safety and clinical benefit of pembrolizumab in advanced cervical cancer was investigated in the open-label, phase II, multicohort KEYNOTE-158 trial. For patients with cervical cancer, an objective response rate (ORR) of 12.2% (95% CI, 6.5%-20.4%), with three complete responses (CR) and nine partial responses (PR), was demonstrated. All 12 responses were in patients with PD-L1–positive tumors with an ORR of 14.6% (95% CI, 7.8%-24.2%).
  - Other PD-1 and PD-L1 therapies have demonstrated promising activity.

- The most active single agents include the following:
  - cisplatin (response rate 20%-30%)
  - carboplatin (response rate 15%-28%)
  - ifosfamide (response rate 15%-33%)
  - paclitaxel (response rate 17%-25%)
- Other agents with activity include irinotecan, vinorelbine, gemcitabine, docetaxel, 5-FU, mitomycin, topotecan, and pemetrexed.
- Tisotumab vedotin, an investigational antibody-drug conjugate directed against tissue factor, adoptive cell transfer therapy, therapeutic HPV vaccines, and cytokines are being investigated for their therapeutic potential in cervical cancer.
- The benefit of chemotherapy with or without radiation versus best supportive care in this patient population has not yet been established.

Special Considerations

- Studies have clearly demonstrated the deleterious effect of anemia on patients receiving radiation therapy. Hemoglobin levels <10 g/dL at the time of radiation therapy impede local disease control and survival. Blood transfusions to raise hemoglobin levels above 10 g/dL are recommended.
- Some patients with small-volume disease in para-aortic lymph nodes and controllable pelvic disease can potentially be cured. Removal of grossly involved para-aortic lymph nodes prior to radiotherapy may be therapeutic.
- Toxicity from extended-field radiation exceeds that of pelvic radiation alone but most commonly is seen in women with prior abdominopelvic surgery.
- Different surgical techniques affect the incidence of complications secondary to para-aortic lymph node extended-field radiation. For example, extraperitoneal lymph node sampling leads to fewer radiation-related posttherapy complications than transperitoneal lymph node sampling.
- IMRT has been shown to reduce sequelae of pelvic and extended-field radiation therapy. Clinical trials evaluating IMRT

are underway in this patient population.

Recurrent Disease

- A 10% to 20% recurrence rate has been reported in stage IB to IIA women with negative nodal sampling treated by primary surgery or radiation therapy.
  - For stage I-IIA disease, the predominant anatomic site of recurrence is local (vaginal apex) or intrapelvic (pelvic sidewall).
- Up to 70% of women with stage IIB, III, or IVA disease with or without positive nodal sampling will ultimately recur.
  - Women with positive lymph nodes at initial diagnosis, particularly para-aortic lymph node involvement, have a higher risk of distant metastases as compared to women with negative lymph nodes.
- Intrapelvic recurrences are typically symptomatic, with 80% to 90% detected by 2 years posttherapy.
- Multiple studies have shown that the distribution of recurrence site as:
  - Central pelvis (vaginal apex)—22% to 56%
  - Regional pelvis (pelvic sidewall)—28% to 37%
  - Distant extrapelvic metastasis—15% to 61%
- In the recurrence setting, favorable prognostic factors include central pelvis disease site, disease not fixed to the pelvic sidewall, the posttherapy disease-free interval is 6 months or longer, and the recurrent tumor measures less than 3 cm.
- More than 90% of women with distant extrapelvic recurrence die of disease within 5 years.
- No curative therapy is available for metastatic disease. In direct contrast, intrapelvic recurrence can potentially be treated with curative intent.
  - For patients with intrapelvic recurrence after radical surgery, cisplatin-based radiochemotherapy has a 40% to 50% durable control rate and long-term survival rate.
  - Pelvic exenteration (resection of the bladder, rectum, vagina, uterus/cervix) is a preferred treatment for centrally located recurrent disease after primary radiation therapy, with a 32% to 62% 5-year survival in select women. Reconstructive procedures include continent urinary conduit, end-to-end rectosigmoid reanastomosis, and myocutaneous graft for a neovagina.
  - High-dose intraoperative radiation therapy combined with surgical resection is offered by some centers for patients whose tumors extend close to the pelvic

sidewalls.

- Surgical resection of limited metastatic disease, such as in the lung, may result in prolonged clinical remission.
- Chemotherapy for distant recurrent disease is palliative, not curative, demonstrating low response rates, short response duration, and low OS rates (see the Palliative Chemotherapy section). Cisplatin is the most active single agent, with a median survival of 7 months.
- Chemotherapy-naive patients have a higher response rate than those exposed to chemotherapy as part of their initial treatment.

TREATMENT DURING PREGNANCY

- Uterine cervix cancer is the most common gynecologic malignancy associated with pregnancy, ranging from 1 in 1200 to 1 in 2200 pregnancies.
- No therapy is warranted for preinvasive lesions; colposcopy, but not endocervical curettage, is recommended to rule out invasive cancer.
- Conization is reserved for suspicion of invasion or for persistent cytologic evidence of invasive cancer in the absence of colposcopic confirmation. Management of dysplasia is usually postponed until postpartum.
- Treatment of invasive cancer depends on the tumor stage and the gestational age at which the diagnosis is made. If cancer is diagnosed before fetal maturity, immediate appropriate cancer therapy for the relevant stage is recommended. However, with close surveillance, delay of therapy to achieve fetal maturity is a reasonable option for patients with stage IA and early IB disease. For more advanced disease, delaying therapy is not recommended unless diagnosis is made in the final trimester. When the fetus reaches acceptable maturity, a cesarean section precedes definitive treatment.

FOLLOW-UP AFTER PRIMARY THERAPY

- Eighty percent to 90% of recurrences occur within 2 years of completing therapy suggesting a role for increased surveillance during this period.
- Follow-up visits, including thorough physical examination, should occur every 3 to 6 months in the first 2 years posttherapy, every 6 to 12 months for the following 3 years, and then annually to detect any potentially curable recurrences.
- Additionally, patients should have annual cervical or vaginal cytology though an exception can be made for those that have undergone pelvic radiation.
- There are insufficient data to support the routine use of radiographic imaging; chest x-ray, CT, and PET or PET/CT should only be used if recurrence is suspected.
- Patients should be counseled about signs and symptoms of recurrence to include persistent abdominal and pelvic pain, leg symptoms such as pain or lymphedema, vaginal bleeding or discharge, urinary symptoms, cough, weight loss, and anorexia.

PREVENTION

- The efficacy and safety of HPV vaccination against HSIL and cancer has been demonstrated in multiple studies.
- HPV vaccine is recommended for routine vaccination at the age of 11 or 12 years. (Vaccination can be started at the age of 9 years.)
- Vaccination through age 26 years if not adequately vaccinated previously is recommended; some adults ages 27 to 45 years may decide to get the HPV vaccine based on discussion with their clinician if they did not get adequately vaccinated when they were younger.

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Vulvar Cancer

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EPIDEMIOLOGY

- Vulvar cancer is the fourth most common gynecologic cancer, accounting for nearly 6% of all female genital tract malignancies and 0.7% of all cancers in women.
- A total of 6120 new cases and 1550 deaths from vulvar cancer are projected for 2021.
- It is most frequently diagnosed in postmenopausal women, with a median age of diagnosis of 68 years.
- One in 333 (0.3%) women will be diagnosed with vulvar cancer during her lifetime (2.4 per 100,000 women per year in the United States).
- The rate of vulvar cancer has remained stable over the past 20 years; however, the incidence of its precursor (vulvar intraepithelial neoplasia 3) has doubled.
- Most patients are diagnosed at an early stage, with a 5-year survival of 72.1%.
- Squamous cell carcinoma is the most common histologic type of vulvar cancer, comprising approximately 75% of all cases.

ETIOLOGY AND RISK FACTORS

- There are two independent pathways of vulvar carcinogenesis:
    1. Mucosal human papillomavirus (HPV) infection—HPV 16 is the most common subtype (73%), followed by HPV 33 (7%) and HPV 18 (5%)

2. Chronic inflammatory or autoimmune processes—most commonly lichen sclerosus and squamous cell hyperplasia

- Premalignant lesions of the vulva are linked to HPV DNA in 70% to 80% of cases. However, the association between HPV and vulvar cancer is observed less frequently, with only 40% to 60% of vulvar cancers testing positive for HPV DNA on molecular analysis.

Risk Factors

- Vulvar high-grade intraepithelial lesions (VIN 2/3) increase the risk of developing invasive vulvar cancer.
- Other risk factors include cigarette smoking, HPV infection, vulvar dystrophies (eg, lichen sclerosus), cervical intraepithelial lesions (CIN), prior history of cervical cancer, immunodeficiency disorders (eg, human immunodeficiency virus [HIV]), and Northern European ancestry.

HISTOLOGY

- Squamous cell carcinomas (SCCs) are the most common histologic type, accounting for at least 75% of all cases. There are two subtypes:
    1. Keratinizing, differentiated, or simplex: more common subtype, occurs in older patients, and unrelated to HPV infection. Strongly associated with vulvar dystrophies and chronic venereal granulomatous disease (in resource-limited countries).
    2. Classic, warty, or Bowenoid: strongly associated with HPV infection (16, 18, and 33), occurs more commonly in younger patients. Patients typically present with early-stage disease.
- Melanomas are the second most common histologic type, accounting for 2% to 10% of all cases. Occur most commonly in postmenopausal, non-Hispanic white patients. Most lesions are pigmented, but amelanotic lesions may also occur.
- The remainder of tumor types include basal cell carcinoma (2%-8%), sarcoma (1%-2%), Bartholin gland carcinoma

(0.1%-5%), extramammary Paget disease (<1%), and verrucous carcinoma (<1%).

VULVAR SCC

- Vulvar SCC is commonly indolent, with slow extension and late metastases. Most patients will present with a vulvar lesion. Lesions are typically unifocal and appear as a plaque, ulcer, or fleshy, warty, or nodular mass. Multifocal lesions occur in approximately 5% of cases, so a thorough inspection of all vulvar and perianal skin surfaces, as well as the cervix and vagina should be performed.
- Other signs and symptoms may include pruritus, pain, bleeding, ulceration, dysuria, and discharge. Many patients are asymptomatic.
- A synchronous second malignancy is found in up to 22% of patients with vulvar SCC (most commonly cervical cancer).

Diagnostic Workup

- A thorough history and physical examination should be performed, with special attention to signs or symptoms of distant metastases.
- All lesions should be measured with care taken to note location and laterality. Biopsies must include adequate tissue to determine histology, grade, and depth of invasion.
- Colposcopic evaluation of the entire lower genital tract is important for identifying subclinical lesions not appreciated on gross visual examination (~5% of cases are multifocal) and to better define the extent of disease to guide biopsies. Areas to evaluate include vulva, vagina, cervix, and perianal area.
- Given the strong association with HPV infection, ensure cervical cytology is current.
- Additional imaging should be considered for patients with large lesions (>4 cm), evidence of local extension, palpable groin

nodes, symptoms of distant metastases (eg, shortness of breath). Positron emission tomography/computed tomography or magnetic resonance imaging may be useful to better delineate tumor size, local extension, presence of lymph node (LN) involvement, or distant metastases.

Indications for Biopsy of Vulvar Lesions

- Any grossly suspicious lesion
- Skin discoloration (eg, red, white, dark brown, or black)
- Areas firm to palpation
- Persistently pruritic areas
- Ulcerated or bleeding lesions
- Any nevi in the genital tract, particularly if a change in color, elevation, or surface of the lesion is noted
- Enlarged or thickened areas of Bartholin glands, especially in postmenopausal women

Location and Metastatic Spread Pattern of Vulvar SCC

- Vulvar SCC is found most commonly on the labia majora (50%), followed by the labia minora (15%-20%), and rarely on the clitoris and perineum.
- Vulvar SCC tends to grow locally via direct extension to nearby structures (eg, vagina, urethra, clitoris, anus), with early spread to inguinal, femoral, and pelvic LNs.
- Hematogenous spread occurs late in the course of disease and is rare in patients without inguinofemoral LN involvement.
- Inguinal and femoral LN involvement is the most important prognostic factor for survival.

Staging

- Vulvar cancer is surgically staged according to the FIGO staging system.
- The revised 2009 FIGO staging system is as follows:

- Stage I: Tumor confined to the vulva
  - IA: Lesions ≤2 cm in size, confined to the vulva or perineum, and with stromal invasion ≤1.0 mm, no nodal metastasis
  - IB: Lesions >2 cm in size or with stromal invasion >1.0 mm, confined to the vulva or perineum, and with negative nodes
- Stage II: Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anus) with negative nodes
- Stage III: Tumor of any size with regional LN metastasis
  - IIIA: (i) One to two LN metastases (<5 mm), or (ii) One LN metastasis (≥5 mm)
  - IIIB: (i) Three or more LN metastases (<5 mm), or (ii) Two or more LN metastases (≥5 mm)
  - IIIC: Lymph node(s) with extranodal extension
- Stage IV: Tumor invades other regional or distant structures
  - IVA: Tumor of any size with extension to any of the following: upper/proximal two-thirds of the urethra, upper/proximal two-thirds of the vagina, bladder mucosa, or rectal mucosa. Also includes tumors fixed to pelvic bone or presence of fixed or ulcerated inguinofemoral LNs.
  - IVB: Any distant metastasis including pelvic LNs.

Prognosis and Survival

- Inguinal and/or femoral LN involvement is the most important prognostic factor for survival. Five-year overall survival is reported to be 70% to 93% for patients without LN involvement and 25% to 41% for those with LN involvement.
- Other prognostic factors include stage, depth of invasion, capillary lymphatic space invasion, and age.
- LN metastases are related to tumor size (>4 cm is associated with 30%-50% rate of inguinofemoral metastases), clinical stage, and depth of invasion.
- Studies suggest a high overall incidence of local recurrence following primary surgical treatment. Disease presence at the excised tumor margin has been postulated as a significant prognostic factor for recurrence.
- Current data suggest that outcomes may be improving despite less aggressive surgical management, possibly due to advances in adjuvant therapy as well as shifting patient demographics (younger patients, less advanced disease).

Management

High-Grade Squamous Intraepithelial Neoplasia

- The goal of treating vulvar high-grade squamous intraepithelial neoplasia (HSIL) is to prevent the development of invasive disease while preserving normal vulvar anatomy and function.
- Management options include surgical excision (eg, wide local excision, skinning vulvectomy), ablative therapy (CO_2 laser or argon beam coagulator), and topical treatment (topical imiquimod, cidofovir, or 5-FU cream). The approach to treatment should be individualized based upon the level of concern for invasive disease and taking biopsy results, prior treatments, and disease location into account.
- Invasive cancer is present in 10% to 22% of women with VIN on initial biopsy; therefore, surgical excision should be treatment of choice for patients at high risk for invasive disease (previous vulvar HSIL, differentiated VIN, or vulvar carcinoma; immunosuppression; or lichen sclerosus).
- Recurrences are seen in up to 35% of women regardless of initial treatment modality. The most common sites of recurrence are perineal skin and clitoral hood.

Stage I (Lesions Confined to Vulva)

- ≤1 mm depth of invasion (stage IA): simple partial vulvectomy
  - Excise down to inferior fascia of urogenital diaphragm.
  - Strive for 1 to 2 cm clear margins to minimize risk of local recurrence.
  - No inguinofemoral lymphadenectomy (LND) or sentinel lymph node biopsy (SLNB) is necessary as LN metastases are rare in this population (<1%).
- > 1 mm depth of invasion (stage IB): simple partial vulvectomy + inguinofemoral LN assessment (risk of LN metastases >8%)
  - Ipsilateral inguinofemoral LND for lateral lesions (located ≥2 cm from vulvar midline).
  - Bilateral inguinofemoral LND for centrally located lesions.
  - SLNB is an emerging technique in early-stage vulvar cancer and may obviate the need for full nodal dissections in many women. SLNB can be offered to patients with vulvar cancer if tumor diameter is <4 cm, >1 mm depth of invasion, no palpable LNs, unifocal disease, and surgeon has sufficient expertise (completed at least 10 procedures under supervision).
  - Patients with close or positive surgical tumor margins (<8 mm from tumor) can undergo reexcision or, if unresectable, adjuvant radiation therapy (RT). Primary

goal is to decrease the risk for disease recurrence while minimizing morbidity and disfigurement.

Special Considerations

- Poor surgical candidates can be treated with chemoradiation, achieving long-term survival.
- Surgical complications include mortality (2%-5%), wound breakdown or infection, sepsis, thromboembolism, chronic leg lymphedema (use of a separate incision for the groin LN dissection reduces wound breakdown and leg edema), urinary tract infection, stress urinary incontinence, and poor sexual function.

Stage II (Extension to Adjacent Perineal Structures)

- Lateral lesion ≥2 cm from vulvar midline—radical partial vulvectomy and ipsilateral inguinofemoral LN evaluation (SLNB vs inguinofemoral LND).
- Central vulvar lesion—radical partial vulvectomy and bilateral inguinofemoral LN evaluation (SNLB vs bilateral inguinofemoral LND).
- As above, reexcision when feasible is recommended for close or positive surgical margins. For positive, unresectable margins, adjuvant RT is recommended.
- Adjuvant RT should also be considered for patients at high risk for disease recurrence to include tumor size >4 cm, close tumor margins (≤8 mm), lymphovascular invasion, depth of invasion, nodal involvement, and pattern of invasion (spray or diffuse).

Stage III (Inguinofemoral LN Involvement)

- Modified radical vulvectomy and bilateral inguinofemoral LND are standard.
- Adjuvant chemoradiation is recommended for women with involved LNs and most commonly involves cisplatin 40 mg/m^2

concurrently with RT to the inguinal, external iliac, internal iliac, and obturator regional bilaterally.

Stage IVA

- Radical vulvectomy and bilateral inguinofemoral LND can be used if ≥1 cm of negative margins can be achieved with preservation of midline structures.
- As in stage II and III vulvar cancers, adjuvant chemoradiation is recommended for women with LN involvement or surgical margins <8 mm.
- Neoadjuvant chemoradiation, with cisplatin concurrently with RT to the vulva, groin, and LNs, may improve operability and should be considered in patients with:
    - Anorectal, urethral, or bladder involvement
    - Disease fixed to the bone
    - Gross inguinal or femoral LN involvement

Special Considerations

- Management of positive groin nodes: Positive LNs require RT to primary tumor/groin/pelvis + concurrent chemotherapy.
- Suggested doses of localized adjuvant radiation are 45 to 50 Gy.
- Neoadjuvant chemoradiation can be used in stages III and IV disease to improve the operability of the tumor. Recent Gynecologic Oncology Group trials have successfully used cisplatin and 5-FU concurrently with RT.
- Patients with inoperable disease can achieve long-term survival with radical chemoradiation therapy.
- Radiation fraction size of ≤180 cGy has been proven to minimize the radiation complication rate (ie, late fibrosis, atrophy, telangiectasia, and necrosis). Total doses of 54 to 65 Gy should be used.
- Radical vulvectomy and pelvic exenteration are not commonly used due to extensive morbidity and uncertain survival benefit.

Stage IVB (Metastatic) and Recurrent Disease

Therapy recommendations depend on sites of metastasis or recurrent disease and disease-related symptoms. All patients should be considered for clinical trials.

- Distant metastasis or recurrence: RT for locoregional control/symptom palliation and/or chemotherapy or best supportive care. Chemotherapy choices for advanced, recurrent/metastatic disease commonly include cisplatin, carboplatin, cisplatin/paclitaxel, carboplatin/paclitaxel, or cisplatin/paclitaxel/bevacizumab. These patients are also appropriate candidates for clinical trials.
- Biomarker-directed systemic therapy may be considered for those with disease progression on or after chemotherapy and may include pembrolizumab (for tumor mutational burden high, PD-L1 positive, microsatellite instability high, or mismatch repair-deficient tumors), nivolumab (for HPV-related advanced or recurrent/metastatic vulvar cancer), or larotrectinib or entrectinib (for *NTRK* gene fusion-positive tumors).
- If recurrence is confined locally to the vulva (and LNs are clinically negative), radical excision and unilateral or bilateral inguinofemoral LND (if not done prior) may be employed. This should be followed by RT ± concurrent chemotherapy if LNs are found to be surgically positive or surgical margins are positive.
- Patients with recurrence in groin LNs who have not undergone prior RT can undergo resection of positive LNs ± inguinofemoral LND followed by RT ± concurrent chemotherapy.

VERRUCOUS CARCINOMA

- Variant of SCC with a distinctive cauliflower-like appearance.
- Very rare and often confused with condyloma acuminatum because of its exophytic growth.
- Locally destructive with slow growth rate and rare metastases.
- Associated with HPV type 6.

- Mainstay of treatment is surgical excision. LN dissection is of questionable value unless LNs are obviously involved. RT is contraindicated as it is thought to induce anaplastic transformation resulting in more aggressive disease with an increased likelihood of metastases.
- Recurrences are treated surgically.

PAGET DISEASE

- The vulva is one of the most common extramammary sites of Paget disease.
- Symptoms include pruritus, tenderness, or vulvar lesions (ie, "red velvet," hyperemic, well-demarcated, thickened lesions with areas of induration and excoriation).
- Although it is histologically a preinvasive disease, it should be treated with simple partial vulvectomy with large margins (2 cm is preferred).
- 12% to 58% of patients will have a local recurrence despite negative surgical margins, likely due to microscopic extension of the disease beyond the clinically visible margins and the multifocal nature of the disease.
- Annual surveillance and follow-up are recommended given the high risk for recurrence and increased risk for noncontiguous carcinoma. Paget disease is associated with an underlying invasive adenocarcinoma in up to 25% of patients.

MALIGNANT MELANOMA

- Malignant melanoma of the vulva is a rare tumor (representing <1% of all melanoma cases and 2%-10% of primary vulvar neoplasms).
- Most melanomas are located on the labia minora and clitoris.
- Patients will often present with pruritus, vaginal bleeding, vaginal discharge, dyspareunia, or a mass.

- Staging of vulvar melanoma is the same as for cutaneous melanoma.
- Prognosis depends on the size of lesion, depth of invasion, and stage of disease. Most patients with vulvar melanoma will eventually develop distant metastatic disease regardless of the primary surgical procedure performed; therefore, patient preferences and quality-of-life should guide the extent of surgical management.
- Suggested therapy is simple partial vulvectomy for women without evidence of distant metastases. Radical vulvectomy is typically reserved for large tumors to obtain local disease control.
- Melanomas <1 mm thick should be treated with 1 cm skin margins. This margin should increase to 2 cm for thicker melanomas.
- The role of regional LN evaluation remains unclear. SLNB may be feasible in some women, while regional LND has been found to provide prognostic information without conferring any survival advantage.

BARTHOLIN GLAND CARCINOMA

- Bartholin gland carcinomas are extremely rare, accounting for 0.1% to 5% of all vulvar malignancies.
- Most affected patients have no prior history of benign Bartholin gland disorders. Primarily affects postmenopausal women in their 60s.
- Diagnosis is often delayed given the location of the Bartholin gland deep within the vulva. Most patients will present with a painless vulvar mass (solid, cystic, or abscessed). Solid areas or fixation to the surrounding tissue increases suspicion for malignancy.
- Any enlargement of the Bartholin gland area in a postmenopausal woman requires evaluation to rule out malignancy.

- Therapy includes radical vulvectomy with bilateral inguinal and pelvic LND. Less radical excisions may be effective; however, surgical margins are often involved given close proximity to the anorectum and pubic arch.
- Primary chemoradiotherapy is another therapeutic option that may obviate the need for surgery and spare the function of adjacent structures.
- Metastatic disease is common given the rich vascular and lymphatic network in this region.

Basal Cell Carcinoma

- Basal cell carcinomas of the vulva are locally aggressive but rarely metastasize.
- Radical local excision without LND is typically sufficient treatment as with primary tumors seen in other sites.

Suggested Readings

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21

Sarcomas and Malignancies of the Bone

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EPIDEMIOLOGY

Sarcomas are tumors of mesenchymal tissues and represent about 1% of adult cancers and about 10% of pediatric cancers. Of these sarcomas, about 80% are in the soft tissues and about 20% are in the bone. Most sarcomas are spontaneous and not hereditary.

SOFT-TISSUE SARCOMA

Clinical Presentation

Patients with soft-tissue sarcomas rarely have constitutional symptoms, such as weight loss or fatigue. They may experience pain, paresthesia, or edema from compression by an enlarging tumor. While soft-tissue sarcomas can occur throughout the body, the majority of them are in the extremities. In one series of 4500 sarcomas, 46% were in the groin, thigh, or buttock; 13% in the upper extremity; 18% in the torso; and 13% in the retroperitoneum. Red flags that suggest presence of a soft-tissue sarcoma include the following:

- Mass greater than 5 cm in size
- Rapid growth of the mass
- Mass that is deep to the fascia

- New pain in a previously painless mass
- Recurrence of a mass

Pathology

The World Health Organization classifies soft-tissue sarcomas into over 100 subtypes based on histology with the primary designation of the subtype based on the presumed tissue of origin, such as liposarcoma, synovial sarcoma, peripheral nerve sheath tumors, or angiosarcoma. Pathology should be reviewed by a center that specializes in sarcoma to ensure the proper diagnosis based on morphology, immunohistochemistry, and molecular genetic studies to determine the presence of gene fusions. Soft-tissue sarcomas are characterized by the FNCLCC grading system developed by the French Federation of Cancer Centers Sarcoma Group.

Diagnosis

Patients with a suspected sarcoma of the extremity should have a magnetic resonance imaging (MRI) of the primary site. Masses in the abdomen, pelvis, or retroperitoneum can initially be assessed with a computed tomography (CT) scan. Patients with myxoid liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma should also have a staging CT of the abdomen/pelvis. A CT of the chest should be obtained for staging since this is a frequent site of metastases for soft-tissue sarcoma. Positron emission tomography (PET) scans may help in some situations, such as distinguishing a neurofibroma from a malignant peripheral nerve sheath tumor, but PET scans should not be obtained as a part of routine staging for most subtypes of sarcoma. Imaging of the CNS is not a part of routine staging for most subtypes and should only be obtained if there is a clinical suspicion for metastasis. CNS imaging is recommended for patients with alveolar soft part sarcoma and angiosarcoma. Due to the pattern of metastatic disease, patients with myxoid/round cell liposarcoma should have an MRI of the spine for staging and follow-up.

Tumors should be sampled with image-guided core needle biopsies or an incisional biopsy with a preference for a needle biopsy. The biopsy should be along the axis of a planned resection, if possible. A sentinel lymph node biopsy should be obtained in patients with enlarged nodes by palpation or imaging and sarcomas likely to have lymphatic spread (rhabdomyosarcoma, angiosarcoma, clear cell sarcoma, epithelioid sarcoma, or synovial sarcoma). There are no serum or plasma biomarkers that should be used for diagnosis, assessing treatment response, or monitoring for recurrence of disease.

Treatment

In the absence of concerns for metastatic disease, surgery is the treatment of choice for patients with a primary sarcoma of the extremity or the trunk. Negative surgical margins are associated with improved overall survival, and surgery is usually done with at least a 1-cm margin with consideration for bone or fascia as a margin. For tumors in extremities, involvement of the bone or vasculature or the inability to achieve proper margins necessitates discussion of amputation. Image-guided external beam radiation should be considered either preoperatively or postoperatively for patients with intermediate or high-grade soft-tissue sarcomas. Brachytherapy is an alternative for radiotherapy delivery at the time of surgery either alone or in combination with external beam radiation. Neoadjuvant radiation therapy should also be considered for patients with low-grade tumors if this may improve the likelihood for appropriate surgical margins.

There are conflicting data for the use of neoadjuvant or adjuvant chemotherapy for patients with soft-tissue sarcoma of an extremity. A meta-analysis of 1953 patients enrolled in 18 trials failed to show a survival benefit for treatment with adjuvant doxorubicin, but there was a significant hazard ratio for the combination of doxorubicin and ifosfamide. However, a separate pooled analysis of two large trials of patients treated with adjuvant doxorubicin and ifosfamide was negative. Trials have not identified the patients most likely to

benefit from adjuvant chemotherapy with inconsistent data on the importance of completeness of resection, tumor size, and tumor grade. Ideally, adjuvant chemotherapy would be given in the setting of a clinical trial. Similarly, there is no consensus in the literature on the role of neoadjuvant chemotherapy for most patients with a soft-tissue sarcoma. Even trials enriched for large or high-grade tumors or utilizing more histology-specific chemotherapy failed to show a benefit. As with adjuvant chemotherapy, neoadjuvant chemotherapy should usually be used on a case-by-case basis after multidisciplinary discussion or as part of a clinical trial.

Surgical resection is the only potentially curative treatment for retroperitoneal sarcomas. Surgery for these tumors often requires a multidisciplinary surgical team with planned mobilization, resection, or repair of adjacent organs in order to get appropriate margins with an en bloc resection. Historically, many patients received preoperative radiation therapy due to extrapolation from soft-tissue sarcomas in the extremities. A recent international, randomized, phase III trial showed no difference in recurrence-free survival in patients with radiation followed by surgery compared with surgery alone. This points to a need to change our clinical practice, but also underscores the need to do randomized trials for patients with rare diseases to establish the optimal therapies. Some patients with an unresectable retroperitoneal sarcoma may benefit from systemic chemotherapy with resection in those who respond. In a phase III trial comparing doxorubicin to doxorubicin and ifosfamide in patients with soft-tissue sarcoma, the response rate was 14% and 25%, respectively. Patients should receive the combination of doxorubicin and ifosfamide to optimize the likelihood of subsequent resection. There are no data to support the use of adjuvant chemotherapy for patients with an R0 or R1 resection of a retroperitoneal sarcoma.

There is a lack of specific therapies for most histologies for most patients with metastatic soft-tissue sarcoma. Unfortunately, most of the clinical trials for the therapies approved for treatment of patients with sarcoma have not investigated individual subtypes. In recent

years, this has improved and there are now chemotherapy regimens for patients with angiosarcoma, solitary fibrous tumor, tenosynovial giant cell tumor, epithelioid sarcoma, alveolar soft part sarcoma, and PEComa. The initial treatment for most patients is doxorubicin-based therapy. Clinical trials should always be considered for patients with metastatic soft-tissue sarcoma. Some representative chemotherapy regimens are listed in Table 21.1. It is also important to consider next-generation sequencing to identify targets for therapy, such as ALK mutations or NTRK fusions, and to define microsatellite stability if the patient is a candidate for a checkpoint inhibitor.

TABLE 21.1

Chemotherapy Regimens for Patients With Metastatic Soft-Tissue Sarcoma

Chemotherapy	Indication
AIM (doxorubicin, ifosfamide, mesna)	Preferred initial regimen for most soft-tissue sarcoma with a nonspecific histology
Histology-specific considerations	
Gemcitabine/docetaxel	Consider as initial therapy for leiomyosarcoma
Paclitaxel	Angiosarcoma
Pazopanib	Nonlipogenic sarcomas
Trabectedin	Second-line therapy for liposarcoma or leiomyosarcoma
Eribulin	Second-line therapy for liposarcoma
Sunitinib	Initial therapy for alveolar soft part sarcoma or malignant solitary fibrous tumor
Sirolimus	Initial therapy for perivascular epithelioid cell differentiation (PEComa)
Palbociclib	Well-differentiated/dedifferentiated liposarcoma
Tazemetostat	Epithelioid sarcoma
Pexidartinib	Tenosynovial giant cell tumor

RHABDOMYOSARCOMA

Clinical Presentation

Rhabdomyosarcoma is the most common soft-tissue tumor in children, accounting for about half of soft-tissue sarcomas in this population; however, these are still rare with an incidence of about 350 new cases in the United States per year. Only 2% to 5% of these cases of rhabdomyosarcoma occur in adults, most often as a head and neck tumor.

As with other soft-tissue sarcomas, patients with rhabdomyosarcoma may be asymptomatic or they may have signs and symptoms related to the site of the disease (Table 21.2).

TABLE 21.2

Most Common Sites of Rhabdomyosarcoma, Frequency, and Clinical Presentation

Site	Frequency (%)	Presentation/Symptoms
Head and neck	35-40	Proptosis (orbit), discharge, painless mass
Genitourinary	25	Hematuria, urinary obstruction, vaginal discharge
Extremities	20	Painless mass with erythema of overlying skin

A prognostic stratification has been developed based on stage, clinical group, site of disease, size of tumor, age, histology, presence of metastatic disease, and involvement of lymph nodes. Patients with an excellent prognosis based on this stratification have a >85% event-free survival. Patients with a very good prognosis and good prognosis have a 70% to 85% and 50% to 50% event-free survival, respectively. A poor prognosis is associated with a <30% event-free survival.

Factors associated with poorer prognosis in patients with a relapse of rhabdomyosarcoma include the following:

- Metastatic disease
- Prior alkylating agents and radiation therapy
- Alveolar histology
- Shorter time to relapse
- Higher stage/clinical group at diagnosis

Pathology

Rhabdomyosarcoma is a tumor of mesenchymal origin that is characterized by myogenic differentiation. Morphologically, rhabdomyosarcoma resembles other tumors, such as lymphoma, mesenchymal chondrosarcoma, and Ewing family sarcomas, making it important that the pathology be reviewed at a center with expertise in sarcoma. Rhabdomyosarcoma will usually stain for actin, myosin, desmin, myoglobin, and MyoD. There are pleomorphic and nonpleomorphic rhabdomyosarcomas.

Among nonpleomorphic rhabdomyosarcoma, 80% of patients have an embryonal subtype and about 15% of patients have an alveolar subtype. The embryonal subtype is characterized by 11p15.5 loss of heterogeneity and hyperdiploid DNA. The alveolar subtype is characterized by PAX3/FKHR t(2;13)(q35;q14) and PAX3/FKHR t(1;13)(p36;q14) translocations and tetraploid DNA.

Diagnosis

Open biopsy is the preferred approach for tissue diagnosis and should be undertaken at an oncology center that specializes in sarcoma, if possible. This ensures that the biopsy can be optimally evaluated and the initial surgical approach can be determined by the multidisciplinary team responsible for the patient's subsequent treatment. Patients should have an MRI or CT of the primary site of disease and a PET/CT scan or bone scan to assess for metastatic disease.

Treatment

A pleomorphic rhabdomyosarcoma should be treated like a soft-tissue sarcoma. The diversity of disease sites and surgical and radiotherapy approaches for each primary site underscore the importance of a patient receiving a consult or treatment by a multidisciplinary team accustomed to treating rhabdomyosarcoma. Rhabdomyosarcoma is treated with a combination of chemotherapy, radiation, and surgery due to the poor outcomes with surgery alone

even in cases with a small primary tumor. The intensity and duration of the chemotherapy are determined by the estimated risk of recurrence.

Patients with rhabdomyosarcoma usually have a very long course of systemic treatment. Those with low-risk, intermediate-risk, or high-risk disease receive chemotherapy for 24 to 45 weeks with radiation therapy starting at week 13 (Table 21.3). Most patients also receive radiation therapy starting at week 13 of their therapy, so early consultation with radiation oncology as part of a multidisciplinary team is important.

TABLE 21.3

Chemotherapy Regimens for Patients With Newly Diagnosed Rhabdomyosarcoma

Prognosis Group	Regimen
Low risk (excellent prognosis)	VA for 15 cycles OR VAC/VA for 8 cycles
Low risk (very good prognosis)	VAC for 15 cycles
Intermediate risk (good prognosis)	VAC for 14 cycles OR VAC/VI for 14 cycles
High risk (poor prognosis)	VAC for 14 cycles

VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, and cyclophosphamide; VI vincristine and irinotecan.

OSTEOSARCOMA

Osteosarcoma, a primary malignancy of the bone, represents 1% of all cases of cancer diagnosed in the United States annually. This cancer primarily affects adolescents with a peak incidence between ages 13 and 16 years and in adults older than 65 years. It is the most common primary cancer of the bone in children and young adults. While a primary cancer in children and young adults, osteosarcoma

in adults is often secondary to prior radiation or the presence of Paget disease.

Clinical Presentation

In children, osteosarcoma is most common in the metaphysis of long bones. In adults, osteosarcoma is more common in the axial skeleton or at sites of either prior radiation or abnormalities of the bone. Most patients present with localized pain, often with a long period of pain with intermittent severity. Fever, weight loss, and fatigue are rare. Patients often develop a soft-tissue mass that is painful to palpation. Fifteen to twenty percent of patients have metastatic disease at the time of diagnosis.

Diagnosis

The primary differential diagnosis for patients with osteosarcoma is Ewing sarcoma, lymphoma, and metastatic disease. Plain radiographs may show either a lytic or sclerotic lesion or periosteal elevation from tumor penetration of the cortical bone. Workup should include an MRI of the involved bone, a CT of the chest, and a bone scan or PET/CT to assess for metastatic disease. A biopsy is required to confirm the diagnosis. The biopsy should be done carefully with consideration of how it may impact subsequent definitive surgery and either be a surgical or core biopsy.

Pathology

Osteosarcomas are of mesenchymal origin and can differentiate to fibrous tissue, cartilage, or bone. Histologically, osteosarcomas have a sarcomatous stroma with tumor osteoid and bone. There are no pathognomonic translocations or molecular abnormalities that define osteosarcoma. Osteosarcoma can be defined as low grade with intramedullary and surface involvement, periosteal, high-grade intramedullary, or extraskeletal osteosarcoma. Extraskeletal osteosarcomas are soft-tissue sarcomas that do not involve the bone or periosteum, but produce bone, osteoid, or chondroid material.

Treatment

Limb-sparing surgery is the preferred approach due to better function after surgery, and this can be achieved in 70% to 90% of patients with osteosarcoma. Amputation and limb-sparing resection incorporate wide en bloc excision of the tumor with the biopsy site through normal tissue planes, leaving a cuff of normal tissue around the periphery of the tumor. Wide excision with negative margins improves local tumor control. Amputation is primarily for patients where a wide margin is not possible. Reconstruction may involve allografts or customized prosthetic devices.

Patients with low-grade osteosarcoma of the intramedullary or surface of the bone or with periosteal osteosarcoma should undergo wide excision of the tumor with consideration of adjuvant chemotherapy for those with periosteal osteosarcoma (Table 21.4). If pathology from the resection shows a high-grade tumor, patients should receive chemotherapy.

TABLE 21.4
Chemotherapy Options for Patients With Osteosarcoma

First-line chemotherapy (neoadjuvant or adjuvant therapy or metastatic disease)
Doxorubicin and cisplatin
Doxorubicin, cisplatin, and high-dose methotrexate
Doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide
Second-line/Subsequent therapy
Regorafenib
Etoposide and high-dose ifosfamide
Sorafenib

Patients with a high-grade osteosarcoma involving the intramedullary or surface of the bone should receive neoadjuvant chemotherapy. Those with an unresectable tumor after neoadjuvant chemotherapy should receive radiation therapy or additional chemotherapy. Patients with a resectable tumor after the neoadjuvant chemotherapy should have a wide excision. The use of adjuvant therapy is based on the status of the surgical margins and

response to therapy. The presence of >10% viable tumor in the resected tumor is considered a poor response to systemic therapy. Treatment options for patients with positive margins include additional surgery, radiation therapy, and adjuvant chemotherapy. Patients with negative surgical margins should receive adjuvant chemotherapy with the chemotherapy regimen given preoperatively or with a different regimen if there was a poor response.

Patients with metastatic disease at the time of diagnosis should be evaluated for their eligibility for resection or stereotactic radiation of the metastatic lesions prior to starting chemotherapy. Patients with unresectable disease should receive chemotherapy or radiation therapy with reassessment for resectability of the metastatic disease.

Extraosseous osteosarcoma should be treated like a soft-tissue sarcoma.

EWING FAMILY OF TUMORS

The Ewing family of tumors (EFTs) includes Ewing sarcoma of the bone, peripheral primitive neuroectodermal tumors, and extraosseous Ewing sarcoma. These tumors have similar immunohistochemical and histologic features and chromosomal translocations suggesting they are derived from a common cell of origin. The EFT is the second most common primary bone tumor in children and adolescents.

Clinical Presentation

EFTs are most common in the long bones of the extremities and the bones of the pelvis. In a review of nearly 1000 patients with EFT, 54% of patients had disease in the axial skeleton with 42% having disease in the appendicular skeleton. Typical symptoms of EFT is localized pain or swelling that may be present for weeks to months with an increase in intensity over time. Pain may be worse with exercise or at night. Patients may have a mass that is tender to palpation with some localized erythema. Fatigue, weight loss, and

fever can occur, but are rare. Approximately 20% of patients with EFT have overt metastases at diagnosis with metastatic disease more common in patients with tumors in the pelvis. Of the patients with metastatic disease, about 50% have lung metastases and about 40% have multiple bone lesions and diffuse bone marrow involvement. The peak incidence is in those between 10 and 15 years, with 30% of cases in those older than 20 years.

Diagnosis

Patients with EFT should have a history and physical examination, an MRI with contrast of the primary site, a CT of the chest, and a PET/CT or a bone scan to determine the presence of metastatic disease or bone marrow involvement. Patients preferably have an open biopsy for the tissue diagnosis, ideally at an oncology center where the diagnostic material can be optimally assessed and the initial surgical approach can be determined by a multidisciplinary team responsible for the patient's subsequent treatment. Needle biopsy may limit the amount of fresh and frozen tissue for cytogenetic and molecular genetic investigations that are necessary to diagnose an EFT. Patients should have a consultation about fertility, unless past the age of reproductive potential.

Pathology

Morphologically, EFTs are similar to other small round blue cell tumors including lymphoma, small cell osteosarcoma, undifferentiated neuroblastoma, desmoplastic small round cell tumors, and rhabdomyosarcoma. EFT can be diagnosed by the presence of *EWSR1* translocations, the most common being t(11;22)(q24;q12), leading to the *EWSR1-FLI1* gene fusion. Other members of the *ETS* gene family include *ERG*, *ETV1*, *ETV4*, and *FEV*.

Treatment

Many patients with EFT with apparently localized disease at the time of diagnosis have subclinical micrometastases. Patients with

EFT should be treated with a multidisciplinary approach including systemic chemotherapy, surgery, and radiation therapy.

Patients with either localized or metastatic EFT should be treated initially with combination chemotherapy for at least 12 weeks (Table 21.5). Patients should be restaged with MRI and/or CT of the primary site, a CT of the chest, and possibly PET/CT or bone scan to determine treatment response.

TABLE 21.5

Chemotherapy Options for Patients With Ewing Family of Tumors

First-line therapy for neoadjuvant or adjuvant therapy
VDC/IE (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide)
First-line therapy for metastatic disease at diagnosis
VDC/IE
VAI (vincristine, actinomycin D, ifosfamide)
VIDE (vincristine, ifosfamide, doxorubicin, etoposide)
Second-line therapy for relapsed/refractory or metastatic disease
Cyclophosphamide/topotecan
Irinotecan/temozolomide ± vincristine

Patients with stable disease or a treatment response following the initial chemotherapy should undergo wide excision and continue with definitive radiation and chemotherapy or, in some cases, amputation. Patients with positive margins after wide resection should have adjuvant chemotherapy and radiation therapy with adjuvant chemotherapy alone in patients with negative margins. Patients requiring amputation as local therapy should receive adjuvant chemotherapy with radiation therapy if there are positive margins.

Patients with progressive disease after their initial chemotherapy should be evaluated by radiation therapy or surgery for the management of the metastatic site followed by additional chemotherapy.

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CHAPTER 22

Skin Cancers and Melanoma

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INTRODUCTION

The skin is the largest organ of the human body, embryologically derived from the neuroectoderm and the mesoderm, eventually organized into epidermis, dermis, and subcutis.

Cancer of the skin arises from the cell types of structures in all the three layers (Table 22.1).

TABLE 22.1

Cells of Epidermis and Dermis and Respective Tumor Types

Cells of Epidermis	Tumor-Type/Incidence	Cells of Dermis	Tumor-Types
Melanocytes	Melanoma 5%-7%	Fibroblasts	Benign and malignant fibrous tumor
Epidermal basal cells	Basal cell carcinoma 60%	Histiocytes	Histiocytic tumor
Keratinocytes	Squamous cell carcinoma 30%	Mast cells	Mast cell tumor
Merkel cells	Merkel cell tumor 1%-2%	Vasculature	Angioma, angiosarcoma, lymphangioma
Langerhans cells	Histiocytosis X < 1%	Lymphocytes	Non-Hodgkin lymphoma
Appendage cells	Appendageal tumors < 1%	—	—

Direct exposure of the skin to sun's ultraviolet radiation and a wide variety of environmental carcinogens predisposes to genetic damage and increased risk of cancer. Skin cancers are best divided into melanoma and nonmelanoma.

MELANOMA

Melanoma arises from the melanocyte, a neural crest–derived cell that migrates during embryogenesis predominantly to the basal layer of the epidermal skin and less commonly to the other tissues in the body such as mucosa of the upper aerodigestive and the lower genitourinary tract, the meninges, and the ocular choroid, where melanoma is rarely encountered.

Epidemiology

- Melanoma ranks as the fifth and sixth leading type of cancer in US men and women, respectively.
- Incidence is high in young, middle age, and elderly subjects.

- Estimated lifetime risk of developing invasive melanoma in US whites is about 1 in 27 in males and 1 in 40 in women.
- In 2021, about 106,110 new cases of invasive melanoma are expected to be diagnosed in the United States with about 7180 subjects projected to die from it.
- The incidence of melanoma is higher in men than women, Northern than Eastern and Central Europeans, and more than 10 times greater in whites than in blacks.
- Australia has the highest incidence of melanoma in the world, approximately 40 cases compared to 23.6 cases among US whites per 100,000 population per year.
- The rate of rise in melanoma incidence has decreased from 6% a year in the 1970s to 3% a year between 1980 and 2000 and stabilized after that period in younger subjects.
- In white males over the age of 50 years, the incidence continues to climb at the fastest rate.
- The median age at diagnosis and death from melanoma is 63 and 69 years, respectively.
- The percent of cutaneous melanoma deaths is highest among people aged 75 to 84 years.

Etiology

- Ultraviolet rays' exposure is a major risk factor for melanoma development and is related to (Figure 22.1):
    - Intermittent intense exposure

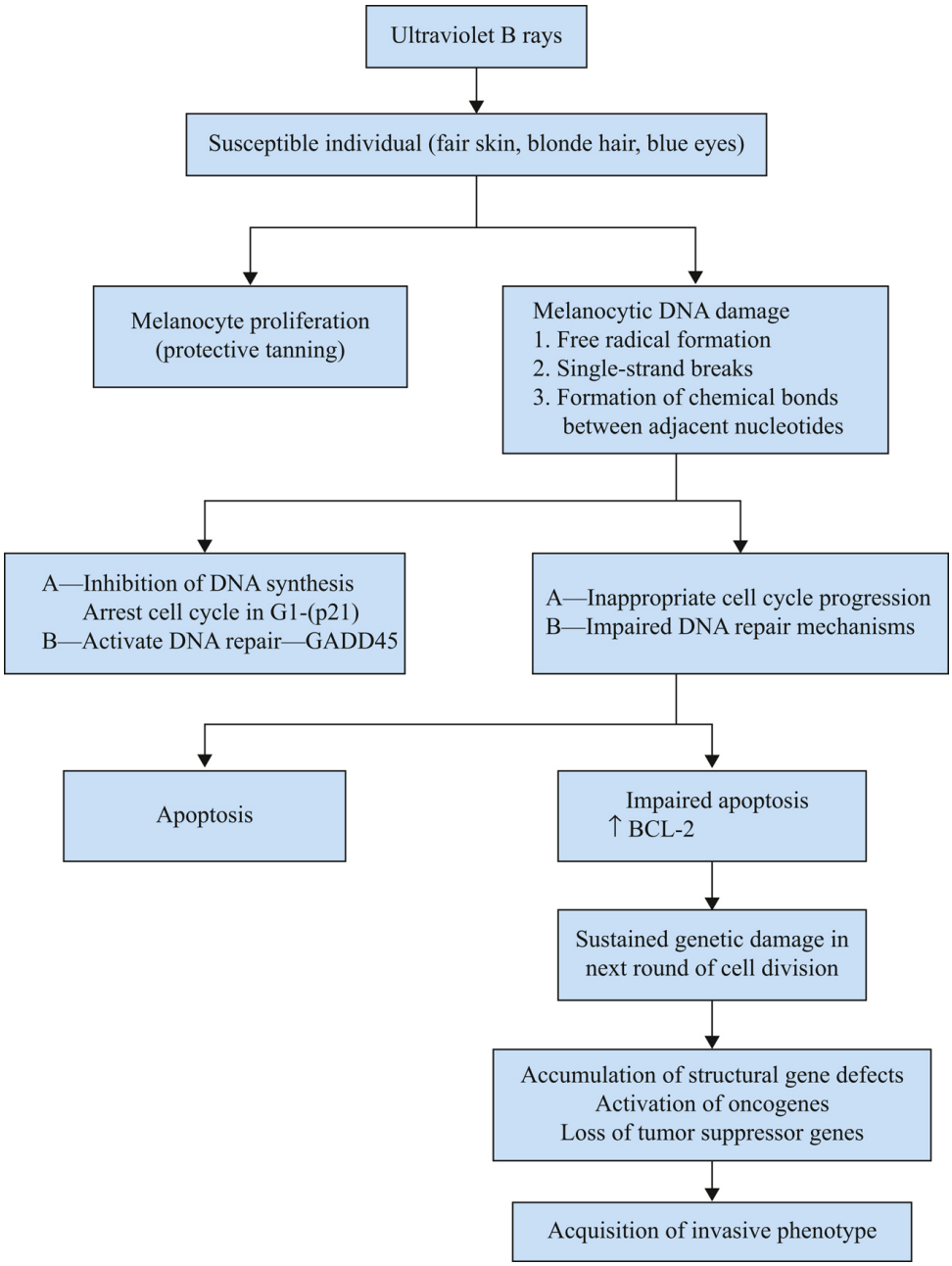

FIGURE 22.1 Model of ultraviolet B light–mediated pathogenesis of cutaneous melanoma.

- Exposure at a young age
- Fair skin, blue eyes, blonde or red hair, propensity for sunburns, and inability to tan

Familial Melanoma

- About 5% to 10% of melanomas are familial among which up to 40% have hereditary basis.
- A tumor suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A) is the most commonly implicated gene located on the short arm of chromosome 9, which could be either mutated or suppressed by epigenetic silencing.
- The protective effect of CDKN2A is mediated by encoded protein $p16^{INK4A}$.

- Other candidate genes in this category include cyclin-dependent kinase 4 (CDK4) and CDKN2A/p14 alternate reading frame CDKN2A/ARF.
- Mutations in the telomere-related genes such as POT1, shelterin complex genes, and TERT have been identified in families with clusters of cutaneous melanoma.
- A high-risk variant of the α-melanocyte–stimulating hormone receptor gene (MC1R) located on chromosome 16q24 and associated with red hair and freckles confers high risk of familial melanoma in families segregating the CDKN2A gene.
- Hereditary basis of melanoma should be suspected in the following circumstances:
  - Individuals with three or more primary cutaneous melanomas
  - Melanoma at a young age and a family history of melanoma (mean age between 30 and 40 years)
  - Individuals with cutaneous melanoma and a family history of at least one invasive melanoma and two or more other diagnoses of melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family
  - Melanoma associated in patients with dysplastic nevi and atypical nevi
- Precursor lesions of melanoma include the following:
  - Dysplastic nevi genetic locus of which resides on short arm of chromosome 1
  - Congenital nevi and acquired melanocytic nevi

Risk Factors for Cutaneous Melanoma

- Xeroderma pigmentosum (caused by mutations in UV damage repair genes)
- Familial atypical mole melanoma syndrome
- Advanced age and immune-suppressed states
- Melanoma in a first-degree relative and previous history of melanoma

Common Chromosomal Abnormalities in Melanoma

- Early chromosomal abnormalities:
  - Loss of 10q and 9p
- Late chromosomal abnormalities:
  - Deletion of 6q, 11q23
  - Loss of terminal part of 1p
  - Duplication of chromosome 7

Clinical Features of Cutaneous Melanoma (ABCDE)

- Most cutaneous melanoma lesions are pigmented and display asymmetry (A); irregular borders (B); variegate colors (C) with shades of brown, black, pink, white, red, or blue have diameter of at least 6 mm (D); and evolve in size, color, nodularity, ulceration, or bleeding (E). Cutaneous melanoma may be painless or, at times, cause itching and discomfort.
- Rarely (<1%) cutaneous melanomas lack pigment (amelanotic) posing diagnostic challenges.
- Cutaneous melanoma is more common in the lower extremities in women, the trunk in men, and the head and neck region in the elderly subjects although it can occur anywhere in the body.

Pathologic Diagnosis of Cutaneous Melanoma

- Morphologically identified melanoma cells express vimentin and are negative for cytokeratin.
- Diagnosis is confirmed by the detection of melanoma-associated antigens such as S-100, premelanosomal protein HMB-45, nerve growth factor receptor, and tyrosinase-related protein 1 (MEL-5) detected by immunohistochemistry.
- In melanoma in situ, the transformed melanocyte is restricted to the basal epidermal layer of the skin.
- Invasive melanoma is defined by its invasion of the dermis quantified by Clark and Breslow.
- Histologic characteristics (microstaging) help prognosticate the tumor and include tumor thickness (Breslow), mitosis, ulceration status, Clark levels, vascular or perineural invasion, lymphocyte infiltration, morphologic variants, and regression.
- Independent variables of melanoma prognosis are Breslow thickness, mitosis, ulceration, and older age (Table 22.2).

TABLE 22.2

Independent Prognostic Factors of Cutaneous Melanoma

Prognostic Factors	Favorable Prognostic Factors	Unfavorable Prognostic Factors
Tumor thickness (Breslow)	Thin tumor (tumor ≤ 1 mm deep)	Thick tumor (tumor > 4 mm deep)
Ulceration	No ulceration of tumor	Tumor ulceration present
Mitosis	No tumor cell mitosis	Tumor mitosis present
Age	Less than 60 y	Sixty years or over
Regional spread to lymph nodes in-transit metastases/satellite or microsatellite lesion seen under microscope	Absent	Present

Clinicohistologic Types of Melanoma

Breslow Thickness

Breslow used an ocular micrometer to measure the vertical depth of penetration of tumor from the granular layer of the epidermis or from the base of the ulcerated melanoma to the deepest identifiable contiguous melanoma cell.

Clark Levels

Clark et al subdivided melanoma invasion of the papillary dermis into a deep group in which tumor cells accumulate at the junction of the papillary and reticular dermis and a superficial group in which tumor cells did not invade deeper layers (Figure 22.2).

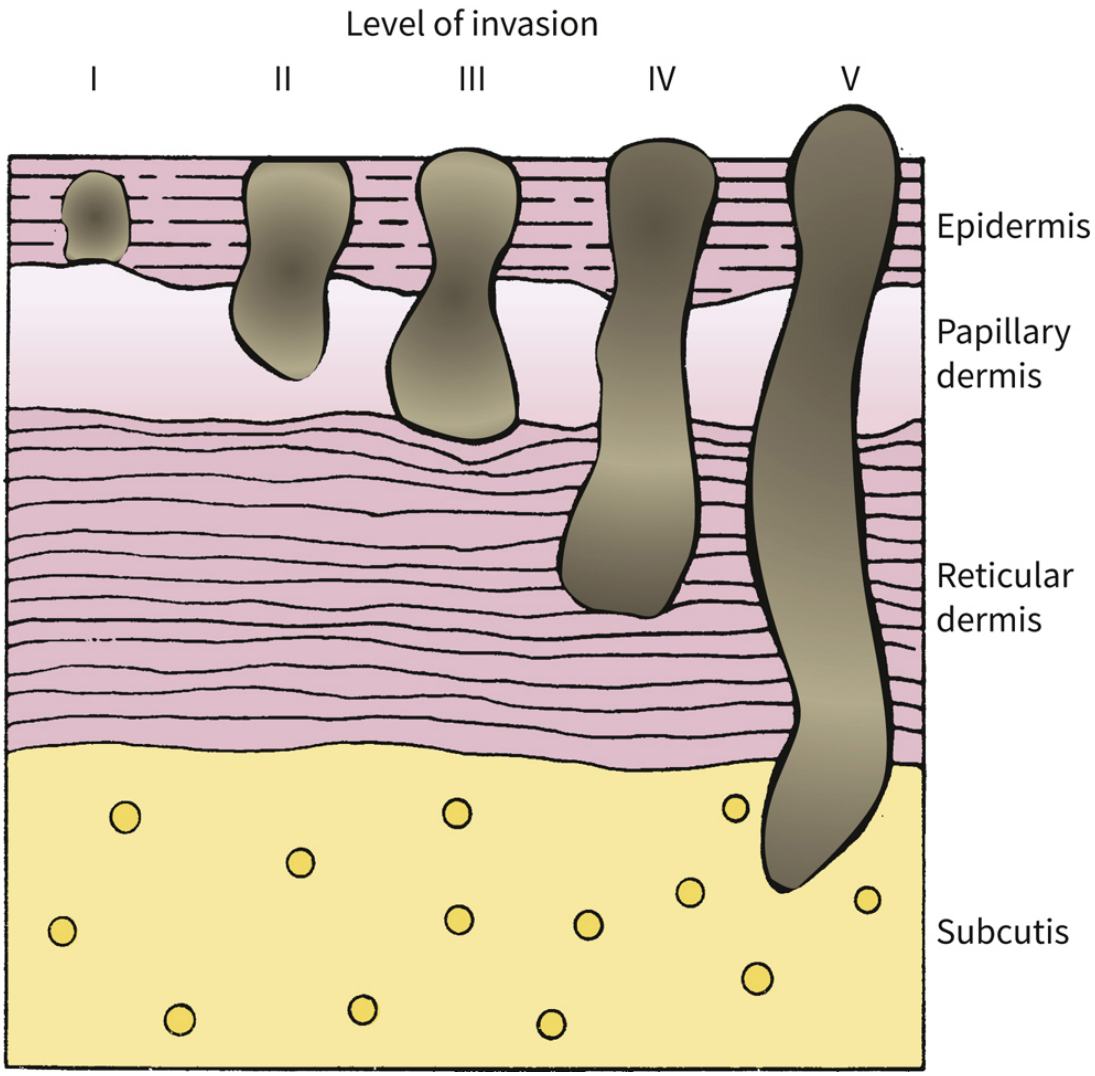

FIGURE 22.2 Schematic diagram of Clark levels of invasion.

Principles of American Joint Committee on Cancer Melanoma Staging

Melanoma stage is based on the information derived from three key categories:

(**TNM**): (**T**) Tumor depth, (**N**) Regional lymph node, (**M**) Distant metastasis—either present or absent.

In the American Joint Committee on Cancer (AJCC) staging, melanoma is divided into five stages:

Stage 0—Melanoma in situ (melanoma limited to epidermis and not invading the dermis)

Stage I—Superficial melanoma without lymph node or distant metastases

- IA (T1a, N0, M0) T1a, <0.8 mm deep without ulcer

- IB—(T1b, N0, M0) T1b, <0.8 mm deep with ulcer or 0.8 to 1 mm with or without ulcer or
  (T2a, N0, M0) T2a, 1-2 mm deep without ulcer

Stage II—Deeper melanoma without lymph node or distant metastasis (IIA, IIB, and IIC)

- IIA (T2b or T3a, N0, M) T2b, 1 to 2 mm with ulcer, T3a, 2 to 4 mm without ulcer
- IIB (T3b or T4a, N0, M0) T3b, 2 to 4 mm with ulcer, T4a > 4 mm without ulcer
- IIC (T4b, N0, M0) T4b > 4 mm with ulcer

Stage III—Melanoma in regional lymph node and/or in-transit/satellite and/or microsatellite metastases

- IIIA (T1a/b-T2a, N1a or N2a, M0) N1a, one occult lymph node, N2a, two to three occult lymph nodes
- IIIB (T0, N1b, N1c, M0) N1b, one occult lymph node, N1c, one satellite, microsatellite or in-transit metastases
- IIIB (T1a/b-T2a, N1b/c or N2b, M0) N2b, two to three lymph nodes, at least one is clinically detected
- IIIB (T2b/T3a, N1a-N2b, M0)
- IIIC (T1a-T3a, N2c, or, N3a/b/c, M0) N2c, one clinically occult or clinically detected lymph node with presence of in-transit metastases, satellite and/or microsatellite metastases
- IIIC (T3b/T4a, any N> or = N1, M0)
- IIIC (T4b, N1a-N2c, M0)
- IIID (T4b, N3a/b/c, M0)

Stage IV, M1a (0 or 1), M1b (0 or 1), M1c (0 or 1), M1d (0 or 1), 0 = normal LDH, 1 = elevated LDH

- M1a distant metastases to skin, soft tissue including muscle, and/or nonregional lymph nodes
- M1b distant metastases to lung with or without M1a site of disease
- M1c distant metastases to non-CNS visceral sites with or without M1a or M1b
- M1d distant metastases to CNS with or without M1a, M1b, or M1c

Sentinel lymph node biopsy (SLNB) is recommended for detection of occult melanoma metastasis in a lymph node when clinical examination is negative.

- Sentinel lymph node is not recommended in a thin, nonulcerated melanoma <0.8 mm since in such a case lymph node metastasis is rare.
- The sensitivity of finding melanoma metastases to the sentinel lymph node either as single cells or in clusters is enhanced by subjecting it for immunohistochemical staining of melanoma-associated antigens.

Prediction of Patient Outcome Based on AJCC Melanoma Staging eighth Edition Cancer Staging Manual (2017) (Figure 22.3)

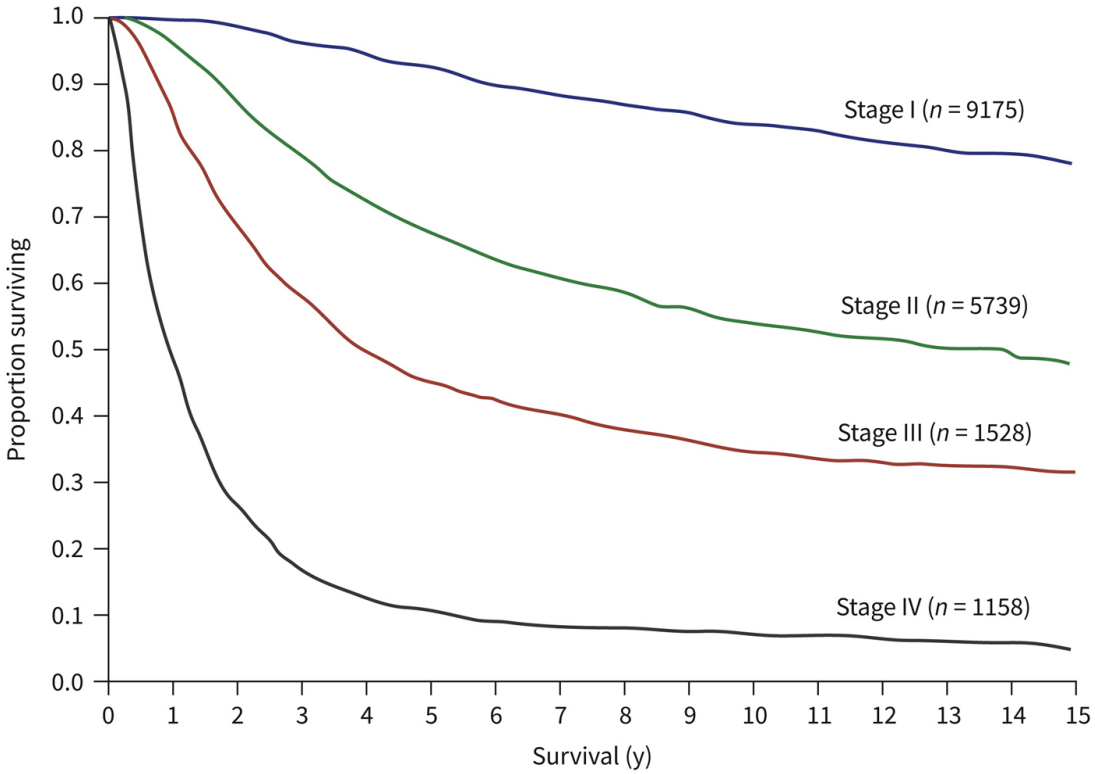

FIGURE 22.3 Relationship between the stage of melanoma and survival.(Reprinted with permission from Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19:3635-3648.)

- Low risk: Stages I and IIA (melanoma-specific mortality less than 15% at 10 years)
- Medium to high risk: Stages IIB, IIC, and III (melanoma-specific mortality between 16% and up to 78%, respectively, at 10 years)
- Poor risk: Stage IV (melanoma-specific mortality more than 80% at 5 years)

Cutaneous Melanoma: Prevention and Early Diagnosis

Public health education measures specific for melanoma include emphasis on spreading awareness of melanoma as a serious cancer, focus on its risk factors such as ultraviolet light exposure and tanning booth use, preventive strategies such as avoiding sun exposure between 10AM and 4PM without sunscreen use (sun avoidance techniques), light clothing, sunscreen use, and early diagnosis by periodic self-skin and total body skin examinations (TBSE).

TBSE performed by a dermatologist provides the opportunity to identify suspicious skin lesions for biopsy and early diagnosis.

- Digital photography helps to track suspicious skin lesions over time in patients with multiple nevi or dysplastic nevus syndrome.
- Dermoscopy (epiluminescence microscopy) improves diagnostic sensitivity and utilizes either a dermatoscope or 10 × ocular scope (microscope ocular eyepiece held upside down) to visualize structures and patterns in pigmented skin lesions not discernible to the eye.

Cutaneous Melanoma Management

An algorithm for melanoma management is presented in Figure 22.4.

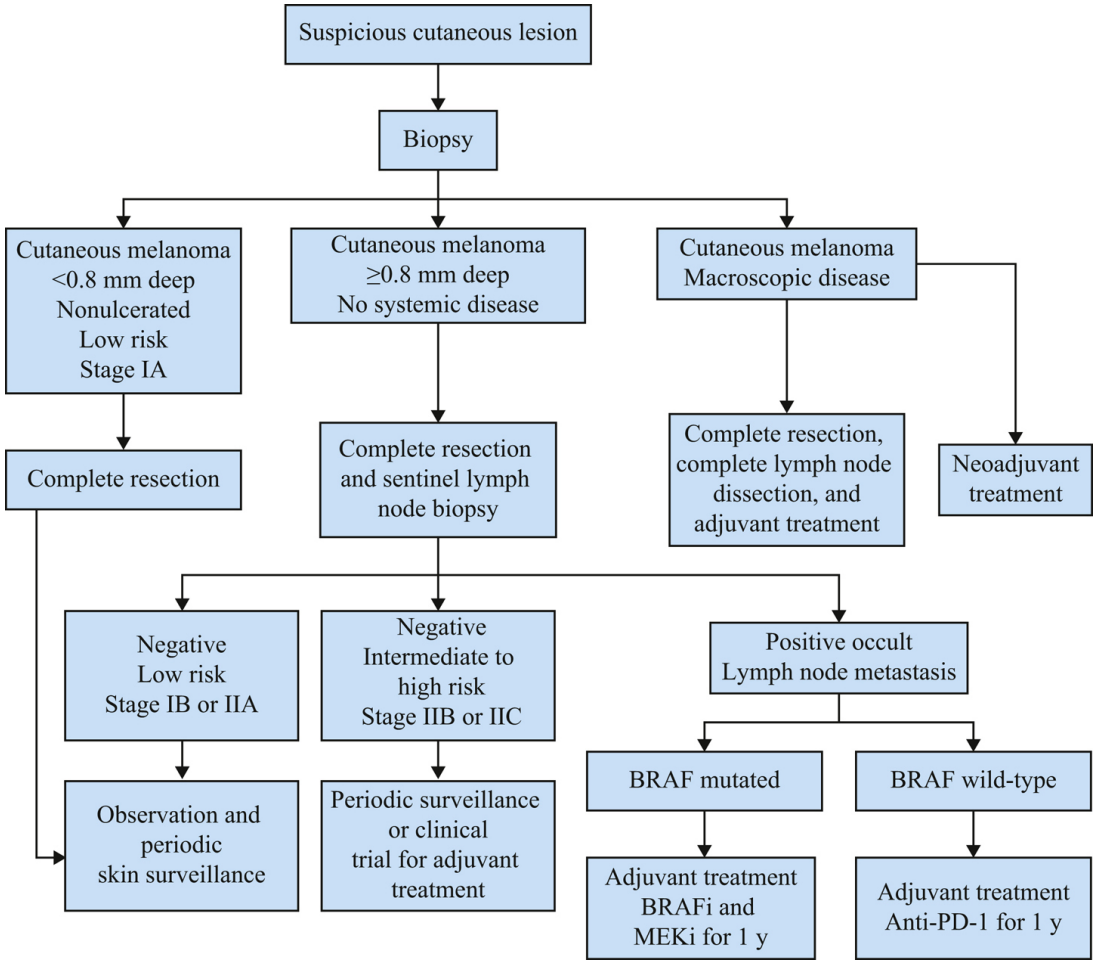

FIGURE 22.4 Algorithm for cutaneous melanoma management.

Primary Surgical Treatment: Principles

- Complete excision of primary melanoma confirmed by comprehensive histologic examination of the entire excised specimen and assessment of melanoma metastasis to the regional lymph node (except in stage IA where the risk of melanoma spread to regional lymph node is low) forms the basis of surgical treatment.

- Recommendations for extent of surgical margins vary by depth of cutaneous melanoma (Table 22.3), but risk of local recurrence relates to completeness rather than extent of surgical margins.

TABLE 22.3

Recommended Margin of Surgical Excision Based Upon Pathologic Stage of Primary Cutaneous Melanoma

Pathologic Stage	Tumor Thickness	Margin of Excision
pTis	Melanoma in situ	5 mm
pT1 and pT2	0-2 mm	1 cm
pT3	2-4 mm	1-2 cm
pT4	>4 mm	2-3 cm

Assessment of the Regional Lymph Node Metastasis and Lymph Node Dissection: Principle

- The risk of regional lymph node metastasis is directly proportional to the depth of invasion, tumor ulceration, and mitosis, all reflecting tumor biology.

Historically, complete excision of primary cutaneous melanoma was followed with elective, therapeutic, or delayed complete lymph node dissection (CLND) from the respective basin.

- Elective CLND consists of removal of all the lymph nodes from the respective basin grounded on a belief that metastasis is present, without positive identification of a sentinel lymph node.
  - Elective CLND procedure carried significant morbidity of the procedure to the patient in the clinical circumstances where cutaneous melanoma did not spread to regional lymph nodes and is no longer recommended.
  - In head and neck melanoma where the site of lymphatic drainage is unpredictable, elective lymph node dissection may be considered on a case-by-case basis.
- Therapeutic CLND is performed if a clinically enlarged lymph node is considered or proven to harbor metastasis.
- Delayed CLND is performed when initially nonpalpable regional lymph nodes become enlarged over a follow-up period due to the delayed onset of lymph node metastasis. With the widespread adoption of SLNB, this scenario is much less common.

Lymphoscintigraphy and SLNB

- Lymphoscintigraphy is a tool to identify SLNB in the corresponding lymph node basin for the detection of occult regional lymph node metastasis.
- Characteristics of a sentinel lymph node:
  - First lymph node in the basin at the greatest risk of metastasis.
  - Easily accessible and identified by lymphoscintigraphy.
  - Pathologic evaluation of this node helps to detect occult melanoma metastasis.
  - Success rate of SLNB is 95% in experienced hands with less than 5% false-negative rates.
- Surgical approach to obtain a SLNB: lymphoscintigraphy
  - Preoperative lymphoscintigraphy uses a vital blue dye injected around the cutaneous melanoma. The blue dye enters the dermal lymphatics to reach the sentinel lymph node/nodes and provides a road map of the

lymph node basin.
    - Intraoperative lymphoscintigraphy uses a radiocolloid injection around the primary tumor that also uses the same dermal lymphatics to reach the sentinel lymph node/nodes. A handheld device tracks the sentinel lymph node by detecting radioactivity.
    - The combination of the radioactivity (hot lymph node) and the vital blue dye helps the surgeon to identify the sentinel lymph node in the respective nodal basin in 95% of cases.
- Implications of SLNB results:
    - Status of the SLNB for melanoma metastases provides important prognostic information. Only those patients with melanoma metastasis to the sentinel lymph node were selected to undergo CLND eliminating the practice of elective CLND.
    - A negative SLNB saves the patient the morbidity of CLND.
    - SLNB-guided information about the extent of lymph node metastasis in nonsentinel lymph nodes in the basin obtained by CLND helped in prognostication of primary melanoma and reduces the risk of recurrence in the lymph node basin. Its impact on overall survival (OS) was not clear.

The Multicenter Selective Lymphadenectomy Trial I (MSLT-1) was designed to find if SLNB followed by early CLND would have an OS benefit in patients with intermediate thickness melanoma (1.2-3.5 mm depth).

- The results showed improved 5-year disease-free survival (DFS) (83.2% vs 53.4%) in subjects assigned to lymphoscintigraphy whose SLNB was negative for metastasis compared to those whose sentinel lymph nodes were positive.
- A subgroup analysis was suggestive of the improved melanoma-specific 5-year survival for patients with node-positive microscopic disease who underwent immediate lymph node dissection compared to the observation arm who underwent lymph node dissection upon macroscopic lymph node metastasis (72.3% vs 52.4%), but this did not translate into an overall melanoma-specific survival (MSS) benefit in the intention-to-treat population.

The changing practice of CLND following detection of a positive sentinel lymph node: Evidence-based practice from emerging new data.

- Is CLND necessary in all sentinel lymph node positive tumors?
- Could tumor bulk in sentinel lymph node determine need for CLND?
- Multicenter Selective Lymphadenectomy Trial-2 (MSLT-2) has evaluated the therapeutic benefit of CLND after positive SLNB. Patients with positive SLNB were randomized to either CLND or nodal observation by periodic ultrasound. The results indicate that at 3 years of follow-up, there was no significant difference in the rate of MSS between the CLND group and the observation group in the per-protocol analysis (86% ± 1.3% and 86% ± 1.2%, respectively: $P = .42$ by the log-rank test). In addition, there was no significant between-group difference detected in distal metastases-free survival (DMFS) (HR, 1.10, 95% CI 0.92-1.31; $P = .31$).
- Only advantage noted was the difference in rate of disease control in the regional nodes at 3 years (92% ± 1.0% in the CLND group vs 77% ± 1.5% in the observation group, $P < .001$).
- Subgroup analysis including an analysis based on sentinel-node tumor burden did not reveal any subgroups that derived significant MSS benefit from CLND.
- The German DECOG study group randomized cutaneous melanoma patients with a positive sentinel lymph node to either CLND or nodal observation. In a final analysis with 72 months of median follow-up, no significant treatment-related differences

were seen in the 5-year DMFS between the observation and CLND arms (67.6% vs 64.9%, respectively: HR, 1.08; P = .87). The 5-year relapse-free survival (RFS) and OS also showed no difference (HR, 1.01 and 0.99, respectively). Grade 3 and 4 adverse effects occurred in 32 patients (13%) in the CLND arm; lymphedema (n = 20) and delayed wound healing (n = 5) were most common and no serious adverse events were noted.

- The Sunbelt Melanoma Trial reported no difference in OS after CLND compared to observation after positive SLNB (although the study was underpowered and this was not to be the main objective of the study).
- Additionally, a large meta-analysis of CLND in sentinel lymph node-positive melanoma showed no benefit of CLND compared to observation on OS and RFS using a random-effects model.

Adjuvant Treatment of Melanoma in Patients at Risk of Recurrence after Surgery (Table 22.4)

TABLE 22.4

FDA-Approved Adjuvant Immune Therapy and Anti-BRAF and Anti-MEK Agents for BRAF V600E or V600K Mutated Cutaneous Melanoma

Treatment Agent	Treatment Regimen and Duration	FDA Approval
Nivolumab (anti–PD-1 agent)	240 mg administered as an IV infusion over 60 min every 2 wk until disease recurrence or unacceptable toxicity, for a maximum of 1 y	December 2017
Pembrolizumab (anti–PD-1 antibody)	200 mg administered as an IV infusion over 30 min every 3 wk until disease recurrence or unacceptable toxicity, for a maximum of 1 y	February 2019
Ipilimumab [a] (anti–CTLA-4 antibody)	Induction phase: Ipilimumab 10 mg/kg IV every 3 wk for four doses followed by Maintenance phase: Ipilimumab 10 mg/kg every 12 wk for up to 3 y	October 2015
High-dose interferon alfa-2b [a]	Induction phase: IFN-α-2b, 20 million units/m^2/dose IV, 5 d/wk × 4 wk (total dose/wk, 100 million units/m^2) followed by Maintenance phase: IFN-α-2b, 10 million units/m^2 SC, three times/wk for 48 wk (total dose/wk, 30 million units/m^2) vs observation	1995
Pegylated interferon alfa-2b [a]	Induction phase: Pegylated interferon alfa-2b, 6 μg/kg/wk SC for 8 wk followed by 3 μg/kg/wk SC for 5 y	2011
Debrafenib plus Trametinib	Debrafenib 150 mg by mouth twice a day plus Trametinib 2 mg by mouth once a day daily until disease recurrence or unacceptable toxicity, for up to 1 y	April 2018

[a]Not preferred treatment due to higher toxicity and less efficacy compared to anti–PD-1 agents Nivolumab and Pembrolizumab.

ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; IV, intravenous; SC, subcutaneous, wk, week.

Historically, adjuvant treatment of melanoma is recommended in stage IIB, IIC, and III patients since follow-up studies following surgical treatment of cutaneous melanoma showed a high rate of relapse and melanoma-specific mortality (35%-75%) in these stage groups.

- Interferon alpha (IFNα)-2b has antiproliferative and immunomodulatory effects and was tested as adjuvant therapy of cutaneous melanoma after surgery in stage IIB, IIC, and III melanoma.
- Large randomized clinical trials showed consistent RFS and DFS benefits, but its impact upon OS has been variable and less consistent.
- Besides toxicities such as flu-like symptoms, chronic fatigue, nausea, bone marrow suppression, liver toxicity, depression caused adverse effects on quality of life.
- Although approved by the Food and Drug Administration (FDA) in 1995 in the adjuvant setting, interferon is not used due to unfavorable risk-benefit ratio compared to the newer approved adjuvant therapies.
- Pegylation of interferon results in increased time the drug remains in blood, reducing frequency of dosing and side effects. A large study designed by the European Organization for Research and Treatment of Cancer (EORTC) 18991 examined benefit of Peginterferon in the adjuvant setting for stage III melanoma.
- Findings indicated persistence of RFS benefit when compared to observation. Peginterferon alfa-2b was FDA approved as adjuvant therapy in 2011.

New-generation adjuvant therapy of melanoma: Immune checkpoint inhibitor agents and anti-BRAF plus anti-MEK agents in BRAF-mutated melanoma.

Ipilimumab (anti–CTLA-4 antibody) as an adjuvant therapy of melanoma: Principles

Based on the survival benefit conferred by Ipilimumab in about 25% of patients with metastatic melanoma, it was investigated as a candidate in the adjuvant setting for stage III sentinel lymph node-positive high-risk cutaneous melanoma patients following CLND (patients with lymph node metastases less than or equal to 1 mm or in-transit metastases were excluded). The results were as follows:

- Ipilimumab administered intravenously at a dose of 10 mg/kg body weight every 3 weeks for four doses (induction phase) followed by the same dose given every 12 weeks for up to 3 years (maintenance phase) improved RFS and OS compared to placebo.
- At 5 years of follow-up, Ipilimumab treatment-led RFS was translated into DMFS and OS compared to placebo. The OS rate at 5 years was 65.4% in the Ipilimumab group, as compared with 54.4% in the placebo group (HR for death from any cause, 0.72, P = .001). At a median follow-up of 6.9 years, OS, RFS, and DMFS advantage was preserved in patients who received high-dose Ipilimumab compared to the placebo.
- Ipilimumab-induced survival advantage occurred in all subgroups of stage III patients including those with microscopic as well as macroscopic recurrences and irrespective of ulceration of the primary melanoma. Ipilimumab was FDA approved for stage III melanoma in 2016 (see Table 22.4).
- Serious autoimmune side effects referred to as immune-related adverse events (irAE) of Ipilimumab led to discontinuation of treatment in 52% of patients (39% patients in induction phase and 13% during maintenance phase).
- Common irAE involved gastrointestinal system (16%), liver (11%), and endocrine organs (8%).
- Five patients (1%) died of severe irAE including three from colitis two of whom had perforation, one patient of myocarditis and one developed Guillain-Barré syndrome

and multiorgan failure.
- Anti–PD-1 agent as adjuvant treatment of high-risk cutaneous melanoma:

In a randomized, double-blind phase III trial of the EORTC Melanoma Group, patients with completely resected stage IIIA (>1 mm focus of metastases in the sentinel lymph node), IIIB/C melanoma were randomly assigned to receive 200 mg Pembrolizumab (514 patients) or placebo (505 patients) intravenously every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence or unacceptable toxic effects occurred.

A regional CLND was performed within 13 weeks before the start of adjuvant treatment. Patients were stratified by PD-L1 expression and by BRAF status. At relapse, patients were unblinded and allowed to cross-over to the active treatment arm if on placebo.

- At a median follow-up of 15 months, Pembrolizumab was associated with significantly longer RFS compared to placebo in the overall intention-to-treat population in all stratified groups.
- Analysis of these data at 3-year median follow-up indicates increased RFS benefit of 20% compared to placebo with an HR of 0.56 (3-year RFS rate, 63.7% vs 44.1 with Pembrolizumab vs placebo, respectively). With longer follow-up of these data, it is projected to result in OS and DMFS in patients across all stratified groups.
- Based on the results of this study, Pembrolizumab was FDA approved as adjuvant treatment for stage III melanoma in February 2019.

Ipilimumab versus Nivolumab as adjuvant therapy of cutaneous melanoma: In a phase III study of high-risk cutaneous melanoma (stage IIIB, IIIC, and resected stage IV), patients were randomized to receive Nivolumab or Ipilimumab for 1 year (Checkmate 238 study). Patients with stage III melanoma underwent CLND of the respective regional lymph node basin before starting adjuvant treatment.

- At a median follow-up of 12 months, the RFS was 70.5% in the Nivolumab group versus 60.8% in the Ipilimumab group. At 24 months, RFS was 62.6% in the Nivolumab group versus 50.2% in the Ipilimumab arm.
- This benefit was found regardless of stage, PD-L1 status, or BRAF status. Grade 3 or 4 autoimmune side effects were much less in the Nivolumab group compared to Ipilimumab group (14.4% vs 45.9%, respectively).
- Based on the results of this study, FDA approved Nivolumab as adjuvant treatment of high-risk cutaneous melanoma (stage IIIB, IIIC, and resected stage IV) following CLND in December 2017.
- Ipilimumab is no longer recommended in the adjuvant setting given the superiority of anti–PD-1 agents Nivolumab or Pembrolizumab and their better safety profile.

Anti-BRAF plus anti-MEK as adjuvant therapy of BRAF-mutated cutaneous melanoma patients

- COMBI-AD is a double-blind, placebo-controlled phase III trial that randomly assigned 870 patients with completely resected stage III melanoma with BRAF V600E or V600 K mutations to receive oral dabrafenib at 150 mg twice daily plus Trametinib

at a dose of 2 mg once daily (combination therapy, 438 patients) or two matched placebo tablets (432 patients) for 12 months.

- Patients with stage IIIA cutaneous melanoma required >1 mm focus of metastases in the lymph node to be eligible for the study. The primary endpoint is RFS. Secondary endpoints included OS, DMFS, freedom from relapse, and safety.
- After a median follow-up of 2.8 years, estimated 3-year rate of RFS is 58% in combination-therapy group and 39% in the placebo group (HR for relapse or death is 0.47; 95% confidence interval [CI], 0.39-0.58; $P < .001$). The 3-year OS rate was 86% in the combination group and 77% in the placebo group (HR for death 0.57; 95% CI, 0.42-0.79; $P = .0006$). Rate of DMFS and freedom from relapse were also higher in the combination group than in the placebo group.
- The safety profile of dabrafenib plus trametinib was consistent with that observed in combination in patients with metastatic melanoma.
- Based on the results of this study, FDA approved dabrafenib plus trametinib as adjuvant treatment of patients with BRAF V600E or V600K-positive stage III cutaneous melanoma following complete resection in April 2018.

Clinically effective adjuvant therapy is now available in high-risk stage III melanoma patients and include anti–PD-1 agents and anti-BRAF plus anti-MEK agents in BRAF-mutated melanoma. However, high-risk stage II melanoma patients do not have clinically effective FDA-approved treatment. Clinical trials are now ongoing to test clinical benefit of anti–PD-1 agents and anti-BRAF plus anti-MEK agents for high-risk stage II patients (IIB and IIC melanoma).

- BRIM-8 plans to randomize 725 patients with stage IIC and III BRAF V600 mutation-positive melanoma to adjuvant vemurafenib versus placebo. The primary endpoint is DFS.
- An additional adjuvant trial, KEYNOTE 716, is currently enrolling patients in a trial of stage IIB and IIC disease with resected melanoma. Diseases are staged according to the AJCC eighth edition, and all patients must have a negative SLNB. The trial randomly assigns patients to receive Pembrolizumab versus placebo for 1 year. The primary outcome is RFS.

Neoadjuvant Treatment of Melanoma: Principles

- Locally advanced cutaneous melanoma patients have high risk of recurrences following surgery. Although adjuvant therapy has reduced risk of recurrences, patients with high-risk stage III patients (stage IIIB, IIIC, and IIID) as well as surgically resected stage IV melanoma patients still remain at high risk of recurrences and poor outcome following adjuvant treatment.
- This selected melanoma patient group remain ideal candidates for neoadjuvant treatment approaches that are based on rapid and effective reduction in local tumor volume to facilitate later surgery and reduce or eliminate systemic micrometastases, thus improving long-term survival. This is particularly true since combined immune checkpoint inhibitor and mutated BRAF-directed targeted therapy confer high and rapid responses suitable for neoadjuvant approach.

- The availability of tissue pre and post neoadjuvant therapy provides valuable information about genetic and immune biomarkers that are useful to develop strategies for long-term survival. It also provides critical insights into mechanisms of response as well as resistance to treatment and provide opportunities for biomarker discovery for treatment response.
- Potential disadvantages of neoadjuvant treatment approaches include tumor progression both locally or systemically if the surgery is delayed due to initiation of neoadjuvant treatment or to manage severe toxicities resulting from it or if neoadjuvant treatment becomes ineffective.
- Selection of appropriate candidates for neoadjuvant treatment is important and close monitoring of toxicity and tumor response are critical for success of this strategy. Survival endpoints include RFS, event-free survival, DMFS, and OS.
- According to the International Melanoma Neoadjuvant Consortium recommendations, a 6- to 8-week duration of preoperative neoadjuvant therapy is recommended followed by surgery, while some studies have included adding adjuvant therapy component postsurgery for a total duration of treatment of 1 year.
- Preliminary data from a pooled analysis of four trials (two with targeted therapy and two with combined immune therapy) showed that high rates of complete responses could be obtained with either of these regimens and that complete pathologic responses resulted in improved RFS.

Role of Radiation Therapy in Melanoma

Radiation therapy of melanoma may be used in the following clinical scenarios:

- Following surgery of bulky/matted and/or four or more lymph node metastasis or extracapsular spread of melanoma in a lymph node.
- Local recurrence of melanoma in a previously dissected lymph node basin.
- After surgical resection of desmoplastic melanoma with neurotropism.
- For pain relief from melanoma metastasis to the musculoskeletal region.
- Brain metastasis of melanoma (discussed later).

Isolated Limb Perfusion or Infusion as a Treatment of Melanoma: Principles

To deliver maximally tolerated chemotherapy in patients with locally advanced and metastatic melanoma to a regionally confined tumor area such as a limb while limiting systemic toxicity.

- Isolated limb perfusion (ILP): Involves hyperthermia and oxygenation of the circulation that potentiates the tumoricidal effects of the chemotherapeutic agents such as Melphalan (L-PAM), Thiotepa, Mechlorethamine with or without tumor necrosis factor (TNF)-α, and IFN-γ.
- Isolated limb infusion (ILI): Is a simplified and minimally invasive procedure developed at the Sydney Melanoma Unit intended to obtain the benefits of ILP without major disadvantages. It is a low-flow ILP procedure performed via percutaneous catheters without oxygenation.

Both procedures may help improve the patient's quality of life by controlling the local pain following effective shrinkage of local tumor metastasis that is not possible with surgery or at high risk of recurrence after surgery. It does not provide a survival advantage.

Potential complications of the procedure include ischemia of the limb, peripheral neuropathy, and bone marrow suppression.

Management of Patients With Metastatic Melanoma

The management options for a patient with metastatic melanoma have expanded following the recent FDA approvals of immune-based and targeted therapy (Figure 22.5).

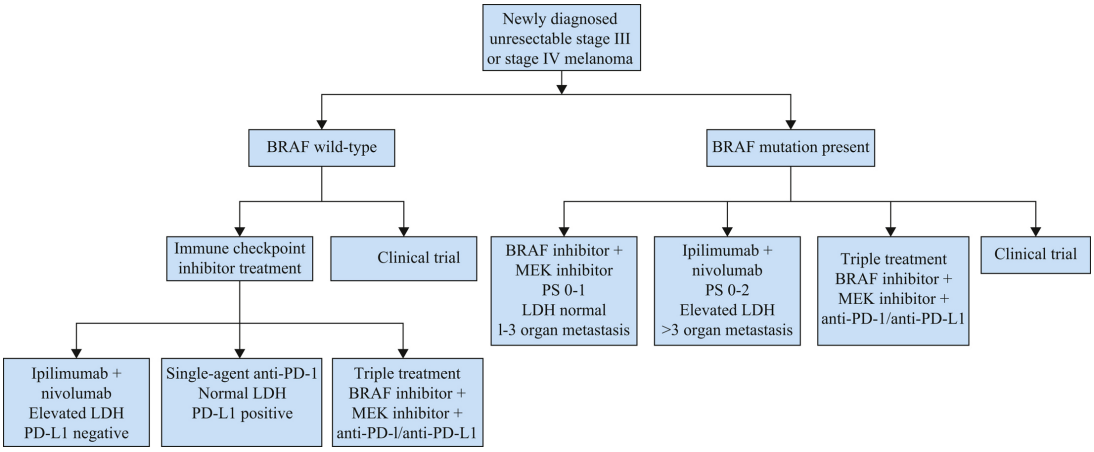

FIGURE 22.5 Algorithm for treatment of newly diagnosed unresectable stage III/IV melanoma.

Surgery has a role in resection of isolated metastasis, while chemotherapy may have a role in palliative treatment of selected patients who have failed upfront therapy.

Immune-Based Therapy of Metastatic Melanoma: Principles

- Melanoma is considered to be an ideal model of an immunogenic tumor attracting T lymphocytes at both the primary and metastatic sites.
- Effector T cells mediate clinically relevant antitumor immune response.
- A number of well-defined melanoma antigens have been identified both at a protein and gene level that evoke an effector T cell (cellular immunity) antimelanoma response (Table 22.5).

TABLE 22.5
Melanoma-Associated Antigens, Peptides, and Presenting MHC Molecules

Melanoma Antigens	Peptides	Presenting MHC Molecules
MAGE-A1 [a]	EADPTGHSY	HLA-A1 and B37
MAGE-A1 [a]	TSCILESLFRAVITK	HLA-DP4
MAGE-A3 [a]	EVDPIGHLY	HLA-A1
NY-ESO-1 [a]	SLLMWITQC	HLA-A2
NY-ESO-1 [a]	MPFATPMEA	HLA-B51

Melanoma Antigens	Peptides	Presenting MHC Molecules
Melan-A/MART-1 [b]	EAAGIGILTV	HLAB35
Melan-A/MART-1 [b]	ILTVILGVL	HLA-A2
Tyrosinase [b]	MLLAVLYCL	HLA-A2
Gp100/pmel17 [b]	KTWGQYWQV	HLA-A2
β-Catenin [c]	SYLDSGIHF	HLA-A24

[a]Shared antigens.

[b]Differentiation antigens.

[c]Mutated antigens.

- Antigen-specific CD8+ cytotoxic T lymphocytes (CTLs) lead the antimelanoma response with critical help from CD4+ helper T cells and antigen-presenting cells (APCs).

Activation of CTLs against melanoma requires two signals: priming and activation

- Signal 1: Priming of CD8+ or CD4+ CTL requires presentation of melanoma antigen (peptide epitope) either by the tumor cell or by the APCs at the MHC class I or MHC class II molecules, respectively, to the T-cell receptor of CD8+ CTL or CD4+ T cells.
- Signal 2: Activation of antigen-primed CD8+ or CD4+ CTL requires costimulatory signaling through binding of its CD28 molecules with costimulatory molecules B7.1 (CD80) and B7.2 (CD86) on the APCs forming a tight synapse between the two cells critical for signal transduction to the T cell nucleus.
- The transcribed genes include those of cytokines and effector molecules necessary for T cell growth, proliferation, and survival as well as tumor killer activity.
- Activated CD8+ CTLs kill tumor cells directly through production of perforins and granzyme and indirectly by the elaboration of secreted cytokines such as TNF-α, IFN-γ, granulocyte-macrophage colony-stimulating factor (GMCSF), and IL-2 all of which help shape the composition of tumor immune microenvironment.

Immune-Based Treatment Strategies of Metastatic Melanoma: Two Approaches

Specific immunity evoked by melanoma vaccines:

- Administration of one or more (monovalent or polyvalent) melanoma antigens as a tumor vaccine either directly or after being pulsed on to monocyte-derived APCs (dendritic cell vaccine) in the subcutis or in the dermis evokes melanoma antigen-specific CTLs.
- Adjuvants are intended to enhance the immune response and are either premixed with vaccine or preapplied to the skin at the site of the vaccine.

Although successful in a mouse model, induction of antimelanoma-specific immunity by vaccine treatment has been unpredictable and not uniformly successful in humans. Also, generation of melanoma-specific T-cell activity did not always correlate with patient responses.

Nonspecific immunity is evoked by immune checkpoint inhibitor agents (Table 22.6) and involves reactivation and proliferation of effector T lymphocytes by the following:

TABLE 22.6

FDA-Approved Systemic Immune Therapy of Metastatic Melanoma

High-Dose IL-2	Pembrolizumab	Nivolumab	Ipilimumab + Nivolumab	Atezolizumab Plus Vemurafenib plus Cobimetinib
High-dose IL-2 administered at 600,000-720,000 units/kg 15 min bolus IV infusion every 8 h on days 1-5 and 15-19. Treatment courses repeated at 8- to 12-wk intervals in responding patients until complete response is achieved or toxicity sets in that the physician decides to stop treatment for safety reasons	2 mg/kg dose IV over 30 min every 3 wk for up to 2 y unless disease progression or unacceptable toxicity occurred	3 mg/kg IV over 30 min every 2 wk for up to 2 y unless disease progression or unacceptable toxicity occurred	*Induction phase:* Ipilimumab 3 mg/kg IV over 90 min plus Nivolumab 1 mg/kg IV over 30 min every 3 wk × 4 doses, followed by *Maintenance phase:* Nivolumab at 3 mg/kg IV every 2 wk for up to 2 y unless disease progression or unacceptable toxicity occurred	Vemurafenib 960 mg PO bid plus Cobimetinib 60 mg once daily for 21 d. Then Vemurafenib at 720 mg bid plus Comitenib 60 mg daily for 7 d until day 28 Cycle 2 onward Atezolizumab at 840 mg day 1 and day 15 of every 28-d plus Vemurafenib 720 mg bid plus Cobimetinib 60 mg day for 21 d of 28-d cycle

- T cell growth factors such as IL-2 and IFN-α.
- T cell checkpoint–blocking monoclonal antibodies such as Ipilimumab against CTLA-4, Pembrolizumab, and Nivolumab against PD-1 receptors or Atezolizumab or Avelumab against PD-L1 ligand, respectively.

Biologic Agents in the Treatment of Metastatic Melanoma

IFN-α was the first recombinant cytokine investigated in phase I and II clinical trials of patients with metastatic melanoma based on its antiproliferative and immunomodulatory effects. Unfortunately, IFN-α is not used as primary therapy of metastatic melanoma due to suboptimal effects and significant toxicity.

Interleukin 2 (IL-2) is a T cell growth factor produced by T lymphocytes that help growth and expansion of T cells including antigen-specific CD8+ CTL precursors and lymphokine-activated killer cells.

Multiple large single-institution studies confirmed the capability of high-dose IL-2 to cure metastatic melanoma in a small subset of patients, leading to its FDA approval in 1998 to treat this disease.

- The overall response rate is about 16% that include complete response of about 6%.
- Subcutaneous, lymph node, and lung metastasis (M1a or M1b) are more likely to respond.
- Complete responses are durable in the majority of patients leading to potential cure.
- Good baseline performance and treatment naive status of melanoma patients are predictive of response to high-dose IL-2 treatment.

Toxicity of high-dose IL-2 is dose limiting and is mediated by endothelial damage that results in vascular leak in multiple organs. Patients with active comorbidities involving heart, lung, kidney, and liver or those with untreated hemorrhagic brain metastasis with vasogenic edema are excluded from high-dose IL-2 treatment due to elevated risk of life-threatening complications. Common manifestations of toxicity include the following:

- High fevers and nausea, vomiting, diarrhea (gastrointestinal), hypotension, cardiac arrhythmias (cardiac), hypoxemia, pleural effusions (pulmonary), azotemia and renal failure (renal), confusion and delirium (central nervous system).
- IL-2–induced defects of neutrophil chemotaxis function require prompt management of infections with antibiotics.
- Common autoimmune side effects include hypothyroidism, vitiligo, and uveitis besides others that require prompt management.

Clinical effectiveness of immune checkpoint inhibitors and anti-BRAF and anti-MEK agents in BRAF-mutated melanoma has replaced IFN-α and high-dose IL-2 therapy of melanoma. However, IFN-α and IL-2 may be used in selected patient scenarios where melanoma patients have run out of available treatment options.

Barriers to Achieving a Successful Anti-Melanoma Immune Response: Immune Tolerance

Antigen-activated CTLs are "highly regulated" or held in check by a number of biological processes so as to maintain immune homeostasis and prevent body injury associated with uncontrolled inflammation. These regulatory processes arise from mechanisms either intrinsic to CTL or by distinct group of immune cells derived from peripheral blood (T regulatory cells). Tumor cells or its microenvironment also imparts negative influence on the immune system.

Intrinsic T cell regulation by immune checkpoints:

- Cytotoxic T-lymphocyte-associated antigen-4 (CTLA- 4) is a high-affinity molecule rapidly expressed by activated T lymphocytes to mediate its own (CTL) inhibition by outcompeting CD28 molecular binding to costimulatory molecules CD80 and CD86 on APCs.
- Programmed cell death protein-1 (PD-1) receptor is expressed on activated melanoma-specific CTL that traffic into tumor tissue expressing PD-L1 and PD-L2 either constitutively or in response to immune stimulatory cytokines (such as interferons).
- Ligation of PD-L1/L2 with PD-1 on CTL results in its exhaustion, premature death, and abrogation of antimelanoma immunity.

Extrinsic Mechanisms That Regulate the Immune Response: T Regulatory Cells

- CD8+ CTL responses are regulated by thymus-derived, naturally occurring CD4+CD25+ T cells referred to as nTreg as well as by CD4+ T cells that acquire

inhibitory properties upon encountering antigen, referred to as induced T regulatory cells (iTreg).
- Regulatory T cells cause CTL inhibition through generation of inhibitory cytokines or directly by contact inhibition mediated by transcription factor FOXP3.

Tumor and its immune microenvironment mediated immune tolerance:

- Antigen presentation to CTL is seriously compromised by downregulation of MHC class I molecules by tumor and APCs. Immune tolerance is facilitated by inhibitory cytokines such as IL-10, TGF-β, IL-6, and VEGF produced by tumor cells, tissue hypoxemia, and myeloid-derived suppressive cells.
- Indoleamine 2,3-dioxygenase (IDO) is an immune-suppressive molecule secreted by the tumor cells, stromal cells, macrophages, and APC in the tumor microenvironment that starve T cells from an important amino acid tryptophan critical for a rate-limiting step in the de-novo biosynthesis of nicotinamide adenine dinucleotide. Additionally, accumulation of *N*-formyl-kynurenine, an IDO-induced byproduct of tryptophan catabolism, inhibits T cell activity.

Reactivating antimelanoma immunity: Successful reactivation of antimelanoma immunity has become possible by effective blockade of inhibitory immune checkpoints (CTLA-4, PD-1, and PD-L1) expressed on activated T cell or on tumor cells through monoclonal antibodies.

Two classes of monoclonal antibodies are approved by the FDA (Table 22.7).

TABLE 22.7

FDA-Approved Immune Therapy and Their Efficacy in Unresectable Stage III and Metastatic Melanoma

Treatment	Complete Remission (%)	Partial Remission (%)	Stable Disease (%)	Clinical Benefit (%)	MPFS Months	MOS Months	1-y Survival (%)	5-y Survival Rates (%)
High-dose Interleukin-2 (IL-2)	6	10	NA	20	13.1	11.4	50	6
Ipilimumab	1.5	9.5	17.5	28.5	2.9	10.1	45.6	23.5
Pembrolizumab	6.1	26.8			4.1	NR	68.4	41
Nivolumab	7.6	32.4	16.7	56.7	5.1	NR	72.9	44
Ipilimumab + Nivolumab	11.5	46.2	13.1	70.8	11.5	NR	NR	52
T-VEC* (intratumoral injection)	10.8*	15.6	NR	26.4	NA	NA	NA	NA
Atezolizumab plus Vemurafenib plus Cobimetinib	15.7	50.6	22.7	88.8	16.1	NA	NA	NA

MOS, median overall survival; MPFS, median progression-free survival; NA, not available; NR, not reached.

- Ipilimumab is an IGG1 monoclonal antibody designed to block inhibitory checkpoint CTLA-4 antigen on activated CD8+ CTLs leading to their reactivation.
- Pembrolizumab and Nivolumab are two highly selective humanized IgG4-kappa isotype antibodies against PD-1 receptor expressed on the membrane of activated

CTLs designed to block its engagement with two of its known inhibitory ligands expressed in tumor cells namely, PD-L1 and PD-L2. The interruption of the PD-1-PD-L1/2 axis reverses adoptive T cell resistance and restores antimelanoma activity.

Ipilimumab treatment of melanoma: In two large randomized phase III clinical trials, Ipilimumab improved both progression-free survival (PFS) and OS in patients with unresectable stage III and stage IV melanoma compared to a glycoprotein 100 (gp100) peptide vaccine or chemotherapy.

In March 2011, Ipilimumab was approved by the FDA for the treatment of unresectable stage III or IV melanoma administered intravenously at 3 mg/kg dose every 3 weeks for four doses.

Important facts about Ipilimumab treatment of patients with metastatic melanoma:

- Objective responses occur in between 10% and 16% patients, while stabilization of tumor in about 15% of patients results in long-term survival benefit in 20% to 25% of melanoma patients.
- Immune responses sometimes continued beyond 24 weeks converting nonresponsive disease to stable, stable disease to partial responses, and partial to complete responses.
- Responses are seen in treatment naïve or previously treated patients including those with high-risk visceral metastasis and elevated serum LDH levels.
- The onset of response is slow and mediated by antigen-specific tumor infiltrating CD8+ CTLs consistent with the proposed mechanism.
- Reinduction therapy with Ipilimumab at the time of disease progression can result in further benefit in a proportion of patients (reinduction is not FDA approved).
- The effect on OS is independent of age, sex, baseline serum LDH levels, metastatic stage, and previous treatment with IL-2 therapy.
- The nonspecific activation of presensitized CTL against both tumor as well as host (shared antigens) results in loss of self-tolerance manifesting as serious irAEs in organs.
- Ipilimumab caused irAE in about 60% but severe grade 3/4 toxicity occurred in 20% to 30% patients.
- Common irAEs involve skin, gastrointestinal tract, liver, and endocrine organs although careful symptom evaluation is important to detect other organ involvement.
- Skin irAEs manifest as rashes and are first to appear after 3 to 4 weeks of treatment followed by colitis, liver (hepatitis), and endocrine organ involvement in that order. Colitis symptoms should be distinguished from diarrhea by the presence of fever, abdominal cramps, distension, and blood in stools and can progress to intestinal obstruction or perforation.

Anti–PD-1 treatment of metastatic melanoma: Phase I/II and randomized phase III studies of anti–PD-1 agents Pembrolizumab and Nivolumab in treatment naïve and previously treated patients reported response rates between 52% and 38%, respectively.

- Responses were seen in those with high-risk features such as visceral metastasis (stage M1c), elevated LDH, and those with history of brain metastasis.
- The effect on OS is independent of age, sex, baseline LDH levels, stage, and previous treatment with Ipilimumab therapy.
- Responses were durable even after stopping treatment leading to PFS and OS.
- Common irAE included skin rashes, fatigue, diarrhea, and pruritus while serious grade 3/4 toxicity in 5% to 15% patients was lower than seen with Ipilimumab treatment (20%-30%).
- Unusual irAE included autoimmune pneumonitis (presenting as cough, shortness of breath, and even fatal respiratory failure) and endocrine toxicity that appeared higher than with anti–CTLA-4 antibody. Unusual irAEs included diabetes mellitus, nephritis besides others.

Management of immune-related adverse events of immune checkpoint inhibitors

- Patient education about toxicity is critical, and prompt reporting of side effects improves outcomes from early initiation of immune-suppressive treatment.
- Every autoimmune toxicity must be graded and treatment initiated with oral steroids at 1 to 2 mg/kg dose or its parenteral equivalent in grade II, III, or grade IV toxicity. This should be followed by gradual taper over 4 to 6 weeks. irAE are best managed with a multidisciplinary team approach.
- Patients not responsive to steroids within 2 to 3 days may need to be administered higher level of immune suppression with agents such as anti–TNF-α antibody infliximab, antimetabolite Mycophenolate mofetil, calcineurin inhibitor Tacrolimus, and Cyclosporine. Rarely, T-cell depleting antibody such as antithymocyte globulin has been used to achieve effective T cell suppression.
- The median time to resolution of severe irAEs of grade 2, 3, or 4 after initiation of immune-suppressive therapy is about 6.3 weeks and sometimes longer.

Combined Immune Checkpoint Inhibition and Metastatic Melanoma: Principles

Hypothesis: Since CTLA-4 and PD-1 are two nonredundant inhibitory pathways affecting activated CTL, their combined inhibition might result in superior antimelanoma response.

- Proof of this hypothesis obtained in preclinical models was confirmed in humans.
- Phase I/II as well as randomized phase III studies showed superior clinical benefit of Ipilimumab + Nivolumab compared to single-agent Nivolumab or Ipilimumab. The response rates were higher including complete responses of 11% to 22% and PFS reached highest ever compared to single agents (11.5 vs 6.9 vs 2.9 months, respectively).
- Onset of responses was earlier and the majority of responses were deep (more than 80% tumor reduction).
- At a minimal follow-up of 60 months, the median OS was more than 60 months (median OS not reached) with Ipilimumab plus Nivolumab compared to 36.9 and 19.9 months with Nivolumab and Ipilimumab alone, respectively.
- OS at 5 years was 52% with Ipilimumab plus Nivolumab compared to 44% in the Nivolumab alone group and 26% in the Ipilimumab alone group.

- The adverse prognostic effects of elevated LDH and negative PD-L1 expression affecting single-agent Ipilimumab or Nivolumab treatment were not seen with the combination.
- Serious irAE were much higher with Ipilimumab + Nivolumab versus Ipilimumab (54% vs 24%).
- irAE led to discontinuation of treatment in 36.4% patients receiving Ipilimumab + Nivolumab. No new late toxicity nor sustained deterioration of health-related quality of life was observed during or after treatment with Ipilimumab plus Nivolumab or Nivolumab alone.
- The combined use of Ipilimumab and Nivolumab was approved by the FDA in 2015 for BRAF wildtype and subsequently in January 2016 for treatment of BRAF wild-type and BRAF V600 mutation positive unresectable or metastatic melanoma.
- The choice between using monotherapy with a PD-1 inhibitor or combination anti-CTLA4 and PD-1 remains controversial and dependent upon risks of autoimmunity and its management in a given patient.
- Data on PD-L1 staining of tumors suggest that patients with low staining (less than 1%), high LDH, and multiorgan metastases are high risk and likely to benefit from combined immune checkpoint blockade, while those tumors with high PD-L1 staining (>5%), normal LDH, and oligometastases may do equally well with anti–PD-1 monotherapy.

Oncolytic Therapy and Antimelanoma Immune Responses: Principles

Oncolytic therapy is intralesional injection of agents that may produce both, a local and a systemic response. They could be viral- or nonviral-based.

Oncolytic viruses are modified live viruses designed to selectively replicate in tumor cells after intratumoral administration, leading to release of tumor antigens in the proximity of tumor and evoking regional and systemic antimelanoma immunity. The immune response is facilitated by insertion and expression of gene encoding human GM-CSF, local production of which helps recruit and activate APCs.

T-VEC is a first in class FDA-approved agent for intratumoral injection and contains a modified herpes simplex virus (HSV) type I through the deletion of two nonessential viral genes.

- Functional deletion of herpes virus neurovirulence factor gene (ICP34.5) attenuates viral pathogenicity and enhances tumor-selective replication.
- Deletion of the ICP47 gene helps to reduce virally mediated suppression of antigen presentation and increases the expression of the HSV US11 gene.

A multicenter, open-label study assigned eligible surgically unresectable stage IIIB, IIIC, or IV melanoma patients suitable for direct or ultrasound-guided injection of T-VEC (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions more than or equal to 10 mm in diameter) versus subcutaneous injection of recombinant GM-CSF at a dose of 125 $\mu g/m^2$ randomly at a two-to-one ratio every 3 weeks after the first dose and then every 2 weeks until tumor progression or occurrence of toxicity.

- Overall response rate was 26.4% with T-VEC versus 5.7% with GM-CSF, with durable responses of at least 6 months duration seen in 16.3% and 2.1% in each arms, respectively.
- Unresectable and treatment naïve stage IIIB, IIIC, and IV, M1a patients experienced more benefit compared to previously treated patients or stage IV M1b or M1c patients.
- Systemic immune effects were seen in 15% uninjected measurable lesions in systemic visceral sites that shrunk by ≥50% size.
- Side effects of T-VEC were minor and included chills, fever, injection-site pain, nausea, influenza-like illness, and fatigue. Vitiligo was reported in 5% of patients.
- Grade 3/4 irAE were seen, respectively, in 11% and 5% patients after T-VEC and GM-CSF.
- A pattern of pseudoprogression seen in some responding patients suggested continued treatment in clinically stable patients even if lesions appeared to grow or new lesions appeared.
- Vitiligo and increased numbers of MART-1–specific T cells as well as decreased CD4+ and CD8+ FoxP3+ regulatory T cells in injected lesions suggested systemic antitumor immunity.
- Noninjected skin lesions demonstrated increased CD8 infiltrating lymphocytes and PD-L1 expression suggesting likely clinical benefit may be seen of oncolytic therapy combination with anti–PD-1 or anti–PD-L1 agents.

Several other oncolytic agents are in clinical trials at this time both as monotherapy and in combination with checkpoint inhibitors.

Adaptive Cell Therapy of Metastatic Melanoma: Principles

Adaptive cell therapy refers to boosting antitumor immunity by transfer of autologous melanoma-specific T cells obtained from the tumor (tumor infiltrating lymphocytes) or from the peripheral blood, back to the patient after their expansion ex vivo to large numbers. Conditioning regimens help provide space and favorable growth factors for survival of the infused T cells. This treatment is based on the following fundamental facts:

- In animal systems, tumors can be controlled with adoptively transferred syngeneic T cells.
- T cells capable of recognizing autologous tumors in humans exist, and they can be activated and expanded ex vivo, as well as engineered to express a set of highly avid T cell receptors for targeting tumor-expressed epitopes displayed canonically on their MHC molecules. Pioneered at the National Cancer Institute, response rates of as high as 50% were seen with this treatment modality with durable responses in subset of patients that are refractory to other treatments.

Resistance to immune checkpoint inhibitor treatment is a major challenge to successful immunotherapy of cancer in the clinic. Resistance can be primary or secondary and intrinsic or extrinsic to the T cells.

- Primary resistance: when no response is observed following initiation of immune therapy.

- Acquired resistance: when initial response to immune therapy is followed by tumor progression or relapse.

A number of factors influence immune response and immune resistance. Some factors are intrinsic to the immune system and tumor cells, while others are due to the constituents of the tumor microenvironment.

Factors that are associated with likelihood of immune response include the following:

- High tumor mutational burden (TMB) such as seen in cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC), Merkel cell carcinoma (MCC) (human polyoma virus negative) that are associated with cumulative ultraviolet light exposure-associated mutagenesis.
- Tumor mismatch repair gene defect and those expressing mutation of DNA repair genes such as BRCA II. Nonsynonymous mutations in tumors result in increased generation of tumor neoantigens that improve chances of cytotoxic T cells to respond to them.
- Hot tumor microenvironment consists of high number of effector lymphocyte trafficking to the tumor resulting in increased effector to regulatory T cell ratio, low or absent regulatory T cells, myeloid-derived suppressor cells (MDSCs), and vascular endothelial growth factors of angiogenesis, and favorable cytokine milieu that facilitates immune cell recruitment and antitumor immune responses.

Factors that are associated with immune resistance:

- Mutations in the T cell receptor binding domain of MHC-1 that result in lack of antigen presentation to the T cells
- Impaired IFN-γ signaling pathway in T cells due to the loss of JAK/STAT signaling. This result in resistance to anti–PD-1 and anti–CTLA-4 agents through downregulation of MHC-1 and PD-L1 expression
- T cell overexpression of alternative checkpoints such as T-cell immunoglobulin, mucin domain-3 protein (TIM-3), lymphocyte-activation gene 3 (LAG-3), B and T lymphocyte attenuator (BTLA) among them.
- Unfavorable tumor microenvironment milieu caused by few or absent T cells, decreased effector to regulatory T cell ratio, unfavorable tumor-associated macrophages (M2), cytokines such as TGF-β, VEGF, MDSCs, T regulatory cells, and chemokines such as CCR4, CCL5, CCL17,CCL22, and CXCL8 and CXCL12.

Targeted Therapy of Melanoma: Principles

Targeted therapy of melanoma is based upon a better understanding of functional cellular genetic machinery critical for transducing signals of cellular growth from outside of the cells to the nucleus leading to the transcription of key genes important for maintaining cellular homeostasis through control of proliferation, differentiation, and cell death.

- The mitogen-activated protein kinase (MAPK) pathway is an important signaling cascade containing Ras/Raf/MEK/ERK proteins.

- B-Raf is a serine/threonine kinase occupying a central place in the MAPK pathway that harbors activating mutations in 50% to 60% of cutaneous melanomas conferring RAS-independent proliferation and survival of melanoma cells.
- Molecular identity of BRAF mutations led to its targeted inhibition through the design of small inhibitory molecules.
- About 90% of mutations in BRAF result in the substitution of glutamic acid for valine at codon 600 (BRAF V600E). Other BRAF mutations include V600 K and V600D/V600R variants.
- Vemurafenib (first-in-class) and dabrafenib are two FDA-approved reversible oral small molecule BRAF kinase inhibitors that selectively target cells harboring BRAF mutation. The resulting tumor cell death and inhibition of growth translated into survival in patients.
- Results from randomized clinical trials showed high response rates of up to 55%, and tumor stabilization of 30% for a clinical benefit to 80% to 90% of metastatic melanoma patients resulting in improved PFS and OS compared to Dacarbazine treatment (Table 22.8).

TABLE 22.8

FDA-Approved Targeted Therapy of Metastatic BRAF Mutated Melanoma and Their Clinical Efficacy

Treatment	Complete Remission (%)	Partial Remission (%)	Stable Disease (%)	MPFS months	MOS months	12-mo Survival (%)	24-mo Survival (%)	3-y Survival Rates (%)
Vemurafenib 960 mg PO BID	8	44	30	7.3	13.6	65	38	43.2
Dabrafenib 150 mg PO BID	3	47	42	5.1	18.7	68	NA	42
Trametinib 2 mg PO daily	2	20	56	4.8	16.1	60.9	32	20.6
Dabrafenib 150 mg PO BID + Trametinib 2 mg PO daily	13	51	26	11.4	25.1	74	50	51
Vemurafenib 960 mg PO BID + Cobimetinib	16	54	18	12.3	22.3	75	49	41.5

MOS, median overall survival; MPFS, median progression-free survival.

The FDA-approved vemurafenib at a dose of 960 mg administered orally twice a day, while dabrafenib is approved at a dose of 150 mg administered orally twice a day for metastatic melanoma.

Important facts about BRAF kinase inhibitor treatment of metastatic melanoma:

- The survival benefit of vemurafenib and dabrafenib was observed in each prespecified subgroup according to age, sex, performance status, tumor stage, serum levels of lactate dehydrogenase, and geographic region.
- Patient compliance with medication is important to maintain continued inhibition of MAPK pathway in tumor cells to ensure continued clinical benefit to the patient.

- Acquired drug resistance to BRAF inhibitor agent frequently leads to treatment failures due to resumption of increased signaling through the MAPK pathway.
- Mechanisms underlying acquired drug resistance include mutations of NRAS (17%), KRAS (2%), BRAF splice variants (16%), BRAF amplifications (13%), MEK 1/2 mutations (7%), and non-MAPK pathway alterations (11%) that include upregulation of platelet-derived growth factor receptor beta (PDGFRβ) and alterations in the PI3K-AKT pathway.
- Toxicities of BRAF inhibitor agents include hyperproliferative skin lesions such as hyperkeratosis, keratoacanthoma, squamous cell carcinoma, and palmar-plantar erythrodysesthesia believed to be due to paradoxical activation of the MAPK pathway in normal cells bearing wild-type BRAF. Secondary cancers occur in RAS-mutated organs.
- Photosensitivity, muscle pain, arthralgia, pruritus, fatigue, alopecia, diarrhea, and nausea and electrolyte abnormalities were other side effects.
- Fever is a side effect seen with dabrafenib in 16% to 26% patients (grade 2/3 in 11% patients).
- Caution must be used with concomitant use of medications affecting CYP3A4, CYP2C8, and CYP2C9 metabolic pathways for concerns of change in dabrafenib concentrations leading to its inefficacy or toxicity.
- Toxicity led to modification or interruption of vemurafenib dose in about 38% of patients and dose reductions and discontinuation of dabrafenib in 28% and 3%, respectively.

MEK is the downstream of BRAF and a therapeutic gene target in the MAPK pathway. Trametinib, Cobimetinib, and Binimetinib are three orally selective reversible kinase inhibitors targeting MEK1 and MEK2 activation leading to decreased phosphorylated ERK and thus decreased tumor growth.

- In a large phase III open-label trial of patients diagnosed with BRAF-mutated metastatic melanoma, Trametinib treatment resulted in 22% responses and 56% stabilization of disease translating into both PFS and OS benefit compared to Dacarbazine chemotherapy. Trametinib is approved for the treatment of metastatic melanoma for patients not able to tolerate BRAF inhibitor agents.
- Side effects were skin rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform.
- No squamous cell carcinoma or hyper proliferative skin lesions occurred.
- Ocular events such as blurred vision and reversible chorioretinopathy in 9% of patients.
- Cardiac toxicity in 7% patients included decreased ejection fraction, ventricular dysfunction.
- Toxicity led to dose interruptions and dose reductions in 35% and 27% of patients, respectively.

Combined inhibition of mutated BRAF and downstream MEK protein consolidates inhibition of MAP kinase pathway leading to delayed emergence of resistance to BRAF inhibitor. In two large randomized phase III studies, combined BRAF and MEK inhibition resulted in higher overall response rate of about 69% compared to dabrafenib alone (53%)

and translated into superior PFS and OS with combination compared to single-agent dabrafenib.

- The incidence of cutaneous hyperproliferative lesions and squamous cell carcinoma following BRAF blockade decreased dramatically following MEK inhibition, consistent with inhibition of paradoxical MAPK pathway activation by anti-BRAF agent in normal BRAF wild-type cells.
- Incidence of fever increased in dabrafenib plus trametinib (71%) compared to 24% for single-agent dabrafenib.
- Fever is believed to be likely from a metabolite of dabrafenib (hydroxyl dabrafenib) clearance of which might be impaired in the presence of a MEK inhibitor.
- 58% of patients on combined dabrafenib/Trametinib required dose reduction and 7% discontinued treatment permanently out of which pyrexia contributed in 4%.
- Pyrexia management following dabrafenib or dabrafenib/trametinib consists of holding dabrafenib if fever is over 38.5 °C, while trametinib is continued until fever is resolved. Nonsteroidal anti-inflammatory drugs or acetaminophen are used for short-term fever management, but lower dose steroids, sometimes even prophylactically, may be used for persistent fevers.

Long-term follow-up data of anti-BRAF plus anti-MEK treatment in BRAF-mutated treatment naïve melanoma patients:

- Two large (COMBI-d and COMBI-v) trials involving previously untreated metastatic melanoma patients with BRAF mutations receiving dabrafenib at 150 mg twice a day plus Trametinib 2 mg once daily were analyzed for PFS and OS.
- Out of total of 563 randomly assigned patients to receive dabrafenib plus Trametinib, the PFS rates were 21% at 4 years and 19% at 5 years. The OS rates were 37% at 4 years and 34% at 5 years.
- A complete response occurred in 109 patients (19%) and was associated with an improved long-term outcome with an OS rate of 71% at 5 years.
- In multivariate analysis, performance status, age, sex, number of organ sites with metastases, and lactate dehydrogenase level were significantly associated with both PFS and OS.

Triple therapy of melanoma: Rationale for combining immune checkpoint inhibitors and anti-BRAF plus anti-MEK targeted therapy in metastatic melanoma.

- Although immune checkpoint inhibitor treatment and anti-BRAF plus anti-MEK treatment in BRAF-mutated melanoma lead to improved survival in melanoma patients, treatment failure results from adaptive immune tolerance and acquired resistance to anti-BRAF plus anti-MEK treatment, respectively, in a significant proportion of patients.
- Preclinical studies indicate that anti-BRAF plus anti-MEK agents result in (1) trafficking of CD4 and CD8 T cells into the tumor microenvironment fostering a cytokine shift toward an inflammatory IFN-γ type response and (2) upregulate melanoma antigens as well as major histocompatibility complex class I and class II

molecules on tumor cells facilitating tumor antigen presentation to the effector T cells.

- PD-L1 is expressed in resistant melanoma clones following anti-BRAF plus anti-MEK treatment.
- Combination of anti-BRAF plus anti-MEK treatment with anti–PD-L1 or anti–PD-1 agents is studied in concurrent and sequential setting. Biomarker studies indicate anti-BRAF plus anti-MEK treatment result in favorable changes in the tumor microenvironment that predict enhanced antimelanoma immune responses in animal studies.
- A phase Ib study evaluated the safety and antitumor activity of combining Atezolizumab (anti–PD-L1 agent) with either vemurafenib (BRAF inhibitor) or cobimetinib (MEK inhibitor) and vemurafenib (triple combination), in treatment naïve metastatic melanoma patients with BRAF V600E mutation. The results showed that the toxicity was manageable and that the triple combination resulted in improved outcomes compared to doublets.
- Exploratory biomarker study showed cobimetinib plus vemurafenib run-in of 28 days prior to anti–PD-L1 agent Atezolizumab was associated with increase in CD4−positive T cells in the tumor microenvironment. The objective response rate was 71.8%, and with 29.9-month follow-up, estimated median duration of responses was 17.4 months with ongoing responses seen in 39.3% patients.
- In a randomized, double-blind, placebo-controlled phase III study (IMspire 150) done at 112 institutes in 20 countries, newly diagnosed treatment naïve melanoma patients with unresectable stage IIIC-IV with BRAF mutation at V600E were randomly assigned 1:1 to 28 day cycles of anti–PD-L1 agent atezolizumab, vemurafenib, and cobimetinib (Atezolizumab group) or atezoliumab placebo plus vemurafenib plus cobimetinib (control group). In cycle 1, all patients received vemurafenib plus cobimetinb only. Randomization was stratified by LDH and geographical location.
- At median follow-up of 18.9 months, PFS was 15.1 months in the Atezolizumab group (triple combination therapy) compared to 10.6 months in the control group (anti-BRAF plus anti-MEK, HR 0.78, $P = .025$).
- Based on these results, in June 2020, FDA approved triple therapy consisting of PD-L1 inhibitor Atezolizumab plus the MEK inhibitor cobimetinib and the selective BRAF kinases inhibitor vemurafenib for the treatment of patients with advanced BRAF V600 mutation-positive melanoma.

Brain metastasis of melanoma and its management:

- The high incidence of brain metastasis of melanoma is reflected by more than 50% to 55% melanoma patients documented to have brain metastasis in autopsy studies. Historically, patients with melanoma metastases to brain have done poorly with limited survival ranging from about 3 to 6 months with the available treatment options such as surgery and external radiation therapy.
- Skibber et al and others showed that external radiation to the whole brain after resection of solitary brain metastasis of malignant melanoma has survival benefits.
- Whole-brain radiation is favored if multiple and/or large size brain metastases are present.

- Stereotactic brain radiation therapy is preferred in small-sized or fewer (two to three) brain metastases.

Melanoma brain metastases in the era of immune checkpoint inhibitor and targeted therapy

- Both immune checkpoint inhibitor agents and BRAF-targeting agents have documented intracranial effects in proportion of melanoma patients with brain metastasis resulting in improved quality of life and survival advantage.
- Anti-BRAF agent dabrafenib has a 39% response rate in patients with brain metastasis that was durable and concordant with systemic effects.
- Pembrolizumab and Ipilimumab have reported activity of 22% and 24%, respectively, in the brain that is concordant with systemic activity. Although smaller metastasis respond better, occasional responses are seen in larger tumors leading to survival benefit.
- Combined use of anti–CTLA-4 antibody and anti–PD-1 antibody have shown high response rates in melanoma brain metastases with durable survival benefit.
- Anti–CTLA-4 or anti–PD-1 treatment may be administered concurrently with external beam radiation therapy and benefit from compounding effect of antigen release by radiation therapy.
- Anti-BRAF plus anti-MEK treatment of melanoma should not be used concurrently with radiation therapy for concerns of risk of radiation necrosis.
- In an ongoing clinical trial of BRAF-mutated melanoma brain metastases, the benefit of central nervous system penetrant anti-BRAF molecule combined with anti-MEK agent is under study.
- Patients diagnosed with cutaneous melanoma brain metastases deserve multidisciplinary treatment.

Chemotherapy of Metastatic Melanoma: Single-Agent Chemotherapy

Chemotherapy of melanoma does not lead to durable responses and therefore does not confer survival advantage to patients. A chemotherapy option might be used as a bridge to potentially effective experimental treatments in patients who fail presently available treatment of melanoma.

Dacarbazine is the only FDA-approved chemotherapeutic agent for melanoma treatment that has a response rate of about 10% to 20% without OS benefit.

Temozolomide is a synthetic analog of Dacarbazine that is orally bioavailable, crosses the blood-brain barrier, has comparable efficacy, and has a reduced toxicity profile.

Multiagent chemotherapy of melanoma results in higher response rates compared to single agents but with increased toxicity and without survival advantage.

Combination Chemotherapy Regimens of Metastatic Melanoma

- MD Anderson regimen: Cisplatin, Vinblastine, Dacarbazine (CVD)
- Dartmouth regimen: Cisplatin, Carmustine, Dacarbazine, and Tamoxifen (CBDT)

- A phase III multicenter randomized clinical trial of Dacarbazine alone versus the Dartmouth regimen in patients with metastatic melanoma showed higher response rates of 25% to 30% and increased toxicity with Dartmouth regimen without significant survival benefit.
- A phase III trial of melanoma patients treated with nab-Paclitaxel (Abraxane) versus Dacarbazine showed improved PFS for nab-Paclitaxel compared to Dacarbazine. Although a trend toward improved OS was seen, this did not achieve statistical significance

Combining Chemotherapy and Biologic Agents in Metastatic Melanoma

Bio-chemotherapy: Rationale

- Preclinical studies suggested that combining chemotherapeutic and biologic agents (biochemotherapy) may confer additive or synergistic effects against melanoma.
- Chemotherapeutic and biologic agents have different mechanisms of antimelanoma effects without overlapping toxicity or cross-resistance.
- Early studies in metastatic melanoma by Falkson et al indicated improved response rates and their duration when Dacarbazine was combined with IFN-α-2b compared to Dacarbazine alone. However, the single-institution study results could not be reproduced.
- The CVD regimen of chemotherapy plus continuous intravenous infusion of moderate dose IL-2 and IFN-α administered subcutaneously showed high response rates and durable survival of between 10% and 20% in selected patients.
- The toxicity associated with biochemotherapy regimens and the lack of reproducibility of survival benefit among investigators has dampened interest in its universal use.
- A meta-analysis of 18 clinical trials and a phase III randomized clinical trial comparing biochemotherapy to CVD chemotherapy in stage IV melanoma confirmed high response rates of 40% to 50% and increased toxicity with biochemotherapy without OS advantage.

Uveal Choroidal Melanoma

Uveal choroidal melanoma is the most common primary malignancy of the eye.

- Estimated incidence in the United States is six to seven cases per 1 million people.
- Depth and diameter determine the treatment indication and prognosis (Table 22.9).

TABLE 22.9
Relationship of Depth and Diameter of Uveal Melanoma and Survival

Uveal Choroidal Melanoma (Size)	Diameter (mm)	Depth (mm)	10-y Survival (%)
Small	<10	<3	80
Medium	10-15	3-5	60
Large	>15	>5	34.8

- Benign choroidal nevi are up to 5 and 1 mm in diameter and depth, respectively.

- Monosomy of chromosome 3 is a common cytogenetic abnormality and confers poor DFS and high risk of death from melanoma.
- Other cytogenetic abnormalities involve chromosomes 1, 6, and 8.
- The most common site of metastasis is the liver although in later stages the tumor can spread to other sites such as the lungs, bones, and skin.

Management of Uveal Choroidal Melanoma

- Local ablative treatment such as brachytherapy (iodine-125 plaque therapy), photoradiation, cryotherapy, and ultrasonic hyperthermia.
- Surgical treatments that include local resection or enucleation of the eye.
- Systemic chemotherapy or biologic therapy is ineffective in metastatic uveal melanoma.
- Experimental therapies for liver metastasis include in situ ablative therapies such as radiofrequency ablation and isolated perfusion using Melphalan.

A randomized trial evaluated the use of liver chemosaturation with Melphalan using a specialized approach of isolating the liver using a system of catheters (percutaneous hepatic perfusion) in patients with melanoma (mostly uveal) metastasis to the liver. The trial showed high response rates and improved liver-specific PFS.

Follow-up of patients with uveal choroidal melanoma after local treatment includes close surveillance for liver metastasis with liver function tests and imaging studies of the liver that include sonography every 6 months in the first 5 years for early diagnosis of liver metastasis. However, late relapses may occur.

Indications for Enucleation of the Eye

- Tumor growing in a blind eye
- Melanoma involving more than half of the iris
- Tumor involving the anterior chamber of the eye or extraocular extension
- Failure of previous local therapy

NONMELANOMA SKIN CANCER

There are three major types of nonmelanoma skin cancers: BCC, CSCC, and MCC. BCC and CSCC together account for nearly 1 million cases in the United States per year although recent estimates indicate this number to be much higher. One important reason for increasing incidence of nonmelanoma skin cancer includes rapid expansion of aging population who have cumulative exposure to ultraviolet light—a well-known carcinogen. A weakened immune system is believed to play an important role in their causation as seen by higher prevalence of these cancers in immune-suppressive states such as aging populations and transplant recipients who receive immunosuppressive therapy. Histologically, regressing nonmelanoma skin cancers show infiltration of the tumor by activated T cells and cytokines such as IFN-α, TNF-β, and IL-2. BCC, CSCC, and virus-negative MCC exhibit highest TMB among all cancers.

Basal Cell Carcinoma

- BCC is the commonest cancer in the US white population of over the age of 50 years, accounting for 75% of the 1 million new cases of nonmelanoma skin cancers.
- BCCs are keratinocyte tumors most commonly diagnosed in people of European ancestry.
- Ultraviolet rays are the most important risk factor followed by ionizing radiation and arsenic.
- Majority of BCCs are driven by increased activity of Sonic Hedgehog (HH) signaling pathway that was originally identified in its familial form—Gorlin syndrome.
- Usual location of BCC is the skin of the head and neck region (sun-exposed area).
- BCC is highly cured by surgery and death rate is very low despite its high incidence.
- When locally advanced or metastatic (rare occasions), local invasion can lead to tissue destruction that makes surgical treatment difficult and outcomes poor.

Clinical Presentations of BCC

- Typical presentation of BCC is a shiny pink translucent papule with telangiectasia, while other types include nodular variants (at times pigmented), sclerosing or morphea type (might go undiagnosed for longer time), and less commonly, hyperkeratotic type affecting head and neck region. Surgery is the primary treatment modality and may include Mohs surgery.

BCC as a Heritable Disorder

- A rare familial presentation of BCC is called basal cell nevus syndrome also known as Gorlin syndrome characterized by a high incidence of BCCs and medulloblastomas.
- Autosomal-dominant inheritance results from uncontrolled activation of the Hedgehog (HH) signaling pathway.
- The genetic defect underlying this condition is linked to mutation of a tumor suppressor gene called patched 1 (PTCH1) mapped to human chromosome 9q22.
- The mutations of PTCH1 and TP53 genes critical to BCC carcinogenesis are believed to be produced by exposure to UV radiation, elucidating the role of UV exposure in its causation.

Cutaneous Squamous Cell Carcinoma

- Usually found as single or multiple lesions in elderly white men with sun-damaged skin.
- Common sites include back of the hand, forearm, face, and neck.
- Presents as a firm, indurated, expanding nodule, often at the site of actinic keratosis.
- Nodules may be ulcerated, and regional lymph nodes may be enlarged.

Squamous Cell Carcinoma of a Mucocutaneous Site

- Common in elderly men with history of smoking, alcohol use, chewing of tobacco or betel nut.
- Mouth and lower lip are common sites where it typically start as an ulcerated nodule or erosion.
- Other sites of origin include the sole of the foot (verrucous form) and male genitalia related to human papillomavirus in underlying condylomata of Buschke-Lowenstein tumor.

Diagnosis of Nonmelanoma Skin Cancer

- A detailed history should include ethnic background and skin type as well as duration of the skin lesion, pain, itching, and recent changes.
- Excessive exposure to sun, radiation, and arsenic and occupational and recreational activities.
- Examination of scalp, ears, palms, sole's interdigital areas, and mucous membranes; assess the extent of sun damage (ie, solar elastosis, scaling, erythema, telangiectasia, and solar lentigines)
- Assessment of the locoregional lymph nodes and distant metastases

Biopsy: An excisional or incisional biopsy in a small or large tumor, respectively, is obtained for histologic diagnosis. A shave biopsy may be used in noduloulcerative, cystic, or superficial lesions.

Complete surgical resection with negative margins of at least 4 to 6 mm is recommended with regional lymphadenectomy if metastasis to the regional lymph node/nodes is present.

Mohs Surgery

- Mohs surgery allows excision of the tumor until negative margins are achieved. It includes micrographic surgery guided by frozen section to ascertain complete resection.
- Superficial BCC: Imiquimod is an FDA-approved agent for the treatment of superficial BCC when used in cream form. The drug works via toll-like receptor agonistic activity and causes stimulation of the innate and adaptive immune system. Common side effects include local skin rashes, burning sensation, erythema, edema, induration, erosion, and pruritus.

Radiation Therapy

X-rays delivered at a total dose of 2000 to 3000 cGy penetrate up to 2 to 5 mm, the level to which most of the basal cell and squamous cell carcinomas infiltrate. The total dose is divided into multiple smaller doses, usually over 3 to 4 weeks, to reduce side effects.

Hedgehog Signaling and Targeted Therapy of Locally Advanced and Metastatic BCC

- HH signaling is a pivotal abnormality in BCC resulting in carcinogenesis due to uncontrolled proliferation of the basal cells of the epidermis.
- The HH pathway is activated after binding of HH ligand to the PATCHED 1 protein encoded by PTCH1 tumor suppressor gene present on target cells.
- In the absence of excessive HH ligand, PTCH1 inhibits a downstream protein called smoothened (SMO) and prevents its translocation into the cilium.
- Binding of the HH ligand to PTCH1 inhibits its protective activity of inhibiting SMO allowing uninhibited SMO to translocate to the primary cilium.
- Downstream effects of SMO activity lead to increased transcription factors GLI1 and GLI2, both of which cause transcription of genes important in proliferation and cell survival.

Approximately, 90% of sporadic BCCs have at least one allele of PTCH1 mutated, while about 10% of BCCs have mutations in the downstream SMO protein that makes SMO resistant to inhibition by PTCH1. Targeted therapy of BCC is directed toward inhibition of HH signaling.

- Cyclopamin (plant alkaloid) is a competitive inhibitor of SMO signaling that binds directly to the protein PTCH1 or SMO and cause regression of the tumor upon local application.
- Vismodegib (first-in-class) and Sonidegib are two FDA-approved small molecule inhibitors of SMO for metastatic or locally advanced BCC.
- In locally advanced BCC, Vismodegib at a daily 150 mg oral dose produced a response rate of 58% with median duration of response of about 12.8 months.
- Vismodegib has lower activity in metastatic BCC (response 30%, median duration 7.6 months)
- Oral daily administration of Sonidegib at 200 mg in locally advanced or metastatic BCC showed response rate of 58% that coincided with decrease in GLI1 expression in the tumor.
- HH pathway inhibitor treatment is continued daily until disease progression or intolerable toxicity occurs.
- Common toxicity of HH inhibitors includes alopecia, dysgeusia (taste disturbance), muscle spasms, fatigue, weight loss, and hair loss. Vismodegib led to serious adverse events in 25% of patients that included deaths.
- Sonidegib also cause nausea, anorexia, vomiting, myalgia, and raised serum creatinine kinase. Grade 3/4 toxicities include weight loss, myalgia, hyperbilirubinemia, dizziness, and fatigue.
- Adverse events result in discontinuation of treatment in a significant number of patients (63%)
- Acquired mutations of SMO result in resistance to the treatment and recurrence of disease.
- Antifungal agents, Itraconazole and Pociconazole, have anti-SMO effects and show promising activity in BCC refractory to Vismodegib or Sonidegib treatment.

Immune checkpoint inhibitor treatment of recurrent or locally advanced and metastatic BCC: Rationale

- BCC shows high TMB due to cumulative sun-induced damage of the epidermal keratinocyte from which it arises.
- However, tumor microenvironment of BCC reveals features favoring immune tolerance such as a decrease in CD8 positive effector lymphocytes, an increase in Treg cells, and a decrease in expression of MHC-1.
- Additionally, increased expression of IL-10 in the tumor microenvironment is linked to the presence of immature dendritic cells fostering immune tolerance.
- Treatment of BCC with HH inhibitor results in increase of CD8 and CD4 T cells and IFN-γ production promoting reversal of immune tolerance. Patients previously treated with HH pathway inhibitor agents are likely to respond to immune checkpoint inhibitor agents.
- Cemiplimab is a high-affinity and potent human monoclonal antibody directed against programmed death 1 receptors.
- In an ongoing open-label multicenter trial of patients with advanced BCC who progressed on HH pathway inhibitor therapy, efficacy of anti–PD-1 agent Cemiplimab-rwlc is assessed (study 1620).
- All eligible patients received Cemiplimab-rwlc 350 mg every 3 weeks for up to 93 weeks until disease progression or unacceptable toxicity or completion of planned treatment.
- Among 84 patients, overall response rate was 29% with median duration of response not reached and 79% responders maintaining response for at least 6 months.
- In patients with metastatic disease, response rate was 21% with a median duration of response not reached and all responders maintained the response for at least 6 months.
- In February 2021, FDA granted regular approval to Cemiplimab-rwlc for patients with locally advanced or metastatic BCC after failure of an HH pathway inhibitor or for whom HH pathway inhibitor is not appropriate. The recommended dose of Cemiplimab–rwlc is 350 mg as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity (Table 22.10).

TABLE 22.10

FDA-Approved Immunotherapy of Nonmelanoma Skin Cancer

Non-Melanoma Skin Cancer (NMSK)	FDA-Approved Treatment	Dose, Frequency, and Duration	Approval Date
Cutaneous squamous cell carcinoma (CSCC) Locally advanced or metastatic not amenable for curative surgery or radiation treatment	Cemiplimab-rwlc (anti–PD-1 agent) Pembrolizumab (anti–PD-1 agent)	350 mg as an intravenous infusion over 30 min every 3 wk for 2 y or until disease progression or toxicity 200 mg every 3 wk or 400 mg every 6 wk for 2 y or until disease progression or toxicity	FDA approval in June 2018 FDA approval in June 2020
Basal cell carcinoma (BCC) Locally advanced and metastatic following treatment with hedgehog inhibitor or who are not suitable for hedgehog inhibitor treatment	Cemiplimab-rwlc (anti–PD-1 agent)	350 mg over 30 min every 3 wk until disease progression or toxicity	FDA approval in February 2021

Non-Melanoma Skin Cancer (NMSK)	FDA-Approved Treatment	Dose, Frequency, and Duration	Approval Date
Merkel Cell carcinoma (MCC) Locally advanced or metastatic	Avelumab (anti–PD-L1 agent) Pembrolizumab (anti–PD-1 agent)	10 mg/kg every 2 wk for 2 y or disease progression or toxicity 200 mg every 3 wk 30 min infusion for 2 y or until disease progression or unacceptable toxicity	FDA approval in March 2017 FDA approval in December 2018

CSCC harbors high mutation burden and is strongly associated with immunosuppressive states. Hence anti–PD-1 treatment has been tried in patients with locally advanced or metastatic cutaneous SCC with isolated reports published in the literature indicating efficacy.

- In a phase I study of Cemiplimab-rwlc (anti–PD-1 agent) for locally advanced or metastatic CSCC as well as from the results of the pivotal phase II study of a cohort of patients with metastatic disease (metastatic-disease cohort), Cemiplimab was administered at 3 mg/kg body weight every 2 weeks and responses assessed every 8 weeks. In phase II study, the primary endpoint was response rate.
- A response rate of 50% was obtained in phase I study, and in the metastatic-disease cohort of phase II, a response rate of 47% was seen.
- The median follow-up was 7.9 months in the metastatic disease cohort of phase II study. Durable responses exceeding 6 months were seen in 57% patients and 82% continued to have a response and to receive Cemiplimab at the time of data cutoff.
- Autoimmune side effects typical of immune checkpoint inhibitors were seen in 15% of patients and the treatment required to be discontinued due to side effects in 7% patients.
- Based on these data, Cemiplimab was approved by the FDA for treatment of locally advanced or metastatic CSCC in June 2018.
- In a multicenter, multicohort, nonrandomized, open-label trial (KEYNOTE-629), patients diagnosed with recurrent or metastatic CSCC that are not cured by surgery or radiation therapy were treated with Pembrolizumab at 200 mg intravenously every 3 weeks for 24 months.
- The objective response rates were 34% and median response duration was not reached. Adverse reactions were similar to those occurring in patients receiving single-agent Pembrolizumab in other clinical trials.

Based on these results, in June 2020, anti–PD-1 agent Pembrolizumab was approved by the FDA for patients with recurrent or metastatic CSCC that is not cured by surgery or radiation therapy (see Table 22.10).

MERKEL CELL CARCINOMA

MCC occurs due to the neoplastic proliferation of the Merkel cells located in the basal layer of the epidermis and hair follicles. These cells, which originate from the neural crest,

are a member of the amine precursor uptake and decarboxylation cell system. Merkel cells serve as tactile sensory cells in lower animals, and they function as a mechanoreceptor in humans. About 2000 new cases of MCC are diagnosed in the United States and the incidence is rising.

Characteristics of MCC

- MCC is an aggressive type of skin cancer.
- Affects older patients in chronically sun-damaged skin of the head and neck region.
- Less common sites are extremities and genitalia.
- Typical presentation is a 0.5 to 1 cm intracutaneous, firm, bluish-purple, nontender nodule.
- Histologically, a small round cell tumor containing neurosecretory cytoplasmic granules that may look similar to small cell carcinoma, melanoma, Ewing sarcoma, and lymphoma.
- Tumor cells stain positive for neuron-specific enolase and anticytokeratin antibody CAM 5.2.
- Polyomaviral DNA integration in >80% of tumor cells supports its role in etiology.
- Polyomavirus-associated MCC has low TMB but likely to express PD-L1.
- In the Polyoma virus-negative MCC, ultraviolet light-mediated DNA damage is believed to result in high TMB.
- Higher incidence of MCC in older subjects suggests clinical relevance of the weakened aging immune system.
- Early spread occurs to locoregional lymph nodes and hematogenously to the distant sites.

Management of MCC: Surgery

- Complete surgical excision of the tumor with lymph node assessment for metastasis by the sentinel lymph node procedure forms the primary treatment.
- In the absence of systemic metastasis, if sentinel lymph node is positive, lymph node dissection from the respective lymph node basin is recommended.
- Adjuvant radiation to the excised site of primary tumor is recommended to prevent local recurrence arising from incomplete resection of tumor or larger size tumor (2 cm or more).

Metastatic MCC: Historically, Cisplatin and Etoposide combination was preferred treatment of MCC due to its high response rates, but frequent recurrences limited median survival to between 8 and 10 months. Other chemotherapeutic agents that have efficacy in MCC include Adriamycin, Cyclophosphamide, Vincristine, and Irinotecan.

Immune therapy of metastatic MCC: Rationale

- PD-L1 is expressed in the tumor microenvironment exhibiting signs of inflammation.
- The infiltrating T lymphocytes demonstrate Polyoma virus large T antigen-specific T cells that exhibit exhaustion markers such as PD-1 and TIM-3.

- Targeting PD-1-PD-L1/2 pathway by anti–PD-1 and anti–PD-L1 agents is now possible and show promising results.
- Polyoma virus-negative MCCs harbor high mutation burden since these tumors are associated with cumulative ultraviolet light exposure.

Avelumab is a fully human anti–PD-L1 IgG1 monoclonal antibody that activates CTL by blocking PD-1–PD-L1 interaction as well as by antibody-mediated cellular toxicity.

- In a phase II open label study of Avelumab at 10 mg/kg dose infused over 1 hour, every 2 weeks in refractory MCC (JAVELIN Merkel 200 study) objective response rate was 31.8% (includes 8 complete responses and 20 partial responses).
- The responses were ongoing in 82% patients and 92% of responses were durable for at least 6 months. Serious irAE occurred in five patients (6%) that included enterocolitis, infusion-related reaction, elevated aminotransferases, chondrocalcinosis, synovitis, and interstitial nephritis in one each.
- In March 2017, Avelumab was approved by the FDA as a first-line treatment of metastatic MCC based on the results of the JAVELIN Merkel 200 study (see Table 22.10).
- Updated analysis of JAVELIN Merkel 200 study confirmed durable responses in patients of recurrent MCC treated with Avelumab. The median OS was 12.9 months, 1 year PFS was 30%, and 1 year OS was 52%.
- Higher probability of responses were seen in patients with lower baseline disease burden, fewer lines of treatment, and PD-L1 positivity. However, durable responses were seen in patients irrespective of above factors.

Pembrolizumab in MCC: In a multicenter nonrandomized open label trial of Pembrolizumab in recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease (KEYNOTE 017 study)

- Objective responses of 56% included complete responses of 24% and partial response of 32%. Median follow-up time was 14.9 months. The 24-month PFS rate was 48.3% and median PFS time was 16.8 months. The 24-month OS was 68.7%.
- Tumor polyoma virus status did not correlate with overall response rate, PFS, or OS. There was a trend toward improved PFS and OS in patients with PD-L1–positive tumors.
- In December 2018, Pembrolizumab was approved by the FDA as a treatment of recurrent locally advanced or metastatic MCC

RARE TUMORS ARISING FROM THE SKIN

Rarely, tumors arise from skin appendages such as in hair follicles, erector pili muscles, apocrine sweat glands, and sebaceous glands. Most of these tumors are benign. The treatment principle is complete surgical excision and lymph node assessment as in melanoma.

Dermatofibrosarcoma Protuberans

This is a rare fibrohistiocytic tumor of the skin and subcutaneous tissue affecting trunk and extremities, demonstrating slow growth and intermediate malignant potential. The t(17:22) cytogenetic abnormality is present in more than 90% patients.

- The translocation t(17;22) between chromosomes 17 and 22 places platelet-derived growth factor-β (PDGF-β) under the control of COL1A1, resulting in upregulation, expression, and activation of tyrosine kinase PDGF-β.
- Imatinib Mesylate is a potent and specific inhibitor of PDGFR-β that is effectively used in neoadjuvant settings and in patients with recurrent disease after surgery.

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23

Acute Leukemia

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INTRODUCTION

Acute leukemia represents a very aggressive, malignant transformation of an early hematologic precursor. The malignant clone is arrested in an immature blast form, proliferates abnormally, and no longer has the ability to undergo maturation. In contrast, the chronic leukemias are characterized by resistance to apoptosis and by accumulation of nonfunctional cells, with the emphasis on proliferation, in contrast to the block in differentiation seen with acute leukemias. Accumulation of the blasts within the bone marrow results in progressive hematopoietic failure, with associated infection, anemia, and thrombocytopenia. These are the complications that often prompt evaluation in newly diagnosed patients.

Acute leukemia continues to be a grave diagnosis because of its rapid clinical course. Patients, particularly those who are younger, require aggressive and urgent evaluation and treatment initiation. As a general rule, treatment is expected to improve quality of life and prolong survival. Unfortunately, many patients present at an advanced age and with comorbid conditions, making cytotoxic approaches difficult. Older or unwell patients who are given the best supportive care survive for a median of only a few months.

The immature, clonally proliferating cells that form blasts are derived from myeloid or lymphoid cell lines. Transformation of granulocyte, RBC, or platelet (myeloid) precursors results in acute

myeloid (myelogenous) leukemia (AML). Acute lymphoblastic (lymphocytic) leukemia (ALL) originates from B or T lymphocytes. This general division has implications for different treatment and diagnostic approaches. It is the first step in classifying the leukemic process occurring in the patient.

EPIDEMIOLOGY

- Estimated new cases in the United States in 2021 are 20,240 for AML (1.1% of all new cancer cases) and 5690 for ALL (0.3% of all new cancer cases).
- AML accounts for 11,400 deaths and ALL accounts for 1530 deaths annually in the United States.
- The risk of developing AML increases with advanced age, the median age being 67 years.
- Seventy-five percent of newly diagnosed patients with AML are older than 60 years.
- ALL is more common in children; 60% to 70% are diagnosed in patients younger than 20 years.

RISK FACTORS

Most patients will have no identifiable risk for developing acute leukemia. Table 23.1 lists the conditions that are associated with an increased risk for developing acute leukemia. Most epidemiologic studies have evaluated the relationship between the risk factors and AML. The conditions that are most commonly associated with AML are chemotherapy or radiation therapy for other cancers (which account for >90% of therapy-related AML), followed by environmental exposures, such as chronic benzene exposure or exposure to ionizing radiation.

TABLE 23.1

Risk Factors for Acute Leukemia

Exposure
Ionizing radiation, benzene, cytotoxic drugs, alkylating agents, cigarette smoking, ethanol use by the mother
Acquired disorders
Myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria, polycythemia vera, chronic myelogenous leukemia, myeloproliferative disorders, idiopathic myelofibrosis, aplastic anemia, eosinophilic fasciitis, myeloma, primary mediastinal germ cell tumor (residual teratoma elements evolve into myeloid progenitors that evolve into AML years later)
Genetic predisposition
Down syndrome, Fanconi anemia, Diamond-Blackfan anemia, Kostmann syndrome, Klinefelter syndrome, chromosome 21q disorder, Wiskott-Aldrich syndrome, ataxia-telangiectasia, dyskeratosis congenita, combined immunodeficiency syndrome, von Recklinghausen disease, neurofibromatosis 1, Shwachman syndrome
Familial
Nonidentical sibling (1:800), monozygotic twin (1:5), first-degree relative (three times increased risk)
Infection
Human T-cell leukemia virus and T-cell ALL

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Ionizing Radiation Exposure Explored in Atomic Bomb Survivors

- Ionizing radiations have a latency period of 5 to 20 years and a peak period of 5 to 9 years in atomic bomb survivors.
- They exhibit a 20- to 30-fold increased risk of AML and chronic myelogenous leukemia (CML).

Chemotherapy

- Therapy-related AML may account for 10% to 20% of new cases.
- Leukemia associated with alkylating agents may be associated with cytogenetic changes of chromosomes 5, 7, and 13. Often there is a multiyear, latent-phase myelodysplastic syndrome preceding the development of AML.
- Topoisomerase II agents, often with an abnormal chromosome 11q23 in the blasts, can rapidly evolve after initial therapy, at a

median of 2 years following exposure.
- Previous, high-dose therapy with autologous transplant leads to a cumulative risk of 2.6% by 5 years, especially with total body irradiation–containing regimens.

CLINICAL SIGNS AND SYMPTOMS

- Ineffective hematopoiesis: Results from marrow infiltration by the malignant cells and a block in differentiation
- Anemia: Pallor, fatigue, and shortness of breath, rarely myocardial infarction or stroke
- Thrombocytopenia: Epistaxis, petechiae, and easy bruising
- Neutropenia: Fever and pyogenic infection
- Infiltration of other organs
- Skin: Leukemia cutis in 10%
- Gum hypertrophy: Especially in monocytic leukemias
- Myeloid (granulocytic) sarcoma: Localized tumor composed of blast cells; will present with prominent extramedullary disease; occasionally associated with chromosome 8;21 translocation; approach to treatment is the same as with overt bone marrow involvement with AML
- Enlarged liver, spleen, and lymph nodes: Common in ALL, occasionally in monocytic leukemia
- Thymic mass: Present in 15% of T-ALL in adults
- Testicular infiltration: Also, a site of relapse for ALL (sanctuary site)
- Retinal involvement
- Central nervous system (CNS) and meningeal involvement
    - 5% to 10% of ALL cases at diagnosis; <5% AML, associated with inv(16), high-blast count, or myeloid sarcoma abutting spine
    - Cerebrospinal fluid (CSF) analysis and prophylaxis are given in every patient with ALL to decrease CNS relapse
    - Symptoms: Headache and cranial nerve palsy, but mostly asymptomatic
- Disseminated intravascular coagulation (DIC) and bleeding
    - Common with acute promyelocytic leukemia (APL) or other AML with blasts whose cytoplasms contain granules; the mechanism is related to tissue factor

release by granules and fibrinolysis; generally improves with all-trans retinoic acid (ATRA, for APL only), the early initiation of which is imperative
    - Can be present in AML inv(16) or monocytic leukemias or can be related to sepsis
- Patients may present with the medical emergencies of tumor lysis syndrome or leukostasis (reviewed later in this chapter)

DIAGNOSTIC EVALUATION

- A complete history and physical examination are an essential part of diagnosis of acute leukemia, including a detailed family history and history of previous chemotherapy or radiation therapy, or of environmental exposures.
- Complete blood count, differential and manual examination of peripheral smear, and peripheral blood flow cytometry are considered when circulating blasts are sufficiently abundant to rapidly establish a diagnosis.
- Coagulation tests include prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, and fibrinogen.
- Complete metabolic panel with calcium, magnesium, phosphorus, and uric acid. Pseudohyperkalemia, as well as a spuriously low glucose and Po_2 (partial pressure of oxygen) can occur with high blast count.
- Bone marrow biopsy and aspirate (with analysis for morphology), cytogenetics (metaphase karyotype), flow cytometry, and cytochemical stains (Sudan black, myeloperoxidase, acid phosphatase, and specific and nonspecific esterase) are used for diagnosis.
- Gene mutation analyses (such as next generation sequencing) of blasts are essential for risk-stratification and are needed to determine subsequent management including treatment with targeted therapy and role of bone marrow transplant.
- Human leukocyte antigen (HLA) testing of patients who are transplant candidates—the test is performed before the patient

becomes cytopenic. Specimen requirements are minimal when DNA-based HLA typing is performed.

- Hepatitis B and C and human immunodeficiency virus antibody titers are obtained.
- Pregnancy test (β-human chorionic gonadotropin), if applicable.
- Electrocardiogram (ECG) and analysis of cardiac ejection fraction should be done prior to the treatment with anthracyclines for AML and ALL patients.
- Lumbar puncture (LP): Performed when signs and symptoms of neurologic involvement are present. Thrombocytopenia and fibrinogen should be corrected prior to the procedure, which should be performed after reduction of peripheral blast count to avoid theoretical inoculation of blasts into uninvolved CSF. Note, in the pediatric patients, LP with intrathecal (IT) chemotherapy is often performed at diagnosis. Obtain cell count, opening pressure, protein level, and submit cytocentrifuge specimen for cytology pathology to review.
- Central venous access should be obtained. Coagulation abnormalities should be corrected if present. It is often possible to initiate induction therapy with normal peripheral veins and await subsidence of coagulopathy to reduce risk of procedural complications.
- Supplemental fluorescent in situ hybridization (FISH) or other assay for PML-RARa, or t(15;17), is performed when APL is suspected; testing for BCR-ABL1, or t(9;22), is performed when CML in blast phase; and when ALL is suspected, check for BCR-ABL, Ph-like signature, and typically FISH for mixed-lineage leukemia (MLL, also known as KMT2) gene rearrangements.

INITIAL MANAGEMENT

The initial management of acute leukemia involves the following:

- Hydration with IV fluids (2-3 L/m^2 per day).

- Tumor lysis prophylaxis and relevant laboratory monitoring should be started.
- Blood product support: Suggestions for prophylactic transfusions are a hemoglobin level of <8 g/dL and a platelet level of <10,000/μL. Platelet transfusion threshold can be higher in the context of fever or bleeding, cryoprecipitate can be used if fibrinogen level is less than normal, and fresh frozen plasma can be used to immediately correct significantly elevated levels of PT and PTT. Platelet transfusion threshold should be increased in APL patients to <50,000/μL in the setting of DIC. The minimum "safe" platelet level required to prevent spontaneous hemorrhage is not known. Additional platelet optimization strategies include avoidance of nonsteroidal anti-inflammatory drugs, aspirin, and clopidogrel-like agents. Deep venous thrombosis prophylaxis with anticoagulants or leg compression devices should be avoided.
- Blood products should be irradiated and given with a white blood cell (WBC) filter (leukopoor or leukoreduced).
- Episodes of fever require blood and urine cultures, followed by treatment with appropriate antibiotics, particularly in the setting of neutropenia (see Chapter 37), and imaging.
- Therapeutic anticoagulation should be given with extreme caution in patients during periods of extreme thrombocytopenia. Adjustment of prophylactic platelet transfusion thresholds or anticoagulants may be required.
- Suppression of menses: High doses of an oral contraceptive pill (combination of ethinyl estradiol and ethynodiol diacetate) can be used for heavy or irregular uterine bleeding during chemotherapy. Leuprolide acetate 3.75 mg intramuscularly every 28 days can also be used to suppress menses.

Tumor Lysis Syndrome

- Tumor lysis syndrome can be spontaneous or can be induced by chemotherapy.

- Risk factors include elevated uric acid, high WBC count, elevated lactate dehydrogenase (LDH), and high tumor burden.
- Laboratory tests indicate elevated potassium (or low potassium with monocytic leukemias), LDH, phosphorus, and uric acid, with a resulting decrease in calcium.
- Patients should be initiated on allopurinol 300 mg daily until WBC falls to below normal levels.
- For hydration, alkalinizing fluids (0.5 NS with 50 mEq sodium bicarbonate, D5W with up to 150 mEq sodium bicarbonate) could be considered to increase solubility of uric acid, minimizing intratubular precipitation. Caution should be taken as alkanizing the urine also promotes calcium-phosphate complex deposition, and normal saline is a viable alternative.
- Uricolytic agents (rasburicase) can be considered if the patient has hyperuricemia (>12) and an elevated creatinine on presentation or has hyperuricemia uncontrolled with allopurinol. Prophylactic rasburicase is not necessary with proper uric acid monitoring due to the quick onset of action of rasburicase.
- Hemodialysis may be required in refractory cases or urgently in the setting of life-threatening hyperkalemia or volume overload if oliguric (see Chapter 39).

Leukostasis

- Occurs with elevated blast counts.
- Symptoms result from capillary plugging by leukemic cells.
- Common signs: dyspnea, headache, confusion, chest pain, and/or hypoxia.
- Initial treatment includes aggressive hydration, chemotherapy to rapidly lower the circulating blast percentage (eg, oral hydroxyurea), or leukapheresis if readily available.
- Transfusions should be avoided, as these may increase viscosity.
- Leukapheresis has not been shown to be superior to chemotherapy for the treatment of leukostasis. However, it can be considered in the setting of organ dysfunction or

hemodynamic instability with an elevated WBC count of >50 to 100. If used, it may be repeated daily in conjunction with chemotherapy until the blast count is <50,000. Leukapheresis should not be used for patients with APL because it may worsen the intrinsic coagulopathy associated with this subtype of leukemia.

CLASSIFICATION

Acute Myeloid Leukemia

Over time, the pathologic classification system from the World Health Organization (WHO) has replaced the French-American-British (FAB) one. The WHO classification system emphasizes recurrent karyotypic and genetic abnormalities over morphology, due to their prognostic relevance (Table 23.2), while still retaining elements of the FAB system to further stratify cases without recurrent genetic abnormalities. Marrow blasts should comprise 20% of the nucleated cells within the aspirate unless t(8;21) or inv(16) is present. The blasts may be characterized as myeloid lineage by the presence of Auer rods; a positive myeloperoxidase, Sudan black, or nonspecific esterase stain; and the immunophenotype shown by flow cytometry. Cell surface markers associated with myeloid cell lines include CD13, CD33, CD34, c-kit (CD117), and HLA-DR. Monocytic markers include CD64, CD11b, and CD14. CD41 (platelet glycophorin) is associated with megakaryocytic leukemia, and glycophorin A is present on erythroblasts. HLA-DR–negative blast phenotype is commonly seen in APL and serves as a rapidly available test corroborating suspicion of this subtype requiring a specific induction therapy.

TABLE 23.2

The World Health Organization (WHO) Classification of Acute Myeloid Leukemia

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
AML with t(6;9) (p23;q34.1); *DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified (NOS)
AML with minimal differentiation (FAB M0)
AML without maturation (FAB M1)
AML with maturation (FAB M2)
Acute myelomonocytic leukemia (FAB M3)
Acute monoblastic/monocytic leukemia (FAB M5)
Pure erythroid leukemia (FAB M6)
Acute megakaryoblastic leukemia (FAB M7)
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

AML, acute myeloid leukemia; FAB, French-American-British.

Acute Lymphoblastic Leukemia

The WHO classification of ALL broadly divides the disease into B-cell, T-cell, and NK-cell leukemias, with subsets being defined by recurrent genetic abnormalities, in particular the presence of BCR-ABL (the *Philadelphia chromosome*). Immunophenotyping of B-lineage ALL reveals the typical lymphoid markers CD19, CD20, CD10, TdT, and immunoglobulin. T-cell markers include TdT, CD2, CD3, CD4, CD5, and CD7.

PROGNOSTIC GROUPS

Acute Myeloid Leukemia

Patients who are older (>60 years) and those with an elevated blast count at diagnosis (>20,000) have a worse prognosis. Therapy-related AML and those with a prior history of myelodysplastic syndromes (MDS) have a worse chance of obtaining a complete remission (CR) and shorter long-term survival. Table 23.3 illustrates the prognostic groups according to cytogenetics and molecular markers.

TABLE 23.3
Risk Groups in Newly Diagnosed Adult Acute Myeloid Leukemia

Risk Category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} [a]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} [a]
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} [a] (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* [b]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, [c] monosomal karyotype [d]
	Wild-type *NPM1* and *FLT3*-ITD^{high} [a]
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

[a]Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5).

[b]t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

[c]Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

[d]Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding, t(8;21), inv(16) or t(16;16)).

Acute Lymphoblastic Leukemia

As in AML, patients with ALL have a worse prognosis when presenting with advanced age or an elevated WBC count. Burkitt-cell (mature B-cell) leukemia or lymphoma has an improved prognosis with intensive chemotherapy and CNS treatments; it usually has a translocation involving chromosome 8q24. Table 23.4 lists the prognostic groups according to cytogenetic analysis.

TABLE 23.4

Prognostic Groups by Cytogenetics in Adult Acute Lymphoblastic Leukemia

Good Risk
8q24 translocations
t(12;21)
t(10;14)
t(7;10)
Hyperdiploidy
Poor Risk
t(9;22) (Philadelphia [Ph] chromosome)
t(4;11)
Hypodiploidy
t(1;19)
9p abnormalities (del(9p), add(9p), der(9)t(V;9)(V;p), i(9q))
Intrachromosomal amplification of chromosome 21 (iAMP21)
Complex karyotype (five or more chromosomal abnormalities)
BCR-ABL1-like (Ph-like) ALL
t(17;19)
Alterations of *IKZF1*
t(v;14q32)/IgH

The presence of t(9;22) (Philadelphia chromosome, Ph, BCR-ABL1 fusion) is the most common abnormality in adults, occurring in 20% to 30% of patients with ALL and in up to 50% of patients in the B-cell lineage. Long-term survival is dismal in this group if treated by

chemotherapy alone. The introduction of tyrosine kinase inhibitors into treatment regimens has improved outcomes, and patients may be recommended to undergo allogeneic transplantation if they are a candidate and have a suitable in first CR. Ph-like (also called BCR/ABL1-like) ALL lacks the hallmark BCR-ABL1 oncoprotein; however, it shares a similar gene expression profile and poor prognosis as Ph-positive ALL. This subtype of ALL frequently harbors *IKZF1* and *CRLF2* alterations and comprises 10% to 15% of pediatric patients and 20% to 30% of adolescents and adults with B-cell ALL.

TREATMENT

AML (Excluding APL)

The goal of "induction" chemotherapy is to obtain a remission, which is correlated with improved survival. Complete response (CR) is defined as the elimination of the malignant clone (marrow blasts <5%) and recovery of normal hematopoiesis (absolute neutrophil count > 1000/μL and platelet count > 100,000/μL). Patients typically have a leukemia cell burden of approximately 10×10^{12} that is reduced to approximately 10×10^{9} by induction. This residual disease may be undetectable morphologically but will certainly lead to relapse in a few months if more therapy is not administered. Additional intensive "postremission" or "consolidation" cycles of chemotherapy are given to further reduce the residual burden in the hope that host-immune mechanisms can suppress the residual leukemia population, thereby leading to sustained, maintenance-free remission. The general approach to induction chemotherapy for adults is shown in Table 23.5. All patients should be considered for clinical trials if available.

TABLE 23.5

Standard Induction for Acute Myeloid Leukemia

"7 + 3," 7 d of infusional cytarabine and 3 d of anthracycline
Cytarabine 100-200 mg/m^2 daily as continuous infusion × 7 d with
Idarubicin 12 mg/m^2 daily bolus for 3 d
OR
Daunorubicin 60-90 mg/m^2 daily bolus for 3 d

In general

- Addition of high-dose cytarabine (HiDAC) or etoposide has been evaluated in published regimens for induction but have not been conclusively shown to be superior to the backbone of 3 days of an anthracycline and 7 days of cytarabine.
- The FLT3-inhibitor midostaurin may be added to chemotherapy and is associated with improved survival in patients whose blasts express this marker.
- Bone marrow aspiration should be repeated at approximately day 14 of induction chemotherapy. If significant residual blasts are present (generally defined as >5%), induction chemotherapy should be repeated ("7 + 3" or can consider "5 + 2" in Table 23.6 for older or frail patients). If significant disease is present (<50% reduction in disease volume), a change in the regimen to age-appropriate HiDAC may be considered.

TABLE 23.6

Consolidation for Acute Myeloid Leukemia

Age < 60
Cytarabine 3 g/m^2 infused over 3 h, q12h on days 1, 3, and 5 (six doses)
Creatinine 1.5-1.9 mg/dL: Decrease cytarabine 1.5 g/m^2 per dose
Age > 60
"5 + 2": Cytarabine 100 mg/m^2 daily as continuous infusion for 5 d and anthracycline (idarubicin 12 mg/m^2 or daunorubicin 45-90 mg/m^2) bolus daily for 2 d
OR
Intermediate-dose cytarabine: 1-1.5 g/m^2 q12h on days 1, 3, 5 OR 1-1.5 g/m^2 daily × 4-5 days

- Older patients (>60 years) may benefit from intensive induction and consolidation treatment. Postremission cytarabine requires dose reduction due to CNS toxicity.

- Older patients or patients who decline intensive induction chemotherapy (ie, 7 + 3) may be candidates for therapy with low-dose cytarabine or hypomethylating agents (azacitidine or decitabine). These agents have lower CR rates (approximately 10%-20%) but lower therapy-related mortality and may be administered in the outpatient setting.
- Older patients or patients who decline intensive therapy may also be candidates for azacitidine plus venetoclax with overall response rate (ORR) rates (approximately 67%) higher than single azacitidine, which is now FDA approved. Patients achieved superior overall survival, a higher rate of remission, more rapid and durable responses, and comparable quality of life. Similar findings were found with decitabine plus venetoclax. Important to note that this regimen is usually administrated initially in the hospital due to the risk of tumor lysis syndrome.

Supportive Care

- Infection is a major cause of morbidity and mortality. Prophylactic antibacterials (quinolones), antifungals (itraconazole, fluconazole, posaconazole, or isavuconazonium), and antivirals (acyclovir) may be given during these periods of prolonged neutropenia. Broad-spectrum antimicrobials are used for neutropenic fever (see Chapter 36).
- Growth factors such as granulocyte colony-stimulating factor (G-CSF) can be considered in the setting of neutropenia and severe infection. They may be used rarely to aid in count recovery. Patients should be off growth factors for a minimum of 7 days prior to a bone marrow biopsy that is being used to document remission as it can confound the interpretation of bone marrow morphology.
- Steroid eye drops are required during HiDAC infusions to reduce the risk of exfoliative keratitis.

AML Postremission Therapy (Excluding APL)

The consolidation options for those patients who enter CR are shown in Table 23.6. HiDAC especially may benefit those patients with good-risk disease [t(8;21), inv(16), *NPM1* mutated/*FLT3* wild-type]. These good-risk patients should not receive allogeneic transplantation in CR1. Consolidation usually consists of four cycles (the minimum effective dose and the number of cycles are not clear). Older patients do not seem to benefit from more than one to two consolidation cycles of a lower-dosed cytarabine-based regimen. Patients with preceding MDS or poor-risk cytogenetics should receive an allogeneic transplantation in CR1, if possible. Patients with intermediate-risk cytogenetics should be considered for an allogeneic transplant, especially if they have a matched sibling donor, though it remains unclear if this provides an advantage for this subpopulation over standard chemotherapy consolidation. Gene mutations may assist in the proper identification of standard-risk patients who would or would not benefit from allogeneic transplant in CR1 (see the Allogeneic Transplantation section).

APL, t(15;17)

The t(15;17) brings together the retinoic acid receptor-α and the promyelocytic leukemia genes, allowing for transduction of a novel protein (PML-RARα). The protein plays a role in blocking differentiation of the promyelocyte, thereby promoting abnormal accumulation within the marrow space. Because the characteristic translocation occurs in this subgroup of AML, therapy incorporates ATRA and/or arsenic trioxide (ATO), which act as differentiating agents. Table 23.7 shows a treatment summary in APL.

TABLE 23.7

Treatment of Acute Promyelocytic Leukemia

	Low to Intermediate Risk	High Risk
Induction	ATRA + ATO	ATRA + anthracycline (idarubicin or daunorubicin) ± cytarabine

	Low to Intermediate Risk	High Risk
		Or
		ATRA + idarubicin + ATO
Consolidation	ATRA + ATO (28 weeks)	ATRA + anthracycline × 3 cycles ± cytarabine
		Or
		Arsenic × 2 cycles followed by anthracycline × 2 cycles
Maintenance (2 y)	None	ATRA 45 mg/m^2 daily for 15 d q3mo + mercaptopurine 50 mg/m^2 daily + MTX 15 mg/m^2 weekly

6-MP, 6-mercaptopurine; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; MTX, methotrexate.

- Therapy with ATRA should be started immediately upon suspicion of APL; therapy can be tailored pending genetic confirmation.
- ATRA + ATO is used for low- to intermediate-risk patients (WBC ≤ 10 × 10^9/L at presentation) as well as an alternative option for higher-risk patients unable to tolerate anthracyclines.
- ATRA + chemotherapy (anthracycline and cytarabine) is used for higher-risk patients (WBC >10 × 10^9/L)
- Time to attain remission may be more than 30 days and a bone marrow biopsy is not performed on day 14.
- Polymerase chain reaction (PCR) should be followed for PML-RARα: Reinduction therapy or allogenic transplantation should be considered if PCR is still positive postconsolidation (but not postinduction); levels should be followed during the maintenance phase. A return of the transcript to positive heralds relapse.
- ATRA (or ATO) syndrome (differentiation syndrome) consists of capillary leak and cytokine release, resulting in fever, leukocytosis, respiratory compromise (dyspnea and infiltrates), weight gain, effusions (pleural and pericardial), renal failure, and hypotension. This syndrome occurs in upward of 25% of patients during induction, with peak occurrences between 1 and 3 weeks into therapy, and is associated with a rapidly rising

neutrophil count. Treat with dexamethasone 10 mg IV BID × 3 days, and then taper over 2 weeks. Discontinuation of ATRA can be considered in severe cases. ATRA may still be safely employed in consolidation or maintenance-phase therapy because the ATRA syndrome is limited to the induction-period neutrophilia.

- A similar differentiation syndrome, not involving ATRA, is seen with the use of ATO.
- Prognosis with APL is very good, with >90% of patients attaining a CR and >70% long-term disease-free survival.
- Patients are typically classified as high-risk (WBC ≥ 10,000), intermediate-risk (WBC < 10,000 and platelets ≤ 40), or low-risk (WBC < 10,000 and platelets > 40) disease at diagnosis.

Relapsed Disease

- ATO 0.15 mg/kg/d until second CR.
- Median of 57 days to remission.
- Baseline electrolytes (Ca, K, Mg), creatinine, and ECG (for prolonged QT interval).
- Monitoring: At least weekly electrolytes and ECG. Keep K > 4.0 mEq/L and Mg > 2.0 mg/dL and reassess if QTc interval > 500.
- Patients commonly develop APL differentiation syndrome similar to ATRA.
- Eighty-five percent of patients achieve CR.
- ATO may be given as consolidation at a dose of 0.15 mg/kg/d, 5 days per week (Monday through Friday) for 25 doses.
- Patients achieving CR (PCR negative) should receive consolidation with an autologous transplant, if eligible. Patients with persistent positive PCR results should be considered for an allogeneic transplant.

Relapsed or Refractory AML

Relapse of AML after initial CR is common (60%-80% of all cases). Relapse occurring within 6 months of induction or a patient never

attaining remission with induction (refractory disease) complicates many reinduction attempts. The prognosis for long-term survival in this subset of patients is poor with chemotherapy alone, and all patients who are able to tolerate the treatment should be evaluated for allogeneic transplantation. Some treatment approaches are described below.

- Reinduction with "7 + 3" or HiDAC.
- Reinduction may be an option for those patients who relapse more than 6 to 12 months after initial induction.
- Subsequent remissions are usually of shorter duration (<50% of the duration of the preceding remission).
- Etoposide, mitoxantrone, ± cytarabine (EM or MEC).
- FLAG: fludarabine, cytarabine, and G-CSF (can be combined with idarubicin or mitoxantrone).
- Clofarabine ± cytarabine or cyclophosphamide.
- FLT3 inhibitor gilteritinib has been approved in this setting, while others such as sorafenib, midostaurin, and quizartinib are currently under investigation.
- IDH 1 and 2 inhibitors ivosidenib (also approved in the upfront setting for newly diagnosed AML patient not eligible for intensive therapy) and enasidenib are approved.
- In cases of isolated CNS relapse, it should be considered that systemic relapse almost always follows soon and that a systemic therapy is also required.

Acute Lymphoblastic Leukemia

General scheme: induction, consolidation, maintenance, and CNS treatment.

Several strategies exist for the treatment of adult ALL. Table 23.8 illustrates the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen used at many North American centers. Modification of the Larson regimen reported by Cancer and Leukemia Group B (CALGB, now Alliance for Clinical Trials in Oncology) Study 19802, shown in Table 23.9, is also

commonly used. Other options based on the Hoelzer and Linker regimens are also available. Adolescent and young adult patients (age ≤ 40) with ALL should be treated with a pediatric-like regimen such as CALGB 10403. Patients with Ph + ALL or Ph-like ALL should be treated with a tyrosine kinase inhibitors targeting Philadelphia chromosome along with the chemotherapy regimen. Rituximab, a monoclonal antibody targeting CD20, may also be incorporated into treatment for ALL patients with positive immunophenotype expressing CD20.

TABLE 23.8
The Hyper-CVAD and MTX/HIDAC Regimen

Cycles 1, 3, 5, and 7
Cyclophosphamide 300 mg/m^2 IV over 3 h q12h on days 1-3 (six doses)
Mesna 600 mg/m^2/d IV as continuous infusion on days 1-3
Vincristine 2 mg IV on days 4 and 11
Doxorubicin 50 mg/m^2 IV on day 4
Dexamethasone 40 mg PO daily on days 1-4 and 11-14
G-CSF 10 μg/kg/d SQ starting after chemotherapy
Cycles 2, 4, 6, and 8
Methotrexate 200 mg/m^2 IV over 2 h on day 1, followed by
Methotrexate 800 mg/m^2 IV over 22 h on day 1
Leucovorin 50 mg starting 12 h after methotrexate completed, followed by leucovorin 15 mg every 6 h × eight doses, dose adjusted on the basis of methotrexate levels
Cytarabine 3 g/m^2 IV over 2 h every 12 h on days 2 and 3 (four doses)
Methylprednisolone 50 mg IV twice daily on days 1-3
G-CSF 10 μg/kg/d SQ starting after chemotherapy
CNS prophylaxis [a]
Methotrexate 12 mg intrathecal (IT) on day 2
Cytarabine 100 mg IT on day 8
Maintenance therapy [b] **(POMP) × 2 y**
Mercaptopurine 50 mg PO three times daily
Methotrexate 20 mg/m^2 PO weekly
Vincristine 2 mg IV monthly
Prednisone 200 mg/d for 5 d each month
Dosage adjustments
Vincristine reduced to 1 mg if bilirubin 2-3 mg/dL (omitted if bilirubin >3 mg/dL)
Doxorubicin decreased to 50% for bilirubin 2-3 mg/dL, decreased to 25% if bilirubin 3-5 mg/dL, and omitted if bilirubin >5 mg/dL
Methotrexate reduced to 50% if creatinine clearance 10-50 mL/min, and a decrease to

50%-75% for delayed excretion, nephrotoxicity, or grade ≥3 mucositis with prior courses
High-dose cytarabine decreased to 1 g/m^2 if patient ≥60 y, creatinine ≥1.5 mg/dL, or MTX level >20 μmol/L at the completion of the MTX infusion

CNS, central nervous system; G-CSF, granulocyte colony-stimulating factor; MTX, methotrexate.

[a]Dosing interval based on risk stratification (see text).

[b]Maintenance therapy is not given in Burkitt-cell leukemia/lymphoma.

TABLE 23.9
The Modified Larson Regimen

Modules A1 and A2
Cyclophosphamide 1000 mg/m^2 IV on day 1 [a]
Daunorubicin 60 mg/m^2 IV on days 1-3 [a]
Vincristine 1.5 mg/m^2 (capped at 2 mg) IV days on 1, 8, 15, 22
Prednisone 60 mg/m^2/d PO on days 1-21 [a]
L-Asparaginase (*Escherichia coli*) 6000 IU/m^2 SQ/IM on days 5, 8, 11, 15, 18, 22
G-CSF 5 μg/kg/d SQ starting on day 4
Modules B1 and B2
Methotrexate 15 mg intrathecal (IT) on day 1
Cyclophosphamide 1000 mg/m^2 IV on day 1
Cytarabine 2000 mg/m^2/d IV on days 1-3
G-CSF 5 μg/kg/d SQ starting on day 4
Modules C1 and C2
IT methotrexate 15 mg on days 1, 8, 15
Vincristine 1.5 mg/m^2 (capped at 2 mg) IV on days 1, 8, 15
Methotrexate 1000 mg/m^2 IV over 4 h on days 1, 8, 15
Methotrexate 25 mg/m^2 PO q 6 h × 4 doses beginning 6 h after initiation of IV methotrexate on days 1, 8, 15
Leucovorin 25 mg/m^2 IV on days 2, 9, 16; given 30 h after initiation of IV methotrexate, followed by leucovorin 5 mg/m^2 PO q 6 h until methotrexate level is < 0.05 μM
Prolonged maintenance (continue until 24 mo after diagnosis)
Vincristine 2 mg IV on day 1 of every 4 wk
Prednisone 60 mg/m^2/d PO on days 1-5 of every 4 wk
6-Mercaptopurine 60 mg/m^2/d PO on days 1-28
Methotrexate 20 mg/m^2 PO on days 1, 8, 15, 22

CNS, central nervous system.

[a]Dosage reductions for age ≥ 60 y: no cyclophosphamide, daunorubicin 60 mg/m^2 on days 1 to 3, and prednisone 60 mg/m^2 on days 1 to 7.

Supportive Care

The regimens described previously incorporate growth factors to reduce neutropenia and allow more scheduled chemotherapy to proceed. All patients will require blood product support at some point during the treatment. Those patients treated with hyper-CVAD receive prophylactic antimicrobials (ie, levofloxacin 500 mg daily, fluconazole 400 mg daily, bactrim DS or pentamidine and valacyclovir 500 mg bid).

CNS Disease

- The CNS is a sanctuary site.
- CNS disease is diagnosed by the presence of neurologic deficits at diagnosis *or* by five or more blasts per microliter of CSF.
- Therapy for CNS disease is IT, methotrexate (MTX), or cytarabine (Ara-C), often alternating. These will be given twice weekly until disease clears, then weekly for 4 weeks, and then resume the prophylaxis schedule. Radiation (fractionated to 2400-3000 cGy) can also be considered, being aware of potential late-term cognitive toxicities.
- Prophylaxis with IT chemotherapy decreases CNS relapse and decreases the use of prophylactic cranial irradiation. The prophylactic chemotherapy schedule is dependent on the relapse risk and type of leukemia.
- In the hyper-CVAD regimen, patients with high-risk disease (ie, LDH level >2.3 times upper limit of normal or elevated proliferative index) should receive eight prophylactic IT treatments, and those with low-risk disease (no factors) receive six prophylactic IT treatments. Patients with mature B-cell disease or a history of documented CNS involvement will require 16 IT therapies. No prophylactic cranial irradiation is given.

Relapsed ALL

The bone marrow is the most common site of relapse but relapse can occur in the testes, eye, and CNS. Patients with late relapse (more than 6 months to 1 year from induction) may respond to reinduction with the original regimen, but most patients are enrolled onto clinical trials. Early relapse or refractory disease will require changing the treatment plan and evaluation for allogeneic transplantation once remission is achieved. For patients with relapsed B-ALL, blinatumomab and inotuzumab ozogamicin are increasingly being used followed by other chemotherapeutic agents including evaluation for clinical trials. Whereas with relapsed T-ALL, nelarabine is considered followed by chemotherapy including trials. Several chemotherapy options are available, including the following:

- Blinatumomab
- Inotuzumab ozogamicin
- Chimeric antigen receptor (CAR) T-cells
- HiDAC with or without idarubicin, mitoxantrone, or fludarabine
- MTX, vincristine, asparaginase (not PEG), steroids (MOAD)
- Dasatinib, imatinib, nilotinib, or ponatinib (if Ph-positive)
- Hyper-CVAD, if not given initially
- Vinorelbine with mitoxantrone, fludarabine, steroids, or rituximab
- Nelarabine (for T-ALL)
- Clofarabine ± cytarabine or cyclophosphamide
- Liposomal vincristine
- Venetoclax in combination with chemotherapy

Use of Targeted Therapy and Immunotherapy in ALL

1. Blinatumomab (Blincyto)
    - Bispecific T-cell engager (BiTE) monoclonal antibody directed at both CD19 on B-cell ALL cells, and CD3 on the patient's T-cells, which enables the T-cells to recognize the malignant B-cells that express CD19. After the T-cell links with the malignant cell, it is activated and exerts cytotoxic activity on the ALL cell.

- Compared to chemotherapy-based regimen (FLAG ± anthracycline; high-dose cytarabine-based; high-dose MTX-based; or clofarabine monotherapy–based), blinatumomab was shown to have an improved CR with full hematologic recovery (34% vs 16%), as well as CR with incomplete hematologic recovery (44% vs 25%), leading to an improved overall survival in a randomized study.
- It is given as a continuous intravenous infusion over 4 weeks, followed by a 2-week treatment-free interval; maintenance treatment may continue as 4-week continuous infusions every 12 weeks for about four cycles.
- Unique and serious side effects include cytokine release syndrome and neurological toxicities. Patients are hospitalized for the first 9 days of the continuous infusion to monitor for cytokine release syndrome and neurologic toxicity.

2. Rituximab (Rituxan)

- Anti-CD20 chimeric murine–human monoclonal antibody
- Given in addition to the previously noted regimens in frontline treatment if CD20+ B-ALL

3. Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib

- Tyrosine kinase inhibitors targeting the Philadelphia chromosome [t(9;22)].
- Dasatinib or imatinib should be considered in addition to previously noted regimens in frontline treatment if Ph positive.
- Role in maintenance therapy could be considered as maintenance therapy in the nontransplant and postallogeneic transplant setting.
- May be used as treatment or palliation in combination with steroids for patients unable to tolerate aggressive chemotherapy.
- Choice of tyrosine kinase inhibitor agent should be selected based on BCR/ABL mutation analysis in the relapse setting. Second- and third-generation TKIs typically have improved clinical responses and outcomes. However, when selecting a TKI, consider the clinical scenario and discuss the adverse events prior to initiating therapy.

4. CAR T-cells

- This technology involves collecting a patient's T-cells, "reprograming" them with a genetically engineered immunoreceptor using a viral vector, expanding them, then reinfusing them into the patient.
- Studies with CD19-directed CAR T-cells are ongoing and are available only at certain centers with infrastructure for cellular therapy.
- A phase II multicenter study evaluated the use of CD19-directed CAR-T cells in 75 children and young adults with relapsed or refractory B-ALL. The ORR was 81%, with all patients whose disease responded achieving negative MRD. The 24-month relapse-free survival and OS rates were 62% and 66%, respectively.
- Tisagenlecleucel is FDA approved for the treatment of patients up to the age <26 years for relapsed/refractory B-ALL.
- As with blinatumomab, cytokine-release syndrome and neurological toxicities do occur early in the treatment course. Severe cytokine-release syndrome can be treated with the anti-interleukin-6 receptor antibody tocilizumab.
- Relapses were a result of tumor cell evasion of the CAR T-cells (loss of expression of CD19).

- Larger trials with long-term follow-up are needed to verify the efficacy of this treatment.
- Second-generation CAR T-cell products are in advanced phases of development.

5. Inotuzumab ozogamicin
    - Humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic agent. The conjugate binds to CD22 and the CD22-conjugate complex is rapidly internalized and the calicheamicin is released. The calicheamicin binds to the minor groove of DNA and thus induces double-strand cleavage and apoptosis.
    - Compared to FLAG, high-dose cytarabine plus mitoxantrone or high-dose cytarabine, inotuzumab ozogamicin was shown to have improved CR or CR with incomplete hematologic recovery was 29.4% vs 80.7%, leading to improved progression-free survival and overall survival.
    - It is dosed on days 1, 8, and 15 of each 3 to 4 weeks up to six cycles.
    - Serious side effects include veno-occlusive disease and increased aspartate aminotransferase, hyperbilirubinemia, and alanine aminotransferase levels.

TRANSPLANTATION

Autologous Transplantation

- Autologous transplant appears to have minimal benefit in acute leukemia in CR1.
- It may be performed in older patients (age > 60).

Allogeneic Transplantation

- Allogeneic transplant has the added benefit of “graft versus leukemia” effect.
- In the setting of unrelated donor searches, the prolonged time needed to identify a donor needs to be considered at the time of diagnosis. Referral to a transplant center is preferred as early as possible in the treatment plan.
- It is considered for all patients with relapsed or refractory disease, as it is the option that may yield long-term survival.
- Reduced-intensity conditioning transplantation is reasonable for patients unable to proceed with ablative treatment secondary to comorbidities or advanced age.

- Outside of possible CAR-T therapy, at the time of relapse, allogeneic bone marrow transplant is the only curative option.

Acute Myeloid Leukemia

- It is performed in the first CR or early in the course for patients with poorer risk cytogenetics or transformation from MDS.
- Patients with good-risk AML [t(8;21), inv(16)), *NPM1* mutated] or APL [t(15;17)] should not be transplanted in CR1.
- Patients with intermediate-risk cytogenetics may be offered allogeneic transplant, especially if they have a sibling donor, though superiority to standard postremission chemotherapy has not been demonstrated prospectively in this group.
- Gene mutations may be able to help stratify intermediate-risk patients with normal cytogenetics as having a poorer or more favorable outcome, assisting in the decision of the usefulness of transplantation in CR1. Patients with *NPM1* and *CEBPA* mutations (without *FLT3*-ITD mutations) may have a good prognosis and may not benefit from transplant in CR1. *FLT3*-ITD mutations are a negative predictor of outcome.
- When transplanted in CR1, overall survival is 50% to 60%; it decreases to 25% to 40% when performed for patients in CR2 and is <10% for patients with refractory disease.
- In a randomized fashion, BMT-CTN 0901 evaluated the role of reduced-intensity conditioning compared to myeloablative preparative regimens for allogeneic transplant in patients with AML. This study was stopped early because of high-relapse incidence with reduced intensity versus myeloablative conditioning (48.3% vs 13.5%). Overall survival was higher with myeloablative regimens, but not significantly. Reduced intensity conditioning resulted in lower complication rates, but due to the higher relapse rates, there was a statistically significant advantage in relapse-free survival with myeloablative conditioning.

Acute Lymphoblastic Leukemia

- Allogeneic HCT is considered in adolescent and young adult (AYA) and adult patients with evidence of high-risk features (including cytogenetics, Ph positive, Ph-like disease, or persistent MRD). HLA tissue typing and bone marrow transplant referral should be considered for newly diagnosed and relapsed patients to ensure timely donor identification, workup, and allogeneic transplant if warranted.

PROGNOSIS AND SURVIVAL

Adults with acute leukemia remain at high risk for disease-related and treatment-related complications. In AML, the prognostic characteristics of the disease are associated with survival. Good-risk AML is associated with an 80% to 90% CR rate, and long-term disease-free survival is 60% to 70% in younger patients treated with HiDAC. Poor-risk features are associated with only a 50% to 60% chance of obtaining a CR, and a high risk of relapse is observed in those patients who enter CR. Additionally, gene mutations have been identified as correlating with prognosis in AML, especially in the intermediate-risk group in which cytogenetics cannot guide postremission therapy. In these patients, *FLT3*-ITD and *TP53* mutations confer a poor prognosis. In patients who are *FLT3*-ITD negative, *NPM1* and *CEBPA* identify a good prognostic subgroup.

CR and long-term outcome have improved for adult patients with ALL who were receiving intensive courses of chemotherapy. With the hyper-CVAD and modified Larson regimens, 85% to 90% of patients will obtain a CR with a median duration of CR of 30 months. Five-year survival is approximately 40%.

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24

Chronic Lymphoid Leukemias

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative neoplasm characterized by the accumulation of monoclonal mature B cells. It is the most common form of leukemia in the Western world, constituting 1.2% of new cancer cases and 0.7% of all cancer deaths. Over the past 2 decades, median survival times have improved, due to major advances in diagnostic techniques, identification of prognostic and predictive markers, and development of novel therapies. This chapter will discuss the diagnosis and management of CLL.

PRESENTATION AND DIAGNOSIS

CLL is generally considered a disease of the elderly, with a median age at diagnosis of 70 years, and affects men twice as often as women. Although the majority of patients present with an asymptomatic lymphocytosis, symptoms typically associated with disease include recurrent infections, fatigue, and constitutional symptoms such as fevers, drenching night sweats, and unintentional weight loss. Other clinical features include nontender lymphadenopathy, hepatosplenomegaly, or autoimmune complications such as hemolytic anemia, pure red cell aplasia, or immune-mediated thrombocytopenia.

According to the guidelines published by the National Cancer Institute–sponsored Working Group (NCI-WG), diagnostic criteria for CLL include the following:

- Absolute lymphocytosis (≥5 × 10^3/μL) in peripheral blood, sustained for at least 3 months
- Peripheral smear demonstrating a mature B-cell phenotype, often with smudge cells
- Flow cytometry with monoclonal expression of CD5, CD19, and CD23 with low levels of CD20, CD79b, and surface immunoglobulin
- Molecular cytogenetics, although not necessary for diagnosis, can identify prognostic chromosomal abnormalities and help distinguish CLL from other lymphoid disorders

As flow cytometry can be performed on peripheral blood, a bone marrow biopsy is not necessary to make the diagnosis. However, a bone marrow biopsy can be helpful in ascertaining the cause of cytopenias and should be considered in patients with anemia or thrombocytopenia. In addition, a bone marrow biopsy is typically performed prior to and after treatment in order to evaluate for response. Monoclonal B lymphocytosis is characterized as <5 × 10^3/μL B lymphocytes in the absence of lymphadenopathy, hepatosplenomegaly, and disease-related cytopenias. Small lymphocytic lymphoma (SLL) is defined by <5 × 10^3/μL B lymphocytes, with nodal, splenic, or other extramedullary involvement in the absence of cytopenias due to bone marrow infiltration.

STAGING AND PROGNOSIS

The most commonly used staging methods include the Rai and Binet staging systems (Table 24.1). In addition, multiple molecular and genetic abnormalities detected by fluorescent in situ hybridization and conventional karyotyping aid in prognostication. Deletion (del)

13q and mutation of immunoglobulin variable heavy chain (IGHV) are associated with favorable outcomes. In contrast, del(11q), del(17p), tumor protein 53 (TP53) mutation, and a complex karyotype (≥3 chromosomal abnormalities) are associated with inferior outcomes. Immunophenotypic expression of CD38 and zeta-associated protein 70, a serum β2 microglobulin level ≥4 mg/L, and NOTCH1 and SFB3B1 mutations have also be identified as poor prognostic markers. The international prognostic index for CLL provides disease risk stratification based on five clinical, biochemical, and genetic parameters.

TABLE 24.1

Rai and Binet Staging of Chronic Lymphocytic Leukemia

Rai stage	**Criteria**
0	Lymphocytosis only (≥5 × 10^3/μL in peripheral blood)
I	Lymphocytosis with lymphadenopathy
II	Lymphocytosis with hepatosplenomegaly
III	Lymphocytosis with anemia (Hgb <11 g/dL)
IV	Lymphocytosis with thrombocytopenia (Plt <100 × 10^3/μL)
Binet stage	**Criteria**
A	Hgb >10 g/dL, Plt >100 × 10^3/μL, and <2 lymph node areas involved
B	Hgb >10 g/dL, Plt >100 × 10^3/μL, and ≥3 lymph node areas involved
C	Hgb >10 g/dL or Plt <100 × 10^3/μL

Hgb, hemoglobin; Plt, platelets.

Computed tomography (CT) scans are not required at diagnosis or for staging purposes but may be useful to evaluate for the presence of internal enlarged lymph nodes not palpable by physical examination. Positron emission tomography scans do not provide beneficial information beyond that of CT scanning and is not indicated except when evaluating for Richter transformation.

COMPLICATIONS

Patients with CLL can develop infectious complications due to an inadequate humoral response, impaired complement activation, hypogammaglobulinemia, and immunosuppressive treatments.

Other complications include disease transformation to large B-cell lymphoma (Richter transformation), prolymphocytic leukemia (PLL), acute lymphoblastic leukemia, and multiple myeloma, which occurs in 10% to 15% of cases. Patients are also at an increased risk of developing solid second primary malignancies, which is associated with inferior survival compared to patients without a preexisting CLL diagnosis.

TREATMENT

CLL often exhibits an indolent course, and most patients can be monitored until there is evidence for symptomatic or progressive disease. The indications for treatment of CLL per the NCI-WG guidelines include the following:

- Significant and persistent fatigue
- Persistent fever >100.5 °F or 38.0 °C for 2 or more weeks without evidence of infection
- Night sweats for more than 1 month without evidence of infection
- Unintentional weight loss of ≥10% in the previous 6 months
- Progressive or symptomatic splenomegaly (>6 cm below costal margin), lymphadenopathy (>10 cm), or extranodal involvement
- Progressive lymphocytosis: Increase of >50% in 2 months or doubling time <6 months
- Progressive marrow failure with worsening or new anemia or thrombocytopenia
- Autoimmune anemia or thrombocytopenia poorly responsive to steroids

Once treatment is indicated, many therapeutic options are available such as small molecule inhibitors, including Bruton's

tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL-2) inhibitors, as well as standard chemoimmunotherapy. Optimal front-line therapy for CLL is dependent on a number of patient-specific factors including age, comorbidities, performance status, and disease molecular profile. For example, the presence of del(17p) or TP53 mutations is associated with resistance to standard chemoimmunotherapy regimens and favorable responses with non-chemotherapeutic agents such as small molecule inhibitors. In contrast, mutation of IGHV predicts for a favorable outcome with fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in younger, fit patients.

Front-Line Therapy

BTK inhibitors such as ibrutinib or acalabrutinib and the BCL-2 inhibitor, venetoclax, in combination with obinutuzumab are preferred treatment options for patients with previously untreated CLL, regardless of del(17p) or TP53 mutation status (Table 24.2).

TABLE 24.2
Treatment for Chronic Lymphocytic Leukemia

Regimen	Dosing
Acalabrutinib ± obinutuzumab	Acalabrutinib: 100 mg PO twice daily until disease progression Obinutuzumab: cycle 2: 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15; cycle 3-7: 1000 mg day 1 *Cycle length = 4 wk*
Ibrutinib	420 mg PO daily until disease progression
Venetoclax + obinutuzumab *(front line)*	Venetoclax: Week 1: 20 mg PO daily starting day 22 of cycle 1 Week 2: 50 mg PO daily Week 3: 100 mg PO daily Week 4: 200 mg PO daily Week 5 and beyond: 400 mg PO daily for 12 cycles Obinutuzumab: cycle 1: 100 mg day 1, 900 mg day 2, then 1000 mg days 8 and 15; cycle 2-6: 1000 mg day 1 *Cycle length = 4 wk; 12 cycles total*

Regimen	Dosing
Venetoclax + rituximab *(relapsed/refractory)*	Venetoclax: Week 1: 20 mg PO daily Week 2: 50 mg PO daily Week 3: 100 mg PO daily Week 4: 200 mg PO daily Week 5 and beyond: 400 mg PO daily until disease progression Rituximab: 375 mg/m^2 IV day 1 of cycle 1 followed by 500 mg/m^2 day 1 of cycles 2-6 (begin after receiving venetoclax at 400 mg daily for 7 d) *Cycle length = 4 wk*
Bendamustine + rituximab	Bendamustine (90 mg/m^2 for previously untreated; 70 mg/m^2 for relapsed/refractory) IV days 1-2 of cycles 1-6 Rituximab 375 mg/m^2 IV day 1 of cycle 1 followed by 500 mg/m^2 IV day 1 of cycles 2-6 *Cycle length = 4 wk; 6 cycles total*
Chlorambucil + obinutuzumab	Chlorambucil: 0.5 mg/kg PO days 1 and 15 of cycles 1-6 Obinutuzumab: cycle 1: 100 mg day 1, 900 mg day 2, then 1000 mg days 8 and 15; cycle 2-6: 1000 mg day 1 *Cycle length = 4 wk; 6 cycles total*
Fludarabine, cyclophosphamide, and rituximab	Fludarabine 25 mg/m^2 IV days 1-3 of cycles 1-6 Cyclophosphamide 250 mg/m^2 IV days 1-3 of cycles 1-6 Rituximab 375 mg/m^2 IV day 1 of cycle 1 followed by 500 mg/m^2 IV day 1 of cycles 2-6 *Cycle length = 4 wk; 6 cycles total*
Idelalisib + rituximab	Idelalisib: 150 mg PO twice daily until disease progression Rituximab: 375 mg/m^2 IV day 1 followed by 500 mg/m^2 every 2 wk × 4 doses followed by every 4 wk × 3 doses
Duvelisib	25 mg PO twice daily until disease progression

BTK Inhibitors

A number of phase III studies have demonstrated the superiority of BTK inhibitors over traditional chemoimmunotherapy in the front-line setting. The RESONATE-2 trial that compared ibrutinib to chlorambucil in previously untreated CLL/SLL patients who were 65 years or older determined ibrutinib to be superior to chlorambucil, in terms of overall response rate (86% vs 35%), progression-free survival (median PFS: not reached [NR] vs 18.9 months; hazard ratio [HR] 0.16; 95% confidence interval [CI] 0.09-0.28), and overall survival (OS: HR 0.16; 95% CI 0.05-0.56). Long-term follow-up at 5 years continued to show a survival benefit

with ibrutinib. The iLLUMINATE trial that compared ibrutinib plus obinutuzumab to chlorambucil plus obinutuzumab (CO) in previously untreated CLL/SLL patients demonstrated longer PFS with ibrutinib plus obinutuzumab (NR vs 19 months; HR 0.23; 95% CI 0.15-0.37) at a median follow-up time of 31.3 months. Interestingly, the Alliance A041202 trial, which demonstrated a PFS benefit with ibrutinib monotherapy and ibrutinib-rituximab over bendamustine-rituximab (BR), suggested that addition of the anti-CD20 monoclonal antibody to ibrutinib did not provide additional benefit. In this phase III study, the 2-year PFS was found to be significantly higher with ibrutinib monotherapy (87% vs 74%; HR 0.39; 95% CI 0.26-0.58) and with ibrutinib-rituximab (88% vs 74%; HR 0.38; 95% CI 0.25-0.59) compared to BR. However, there was no significant PFS difference between ibrutinib and ibrutinib-rituximab (HR 1.00; 95% CI 0.62-1.62), nor a difference in OS between any of the three arms. Overall, ibrutinib was generally well tolerated with low rates of discontinuation. The most common adverse events (≥30%) included neutropenia, anemia, thrombocytopenia, fatigue, nausea, diarrhea, rash, and musculoskeletal pain. Less common but clinically significant adverse events included hemorrhage, infections, cardiac arrhythmias, hypertension, tumor lysis syndrome, and second primary malignancies. The efficacy of ibrutinib in the younger population was demonstrated in the E1912 trial, which compared ibrutinib with rituximab to FCR chemoimmunotherapy in previously untreated CLL patients aged 70 years or younger. At a median follow-up of 33.6 months, ibrutinib-rituximab showed a survival advantage compared to FCR (PFS: HR 0.35, 95% CI 0.22-0.56; OS: HR 0.17, 95% CI 0.05-0.54). This benefit was observed across all subgroup analyses except among patients with IGHV mutation, where no statistical difference was observed between the two treatments.

The second-generation BTK inhibitor, acalabrutinib, was approved for CLL based on the ELEVATE-TN trial, which compared acalabrutinib, monotherapy and in combination with obinutuzumab, to CO in previously untreated CLL. A PFS benefit was observed with

both acalabrutinib containing arms compared to CO after a follow-up time of 28.3 months (acalabrutinib: NR vs 22.6 months, HR 0.2, 95% CI 0.13-0.3; acalabrutinib with obinutuzumab: NR vs 22.6 months, HR 0.1, 95% CI 0.06-0.17).

BCL-2 Inhibitor

Venetoclax, a BCL-2 inhibitor, in combination with obinutuzumab (VO) is an established front-line regimen based on the CLL-14 trial, which demonstrated a PFS benefit with fixed duration VO compared to CO (HR 0.35; 95% CI 0.23-0.53). This PFS benefit was consistently observed among all subgroups including those with del(17p), TP53, and unmutated IGHV. The most common adverse events (≥20%) were related to myelosuppression, which occurred primarily within the first month of therapy and resolved over time. Fatigue, diarrhea, nausea, upper respiratory tract infection, cough, edema, and musculoskeletal pain were also observed. Due to the profound, rapid activity of the drug, venetoclax requires a dose ramp-up over 5 weeks in conjunction with aggressive tumor lysis prophylaxis and rigorous monitoring to prevent serious clinical consequences of tumor lysis syndrome including cardiac arrhythmia and acute renal failure.

Chemoimmunotherapy

Based on the phase III data discussed above, the role of chemoimmunotherapy has decreased substantially in CLL. Chemoimmunotherapy is not recommended for any patients with del(17)p or TP53 mutation due to lack of efficacy. Additionally, the FCR regimen should only be considered as a front-line regimen in younger patients with IGHV mutation. The decision to use BR or CO in older patients who lack high-risk features should be based on pertinent medical comorbidities and/or patient preference.

Relapsed/Refractory Therapy

Despite multiple effective front-line treatment options for CLL, patients inevitably relapse and require additional therapy. All

patients should be evaluated for new cytogenetic abnormalities with initiation of each line of therapy, as up to 50% of patients can develop del(17p) or TP53 mutation over time. In addition, patients who progress while on ibrutinib should be evaluated for mutations associated with acquired resistance to BTK inhibitors. Many of the front-line regimens that were not used as initial therapy can be considered in subsequent lines (Table 24.2).

Ibrutinib was initially approved for relapsed patients based on the RESONATE trial that demonstrated superior outcomes compared to ofatumumab (HR 0.22; 95% CI 0.15-0.32). The MURANO trial, which compared venetoclax and rituximab (VR) to BR in relapsed/refractory CLL, demonstrated a PFS advantage favoring VR (HR 0.17; 95% CI 0.11-0.25). This benefit was maintained across all subgroups including patients with del(17p). The ASCEND trial supported the use of acalabrutinib in patients who did not previously progress on a BTK inhibitor. In this phase III study, patients received either acalabrutinib or investigator's choice of idelalisib with rituximab or BR. A PFS advantage was seen with acalabrutinib compared to investigator's choice therapy (HR 0.31; 95% CI 0.20-0.49). The PI3K inhibitors, idelalisib and duvelisib, are also available for relapsed/refractory CLL. Idelalisib, although originally approved in combination with rituximab, has gone out of favor due to adverse events including serious opportunistic infections, hepatotoxicity, colitis, and pneumonitis. Duvelisib was more recently approved for the treatment of CLL/SLL after at least two prior therapies following the randomized DUO trial in which a longer PFS benefit was seen compared to ofatumumab. At this time, the only therapy that has been proven to be potentially curative in CLL is allogeneic stem cell transplantation. However, this is often not an option for the elderly population that CLL typically affects or patients with multiple comorbidities.

DEVELOPMENTS

Multiple studies are currently investigating doublet and triplet combinations, fixed duration, and measurable residual disease–guided treatment approaches for previously untreated and relapsed CLL/SLL. In addition, the noncovalently binding BTK inhibitor, pirtobrutinib, has demonstrated promising efficacy in heavily pretreated CLL/SLL patients including those who have mutations associated with resistance to ibrutinib (BTK C481). Lastly, the ongoing TRANSCEND CLL-004 study that evaluated the CD19-directed chimeric antigen receptor T-cell therapy, lisocabtagene maraleucel, as monotherapy or in combination with ibrutinib, showed encouraging and potentially durable responses in heavily pretreated disease.

OTHER CHRONIC LYMPHOID LEUKEMIAS

Other rare lymphoid malignancies include PLL and hairy cell leukemia (HCL). B-cell PLL is an aggressive mature lymphoid neoplasm that is generally associated with ≥55% circulating prolymphocytes and TP53 mutation or complex karyotype. Although there is no consensus on the optimal therapy for B-cell PLL, case series have shown ibrutinib to be efficacious. HCL is a rare B-cell lymphoid neoplasm characterized by abundant cytoplasm and "hairy" projections. Front-line treatments include pentostatin and cladribine. Concurrent rituximab in combination with cladribine improves minimal residual disease-negative complete response rates compared to delayed rituximab. Vemurafenib and moxetumomab are effective for relapsed disease.

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Chronic Myeloid Leukemia

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EPIDEMIOLOGY

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by dysregulated proliferation of mature granulocytes secondary to deregulated tyrosine kinase. CML accounts for approximately 15% of newly diagnosed leukemias in adults with a median age at diagnosis of 65 years. The age-adjusted incidence of CML is 3.3 per 1 million person-years, with a male predominance. The average person's lifetime risk of being diagnosed with CML is about 1 in 526. There has been a notable increase in the incidence and prevalence of CML over the past decade, likely related to the increased use of Philadelphia (Ph) chromosome testing and improved survival with the use of tyrosine kinase inhibitors (TKIs).

PATHOPHYSIOLOGY

CML is a clonal disorder of hematopoietic stem cells. The reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22)], the Ph chromosome, is the initiating event and the diagnostic hallmark of CML. This translocation results in the transfer of the Ableson murine leukemia (*ABL1*) gene on chromosome 9 to an area of chromosome 22, termed the breakpoint cluster region (BCR), resulting in the BCR-ABL1 fusion gene. This fusion gene results in the expression of the constitutively active protein tyrosine kinase, BCR-ABL1 oncoprotein, which plays the central role in the

pathogenesis of CML leading to an uncontrolled proliferation of granulocytes, predominantly neutrophils, but also eosinophils and basophils at various maturation stages.

Ninety percent of patients will have a typical Ph chromosome, t(9;22). Five percent will have variant translocations either involving chromosome 22 and a chromosome other than 9 or chromosomes 9 and 22 plus other chromosomes. The remaining usually have a cryptic translocation not identified by routine cytogenetics but can be revealed with interphase fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR). If these are negative, a diagnosis of atypical CML or another etiology should be considered.

Several distinct BCR-ABL1 fusion proteins are generated from alternative chromosome 22 breakpoints. The three most common are the $p210^{BCR\text{-}ABL1}$, $p190^{BCR\text{-}ABL1}$, and $p230^{BCR\text{-}ABL1}$. In CML, the p210 oncoprotein is most commonly seen. This occurs from fusion of exon a2 from the *ABL* gene to either exon b2 or b3, which is the major BCR (M-*bcr*) on chromosome 22, forming b2a2 or b3a2 transcripts which produces p210. Rarely, the p190 variant is seen in CML, which occurs when a2 from the *ABL* gene fuses to the minor BCR (m-*bcr*), exon e1, on chromosome 22 creating the e1a2 transcript, which produces the p190 oncoprotein. The p230 oncoprotein is produced from fusion of a2 to exon 19, which is the micro-BCR (μ-*bcr*), forming the e19a2 transcript. The p230 oncoprotein is most commonly seen in chronic neutrophilic leukemia.

Additional cytogenetic abnormalities may develop in over 80% of patients as they advance to accelerated phase and blast phase, and they can even be seen in approximately 7% of patients at the time of diagnosis. Finding cytogenetic abnormalities at diagnosis or developing clonal cytogenetic evolution while on treatment confers a worse prognosis especially when it includes one of the “major route” abnormalities such as trisomy 8, trisomy 19, duplication of the Ph chromosome, and isochromosome 17q.

DIAGNOSIS AND CLINICAL FEATURES

Symptoms and Signs

Patients with CML present in the chronic phase in over 85% of cases, and the diagnosis is generally incidental. Up to 50% of patients are asymptomatic at presentation. Symptoms are usually related to underlying cytopenias or splenomegaly. The following are the common symptoms at presentation:

- Fatigue and malaise
- Anorexia and weight loss
- Sweats and low-grade fever
- Left upper quadrant discomfort/early satiety associated with splenomegaly
- Dyspnea on exertion
- Bleeding from thrombocytopenia

Laboratory Features

The diagnosis of CML may be accomplished with peripheral blood testing. Patients typically present with leukocytosis and a left-shifted white blood cell differentiation revealing varying degrees of neutrophil maturity from myeloblasts to mature neutrophils. Basophilia can be seen in almost all cases, and eosinophilia can also be seen in a majority of cases. A small population of blasts (typically <5%) can be seen in chronic phase. Although identification of Ph chromosome on cytogenetic analysis or the detection of BCR-ABL fusion transcript by FISH analysis or PCR in peripheral blood may be sufficient for initial presumptive diagnosis, a bone marrow aspiration/biopsy and cytogenetic analysis are mandatory before initiation of treatment for staging purposes and to detect additional chromosomal abnormalities (other than Ph chromosome). This would guide the choice of initial therapy and subsequent disease monitoring, including clonal evolution. The absolute value of the transcript level by PCR testing is not important for initial diagnosis or staging, but it is essential for subsequent evaluation of response.

Differential Diagnosis

- Leukoerythroblastic reaction in response to infection, inflammation, or malignancy
- Chronic myelomonocytic leukemia
- Juvenile myelomonocytic leukemia
- Chronic eosinophilic leukemia
- Chronic neutrophilic leukemia
- Atypical CML
- Idiopathic myelofibrosis
- Essential thrombocytosis
- Polycythemia vera

DISEASE PHASES (STAGING)

CML is characterized by three distinct clinical phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP). CP is generally accepted as <10% blasts and <20% basophils, and BP is generally accepted as >30% blasts. However, there are various accepted criteria for AP in CML. The four main classification systems for the AP are the International Blood and Marrow Transplant Registry, the MD Anderson Cancer Center, the World Health Organization, and the European LeukemiaNet (ELN). These four classification systems are listed in Table 25.1. While over 85% of patients are diagnosed in the more indolent stage termed CP, if left untreated, most patients will eventually progress within 3 to 5 years to an AP, followed by the BP. Twenty to 25% of patients can progress directly from CP to BP. BP can be either a myeloid BP or a lymphoid BP, both of which can also present with extramedullary disease.

TABLE 25.1

Criteria for Accelerated Phase in Chronic Myeloid Leukemia

Criteria	IBMTR	MDACC	ELN	WHO
Blasts (PB or BM)	10%-29%	15%-29%	15%-29%	10%-19%

Criteria	IBMTR	MDACC	ELN	WHO
Blasts plus promyelocytes (PB or BM)	>20%	≥30% with blasts <30%	≥30% with blasts <30%	–
Basophils (PB)	≥20%	≥20%	≥20%	≥20%
WBC	>100 × 10^9/L	>100 × 10^9/L	–	Unresponsive to tx
Thrombocytopenia	<100 × 10^9/L Unrelated to tx	<100 × 10^9/L Unrelated to tx	<100 × 10^9/L Unrelated to tx	<100 × 10^9/L Unrelated to tx
Thrombocytosis	>100 × 10^9/L Unresponsive to tx	–	–	>100 × 10^9/L Unresponsive to tx
Anemia	Hgb <8 g/dL, Unresponsive to tx	–	–	–
Splenomegaly	Unresponsive to tx	Unresponsive to tx	–	Unresponsive to tx
Cytogenetics	CE, on treatment	CE, on treatment	ACA/Ph+ major route, on treatment	ACA/Ph+ major route, complex karyotype, or 3q26.2 abnormalities, at diagnosis; any new ACA/Ph+ on treatment
Response to TKI (provisional criteria)	–	–	–	Failure to achieve CHR to the first TKI, or any hematological, cytogenetic, or molecular indication of resistance to two sequential TKIs, or occurrence of ≥2 mutations in BCR-ABL1 during TKI therapy

ACA/Ph+, additional chromosome abnormalities in Philadelphia-positive cells; BM, bone marrow; CE, clonal evolution; CHR, complete hematologic response; ELN, European

Leukemia Net; IBMTR, International Blood and Marrow Transplant Registry; MDACC, MD Anderson Cancer Center; PB, peripheral blood; WHO, World Health Organization.

The various criteria used to define accelerated phase in CML are listed in Table 25.1.

PROGNOSTIC FACTORS

Prognosis of patients with CML has improved markedly over past 2 decades with the introduction of TKIs. Patients with CP BCR-ABL+ CML in western countries now have a life expectancy close to the general population. However, life expectancy for patients in AP or BP remains relatively poor. For this reason, one of the most important prognostic factors is disease phase at the time of diagnosis. Two other key prognostic factors include acquisition of or presentation with additional chromosomal abnormalities and response to treatment. The additional chromosomal abnormalities of concern in CML are +8, +Ph (second Ph chromosome), isochrome 17q, +19, −7/7q−, 11q23, 3q26.2, and complex karyotypes. These chromosomal abnormalities have been linked to shorter survival and poorer response to TKIs.

For survival risk estimation in CP CML, various risk scores have been validated. The Sokal and Hasford risk scores are derived from patients treated with conventional chemotherapy or recombinant interferon alpha (rIFNα), and these risk scores use clinical and laboratory features at diagnosis such as age, spleen size, platelet count, and blast percentage in peripheral blood. The Hasford score also includes eosinophilia and basophilia. The Sokal score was used in most of the TKI trials given its general acceptance. The European Treatment and Outcome Study (EUTOS) and the newer EUTOS long-term survival (ELTS) scores are also available. The ELTS score is particularly helpful to estimate the risk of death from CML (leukemia-related death) in patients treated with TKIs, as many patients treated with TKIs die from other causes. For this reason, the ELN recommends using the ELTS risk score in their ELN 2020

recommendations for treating CML. The four risk scores (Sokal, Hasford, EUTOS, ELTS) are compared in Table 25.2.

TABLE 25.2
Risk Scores

Risk Category	Variables	Risk Index	Classification
Sokal			
	Age, spleen size, blast percentage, platelet count	<0.8	Low
		0.8-1.2	Intermediate
		>1.2	High
Hasford			
	Age, spleen size, blast percentage, platelet count, eosinophils, basophils	≤780	Low
		781-1480	Intermediate
		>1480	High
EUTOS			
	Spleen, basophils	>87	High
		≤87	Low
ELTS			
	Age, spleen, platelets, blasts	≤1.5680	Low
		>1.5680 but ≤2.2185	Intermediate
		>2.2185	High

Sokal risk index was defined based on patients treated with conventional chemotherapy. Hasford risk index was defined based on patients treated with rIFNα-based regimens. EUTOS was defined based on patients treated with imatinib.

Sokal score: EXP [0.0116 × (age − 43.4) + 0.0345 × (spleen size [cm below costal marigin] − 7.51) + 0.188 × [(platelet count/700)^2 − 0.563] + 0.0887 × (myeloblasts − 2.1)].

Hasford score: [0.666 when age ≥50 y + 0.042 × (spleen size [cm below costal marigin]) + 1.0956 (when platelet count ≥1500 × 10^9/L) + 0.0584 × myeloblasts + 0.2039 (when basophils ≥3%) + 0.0413 × eosinophils (%)] × 1000.

EUTOS score: (7 * basophils) + (4 * spleen size).

ELTS score: 0.0025 × (age/10)3 + 0.0615 × spleen size below costal margin + 0.1052 × blasts in peripheral blood + 0.4104 × (platelet count/1000) − 0.5.

TREATMENT

Overview

Historically, treatment options for CML included conventional cytotoxic chemotherapy with hydroxyurea, busulfan, and interferon α. Allogeneic hematopoietic stem cell transplantation was used as the only potentially curative option. In the past 2 decades, TKIs have revolutionized the treatment of CML as well as changing treatment algorithms, treatment goals, monitoring tools, and the expectations of patients and physicians. The response criteria for CML are reviewed in Table 25.3. For most patients, current guidelines recommend starting treatment with a TKI. When selecting an initial TKI, the disease state, risk score (if in CP), patient comorbidities, medications, and underlying mutations will be important in determining which TKI to begin with. The TKIs are generally well tolerated with significant improvement in efficacy over time. The second-generation TKIs have efficacy against certain mutations, which are reviewed in Table 25.4. Myelosuppression is common to all agents, but each TKI has its own unique side effects which are reviewed below.

TABLE 25.3
CML Response Criteria

<table>
<tr><th>Hematologic Response</th><th colspan="2">Cytogenetic Response</th><th>% Ph (Bone Marrow)</th><th>Molecular Response</th><th>% BCR-ABL1 (IS) (Peripheral Blood or Marrow)</th></tr>
<tr><td rowspan="8">Complete:
• WBC <10 × 10^9/L
• Basophils <5%
• No immature granulocytes
• Platelet count <450 × 10^9/L
• Nonpalpable spleen</td><td colspan="2">Minimal</td><td>66-95</td><td></td><td rowspan="2">>10</td></tr>
<tr><td colspan="2">Minor (mCyR)</td><td>36-65</td><td></td></tr>
<tr><td rowspan="6">Major</td><td>Partial (PCyR)</td><td>1-35</td><td></td><td>1 to <10</td></tr>
<tr><td rowspan="5">Complete (CCyR)</td><td rowspan="5">0</td><td></td><td>>0.01 to <1</td></tr>
<tr><td>Major (MMR; MR^3)</td><td>≤0.1</td></tr>
<tr><td>MR^4</td><td>≤0.01</td></tr>
<tr><td>$MR^{4.5}$</td><td>≤0.0032</td></tr>
<tr><td>Undetectable</td><td>0</td></tr>
</table>

The response criteria for treatment of chronic myeloid leukemia. A complete hematologic response is defined by the laboratory and clinical criteria listed. A cytogenetic response depends on the percentage of Ph+ cells, which can be assessed with chromosome banding analysis from bone marrow samples. A molecular response is assessed by Q-PCR of the ratio of BCR/ABL1 to ABL1 transcripts, represented on a log scale (IS).

TABLE 25.4
BCR-ABL1 Resistance Mutations and Sensitive TKIs

Mutation	Recommended Treatment Options
T315I	Ponatinib
Y253F, F359V	Dasatinib, bosutinib, ponatinib
E255V	Dasatinib
F317L	Bosutinib, nilotinib, ponatinib
V299L	Imatinib, nilotinib, ponatinib

There are various mutations which have been identified which render certain TKIs resistant. The more common mutations that are paired with TKIs with known sensitivity are listed in this table.

Adapted from Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *J Clin Oncol*. 2009;27(3):469-471. doi:10.1200/JCO.2008.19.8853

Historic Treatments

Hydroxyurea

Hydroxyurea is a cytotoxic antiproliferative agent that is administered orally and is used when a patient has an elevated white blood cell count (>80 × 10^9/L) to allow rapid control of blood counts. It induces hematologic responses in 50% to 80% of patients and is continued until confirmation of diagnosis; however, it does not alter the disease course. Allopurinol may be added to prevent tumor lysis syndrome when starting hydroxyurea.

Interferon

rIFNα-based regimens were the standard therapy for CP CML before the discovery of imatinib. Majority of patients achieved complete

hematologic response (CHR) although complete cytogenetic responses (CCyR) were noted in only a minority of patients. While effective and even curative in some patients, with earlier studies showing 10-year overall survival (OS) in >70% of patients who achieve CCyR, these agents had significant adverse effects that greatly impaired quality of life and adherence to treatment. IFN is no longer recommended as frontline treatment in CML. However, it can be considered in specific circumstances such as pregnancy, given its relative safety compared to TKIs.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation has been the only potentially curative treatment for CML for decades. It remains the most viable treatment option for patients diagnosed in advanced phase (accelerated or blast) and patients who have failed at least two TKIs. CML is a disease in which graft-versus-leukemia effect plays an important role, and there are multiple reports of the use of donor lymphocyte infusions leading to durable complete remissions. An analysis from the Center for International Blood and Marrow Transplant Research reported outcomes on 2444 patients who received myeloablative allogeneic stem cell transplant in first CP and survived in continuous complete remission for ≥5 years. OS for the entire patient population was 94% at 10 years and 87% at 15 years. Compared to matched general population, these patients had a 2.5 times higher risk of death at 10 years due to complications such as multiorgan failure, infection, graft-versus-host disease, relapsed disease, and secondary malignancies. However, mortality rates approached that of the general population at 15 years post–allogeneic transplant for those who survived. Improvements in HLA typing, management of infections, supportive care, conditioning regimens, and immunosuppressive agents have contributed to a significant improvement in transplant outcomes. Reduced-intensity regimens have been safely used in older patients and patients with comorbidities. In recent years, advances in alternative donor transplantation including the use of haploidentical donors and

unrelated umbilical cord blood as stem cell sources have made allogeneic transplants available to patients that previously were unable to find a matched related or unrelated donor. While there have been no randomized, controlled trials supporting the use of maintenance TKI therapy posttransplant, some centers recommend posttransplant TKI maintenance based on small, observational studies in patients who had advanced phase disease prior to transplant or detectable BCR-ABL1 mRNA by RT-PCR following transplant due to a higher probability of relapse. This remains an area for further evaluation with randomized, controlled trials.

Tyrosine Kinase Inhibitors

Imatinib

Imatinib was the first TKI to receive Food and Drug Administration (FDA) approval for CP CML in 2001. Imatinib is a phenylaminopyrimidine derivative that inhibits the BCR-ABL tyrosine kinase by competitive binding at the ATP-binding site, as well as the receptor tyrosine kinase for c-kit, platelet-derived growth factor, and stem cell factor. The phase 3 International Randomized Study of Interferon and STI571 was the landmark trial for imatinib in CML which compared imatinib 400 mg/d to interferon-α (IFN- α) plus low-dose cytarabine. At 18 months, imatinib was favored based on an improved rate of CCyR (76.2% vs 14.5%, $P < .001$) and freedom from progression to AP or BP (96.7% vs 91.5%, $P < .001$). In a long-term follow-up analysis (median follow-up of 10.9 years), patients who received imatinib had an estimated OS rate of 83.3%, a CCyR rate of 83%, and a 10-year major molecular response (MMR) rate of 93%. Of note, only 48.3% of patients remained on imatinib at the time of median follow-up.

Imatinib 400 mg daily is the recommended starting dose as first-line therapy for CP CML and 600 mg daily in AP or BP. Major side effects include edema/fluid retention, myelosuppression, hepatotoxicity, gastrointestinal symptoms, muscle cramps, arthralgias, rash, and fatigue. In patients with significant underlying

renal impairment, another TKI should be considered in the first-line setting. Some of these side effects will resolve over time, and some will resolve with a drug holiday. Imatinib generics are also available now and have similar efficacy and safety as branded imatinib.

Dasatinib

Dasatinib is a second-generation TKI approved for first-line treatment in CML. Dasatinib also inhibits the Src family kinases and was proven to be significantly more potent than imatinib in vitro. The Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION) trial was the pivotal phase 3 trial which compared dasatinib 100 mg daily to imatinib 400 mg daily in newly diagnosed CP CML. Dasatinib showed improved 12-month confirmed CCyR (cCCyR) versus imatinib (77% vs 66%, P = .007), which was the primary outcome. In a planned 5-year follow-up analysis, dasatinib had higher rates of MMR (76% vs 64%, P = .0022) and $MR^{4.5}$ (42% vs 33%, P = .025), higher proportion of BCR-ABL1 transcript IS ≤10% at 3 months (84% vs 64%, P < .0001), and fewer transformation to AP or BP (4.6% vs 7.3%). Despite the more rapid and deeper response, there was no improvement in OS (91% vs 90%, HR 1.01) or progression-free survival (PFS) (85% vs 86%, HR 1.06). These results were also confirmed by several other investigators.

Dasatinib 100 mg daily is the recommended starting dose as first- and second-line treatment for CP CML and 140 mg daily in AP or BP. The major side effects associated with dasatinib include fluid retention (specifically, pleural and pericardial effusions), QTc prolongation, pulmonary arterial hypertension, and bleeding secondary to platelet dysfunction from SRC inhibition. Underlying history of congestive heart failure or other cardiopulmonary disease is a contraindication for using dasatinib in the first line. Patients on antiplatelet agents or anticoagulants should be monitored closely.

Nilotinib

Nilotinib is another second-generation TKI, which is a structural analog of imatinib with improved potency compared to imatinib. Nilotinib in two dosages (300 mg twice daily or 400 mg twice daily) was compared to imatinib in the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) trial. This trial favored nilotinib (both dosages) over imatinib with improvement in rates of MMR at 12 months (44% for 300 mg dose vs 43% for 400 mg dose vs 22% for imatinib) and CCyR by 12 months (80% for 300 mg dose vs 78% for 400 mg dose vs 65% for imatinib). After 10 years of follow-up data, nilotinib 300 mg twice daily had improved cumulative rates of MMR (77.7% vs 62.5%, $P < .0001$) and $MR^{4.5}$ (61% and 39.2%, $P < .0001$). Like the results seen with dasatinib, there was no significant improvement in 10-year PFS (86.2% vs 89.9% vs 87.2%) or OS (87.6% vs 90.3% vs 88.3%).

Nilotinib 300 mg BID is the recommended dose for first-line CP CML and 400 mg BID is the recommended starting dose for AP or second-line treatment. Major side effects include cardiovascular events (occurred in 20% of patients over 10 years), headache, skin rashes, indirect hyperbilirubinemia, hyperglycemia, and pancreatitis. Given the rates of cardiovascular complications, underlying coronary artery disease, cerebrovascular disease, and peripheral arterial disease are contraindications to starting nilotinib in the first-line setting. Uncontrolled diabetes and history of pancreatitis are also contraindications to starting nilotinib first-line.

Bosutinib

Bosutinib is the third second-generation TKI approved in the first-line setting for CML. It is another potent BCR-ABL1 and Src family kinase inhibitor. It was approved with the results of the Bosutinib Trial in First-Line Chronic Myelogenous Leukemia Treatment (BFORE) trial which compared bosutinib 400 mg daily versus imatinib 400 mg daily. The MMR rate at 12 months for bosutinib was greater than imatinib (47% vs 37%, $P = .02$), and the rate of CCyR at 12 months was also improved (77% vs 66%, $P = .0075$). The 2-year cumulative rates of CCyR favored bosutinib (76% vs 66%, $P = .005$),

as did the 2-year cumulative MMR (57% vs 34%, P = .0036), MR^4 (27% vs 10%, P = .0249), and $MR^{4.5}$ (15% vs 3%, P = .0542). Similar to the other second-generation TKIs, the estimated 2-year OS were not different (99% vs 97%).

Bosutinib 400 mg daily is the recommended dose for first-line CP CML and 500 mg daily is recommended for second-line, AP, and BP. Significant side effects include transient diarrhea, elevations in transaminases, and renal dysfunction. Bosutinib should be avoided in the first-line in patients with underlying inflammatory bowel disease or renal dysfunction.

Ponatinib

Ponatinib is a third-generation TKI approved for patients with CML who were resistant to two or more TKIs or if a T315I mutation is present as this is the only TKI with activity against this mutation. In the Ponatinib Ph+ ALL and CML Evaluation (PACE) trial, patients with either resistance/intolerance to dasatinib or nilotinib or T315I mutation were treated with ponatinib 45 mg daily. 56% of patients achieved a major cytogenetic response (MCyR) by 12 months. In a 5-year follow-up, 60% of patients achieved MCyR at any point and 82% remained in MCyR at 5 years. The estimated 5-year OS was 73%.

Ponatinib 45 mg daily is the recommended dose for patients who were resistant or intolerant to at least two prior TKIs or harbor a T315I mutation. Arterial occlusive events occurred in 31% of patients, most of which were serious. Other notable side effects include hepatotoxicity, heart failure, venous thromboembolic events, and skin rash.

Response Assessment

Patients should have a complete blood count monitored regularly (eg, every 2 weeks) after starting treatment to watch for myelosuppression from TKIs and evaluate for a hematologic response. Regular bone marrow examination is not necessary given

the accuracy of RT-PCR testing in peripheral blood; however, patients require monitoring of quantitative RT-PCR every 3 months until an MMR is obtained, then it can be monitored every 3 to 6 months. ELN 2020 CML treatment milestones are listed in Table 25.5. If a patient does not respond adequately, has a suboptimal response, or progresses after initial response to TKI, reevaluation is warranted with bone marrow examination, cytogenetics, and BCR-ABL1 kinase domain mutational analysis.

TABLE 25.5

Milestones for CML Treatment Using BCR-ABL1 (IS)

	Optimal Response	Warnings	Failure
Baseline	Not applicable	High-risk ELTS score High risk ACA	Not applicable
3 Mo	BCR-ABL1 ≤10%	BCR-ABL1 >10%	>10% if confirmed within 1-3 mo
6 Mo	BCR-ABL1 ≤1%	BCR-ABL1 1%-10%	BCR-ABL1 >10%
12 Mo	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1%	BCR-ABL1 >1%
Then, and at any time	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1%, loss of ≤0.1% (MMR)	>1%, resistance mutations, high-risk ACA

The definitions are the same for patients in chronic phase, accelerated phase, and blast phase and apply also to second-line treatment, when first-line treatment was changed for intolerance.

Adapted from Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-984. doi:10.1038/s41375-020-0776-2. https://creativecommons.org/licenses/by/4.0/

Treatment Discontinuation

Given the success of TKIs in CP CML in combination with the financial burden of long-term treatment and the potential for side effects, multiple trials were conducted to determine the feasibility of TKI discontinuation, otherwise known as "treatment-free remission." The Stop Imatinib 1 trial, the EURO-SKI trial, and another large meta-analysis by Campiotti et al were the first few

trials to address this issue. These studies showed that approximately half of patients were able to maintain a long-term remission after stopping TKIs. In the patients who relapsed, most of which occurred in the first 6 months, they were able to achieve and maintain a durable response after restarting their prior TKI. The National Comprehensive Cancer Network® (NCCN®) criteria for TKI discontinuation are listed in Table 25.6. When discontinuing TKIs, 20% to 30% of patients experienced withdrawal symptoms of musculoskeletal pain and/or arthralgias. However, these symptoms resolved over time with supportive care.

TABLE 25.6

National Comprehensive Cancer Network® (NCCN®) Criteria for Discontinuing Tyrosine Kinase Inhibitors

Age ≥18-years-old.
Chronic phase CML. No history of accelerated or blast phase.
On approved TKI therapy for at least 3 y.
Prior evidence of quantifiable BCR-ABL1 transcript.
Stable molecular response (MR^4) for ≥2 y, documented on at least four tests performed 3 mo apart.
Access to a reliable qPCR test with a sensitivity of detection of at least $MR^{4.5}$ and that provides results within 2 wk.
Monthly molecular monitoring for the first 6 mo following discontinuation, bimonthly during months 7-12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR^3).
Prompt resumption of TKI within 4 wk of a loss of MMR with monthly molecular monitoring until MMR is reestablished, then every 3 mo thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 mo of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed and monthly molecular monitoring should be continued for another 6 mo.

Note: The current guidelines version is 2.2022. There is no change to the content referenced above between V1.2022 and V 2.2022.

Omacetaxine

Omacetaxine is a semisynthetic form of homoharringtonine, which is a natural alkaloid obtained from various *Cephalotaxus* species. It binds to the A-site cleft of the ribosomal subunit, leading to a reversible inhibition of protein synthesis and promotion of apoptosis. The semisynthetic derivative, omacetaxine, has been shown to have benefit in imatinib-resistant CML and for those patients with T315I mutation. Evidence is based on two phase 2 studies. The first study examined the use of omacetaxine in patients with imatinib-resistant CML harboring T315I mutation and showed favorable complete hematologic response, MCyR, and CCyR in 77%, 23%, and 16%, respectively. The second phase 2 study included patients who had failed or were intolerant to at least two TKIs. The CHR, MCyR, and CCyR were 70%, 18%, and 8%, respectively, with a median duration of response of 11 months. Omacetaxine was found to be effective in patients with advanced-phase CML, particularly AP, with median PFS and OS of 3.6 and 14.3 months, respectively. The most frequent grade 3/4 toxicities are thrombocytopenia, neutropenia, anemia, and diarrhea. Omacetaxine is FDA approved for CML patients in CP or AP who had failed or were intolerant to at least two TKIs.

SUMMARY

Treatment of CML has advanced dramatically in the past 2 decades with the development of TKIs. As reported above, the average life expectancy of patients with CP CML is now similar to age-matched controls. Imatinib, dasatinib, nilotinib, and bosutinib are the TKIs approved for the first-line treatment. The second-generation TKIs have also shown efficacy against some of the common resistance mutations. There are new TKIs on the horizon, such as asciminib, with different binding sites which have shown promise in phase 1 studies. Omacitaxine and IFN-α still have a role in certain clinical scenarios. Allogeneic stem cell transplantation still has a role in patients with advanced phase disease, accelerated or blast, or after

the failure of two prior TKIs. Future strategies are focusing on combination therapy and newer agents with the hope of achieving deeper responses and an ability to cure CML.

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26

Chronic Myeloproliferative Neoplasms

Yogen Saunthararajah

INTRODUCTION

Chronic myeloproliferative neoplasms (MPNs) are clonal proliferations of myeloid precursors that stand out clinically because of an increase in at least one peripheral blood count or a substantial increase in bone marrow fibrosis. The World Health Organization (WHO) recognizes the following entities (Table 26.1):

TABLE 26.1

The 2016 World Health Organization Classification Scheme for Myeloid Neoplasms (Subtypes of AML and MDS Not Shown)

1.Myeloproliferative neoplasms (MPN)1.1 Chronic myeloid leukemia (CML), *BCR-ABL* $^{+}$1.2 Polycythemia vera (PV)1.3 Essential thrombocythemia (ET)1.4 Primary myelofibrosis (PMF) PMF, prefibrotic/early stage; PMF, overt fibrotic stage1.5 Chronic neutrophilic leukemia (CNL)1.6 Chronic eosinophilic leukemia, not otherwise specified (NOS)1.7 MPN, unclassifiable
2.MDS/MPN2.1 Chronic myelomonocytic leukemia (CMML)2.2 Juvenile myelomonocytic leukemia2.3 Atypical chronic myeloid leukemia (aCML), *BCR-ABL* $^{-}$2.4 MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)2.5 MDS/MPN unclassifiable
3.Myeloid neoplasms associated with eosinophilia and abnormalities of *PDGFRA, PDGFRB, or FGFR1*3.1 Myeloid neoplasms associated with *PDGFRA* rearrangement3.2 Myeloid neoplasms associated with *PDGFRB* rearrangement3.3 Myeloid neoplasms associated with *FGFR1* rearrangement (8p11 myeloproliferative syndrome)
4.Myelodysplastic syndromes (MDS)
5.Acute myeloid leukemia (AML)

1. Chronic myelogenous leukemia (CML), *BCR-ABL* positive
2. Chronic neutrophilic leukemia (CNL)

3. Polycythemia vera (PV)
4. Primary myelofibrosis (PMF)—PMF, prefibrotic early stage; PMF, overt fibrotic stage
5. Essential thrombocythemia (ET)
6. Chronic eosinophilic leukemia, not otherwise specified (NOS)
7. MPN, unclassifiable

CML is discussed in Chapter 25 because of its unique treatment paradigm. This chapter is limited to a discussion of the three "classical" and more common MPNs: PV, ET, and PMF. These three neoplasms share clinical characteristics, including propensities to thrombosis and hemorrhage, splenomegaly, debilitating systemic symptoms, cytopenias of some lineages even as others are increased, and a risk of leukemic transformation. The overlap in clinical features, which sometimes confounds attempts at disease classification, reflects overlap at the level of causative mutations, illustrated by a common high frequency of the *JAK2* V617F mutation. Shared biologic strands are revealed also by evolution of both PV and ET into PMF in some patients and a common risk for transformation into acute myeloid leukemia (AML). Overlap can also occur with myelodysplastic syndromes (MDS), and MDS/MPN overlap neoplasm is a classification recognized by the WHO.

PATHOPHYSIOLOGY AND DIAGNOSIS

Molecular Mechanism

The MPNs are clonal diseases driven by combinations of molecular abnormalities, most of which can be found in all the MPN subtypes, although individual mutations do have specific clinicopathologic associations. For example, the *JAK2* mutation that substitutes phenylalanine for valine at position 617 (V617F) causes cytokine-independent (constitutive) activation of downstream messengers through the JAK-STAT, PI3K, and AKT pathways and is found in 95% of patients with PV and 50% to 60% with ET or idiopathic

myelofibrosis. Mutated *JAK2* is found in >50% of patients with Budd-Chiari syndrome suggestive of a masked myeloproliferative disorder. The *CSF3R* mutation is strongly linked with CNL. Inactivating mutations in *EZH2* (a polycomb repressor complex component which is also deleted by chromosome 7q loss) are more evenly distributed but do have an association with increased platelet counts. Inactivating mutations in another polycomb repressor component *ASXL1* are highly associated with PMF, and interestingly, with transformation of PV or ET into PMF. Increasing knowledge regarding the molecular basis of MPNs is useful for diagnosis and prognosis (Table 26.2) and hopefully will prove increasingly useful in guiding therapy. Testing for the *JAK2* V617F mutation by different techniques (polymerase chain reaction, restriction enzyme digestive pyrosequencing) is sensitive and specific and readily available as a diagnostic tool.

TABLE 26.2

WHO Diagnostic Criteria for Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF)

	PV (Requires All 3 Major, or First 2 Major and the Minor Criterion	ET (Requires All 4 Major Criteria, or First 3 Major and the Minor Criterion)	PMF (Requires All 3 Major and at Least 1 Minor Criteria)

	PV (Requires All 3 Major, or First 2 Major and the Minor Criterion	ET (Requires All 4 Major Criteria, or First 3 Major and the Minor Criterion)	PMF (Requires All 3 Major and at Least 1 Minor Criteria)
Major criteria	1. Hgb >16.5 g/dL (men), >16.0 g/dL (women) OR hematocrit >49% (men), >48% (women) OR increased red cell mass >25% above mean normal predicted value 2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes 3. Presence of *JAK2V617F* or *JAK2* exon 12 mutation	1. Platelet count ≥450 × 10^9/L 2. BM biopsy showing proliferation mainly of megakaryocytes with large and mature morphology; no significant increase or left shift in neutrophil or erythroid proliferation, and very rarely, minor (grade 1) increase in reticulin fibers. 3. Not meeting WHO criteria for *BCR-ABL* $^+$ CML, PV, PMF, MDS, or other myeloid neoplasms 4. Presence of *JAK2, CALR, or MPL* mutation	1. Megakaryocyte proliferation and atypia (pre PMF = without reticulin fibrosis >grade1; overt PMF = reticulin and/or collagen fibrosis ≥grade2), accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often, decreased erythropoiesis 2. Not meeting WHO criteria for *BCR-ABL* $^+$ CML, PV, ET, MDS, or other myeloid neoplasms. 3. Presence of *JAK2, CALR, or MPL* mutation OR in the absence of these mutations, presence of another clonal marker OR absence of minor reactive BM reticulin fibrosis

	PV (Requires All 3 Major, or First 2 Major and the Minor Criterion	ET (Requires All 4 Major Criteria, or First 3 Major and the Minor Criterion)	PMF (Requires All 3 Major and at Least 1 Minor Criteria)
Minor criteria	1. Subnormal serum erythropoietin level	1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis	1. Anemia, not attributed to comorbidity 2. Leukocytosis ≥11 × 10^9/L 3. Palpable splenomegaly 4. LDH above upper limit of normal 5. Leukoerythroblastosis (criterion for overt PMF)

BM, bone marrow; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome

Diagnosis and Distinguishing Between the MPNs

The clinical presentation of MPNs can be with incidentally noted abnormal blood counts with patterns that vary depending on the particular MPN (Table 26.3) or with a complication, for example, Budd-Chiari syndrome.

TABLE 26.3

Distinguishing Clinical Features of the Myeloproliferative Neoplasms

	CML	PV	ET	PMF
Hematocrit	N or ↓	↑↑	N	↓
WBC count	↑↑↑	↑	N	↑ or ↓
Platelet count	↑ or ↓	↑	↑↑↑	↑ or
Splenomegaly	++++	+	+	++++
Cytogenetic abnormality	Ph chromosome	±	−	±
LAP score	↓	↑↑	N or ↑	N or ↑
Marrow fibrosis	±	± or ↓	±	++++ (Dry tap)
Marrow cellularity	↑↑↑ Myeloid	↑↑	↑↑ Megakaryocytes	N or ↓

	CML	PV	ET	PMF
Basophils ≥2%	+	±	±	Usually +

CML, chronic myeloid leukemia; ET, essential thrombocytopenia; LAP, leukocyte alkaline phosphatase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; N, normal; PV, polycythemia vera; WBC, white blood cell.

- **Symptoms and Signs:** Increased red blood cell mass and thus viscosity in PV can produce headaches, vertigo, tinnitus, and blurred vision. Another characteristic of PV in some patients is pruritus (histamine release) aggravated by hot water. Increased number of abnormal platelets in ET can cause arterial thrombotic events such as cerebrovascular ischemia, digital ischemia/erythromelalgia, and spontaneous abortions. ET with very high platelet counts and consequent acquired von Willebrand syndrome (VWS) can present with spontaneous hemorrhage into a muscle or other site. In both PV and ET, presenting symptoms and signs can be those of overt arterial or venous thrombo-occlusion. Anemia in patients with MF may cause fatigue and shortness of breath and splenomegaly can cause abdominal discomfort or early satiety. Hypermetabolic symptoms such as weight loss and sweating can not only be seen in MF but also in the other MPNs. MPN (like MDS or MDS/MPN) presentation can be with cutaneous/subcutaneous inflammatory complications, for example, erythema nodosum or pyoderma gangrenosum. Symptom burden can be semiquantified using the MPN Symptom Assessment form for 20 items (MPN-SAF). Obviously, prior transfusion and treatment history is highly pertinent information.
- **Bone marrow aspirate and biopsy:** Morphologic examination should incorporate trichome and reticulin stains. Standard metaphase karyotyping can be supplemented with fluorescence in situ hybridization (FISH), especially if *BCR-ABL* $^{+}$ CML is in the differential diagnosis.
- **Molecular testing:** For *JAK2* V617F mutation, and if negative, for *CALR* and *MPL* mutations if clinical impression is of ET or MF, and for *JAK2* Exon 12 mutations if clinical impression is of

PV. Nowadays, targeted next generation exon sequencing of a panel of >50 genes recurrently mutated in myeloid malignancies is often feasible, which can assist in demystifying overlap features, for example, with MDS.

- **Other relevant labs:** Besides complete blood counts with differentials and peripheral smear, reticulocyte counts, lactate dehydrogenase, and D-dimer levels can be useful parameters to assist with evaluation and tracking of tumor burden and risks over time. Serum erythropoietin levels (which should be >200 mU/mL if there is anemia) and iron studies are pertinent also to diagnosis and management. Serum vitamin B_{12} levels are frequently elevated in MPN patients because of increased amounts of the carrier-protein haptocorrin that is produced in myeloid cells but can disguise functional vitamin B_{12} deficiency, since haptocorrin-bound vitamin B_{12}, in contrast to transcobalamin II-bound vitamin B_{12}, is less available for cellular uptake. If there is clinical concern for vitamin B_{12} deficiency, methylmalonic acid (MMA) can be measured (MMA is elevated with B_{12} deficiency). Finally, evaluation by a stem cell transplant team (with human leukocyte antigen testing) is appropriate for patients with PMF who might be stem cell transplant candidates.
- **Risk stratification** is discussed below in the context of management.

Diagnosis Summary

As outlined earlier, there is overlap in the molecular underpinnings of MPNs, and thus, not surprisingly, in clinical behaviors. Nonetheless, the various MPN individual diagnoses do have differing types of complication, risks of complication, and prognoses. For example, prefibrotic (early) PMF, distinguishable from ET on the basis of BM morphology, has a higher risk of progressing to overt PMF or AML and has poorer survival than ET. Thus, there is predictive value in establishing a best-fit specific diagnosis. CML should be ruled out by performing a FISH analysis

for *BCR-ABL* in JAK2 mutation-negative thrombocytosis or bone marrow fibrosis. Even with a positive JAK2 mutation or other clinical and peripheral blood observations to favor a particular MPN classification, bone marrow biopsy with cytogenetic analysis should be considered, to not miss a diagnosis of CML or MDS with accompanying prognostic and treatment implications. Platelet function tests or bleeding times are of little use in diagnosing or in guiding the management of MPNs.

PROGNOSIS

Median Survivals

- Patients with PV have a median survival of 1.5 to 13 years. In a recent multicountry prospective study of 1638 patients with PV, the 5-year event-free survival was 82%, with a relatively low risk of death from cardiovascular disease and a high risk of death from noncardiovascular causes (mainly hematologic transformations).
- Patients with ET have a median survival of more than 10 years.
- Patients with MF have a median survival between 3 and 5 years.

Rate of Transformation to Acute Leukemia

- The estimated incidence of acute leukemia in 1638 patients with PV prospectively followed in the European collaboration study on low-dose aspirin in polycythemia (ECLAP) study was 1.3%, with an estimated annual incidence of 0.5 per 100,000 per year. Older age and exposure to P32, busulfan, or pipobroman were independent risk factors.
- The cumulative rate of transformation for patients with ET is 2% to 4% at 10 and 20 years from diagnosis, respectively.
- The cumulative rate of transformation for patients with MF is 10% at 10 years (please also see discussions on treatment regarding transformation risk).

Transformation of PV or ET Into PMF

Both PV and ET may progress to post-PV PMF or post-ET PMF, previously referred to as the spent phase, which clinically resembles PMF and is characterized by progressive cytopenias, splenomegaly, and marrow fibrosis. The cumulative rate of transformation is 5% and 10% at 10 to 20 years, respectively, for ET, and 10% to 20% for the same time line for PV.

Risk Factors for Thrombosis

In two prospective studies, the ECLAP study and the MRC-PT1, the cumulative rate of cardiovascular events in patients with PV ranged from 2.5% to 5% per patient-year and from 1.9% to 3% per patient-year for patients with ET. Arterial thrombosis accounts for 60% to 70% of the events and is the major cause of death.

- In PV, older age (>60), a hematocrit ≥45%, and a previous history of thrombosis are risk factors.
- In ET, age over 60 years and the presence of other cardiovascular risk factors (eg, smoking and previous thrombosis) increase the risk for thrombosis.

In ET, an association between platelet count and thrombosis has not been established, but platelet cytoreduction on treatment with hydroxyurea (HU) has been associated with a *reduced* risk.

Risk Factors for Hemorrhage

- In ET, a platelet count >2 × 10^6/μL is a risk factor for hemorrhage (please also see the recommendations regarding treatment).

TREATMENT

The goals of therapy of PV, ET, PMF, or overlaps thereof, can be usefully framed as **(1)** alleviating symptoms present in the individual patient (eg, symptoms from splenomegaly, pruritus,

cytopenias, inflammation); **(2)** anticipating and preventing potential life-threatening complications or risks such as thrombosis or hemorrhage; and **(3)** reducing pressures for disease evolution/progression—this latter goal is implicit in recommendations to avoid cytoreducing drugs that damage DNA in patients <60 years old if possible and in consideration of noncytotoxic treatments such as pegylated interferon alpha 2a (IFN-α). In accordance with these goals, there are systems for formal assessment of risk, as described below. Following is a definition of risk categories and recommended treatments, with an overview provided in Table 26.4.

TABLE 26.4

Current Management Depending on Risk Stratification in PV, ET, and PMF

Risk Category	PV	ET	PMF
Low	Low-dose aspirin (81-100 mg/d) + phlebotomy to maintain hematocrit <45% (consider <42% for females or if symptoms persist or progress)	Observation or low-dose aspirin (also for very low risk)	Individualize per predominant symptoms (eg, anemia, splenomegaly, constitutional). Managing patients with both splenomegaly and cytopenias is where difficulties arise—consider DNMT1-depleting drugs (decitabine or 5-azacytidine) in such subjects. Please see text
Intermediate		Low-dose aspirin ± HU	Consider stem cell transplant in transplant eligible intermediate-2 or high-risk subjects.
High	Low-dose aspirin + phlebotomy + HU. Alternatives to HU for cytoreduction are pegylated IFN-α or ruxolitinib	Low-dose aspirin + HU Alternative to HU for cytoreduction is pegylated IFN-α especially for patients <60 years old	

ET, essential thrombocytopenia; HU, hydroxyurea; PMF, primary myelofibrosis; PV, polycythemia vera.

Polycythemia Vera

- **Low risk:** Age <60 years and no personal history of vascular events, and who do not have additional risk factors for cardiovascular disease. *Recommended treatment*: phlebotomy (target hematocrit <45%), low-dose aspirin (81-100 mg/d, unless there is a contraindication to its use), and reduction of other cardiovascular risk-factors, for example, smoking cessation, avoidance of estrogen-containing oral contraceptives.
- **High risk:** Age ≥60 years and/or a prior history of thrombosis. *Recommended treatment*: all the treatments as for "Low risk," and in addition, cytoreducing drugs, described below.

Hematocrit targets: Maintaining a hematocrit <45% dramatically decreases the incidence of thrombotic complications. This is important since in PV, 35% of initial thrombotic events are fatal. For females, a lower threshold of <42% can be considered, especially if there are persistent or progressive symptoms. Surgery should be avoided in patients until a hematocrit <45% has been maintained for more than 2 months. Standard "1 U" phlebotomy removes 500 mL of whole blood, expected to reduce hematocrit by 3%. If there is heart disease or low body weight and a concern as to whether removal of 1 U will be tolerated, 250 mL of whole blood can be removed instead. Phlebotomy can be followed by intravenous hydration and can be performed once a week toward hematocrit goals. Phlebotomy controls hematocrit via iron deficiency (the goal is mild iron deficiency to suppress erythropoiesis).

Aspirin: A randomized study of 518 patients with PV has shown that treatment with low-dose aspirin (100 mg/d) lowers the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Do not give aspirin if a patient has acquired VWS (see section on Essential Thrombocythemia treatment).

Anticoagulation: Management of an acute thrombosis is as for non-MPN patients, that is, low-molecular weight heparin followed by early initiation of vitamin K antagonists (coumadin) for an international normalized ratio of 2.5 (range 2.0-3.0) (there are limited published data regarding use of direct oral anticoagulants in MPN patients). In deciding on long-term oral anticoagulation together with low-dose aspirin, take into consideration the circumstances (provoked/unprovoked) and site (proximal/distal) of the thrombotic event, control/progression of the MPN, hemorrhage risks, and D-dimer levels.

Cytoreducing drugs: **(1)** *HU*: the cytoreducing agent for which there is the longest clinical experience in MPN is a ribonucleotide reductase inhibitor that produces cytotoxicity and cytostasis via DNA damage. A nonrandomized study of HU in 51 PV patients by the PV study group reported thrombotic events in 10% versus 33% in a historical control group treated with phlebotomy alone. A standard starting dose is 15 mg/kg/d (eg, 500 mg 2×/d) (lower in patients with renal impairment), with dose adjustments toward hematocrit goals and to avoid neutropenia. Adverse events include cytopenias, nausea, diarrhea, mucocutaneous ulcers, and rare severe pulmonary toxicity; **(2)** *Ruxolitinib* is approved in the United States for treatment of adults with PV resistant to or intolerant of HU. It may be appropriate to start at lower doses than in the package insert, for example, at 5 mg 2×/d instead of 10 mg 2×/d, then increase toward goals-of-care. Ruxolitinib has anti-inflammatory effects, and there can be rebound inflammatory symptoms. Thus, it should be administered twice a day in accordance with its pharmacokinetics to avoid this phenomenon. Also, for this reason, drug should be tapered off rather than discontinued abruptly. Ruxolitinib can increase appetite and cause weight-gain; **(3)** *Pegylated IFN-α* is a natural ligand for interferon receptors that signal through the JAK-STAT network that mediates erythropoietin and thrombopoietin receptor signaling also. Pegylated IFN-α has a favorable toxicity profile compared to its unpegylated counterpart and is clinically active with once a week or once every 2-week administration.

Reasons to prefer pegylated IFN-α for cytoreduction include desire to avoid DNA-damage and teratogenic risks inherent with HU (considerations especially in younger patients) and a growing body of data demonstrating long-term efficacy and safety. A standard initial subcutaneous dose is 45 μg/wk. Adverse event concerns include autoimmune phenomena, depression, and myalgias.

Symptom-specific treatments: **(1)** *Pruritus*: Intractable pruritus responds to pegylated IFN-α in up to 81% of patients. Paroxetine, a selective serotonin reuptake inhibitor, can also frequently alleviate this symptom; **(2)** *Hyperuricemia*: Allopurinol can be used to reduce the risk of gout and urate nephropathy. Standard dose is 300 mg/d, dose-reduced in renal insufficiency; **(3)** *Mucosal or cutaneous ulcers*: Consider alternatives to HU for cytoreduction—ruxolitinib, pegylated IFN-α, or in patients with MDS/MPN overlap features, subcutaneous decitabine by noncytotoxic dose and schedule.

Essential Thrombocythemia

Treatment is primarily directed at preventing thrombosis and/or hemorrhage, and risk stratification is mostly a means to guide the use of cytoreducing drugs, to avoid their likely unnecessary early application. As per PV, cardiovascular risk factors should be concurrently managed.

- **Very low risk:** Age ≤60 years, no *JAK2* mutation, no history of thrombosis. *Recommended treatment*: observation or low-dose aspirin (81-100 mg/d), especially if there are symptoms or cardiovascular risk factors (eg, smoking). Cytoreductive drugs are not routinely recommended but could be needed for platelet counts to ≥1500 × 10^9/L, which can cause acquired VWS (ristocetin cofactor activity <30%). Other reasons to consider cytoreductive therapy are symptomatic splenomegaly, B-symptoms, new thrombosis or hemorrhage, or progressive leukocytosis. If cytoreductive treatment is needed, consider pegylated IFN-α rather than HU in these younger patients.

- **Low risk:** As above but with *JAK2* mutation. *Recommended treatment*: As described for "Very Low Risk."
- **Intermediate risk:** Age >60 years, no JAK2 mutation, no history of thrombosis. *Recommended treatment*: Aspirin 81 to 100 mg/d. In addition, cytoreductive therapy with HU or pegylated IFN-α could be an upfront consideration.
- **High risk:** Age >60 years and/or a previous history of thrombosis. *Recommended treat*ment: Aspirin 81 to 100 mg/d, and in addition, cytoreduction with HU or pegylated IFN-α.

Cytoreduction to reduce thrombotic risk in ET: **(1)** *HU*: A randomized trial of HU versus placebo in 114 high-risk patients showed a significant reduction of thrombotic events in the treatment arm (3.6% vs 24%). The HU dose was adjusted to achieve a platelet count of $<600 \times 10^9$/L; **(2)** *Anagrelide* is a nonmutagenic orally active agent that produces selective platelet cytoreduction by interfering with megakaryocyte maturation. In a randomized study of 809 patients with high-risk ET, HU plus low-dose aspirin was superior to anagrelide plus low-dose aspirin; **(3)** *Pegylated IFN-α* can also effectively reduce platelet mass and is preferred in younger patients for the reasons described for PV. The therapeutic target platelet count in this trial was $<400 \times 10^9$/L; **(4)** *Plateletpheresis* is used as an emergency therapy when ongoing thrombosis cannot be adequately managed with cytoreductive drugs and antithrombotic agents.

Aquired VWS: Increased platelets in ET can cause acquired VWS and accompanying risk for spontaneous hemorrhage. The functional VW factor:ristocetin cofactor activity (VWF:RCo) assay, with a result of <30%, suggests acquired VWS. The possibility of acquired VWS should be evaluated in ET patients with platelet counts $>1.5 \times 10^9$/L since it is a reason to withhold low-dose aspirin therapy. Acquired VWS can occur, however, even with platelet counts $<1.5 \times 10^9$/L. Cytoreducing therapy, for example, with pegylated IFN-α or HU, is indicated in ET patients with acquired VWS/hemorrhage, with a usual platelet target of $<400 \times 10^9$/L.

Myelofibrosis

Risk stratification by the Dynamic International Prognostic Scoring System Plus (DIPSS Plus) determines whether a patient should be considered upfront for stem cell transplant if they are a transplant candidate (DIPSS intermediate-2 or high-risk patients). Otherwise, for low risk or intermediate-1 risk patients or nontransplant candidate higher risk patients, management is directed toward relieving symptoms caused by splenomegaly or cytopenias and decreasing risk of further progression.

- Risk stratification by DIPSS Plus: one point each for age >65 years, white blood cell count >25 × 10^9/L, circulating blast cells ≥1%, presence of constitutional symptoms, unfavorable karyotype, platelet count <100 × 10^9/L, and transfusion dependence and two points for hemoglobin <10 g/dL.

***Low risk*:** 0 points, median survival 20 years. ***Intermediate risk-1*:** 1 point, median survival 6.5 years. ***Intermediate risk-2*:** 2 to 3 points, median survival 2.9 years. ***High risk*:** 4 to 6 points, median survival 1.7 years.

Anemia: **(1)** *Erythropoietin:* Erythropoietin levels should normally rapidly increase in response to anemia. Thus, levels <500 mU/mL in the setting of anemia can be considered as inappropriately low (renal endocrine deficiency), warranting consideration of erythropoietin replacement; **(2)** *Other replacement therapies*: MPN patients can develop the same deficiencies frequently in the general population, for example, of thyroid hormone or of vitamin B_{12}. Evaluating for vitamin B_{12} deficiency is confounded by high amounts of the carrier protein haptocorrin in MPN patients, so consider MMA levels to evaluate for vitamin B_{12} deficiency (see "Other relevant labs" above); **(3)** *Androgens (eg, danazol)* alone or combined with prednisone (prednisone is tapered after a few weeks) is an option, with the caution that danazol can potentially exacerbate thrombotic risk. Consider starting danazol at 50 mg 2×/d; **(4)** *Decitabine or 5-azacytidine* are DNA methyltransferase 1–depleting drugs

(hypomethylating agents or HMA) approved in the United States to treat MDS or AML in combination with the BCL2-inhibitor venetoclax. HMAs are particularly useful when the goal is to reduce some blood count lineages but increase others, for example, in patients with PMF or MDS/MPN with increasing white blood cells/myeloblasts but worsening anemia and/or thrombocytopenia. For these goals of care, decitabine can be administered subcutaneously at low, noncytotoxic doses (0.2 mg/kg once a week) instead of by the higher, pulse-cycled, intravenously infused doses described in the approved label, a practical regimen that is suited also to quality-of-life goals of care. Decitabine and 5-azacytidine reconfigure myelopoiesis to favor red cell and platelet production over granulocytes and monocytes; thus, neutropenia is a frequent side-effect, even with noncytotoxic dosages; **(5)** *Lenalidomide* is approved to treat MDS with isolated 5q-abnormality, a subtype of MDS characterized by anemia and normal or elevated platelet counts. Lenalidomide could have a role in PMF patients with features of MDS with 5q-. Consider starting at a low dose of 5 mg/d for 21 of every 28 days. Adverse events include diarrhea, neutropenia, thrombocytopenia, renal dysfunction, and thrombophilia; **(6)** *Luspatercept* has actions that include binding of transforming growth factor-β superfamily ligands to promote late-stages of erythroid maturation and is approved in the United States to treat MDS (or MDS/MPN) with ring sideroblasts (MDS that is enriched for maturation-impeded erythroid precursors). The most common adverse events are fatigue, headache, and musculoskeletal pain; **(7)** *Iron-chelation* may be indicated for transfusion-dependent patients.

Splenomegaly: **(1)** *Ruxolitinib*: if there is no significant anemia and platelets are >50 × 10^9/L, although the currently approved dosages may be unnecessarily high, and it may be appropriate to start with lower than standard dosages, for example, 5 mg 2×/d, with an escalation if necessary. Please see Polycythemia Vera treatment; **(2)** *Fedratinib* is approved in the United States to treat PMF splenomegaly with platelet counts >50 × 10^9/L at a dose of 400 mg/d.

The label includes a warning for rare, serious, and fatal encephalopathy, including Wernicke encephalopathy, requiring monitoring of thiamine levels. The most common adverse events were diarrhea, nausea, anemia, and vomiting. Dose reduction is recommended for patients taking strong CYP3A inhibitors or with severe renal impairment; **(3)** *Decitabine or 5-azacytidine*: see above—a consideration if a concurrent goal is to alleviate anemia and/or thrombocytopenia; **(4)** *Lenalidomide*: see above—a consideration if there is overlap with MDS with 5q-features; **(5)** *HU*: As with ruxolitinib or fedratinib, difficulties arise when confronted with concurrent anemia or thrombocytopenia (consider decitabine or 5-azacytidine instead in that circumstance); **(6)** *Pegylated IFN-α.* As with HU or ruxolitinib or fedratinib, difficulties arise if there is a concurrent goal of alleviating cytopenias; **(7)** *Splenectomy* is an option to alleviate pain and early satiety, depending on local surgical experience and thus surgical risk. Secondary progressive hepatomegaly is a potential long-term complication of splenectomy. Increasing white blood cell counts and platelet counts after splenectomy may necessitate cytoreducing drugs. Also a possible consideration depending on local expertize is splenic artery embolization via interventional radiology. Analgesia may be required for splenic infarct pain, whether or not a patient has splenic artery embolization.

Curative therapy with allogeneic transplantation should be considered for intermediate-2 or high-risk patients who are transplant candidates. Five-year survivals with a related or an unrelated matched transplant have been reported at 54% and 48%, respectively, by the European Group for Blood and Marrow Transplantation. A recommendation for transplantation is not clear-cut in lower risk patients because the median survival in this group is >14 years with nontransplant therapy. In other words, risk classification should be considered, and although the outcome with transplantation is adversely affected by risky characteristics, risk factors such as hemoglobin level <10 g/dL; white blood cell count $<4 \times 10^3/\mu L$ or $>30 \times 10^3/\mu L$; more than 10% of circulating blasts,

promyelocytes, or myelocytes; or abnormal cytogenetics should prompt consideration for transplantation. Pretransplantation splenectomy, although not necessary in every patient, is associated with faster engraftment and can be considered in those with massive splenomegaly. Marrow fibrosis is reversible with transplantation.

Suggested Readings

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7. Vannucchi AM, Harrison CN. Emerging treatments for classical myeloproliferative neoplasms. *Blood*. 2017;129(6):693-703.

CHAPTER 27

Multiple Myeloma

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INTRODUCTION

Multiple myeloma (MM) is characterized by clonal proliferation of plasma cells in the bone marrow, often producing a monoclonal immunoglobulin. This can result in hypercalcemia, renal dysfunction, anemia, or extensive skeletal destruction with osteolytic lesions that are the major presenting signs of the disease. Unlike most other malignancies, diagnosis require the presence of these clinical features and its attribution to clonal plasma cell proliferation in order to distinguish it from the precursor phases—-monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). More recently, the diagnostic criteria have been updated to include biomarkers predictive of high risk of developing clinical features. Newer active agents and autologous stem cell transplantation (ASCT) have led to improved outcomes, including a median survival of 3 years in the late 1990s to 8 to 10 years currently, a metric that continues to improve.

EPIDEMIOLOGY

MM accounts for approximately 2% of all cancers and about 10% of all hematologic malignancies. In 2021, it is estimated that 34,920 new cases and 12,410 deaths from MM will occur in the United States. The annual age-adjusted incidence in the United States is approximately 6.9 per 100,000 and has increased over the past 2 decades. The median age at diagnosis is about 68 years and MM is slightly more common in men than in women (1.2:1). Incidence in the African American population is twofold higher than that in Caucasians, whereas it is lower in Asians. The risk of developing MM is approximately two- to fourfold higher in individuals with a first-degree relative with MM.

PATHOPHYSIOLOGY

MM is characterized by the proliferation and accumulation of clonal plasma cells in the bone marrow. All patients with MM evolve from an underlying premalignant state called MGUS. Prevalence of MGUS is over 3% above the age of 50 years, and the rate of progression to MM is roughly 1% per year, a risk that does not change with time from diagnosis. Studies suggest that patients with myeloma typically have MGUS for an average of 15 years before development of symptomatic myeloma. Some patients may also develop an intermediate, more advanced stage referred to as SMM that is defined clinically (Table 27.1). Since reclassifying patients with ultrahigh-risk SMM as MM, the risk of progression is approximately 22% at 2 years, 42% at 5 years, and 64% at 10 years from diagnosis.

TABLE 27.1

International Myeloma Working Group Criteria for Diagnosis of Multiple Myeloma and Related Plasma Cell Disorders

Terminology	Definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS) [a]	• Serum monoclonal protein (non-IgM type) < 3 g/dL AND • Clonal bone marrow plasma cells < 10% AND • Absence of end-organ damage (hypercalcemia, renal insufficiency, anemia, and bone lesions [CRAB]) attributable to the plasma cell proliferative disorder
Smoldering multiple myeloma	• Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL or urinary monoclonal protein ≥ 500 mg/24 h and/or clonal bone marrow plasma cells 10%-59% AND • Absence of myeloma defining events or amyloidosis

Terminology	Definition
Multiple myeloma	• Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma [b] AND • One or more of the myeloma defining events (MDEs): 1. Evidence of end organ damage attributable to the underlying plasma cell proliferative disorder, specifically: a. Hypercalcemia: serum calcium > 1 mg/dL higher than the upper limit of normal or >11 mg/dL b. Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine > 2 mg/dL c. Anemia: hemoglobin > 2 g/dL below the lower limit of normal or a hemoglobin < 10 g/dL d. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) 2. One or more of the biomarkers of malignancy a. Clonal bone marrow plasma cell percentage ≥ 60% b. Involved: uninvolved serum-free light chain (FLC) ratio ≥ 100 (involved free light chain level must be > 10 mg/dL) c. >1 focal lesions on magnetic resonance imaging (MRI) studies
Light Chain MGUS	• Abnormal free light chain (FLC) ratio (<0.26 or >1.65) AND • Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) AND • No immunoglobulin heavy chain expression on immunofixation AND • Absence of end-organ damage attributable to the plasma cell proliferative disorder AND • Clonal bone marrow plasma cells < 10% AND • Urinary monoclonal protein < 500 mg/24 h
Solitary plasmacytoma [c]	• Biopsy proven solitary lesion of clonal plasma cells involving bone or soft tissue AND • No evidence of clonal plasma cells in bone marrow AND • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) AND • Absence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) attributable to a plasma cell proliferative disorder

[a]IgM MGUS is defined by IgM monoclonal protein < 3 g/dL in serum, <10% bone marrow infiltration by lymphoplasmacytic cells, and absence of any end organ damage that can be attributed to underlying lymphoproliferative disorder.

[b]Approximately 4% of patients may have fewer than 10% bone marrow plasma cells since marrow involvement may be focal, or they may have multifocal plasmacytomas. Such patients should undergo repeat bone marrow biopsy or CT/MRI-guided biopsy of a bony or extramedullary lesion.

[c]Solitary plasmacytoma with minimal marrow involvement is defined as a biopsy proven bony or soft tissue plasmacytoma with <10% clonal bone marrow plasma cells and no other myeloma defining event other than the primary solitary lesion. Solitary lesion with ≥10% clonal plasma cells is considered as multiple myeloma.

Adapted from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538-e548.

The clonal plasma cells in MM are characterized by genetic abnormalities, with most patients having one or more well-characterized abnormalities. Current understanding of genomics suggests that initial genetic changes responsible for clonal plasma cell disorders occur in second or third decade of life. Interphase fluorescence in situ hybridization (FISH) of sorted plasma cells is the most common technique used to detect chromosomal abnormalities in clinical practice. Five recurrent translocations involving the immunoglobulin heavy chain (IgH) locus on chromosome 14 have been identified and are present in approximately 40% of all MM. These translocations are mutually exclusive and place various genes under the transcriptomic control of the IgH locus which are implicated in driving clonal proliferation. Trisomies of odd-numbered chromosomes are detected in nearly half of the patients. IgH translocations and trisomies are labeled as primary abnormalities as they occur in precursor states such as MGUS and SMM. Over time, the clonal plasma cells acquire additional genetic changes. Abnormalities such as partial deletion of chromosomes 13q, 17p, and 1p and gain of 1q are considered secondary abnormalities. Detection of these abnormalities by FISH is crucial in defining prognosis. Next generation sequencing (NGS) has allowed us to better define the genomic landscape of MM and propose mechanisms related to progression from MGUS and SMM. Mutations involving the *RAS* and nuclear factor-κB pathways are common in MM. Primary genetic events are often associated with additional genetic events—t(4;14) with mutations in *FGFR3*, *DIS3*, and *PRKD2*; t(11;14) with mutations in *CCND1* and *IRF4*; t(14;16) with mutations in *MAF*, *BRAF*, *DIS3*, and *ATM*; and hyperdiploidy with gain 11q, mutations in *FAM46C*, and *MYC* rearrangements—suggesting secondary genetic abnormalities accumulate leading to clonal evolution and progression. Using NGS, several molecular subtypes of MM have been defined with distinct cooperating events.

The clinical features of MM are a result of bone marrow infiltration by the malignant clone; damage from high levels of immunoglobulins or free light chains in the circulation or glomeruli; the secretion of osteoclast-activating factors such as RANKL (receptor activator of nuclear factor-κB ligand) and MIP-1 (macrophage inflammatory protein-1) with resultant bone damage; decreased production of the natural RANKL inhibitor OPG (osteoprotegerin); overexpression of dickkopf 1 inhibiting osteoblast differentiation and new bone formation; and impaired immunity, both cell-mediated and humoral.

CLINICAL FEATURES

Bone pain, particularly in the back or chest, and less often in the extremities, is present in nearly 60% of patients with MM. Patients may present with pathologic fractures and can also have loss of height because of vertebral collapse. Other common clinical features include fatigue (32%), weight loss (24%), normocytic normochromic anemia (73%), and hypercalcemia (28%). MM can also result in a low anion gap due to severe hypercalcemia and/or the cationic immunoglobin molecule. Renal insufficiency is seen in almost half the patients with MM at diagnosis and is commonly caused by hypercalcemia and related dehydration or light chain cast nephropathy. Other etiologies of renal dysfunction may include renal amyloidosis, light chain deposition disease, cryoglobulinemia, or drug-induced kidney injury. In some patients, concurrent light chain amyloidosis can cause a nephrotic syndrome (<5%). Acquired Fanconi syndrome with glycosuria, phosphaturia, and aminoaciduria can also occur with MM. MM patients are at an increased risk for infection due to impaired lymphocyte function, suppression of normal plasma cell function, and hypogammaglobulinemia. Patients can also present with radiculopathy or spinal cord compression that can result from compression by paravertebral plasmacytoma or by fractured vertebral body. Peripheral neuropathy can be present at diagnosis, related to the monoclonal protein or due to concomitant amyloidosis.

DIAGNOSIS AND WORKUP

Diagnosis of MM requires evidence of a clonal plasma cell disorder with the presence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) attributable to the plasma cell disorder or presence of biomarkers predicting high risk of progression to symptomatic myeloma. The International Myeloma Working Group (IMWG) updated criteria for diagnosis of monoclonal gammopathies in 2014 (Table 27.1). When MM is suspected, the diagnostic workup should include a thorough history and physical examination with specific attention to complaints of bone pain, constitutional symptoms, neurologic symptoms, and infections. For diagnosis and staging, these laboratory tests should be performed: complete blood count with differential; serum electrolytes, blood urea nitrogen, serum creatinine, calcium, phosphate, magnesium, uric acid, albumin, β_2-microglobulin, and lactate dehydrogenase (LDH); serum protein electrophoresis (SPEP) and immunofixation (IFE); serum free light chain assay; 24-hour urine protein electrophoresis (UPEP) and IFE; quantitative

immunoglobulins; radiographic skeletal survey; and bone marrow aspirate and biopsy with FISH testing of the plasma cells.

SPEP is useful in detecting and quantifying the presence of a monoclonal protein (M-protein) that is visualized as an M-spike in the gamma region. Serum IFE confirms the presence of the monoclonal immunoglobulin and determines its type (Figure 27.1). Approximately 15% of patients have only light chains (light chain MM), which may rapidly be cleared from the plasma to the urine. Hence, serum free light chains, UPEP, and/or urine IFE should be performed in all patients and are very useful in such patients. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry is a more sensitive method of detecting monoclonal proteins in serum and urine. It can also distinguish therapeutic monoclonal antibodies and may replace SPEP, UPEP, and IFE for diagnosis and monitoring of plasma cell disorders in the future.

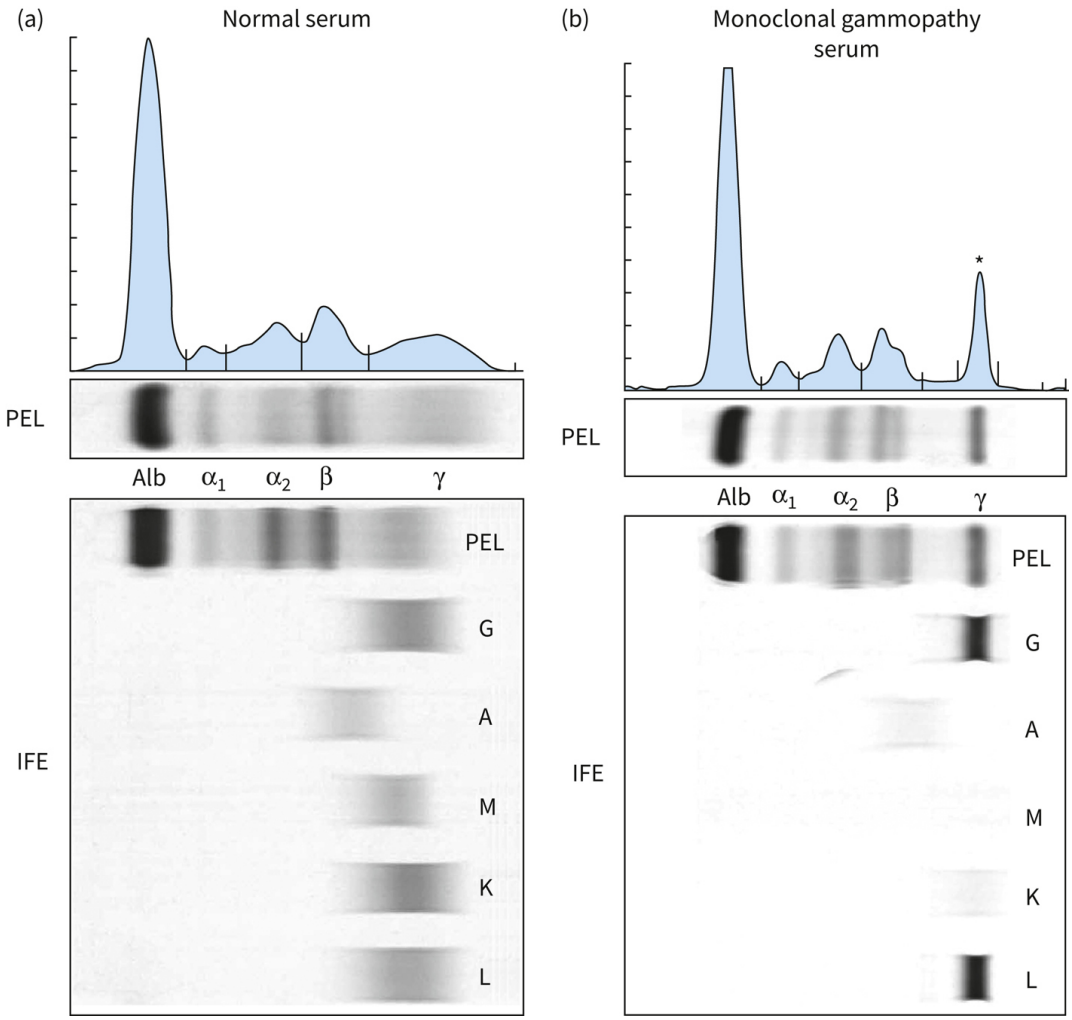

FIGURE 27.1 Electrophoretic pattern of (A) normal human serum and (B) immunoglobulin G (IgG lambda) multiple myeloma.Asterisk indicates M spike in the gamma region.

SPEP detects an M-spike in 82% of patients with MM. Addition of serum IFE increases the sensitivity to 93%. The sensitivity increases to 97% or more if either the serum free light chain assay or 24-hour UPEP/urine IFE is performed in addition. Patients who lack detectable M-protein by any of these tests but have end-organ damage and clonal plasma cells in the bone marrow are considered to have nonsecretory myeloma. The circulating M-protein on IFE is IgG in 52% of cases, IgA in 21%, light chain only (kappa or lambda) in 16%, IgD in 2%, and biclonal in 2%. IgM myeloma is exceedingly rare and is seen in <1% of cases. Kappa is the predominant light chain isotype compared with lambda (ratio 2:1), except in IgD myeloma, where lambda isotype is more common.

Bone marrow studies should report the plasma cell percentage on bone marrow aspirate and biopsy. The clonality of plasma cells should be

established using light chain restriction by immunohistochemistry or immunofluorescence or by flow cytometry. Interphase FISH designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), hyperdiploidy, deletion 13q, 1q amplification, 1p deletion, *MYC* translocation, and deletion 17p is essential at diagnosis. Plasma cell proliferation rate is another test with prognostic value available in some laboratories. Gene expression profiling, when available, can add prognostic information. Two gene expression profiles, GEP70 and SKY92, have been incorporated into some prognostic models. Mutation panels that examine the plasma cells for common recurrent mutations have become available, but their clinical utility remains to be demonstrated.

Radiologic changes seen on a skeletal survey include punched-out lytic lesions, severe osteopenia or osteoporosis, and pathologic fractures. Conventional skeletal survey in the evaluation of plasma cell disorders has been superseded by modalities such as whole-body low-dose computed tomography, ^{18}F-fluoro deoxyglucose–positron emission tomography (FDG PET) CT scan and whole-body magnetic resonance imaging (MRI). CT scan is sensitive in detecting skeletal lesions. PET-CT can detect metabolically active skeletal and extramedullary lesions. MRI is highly sensitive for bone marrow imaging. In patients with MM, whole-body PET-CT is the initial imaging modality of choice, and if negative, patients should undergo whole body or axial skeletal MRI. Subsequently, prior to initiation of maintenance treatment and at relapse, patients should be imaged with either PET-CT or MRI to detect new lesions, which can help in response assessment. Any patient with significant back pain should undergo MRI of the spine to evaluate for cord compression. Imaging strategy using whole body CT and MRI is recommended in patients with smoldering myeloma to rule out presence of more than one focal lesion, which would reclassify a patient as having MM. In patients with solitary plasmacytoma, PET-CT is recommended for patients with extramedullary plasmacytoma and whole-body MRI is recommended for skeletal plasmacytoma.

STAGING

Three main staging systems exist for MM that primarily reflect tumor burden: the International Staging System (ISS) that is based on serum albumin and β-2–microglobulin levels, and the Durie-Salmon staging system, predominantly a clinical system. Both provide prognostic information but are not helpful in making therapeutic choices. Recently, the ISS has been

revised with the inclusion of cytogenetic abnormalities and LDH, resulting in the revised ISS (R ISS) that incorporates some aspects of disease biology and provides both prognostic and staging information (Table 27.2).

TABLE 27.2
Staging Systems for Multiple Myeloma

Stage	Criteria	Percentage of Patients	Median Survival (months)
	Durie and Salmon staging		
I	Low measured myeloma cell mass PLUS all of: Hemoglobin > 10 g/dL Serum calcium < 12 mg/dL On x-ray, normal bone structure or solitary plasmacytoma only Low M-component production (IgG < 5 g/dL, IgA < 3 g/dL, and urine M-component < 4 g/24 h)		
II	Intermediate myeloma cell mass—fitting neither stage I or stage III [a]		
III	High myeloma cell mass—one or more of: Hemoglobin < 8.5 g/dL Serum calcium > 12 mg/dL Advanced lytic bone lesions High M-component production (IgG > 7 g/dL, IgA > 5 g/dL, and urine M-component > 12 g/24 h)		
	International Stating System (ISS)		
I	Serum β_2-microglobulin <3.5 mg/L	28	62
	Serum albumin ≥ 3.5 g/dL		
II	Not fitting stage I or III	33	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	39	29
	Revised International Staging System (R-ISS) [b]		
I	ISS stage I and no high risk cytogenetics by iFISH and normal LDH	28%	Not reached
II	Not R-ISS stage I or II	62%	83
III	ISS stage and either high risk cytogenetics by FISH or high LDH	10%	43

iFISH, interphase fluorescent in situ hybridization; LDH, lactate dehydrogenase.

[a]Durie and Salmon stage II is subdivided into IIA (serum creatinine < 2 mg/dL) and IIB (serum creatinine ≥ 2 mg/dL).

[b]High-risk cytogenetics on interphase fluorescent in situ hybridization (iFISH) of plasma cells is defined as presence of del(17p) and/or t(4;14) and/or t(14;16).

Adapted from Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36:842; Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23(15):3412-3420; Palumbo A, Avet-Loiseau H, Oliva S, et al.

Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863.

PROGNOSIS

Prognosis in MM depends on a variety of host factors (age, performance status, and comorbidities), disease stage and biology, and response to therapy. Recently, the focus has shifted to using molecular characteristics to risk stratify patients. The inclusion of the high-risk translocations, t(4;14) and t(14;16) and del(17p) in R ISS reflects the importance of disease biology in predicting outcomes. Other abnormalities such as *TP53* gene mutation, amplification of 1q (≥4 copies), and 1p deletion are also classified as high-risk abnormalities. Presence of more than one high-risk abnormality is associated with worse outcomes. A high plasma cell proliferative rate also strongly predicts poor prognosis, but this test is not commonly available. Gene expression analysis has identified several signatures that allow for prognostication in patients with myeloma, and at least two of these (GEP70 and SKY92) are available for use in the clinic. Newly diagnosed patients can be stratified using these markers as having standard-risk or high-risk disease based on the Mayo stratification for myeloma and risk-adapted therapy classification (Table 27.3). Other risk stratification systems such as the IMWG criteria also group patients into standard risk and high-risk myeloma based on genetic and clinical characteristics. Median survival varies from 8 to 10 years for standard-risk patients versus 2 to 3 years for high-risk myeloma. Major progress has been made in understanding the impact of genomic abnormalities on the outcome of patients in MM. For example, mutations in *CCND1* and the DNA repair pathway (*TP53*, *ATM*, *ATR*, and *ZNFHX4* mutations) are associated with negative impact, while *EGR1* and *IRF4* mutations are associated with beneficial impact on survival. *TP53* biallelic inactivation, lambda light chain translocations, mutations of *APOBEC* and *FAM46C,* and deletions of *BIRC* and *PRDM1* have been shown to affect prognosis in MM but have not been incorporated into clinical decision-making. Other laboratory parameters such as creatinine, calcium, LDH, immunoglobulin subtype, plasmablastic morphology, circulating plasma cells, and C-reactive protein have also been shown to be independent risk factors for survival in myeloma. Primary refractory MM and relapse within 18 months of ASCT are also considered high-risk clinical features.

TABLE 27.3

Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Classification of Multiple Myeloma

	High Risk	Standard Risk
Median overall survival (years)	3	8-10
Characteristic	High-risk genetic abnormalities [a, b]: Del 17p t(4;14) t(14;16) t(14;20) Gain 1q TP53 mutation R ISS stage 3 High-risk signature on gene expression profiling High plasma cell S-phase [c]	All others including: Hyperdiploidy t(11;14) [d] t(6;14)

[a]Trisomies may ameliorate.

[b]Chromosomal abnormalities are based on FISH analysis unless specified.

[c]Cut-offs vary.

[d]t(11;14) may be associated with plasma cell leukemia.

Adapted from Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-376. www.msmart.org

TREATMENT

General

Monoclonal Gammopathy of Undetermined Significance

Currently, there is no evidence to screen the general population for MGUS. Risk-stratification models have been proposed for progression of MGUS and assist in detecting patients with higher risk of progression to myeloma, AL amyloidosis or Waldenström macroglobulinemia. Presence of an M protein ≥ 1.5 g/dL and an abnormal free light chain ratio are adverse predictors of long-term risk of progression. For patients with non-IgM MGUS, the risk of progression at 20 years is 30% among those with two risk factors, 20% among those so have only one risk factor, and only 7% among patients who had neither risk factor. For patients with IgM MGUS, presence of two adverse risk factors was associated with a risk of progression at 20 years of 55%,

compared to 41% among those with one adverse factor and 19% among those with neither. Patients with MGUS should be monitored indefinitely without treatment because patients progress at a constant rate of approximately 1% per year. Low-risk patients do not require a bone marrow biopsy at diagnosis. Whole-body CT skeletal survey is recommended in patients with high-risk non-IgM MGUS. Patients should have SPEP, UPEP, and serum free light chains repeated 3 to 4 months after initial diagnosis and if stable can be followed every year for high- or intermediate-risk patients and every 2 to 3 years for low-risk patients (no risk factors present) or when myeloma symptoms arise. Treatment is not indicated unless it is part of a clinical trial.

Smoldering (Asymptomatic) Multiple Myeloma

Patients with SMM have a higher risk of progression to myeloma than MGUS. The risk is highest in the first 2 years after diagnosis and decreases in the subsequent years. These patients should have SPEP, UPEP, complete blood count, and calcium and creatinine measured 2 to 3 months after the initial diagnosis. If the results are stable, the studies should be repeated every 4 to 6 months during the first year and, if stable, evaluation can be lengthened to every 6 to 12 months. The 2018 Mayo Clinic revised risk stratification (20/2/20 model) uses bone marrow plasma cell percentage ≥20%, M-protein > 2 g/dL, and involved to uninvolved free light chain ratio > 20 to stratify the risk of progression to myeloma-related end-organ damage. Presence of two or three of the above risk factors is associated with approximately 50% risk of progression at 2 years. The above model was validated in a large multinational cohort of patients studied by IMWG. Data on high-risk FISH abnormalities can be added to further refine the risk estimation, and the use of the IMWG scoring system provides additional granularity to the risk of progression. Addition of MYC aberrations, MAP kinase pathway mutations and DNA repair alterations to the 2018 Mayo clinic model also improves prediction of progression. In a Spanish trial of patients with high-risk SMM (defined using the PETHEMA model), upfront treatment with lenalidomide and dexamethasone improved progression-free survival (PFS) and overall survival (OS) compared to observation. In the ECOG-ACRIN E3A06 phase 3 trial of patients with high-risk smoldering myeloma, treatment with single-agent lenalidomide improved PFS, especially in the high-risk group defined by the 2018 Mayo Clinic model. Accordingly, in patients with high-risk SMM defined by the Mayo Clinic 2018 criteria, we recommend enrollment in a clinical trial if available or

shared decision-making regarding treatment with single-agent lenalidomide in order to reduce risk of progression to myeloma-related organ damage.

Solitary Plasmacytoma

Patients suspected to have a solitary plasmacytoma should have a PET scan performed to conclusively rule out other lesions, once the initial lesion is biopsied and confirmed to be plasmacytoma. The initial evaluation is similar to that for myeloma, including a bone marrow aspirate and biopsy. These patients are primarily treated with radiation therapy to the affected area, and surgery is reserved for specific situations such as those in case of bone lesions with extensive destruction that require stabilization or soft tissue masses with pressure symptoms. After completion of treatment, patients should be followed by regular monitoring of M-protein and imaging studies as indicated, given the risk of progression to MM. Older patients, bone plasmacytoma especially of the axial skeleton, persistent monoclonal protein after radiation therapy, presence of marrow involvement, increased angiogenesis in the plasmacytoma, and presence of circulating PCs, all suggest a higher risk of progression.

Multiple Myeloma

The treatment of MM has undergone a significant shift in the last decade, primarily driven by increased availability of new drugs, development of effective multidrug combinations, and the concept of continuous therapy. The introduction of novel highly active drugs along with the increasing application of ASCT has significantly improved the outcome of patients with MM. The important classes of drugs used in treatment of MM are proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), corticosteroids (usually dexamethasone or prednisone), anti-CD38 monoclonal antibodies (daratumumab and isatuximab), anti-SLAMF7 antibody (elotuzumab), and alkylating agents (cyclophosphamide, melphalan, and bendamustine). High-dose melphalan is the most used conditioning regimen prior to ASCT for MM. There is increasing use of aggressive multidrug treatment upfront to achieve deep responses versus a sequential disease control approach. Patients with high-risk disease have better long-term OS if they achieve a deep response, justifying an aggressive strategy upfront. The treatment choice for symptomatic myeloma patients largely depends on eligibility for high-dose melphalan and ASCT and risk stratification (Figure 27.2). In the transplant-eligible patients, the current

approach includes initial therapy with a triplet, followed by ASCT which is followed by maintenance therapy of variable duration. In the non–transplant-eligible patients, initial therapy typically uses a triplet or a doublet- if frail, given for a defined duration followed by maintenance for variable duration. Eligible patients should always be considered for enrollment in clinical trials that evaluate novel treatment strategies.

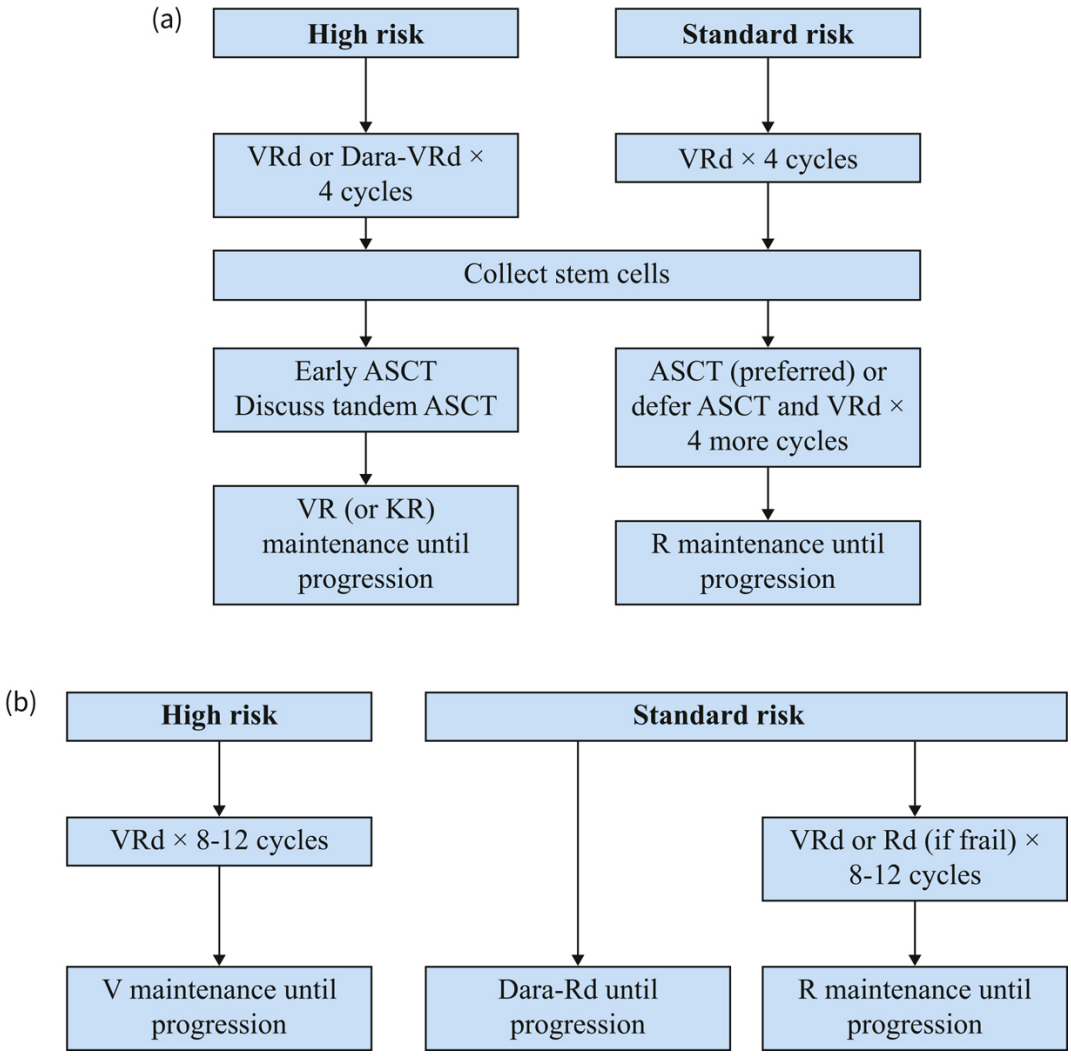

FIGURE 27.2 A suggested treatment algorithm for newly diagnosed multiple myeloma patients.Transplant eligible (A) and transplant ineligible (B). All patients should receive supportive care and must be considered for bisphosphonate treatment and clinical trials. (*Dexamethasone is usually discontinued after 12 months. ASCT, autologous stem cell transplantation; Dara-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; KR, carfilzomib and lenalidomide; R, lenalidomide; Rd, lenalidomide, dexamethasone; V, bortezomib; VR, bortezomib and lenalidomide; VRd, bortezomib, lenalidomide, dexamethasone.)(Adapted from msmart.org)

As a result of the improved therapies, we have been able to achieve deep responses, not previously seen with the older therapies. This exposed the limitations of the previous response assessment approaches that relied primarily on the serologic and/or urine monoclonal protein assessment along with marrow assessment using methods with low sensitivity. This coupled with improvements in flow cytometry as well as development of NGS to identify VDJ recombination regions have allowed us to detect measurable

residual disease (MRD) involvement in the bone marrow with detection of 1 in 10^5 to 10^6 cells. This sensitive marrow assessment has been combined with imaging in the revised IMWG response criteria to assess the extramedullary compartment to provide a more thorough evaluation of disease status. The revised criteria by the IMWG for evaluating disease response and progression in myeloma patients are outlined in Table 27.4. Achieving MRD negativity with treatment predicts longer PFS and OS and mitigates some of the poor prognosis conferred by high-risk cytogenetic abnormalities at diagnosis.

TABLE 27.4

International Myeloma Working Group Consensus Criteria for Response Assessment

Response Subcategory	Response Criteria
	IMWG MRD criteria (requires a complete response as defined below)
Sustained MRD negative	MRD negative in the marrow (NGF, NGS, or both) AND by imaging, confirmed at least 1 y apart
Flow MRD negative	Absence of aberrant plasma cells by NGF on bone marrow aspirates using a validated method with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD negative	Absence of aberrant plasma cells by NGS on bone marrow aspirates using a validated method with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging plus MRD negative	MRD negativity by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
	Standard IMWG response criteria
Stringent complete response (sCR)	CR as defined below AND normal FLC ratio AND absence of clonal cells in bone marrow by immunohistochemistry
Complete response (CR)	Negative immunofixation on the serum and urine AND disappearance of any soft-tissue plasmacytomas AND <5% plasma cells in bone marrow
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR ≥90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h

Response Subcategory	Response Criteria
Partial response (PR)	≥50% reduction in serum M-protein AND reduction in 24-h urine M-protein by ≥90% or to <200 mg/24 h If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein and serum free-light-chain assay are unmeasurable, ≥50% reduction in plasma cells in the bone marrow provided baseline percentage was ≥30% In addition to the above listed criteria, if present at baseline, ≥50% reduction in the size of soft-tissue plasmacytomas
Minimal response (MR)	≥25% but ≤49% reduction of serum M-protein AND reduction in 24-h urine M-protein by 50%-89% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or PD
Progressive disease (PD)	One or more of: 25% increase from lowest response level in any of: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Urine M-protein (absolute increase must be ≥200 mg/24 h) • In patients without measurable serum or urine M-protein levels, the difference between the involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum or urine M-protein levels, and without measurable involved FLC levels, bone marrow plasma cell percentage (absolute increase must be ≥10%) Development of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	One or more of: CRAB features related to underlying plasma cell proliferative disorder New soft tissue plasmacytomas or bone lesions Definite increase (>50% and ≥1 cm) in size of existing plasmacytomas or bone lesions Hypercalcemia (>11 mg/dL) Decrease in hemoglobin > 2 g/dL (not related to therapy or a cause other than myeloma) Rise in serum creatinine ≥ 2 mg/dL attributable to myeloma Hyperviscosity related to serum paraprotein
Relapse from CR [a]	One or more of: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥5% plasma cells in the bone marrow Any other sign of progression
Relapse from MRD [a]	One or more of: Loss of MRD negativity Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥5% plasma cells in the bone marrow Any other sign of progression

CRAB, calcium elevation, renal failure, anemia, lytic bone lesions; FLC, free light chain; IMWG, International Myeloma Working Group; MRD, minimal/measurable residual disease; NGF, next generation flow; NGS, next generation sequencing; PET-CT, positron emission tomography-computed tomography; SUV, standardized uptake value; SPD, sum of the products of the maximal perpendicular diameters. All response categories require two consecutive assessments made at any time before the institution of any new therapy. All categories also require no known evidence of new or progressive bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy the response requirements. Bone marrow assessments need not be confirmed. Each category other than SD will be considered unconfirmed until the confirmatory test is performed.

[a]To be used for calculation of disease-free survival only; progression should be defined using criteria for progressive disease.

Adapted from Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016; 17(8):e328-e346.

Initial Therapies

Induction Treatment for Patients Eligible for Transplantation

Initial therapy of myeloma has moved from doublets of thalidomide, lenalidomide or bortezomib, and dexamethasone to triplets that incorporate one or more of different drug classes in addition to dexamethasone. A summary of these regimens is shown in Table 27.5.

TABLE 27.5

Currently Recommended Regimens for Induction Therapy in Transplant Eligible Myeloma Patients

Regimen	ORR (PR + VGPR + CR) [a]	CR + VGPR [a]	PFS/EFS (months)	OS (months)	Reference(s)
VRD vs Rd (SWOG S0777)	81% vs 71%	43% vs 32%	41 vs 29	NR vs 69	Durie et al 2017; Durie. 2020.
VCRD vs VRD vs VCD-mod (EVOLUTION; phase 2)	88% vs 85% vs 100%	58% vs 51% vs 53%	12-mo: 86% vs 83% vs 100%	12-mo: 92% vs 100% in all other arms	Kumar et al 2012.
VTD vs TD (GIMEMA-MMY-3006)	93% vs 79%	62% vs 28%	60 vs 41	NR vs 110	Cavo et al 2010; Tacchetti et al 2020.
VTD vs TD (PETHEMA/GEM)	85% vs 62%	60% vs 29%	56 vs 28	4-y: 74% vs 65%	Rosiñol et al 2012.

Regimen	ORR (PR + VGPR + CR) [a]	CR + VGPR [a]	PFS/EFS (months)	OS (months)	Reference(s)
VTD vs VCD (IFM2013-04)	92% vs 83%	66% vs 56%	NA	NA	Moreau et al 2016.
RD vs high-dose dexamethasone (S0232)	78% vs 48%	63% vs 16%	3-y: 52% vs 32%	3-y: 79% vs 73%	Zonder et al 2010.
Rd vs RD (E4A03)	70% vs 81%	40% vs 50%	25 vs 19	1-y: 96% vs 87%	Rajkumar et al 2010.
VRd vs KRd (ENDURANCE)	84% vs 87%	65% vs 74%	34 vs 35	3-y OS: 84% vs 86%	Kumar et al 2020.
IRd (phase 1/2)	90%	35%	35	4-y: 84%	Kumar et al 2014; Kumar et al 2019.
Dara-VTd vs VTd (CASSIOPEIA)	93% vs 90%	83% vs 78%	NR vs 52 mo	NR in either arm	Moreau et al 2019; Moreau et al 2021.
Dara-VRd vs VRd (GRIFFIN; phase 2)	99% vs 91%	90% vs 73%	2-y PFS: 96% vs 90%	NR in either arm	Voorhees et al 2020.
Dara-KRd (MASTER; phase 2)	100%	90%	NA	NA	Costa et al 2019.
KCd (CARDAMON; phase 2)	87%	59%	2-y PFS of 70% and 76% in consolidation and transplant arms	NA	Yong et al 2019.

CR, complete response; Dara, daratumumab; IRd, ixazomib, lenalidomide, and dexamethasone; KCd,carfilzomib, cyclophosphamide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; ORR, overall response rate; PR, partial response; RD, lenalidomide and high-dose dexamethasone; Rd, lenalidomide and low-dose dexamethasone; TD, thalidomide and dexamethasone; VCD, bortezomib, cyclophosphamide, and dexamethasone; VCRD, bortezomib, cyclophosphamide, lenalidomide, and dexamethasone; VD, bortezomib and dexamethasone; VGPR, very good partial response; VRD/VRd, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone; vtD, contains reduced doses of bortezomib and thalidomide, and dexamethasone.

[a]The results given are for best response after induction unless specified otherwise.

Commonly Used Combinations for Upfront Treatment

The most used induction therapy in the United States is the combination of bortezomib, lenalidomide, and dexamethasone (VRd). This combination is very effective with over 90% of the patients obtaining a partial response to therapy and over a third reaching complete response in some of the trials. In a phase 3 trial, VRd was associated with improved PFS and OS, supporting its use as the current standard of care. In the phase 3 ENDURANCE trial,

combination of carfilzomib, lenalidomide, and dexamethasone (KRd) did not offer significant advantage over VRd in patients with standard risk disease, establishing VRd as the current standard of care. European trials have predominantly used the combination of bortezomib, thalidomide, and dexamethasone (VTd) in their phase 3 trials as induction therapy, and this regimen is very effective in inducing responses in newly diagnosed MM. Another regimen that has been commonly used around the globe is the combination of bortezomib, cyclophosphamide, and dexamethasone (VCd). All the recent regimens have used dexamethasone weekly compared to the earlier use of 4 days on -4 days off regimen, with phase 3 trials demonstrating an improved OS associated with the lower dose of dexamethasone. It is also important to note that the use of bortezomib has shifted to mostly subcutaneous route of administration due to reduced risk of neuropathy with preserved efficacy.

Typically, patients receive three to four cycles of induction therapy and proceed to stem cell collection and ASCT. The ideal duration of induction therapy remains a subject of debate with retrospective trials demonstrating no impact of the initial response on the outcomes of transplantation.

Novel Combinations in Clinical Trials

The past few years have witnessed an ongoing effort to further improve the efficacy of the induction regimens by adding new drug classes to the upfront combinations. KRd and carfilzomib, cyclophosphamide and dexamethasone (KCd) have yielded better response rates but have failed to yield a survival benefit in phase 3 trials. Ixazomib has been combined with lenalidomide and dexamethasone (IRd) providing a well-tolerated and efficacious all-oral regimen. Addition of the anti-CD38 monoclonal antibody, daratumumab (Dara), has led to deeper responses and improved PFS compared to VTd alone. Phase 2 results of daratumumab added to VRd and KRd are also promising. We currently consider addition of daratumumab to VRd induction for high-risk MM. It is likely that Dara-VRd may become the standard of care for induction in MM soon.

Autologous Stem Cell Transplantation

The Inter Groupe Francophone du Myelome 90 (IFM 90) trial and the Medical Research Council Myeloma VII Trial, demonstrated that high-dose therapy (HDT) followed by ASCT improves response rate and OS compared to conventional chemotherapy in myeloma patients younger than 65 years with good performance status (Table 27.6). However, two clinical trials

published later failed to show an OS benefit in patients receiving ASCT. One of them showed a trend to better event-free survival and a longer period without symptoms or treatment-related toxicity. The IFM 95 randomized trial showed that 200 mg/m^2 of melphalan is less toxic and as effective a conditioning regimen as total body irradiation with 140 mg/m^2 melphalan before ASCT. Although ASCT is commonly performed following three to four cycles of induction chemotherapy, a randomized trial comparing early versus late transplantation demonstrated that ASCT could be delayed until relapse without compromising survival provided that the stem cells are harvested and cryopreserved early in the disease course. Therefore, the timing of ASCT is based on patient preference and other factors, including response to initial induction therapy.

TABLE 27.6

Results for Chemotherapy Versus High-Dose Therapy (HDT) Followed by Stem Cell Transplantation (SCT)

Treatment	ORR (CR + VGPR PR)	CR + VGPR [a]	Median EFS/PFS (months)	Median OS (months)	Reference
CC vs ASCT (IFM 90)	57% vs 81%	14% vs 38%	18 vs 28	44 vs 57	Attal et al 1996.
CC vs ASCT (MRC VII)	48% vs 86%	8% vs 44%	20 vs 32	42 vs 54	Child et al 2003.
CC vs ASCT (MAG)	58% vs 62%	4% vs 6%	18.7 vs 25.3	47.6 vs 47.8	Fermand et al 2005.
CC vs ASCT (SWOG9321)	76% in both arms	11% in both arms	14% vs 17% at 7 y	38% at 7 y in both arms	Barlogie et al 2006.
MPR vs ASCT (GIMEMA RV-MM-PI-209)	91% vs 93%	63% vs 59%	22 vs 43.0	65% vs 82% at 4 y	Palumbo et al 2014.
CRd vs single or double ASCT (RV-MM-EMN-441)	89% vs 91%	50% vs 54%	29 vs 43	73% vs 86% 4-y OS	Gay et al 2015.
VCd induction followed by, VMP vs single or double ASCT (EMN02/HO95 MM)	95% vs 96%	77% vs 84%	42 vs 57	5-y OS: 72% vs 75%	Cavo et al 2016; Cavo et al 2020.
VRD-ASCT vs VRD alone, followed by lenalidomide maintenance (IFM 2009)	99% vs 97%	59% vs 48%	47 vs 35	8-y OS: 62% vs 60%	Attal et al 2017; Perrot et al 2020.

Treatment	ORR (CR + VGPR PR)	CR + VGPR [a]	Median EFS/PFS (months)	Median OS (months)	Reference
KCd-ASCT-K maintenance vs KCd- KCd consolidation-K maintenance (CARDAMON)	96% vs 90%	90% vs 78%	2-y PFS: 76% vs 70%	NA	Yong et al 2021.
KRd-ASCT vs KRdx 12 vs KCd-ASCT (FORTE)		89% vs 87% vs 76%	3-y PFS: 78% vs 68% vs 58%	3-y OS: 92% vs 90% vs 83%	Gay et al 2020.

[a]May include only complete response if VGPR was not reported in the trial. ASCT, autologous stem cell transplantation; CC, conventional chemotherapy; CR, complete response; CRd, cyclophosphamide, lenalidomide, and dexamethasone; EFS, event-free survival; K, carfilzomib; KCd, carfilzomib, cyclophosphamide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; MPR, melphalan, prednisone, and lenalidomide; ORR, overall response rate; PFS, progression-free survival; PR, partial response; OS, overall survival; TD, thalidomide and dexamethasone; V, bortezomib; VD, bortezomib and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

The above-mentioned trials were conducted when novel agents including thalidomide, lenalidomide, and bortezomib were not available. Novel agent-based chemotherapy improves event-free survival and is associated with deeper remissions compared to conventional chemotherapy prior to ASCT. In the IFM 2005-01 trial where patients were randomized to bortezomib with dexamethasone (VD) or conventional chemotherapy (VAD) before ASCT, the overall response in the VD arm was better, and there was a trend toward improved PFS in the VD arm. In the PETHEMA/GEM study, patients receiving bortezomib, thalidomide, and dexamethasone (VTD) had a PFS of 56 months compared to 28.2 months in the thalidomide with dexamethasone (TD) arm and 35.3 months in the conventional therapy with bortezomib arm.

Multiple trials have compared ASCT with novel agent-based chemotherapy as a consolidation strategy. In the RV-MM-EMN-441 trial, patients received lenalidomide and dexamethasone (Rd) as induction, and (single or double) ASCT was compared with cyclophosphamide, lenalidomide, and dexamethasone (CRd) as consolidation strategy, followed by R-maintenance. The patients in the ASCT arm had improved PFS and OS. In the GIMEMA RV-209 trial comparing melphalan, with prednisone and lenalidomide (MPR) against ASCT as consolidation followed by lenalidomide maintenance, OS was prolonged in patients in the ASCT arm. Another study which compared bortezomib, melphalan, and prednisone (VMP) against single- or double-ASCT, found deeper responses and improved PFS in patients in the ASCT arm. In the IFM DFCI 2009 study, VRD followed by ASCT and lenalidomide maintenance resulted in improved

PFS with similar OS when compared to RD consolidation and lenalidomide maintenance. In the CARDAMON study, induction with KCd followed by consolidation with KCd was non-inferior to ASCT with respect to PFS. In the FORTE study, there was a clear PFS benefit in the KRd + ASCT arm compared to KRd for 12 cycles, albeit with similar 3-year OS. These studies show that consolidation with SCT provides a clear PFS benefit even when compared to novel agent-based chemotherapy. The recent trials may show an OS benefit as the long-term follow-up data are available. Hence HDT with ASCT, either early or at first relapse, is the current standard of care in treatment of MM.

The question of using single SCT versus tandem SCT (planned second HDT and SCT done within 6 months of the first ASCT) in MM is controversial. The IFM 94 trial and the Bologna 96 Clinical study showed that tandem ASCT is superior to single ASCT after conventional chemotherapy, providing benefit in PFS as well as OS. However, the GMMG-HD2 trial which randomized patients after conventional chemotherapy to single ASCT or tandem SCT did not show any difference in survival. The BMT CTN 0702 (STaMINA) trial, which addressed the role of tandem SCT in the era of novel agents, randomized patients after an ASCT to R-maintenance, VRD consolidation and R-maintenance, or a second ASCT followed by R-maintenance. STaMINA showed similar PFS and OS at long-term follow-up, further suggesting that a tandem ASCT may not have distinct advantage over single ASCT. The per-protocol analysis in the high-risk subgroup showed improvement in PFS and OS. The EMN02 trial, on the other hand, showed a PFS advantage for tandem transplant, and this was driven by benefit in patients with high-risk cytogenetics. This is consistent with a meta-analysis of European randomized trials, which showed better OS with the tandem approach, among patients with t(4;14) or del17p. Tandem ASCT can be considered for patients with high-risk cytogenetics and those younger than 60 years who fail to achieve a deep response after first ASCT (Table 27.7).

TABLE 27.7

Results for Single Versus Double Autologous Stem Cell Transplantation (ASCT)

Treatment	ORR (CR + VGPR PR)	CR + VGPR/nCR	Median EFS/PFS (months)	Median OS (months)	TRM	Reference

Treatment	ORR (CR + VGPR PR)	CR + VGPR/nCR	Median EFS/PFS (months)	Median OS (months)	TRM	Reference
Single vs double ASCT (IFM 94)	84% vs 88%	42% vs 50%	25 vs 30	48 vs 58	4% vs 6%	Attal et al 2003.
Single vs double ASCT (Bologna 96)	NA	33% vs 47%	23 vs 35	65 vs 71	3% vs 4%	Cavo et al 2007.
Single ASCT vs double ASCT (GMMG HD2)	93% vs 91%	CR- 16% vs 19%	25.0 vs 28.7	73 vs 75.3	2% vs 5%	Mai et al 2016.
VRd induction with first ASCT followed by: ASCT vs VRd vs no additional consolidation; R maintenance in all arms (BMT CTN 0702/STaMINA)	NA	NA	5-y: 47% vs 44% vs 45%	5-y OS: 75% vs 75% vs 76%	3 vs 4 vs 1	Stadtmauer et al 2019; Hari et al 2020.
VCd induction followed by single vs double ASCT (EMN02/HO95 MM)	87% vs 100%	46% vs 90%	5-y: 45% vs 54%	5-y: 73% vs 80%	NA	Cavo et al 2017; Cavo et al 2020.

ASCT, autologous stem cell transplantation; CR, complete response; EFS, event-free survival; nCR, near-complete response; ORR, overall response rate ; OS, overall survival; PFS, progression-free survival; PR, partial response; R, lenalidomide; TRM, treatment-related mortality; VCd, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response; VRD, bortezomib, lenalidomide, and dexamethasone.

Initial Treatment for Patients Not Eligible for Transplantation

For a long time, melphalan-based regimens formed the cornerstone of therapy in patients with MM who were ineligible for an ASCT. Addition of novel agents to melphalan resulted in deeper responses and improvement in PFS and OS. Currently, novel agent-based triplets are the preferred initial therapy in this group of patients. The recommendations are based on trials conducted in transplant-ineligible patients as well as trials which included a significant proportion of patients with advanced age (Table 27.8). We recommend upfront therapy with Dara-Rd until progression or VRd for 8 to 12 cycles followed by Rd in patients who are transplant-ineligible. In patients with high-risk cytogenetics, Dara-Rd until progression or VRd followed by bortezomib maintenance can be used. In general, the newer agents improve PFS and OS in transplant-ineligible patients but with some increased risk of toxicity. The recommendations for use of Dara-Rd upfront are based on the results of the phase 3 MAIA trial which showed improved PFS and OS in the

Dara-Rd arm compared to Rd alone. This is also supported by the results of ALCYONE which showed improved outcomes with Dara-VMP compared to VMP alone. In the SWOG S0777 trial, VRd improved PFS and OS in patients with age ≥ 65 years. IRd showed improvement in PFS, with no benefit in OS in the TOURMALINE MM-2 trial. The doses of individual drugs in triplets can be modified to limit toxicity. Reduced intensity regimens using a single-novel agent such as Rd or Vd should be reserved for frail patients who cannot tolerate triplets. In the FIRST trial, continuous Rd was better than fixed duration Rd (72 weeks) and melphalan, prednisone, and thalidomide (MPT). In the UPFRONT trial, Vd was comparable to VTd and VMP. MP alone may still be considered in elderly patients without access to or who are not candidates for novel agents due to comorbidities.

TABLE 27.8

Regimens Evaluated in Newly Diagnosed Transplant Ineligible Patients With Multiple Myeloma

Regimen	ORR (CR + PR)	CR + VGPR	EFS/PFS/TTP (months)	OS (months)	Reference
Rd-continuous vs Rd for 18 mo vs MPT (FIRST)	81% vs 79% vs 67%	48% vs 47% vs 30%	26 vs 21 vs 22	59 vs 62 vs 49	Facon et al 2018.
VD vs VTD vs VMP (UPFRONT)	73% vs 80% vs 70%	37% vs 51% vs 41%	14.7 vs 15.4 vs 17.3	49.8 vs 51 vs 53.1	Niesvizky et al 2015.
VCD	95%	70%	12	NA	Jimenez Zepeda et al 2014.
IRd vs Rd	82% vs 80%	63% vs 48%	35 vs 22	5-y: approximately 60% in both arms	Facon et al 2021.
KMP vs VMP (CLARION)	84% vs 79%	NA	22 vs 22	22% and 20% died at median of 27 mo	Facon et al 2019.
MPT vs MP (GISMM2001-A)	70% vs 48%	29% vs 11%	22 vs 14.5	45 vs 48	Palumbo et al 2008.
MPT vs MP (IFM 99-06)	76% vs 35%	47% vs 7%	27 vs 18	52 vs 33	Facon et al 2007.
VMP vs MP (VISTA)	74% vs 39%	41% vs 8%	24 vs 17	83% vs 70% at 24 mo	San Miguel et al 2008.
VMP-VT vs VMP	89% vs 81%	59% vs 50%	35 vs 25	5-y OS: 61% vs 51%	Palumbo et al 2010; Palumbo et al 2014.

Regimen	ORR (CR + PR)	CR + VGPR	EFS/PFS/TTP (months)	OS (months)	Reference
MPR	81%	48%	92% at 12 mo	100% at 12 mo	Palumbo et al 2007.
Dara-Rd vs Rd (MAIA)	93% vs 82%	81% vs 57%	4-y PFS: 60% vs 38%	NA	Facon et al 2019; Kumar et al 2020.
Dara-VMP vs VMP (ALCYONE)	91% vs 74%	73% vs 50%	3-y: 51% vs 19%	3-y: 78% vs 68%	Mateos et al 2020.

CR, complete response; Dara-Rd, daratumumab, lenalidomide and dexamethasone; Dara-VMP, daratumumab, bortezomib, melphalan and prednisone; EFS, event-free survival; IRd, ixazomib, lenalidomide, and dexamethasone; KMP, carfilzomib, melphalan, and prednisone; KRd, carfilzomib, lenalidomide, and dexamethasone; MP, melphalan and prednisone; and MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Rd, lenalidomide and low dose dexamethasone; TTP, time to progression; VCD, bortezomib, cyclophosphamide, and dexamethasone; VD, bortezomib and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VTD, bortezomib, thalidomide, and dexamethasone.

In patients with renal insufficiency, VCd or Vd is preferred; for patients with history of peripheral neuropathy, Rd can be considered; if cost is a concern, MPT is least expensive; if oral therapy is desired, IRd, MPT, or MPR would be good choices.

Maintenance Therapy

Multiple trials have evaluated the role of maintenance treatment in transplant-eligible patients as well as in patients receiving non-transplant primary therapy (Table 27.9). In contrast to prior practice, maintenance treatment with lenalidomide after initial induction with or without consolidation with ASCT is the current standard of care in transplant-eligible patients with MM. Treatment is continued until progression or intolerable side-effects. In patients undergoing ASCT, lenalidomide maintenance has shown a consistent PFS benefit. A meta-analysis which included IFM2005-02, CALGB 100104, and GIMEMA RV-MM-PI-209 trials showed a median PFS of 52.8 months for the maintenance group and 23.5 months for the placebo/observation group. The OS was not reached in the lenalidomide group compared to 86 months in the placebo/observation group. Second primary malignancies were common in lenalidomide group (6.1% vs 2.8%). However the risk of developing progressive MM was lower and the time to death from MM was longer in patients receiving lenalidomide maintenance. Only one randomized study has been published which evaluates the role of long-term bortezomib therapy after ASCT. The HOVON-65/GMMG-HD4 trial randomized patients to bortezomib-based and conventional therapy

followed by ASCT. This was followed by bortezomib and thalidomide, respectively, as maintenance in the two arms. The PFS was better in the bortezomib arm (35 vs 28 months) and the incidence of peripheral neuropathy was lower with bortezomib. Bortezomib significantly improved PFS and OS in high-risk subgroups including patients with renal failure at diagnosis and those with del(17p) on FISH. There was no randomization prior to starting maintenance in this trial. So, it is difficult to attribute the improved outcomes to maintenance with bortezomib alone. Oral ixazomib improves PFS when used as maintenance after SCT and can be considered in patients with high-risk cytogenetics as well. Based on the results of the FORTE study which showed improvement in PFS with KR over R alone, maintenance with a combination of a proteasome inhibitor and lenalidomide is an option especially in patients with high-risk cytogenetics.

TABLE 27.9

Randomized Trials Evaluating Maintenance in Transplant and Nontransplant Settings

Maintenance Strategy	PFS (months)	OS (months)	Second Primary Malignancy	Reference
Maintenance after ASCT				
R maintenance vs placebo (IFM2005-02)	46 vs 24	82 and 81	13% vs 7%	Attal et al 2012; Attal et al 2013.
R maintenance vs placebo (CALGB 100104)	57 vs 29	114 vs 84	14% vs 8%	McCarthy et al 2012; Holstein et al 2017.
ASCT vs MPR followed by R maintenance vs no maintenance (GIMEMA RV-MM-PI-209)	42 vs 22	88% vs 79% at 3 y	Five patients in either arm	Palumbo et al 2014.
R maintenance vs observation (myeloma XI)	57 vs 30	3-y: 88% vs 80%	NA	Jackson et al 2019.
VAD + ASCT and thalidomide maintenance vs PAD + ASCT and Bortezomib maintenance (HOVON-65/GMMG-HD4)	28 vs 34	8-y OS: 45% vs 48%	7% vs 7%	Sonneveld et al 2012; Goldshmidt et al 2018.
Ixazomib vs Placebo (TOURMALINE-MM3)	27 vs 21	NA		Dimopoulos et al 2019.
R 2 y vs R till CR (GMMG-MM5)	3-y: 56% vs 49%	3-y: 84% vs 76%	6% vs 6%	Goldschmidt et al 2020.
KR vs R (FORTE)	3-y: 75% vs 66%	3-y: 90% in both arms.	NA	Gay et al 2020.
Maintenance after non-transplant primary treatment				

Maintenance Strategy	PFS (months)	OS (months)	Second Primary Malignancy	Reference
MP followed by placebo vs MPR vs MPR followed by R maintenance (MM-015)	13 vs 14 vs 31	66% vs 62% vs 70%	3% vs 7% vs 7% at 3 y	Palumbo et al 2012.
Rd indefinitely vs Rd for 72 wk vs MPT only (FIRST)	26 vs 21 vs 22	59 vs 62 vs 49	7% vs 7% vs 9%	Benboubker et al 2014; Facon et al 2018.
MPR and R maintenance vs MPT and thalidomide maintenance (HOVON87/NMSG-18)	23 vs 20	4-y OS: 56% vs 52%	6% vs 7%	Zweegman et al 2016.
MPT and thalidomide maintenance vs MPR and R maintenance (ECOG E1A06)	21 vs 19	53 vs 48	3.5 vs 2/100 person years	Stewart et al 2015.
R maintenance vs observation (Myeloma XI)	26 vs 11	3 y: 67% vs 70%		Jackson et al 2019.
Ixazomib × 24 mo vs placebo (TOURMALINE MM4)	17 vs 9	N/A	5% vs 6%	Dimopoulos et al 2020.
Dara-VMP-Dara vs VMP (ALCYONE)	3-y PFS: 51% vs 19%	3-y OS: 78% vs 68%	5% vs 5%	Mateos et al 2020.
Dara-VTd vs VTd followed by Dara vs no maintenance (CASSIOPIEA)	NR vs 47	N/A	5% vs 3%	Moreau et al 2021.

ASCT, autologous stem cell transplantation; CR, complete response; Dara, daratumumab; Dara-VMP, daratumumab, bortezomib, melphalan, and prednisone; Dara-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; KR, carfilzomib and lenalidomide; MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; OS, overall survival; PAD, bortezomib, doxorubicin, and dexamethasone; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.

Lenalidomide has shown improvement in PFS in at least two clinical trials in patients who do not receive ASCT as part of the primary therapy. The MM-015 trial assigned patients randomly to MP followed by placebo versus MPR followed by lenalidomide maintenance. The patients in the maintenance arm had prolonged PFS, while there was no improvement in OS at 3 years. In the FIRST trial, patients who received lenalidomide indefinitely had better PFS when compared to those who received lenalidomide for a fixed duration. In both these studies, the incidence of send primary cancers was higher in the lenalidomide maintenance arm. The UPFRONT trial is the only study which has used bortezomib maintenance in the transplant ineligible population. Patients received Vd, VTD, or VMP for induction, followed by bortezomib maintenance. Bortezomib sustained the responses or deepened the responses during maintenance with little additional toxicity.

Notably, there was no randomization prior to maintenance treatment. Ixazomib as maintenance has also been shown to improve PFS in transplant-ineligible patients. In the transplant-ineligible population, a continuous treatment strategy with daratumumab improves survival based on the results on the ALCYONE trial. However, CASSIOPIEA trial which randomized patients after Dara-VTd or VTd induction to daratumumab or placebo maintenance showed that the benefit of daratumumab maintenance was seen only in those patients who were not exposed to it during the initial induction phase, bringing into question of utility of daratumumab as maintenance if used as part of induction.

Potential risks and benefits, patient characteristics that influence outcomes, and patient preference should be taken into consideration while making a decision to institute maintenance therapy. Maintenance with lenalidomide is preferred after upfront therapy irrespective of the use of ASCT. Bortezomib is a viable alternative, especially in patients who have renal dysfunction, those with high-risk cytogenetics, or for patients who are intolerant to lenalidomide. Ixazomib, daratumumab, and dual maintenance with a PI and an IMiD can be considered based on a case by case basis. For frail patients, observation after initial treatment remains a reasonable option.

Supportive Measures

Intravenous pamidronate given monthly reduces bone pain and the incidence of pathologic fractures and the need for surgery or irradiation to the bone in patients with advanced myeloma. A randomized trial demonstrated that zoledronic acid is as effective as pamidronate in reducing skeletal complications, in addition to having the advantage of a shorter administration time. However, zoledronic acid is associated with an increased risk of osteonecrosis of the jaw when compared to pamidronate. The long-term outcomes of MRC myeloma IX trial, which randomized patients with MM regardless of bone lesions, showed improved PFS and OS, and higher rates of osteonecrosis in patients receiving zoledronic acid. Based on the above trials and a meta-analysis that demonstrated benefit of bisphosphonates, they are recommended in all patients with MM, regardless of the presence of bone disease. Patients should have a dental examination prior to therapy and should be monitored for osteonecrosis of jaw and renal dysfunction during therapy. Bisphosphonate should be given monthly for at least 2 years. Bisphosphonates should be restarted at relapse. The RANK-ligand inhibitor denosumab was non-inferior to zoledronic acid with respect to the time to first skeletal-related event. Denosumab was associated with

lower rates of renal adverse events, especially in those with a creatinine clearance ≤ 60 mL/min. Cost is a limiting factor in using denosumab. It can be used in patients where zoledronic acid is contraindicated.

Infection prophylaxis is crucial during induction therapy. All patients should receive antibacterial prophylaxis with levofloxacin 500 mg/d for 3 months. Trimethoprim-sulfamethoxazole (one single strength tablet daily) is the preferred agent for prophylaxis against *Pneumocystis jirovecii* pneumonia for patients on dexamethasone. Herpes zoster prophylaxis with acyclovir 400 mg twice a day or valacyclovir 500 mg daily should be used in patients receiving bortezomib- or daratumumab-containing regimens. Intravenous immunoglobulin therapy may be used in patients with recurrent life-threatening infections and immunoparesis.

Other supportive measures in myeloma include adequate analgesia with or without local irradiation for bone pain, limited field radiation or surgery for spinal cord compression, vertebroplasty or kyphoplasty for impending vertebral pathologic fractures, treatment and prevention of hypercalcemia, avoidance of dehydration by a high fluid intake to maintain renal function, and dialysis if necessary.

Prophylactic anticoagulation to decrease the risk of thrombotic complications is recommended for myeloma patients receiving therapy. The National Cancer Center Network guidelines for cancer-associated venous thromboembolic disease may be used to choose thromboprophylaxis. Patients receiving immunomodulator-based therapy or with one individual risk factor should receive prophylaxis with aspirin (81-325 mg once daily). Low–molecular-weight heparin (equivalent of enoxaparin 40 mg/d) or warfarin (INR goal: 2-3) is recommended for patients with ≥2 patient-related risk factors, or those receiving highly prothrombotic therapy (an immunomodulatory drug in combination with high-dose dexamethasone [≥480 mg/mo] or doxorubicin or multiagent chemotherapy). IMPEDE-VTE and SAVED are two scoring systems validated in patients with MM based on large databases and may be used for identifying patients at high risk of thrombosis. Novel oral anticoagulants such as apixaban and rivaroxaban can be considered in place of low–molecular-weight heparin and warfarin although prospective data in patients with MM are lacking.

REFRACTORY AND/OR RELAPSED MULTIPLE MYELOMA

Relapsed MM is defined as previously treated MM that progresses (biochemical progression or clinical relapse) and requires salvage therapy. MM is said to be refractory to a drug if the patient fails to attain at least a minimal response to therapy or attains a response but progresses while on therapy or within 60 days of stopping therapy. Almost all patients with MM relapse after primary therapy. Even with the availability of multiple active agents, the outcome of patients who have relapsed multiple times and are refractory to multiple drugs is poor.

All patients with relapsed MM should undergo a comprehensive evaluation for factors that aid in deciding the choice of therapy and defining the prognosis. This would include bone marrow biopsy with FISH testing for high-risk secondary cytogenetic abnormalities like del(17p), 1q gain, 1p deletion and MYC rearrangement, serum LDH, flow cytometry for circulating plasma cells, and an appropriate imaging such as whole-body PET-CT for evaluation of extramedullary disease. High-risk cytogenetic abnormalities, circulating plasma cells, extramedullary plasmacytoma(s), elevated LDH, refractoriness to primary therapy, and relapse within 18 months of an ASCT indicate high-risk disease and require aggressive therapy. All patients should be encouraged to explore the option of enrolling in a clinical trial investigating newer drugs and drug-combinations. We have summarized the results of clinical trials supporting the current off-protocol treatments in patients with RRMM (Table 27.10). We do not have robust evidence from trials investigating best sequence of therapies in patients with RRMM. The current recommendations on the preferred combinations are based on subgroup analyses of large clinical trials. Triplet combinations should be used whenever possible. Doublets have shown efficacy in clinical trials but should be reserved for patients who cannot tolerate a triplet. Patients who did not receive an upfront ASCT should be considered for ASCT after reinduction.

TABLE 27.10

Important Clinical Trials in Relapsed And/Or Refractory Multiple Myeloma

Regimen	EFS/PFS (months)	OS (months)	Reference
Dara-Kd vs Kd (CANDOR)	28 vs 15	18-mo: 80% vs 74%	Dimopoulos et al 2020.
Lenalidomide-refractory	28 vs 11 mo	NA	

Regimen	EFS/PFS (months)	OS (months)	Reference
PVd vs Vd (OPTIMISMM)	11 vs 7	NA	Richardson et al 2019.
Lenalidomide-refractory	18 vs 10	NA	Dimopoulos et al 2021.
Isa-Kd vs Kd (IKEMA)	2-y: 69% vs 46%	NA	Moreau et al 2021.
Lenalidomide refractory	NR vs 16	NA	
Dara-Pd vs Pd (APOLLO)	12 vs 7	NA	Dimopoulos et al 2021.
Lenalidomide refractory	10 vs 7	NA	
Dara-Vd vs Vd (CASTOR)	17 vs 7 mo	NR	Palumbo et al 2016.
Refractory to IMiD	9 vs 5	2-y: 62% vs 47%	Mateos et al 2020.
Kd vs Vd (ENDEAVOR)	18.7 vs 9.4	47.6 vs 40	Dimopoulos et al 2016; Dimopoulos et al 2017; Orlowski et al 2020.
Lenalidomide refractory	NA	29 vs 21	Orlowski et al 2020.
Dara-Rd vs Rd (POLLUX)	45 vs 18 mo	42-mo: 65% vs 57%	Dimopoulos et al 2016; Bahlis et al 2020.
KRd vs Rd (ASPIRE)	26 vs 17	48 vs 40	Stewart et al 2015; Dimopoulos et al 2017; Siegel et al 2018.
IRd vs Rd (TOURMALINE MM1)	21 vs 15	54 vs 52	Moreau et al 2016; Richardson et al 2021.
Elo-Rd vs Rd (ELOQUENT-2)	19 vs 15	48 vs 40	Lonial et al 2015; Dimopoulos et al 2010.
SVd vs Vd (BOSTON)	14 vs 9	NR vs 25 mo	Grosicki et al 2020.
Venetoclax + Vd vs Vd (BELLINI)	22 vs 12	2-y approx. 75% vs 90%	Kumar et al 2020.
t(11;14) and BCL-2 expression	NR vs 10 mo and 22 vs 10 mo.	NA	
Isa-Pd vs Pd (ICARIA)	12 vs 6	25 vs 18	Attal et al 2019; Richardson et al 2021.
Lenalidomide refractory	11 vs 6	NA	
Rd, ASCT, and R vs Rd (GMMG ReLapse)	21 vs 19	3-y: 72% vs 72%	Goldschmidt et al 2020.
ASCT vs oral cyclophosphamide (Myeloma X relapse)	19 vs 11	3-y: 80% 63%	Cook et al 2014.
Phase 2 studies			
Elo-Pd vs Pd (ELOQUENT-3)	10 vs 5	NA	Dimopoulos et al 2018.
Dara-Pd (EQUULEUS)	9	18	Chari et al 2017.

Regimen	EFS/PFS (months)	OS (months)	Reference
Sd (STORM)	4	9	Chari et al 2019.
Melflufen with dexamethasone (HORIZON)	4	12	Richardson et al 2021.
Idecabtagene vicleucel/ide-cel (KarMMa-2)	9	25	Munshi et al 2021.
Belantamab mafodotin 2.5 mg/kg 3.4 mg/kg (DREAMM-2)	3 5	14 NA	Lonial et al 2020.

ASCT, autologous stem cell transplant; Dara-Kd, daratumumab, carfilzomib, and dexamethasone; Dara-Pd, daratumumab, pomalidomide and dexamethasone; Dara-Rd, daratumumab, lenalidomide and dexamethasone; Dara-Vd, daratumumab, bortezomib, and dexamethasone; EFS, event-free survival, Elo-Pd, elotuzumab, pomalidomide, dexamethasone; Elo-Rd, elotuzumab, lenalidomide and dexamethasone; IRd, ixazomib, lenalidomide and dexamethasone; Isa-kd, isatuximab, carfilzomib, and dexamethasone; Isa-Pd, isatuximab, pomalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide and dexamethasone; Sd, selinexor and dexamethasone; SVd, selinexor, bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.

Based on the International Myeloma Working Group guidelines for relapsed and/or refractory multiple myeloma. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol*. 2021;22(3):e105-e118.

In general, patients who relapse while on therapy or within 6 months of last therapy should receive a triplet regimen containing ≥1agent(s) belonging to separate classes of drugs or at least drugs belonging to the next generation within the same class. Since maintenance treatment with lenalidomide is the current standard, an important criterion to decide next treatment at first relapse is whether the patient is refractory to lenalidomide or not (Figure 27.3). Drug regimens based on anti-CD38 monoclonal antibodies and either proteasome inhibitors or pomalidomide are preferred in this setting. For patients who are not refractory to lenalidomide, drug combinations incorporating lenalidomide are preferred at first relapse. Dara-Rd, IRd, ixazomib, cyclophosphamide, and dexamethasone (ICd) and the anti-SLAMF7 antibody elotuzumab with Rd (Elo-Rd) are triplet combinations that may be tolerated in frail patients. For subsequent relapses, therapy should be decided based on prior refractoriness and likelihood of response based on the tumor biology. In patients who are refractory to multiple agents, efforts should be made to choose drug combinations which contain as many drugs as possible to which the patient is not refractory. Venetoclax-based combinations are highly active in patients with t(11;14) or expressing

BCL-2. Currently, the autologous anti-B–cell membrane antigen chimeric antigen receptor (CAR) T-lymphocyte product idecabtagene vicleucel (ide cel) is approved for use in patients exposed to at least four prior lines of therapy. The antibody drug conjugate belantamab mafodotin (belamaf) is also approved for a similar patient population. Patients who received an ASCT as part of primary therapy would benefit from a second ASCT if they derived a meaningful PFS from their first ASCT. Aggressive therapies like VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) or its modifications may be used in patients with quadruple refractory disease, secondary plasma cell leukemia, or with extensive extramedullary disease for cytoreduction and as a bridge to stem cell transplantation.

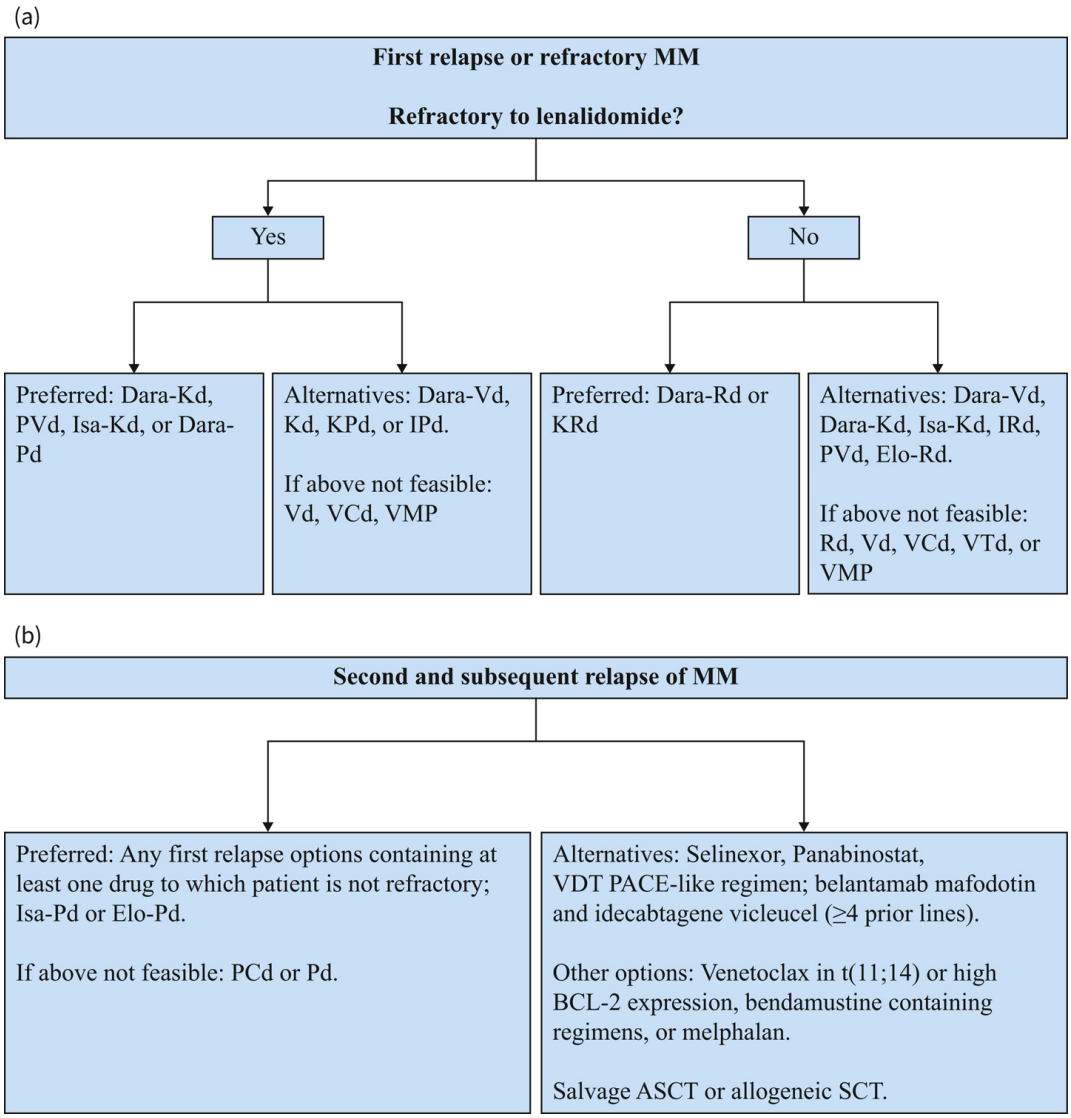

FIGURE 27.3 Recommended treatment options for relapsed and/or refractory multiple myeloma patients at first relapse (A) and at second and subsequent relapses (B).ASCT, autologous stem cell transplant; Dara-Kd, daratumumab, carfilzomib, and dexamethasone; Dara-Pd, daratumumab, pomalidomide, and dexamethasone; Dara-Rd, daratumumab, lenalidomide, and dexamethasone; Dara-Vd, daratumumab, bortezomib, and dexamethasone; Elo-Pd, elotuzumab, pomalidomide, dexamethasone; Elo-Rd, elotuzumab, lenalidomide, and dexamethasone; IRd, ixazomib, lenalidomide, and dexamethasone; Isa-kd, isatuximab, carfilzomib, and dexamethasone; Isa-Pd, isatuximab, pomalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PCd, pomalidomide, cyclophosphamide, and dexamethasone; Pd, pomalidomide and dexamethasone; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide and dexamethasone; SCT, stem cell transplantation; Sd, selinexor and dexamethasone; SVd, selinexor, bortezomib, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VDT PACE, bortezomib,

dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.(Based on the International Myeloma Working Group guidelines for relapsed and/or refractory multiple myeloma. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol*. 2021;22(3):e105-e118.)

Myeloablative as well as nonmyeloablative allogeneic stem cell transplantation may benefit a small percentage of patients with relapsed MM because of a powerful graft-versus-myeloma effect, with attendant risks of transplant-related mortality and graft-versus-host disease. Allogeneic transplantation especially under the purview of a clinical trial may be considered as a salvage option in younger, fit patients, with high-risk markers who are refractory to commonly used regimens.

CONCLUSION

Recent advances in understanding of tumor biology, availability of newer drugs, and widespread use of ASCT are improving the survival in patients with MM. Novel agent-based triplets form the backbone of initial therapy as well as treatment of relapsed disease. Monoclonal antibodies are a recent addition to the therapeutic armamentarium, with the potential to induce deep and lasting remissions. Newer therapies such as CAR T-cells, bispecific antibodies, and antibody-drug conjugates may further improve outcomes for patients. However, a proportion of patients have high-risk features, and their outcomes remain poor. Development of biomarkers and targeted drug development are necessary to improve the survival in this patient population.

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28

Non-Hodgkin Lymphoma

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INTRODUCTION

The term *non-Hodgkin lymphoma* (NHL) encompasses a diverse group of lymphoproliferative disorders of B-cell, T-cell, and NK-cell origin that together account for approximately 90% of all lymphomas diagnosed in the United States. Although unified in their histopathologic distinction from Hodgkin lymphoma, these disorders vary considerably in morphologic appearance, clinical behavior, therapeutic options, and prognosis. Our understanding of the genetic and molecular basis of different NHL subtypes continues to advance, and as a result, so does the therapeutic landscape.

EPIDEMIOLOGY AND RISK FACTORS

NHL is the seventh most common adult malignancy in the United States, with 77,240 new cases diagnosed in 2020. The overall incidence of NHL has increased substantially over the past several decades, almost doubling between 1975 and 1995. Since the mid-1990s, however, this trend has become progressively less pronounced, with overall incidence rates stabilizing between 2005 and 2009. Although incompletely understood, these changes in NHL incidence have been attributed to a variety of factors such as the emergence of (and subsequent advancements in therapy for) HIV/AIDS, improvements in detection and reporting of NHL, and reduction in mortality rates from other causes.

The risk of developing NHL increases with each decade of adult life. Certain subtypes of NHL, however, such as primary mediastinal B-cell lymphoma (PMBL) and Burkitt lymphoma (BL), tend to occur in younger patients. There is considerable geographic disparity in NHL incidence, with the highest rates seen in North America, Australia, and Western Europe and the lowest rates seen in Asia, South America, and the Caribbean.

Disorders of the immune system, often in conjunction with chronic viral infection, are associated with increased risk of NHL. Higher rates of NHL are seen in patients with congenital and acquired immunodeficiencies and with diseases of immune dysregulation. Though most of these lymphomas are of B-cell lineage, there are notable exceptions like enteropathy-associated T-cell lymphoma (EATL), which occurs most commonly in patients with gluten enteropathy, and hepatosplenic T-cell lymphoma, which often occurs in patients with inflammatory bowel disease or post–solid organ transplantation.

Epstein-Barr virus (EBV), an oncogenic driver in multiple subtypes of NHL, and EBV-associated NHL can occur in both immunocompetent and immunocompromised patients. In BL, virtually all cases of endemic BL, 30% of sporadic BL, and 40% of immunodeficiency-related BL are associated with EBV infection. In diffuse large B-cell lymphoma (DLBCL),

between 5% and 15% of cases are EBV-associated. Among HIV-related lymphomas, EBV infection is seen in nearly all cases of primary CNS lymphoma (PCNSL) and plasmablastic lymphoma, oral type, and is also seen in immunodeficient patients with primary effusion lymphoma (PEL), plasmablastic lymphoma, and posttransplant lymphoproliferative disorder. One oncogenic mechanism of EBV in NHL involves constitutive activation of the NF-κB pathway although the entire spectrum of oncogenic mechanisms remains unknown.

Other infections besides EBV have been implicated in the development of specific NHL subtypes. PEL and adult T-cell lymphocytic leukemia are nearly always seen in conjunction with HHV-8 and HTLV-1 infections, respectively. Marginal zone lymphomas (MZL) also are frequently associated with viral or bacterial antigens; for example, splenic and nodal MZL variants with HCV, gastric mucosa-associated lymphoid tissue (MALT) lymphoma with *Helicobacter pylori*, and ocular adnexal MALT lymphoma with *Chlamydia psittaci* (Table 28.1).

TABLE 28.1

Risk Factors Associated With NHL Development

Immunosuppression/Immunodeficiencies	Drugs	Environmental/Exposures	Infections	Other
Congenital • Ataxia telangiectasia • Wiskott-Aldrich syndrome • SCID • CVID • Hyperimmunoglobulin M (Job syndrome) • X-linked hypogammaglobulinemia • X-linked lymphoproliferative syndrome acquired • Solid organ transplantation • Stem cell transplantation • AIDS • Sjögren syndrome • Rheumatoid arthritis • Hashimoto thyroiditis • IBD • Celiac sprue	Immuno-suppressive agents Phenytoin Methotrexate TNF inhibitors	Radiation therapy Occupational exposures • Herbicides • Pesticides • Wood dust • Epoxy glue • Solvents • Agent orange • Farming • Forestry • Painting • Carpentry • TanningSilicone breast implants	EBV HTLV-1 *Helicobacter pylori* HCV HHV-8 HIV *Borrelia burgdorferi* *Chlamydia psittaci* *Chlamydia trachomatis* *Chlamydia pneumonia* *Campylobacter jejuni*	Advanced age Male gender Previous history of NHL Family history of NHL

AIDS, acquired immunodeficiency syndrome; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HTLV-1, human T-cell lymphotropic virus type I; IBD, inflammatory bowel disease; SCID, severe combined immunodeficiency; TNF, tumor necrosis factor.

PATHOGENESIS AND MOLECULAR CHARACTERIZATION

NHL pathogenesis involves a complex array of genetic aberrations that disrupt the normal cellular pathways of proliferation, differentiation, and apoptosis. These genetic events are usually acquired and result in functional activation of proto-oncogenes and/or inactivation of tumor suppressor genes. Balanced chromosomal translocations are early genetic events that initiate lymphomagenesis in certain types of NHL. Up to 85% of patients with follicular lymphoma (FL) carry a t(14;18) translocation, and nearly every case of mantle cell lymphoma (MCL) is characterized by a t(11;14) translocation. High-throughput genetic

sequencing has revealed a broad genomic landscape in NHL, with considerable heterogeneity within and across subtypes. Further characterization of lymphomagenesis with emerging technologies promises more precision in diagnosis, prognosis, and treatment selection.

CLASSIFICATION

Individual NHL are defined in the World Health Organization (WHO) classification system, most recently updated in 2016. Initially established in 2001, this system constituted the first international consensus on diagnosis and classification of lymphoma. Within this system, NHL is classified primarily by cell lineage and maturity (B- vs T/NK cell, mature vs precursor cell of origin) and then further subcategorized according to a combination of morphologic, immunophenotypic, genetic, molecular, and clinical features. It is expected that the classification system for NHL will continue to evolve as our knowledge of the genetic and molecular basis of these diseases continues to improve.

DIAGNOSIS

An excisional lymph node biopsy remains the gold standard for diagnosing lymphoma. Some centers have adopted the practice of obtaining a combination of core-needle biopsy and fine-needle aspiration as an alternative to surgical lymph node excision, reserving the latter for nondiagnostic cases. Although this approach is relatively sensitive and cost-effective, a definitive diagnosis is unobtainable in approximately 20% to 25% of patients. Consequently, perioperative risk, institutional experience with core-needle biopsy, and the harm of diagnosis delay should be considered when deciding the diagnostic approach.

The pathologic classification of NHL subtype primarily relies on morphologic appearance and immunophenotyping using immunohistochemistry (IHC) and flow cytometry. Additional studies that confirm clonality and further subclassify tumor type include cytogenetic analysis and molecular studies.

WORKUP AND STAGING

Initial workup and staging evaluation of NHL should include a complete history and physical examination and clinical laboratory assessment of organ function. The following tests should be performed:

- Complete blood count with differential
- Complete metabolic panel including lactate dehydrogenase (LDH)
- Serologies for HIV, HBV, HCV (regardless of exposure history)
- Computed tomography (CT) scan of the chest, abdomen, and pelvis
- Whole-body fluorodeoxyglucose–positron emission tomography (FDG-PET) scan
- Bone marrow (BM) aspirate and biopsy
- Lumbar puncture with cerebrospinal fluid (CSF) cytology and flow cytometry (in select cases only)

The Ann Arbor staging system, originally designed for Hodgkin lymphoma, is standardly used in newly diagnosed NHL (Table 28.2). Although this system is often of limited prognostic value in NHL due to the lack of contiguous orderly spread through lymph node regions, it nevertheless remains an integral component of the validated international prognostic indices (IPIs) for aggressive NHL and FL.

TABLE 28.2

Staging Classification of Lymphoma

Stage	Ann Arbor Classification	Cotswold Modification
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (II_E)	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is considered a single site, whereas the hilar lymph nodes are considered bilaterally); the number of anatomic sites should be indicated by a subscript (eg, II_3)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S); a limited contiguous extralymphatic organ or site (III_E); or both (III_{ES})	Involvement of lymph node regions on both sides of the diaphragm: III_1 (with or without involvement of splenic hilar, celiac, or portal nodes) and III_2 (with involvement of para-aortic, iliac, and mesenteric nodes)
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without lymphatic involvement	Involvement of one or more extranodal sites in addition to a site for which the designation E has been used

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant fever (>38.0 °C [100.4 °F]), night sweats, and unexplained weight loss exceeding 10% of normal body weight within the previous 6 months. The clinical stage (CS) denotes the stage as determined by all diagnostic examinations and a single diagnostic biopsy only. In the Ann Arbor classification, the term pathologic stage (PS) is used if a second biopsy of any kind has been obtained, whether negative or positive. In the Cotswold modification, the PS is determined by laparotomy; X designates bulky disease (widening of the mediastinum by more than one-third or the presence of a nodal mass >10 cm), and E designates involvement of a single extranodal site that is contiguous or proximal to the known nodal site.

Restaging for Response Evaluation

Upon completion of therapy, CT scans should be repeated to categorize the response. BM biopsy is required to determine complete response (CR) if the marrow was involved prior to therapy. In accordance with the Revised Response Criteria for Malignant Lymphoma, FDG-PET is mandatory for the evaluation of residual masses at the completion of therapy. Response to therapy is determined based on changes in the sum of the product of the diameters of the masses, as well as resolution of hepatosplenomegaly and BM involvement. FDG-PET was formally incorporated into staging and response assessment with the Lugano classification, wherein responses are assessed by changes in the lesions' FDG uptake in relation to the mediastinal blood pool and liver. This classification was also subsequently refined to incorporate changes, such as tumor flare or pseudoprogression, that can occur with modern immunotherapy treatments. In cases of suspected disease relapse or refractoriness to initial therapy, repeat biopsy should be strongly considered for confirmation.

PROGNOSTIC FEATURES

IPI is a clinical prognostic index that has been validated in aggressive lymphoma. Five clinical factors comprise the IPI and 1 point is assigned to each factor:

- Age >60 years
- Eastern Cooperative Oncology Group (ECOG) performance status 2 or higher
- LDH level greater than normal
- Two or more extranodal sites
- Ann Arbor stage III or IV disease

Scores of 0-1, 2, 3, and 4-5 correspond to 5-year survivals of 73%, 51%, 43%, and 26%, respectively, in DLBCL. A validated clinical prognostic index also has been applied to patients with untreated FL. The Follicular Lymphoma International Prognostic Index (FLIPI) is scored according to the following:

- Age >60 years
- Ann Arbor stage III or IV disease
- LDH level greater than normal
- Hemoglobin <12 g/dL
- Five or more nodal areas involved

The FLIPI score reliably predicts survival in FL with scores of 0-1, 2, and 3-5 corresponding to 5-year survivals of 91%, 78%, and 53%, respectively. Gene expression profiling (GEP) has emerged as a useful means of identifying molecularly distinct subclassifications of NHL and can be used to identify individuals who may benefit from treatment intensification or addition of novel agents given their poor prognosis with current standard therapies. Integration of somatic mutation profiles that correlate with individual subtypes has the potential to further refine these prognostic models.

MANAGEMENT

Indolent B-Cell NHL

Follicular Lymphoma

FL is the most common of the indolent lymphomas, constituting approximately 70% of cases, and is considered an incurable lymphoma. Patients are typically older (median age of 60) with disseminated lymphadenopathy at diagnosis. Constitutional symptoms and extranodal involvement can occur but are uncommon. Many patients are asymptomatic at diagnosis. FL is graded (1-3) according to the number of centroblasts per high-power field. Therapeutic approaches to grades 1 to 3A are similar, whereas grade 3B should be treated as DLBCL.

FL exhibits a wide range of clinical behavior. The median survival is currently greater than 10 years, but approximately 20% of patients will progress within 2 years of initial therapy and these patients have a much poorer prognosis compared to those without early progression. Histologic transformation to a more aggressive NHL subtype (typically

DLBCL) occurs at an approximate cumulative rate of 3% per year and is generally associated with an inferior prognosis.

Even though FL is considered generally incurable, those who present with truly limited stage disease (stage 1) may achieve prolonged remissions and long-term survival with radiation treatment to the affected areas. Multiple studies have reported a 15-year overall survival (OS) rate of approximately 50% in these patients and only a few relapses reported after 10 years. For most patients with FL, however, this is not an option since the disease is advanced stage at the time of diagnosis. For patients with advanced stages of FL but without symptoms, immediate therapy is not mandatory. Randomized trials have assessed early initiation of therapy in advanced stage FL compared to observation and have not shown an improvement in OS.

The anti-CD20 monoclonal antibody, rituximab, has demonstrated both safety and efficacy in previously untreated, advanced-stage, low-grade FL and can be considered as monotherapy for patients with low-volume disease. Rituximab monotherapy, however, is less effective in patients with high tumor burden, and these patients should be treated with combination therapy. Bendamustine with rituximab (BR) and rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) are commonly used standard first-line treatment regimens. In two separate randomized phase 3 trials directly comparing BR with R-CHOP in indolent NHL, BR demonstrated better or noninferior progression-free survival (PFS) and overall toxicity across all histological subtypes, including FL, but no statistically significant difference in OS. Patients receiving BR had a slightly higher rate of secondary malignancies and opportunistic infections. Subsequently, the GALLIUM trial assessed whether the efficacy of chemoimmunotherapy could be improved by replacing rituximab with obinutuzumab, a glycoengineered anti-CD20 antibody with greater direct B-cell killing effects than rituximab. Patients were randomized to either rituximab or obinutuzumab in combination with investigator's choice of chemotherapy (bendamustine, CHOP, or CVP). The obinutuzumab arm had a better PFS, but no difference in response rates at the end of induction therapy, and a higher rate of grade 3-5 adverse events. More recently, lenalidomide in combination with rituximab (R2) has emerged as another first-line treatment option. In a multicenter, international randomized phase 3 trial, R2 demonstrated similar response rates and 3-year interim PFS compared to BR, R-CHOP, or R-CVP, with lower rates of grade 3-4 neutropenia and febrile neutropenia and higher rates of cutaneous reactions (Table 28.3).

TABLE 28.3

First-Line Treatment Regimens for Follicular Lymphoma

Regimen	Number of Patients	Outcome	Reference
Watchful waiting vs rituximab induction vs rituximab induction and maintenance	379	WW: 3-y TTNT 46% Induction: 3-y TTNT 78% Induction + maintenance: 3-y TTNT 88%	Ardeshna et al, 2014
BR vs R-CHOP	279	BR: Median PFS NR R-CHOP: Median PFS 40.9 mo	StiL Study Rummel et al, 2013
BR vs R-CHOP/R-CVP	447 with BCL (371 with iNHL)	BR: 5-y PFS 66% R-CHOP/CVP: 5-y PFS 56%	BRIGHT Study Flinn et al, 2019

Regimen	Number of Patients	Outcome	Reference
Lenalidomide + rituximab (R^2) vs chemotherapy + rituximab	1030	R^2: 3-y PFS 77% R-chemo: 3-y PFS 78%	RELEVANCE Study Morschhauser et al, 2018
Obinutuzumab + chemo vs rituximab + chemo followed by maintenance	1202	O + chemo: 3-y PFS 80% R + chemo: 3-y PFS 73%	GALLIUM Study Marcus et al, 2017
Rituximab maintenance vs observation following R-CHOP/CVP	1217	Maintenance: 3-y PFS 75% Observation: 3-y PFS 58%	PRIMA Study Salles et al, 2010

BCL, B-cell lymphoma; BR, bendamustine and rituximab; iNHL, indolent non-Hodgkin lymphoma; NR, not reached; PFS, progression-free survival; R^2, rituximab and Revlimid (lenalidomide); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; TTNT, time to next treatment.

An important issue surrounding frontline therapy for FL is whether to use extended duration or "maintenance" therapy. The RESORT trial addressed this question in patients with low tumor burden FL who were first treated with rituximab monotherapy. Patients who responded to initial doses of rituximab were then randomized to a planned scheduled of rituximab maintenance or a schedule that initiated rituximab only at the time of disease progression. At a median follow-up of 5 years, the treatment failure was similar between the two groups. The PRIMA trial later assessed the benefit of maintenance rituximab following induction chemoimmunotherapy (R-CHOP, R-CVP, R-FCM) in patients with high tumor burden. Following induction therapy, responding patients were randomized to 2 years of rituximab maintenance or observation. Although rituximab maintenance led to improved PFS, this did not translate into an OS benefit and was associated with increased toxicity and infections.

Patients with relapsed/refractory FL can be treated with alternative chemoimmunotherapy regimens, single-agent rituximab, radioimmunotherapy (RIT), or targeted therapy. Selection of therapy depends on multiple factors including disease burden, prior treatment received, and how quickly the patient relapsed after frontline treatment. For patients with low disease burden and a long response to initial therapy, retreatment with rituximab alone may be sufficient. R-CHOP, BR, and lenalidomide plus rituximab also have shown efficacy in relapsed/refractory FL. For patients with rituximab-refractory disease, obinutuzumab-based chemoimmunotherapy may be preferable. O-CHOP yielded an overall response rate (ORR) of 96% in the relapsed/refractory setting, and all patients with rituximab-refractory disease achieved at least a PR. The phase 3 GADOLIN trial evaluated obinutuzumab plus bendamustine followed by obinutuzumab maintenance in patients with rituximab-refractory indolent NHL; the median PFS was 25 months. Alternatively, the RIT agent ^{90}Y-ibritumomab tiuxetan, an anti-CD20 antibody conjugated to a radioactive isotope, demonstrated an ORR superior to rituximab (80% vs 56%) in a phase 3 randomized trial in patients with relapsed or refractory follicular or transformed lymphoma.

For patients with relapsed/refractory FL already treated with at least two prior therapies, there now are several targeted therapy options. The first targeted therapies to be FDA-approved in this setting were the phosphatidylinositol-3-kinase (PI3K) inhibitors idelalisib,

copanlisib, and duvelisib, which showed ORRs of 56%, 59%, and 42%, respectively. The 12-month PFS for both idelalisib and copanlisib was 11 months and for duvelisib was 9.5 months. Umbralisib is an inhibitor of PI3K-delta and casein kinase CK1-epsilon approved for relapsed/refractory FL that has received at least three prior therapies, based on an open-label trial that demonstrated an ORR of 43% and median duration of response (DOR) of 11 months. Approximately 20% of FL tumors harbor a gain-of-function mutation in the enzymatic domain of *EZH2*. Tazemetostat is an EZH2 inhibitor that was approved for patients whose tumors harbor a EZH2 mutation and have received at least two prior therapies and for patients with relapsed/refractory FL who have no alternative treatment options. The ORR in EZH2-mutated patients was 69% with a median DOR of 11 months, and in patients with EZH2 wild-type tumors, the ORR was 34% and median DOR 13 months. Targeted cellular therapy is the latest treatment option for relapsed/refractory disease; ZUMA-5 is a phase 2 study of the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel in patients with relapsed/refractory indolent NHL. Among the 124 patients with FL, the ORR was 91% and the CR rate was 74%. Longer follow-up is needed, but the estimated 12-month DOR among all patients was 72% (Table 28.4).

TABLE 28.4

Novel Treatments for Relapsed/Refractory Follicular Lymphoma

Regimen	Number of Patients With FL	Outcome	Reference
Idelalisib	72	ORR 57%, CR 6% Median DOR 12.5 mo	Gopal et al, 2014
Copanlisib	104	ORR 59% Median DOR 12.2 mo	CHRONOS-1 Study, Dreyling et al, 2020
Duvelisib	83	ORR 42%, CR 1%	DYNAMO + R Study
R^2	295	ORR 80%	AUGMENT Study, Leonard et al, 2019
Lenalidomide + Obinutuzumab	86	ORR 79%, CR 38% DOR at 2 years 70%	GALEN Study, Morschhauser et al, 2019
Bendamustine + Obinutuzumab	155	ORR 79%, CR 16% Median DOR NR	GADOLIN Study, Sehn et al, 2016
Tazemetostat	42 EZH2 mutant	ORR 69%, CR 12% Median DOR 10.9 mo	Morschhauser et al, 2020
	53 EZH2 WT	ORR 34%, CR 4% Median DOR 13 mo	
Umbralisib	117	ORR 43%, CR 3% Median DOR 11.1 mo	UNITY-NHL Study, Zinzani et al, 2020
Axicabtagene ciloleucel	84	ORR 94%, CR 80% Median DOR NR	ZUMA-5 Study, Jacobson et al, 2020

CR, complete response; DOR, duration of response; FL, follicular lymphoma; NR, not reached; ORR, overall response rate; R^2, rituximab and Revlimid (lenalidomide); WT, wild type.

Patients who have refractory disease, early relapsing disease, or who have relapsed from multiple therapies can be considered for consolidative autologous or allogeneic stem cell transplant. Autologous stem cell transplant has been shown to improve PFS and OS in relapsed/refractory disease although much of the data predate more contemporary treatment options. Allogeneic stem cell transplant is a potentially curative treatment but has not been studied in any randomized trials and is associated with a higher rate of nonrelapse mortality.

Lymphoplasmacytoid Lymphoma/Waldenström Macroglobulinemia

Lymphoplasmacytoid lymphoma (LPL) is an indolent but incurable lymphoma composed of mature plasmacytoid lymphocytes that typically involves the BM but may also involve the lymph nodes and spleen. When LPL is associated with a monoclonal IgM production, it is termed Waldenström macroglobulinemia (WM). LPL/WM primarily affects older patients. Patients typically present with symptoms of increased tumor burden (cytopenias due to marrow involvement, hepatosplenomegaly, lymphadenopathy, constitutional symptoms) and/or symptoms attributable to the secreted monoclonal immunoglobulin (hyperviscosity syndrome, autoimmune neuropathy, mucocutaneous bleeding). Asymptomatic patients are considered to have "smoldering" WM and are observed. 10% of patients managed with watchful waiting will not require treatment for 10 years. Approximately 50% of patients will develop symptomatic disease requiring treatment within 3 years of diagnosis.

The vast majority of LPL/WM tumors harbor a mutation in the *MYD88* (L265P) gene. This mutation is rare to absent in paired normal tissue, normal B-cells from healthy donors, and other B-cell disorders, and thus is a useful diagnostic marker. *MYD88* mutations lead to constitutively active IRAK-mediated NF-κB signaling, thereby promoting B-cell survival and also conferring sensitivity to BTK inhibition. A prospective trial of ibrutinib monotherapy in 63 previously treated patients with WM showed an ORR of 91% and 2-year PFS 69%, and a separate phase 2 trial of ibrutinib in 30 patients with treatment-naïve WM showed an ORR of 100% and an 18-month PFS of 92%. Subsequently, the phase 3 iNNOVATE trial compared ibrutinib/rituximab to rituximab/placebo in both treatment-naïve and previously treated WM patients. The ibrutinib/rituximab combination was markedly superior, with an ORR of 95% (vs 48% in the rituximab/placebo arm) and a 30-month PFS of 79% (vs 41%). Based on these data, ibrutinib with or without rituximab is a preferred first-line treatment for LPL/WM and an option for relapsed/refractory cases. Approximately 40% of LPL/WM patients have an activating mutation in *CXCR4*, and patients with such mutations may have lower or slower responses to ibrutinib and shorter PFS.

Other options for therapy include single-agent rituximab, chemoimmunotherapy regimens such as BR and rituximab/cyclophosphamide/dexamethasone, and rituximab/dexamethasone combined with a proteasome inhibitor such as bortezomib. When rituximab is used, the patient must be observed carefully for development or worsening of hyperviscosity symptoms, as serum IgM levels can increase abruptly and substantially prior to declining. Plasmapheresis prior to rituximab-containing therapy should be strongly considered for any patient presenting with symptoms of hyperviscosity or high baseline serum IgM.

Marginal Zone Lymphomas

All MZL are indolent and comprise approximately 10% of NHL. There are three subtypes of MZL: extranodal MZL (EMZL) or MALT lymphomas, splenic MZL, and nodal MZL. The majority of EMZL occurs within the gastrointestinal (GI) tract (most commonly the stomach) but can also occur in the parotid and salivary glands, thyroid, lungs, ocular adnexae, and breast. Most patients present with localized disease, and 5-year survival is approximately 90%. EMZL frequently is antigen driven and often is associated with a chronic infection such as *Helicobacter pylori* gastritis (causing gastric MALT lymphoma) or

Chlamydia psittaci (causing ocular adnexae MALT lymphoma). Treating the infection is the first step in management. In early-stage gastric MALT lymphoma, approximately 62% of patients will achieve complete remission with bacterial eradication alone. A subset of cases are associated with a t(11;18) translocation and are less likely to respond to antibiotic therapy; these cases should be considered for alternative treatment. In ocular adnexae MALT lymphoma, eradication of *C. psittaci* with doxycycline can induce complete remission in 22% of patients, partial remissions in another 22%, and minimal responses (<50% regression) in 33%. For patients with advanced or antibiotic-refractory disease, or those with EMZL subtypes not associated with known infectious agents, therapeutic options include rituximab, radiation, surgical resection in sites amenable to complete resection, chemoimmunotherapy, and targeted therapy (discussed below).

Splenic MZL accounts for approximately 20% of MZL and typically presents with splenomegaly and BM involvement. Five-year OS is around 80%. Splenectomy has been the historical standard of care but increasingly is being supplanted by rituximab, either alone or as an adjunct to surgical therapy. In a retrospective trial of 43 patients with splenic MZL, rituximab monotherapy led to an ORR of 100% and CR rate of 79% and was as efficacious as rituximab/chemotherapy combinations while conferring significantly less toxicity. Rituximab monotherapy also had a substantially better 3-year disease-free survival than splenectomy or chemotherapy alone (79% vs 29% vs 25%). Like EMZL, splenic MZL can also be antigen driven; approximately one-third of cases are associated with HCV, and many of these patients can enter remission with antiviral therapy alone. Nodal MZL is the least common MZL and is characterized by nodal disease in the absence of a mucosal component. The clinical course of nodal MZL tends to be more aggressive than its extranodal or splenic counterparts, and 5-year OS is slightly lower at 77%. Nodal MZL is not typically associated with a known infectious etiology, but up to 20% of cases may be associated with HCV infection. The therapeutic approach for nodal MZL generally follows that of FL.

For MZLs that require chemoimmunotherapy, preferred first-line regimens include BR, R-CHOP, R-CVP, and R2. For cases that are relapsed/refractory following prior anti-CD20-based treatment, there are now multiple targeted therapy options including PI3K inhibitors (copanlisib, idelalisib, duvelisib), umbralisib, and ibrutinib. Ibrutinib was the first targeted therapy approved in MZL based on a phase 2 study in 63 patients with relapsed/refractory MZL who received single-agent ibrutinib continuously; MALT, nodal MZL, and splenic MZL were all represented. The median time to initial response was 4.5 months, ORR 58%, and median DOR 28 months.

Aggressive B-Cell NHL

Diffuse Large B-Cell Lymphoma

DLBCL is the most common NHL subtype, accounting for approximately 30% of all cases. Although it is most often diagnosed in the seventh decade of life, DLBCL can present at any age. DLBCL occurs either de novo or as a transformation from a more indolent NHL subtype. In recent years, there has been increasing appreciation of the molecular heterogeneity within DLBCL and increasing efforts to better characterize DLBCL molecular subtypes, as they can vary widely in clinical behavior and response to therapy. The first step in this direction came with the advent of GEP, which was used to classify 80% to 85%

of DLBCL cases into two molecularly distinct subtypes, termed germinal center B cell (GCB) and activated B cell (ABC). Subsequent studies refined this taxonomy and identified four genetic subtypes of DLBCL, each featuring recurrent genetic aberrations: MCD (*MYD88* and *CD79B* mutations), BN2 (*BCL6* translocations and *NOTCH2* mutations), EZB (*EZH2* mutations and *BCL2* translocations), N1 (*NOTCH1* mutations). Further genomic analyses are ongoing to characterize DLBCL subtypes with even greater granularity and precision.

All DLBCL, regardless of stage, is treated with systemic chemoimmunotherapy with curative intent. The first curative regimen, CHOP, was developed in the early 1970s and efforts to improve upon CHOP largely failed until the introduction of rituximab in 2006. Rituximab + CHOP (R-CHOP) was shown to significantly improve response rates (76% vs 63%), PFS, and OS compared to CHOP alone in newly diagnosed patients, and since then has been considered the standard first-line treatment regimen. In a randomized phase 3 trial in young patients with favorable prognosis (stage I-II nonbulky disease, normal LDH, and ECOG 0-1), four cycles of R-CHOP were found to be non-inferior to six cycles of R-CHOP, and the 3-year PFS was 96%. In patients with advanced disease, R-CHOP is curative 60% to 70% of the time, but those not cured with R-CHOP tend to have a poor prognosis. More intensive chemotherapy regimens may be beneficial in certain DLBCL molecular subtypes. For example, dose-adjusted (DA) EPOCH-R (rituximab, dose-intensive etoposide/doxorubicin/vincristine, and cyclophosphamide) had similar efficacy to R-CHOP when compared in a randomized phase 3 trial, but other retrospective studies suggest that DA EPOCH-R may be more effective in the particularly aggressive "double-hit" DLBCL (DLBCL harboring dual chromosomal rearrangements of *MYC* and either *BCL2* or *BCL6*). The regimen R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) demonstrated superior 3-year PFS and OS in untreated DLBCL patients aged 18 to 59 years with low-intermediate IPI compared to R-CHOP (although with more than twice as many serious adverse events), and this survival benefit was especially pronounced in patients with non-GBC subtype DLBCL.

PMBL is a subtype of DLBCL that clinically and biologically more closely resembles classical Hodgkin lymphoma than other subtypes of DLBCL. Standard treatment approaches in the past have involved chemotherapy followed by mediastinal radiation. While combined modality therapy has been very effective in most patients, mediastinal radiation is associated with long-term sequelae like increased risks of cardiac disease and secondary tumors, particularly breast cancer in females. In a phase 2 study, DA-EPOCH-R demonstrated high efficacy in this disease with 5-year event-free survival (EFS) 93% and OS 97%, obviating the need for radiation in almost all patients.

The most recent efforts to improve first-line treatment have focused on adding targeted therapy to chemotherapy, leveraging our evolving understanding of DLBCL pathogenesis. This is especially true for ABC-DLBCL, which has 5-year PFS and OS rates of only 45% and 50%, respectively, and is characterized by constitutive activation of NF-κB, often resulting from activating mutations in the B-cell receptor (BCR) or MYD88 pathways. Both ibrutinib and lenalidomide target these oncogenic mechanisms. The efficacy of R-CHOP plus ibrutinib was assessed in the PHOENIX study, a randomized phase 3 trial in patients with untreated non-GCB (mostly ABC) DLBCL. Compared to R-CHOP, the combination R-CHOP plus ibrutinib did not improve outcomes in the overall patient population but did improve PFS and OS in the subset of patients <60 years old. The efficacy of lenalidomide

plus R-CHOP (R2-CHOP) versus R-CHOP alone specifically in ABC-DLBCL was assessed in the phase 3 ROBUST study. There was no significant difference in PFS, but there was a trend favoring R2-CHOP in patients with high-risk disease. In a separate phase 2 study randomizing patients to R2-CHOP or R-CHOP, the R2-CHOP arm was associated with a 34% reduction (HR 0.66) in risk of progression or death after a median follow-up of 3 years, with 3-year PFS 73% versus 61% and 3-year OS 83% versus 75%. Among the subset of patients with ABC-DLBCL, the PFS HR was 0.67, also favoring R2-CHOP. Further randomized studies are needed to establish the role of lenalidomide in the frontline setting.

For relapsed/refractory DLBCL, the standard approach involves salvage chemotherapy followed by HDC/SCT in transplant-eligible patients with chemosensitive disease. Commonly used salvage chemotherapy regimens include R-GDP, R-ICE, R-DHAP, and R-ESHAP. HDC/SCT outcomes vary depending on myriad factors including how long after first-line therapy the patient relapsed, presence of *MYC* rearrangement, cell of origin (GCB vs ABC subtype), whether the patient received rituximab, and age-adjusted IPI. The results of the CORAL study indicate that the benefit of HDC/SCT may be significantly limited in the rituximab era, as patients in this trial who were previously treated with rituximab had a 3-year EFS of only 21% after HDC/SCT. Furthermore, approximately 50% of patients do not adequately respond to salvage chemotherapy and thus are not candidates for HDC/SCT. In the past, these patients would be managed with palliative chemotherapy, but the approach to relapsed/refractory DLBCL is changing dramatically and HDC/SCT is playing an increasingly smaller role in management.

The most impactful recent change in relapsed/refractory DLBCL management has been the introduction of CAR T-cell therapy. CAR-T cells are patient-derived T-cells that are harvested via leukapheresis, genetically engineered to express a specific antigen receptor (in lymphoma, a receptor for CD-19), and infused back into the patient. The first CAR-T cell therapy for lymphoma, the anti-CD19–expressing product axicabtagene ciloleucel, was approved in 2017 for patients with relapsed/refractory DLBCL that had failed at least two prior lines of treatment. Its approval was based on the single-arm, multicenter ZUMA-1 trial, which showed an 83% ORR, 58% CR rate, and median DOR of 11 months. Importantly, in patients that achieved CR, the median DOR was not reached after 2 years of follow-up and 37% of patients had ongoing CR, indicating that CAR-T therapy can lead to durable responses in a significant percentage of patients. Since then, two other CD19 CAR-T cell products (tisagenlecleucel and lisocabtagene maraleucel) have been FDA-approved in the third-line setting. All three products are currently being compared to chemotherapy plus HDC/SCT in the second-line setting.

Several other novel therapies have recently been approved for relapsed/refractory DLBCL. Polatuzumab is a CD79b-directed antibody-drug conjugate (ADC) that is approved in combination with bendamustine and rituximab (BR). 80 patients were randomized to receive polatuzumab + BR or BR alone, and the polatuzumab + BR arm had superior ORR and CR rates (ORR 63% vs 25% and CR 40% vs 18%), with 48% of responses continuing at 12 months. Tafasitamab-cxix is a cytolytic CD-19 targeting monoclonal antibody approved in combination with lenalidomide based on a single-arm phase 2 study that found an ORR 55%, CR rate 37%, and median DOR of 21.7 months. Selinexor, an oral selective inhibitor of nuclear export, is approved as a monotherapy based on a phase 2 study that found an ORR 29% and CR rate 13% in 127 patients; of note, nearly half of patients developed grade 3-4 thrombocytopenia and only 15% of responses were ongoing at 12 months. Finally,

loncastuximab tesirine-lpyl is a CD19-directed ADC that conferred an ORR 48%, CR rate 24%, and median DOR of 10.3 months in its phase 2 trial. Importantly, durable responses were seen in nearly half of patients that had progressed following CAR-T (Table 28.5). Ibrutinib and/or lenalidomide plus rituximab is another option, especially in patients with ABC-DLBCL. In patients with disease that has relapsed following multiple lines of therapy, consolidative alloSCT should be considered.

TABLE 28.5

Targeted Therapies for Relapsed/Refractory DLBCL

Regimen	Number of Patients	Outcome	Reference
Axicabtagene ciloleucel	101	ORR 83%, CR 58% Median DOR 11 mo	ZUMA-1 Study Locke et al, 2019
Tisagenlecleucel	68	ORR 52%, CR 40% DOR at 12 mo 65%	JULIET Study Schuster et al, 2019
Lisocabtagene maraleucel	256	ORR 73%, CR 53% DOR at 12 mo 55%	TRANSCEND Study Abramson et al, 2020
Polatuzumab vedotin-piiq + bendamustine/rituximab	80 randomized 1:1 to P-BR or BR	ORR 63%, CR 40% (vs ORR 25%, CR 18% with BR alone) DOR at 12 mo 48%	Sehn et al, 2020
Selinexor	134	ORR 29%, CR 13% DOR at 12 mo 15%	SADAL Study Kalakonda et al, 2020
Tafasitamab-cxix + lenalidomide	81	ORR 55%, CR 37% Median DOR 21.7 mo	L-MIND Study Salles et al, 2020
Loncastuximab tesirine-lpyl	145	ORR 48%, CR 24% Median DOR 10.3 mo	LOTIS-2 Study

BR, bendamustine/rituximab; CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; P-BR, polatuzumab + bendamustine/rituximab; PFS, progression-free survival.

Primary CNS Lymphoma

PCNSL is a rare and aggressive lymphoma that originates in the CNS (brain parenchyma, meninges, cranial nerves, eyes, spinal cord). Over 95% of cases have DLBCL histology and are of the activated B-cell subtype by IHC. PCNSL can occur in both immunocompetent and immunocompromised patients and most commonly affects the brain parenchyma, although approximately 20% of cases can have concomitant or isolated leptomeningeal involvement. Intraocular involvement is also common, and in some cases can predate the development of brain lesions by months.

PCNSL is not effectively treated by standard first-line DLBCL regimens because many of the component agents poorly penetrate the blood-brain barrier. There are very few randomized trials comparing PCNSL therapies, and treatment preferences vary among institutions. However, the universal backbone of induction therapy is high-dose methotrexate (HD-MTX) 3 to 8 g/m^2, often combined with other chemotherapy agents (commonly temozolomide or procarbazine/vincristine) and/or rituximab. HD-MTX–based regimens can produce rapid responses and high ORRs but only produce durable remissions

in around 50% of patients. Consolidation treatment with additional chemotherapy (typically cytarabine or cytarabine/etoposide), HDC/ASCT, or whole brain radiation therapy (WBRT) may improve PFS. Choice of consolidative therapy (or observation) depends upon a patient's age, functional status, and comorbidities. For example, HDC/ASCT is an option only in younger (<60-70 years old), fit patients. Clinical trials comparing consolidative HDC/ASCT to consolidative chemotherapy are ongoing. WBRT can lead to long-term neurocognitive deficits and does not effectively address CSF-disseminated disease. Furthermore, a randomized phase 3 study assessing consolidative WBRT after HD-MTX did not demonstrate improved OS.

Patients who relapse following first-line therapy generally have a poor prognosis. For those who experienced a prolonged remission with initial HD-MTX, a rechallenge with additional HD-MTX is reasonable. For those with refractory disease or who relapsed shortly after HD-MTX, clinical trials should be considered. A better understanding of PCNSL pathogenesis has led to a broader landscape of potential treatments including targeted therapy and immunotherapy. PCNSL cells heavily rely on chronic active BCR signaling and inhibiting this pathway with ibrutinib has yielded ORRs of 60% to 80% in phase I trials. The PFS with ibrutinib monotherapy is brief (3-4 months), and ibrutinib currently is being studied in combination with immunochemotherapy regimens like ibrutinib/methotrexate/rituximab and TEDDI-R, which have shown improved response durability. Phase 1 and 2 trials of rituximab plus the immunomodulatory drug lenalidomide have shown ORRs around 65% and PFS of 6 to 8 months. Many EBV-negative PCNSL specimens overexpress PD-L1 and PD-L2, and the PD-1 inhibitor pembrolizumab was recently shown in a phase 2 trial to be tolerable and modestly efficacious (ORR 26%) in relapsed/refractory PCNSL. Trials with checkpoint inhibitor-based combination therapies are ongoing. Finally, CD19-targeted CAR T-cell products also are being evaluated in early phase clinical trials.

Burkitt Lymphoma

BL is a rare and highly aggressive but curable lymphoma. Most cases in the United States and Western countries are either sporadic or associated with immunodeficiency and typically affect children and young adults. Approximately 30% of cases of sporadic BL are associated with EBV infection. Endemic BL, by contrast, is highly prevalent in young children in equatorial Africa and is strongly associated with EBV infection. Whereas endemic BL presents most commonly with jaw and facial bone disease, sporadic BL tends to present with bulky abdominal disease. Involvement of the BM, GI tract, and CNS is also common. All variants of BL are characterized by acute clinical onset and rapid disease progression without therapy.

BL derives from a germinal center B-cell and its genetic hallmark is a *MYC* translocation, most commonly arising from an (8,14) translocation. RNA sequencing has identified multiple pathways that cooperate with *MYC* in oncogenesis. Around 70% of sporadic BL cases harbor mutations in the transcription factor *TCF3* or its negative regulator *ID3*, leading to activation of the prosurvival PI3K pathway. Another frequently mutated gene in both sporadic and HIV-associated BL is *CCND3*, which encodes the cell-cycle regulator cyclin D3. Mutant cyclin D3 isoforms drive cell cycle progression and confer a proliferation advantage. Gaining more insight into the pathogenesis of BL may lead to novel treatment strategies in the future.

The classic chemotherapies for BL, CODOX-M/IVAC and hyper-CVAD, are highly dose-intensive multiagent regimens that incorporate HD-MTX, high-dose cytarabine, and intrathecal chemotherapy and lead to long-term survival in approximately 70% to 80% of patients. A randomized phase 3 trial in HIV-negative BL patients later demonstrated that adding rituximab improves EFS, and this is now standard in most BL regimens. While effective, these regimens are highly toxic, especially in older patients and those with comorbid conditions like HIV and can have long-term sequelae like secondary malignancies and infertility. To mitigate toxicity, efforts are now focused on developing less-intensive regimens. Recently, a multicenter single-arm trial demonstrated that risk-adapted DA-EPOCH-R has efficacy comparable to more intensive regimens; EFS and OS were 85% and 87%, respectively, at a median follow-up of 59 months. Hence, risk-adapted DA-EPOCH-R is now a reasonable first-line treatment for both sporadic and HIV-associated BL. BL has a high propensity for CNS involvement, and all first-line treatment regimens should incorporate CNS prophylaxis. Patients that do not receive prophylaxis have a 30% to 50% risk of CNS relapse, and this usually occurs within the first year after completing treatment.

Mantle Cell Lymphoma

MCL is an incurable and variably aggressive lymphoma. The median age at diagnosis is 60, and most of those affected are men. Patients commonly present with advanced disease, splenomegaly, and involvement of the BM, peripheral blood, and GI tract. The vast majority of MCL cases harbor t(11;14), resulting in aberrant expression of cyclin D1. Despite this unifying event, MCL is biologically and clinically heterogeneous. Some patients have an indolent disease course and can be managed with watchful waiting, while other patients have an aggressive disease course despite treatment with intensive chemotherapy. The mantle cell IPI classifies patients into prognostic categories based upon age, performance status, LDH, and WBC count and can aid in therapeutic decision-making.

For patients that require systemic treatment, the standard first-line approach has been chemoimmunotherapy. There is no single preferred first-line regimen; treatment choice primarily depends on a patient's ability to tolerate aggressive chemotherapy and whether they would be candidates for subsequent HDC/SCT. In younger patients, regimens that utilize cytarabine are generally superior to those that do not (eg, R-CHOP). These include alternating R-CHOP and R-DHAP, rituximab/dexamethasone/cytarabine plus a platinum-based agent, dose-intensified R-CHOP alternating with high-dose cytarabine (the Nordic regimen), and R-hyperCVAD. The latter regimen yielded impressive results (median OS of 10.7 years) but also conferred considerable toxicity. HDC/SCT after induction chemotherapy has been studied extensively and can extend PFS over chemotherapy alone when used in first remission but is not curative and will likely play less of a role in treatment as more novel therapies are adopted. Nonmyeloablative allogeneic SCT is still considered investigational, although at this time, it remains the only potentially curative option.

Many MCL patients are older than 65 years and cannot tolerate highly dose-intensive therapies. Thus, alternative regimens have been developed for patients considered unfit for dose-intensive therapy or for those who wish to avoid dose-intensive therapy in the frontline setting. In a randomized phase 3 noninferiority trial comparing BR to R-CHOP in the first-line setting, BR was associated with improved PFS (median PFS 35 vs 22 months)

and less overall toxicity. The proteasome inhibitor bortezomib and the immunomodulatory agent lenalidomide both have shown activity in MCL and have been used as frontline therapy in combination with chemoimmunotherapy and rituximab, respectively. In a randomized, phase 3 study of R-CHOP versus VR-CAP (substituting bortezomib for vincristine) in patients with newly diagnosed MCL ineligible for HDC/SCT, the bortezomib-containing regimen had superior PFS (median 25 vs 14 months) and OS (median 91 vs 56 months). In a multicenter, phase 2 study of lenalidomide and rituximab induction plus maintenance therapy, untreated patients receiving this doublet had high response rates and durable responses, with ORR 92% (CR 64%) and estimated 7-year PFS and OS rates of 60% and 73%, respectively.

In relapsed/refractory disease, the treatment landscape is evolving rapidly. Both targeted therapies and cell-based therapy display impressive activity in relapsed/refractory MCL and soon will likely change the approach to untreated disease, as well. Lenalidomide and bortezomib were among the first targeted agents tested and FDA-approved in the relapsed/refractory setting. A randomized, phase 2 study demonstrated that lenalidomide conferred a longer PFS than chemotherapy (9 vs 5 months); however, neither lenalidomide nor bortezomib, either alone or in combination with rituximab, has been able to extend PFS beyond 1 year. Since then, the BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib have been FDA-approved for relapsed/refractory MCL. As monotherapies, ibrutinib, acalabrutinib, and zanubrutinib have shown OR rates of 66%, 80%, and 84%; CR rates of 30%, 40%, and 69%; and median PFS of 13, 20, and 22 months, respectively. In a pooled analysis of 370 patients treated with ibrutinib across three studies, the patients who received ibrutinib as second-line therapy experienced better outcomes than the patients who had already received at least two lines of therapy (median PFS 25 vs 12 months), and hence, BTK inhibitors have become the preferred agents for second-line therapy. Venetoclax also shows significant activity in MCL but is not currently FDA-approved in this setting. In a phase 1 trial involving 28 patients with relapsed/refractory MCL, venetoclax monotherapy resulted in an ORR of 75% (21% CR) and median PFS of 14 months. Currently, efforts to improve MCL treatment are focused on combining these targeted therapies to achieve synergy and overcome cellular resistance mechanisms. A phase 2 study of ibrutinib plus venetoclax in 24 patients with MCL showed a CR rate of 67%, with 38% of patients negative for minimal residual disease (MRD) in the blood as assessed by polymerase chain reaction. Another phase 1/2 study of obinutuzumab plus ibrutinib in relapsed/refractory MCL and obinutuzumab plus ibrutinib plus venetoclax in relapsed/refractory and untreated MCL showed CR rates ranging 67% to 90% and MRD negativity rates 66% to 100%. The combination of lenalidomide, ibrutinib, and rituximab in 50 patients with high-risk MCL yielded a CR rate of 54%, and 68% of responding patients remained MRD-negative in the BM at 12 months. Longer follow-up will show whether these high rates of MRD negativity will translate into longer remissions. Finally, the anti-CD19–directed T-cell product brexucabtagene autoleucel was recently approved for relapsed/refractory MCL based on the ZUMA-2 multicenter trial of 74 patients who had previously received chemotherapy, anti-CD20 therapy, and a BTK inhibitor. The ORR was 85% and CR rate 59%, and at 12 months, the estimated PFS and OS were 61% and 83%, respectively (Table 28.6).

TABLE 28.6

FDA-Approved Targeted Therapies for Relapsed/Refractory Mantle Cell Lymphoma

Regimen	Number of Patients	Outcome	Reference
Bortezomib	155	ORR 35%, CR/CRu 8% Median DOR 9.2 mo	PINNACLE Study Goy et al, 2006
Lenalidomide	134	ORR 28%, CR/CRu 8% Median DOR 16.6 mo	EMERGE Study Goy et al, 2013
Ibrutinib	111	ORR 68%, CR 21% Median DOR 17.5 mo	Wang et al, 2013
Acalabrutinib	124	ORR 81%, CR 40% PFS at 12 mo 67%	Wang et al, 2018
Zanubrutinib	86	ORR 84%, CR 59% Median DOR 19.5 mo	Song et al, 2020
Brexucabtagene autoleucel	60	ORR 93%, CR 67% PFS at 12 mo 61%	ZUMA-2 Study Wang et al, 2020

CR, complete response; CRu, complete response unconfirmed; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival.

Peripheral T-Cell Lymphomas

The term "peripheral T-cell lymphoma" (PTCL) encompasses the various lymphomas derived from mature T and natural killer (NK) cells. T-cell lymphomas are less common than B-cell lymphomas, accounting for approximately 10% to 15% of NHL. Their behavior ranges from indolent to aggressive, although the majority are aggressive lymphomas with low response rates to chemotherapy and poor OS relative to B-cell lymphomas. There are notable exceptions, however, such as anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and mycosis fungoides (MF) with limited skin disease, which have excellent prognoses. Although various distinct disease entities exist within the realm of PTCL, the most common subclassification remains "PTCL-not otherwise specified," underscoring the need for further elucidation of the genetic and molecular basis of these diseases.

Anaplastic Large Cell Lymphoma

ALCL is a CD30-positive subtype of PTCL that encompasses two biologically distinct diseases: ALCL overexpressing ALK-positive ALCL, usually due to t(2;5), and ALK-negative ALCL. The former is typically a disease of children and young adults, while the latter tends to affect older individuals. Patients with both forms typically present with diffuse lymphadenopathy, extranodal disease, and systemic symptoms. ALK-positive ALCL has an excellent prognosis compared to most PTCL subtypes, with a 5-year OS of approximately 70% after anthracycline-based chemotherapy. Standard first-line treatment for systemic ALCL (sALCL) was established by the 2019 ECHELON-2 study, a multicenter, phase 3 trial in which 452 patients with CD30-positive tumors (70% ALCL) were randomly assigned to the anti-CD30 ADC brentuximab vedotin (BV) plus CHP (CHOP without vincristine) versus CHOP alone. BV + CHP conferred a superior median PFS (48 vs 21 months) across all patients and a PFS advantage in both ALK+ and ALK-sALCL. Adverse effect profiles were comparable between the two study arms.

Primary cutaneous ALCL is a separate disease entity characterized by indolent behavior, predominantly dermatologic involvement, and excellent long-term survival. Primary breast ALCL is a more recently recognized disease that rarely occurs in women with breast

implants. A study of 87 breast implant-associated ALCL patients showed a 3- and 5-year OS rate of 93% and 89%, respectively, with superior EFS and OS in patients who underwent a complete surgical excision (total capsulectomy and breast implant removal) compared to patients who had a partial capsulectomy, systemic chemotherapy, or radiation.

PTCL, Not Otherwise Specified

This subclassification includes all T-cell lymphomas not identified as clinicopathologically distinct by the WHO classification. These are aggressive nodal lymphomas that can also have extranodal involvement, most commonly skin or GI tract. The current approach to first-line therapy is stratified based on whether the tumor expresses CD30. For CD30-expressing tumors (accounting for 32%-58% of PTCL-NOS [not otherwise specified] cases), the preferred first-line treatment is BV + CHP. This is based on the ECHELON-2 study, although the outcomes in PTCL-NOS were not as impressive as those seen in sALCL; in the 72 patients with PTCL-NOS, the hazard ratio for 5-year PFS was 0.8 (95% CI 0.33-1.46) favoring the arm receiving BV + CHP. For tumors that do not express CD30, the standard treatment is CHOP-like chemotherapy. A post-hoc analysis of PTCL patients treated on trials of the German High-Grade NHL Study Group (DSHNHL) indicated that CHOEP (etoposide added to CHOP) is superior to CHOP (3-year EFS 75% vs 51%) in patients <60 years old with normal LDH levels. Overall, the subset of patients with PTCL-NOS in this study had a poor outcome regardless of treatment regimen, with 3-year EFS 41% and 3-year OS of 54%. Dose-intensive regimens such as hyper-CVAD have not been shown to improve outcomes over CHOP. Patients that achieve CR or PR with initial therapy generally proceed to HDC/ASCT. A phase 2 study of upfront HDC/ASCT demonstrated 5-year PFS and OS rates of 38% and 47%, respectively, in the subset of patients with PTCL-NOS (Table 28.7). In general, the role of radiation in PTCL-NOS is poorly defined, except as consolidative therapy in localized (stage I or II) PTCL-NOS in CR after initial chemotherapy. Ongoing work with GEP will hopefully lead to better prognostication and treatments for this heterogeneous group of PTCLs.

TABLE 28.7

Targeted Therapies for PTCL

Treatment	Patient Population	Outcome	Reference
Pralatrexate	Relapsed/refractory PTCL	ORR 29%, CR 11% Median DOR 10.1 mo Median PFS 3.5 mo Median OS 14.5 mo	PROPEL Study O'Connor et al, 2011
Romidepsin	Relapsed/refractory PTCL	ORR 25%, CR 15% Median DOR 17 mo	Coiffier et al, 2012
Belinostat	Relapsed/refractory PTCL	ORR 26%, CR 11% Median DOR 13.6 mo	BELIEF Study O'Connor et al, 2015
Brentuximab vedotin	Relapsed/refractory sALCL	ORR 86%, CR 57% Median DOR 12.6 mo	Pro et al, 2012
	Relapsed/refractory pcALCL and CD30+ MF	ORR 67%, CR 16% Median PFS 16.7 mo	ALCANZA Study, Prince et al, 2017

Treatment	Patient Population	Outcome	Reference
	Untreated sALCL and other CD30+ PTCL in combination with chemotherapy	Median PFS 48 mo with BV + CHP (vs 21 mo with CHOP)	ECHELON-2 Study, Horwitz et al, 2019

CD30, cluster of differentiation 30; CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) is one of the more common subtypes of PTCL, accounting for 15% to 20% of cases. Median age at diagnosis is 65 years and patients typically present with diffuse lymphadenopathy, hepatosplenomegaly, extranodal involvement, systemic symptoms, rash, and hypergammaglobulinemia. Autoimmune phenomena, both hematologic and nonhematologic, are also common. AITL is thought to arise from T follicular helper cells. In a prospective observational study of 282 patients with AITL, the 5-year OS and PFS were 44% and 32%, respectively. 81% of these patients had received an anthracycline-based chemotherapy regimen. Although prospective trials are lacking, patients that achieve CR with initial therapy seem to benefit from HDC/ASCT; in one retrospective study, the 4-year PFS and OS were 56% and 59%, respectively. Outcomes of patients achieving PR or with refractory disease are less promising. 43% to 63% of AITL expresses CD30, and a phase 2 trial of BV monotherapy in relapsed/refractory CD30+ PTCL showed a 54% ORR in the subset of patients with AITL. Unfortunately, the 54 patients with AITL enrolled on the ECHELON-2 trial did not appear to benefit from the addition of BV to first-line chemotherapy.

Rare Extranodal NK/T-Cell Lymphomas

The two main subclassifications of NK/T-cell lymphoma are extranodal NK/T-cell lymphoma (ENKL), nasal type, and aggressive NK-cell leukemia (ANKL). These diseases are almost always EBV positive and are extremely rare in North America and Europe but prevalent in Asia and Central/South America. ENKL typically involves the nasopharynx, nasal cavity, and palate and can also affect the skin, gastrointestinal tract, and testis. EBV viral load serves as a useful biomarker of disease in the blood and should be measured at diagnosis and followed throughout the course of treatment as a marker of possible persistent disease. The Prognostic Index of Natural Killer Lymphoma (PINK) is a prognostic index for ENKL patients treated with non–anthracycline-based therapy that incorporates four parameters: age >60 years, stage III or IV disease, distant lymph node involvement, and non-nasal type disease. Patients are divided into low- (0 points), intermediate- (1 point), and high-risk (2+ points) groups with 3-year OS rates of 81%, 62%, and 25%, respectively. The newer PINK-E prognostic index also incorporates EBV viral load. Patients with disease confined to the nasal cavity can be successfully treated using involved-field radiation therapy with or without chemotherapy (DeVIC, VIPD, m-SMILE, or GELOX), while those with extranasal disease or ANKL have a very poor prognosis and should be considered for clinical trials. There is no standard chemotherapy for this patient population, but non–anthracycline-based regimens are generally superior to anthracycline-based regimens, and intensive asparaginase-based regimens like SMILE, P-GEMOX, and DDGP have produced superior outcomes in medically fit patients. In newly diagnosed stage IV or relapsed/refractory disease, the SMILE regimen yielded an ORR of 79% and CR

rate of 45%. Patients with advanced or relapsed/refractory disease should be considered for HDC/ASCT or allogenic SCT although prospective trials for both modalities are lacking.

Gamma-Delta T-Cell Lymphomas

These are rare and aggressive T-cell lymphomas that originate from gamma-delta lymphocytes. The WHO 2008 classification divided these lymphomas into two separate entities: hepatosplenic gamma-delta T-cell lymphoma (HSGD-TCL) and primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL). HSGD-TCL typically affects young men and involves the liver, spleen, and BM. Approximately 20% of cases arise in the setting of immunosuppression or immune dysregulation. Histologic diagnosis can often be difficult to obtain, in part because nodal involvement is rare. Prognosis is poor regardless of choice of therapy, with a median OS of approximately 2 years. There is no standard of care although most patients are treated with CHOP-like regimens with or without HDT/ASCR. Relapse rates are high, and patients that respond to chemotherapy should be considered for alloSCT. PCGD-TCL is extremely rare and accounts for <1% of primary cutaneous lymphomas. Cutaneous disease is variable and clinical course is typically aggressive with poor long-term survival (median survival 15 months). Cases are often treated with radiation (if localized disease) or combination chemotherapy. Small single-center studies indicate brentuximab vedotin is another treatment option for chemotherapy-refractory patients whose tumors express CD30.

Intestinal T-Cell Lymphomas

Intestinal T-cell lymphomas are rare, extranodal PTCLs of the small bowel. There are two aggressive variants: EATL, which is strongly associated with celiac disease, and the more recently recognized monomorphic epitheliotropic intestinal T-cell lymphoma. Patients typically present with abdominal pain and anorexia. A large, multicenter cohort study of 61 EATL patients showed overall poor prognosis with 1- and 5-year OS rates of 40% and 11%, respectively. Patients achieving a first remission may benefit from HDC/SCT but prospective, randomized data are lacking. Most EATL strongly expresses CD30 and may benefit from treatment with BV but EATL has been poorly represented in the prior trials of BV in PTCL. A phase 2, single-center study of first-line BV-CHP followed by HDC/ASCT is currently enrolling.

Cutaneous T-Cell Lymphoma/MF

Cutaneous T-cell lymphomas (CTCLs) are typically mature T-cell neoplasms that originate within, and often remain confined to, the skin, with variable spread to the lymph nodes, BM, and peripheral blood. MF constitutes the majority of CTCL. Sezary syndrome (SS) is the much less common leukemic manifestation of MF, accounting for 3% of CTCL. MF is considered an indolent lymphoma although behavior and prognosis are highly variable; patients with limited patch or plaque disease of the skin have excellent long-term survival, while prognosis is poorer for those with erythrodermal skin involvement and extracutaneous disease.

MF is staged according to the revised Mycosis Fungoides Cooperative Group staging system, which incorporates extent of skin, nodal, visceral organ, and peripheral blood involvement. Patients with limited skin disease are typically treated with topical corticosteroids, topical retinoids, topical chemotherapy, phototherapy, or local radiation. Patients with more extensive skin involvement can be treated with the same modalities or

with total skin electron beam therapy. Patients with more advanced disease are treated initially with systemic therapies such as extracorporeal photopheresis, oral retinoids, interferon, or HDAC inhibitors, with chemotherapy being reserved for patients who progress on these agents or for those with aggressive disease with visceral organ involvement. Systemic chemotherapy agents used include alemtuzumab, brentuximab, bortezomib, doxil, gemcitabine, low-dose methotrexate, pentostatin, and temozolomide. The recent ALCANZA study, a phase 3 trial of BV versus physician's choice of methotrexate or bexarotene in patients with relapsed/refractory CD30+ MF or cutaneous ALCL, showed that MF patients with at least 10% CD30 expression on one biopsy had significantly improved ORR and PFS (16 vs 4 months) when treated with BV. Allogeneic HSCT is a potentially curative option in advanced stage MF and SS, but relapse rates remain high and only a minority of patients achieve long-term remissions; a recent series of 113 patients reported 5-year OS and PFS of 38% and 26%, respectively.

TREATMENT APPROACHES FOR RELAPSED PTCL

Most patients with PTCL eventually relapse. HDC/SCT is an option for patients that did not receive HDC/SCT in first remission and respond to salvage chemotherapy. HDC/SCT in second remission has been associated with an improved 3-year survival (48% vs 18% in those not undergoing transplant), but long-term outcomes remain poor. Patients should be considered instead for alloSCT, which has been associated with 5-year PFS rates around 50%. For patients that are transplant-ineligible or who relapse following transplant, there are several novel agents that recently have been approved for relapsed/refractory PTCL. These include the histone deacetylase inhibitors, romidepsin and belinostat, and the novel antifolate, pralatrexate. Romidepsin was approved based on a phase 2 trial showing an ORR of 25% with median DOR of 17 months, with responses seen independent of number of prior therapies or ASCT. PTCL patients treated on the phase 2 BELIEF study with belinostat monotherapy had an ORR of 26% with median DOR of 13.6 months. The PROPEL study with pralatrexate demonstrated an ORR of 29% and median DOR of 10.1 months. In patients with tumors expressing CD30+, BV monotherapy is another option; a phase 2 study in relapsed/refractory sALCL found an ORR 86% and CR 57%. In CD30-expressing AITL, the ORR was 54% and median PFS 6.7 months. Many more novel agents are being investigated as monotherapies or in combination with chemotherapy, both in the frontline and relapsed/refractory settings, and patients should be referred for clinical trials whenever possible.

NOVEL TREATMENT APPROACHES AND FUTURE DIRECTIONS

Circulating tumor DNA (ctDNA) is emerging as a powerful tool in the diagnosis and management of NHL. When used as a "liquid biopsy," ctDNA can aid in noninvasive diagnosis and may eventually guide selection of targeted therapy in a precision-directed fashion. ctDNA also has prognostic potential both at diagnosis and following therapy. In a correlative biomarker study comparing ctDNA to CT scans in previously untreated DLBCL patients, interim monitoring of ctDNA revealed significantly improved 5-year time to progression (80% vs 42%) in patients with undetectable interim ctDNA and also detected

early relapse 3.5 months prior to clinical disease when used in the surveillance setting. A later study in 217 patients with DLBCL found that both pretreatment ctDNA and molecular responses after one or two cycles of chemotherapy were independently prognostic of patient outcomes. Further validation is needed in prospective studies, but ctDNA has the potential to transform our current methods of diagnosis, response assessment, and relapse detection in NHL.

In recent years, CAR-T cells have dramatically changed the management of relapsed/refractory NHL and likely will continue to do so in the future. Current efforts include improving safety and tolerability, and increasing efficacy and durability by combining CARs with novel agents or immunotherapy. There also are ongoing preclinical efforts to develop "off the shelf" or allogeneic CAR-T and CAR-NK products, which could improve treatment availability and cost. Other emerging treatments reflect our evolving understanding of NHL cell biology and tumor microenvironment. Chemotherapy-free regimens that combine multiple agents targeting B-cell pathogenic mechanisms are efficacious in both indolent and aggressive NHLs, and clinical trials are ongoing. Further elucidation of pathogenic heterogeneity within NHL subtypes may enable more personalized application of these agents in the future.

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29

Hodgkin Lymphoma

Robert Dean

EPIDEMIOLOGY

Hodgkin lymphoma (HL) is a common lymphoid malignancy, representing 10% of all lymphomas. The National Cancer Institute Surveillance, Epidemiology, and End Results registry estimates that approximately 8830 patients will be diagnosed with HL in 2021 in the United States. Median age at the time of diagnosis is 39 years, with a peak incidence at age 20 to 34 years. The age-adjusted incidence rate of HL is 2.6 per 100,000 individuals per year. Unlike non-Hodgkin lymphoma (NHL), HL incidence has not increased over the past decades. The male-to-female ratio is 1.3:1.0. In the United States, it affects African Americans slightly less commonly than Caucasians.

ETIOLOGY AND RISK FACTORS

The cause of HL remains unknown.

- Epstein-Barr virus is implicated in the pathogenesis of some cases of HL (particularly mixed cellularity and lymphocyte-depleted subtypes).
- Loss of immune surveillance in immunodeficiency states (eg, HIV infection, allogeneic stem cell transplantation, and solid organ transplantation) is associated with a higher risk of developing HL.

- A 15% higher risk of HL is seen in smokers compared with nonsmokers.
- Family history of HL increases the risk to develop disease by threefold to ninefold, mainly among siblings. Identical twin sibling of an HL patient has a 99-fold higher risk of developing HL.

PATHOLOGY

HL is a neoplastic disease of B-cell origin. Classic HL (CHL) is characterized by the presence of Reed-Sternberg (RS) cells and mononuclear variants, amid an inflammatory background consisting of lymphocytes, plasma cells, eosinophils, monocytes, and histiocytes. Nodular lymphocyte-predominant HL (NLPHL) is characterized by RS variants termed "L&H" (lymphocytic and histiocytic) cells in a background of lymphocytes and histiocytes but without other inflammatory cells.

RS cells are derived from follicular center B cells with clonally rearranged immunoglobulin heavy chain genes, but surface B-cell receptor expression is absent. RS cells often exhibit symmetrical bilobed nuclei ("owl's eyes" appearance) (Figure 29.1). RS cells are positive for CD30 and CD15 and typically negative for CD20 and CD45, whereas the L&H cells of NLPHL express B-cell markers including CD20, CD45, and CD79a but are negative for CD30 and CD15.

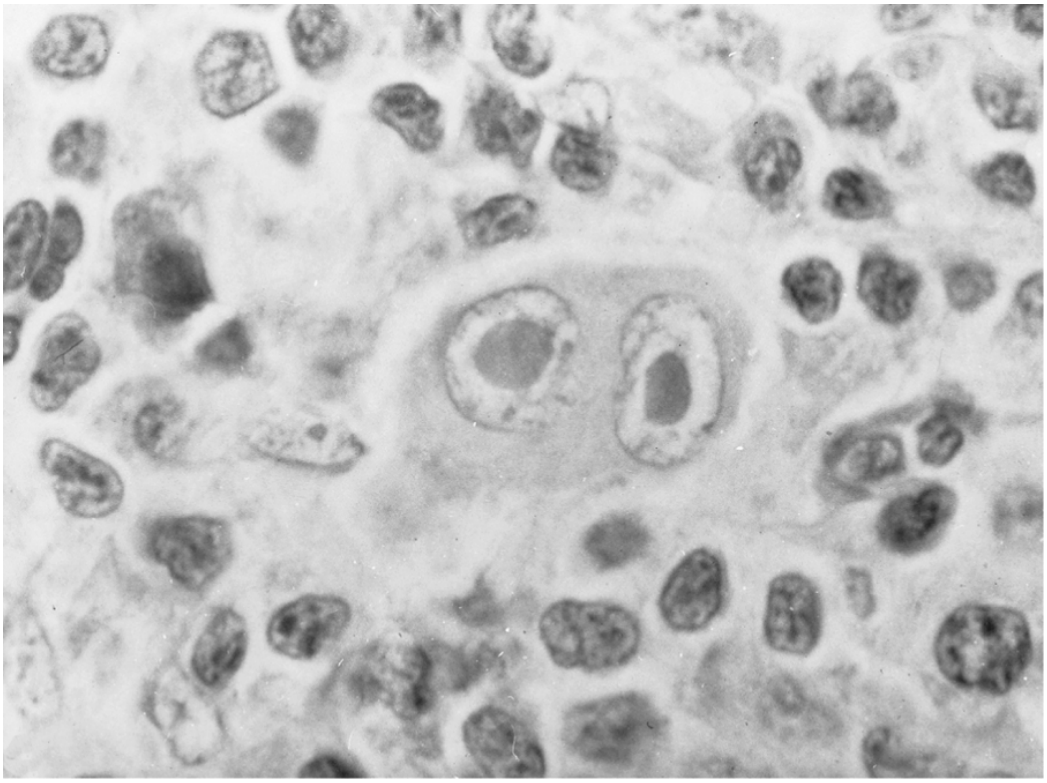

FIGURE 29.1 Diagnostic Reed-Sternberg cell, with “owl’s eye” nucleus, seen in classic types of Hodgkin lymphomas (mixed cellularity, nodular sclerosis, lymphocyte depletion).

Pathologic Classification

The World Health Organization (WHO) classification divides HL into two main types (Table 29.1):

TABLE 29.1
Immunophenotypic Features of Hodgkin Lymphoma

	Classic Hodgkin Lymphoma	Nodular Lymphocyte-Predominant Hodgkin Lymphoma
CD45	Negative	Positive
CD30	Positive	Negative [a]
CD15	Positive (80% of cases)	Negative
CD20	Variable [b]	Positive
CD79a	Negative [a]	Positive
EMA [c]	Rarely positive	Positive (over 50% of cases)

[a]Positive in rare cases.

[b]Present in up to 40% of cases but usually expressed on minority of tumor cells with variable intensity.

[c]Epithelial membrane antigen.

- CHL:
  - CHL is characterized by the presence of RS cells in an inflammatory background and is divided into four histologic subtypes, based mainly on the characteristics of the nonneoplastic reactive infiltrate.
    - Nodular sclerosis HL
    - Mixed cellularity HL
    - Lymphocyte-rich HL
    - Lymphocyte-depleted HL
- NLPHL:
  - NLPHL lacks typical RS cells but is characterized by L&H cells, sometimes referred to as *popcorn cells* based on their irregular nuclear appearance.

Table 29.2 summarizes the clinical and pathologic features of the disease subtypes.

TABLE 29.2
Classification of Hodgkin Lymphoma

Pathologic Type	Pathologic Features	Clinical Features
Classic Hodgkin lymphoma		
Nodular sclerosis	Nodular growth pattern with broad bands of fibrosis	Most common type and has a better prognosis. Common in resource-rich countries. Peak incidence at ages 15-34 y
Mixed cellularity	Typical Reed-Sternberg (RS) cells in a rich inflammatory background and fine reticular fibrosis; 70% are positive for Epstein-Barr virus	Second most common type; more common in patients with HIV infection and in developing countries. Median age is 38 y, with a male predominance
Lymphocyte rich	Scattered RS cells in a usually nodular background consisting of small lymphocytes	Common in elderly; has good prognosis
Lymphocyte depleted	Relative predominance of RS cells with depletion of background lymphocytes	Rare, often associated with HIV infection; has poor prognosis. Median age ranges from 30 to 37 y
Nodular lymphocyte-predominant Hodgkin lymphoma		

Pathologic Type	Pathologic Features	Clinical Features
	No RS cells, but characterized by “popcorn” or lymphocyte-predominant cells (lobulated nucleus)	More common in adult males; often presents with early stage and has good prognosis, but late relapses are not uncommon. Peak incidence at ages 30-50 y

CLINICAL FEATURES

- Lymphadenopathy: Most commonly above the diaphragm (cervical, axillary, or mediastinal). Enlarged nodes are nontender, with a characteristic firm rubbery consistency. Lymph node pain may occasionally be precipitated by alcohol intake.
- Chronic pruritus.
- Most common extranodal sites of involvement are the lung, bone marrow, liver, and skeleton.
- B symptoms:
  - Unexplained weight loss (>10% body weight over 6 months before diagnosis)
  - Fever of >38 °C, intermittent with 1- to 2-week cycles
  - Drenching night sweats

Staging

The modified Ann Arbor staging of lymphoma is used to clinically stage HL (Table 29.3).

TABLE 29.3
Cotswolds-Modified Ann Arbor Staging of Lymphoma

Stage I	Single lymph node region, lymphoid structure (eg,, spleen, thymus, or Waldeyer ring), or a single extralymphatic site (IE)
Stage II	Two or more lymph node regions on the same side of the diaphragm, or localized extranodal extension (contagious to a nodal site) plus one or more nodal regions (IIE)
Stage III	Lymph node regions on both sides of the diaphragm. This may be accompanied by localized extranodal site (IIIE), or splenic involvement (IIIS), or both (IIIE + S)
Stage	Diffuse or disseminated involvement of one or more extranodal organs or tissue

IV	beyond that designated E, with or without associated lymph node involvement
	Each stage is designated A or B, where B means presence and A means absence of B symptom
	X: A mass >10 cm or a mediastinal mass larger than one-third of the thoracic diameter
	E: Extranodal contiguous extension, which can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensive extranodal disease is designated stage IV

Diagnostic Evaluation

Excisional biopsy of an enlarged lymph node is strongly recommended for initial diagnosis. A core biopsy may be appropriate if adequate tissue can be obtained to avoid major surgery, but this may limit accurate classification among CHL subtypes. A fine-needle aspiration is *not* recommended for initial diagnosis.

Laboratory Tests

- Complete blood count (CBC), differential, and platelets.
- Erythrocyte sedimentation rate (ESR): Adverse prognostic biomarker, if elevated.
- Lactate dehydrogenase and albumin.
- Liver function tests: If abnormal, may be associated with liver involvement.
- Alkaline phosphatase: May be nonspecifically high or associated with bone involvement.
- BUN, creatinine, electrolytes, and uric acid.
- Pregnancy test: Women of childbearing age.
- HIV testing in patients with risk factors for HIV.

Radiologic Studies

- Diagnostic computed tomography (CT) scan of the chest, abdomen, and pelvis is recommended for staging. CT scan of the neck may be needed for objective assessment of palpable lymphadenopathy, or in obese patients.

- ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan.

Unilateral Bone Marrow Biopsy and Aspiration

This is recommended if PET/CT shows focal areas of skeletal uptake, or if unexplained cytopenias are present. Generally, this is not needed in clinical stage III or IV. Reactive, uniform bone marrow uptake is commonly present and does not warrant bone marrow biopsy for evaluation in the absence of unexplained cytopenias or focal skeletal lesions.

Evaluation/Procedures for Specific Treatments and Counseling

- Multigated acquisition scan or echocardiography to evaluate left ventricular ejection fraction before anthracycline treatment.
- Pulmonary function tests (spirometry and diffusion capacity) prior to bleomycin-containing treatment.
- Fertility counseling (to discuss sperm, ovarian tissue, and/or oocyte cryopreservation).
- Smoking cessation counseling.

MANAGEMENT

- CHL is sensitive to radiation and many chemotherapeutic agents. Patients should be treated with curative intent, regardless of stage. Cure rates are high (>80%); thus, limiting long-term toxicities is a major consideration of treatment.
- Early-stage disease may be treated with combined-modality chemotherapy and radiation treatment (RT) or chemotherapy alone.
- Advanced-stage disease is usually treated with chemotherapy alone.

- In advanced-stage disease, radiation consolidation can be considered for PET-positive areas following a full course of chemotherapy, particularly in patients who are poor candidates for intensive second-line therapy including autologous transplantation. Radiation consolidation should be omitted in patients with PET-negative residual masses. Based on pre-PET era studies, routine radiation consolidation in patients with bulky (≥10 cm or one-third the diameter of the chest on chest X-ray) disease is widely practiced in North American centers; however, radiation consolidation may not be necessary in PET-negative bulky masses.

Principles of Chemotherapy

- The goal of primary treatment for CHL is complete remission. The standard regimen for CHL in North America is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) since it superseded the MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) regimen in the large randomized trial of the Cancer and Leukemia Group B in 1992 (Table 29.4). ABVD was associated with superior efficacy but less myelosuppression and lower risks of secondary leukemias and infertility compared to MOPP. Prophylactic use of growth factors may increase the risk of pulmonary toxicity with ABVD and is therefore discouraged. Treatment delay and/or dose reduction due to uncomplicated leukopenia is not recommended, given that febrile neutropenia is uncommon with ABVD.
    - The alternate regimen of BV + AVD (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) demonstrated superior progression-free survival to ABVD in a randomized controlled trial for advanced CHL. Overall survival was similar, and BV + AVD increased neurotoxicity and myelosuppression, requiring prophylactic growth factor support.

TABLE 29.4

CALGB Study Comparing Different Regimens in Hodgkin Lymphoma

Regimen	Complete Response Rate (%)	5-y Overall Survival Rate (%)
MOPP	67	66

Regimen	Complete Response Rate (%)	5-y Overall Survival Rate (%)
ABVD	82	73
Alternating MOPP/ABVD	83	75

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CALGB, Cancer and Leukemia Group B; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone.

- The dose-escalated BEACOPP regimen was superior to COPP-ABVD and standard-dose BEACOPP in advanced CHL. However, controlled trials comparing escalated BEACOPP with ABVD have not demonstrated a difference in overall survival, and the significant toxicities of escalated BEACOPP (3% rate of treatment-related death, 2% to 3% rate of secondary leukemias, and nearly universal infertility) have precluded its widespread use in North America. Escalated BEACOPP is not recommended for older CHL patients (≥60 years).

Chemotherapy regimens are described in Table 29.5.

TABLE 29.5

Commonly Used Chemotherapy Regimens for Hodgkin Lymphoma

ABVD (every 28 d)	Doxorubicin 25 mg/m^2/dose IV on days 1 and 15
	Bleomycin 10 units/m^2/dose IV on days 1 and 15
	Vinblastine 6 mg/m^2/dose IV on days 1 and 15
	Dacarbazine (DTIC) 375 mg/m^2/dose IV on days 1 and 15
BV + AVD (every 28 d)	Brentuximab vedotin 1.2 mg/kg/dose IV on days 1 and 15
	Doxorubicin 25 mg/m^2/dose IV on days 1 and 15
	Vinblastine 6 mg/m^2/dose IV on days 1 and 15
	Dacarbazine (DTIC) 375 mg/m^2/dose IV on days 1 and 15
Dose-escalated BEACOPP (every 3 wk)	Bleomycin 10 international units/m^2 IV on day 8
	Etoposide (VP-16) 200 mg/m^2 IV on days 1-3
	Doxorubicin (Adriamycin) 35 mg/m^2 on day 1
	Cyclophosphamide (Cytoxan) 1200 mg/m^2 on day 1
	Vincristine 1.4 mg/m^2 (max 2 mg) on day 8
	Procarbazine 100 mg/m^2 PO on days 1-7
	Prednisone 40 mg/m^2 PO on days 1-14
	Filgrastim (G-CSF) support is needed

Principles of Radiotherapy

- Radiation therapy for HL targets sites with radiographic disease (involved nodal or involved site). Historical approaches included involved areas alone (involved field) or involved *plus* adjacent areas (extended field). Extended fields are either "mantle field" for the cervical, axillary, and mediastinal regions or "inverted-Y field" for spleen, para-aortic, and pelvic regions. When inverted-Y field radiation is given together with mantle field radiation, the combination is called total nodal radiation.
- Dose of RT depends on the extent of the disease. In combined-modality therapy, RT is initiated ideally within 3 weeks of finishing chemotherapy.

Treatment Response Evaluation

Multiple prospective trials support response-adapted modification of treatment according to the results of interim restaging with PET/CT, usually after two cycles of treatment with ABVD. The goals of response-adapted treatment are to maintain efficacy while reducing toxicity for patients with CHL that is responding favorably to treatment and to reserve more intensive and toxic treatment approaches for patients with more resistant disease. All patients (early and advanced stages) should receive interim restaging with PET/CT after two cycles of chemotherapy to evaluate the response to treatment. Responses are scored according to the Deauville 5-point scale to indicate the degree of residual FDG uptake in involved sites relative to normal uptake within the mediastinal blood pool and liver (Table 29.6).

TABLE 29.6
Deauville 5-Point Scale for Response Assessment in Lymphoma

Deauville Score	PET/CT Findings	Interpretation
1	No uptake	Negative
2	Uptake ≤ mediastinum	
3	Uptake > mediastinum but ≤liver	
4	Uptake moderately higher than liver	Positive

Deauville Score	PET/CT Findings	Interpretation
5	Uptake markedly higher than liver and/or new lesions	
X	New areas of uptake unlikely to be related to lymphoma	

CT, computed tomography; PET, positron emission tomography.

Restaging may be repeated after four cycles of chemotherapy to evaluate ongoing response, where applicable. Restaging with PET/CT should be repeated 1 to 2 months after the end of treatment if complete remission is not achieved in the interim assessment.

TREATMENT OF EARLY DISEASE (STAGES I AND II)

Early-stage CHL is stratified as favorable or unfavorable disease, and treatment varies accordingly. Unfavorable risk factors in this subset of patients vary among international clinical trial groups and are simplified in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

National Comprehensive Cancer Network® (NCCN®) Unfavorable Prognostic Features for Early-Stage Disease (I and II)

NCCN unfavourable factors include:

- Bulky mediastinal or >10 cm disease,
- B symptoms,
- ESR ≥ 50, and
- > three sites of disease

2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Early-stage patients with unfavorable risk factors are treated similarly to advanced-stage (stage III/IV) disease. The remaining favorable risk early-stage patients are managed as follows.

Favorable Early-Stage Disease

The cure rate for this subgroup of patients is >90%. These patients may be treated with ABVD × two cycles followed by 20 Gy of involved nodal or involved site radiation. Outcomes for this strategy were noninferior to four cycles of ABVD and a radiation dose of 30 Gy in a prospective trial among favorable early-stage patients (baseline ESR less than 50 mm/h, fewer than three nodal sites, and no extranodal disease).

Chemotherapy without radiation therapy is an alternative for favorable early-stage disease. This option is attractive for patients with abdomen-only disease, and in young patients where radiation to chest or axillae increases the risk of subsequent second cancers (particularly breast cancer in female patients) and premature coronary artery disease.

- ABVD × two cycles, followed by restaging PET/CT.
  - Patients with Deauville scores of either 1 or 2 may be treated with one additional cycle of ABVD.
  - Patients with a Deauville score of 3 should receive two additional cycles of chemotherapy with AVD, excluding bleomycin.
  - Patients with a Deauville score of 4 may continue ABVD for two additional cycles followed by repeat restaging, if PET positivity is limited to a single site, ie, responding to treatment.
  - Patients with a Deauville score of 4 involving multiple initial disease sites, or Deauville score of 5, should undergo repeat biopsy, and alternate therapy should be considered for patients with confirmed treatment failure. For patients

who cannot tolerate intensive second-line therapy, consider involved site radiation therapy at a dose of 30 to 36 Gy.

Unfavorable Early-Stage Disease

Patients with stage I or II CHL with bulky disease and/or B symptoms are treated with ABVD × four cycles followed by 30 Gy of involved nodal or involved site radiation.

Patients with unfavorable early-stage disease may also be treated with chemotherapy alone, without radiation therapy:

- ABVD × two cycles is administered, followed by restaging PET/CT.
  - Patients with Deauville scores of 1 to 3 should receive an additional four cycles of AVD, excluding bleomycin.
  - Patients with Deauville scores of 4 or 5 on interim PET/CT should undergo repeat biopsy to confirm treatment failure, and alternate therapy should be considered as described for patients with favorable early-stage disease, above.

For patients with unfavorable early-stage disease who have a contraindication to bleomycin, a phase II trial indicates that such patients may be treated with BV + AVD, without radiotherapy:

- BV + AVD × four cycles is administered, followed by restaging PET/CT.
  - Patients with Deauville scores of 1 to 3 should receive no further therapy.
  - Patients with Deauville scores of 4 or 5 on end-of-treatment PET/CT should undergo repeat biopsy to confirm treatment failure, and alternate therapy should be considered as described for patients with favorable early-stage disease, above.
- Rarely, in patients who are unfit for chemotherapy, treatment with subtotal nodal or mantle field radiation alone may be considered.

TREATMENT OF ADVANCED DISEASE (STAGES III AND IV)

Mixed cellularity or lymphocyte-depleted histology is more common among patients with advanced CHL and is associated with more aggressive clinical behavior.

Unfavorable Prognostic Features for Advanced Stages (III and IV)

Hasenclever index (also called international prognostic score [IPS]) identifies seven adverse prognostic factors:

- Stage IV disease
- Age > 45 years
- Male gender
- White blood cell (WBC) ≥ 15,000/mm^3
- Lymphopenia (<600/mm^3 or <8% of total WBC)
- Hemoglobin <10.5 g/dL
- Albumin level <4 g/dL

The 5-year overall survival decreases with higher IPS scores as follows: 0 factor (89%), 1 factor (90%), 2 factors (81%), 3 factors (78%), 4 factors (61%), and 5 or more factors (56%).

The primary treatment of advanced-stage CHL is chemotherapy. ABVD is the standard of care in North American centers. The recommended initial treatment course is six cycles, with response-adapted modifications based on the results of interim PET/CT restaging after two cycles. BV + AVD may also be given for six cycles, without response-adapted modification; this regimen improved progression-free survival and decreased pulmonary toxicity compared to ABVD, with similar overall survival, increased neurotoxicity and myelosuppression, and greater cost. Initial therapy with dose-escalated BEACOPP does not improve survival and increases the risk of subsequent myelodysplastic syndrome. Stanford V is a dose-intense regimen with lesser cumulative doses of doxorubicin and bleomycin than in ABVD, incorporating radiation

therapy to macroscopic splenic disease and all nodal sites measuring ≥5 cm in size. In three randomized prospective trials, Stanford V had outcomes compared to ABVD and is thus not currently recommended as initial therapy outside the setting of a clinical trial.

- If PET/CT scan is negative (Deauville score 1, 2, or 3) following two cycles of ABVD chemotherapy, then bleomycin may be discontinued, continuing with AVD to complete six cycles. This approach achieves outcomes comparable to ABVD and merits particular consideration in older adults, who are at higher risk for pulmonary toxicity and mortality with bleomycin-based therapy.
- If interim PET/CT scan is positive after two cycles of ABVD chemotherapy (Deauville 4 or 5), then evidence supports intensification of treatment with either (1) four cycles of dose-escalated BEACOPP or (2) ifosfamide-based chemotherapy followed by high-dose chemotherapy with autologous hematopoietic cell rescue.

Nonbulky advanced-stage patients with a negative PET/CT at the end of chemotherapy do not need radiotherapy consolidation, particularly if interim restaging with PET or PET/CT scan was negative following two cycles of chemotherapy. RT can also be omitted in bulky disease patients with a negative CT or PET/CT after finishing chemotherapy, but this is an area of significant controversy. Bulky HL patients with a positive PET/CT after finishing chemotherapy can be offered 36 Gy of involved nodal or involved site RT.

TREATMENT OF NLPHL

The NLPHL subtype represents 5% of HL. Unlike CHL, NLPHL is strongly CD20 positive and typically behaves like an indolent NHL. While conventional HL approaches continue to be applied to

NLPHL, as outlined below, there are compelling biologic and clinical arguments for a different therapeutic approach.

Conventional Treatment Approaches

- Stages IA and IIA can be treated with radiation therapy alone (involved nodal or involved site, up to 36 Gy).
- Stages IA, IB, IIA, and IIB can be managed with a combined-modality approach (eg, two to four cycles of rituximab with ABVD or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), followed by involved field radiation).
- Watchful waiting in patients with asymptomatic stage III/IV disease is reasonable. Patients with symptomatic advanced-stage disease are managed with systemic chemotherapy. The optimal chemotherapy regimen for NLPHL remains unknown. While ABVD is the "historical" standard, regimens designed for NHLs such as CHOP, cyclophosphamide, vincristine, and prednisone (CVP), or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) with rituximab (because of strong CD20 expression on lymphocyte-predominant Hodgkin cells) are also appropriate. Single-agent rituximab is also active in NLPHL and can be considered in patients with low bulk disease. It is important to recognize the "aggressive" presentations of NLPHL such as those with disseminated disease, including cases involving the bones and bone marrow and transformation to aggressive histologies. Such cases should be managed like aggressive NHLs.

FOLLOW-UP AFTER COMPLETION OF TREATMENT

The purpose of follow-up is the detection of disease relapse and late treatment-related complications.

- Clinical evaluation with CBC and chemistry panel every 3 to 4 months for 2 years, then every 6 months for 5 years.
- There is no evidence to support routine radiographic surveillance following completion of treatment and confirmation of complete remission. Surveillance PET/CT imaging should be avoided because of frequent false-positive results.
- Annual influenza vaccination.
- Thyroid-stimulating hormone annually if neck RT was given (risk of hypothyroidism).
- Annual mammogram screening should start 8 to 10 years after RT or at age of 40 years, whichever is earlier, for patients who received RT above the diaphragm. Annual breast MRI is also recommended by the American Cancer Society in addition to mammogram in female patients who received radiation to chest or axillae between the ages of 10 and 30 years. Breast self-examination should be encouraged.

LATE TREATMENT-RELATED COMPLICATIONS

- Hypothyroidism and thyroid cancer can occur after neck or mediastinal RT.
- Breast cancer can occur in females after chest or axillary RT. The risk is higher in patients who receive RT at younger age. It occurs after an average of 15 years after finishing treatment.
- Lung cancer: High risk is evident in patients who received RT to chest, received alkylating agents, and smoke cigarettes.
- Infertility risk is high after pelvic RT, MOPP regimen, BEACOPP regimen, and autologous transplantation.
- Leukemia and myelodysplastic syndromes (especially with MOPP, BEACOPP, RT, and autologous transplantation).
- Pulmonary toxicity after bleomycin treatment: Risk may be increased when granulocyte colony-stimulating factor (G-CSF)

is used during treatment; hence, G-CSF use is discouraged with ABVD. Supplemental oxygen should be used sparingly when needed, to minimize the risk of inducing pneumonitis.

- Cardiac toxicity secondary to anthracycline is uncommon (total cumulative anthracycline dose is not prohibitive). The risk for premature coronary artery disease and cerebrovascular accidents is increased after mediastinal and cervical RT, respectively.
- Peripheral sensory neuropathy may result from vinblastine and/or brentuximab vedotin and may be irreversible, depending on severity.
- Lhermitte sign: It is an infrequent complication that can occur 6 to 12 weeks after neck RT and resolves spontaneously. Patients feel electric shock–like sensation radiating down the back and extremities when the neck is flexed. This sign is attributed to transient spinal cord demyelinization.
- Encapsulated organism infection (pneumococcal, meningococcal, and hemophilus) can occur in patients not vaccinated after splenic RT or splenectomy (rarely used now).

TREATMENT OF RELAPSED HL

- Relapsed disease must be confirmed by repeat biopsy.
- CHL:
  - In rare cases where RT was the first-line treatment, conventional chemotherapy (ABVD) at the time of relapse can be curative without necessitating autologous transplantation.
  - If conventional chemotherapy (with or without RT) was the primary treatment, second-line chemotherapy such as ICE (ifosfamide, carboplatin, and etoposide), DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin), or GND (gemcitabine, vinorelbine, and liposomal doxorubicin) (Table 29.7) followed by autologous stem cell transplantation is curative for about 50% of patients.

TABLE 29.7

Salvage Chemotherapy Regimens for Hodgkin Lymphoma

ICE (ifosfamide, carboplatin, and etoposide)
DHAP (dexamethasone, high-dose cytarabine, and cisplatin)

ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin)
GND (gemcitabine, vinorelbine, and liposomal doxorubicin)
GCP (gemcitabine, cisplatin, and methylprednisolone)

- For brentuximab vedotin–naïve patients, maintenance therapy with brentuximab vedotin following autologous stem cell transplantation improves progression-free survival, particularly in high-risk patients who do not achieve complete remission with second-line chemotherapy before autologous stem cell transplantation.
- In patients with relapsed or refractory HL, the PD-1 checkpoint inhibitor nivolumab induced remission in 69% resulting in a median progression-free survival of 14.7 months. Similarly, the PD-1 inhibitor pembrolizumab induced responses in 69% of patients with previously treated HL, with 63.4% progression-free survival at 9 months of follow-up. Pembrolizumab improved progression-free survival compared with brentuximab vedotin in a controlled trial of patients who previously underwent autologous stem cell transplantation or were ineligible to do so.
- In patients with relapsed or refractory HL, brentuximab vedotin induced remission in 75% with estimated 3-year overall survival and progression-free survival rates of 73% (95% confidence interval [CI]: 57%, 88%) and 58% (95% CI: 41%, 76%), respectively.
- A small proportion of heavily pretreated, but otherwise healthy HL patients relapsing after an autologous transplant can be cured with an allogeneic stem cell transplant, with better results obtained in those achieving remission first.
- NLPHL: Relapsed disease is best approached as an indolent lymphoma in most patients. Reasonable options include observation, rituximab alone or with chemotherapy, and/or RT. NLPHL may relapse with clinically aggressive disease and histologic features of large B-cell lymphoma on repeat biopsy; such cases should be treated as aggressive NHL, accordingly.

Palliative Treatment

- Sequential single-agent chemotherapy such as brentuximab vedotin, nivolumab or pembrolizumab, gemcitabine, bendamustine, vinblastine, lenalidomide, or everolimus.
- RT can be used to relieve pain or pressure symptoms of bulky masses.
- Investigational treatment is encouraged through enrollment in clinical trials.

Future Directions

- Phase III studies are underway to evaluate combinations of standard chemotherapy with novel agents such as brentuximab

vedotin and checkpoint inhibitors like nivolumab in the first-line setting to improve patient outcomes.

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Hematopoietic Cell Transplantation and Cellular Therapy

Lauren Veltri, Navneet Majhail, Abraham S. Kanate

INTRODUCTION

The effective therapeutic implementation of hematopoietic cell transplantation (HCT) took the concerted efforts of several prominent investigators spanning the 20th century. Seminal work done predominantly on murine models identified the cellular basis of hematopoiesis and raised the possibility of HCT in humans in the first half of the 20th century. The latter half witnessed the successful (albeit with early setbacks) therapeutic application of human HCT. For his pioneering efforts in the field, Dr. E. Donnall Thomas received the Nobel Prize in Physiology or Medicine in 1990. Currently, it is estimated that over 50,000 patients undergo HCT annually worldwide that includes both autologous (auto-HCT) and allogeneic (allo-HCT) transplantation.

HCT is an effective therapeutic option for patients with a wide range of malignant and benign conditions. While high-dose therapy (HDT) and auto-HCT, where the patient serves as the donor, are implemented chiefly in the management of multiple myeloma (MM) and lymphoma; allo-HCT is primarily used in the treatment of leukemia, myelodysplastic syndromes (MDS), and bone marrow failure states and involves the transfer of hematopoietic cells from a donor to the patient. Apart from matched related donor (MRD) allo-HCT, patients may be offered allografts from matched unrelated donors (MUDs), mismatched unrelated donors (MMUDs),

haploidentical-related donors or umbilical cord blood (UCB). The application of HCT has broadened to include older and frail patients with the advent of reduced intensity conditioning (RIC) regimens. Advances in supportive care, human leukocyte antigen (HLA) typing, prevention and treatment of graft-versus-host disease (GVHD), and better management of complications have led to improved survival and outcomes.

While HCT remains a key therapeutic option for patients, new cellular therapies continue to evolve. Collectively called immune effector cell therapy (IECT), only chimeric antigen receptor therapy (CAR-T) is currently Food and Drug Administration (FDA) approved. It involves ex vivo genetic modification of patient's own T-lymphocytes to express a new receptor with antibody fragments showing affinity for specific tumor antigens, thus directing the CAR-T cells to target tumor cells. This therapy has unique side effects including cytokine release syndrome and neurotoxicity but is efficacious in many lymphoid malignancies and its utility continues to develop.

A brief overview of both autologous and allogeneic HCT is provided in this chapter, along with a discussion of the complications and their management. We will also further introduce CAR-T therapy and briefly discuss indications and toxicities.

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells (HSCs) reside within the bone marrow space in close association with stromal cells and extracellular matrix proteins and are capable of producing progenitor cells that can reconstitute the hematopoietic system including lymphoid and myeloid cell lines. True HSCs are characterized by their unlimited self-renewal capacity, pluripotency (ability to differentiate), quiescence, and extensive proliferative capacity. While committed progenitor cells may retain some of the HSC properties and may repopulate the hematopoietic system, they lack self-renewal

capacity. In humans, the HSC immunophenotype is characterized as $CD34^+$, $CD38^-$, Thy-1^{low}, and lacking lineage-specific markers although a population of $CD34^-$ stem cells has also been described. Considering the abundance of hematopoietic cells, true HSCs are relatively rare and constitute only 1 in 10,000 bone marrow cells. The HSC when infused to a recipient retains the ability to migrate and occupy bone marrow niches by virtue of surface adhesion molecules, chemokines, and their receptors. The number of $CD34^+$ cells in the infused graft product has important ramifications on post-HCT outcomes as lower $CD34^+$ cell dose may be associated with a higher risk of graft failure, delayed engraftment, and hematopoietic recovery resulting in higher nonrelapse mortality (NRM).

STEM CELL SOURCES

Bone Marrow

Originally bone marrow was considered the sole source of acquiring HSCs for both autologous and allogeneic transplantation and is obtained via repeated aspiration of the marrow from the posterior iliac crest usually under general anesthesia. The goal is to obtain $>2 \times 10^8$/kg recipient body weight of total mononuclear cells to allow safe engraftment. The maximum volume of marrow that may safely be removed at a given time is 20 mL/kg donor weight. The harvesting procedure is very well tolerated with low-risk of long-term adverse effects. Temporary pain at the procedure site is common, and less common side effects include neuropathy, infection, and anemia. Transplantation with peripheral blood progenitor cells (PBPCs) has largely replaced marrow-derived HSCs as the choice of cells for almost all auto-HCT and majority of the allo-HCT in adult patients. However, marrow remains the chief source of HSCs in pediatric patients and in some adults with nonmalignant hematological disorders such as aplastic anemia. Recent data have also led to resurgent use of marrow-derived products in unrelated and haploidentical-related donor HCT.

Peripheral Blood

Growth factors such as granulocyte colony-stimulating factor (G-CSF) are used to "mobilize" or increase the number of HSCs and progenitor cells in the peripheral blood, which are collected by apheresis. The minimum goal of PBPC collection is 2×10^6/kg recipient body weight of $CD34^+$ cells. The PBPC collection is safe with low risk of long-term adverse effects to the donor. The administration of growth factors to healthy donors may produce minor bone pain, with splenic rupture and myocardial infraction being extremely rare but significant complications. Plerixafor is a chemokine receptor antagonist against CXCR4, which mobilizes HSC and is currently approved in combination with G-CSF prior to auto-HCT in lymphoma and myeloma patients. In the setting of auto-HCT, cytotoxic agents are sometimes used prior to G-CSF mobilization. The postchemotherapy recovery phase improves the PBPC yield and may also provide antineoplastic effects. PBPC grafts generally result in more rapid engraftment and hematopoietic recovery. Based on existing evidence, PBPC is preferred over marrow grafts in auto-HCT. It is more nuanced in the setting of allo-HCT. Due to the 10- to 20-fold higher T-lymphocytes present in the PB product, there is an increased risk of GVHD. Results of early comparative studies in MRD allo-HCT demonstrated earlier engraftment, similar acute GVHD and relapse rates, but increased chronic GVHD with the use of PBPC in some but not all studies. A randomized trial evaluating peripheral blood versus bone marrow allo-HCT in the MUD setting showed increased chronic GVHD with the peripheral blood product, which was offset by delayed engraftment with marrow graft. Although graft source did not impact relapse rate or survival, long-term follow-up suggests improved quality of life parameters with the use of bone marrow allografts. Registry studies have shown increased chronic GVHD and poorer survival in patients receiving PBPC allo-HCT in severe aplastic anemia compared to those receiving bone marrow product, thus making it the graft source of choice in aplastic anemia. A risk-

adapted approach taking into account diagnosis, disease status, and donor type is warranted in choosing the ideal graft source.

Umbilical Cord Blood

UCB obtained from the umbilical cord and placenta after delivery of the baby is another source for HSC, which can be cryopreserved for later use. This represents an enriched source of HSC in a relative small volume of blood in comparison to bone marrow or PBPC. The small product size often correlates to an insufficient HPC dose and thus trials have investigated the successful infusion of two cord blood units. Cord blood is readily available but is an expensive stem cell source.

INDICATIONS FOR TRANSPLANTATION

HCT is considered a therapeutic option in the management of several disease entities. The National Marrow Donor Program (NMDP) website, http://www.bethematch.org, and the American Society for Transplantation and Cellular Therapy (ASTCT) provide a comprehensive list. See Table 30.1 for common indications in adults. Some of the salient features are as follows:

TABLE 30.1

Common Indications for Hematopoietic Cell Transplantation in Adults

Diagnosis	Autologous HCT	Allogeneic HCT
Aplastic anemia	No	Yes
Acute lymphoblastic leukemia	No	Yes; CR1, Ph + CR1, >CR2, Rel/Ref [a]
Acute myeloid leukemia	Yes; CR1 [a]	Yes; High-risk CR1, >CR2, Rel/Ref
Chronic lymphoid leukemia	No	Yes
Chronic myeloid leukemia	No	Yes; TKI intolerance/resistance, >CP1

Diagnosis	Autologous HCT	Allogeneic HCT
Diffuse large B-cell lymphoma	Yes; first relapse/CR2 (chemosensitive)	Yes; >CR2, >second relapse, Ref
Follicular lymphoma	Yes; first relapse/CR2 (chemosensitive)	Yes; >CR2, >second relapse, Ref
Germ cell tumor (Testicular)	Yes; Rel [a]	No
Hodgkin lymphoma	Yes; first relapse/CR2 (chemosensitive)	Yes; >CR2, >second relapse, Ref
Mantle cell lymphoma	Yes; CR1 and >CR1	Yes; >CR1
Multiple myeloma	Yes	No [a]
Myelodysplastic syndrome	No	Yes
Myeloproliferative neoplasms	No	Yes
T-cell lymphoma	Yes; CR1 and >CR1	Yes; >CR1

CP, chronic phase; CR, complete remission; HCT, hematopoietic cell transplantation; Ph, Philadelphia chromosome; Ref, refractory; Rel, relapsed; TKI, tyrosine kinase inhibitor.

[a]Either investigational or ideally considered as part of clinical trial.

- In pediatric population (<20 years), chief indications for auto-HCT are nonhematological malignancies, and for allo-HCT, they are benign hematological and immune system disorders (erythrocyte disorders, inherited immune system defects, congenital metabolic diseases).
- In the adult population, myeloma and lymphoma are common indications for auto-HCT, while acute and chronic leukemias, myeloid neoplasms, lymphomas, MDS, and aplastic anemia are common indications for allo-HCT. Autoimmune diseases such as relapsing multiple sclerosis and severe systemic sclerosis are newer indications for auto-HCT.
- Trends in HCT have changed overtime with therapeutic advances. An important example is: allo-HCT used to be the standard of care for chronic myeloid leukemia (CML) but not so in the era of bcr-abl tyrosine kinase inhibitors. Similarly, CAR-T therapy is expected to impact HCT trends in lymphoid malignancies.

PRETRANSPLANT EVALUATION

Prior to treatment, a thorough discussion highlighting the transplantation procedure as well as risks and benefits associated with the procedure should take place between the physician and the patient.

1. HLA typing of the patient and a search for an HLA-matched donor is required if an allogeneic transplant is being considered. Donor search is initiated with matched siblings as first choice, followed by MUDs and alternative donors (haploidentical, UCB, and MMUD)
2. Medical history and evaluation
    - Age—remains an important predictor of treatment-related morbidity and mortality. However, with improving supportive care, HLA typing, and use of RIC regimens, physiologic age and frailty is considered more important than chronological age
    - Review of original diagnosis and previous treatments, including radiation
    - Concomitant medical problems
    - Current medications, important past medications, and allergies
    - Determination of current disease remission status and restaging (by imaging studies, bone marrow biopsy, flow cytometry on blood or bone marrow, lumbar puncture, tissue biopsy as warranted)
    - Transfusion history and complications, as well as ABO typing and HLA antibody screening
    - Psychosocial evaluation and delineation of a caregiver
3. Physical examination
    - Thorough physical examination including evaluation of oral cavity and dentition
    - Performance status and frailty evaluation
4. Organ function analysis
    - Complete blood count
    - Renal function: preferably creatinine clearance > 60 mL per minute, except in myeloma
    - Hepatic function: alanine aminotransferase and aspartate aminotransferase less than twice the upper level of normal and bilirubin < 2.00 μg/dL preferred
    - Cardiac evaluation; electrocardiogram and echocardiography or multiple-gated acquisition imaging with ejection fraction
    - Chest x-ray and pulmonary function testing, including diffusing capacity of lung for carbon monoxide and forced vital capacity
    - Scoring schemes such as the HCT-specific comorbidity index (HCT-CI), which can predict NRM based on patient factors, may be used to risk stratify patients
5. Infectious disease evaluation

- Cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis, and hepatitis serology
- Serology for herpes simplex virus (HSV), Epstein-Barr virus (EBV), and varicella zoster virus (VZV)
- Assess for prior history of invasive fungal (aspergillus) infection

6. Pregnancy testing for all women of child-bearing age and consideration of referral to reproductive center for sperm banking or in vitro fertilization

AUTOLOGOUS HCT

The principle behind HDT is the administration of maximal tolerated doses of cytotoxic agents and/or radiation to maximize tumor kill and overcome relative tumor resistance, which causes prolonged and lethal cytopenias from which the patient may be rescued with the infusion of autologous progenitor cells to reconstitute the hematopoietic system. HDT regimens typically use combinations of cytotoxic agents with nonoverlapping organ toxicities. Commonly used regimens include (1) BEAM—carmustine + etoposide + cytarabine + melphalan (lymphoma), (2) CBV—cyclophosphamide + carmustine + etoposide (lymphoma), and (3) single-agent melphalan 200 mg/m^2 (myeloma). HDT is usually considered in chemotherapy-sensitive malignancies and/or as consolidation therapy for patients in remission (Table 30.1). HDT is also used in refractory germ cell tumors and other pediatric cancers such as neuroblastoma and to reset the immune system in autoimmune diseases such as scleroderma and multiple sclerosis. Overall, it is well tolerated with a NRM of <5%. Typically, the auto-HCT product is mobilized with G-CSF alone or in combination with either chemotherapy or the chemokine antagonist plerixafor. The mobilized PBPC is collected by apheresis and is cryopreserved viably in dimethyl sulfoxide (DMSO) and thawed just prior to infusion. Complications related to HDT and auto-HCT include the following:

- Rare infusion reactions may include bronchospasm, flushing, hypertension, or hypotension secondary to DMSO.
- Pancytopenia is universal, packed red blood cell (PRBC) and platelet transfusions maybe required. Neutrophil recovery takes 10 to 14 days with G-CSF support.
- Infectious complications—bacterial, viral, and fungal infections may manifest during the cytopenic phase but can be effectively prevented with antimicrobial prophylaxis. Late infections include Pneumocystis jiroveci, and varicella reactivation require continued prophylaxis beyond engraftment.
- Regimen-related toxicities may be (1) acute—infusion reaction (carmustine), hemorrhagic cystitis (cyclophosphamide), hypotension (etoposide) or (2) delayed—pulmonary toxicity (carmustine, total body irradiation [TBI]), sinusoidal obstruction syndrome or SOS (TBI or alkylating agents), and myelodysplasia (TBI, alkylating agents, etoposide).
- Relapse of the primary malignancy remains a major barrier to long-term survival.

ALLOGENEIC HCT

Allo-HCT has progressed from an experimental treatment of last resort to standard of care therapy for several disease conditions (Table 30.1). Extensive planning and coordination of care is required for all transplant candidates, usually involving a network of physicians and support staff. For patients without a MRD, the NMDP is an invaluable resource for the purpose of MUD allo-HCT. All physicians may perform a free initial search for an HLA-matched unrelated donor in the NMDP. As of 2019, the NMDP can search over 35 million MUD and 783,000 UCB units as potential donors through its international networks.

Graft-Versus-Tumor Effect

In the context of malignancies, the major therapeutic benefit of allo-HCT is the potential for the donor immune system to recognize and

eradicate the malignant stem cell clone, the so-called alloreactive graft-versus-tumor (GVT) effect. This immune effect is largely mediated by transplanted donor lymphocytes and is evidenced by the lower relapse rate of hematological malignancies in patients who undergo allo-HCT than in those who undergo auto-HCT, as well as by an increased risk of relapse in syngeneic (identical twin) donor or T-cell depleted allo-HCT. Arguably, the most important and direct evidence for GVT effect comes from the ability of therapeutic donor lymphocyte infusion (DLI) to induce remission in those that relapse after allo-HCT. CML, low-grade lymphomas, chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML) are most susceptible to the GVT effects, whereas acute lymphoblastic leukemia and high-grade lymphomas are relatively resistant. Donor-derived T-lymphocytes predominantly mediate GVT reactions, although evidence supports potential contribution from nonspecific cytokines (host- and/or donor-derived) and alloreactive natural killer (NK) cells (haploidentical allo-HCT).

HLA Typing

The HLA system consists of a series of cell surface proteins and antigen-presenting cells encoded by the major histocompatibility complex located on chromosome 6 and play a vital role in immune recognition and function. A striking feature of the HLA system is its enormous diversity. HLA class-I molecules include HLA-A, -B, and -C antigens and class-II molecules are made up of more than 15 antigens (HLA-DP, -DQ, and -DR). The complexity of the HLA system was revealed with the advent of molecular-based HLA typing, which showed that matched HLA phenotypes by serologic testing (antigen level) were actually diverse when classified by DNA analysis (allele level). The importance of careful HLA matching prior to the selection of a donor cannot be overemphasized and independently impacts graft failure, GVHD, and overall survival (OS). High-resolution HLA typing at the allele level is recommended for all recipients at HLA-A, -B, -C, -DRB1, and -DPB1 at the earliest as it avoids unnecessary delays in identifying a donor. The NMDP

recommends rigorous matching at the allele level for HLA-A, -B, -C, and -DRB1 (8/8 match) for adult patients and donors and updated recommendations also include high-resolution typing for HLA-A, -B, - C, and -DRB1 for UCB units.

Donor Types for Allogeneic HCT

1. Matched related donor
2. In the United States, approximately 25% to 30% of patients will have an HLA-matched sibling and is the preferred donor source. The risk of GVHD is higher with increasing HLA disparity and therefore, most transplant centers prefer at least 6/6 HLA match (HLA-A, -B, -DRB1).
3. Syngeneic donor
4. Rarely, an identical twin may serve as the donor. As the donor and recipient are genetically identical, GVHD does not typically occur (rarely noted, when a parous female serves as the donor) and post-HCT immunosuppression is not required. By the same principle, such HCT lacks GVT effects and malignancy relapse risk tends to be higher.
5. Matched unrelated donor
6. As discussed above, the search for an appropriate MUD is performed through the NMDP. It typically takes 6 to 12 weeks from the time a suitable donor is located to obtaining the allograft, although this period may be shortened when expedited searches are requested. Seventy percent of Caucasians will have a suitable MUD, while it is more difficult for ethnic minorities owing to disparities in registered volunteers in the NMDP registry. High-resolution (allele level) matching at HLA-A, B, C, and -DRB1 (8/8) is considered for MUD. When possible additional matching at -DQ (10/10 match) and -DP (12/12 match) are considered. Recent data suggest high-resolution MUD allo-HCT has similar outcomes to MRD allo-HCT.
7. Alternative donors
8. In the absence of an HLA-matched sibling donor, a MUD is traditionally considered. When a MUD is not available,

alternative donors may be used.

9. Mismatched unrelated donors—are potential alternative donors. Studies have established that donor-recipient HLA mismatches decrease OS and increase the risk of GVHD and graft failure. Most centers consider a 7/8 match in this setting (at -A, -B, -C, and -DRB1) and the NMDP requires a minimum 6/8 match prior to approving a match. In MMUD, it is important to look for (1) presence of recipient HLA antibodies against the donor HLA called donor-specific HLA antibodies (DSA) and (2) matching at secondary HLA loci such as -DQB1, -DRB3/4/5, and -DP. The use of posttransplant cyclophosphamide (PTCy) as GVHD prophylaxis in this setting is considered by many centers.
10. Haploidentical donor—Ready availability of an unrelated donor remains a major concern for patients who are not Caucasians. Haploidentical-related donors (defined as >2 antigen level mismatches) are a less expensive and readily available source for most patients across ethnic and racial barriers. Early reports utilizing haploidentical donors were associated with prohibitive GVHD in T-cell replete grafts. Extensive in vivo or ex vivo T-cell depletion used to mitigate this risk led to a higher risk disease relapse, delayed immune-reconstitution, infectious complications resulting in a higher NRM. Marrow-derived T-cell replete haploidentical allografts with posttransplant administration of high-dose cyclophosphamide selectively target alloreactive T-cells (effector cells implicated in acute GVHD) rapidly proliferating early after an HLA-mismatched transplant, but relatively sparing regulatory T-cells and nondividing hematopoietic cells, has shown encouraging results with prompt engraftment, low GVHD, and favorable NRM. Although lacking prospective data, large observational studies have demonstrated comparable posttransplant outcomes with haploidentical transplantation compared to more traditional MUD and MRD allo-HCT in leukemia and lymphoma. Data from a recent randomized trial demonstrated similar 2-year PFS but lower NRM resulting in improved OS with haploidentical transplantation compared to UCB transplantation.

Haploidentical donor HCT is an attractive choice for ethnic minorities and resource restricted regions.

11. Umbilical cord blood—Obtained and cryopreserved from a newborn's cord, the presence of immunologically naïve immune cells allows for HLA mismatches without increasing the risk of GVHD. Graft rejection and delayed engraftment occur more frequently owing to lower number of nucleated cells. However, the simultaneous use of two UCB (double UCB) units from different donors has shown to improve engraftment. Higher unit quality and total nucleated cell dose as well as better degrees of HLA match are associated with improved transplant outcomes. While the prior standard cord selection included antigen level matching for HLA-A and -B with allele level match for DRB1, newer data support high-resolution typing and the NMDP recommends HLA high-resolution typing for HLA-A, -B, -C and HLA-DRB1.

Donor Evaluation

Careful donor selection and evaluation is an integral part of the pretransplantation workup. The donor must be healthy and able to withstand the apheresis procedure or a bone marrow harvest.

1. HLA typing
2. ABO typing
3. History-relevant information of the donor
4. Any previous malignancy within 5 years, except nonmelanoma skin cancer is considered and absolute exclusion criteria. Age, sex, and parity of the donor impacts HCT outcomes and though are not exclusion criteria; younger men and nonparous women are preferred when available. Comorbidities like cardiac or coronary artery disease, lung diseases, back or spine disorders, medications and complications to general anesthesia to be considered.
5. Infection exposure

6. HIV, human T-lymphotropic virus, hepatitis, CMV, HSV, and EBV serology
7. Pregnancy testing for women

PHASES OF ALLOGENEIC TRANSPLANT

Pretransplant Phase—Conditioning ("The Preparative Regimen")

This phase of HCT precedes the graft infusion and is characterized by the administration of chemotherapeutic agents ± radiation. In the conventional sense, the goals of the conditioning regimen include immunosuppression of the recipient to prevent graft rejection and to eradicate residual disease. Newer conditioning strategies such as RIC/nonmyeloablative (NMA) regimens preserve immunosuppressive effects to aid donor engraftment with minimal or no myelosuppression.

1. Myeloablative conditioning
2. The most commonly used myeloablative conditioning regimens incorporate high-dose cyclophosphamide (120 mg/kg) in combination with TBI (usually 12 Gy) or busulfan. The choice of regimen is guided by factors such as the sensitivity of the malignancy to drugs in the regimen, the toxicities inherent to individual conditioning agents, prior therapies, age and performance status of the patient. Early regimen-related toxicity includes mucositis, nausea, diarrhea, alopecia, pancytopenia, seizures, and SOS. Late effects include pulmonary toxicity, hypothyroidism, growth retardation, infertility, an increased risk of cardiovascular disease, and second malignancies (mostly related to TBI).
3. NMA/RIC
4. RIC or NMA conditioning provides immunosuppression to aid donor engraftment and relies principally on the GVT reactions to eliminate residual malignancy. Cytopenias are limited

requiring no or minimal transfusion support. Commonly used truly NMA regimens incorporate fludarabine combined with low-dose TBI (<2 Gy) or alkylating agent such as cyclophosphamide, busulfan, or melphalan. While the division is somewhat arbitrary, RIC is intermediate between myeloablative and NMA regimens and is usually associated with cytopenias needing transfusion support. The advent of RIC/NMA regimens has broadened the applicability of allo-HCT to include older patients (>60) and those with poor performance status and comorbidities. Regimen-related toxicity and NRM tend to be less. Unique to RIC/NMA is the presence of assortment of donor and recipient hematopoietic cells in the initial months post-HCT (called mixed chimerism). Several reports indicate that persistent mixed chimerism may lead to higher relapse rates. Immunosuppression withdrawal and less commonly DLI are implemented to convert mixed chimerism by the gradual donor-immune–mediated eradication of recipient hematopoietic cells. GVT effects have been observed in several hematologic malignancies, as well as in select metastatic solid tumors such as renal cell carcinoma and neuroblastoma.

Transplant Phase

The transplantation phase is characterized by the intravenous infusion of the graft and usually starts 24 to 48 hours after completing the preparative regimen. Infusion is usually well tolerated by the recipient. The day of transplantation is traditionally referred to as “day 0.”

Posttransplant (Preengraftment) Phase

Early posttransplant phase is characterized by marrow aplasia and pancytopenia. Regimen-related toxicity and infectious complications are common during this phase and usually require intensive support with aggressive hydration, antimicrobial prophylaxis and treatment, GVHD prophylaxis, and transfusion support. All transfused products should be irradiated (to avoid transfusion-associated

GVHD) and leukoreduced (CMV safe). Engraftment is the term used to define hematopoietic recovery after HCT. Earliest to occur and sometimes used synonymously with the term engraftment is myeloid engraftment defined as sustained recovery of neutrophil count of $>0.5 \times 10^9$/L. Platelet engraftment usually lags behind granulocyte recovery and is usually defined as platelet counts of at least $>20 \times 10^9$/L without transfusion for 7 days. Erythrocyte engraftment occurs much later and is characterized by independence from PRBC transfusions. Posttransplant cytopenias depend on conditioning regimen used, diagnosis and disease status, donor source, $CD34^+$ cell dose in the allograft, use of growth factors, and GVHD prophylaxis.

Posttransplant (Postengraftment) Phase

Even after myeloid engraftment occurs, the recipient remains immunosuppressed due to GVHD prophylaxis/treatment and slow immune reconstitution, which may take up to 12 months or more to occur. Notable complications during this phase include infections and GVHD and require continued monitoring. Immunosuppression withdrawal in the absence of GVHD is employed at this stage to facilitate immune reconstitution.

COMPLICATIONS

Figure 30.1 highlights the timeline for some important posttransplant complications after allo-HCT. The following text elaborates the salient features of some key adverse effects and may not be considered comprehensive.

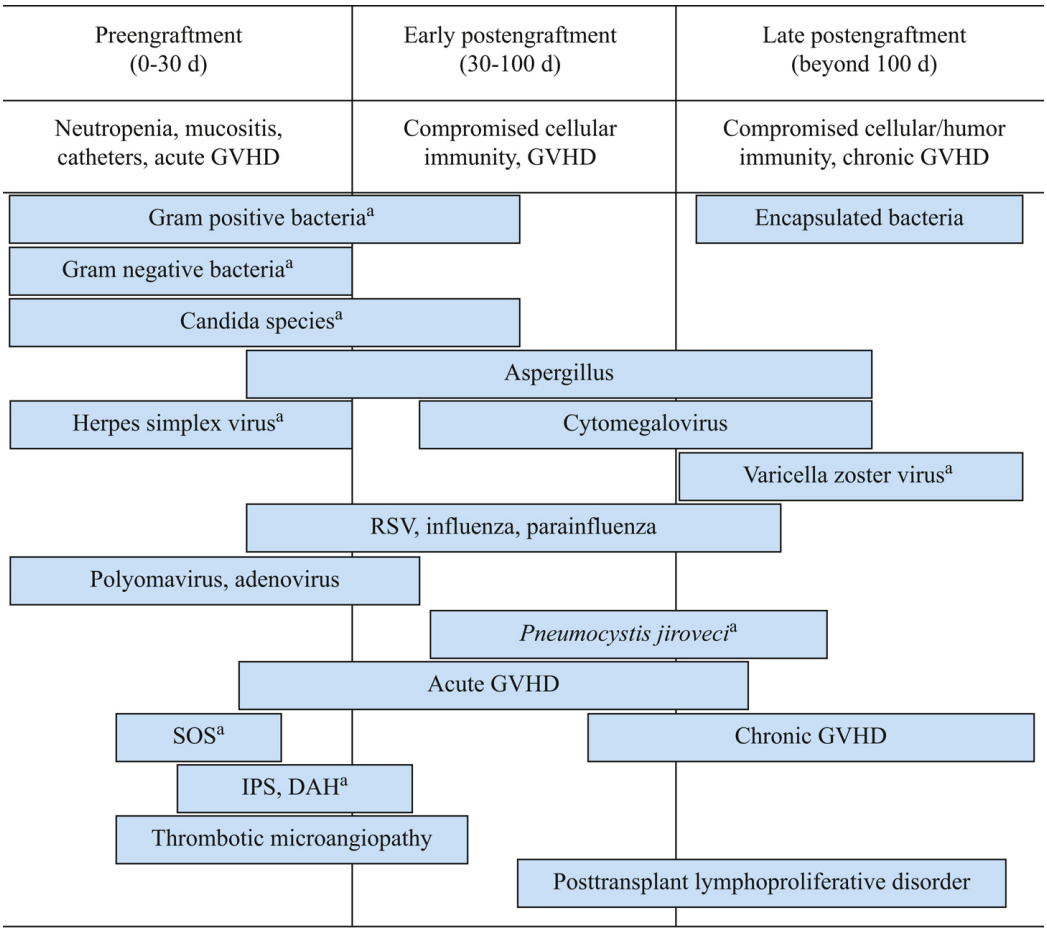

FIGURE 30.1 Timeline of complications after hematopoietic cell transplantation.

Graft Failure

Graft failure is a rare but serious complication characterized by the lack of engraftment and hematopoietic recovery after allo-HCT. Causes include HLA disparity, recipient alloimmunization, low $CD34^+$ dose, T-cell depletion of the graft, inadequate immunosuppression, disease progression, infections, and medications. Graft failure maybe primary (early) when no hematopoietic recovery is noted post-HCT or secondary (late) when the initial hematopoietic recovery is lost. Host immune-mediated

graft rejection is an important cause of graft failure. Growth factor support, manipulating dosage of immunosuppressive agents, $CD34^+$ stem cell boost, DLI, and regrafting represent approaches to the management of graft failure.

Infections

- Infection remains a major cause of morbidity for patients undergoing HCT. Indwelling catheters and transmigration of intestinal flora are common sources of infections, and bacteremia and sepsis may occur during the preengraftment (neutropenic) phase of HCT. Current approaches to minimize the risk of life-threatening infections include the use of prophylactic antibacterial, antifungal, and antiviral agents, as well as aggressive screening and treatment for common transplantation-associated infections.
- CMV infection most commonly occurs due to reactivation in seropositive patients or very rarely because of the transfer of an infection from the donor. The infection usually occurs after engraftment and may coincide with GVHD and/or its treatment. The risk for reactivation is highest up to day +100. CMV pneumonia and colitis can cause significant morbidity and mortality. In addition, it can cause febrile disease, hepatitis, and marrow suppression. A preemptive strategy involving screening for viral reactivation weekly posttransplantation either by CMV antigen levels or by polymerase chain reaction (PCR) was the favored approach for the majority of patients. Initial treatment is with intravenous ganciclovir or oral valganciclovir ± intravenous immunoglobulin. Foscarnet and cidofovir are alternatives (especially in patients with cytopenias). The use of ganciclovir for the initial prophylaxis or preemptive therapy in patients who reactivate CMV posttransplant (ie, become CMV-PCR+) can significantly prevent CMV disease and has resulted in a substantial reduction in CMV-associated morbidity and mortality. A randomized trial comparing letermovir to placebo in patients who are CMV

seropositive demonstrated that letermovir prophylaxis led to a significantly lower risk of clinically significant CMV infection without significant toxicity. This has led to increased use of letermovir prophylaxis in high-risk patients but does not obviate the need for continued monitoring of CMV PCR.

- Invasive fungal infection—With the routine use of fluconazole prophylaxis in HCT patients, once lethal invasive Candida infections are relatively uncommon. Other important pathogens include Aspergillus, Fusarium, and Zygomycetes. Common presentations include pneumonia, rhinosinusitis, skin infections, or fungemia. Patients with GVHD on high-dose steroids are especially at risk for invasive fungal infection and may benefit from expanded selection of antifungal prophylaxis.
- Others—HSV and VZV reactivation is effectively prevented with acyclovir prophylaxis, but late VZV reactivation after cessation of prophylaxis has been noted. EBV reactivation and posttransplant lymphoproliferative disorders are seen more commonly with T-cell–depleted transplants and in cord blood transplant recipients, especially those who receive antithymocyte globulin (ATG).

SOS (Veno-Occlussive Disease)

Hepatic SOS is characterized by jaundice, tender hepatomegaly, and unexplained weight gain or ascites and usually manifests in the first 2 weeks post-HCT. SOS is difficult to treat and typically involves supportive care measures focused on maintaining renal function, coagulation system, and fluid balance. The risk of SOS is higher in combination regimens containing alkylators with higher dose TBI or ablative doses of busulfan. The intravenous use and pharmacokinetic monitoring of busulfan drug levels has dramatically reduced the incidence of SOS. Defibrotide, a deoxyribonucleic acid derivative which is an anticoagulant, was approved by FDA in 2016 for treatment of SOS. Limited prophylactic options exist, but based on a meta-analysis, ursodeoxycholic acid, a naturally occurring hydrophilic bile acid, demonstrated decreased

SOS-associated mortality and reduced incidence of hepatic SOS and is commonly used as prophylaxis.

Pulmonary Toxicity

Bacterial, viral, or fungal organisms may cause infectious pneumonia. Idiopathic pulmonary syndrome, characterized by fever, diffuse infiltrates, and hypoxia may occur in 10% of patients and has an abysmal prognosis in severe cases requiring ventilator support. A subset of patients with diffuse alveolar hemorrhage may respond to high-dose steroids. Other causes such as CMV pneumonitis, transfusion-associated circulatory overload, and transfusion-associated lung injury must be excluded. Risk factors for pulmonary toxicity include ablative conditioning regimen (TBI), older age, prior radiation, a low DLCO, tobacco use, and GVHD.

Graft-Versus-Host Disease

After allo-HCT, donor-derived T-lymphocytes may recognize recipient tissue as foreign and mount an immunologic attack resulting in GVHD. It is one of the main treatment-related toxicities and impacts NRM significantly. Conventionally, acute GVHD was defined as occurring within day +100 and chronic GVHD beyond 100 days of transplant. It is no longer true and the classification should be based on clinical features rather than time of onset.

Acute GVHD: Up to 40% to 50% of MRD allo-HCT can be complicated by acute GVHD. Though varied in clinical presentation, it typically manifests in the first 2 to 6 weeks and affects the skin, liver, and the gastrointestinal system. The consensus criteria for staging/grading of acute GVHD are presented in Table 30.2. Risk factors for acute GVHD include degree of HLA mismatch, infections (CMV, VZV), unrelated donors, older patients, multiparous donor, older donors in MUD transplants, ABO-mismatches, sex-mismatched transplants (female donor → male recipients), and the use of intensive conditioning regimens.

TABLE 30.2

Acute Graft-Versus-Host Disease Staging by Consensus Criteria [a]

Stage	Skin	Liver (Bilirubin)	Gastrointestinal (GI)
0	No skin rash	<2 mg/dL	<50 mL/d or persistent nausea alone
1	Maculopapular rash <25% BSA	2.1-3 mg/dL	500-1000 mL/d, or persistent nausea, vomiting, anorexia, or positive upper GI biopsy [b]
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	1000-1500 mL/d
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	>1500 mL/d
4	Generalized erythroderma, plus bullae, or desquamation	>15 mg/dL	>2000 mL/d, severe abdominal pain ± ileus
Clinical grade	**Skin**	**Liver**	**Gastrointestinal**
I	Stages 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stages 2-3 or	Stages 2-4
IV	Stage 4 or	Stage 4	-

BSA, body surface area.

[a]Reprinted by permission from Nature: Przepiorka D, Weisdorf D, Martin P, et al. Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15(6):825-828. Copyright © 1995 Springer Nature.

[b]milliliter/day of liquid stool.

- Prevention of Acute GVHD
- Strategies to prevent acute GVHD have been established and are more effective than treating acute GVHD. Commonly employed strategies include:
    1. Pharmacologic therapy: Combination therapy of nonspecific immunosuppressive agents (methotrexate, steroids) and T-cell–specific immunosuppressant (calcineurin inhibitors [cyclosporine and tacrolimus], mycophenolate mofetil) are preferred to single-agent therapy. Methotrexate IV on days +1, +3, +6, and +11 with tacrolimus or cyclosporine IV/PO starting day -2 is most commonly used. Sirolimus and mycophenolate are sometimes used in lieu of methotrexate. Drug toxicities and interactions are extremely important

to monitor, and drug levels are followed closely for calcineurin inhibitors and sirolimus.

2. T-cell depletion: Achieved by (1) ex vivo separation by CD34+ selection or the use of monoclonal antibodies to remove T cells or (2) in vivo T cell depletion with the use of monoclonal antibodies such as ATG or alemtuzumab or (3) the administration of posttransplant high cyclophosphamide. Though effective in reducing GVHD, these maneuvers may increase relapse rates and infections due to late immune reconstitution.
3. PTCy mitigates the risk of GVHD by targeting alloreactive T-cells rapidly proliferating early after an HLA-mismatched transplant. Usually administered in combination with tacrolimus and MMF, it has become standard in patients receiving haploidentical-related donor transplant. The use of PTCy for GVHD prevention for mismatched and matched allo-HCT is the subject of active investigation. BMT CTN 1203 was a phase II trial randomizing patients to PTCy/Tacrolimus/MMF, Tacrolimus/MTX/bortezomib, or Tacrolimus/MTX/maraviroc in patients receiving RIC regimen for matched related or unrelated HCT. The PTCy arm appeared superior with the best GVHD-free, relapse-free survival (GRFS). HOVON-96, a phase III randomized trial evaluating conventional prophylaxis with CSA/MMF or PTCy/CSA in HLA-matched transplants with PTCy/CSA demonstrating improved 1-year estimated GRFS (45% vs 22%). To further assess the role of PTCy in related and unrelated HLA-matched transplantations, a phase III multicenter trial, BMT CTN 1703, is ongoing.

- Treatment of Acute GVHD
- Frontline treatment for clinically significant (grades II-IV) acute GVHD is methylprednisolone at a dose of 1 to 2 mg/kg/d and calcineurin inhibitors should be continued or restarted. For patients not responding to treatment, ruxolitinib was approved by the FDA in 2019, after demonstrating superior outcomes compared to the current best available therapy in the randomized trial. Additional agents (MMF, azathioprine, daclizumab, extracorporeal photopheresis, ATG, infliximab, etanercept) are used with variable success. Steroid refractory acute GVHD portends a very poor prognosis. Prophylactic antifungal therapy against aspergillus and Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered in those on corticosteroid treatment.
- **Chronic GVHD:** Use of PBPC allografts, MUD, alternative donor allo-HCT, and prior history of acute GVHD are risk factors. Chronic GVHD thought to be mediated chiefly by donor B-lymphocytes, presents with variable and multisystem organ

involvement and clinical manifestations, and may resemble autoimmune disorders (ie, lichenoid skin changes, sicca syndrome, scleroderma-like skin changes, chronic hepatitis, and bronchiolitis obliterans). Chronic GVHD is often accompanied by cytopenias and immunodeficiency. Treatment involves prolonged courses of steroids and other immunosuppressive agents as well as prophylactic antibiotics (eg, penicillin) and antifungal agents. In patient with steroid refractory disease, ruxolitinib had superior overall response rates compared to best available therapy in a randomized trial and received FDA approval for this indication. Ibrutinib, a B-cell receptor antagonist, also showed clinical activity in phase 1/2 trial prompting FDA to grant breakthrough status for patients with steroid refractory chronic GVHD. Other potentially useful agents include thalidomide, MMF, imatinib mesylate, pentostatin, rituximab, bortezomib, photopheresis, and Psoralen ultraviolet radiation (skin GVHD).

Relapse

Relapse after allo-HCT is ominous, especially for aggressive malignancies such as AML and ALL. Most relapses occur within 2 years of transplantation and those that relapse within 6 months have a worse prognosis. Immunosuppression is typically withdrawn to enhance GVT effect and, in some cases, DLI is administered. DLI administration frequently results in GVHD. The most favorable responses to DLI have been seen in patients with CML, especially those with molecular or chronic phase relapse. Second transplant for relapsed disease rarely results in long-term disease-free survival and is associated with a high risk of NRM.

SURVIVORSHIP

It is estimated that there are over 250,000 patients who are long-term (>5 years) survivors after HCT. While survivors after auto-HCT lead near-normal lives, studies have consistently shown that allograft

recipients have lower life expectancy than age-matched population. Long-term complications depend on the conditioning regimen, age, and presence of chronic GVHD. Some key points are:

1. Auto-HCT survivors are at risk for lung dysfunction, cardiovascular diseases, and secondary myelodysplasia/AML.
2. Major complications afflicting allo-HCT survivors include chronic GVHD, infections, organ dysfunction (pulmonary, cardiovascular, endocrine, and immune systems), secondary myelodysplasia/AML and solid organ malignancies. In addition, the pediatric population is at risk for growth retardation.
3. Immunizations are recommended for auto-HCT patients starting at 6 months and after withdrawal of immunosuppressive agents for allo-HCT. Long-term antibiotic prophylaxis is also needed for patients receiving prolonged immunosuppression for chronic GVHD.
4. Standardized long-term follow-up clinics are optimal and recommended screening and preventive measures for survivors have been established (see reference list). This include routine hemogram, hepatic and renal function tests, endocrine screening (lipid panel, vitamin D, thyroid panel), immunological studies, and others studies (echocardiogram, pulmonary function tests, age-appropriate cancer screening, ophthalmologic evaluation, bone densitometry).

CAR– T-CELL THERAPY

Immune effector cell therapy (IECT) is the collective term used to define infusion of modified immunologically active cells for therapeutic infusion. The therapeutic infusion of genetically engineered T cells with receptors that express antibody fragments with a defined specificity against tumor antigen(s) forms the basis of CAR-T therapy. TCR-engineered T cell therapy (T-cells modified to direct its specificity against tumor antigens) and NK cell therapy are in developmental stages. CAR-T therapy has significantly advanced

the therapeutic paradigm for patients with lymphoid malignancies including MM. Figure 30.2 provides a basic illustration of chimeric antigen receptor T-cell therapy. The process involves leukapheresis of a patient's T-cells ($CD3^+$ lymphocytes), followed by enrichment of these cells and transduction of a genetically engineered CAR fusion protein by means of a viral vector. The T-cells then undergo ex vivo expansion before delivery back to the facility for intravenous infusion to the patient. CAR designs comprised of T-cell signaling domains and an antigen-binding region continue to develop, broadening the indication for therapy. CD19 is expressed on most B-cells and thus has been an excellent target for CAR-T therapy in lymphoid malignancies. The first FDA product approved in August 2017 was tisagenlecleucel followed quickly by axicabtagene ciloleucel with recent approvals of brexucabtagene autoleucel and lisocabtagene maraleucel, all targeting CD19 (CAR containing anti-CD19 antibody fragment). Idecabtagene vicleucel targets BCMA (B-cell maturation antigen) and was recently FDA approved for patients with relapsed/refractory MM. The current approved indications are listed in Table 30.3, while newer treatment indications and additional targets are under investigation.

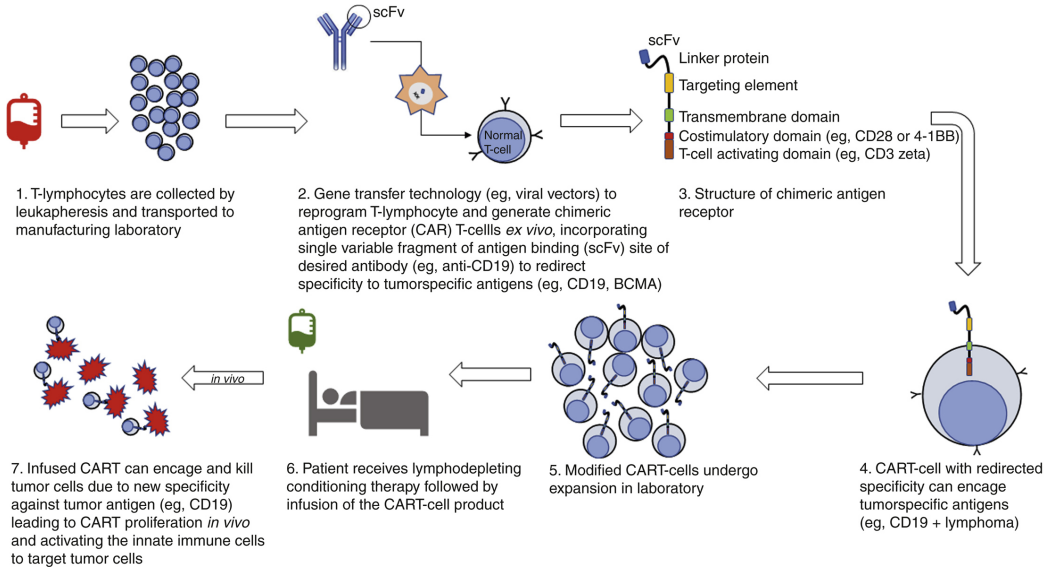

FIGURE 30.2 Illustration of chimeric antigen receptor T-cell therapy.

TABLE 30.3
Current FDA Approved CAR T-Cell Therapy

Product	Target	FDA-Approved Indications
Tisagenlecleucel	CD19	• Pediatric and young adults (≤25 years old) with R/R ALL • R/R DLBCL (at least two prior lines of therapy)
Axicabtagene ciloleucel	CD19	• R/R DLBCL • R/R PMBCL • R/R DLBCL arising from FL • R/R FL after ≥2 lines of therapy
Lisocabtagene maraleucel	CD19	• R/R DLBCL • R/R PMBCL • R/R DLBCL arising from indolent lymphoma • R/R FL Grade 3B
Brexucabtagene autoleucel	CD19	• R/R mantle cell lymphoma
Idecabtagene vicleucel	BCMA	• R/R multiple myeloma >4 prior lines of therapy

ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory.

Prior to infusion of the product, patients receive lymphodepleting conditioning chemotherapy most commonly with fludarabine and cyclophosphamide. Post CAR-T infusion, patients must be monitored closely at a designated facility as severe, life-threatening toxicities can ensue. The more severe toxicities of CAR-T therapy included cytokine-release syndrome (CRS) and neurotoxicity (now called ICANS or immune effector cell associated neurotoxicity syndrome) with other adverse effects including B-cell aplasia, hypogammaglobulinemia, pancytopenia, anaphylaxis, hemophagocytic lymphohistiocytosis, and tumor lysis syndrome. The time to onset, frequency, and severity of these toxicities varies

based on the specific CAR-T product infused, cell dose, underlying disease subtype, and disease burden.

CRS is associated with marked elevation in interleukins (IL2, IL6, IL10), interferon-gamma IFNγ, C-reactive protein, and ferritin and typically occurs within the first 14 days following CAR-T infusion with some cases occurring within the first 24 hours of infusion. The first symptom is typically fever but patients may go on to develop sinus tachycardia, hypotension, hypoxia, depressed cardiac function, pulmonary edema, and end-organ toxicity. Toxicity grading systems have been developed by different centers and ASTCT. Grading systems help guide the management of CRS. Tocilizumab, an IL-6 receptor antagonists, is FDA-approved for the treatment of severe CRS with the ability to lead to rapid resolution of hemodynamic instability in the majority of cases. Corticosteroids may also be considered in conjunction. A second dose of tocilizumab can be administered within 6 to 8 hours of the first dose if there is lack of clinical improvement. In fact, the availability of two doses of tocilizumab at the center is a requirement prior to infusion of the CAR-T therapy.

Neurotoxicity (ICANS) may coincide with CRS or can occur independently. The timeline is highly variable and can appear within 24 hours or 3 to 4 weeks after product infusion. It has also presented in a biphasic manner with initial occurrence with CRS symptoms and then a second occurrence after CRS resolution. A wide range of neurotoxicities have been reported including decreased attention, confusion, delirium, hallucinations, tremors, ataxia, dysphasia, nerve palsies, somnolence, obtundation, and seizures. Tocilizumab has little CNS penetration and thus has limited efficacy in neurologic toxicity. Along with proper imaging, neurologic evaluation, and supportive care, IV corticosteroids can provide additional benefit.

Patients receiving CAR-T infusion are susceptible to infections secondary to cytopenias that can develop from the conditioning regimen as well as prolonged cytopenias being reported. The anti-

CD19 CAR T-cells will also deplete normal B-cells leading to B-cell aplasia and hypogammaglobulinemia after infusion. Patients are monitored closely for infections and any febrile neutropenia ought to be managed according to established standards of care. Antiviral and PJP prophylaxis are necessary and most centers periodically monitor the $CD4^+$ count periodically and continue prophylaxis until the CD4 count is persistently >200. Quantitative immunoglobulin (Ig)G levels should be monitored closely during the first year following treatment with consideration of intravenous immunoglobulin initiation if patient has hypogammaglobulinemia and recurrent infections.

While CAR-T infusion may be administered in the outpatient setting, patients are instructed to be close to the hospital for the first 30 days postinfusion for close monitoring and assessments of blood counts, inflammatory markers, vital signs, and neurologic assessments. Prompt hospitalization and inpatient management with the first signs of CRS and/or neurotoxicity is recommended. Ongoing studies are evaluating ways to mitigate toxicity without compromising efficacy, including early administration of tocilizumab.

Although patients with durable responses have been reported, disease relapse after CAR-T therapy remains a significant challenge. Research to improve the response rates and long-term success is ongoing. CAR-T therapy is currently being studied in many other malignancies including CLL, Hodgkin lymphoma, AML, T-cell lymphoma, and even solid tumors, including thyroid cancer, glioblastoma, and ovarian cancer.

CONCLUSION

HCT has evolved into an effective therapeutic option for a broad range of disease entities. CAR-T and other IEC therapy are rapidly evolving providing further treatment modalities for patients with relapsed or refractory disease who may not have other treatment

options. Both entities require thorough patient evaluation and patient selection. The number of patients who benefit from these procedures will likely continue to increase as future treatment strategies continue to evolve and efforts to broaden indications and minimize adverse events continue.

Suggested Reading

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31

Cancer of Unknown Primary

F. Anthony Greco

DEFINITION

- Cancer of unknown primary (CUP) is a clinical pathologic syndrome defined by the presence of metastatic cancer in the absence of a clinically recognized anatomical primary site of origin.
- CUP represents a heterogeneous group of different cancers, most with a very small (occult) primary tumor site but with the capacity to metastasize. The pathologic diagnosis is made by biopsy of a metastasis.
- Autopsy series of CUP patients revealed small invasive primary sites in 75% with more than 25 cancer types (mostly carcinomas) documented. Very small primary sites which are not visualized or palpated at autopsy are likely missed since it would take hundreds or even thousands of tissue sections through various organs to detect these primaries.

EPIDEMIOLOGY AND PATHOGENESIS

- CUP is relatively common being among the ten most frequently diagnosed advanced cancers worldwide; estimated 50,000 to 75,000 patients annually in the United States.
- The exact incidence is not known since many CUP patients are arbitrarily assigned a specific primary site/cancer type based on

the physician's clinical opinion or pathology report despite the inability to detect an anatomical primary site, and these cancers are not listed in tumor registries as CUP.

- Male to female ratio is about 1.2 to 1.
- The cause of the CUP syndrome remains an enigma. The clinically occult invasive primaries produce metastasis and these grow and become clinically detectable. The very small primary sites usually do not grow and remain occult. Acquired genetic and/or epigenetic alterations are likely to be the basis of the syndrome. However, no specific unique nonrandom genetic alterations have yet been discovered.

CLINICAL FEATURES AND PROGNOSIS

- Nearly, all patients have symptoms related to metastasis which can be present at any site but are most common in lymph nodes, liver, lung, and bone.
- CUP is not a single cancer type but many specific metastatic cancers, which have a common unique feature—an occult clinically undetectable invasive anatomical primary site.
- Most CUP patients (greater than 50%) present with multiple sites of metastasis but a minority have only one to two sites. Although metastatic sites are occasionally atypical for the primary, most CUP cancers metastasize to sites expected for the primary and are otherwise biologically similar to their counterparts with known primaries. The major difference in CUP cancers and metastasis from a known primary cancer appears to be the size of the primary site.
- In the past, all patients were grouped together since the specific type or origin of the cancer was not definable; CUP was considered as a single entity assumed to be biologically similar; a minority (about 15%) of patients were eventually defined within several favorable subsets based on clinicopathological features (discussed later).

- In general, when CUP patients are considered as a single entity/cancer and treated with nonspecific empiric chemotherapy, their median survival time (excluding the favorable subsets) is about 9 months with a 1-year survival of 25% and 5-year survival less than 10%.
- Poor prognostic factors in the past were largely determined from untreated patients or those treated with empiric chemotherapy in the era when the specific cancer type was not possible to define.
- Historically poor prognostic factors included: men, adenocarcinoma histology, increasing number of metastasis to multiple organ sites, hepatic or adrenal involvement, poor performance status, high-serum lactate dehydrogenase, and low-serum albumin; many of these factors also apply to patients with many types of advanced cancer with known primary sites.
- Patients with more favorable prognostic factors included favorable clinical pathologic subsets (discussed later), predominant lymph node involvement without major visceral involvement.

DIAGNOSIS

- The initial diagnostic evaluation recommended is outlined in Table 31.1. If an anatomical primary site is identified, the patient does not have CUP.

TABLE 31.1

Initial Diagnostic Evaluation of a Possible CUP Patient

- Complete history and physical examination
- Laboratory tests: urine analysis, CBC, CMP, LDH, PSA in men, others depending on clinicopathological features
- Computerized tomographic (CT) scans of chest, abdomen, pelvis
- Positron emission tomography (PET) scan in selected patients (squamous carcinoma in cervical/inguinal nodes and those with a suspected single site of involvement)
- Mammography in women; MRI breasts if breast cancer highly suspected
- Biopsy should be generous specimen if feasible; avoid fine needle aspiration
- Pathology evaluation: screening immunohistochemical (IHC) stains of the biopsy on carcinomas (CK7, CK20, TTF-1, CDX-2); other stains or specialized pathology depending on histology and clinicopathological features (see Tables 31.2 and 31.3.)

- Additional clinical, laboratory, and pathologic evaluation based on details from history, physical examination, laboratory testing, and medical imaging
- If an anatomical primary site is not found, the patient has CUP
- Molecular cancer classifier assay on very small biopsy/aspiration/cytology specimens or when a reasonable number of IHC stains is not diagnostic of a single cancer type or tissue of origin
- Next generation sequencing/comprehensive molecular profiling may be important particularly if the cellular context/tissue of origin is known

CBC, complete blood count; CMP, comprehensive metabolic panel; CUP, cancer of unknown primary; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

TABLE 31.2

IHC Staining Patterns Characteristic of a Single Cancer or Tissue of Origin

Prostate	CK7−, CK20−, PSA+
Breast	CK7+, CK20−, GCDFP-15+, mammoglobin+, ER+, PR+, GATA3+ Her-2-neu+
Lung-adenocarcinoma and large cell	CK7+, CK20− TTF-1+, Napsin A+
Colorectal	CK7−, CK20+, CDX2+
Germ cell	PLAP+, OCT4+, SALL4+
Lung-neuroendocrine (small cell/large cell)	Chromogranin+, synaptophysin+, CD56+, TTF-1+
Thyroid carcinoma (papillary/follicular)	Thyroglobulin+, TTF-1+
Melanoma	MelanA+, HMB45+, S100+
Adrenal carcinoma	Alpha-inhibin+, Melan-A+(A103)
Renal cell carcinoma	RCC+, PAX8+
Ovary carcinoma	CK7+, CK20−, WT-1+, PAX8+, ER+
Hepatocellular carcinoma	Hepar-1+, CD10+, CD13+

TABLE 31.3

Additional Evaluation Based on Findings From Initial Diagnostic Evaluation in CUP

Results of Initial Diagnostic Evaluation	Additional Evaluation	
	Clinical	IHC Staining/Other Testing
Features highly suggestive of colorectal carcinoma (peritoneal/liver metastasis; biopsy CK20+, CK7−, CDX2+)	Colonoscopy	KRAS an or BRAF mutation of biopsy Microsatellite status

Results of Initial Diagnostic Evaluation	Additional Evaluation	
	Clinical	IHC Staining/Other Testing
Features highly suggestive of lung carcinoma (mediastinal/hilar adenopathy; biopsy CK7+, CK20−, TTF-1+)	Consider bronchoscopy	Genomic analysis of biopsy for EGFR mutation, ALK/ROS1 rearrangement, and other treatable alterations
Features suggestive of ovarian carcinoma (peritoneal/pelvic metastasis; biopsy CK7+)	Intravaginal/pelvic ultrasound	WT-1, PAX8, ER stains of biopsy BRCA1/2 evaluation
Features suggestive of breast carcinoma (axillary nodes, lung, bone, liver metastasis; CK7+)	Breast MRI	ER, GCDFP-15, mammoglobin, GATA3 stains; Her-2-neu testing of biopsy
Mediastinal and/or retroperitoneal masses in young adults (usually men)	Testicular ultrasound, serum AFP, HCG, LDH	PLAP,OCT4, SALL4 stains of biopsy; FISH for i(12)p of biopsy
Poorly differentiated carcinoma, with or without clear cell features	Serum AFP if liver involvement; gallium PET DOTATATE scan if neuroendocrine stains+	Chromogranin, synaptophysin, RCC, PAX8, Hepar1, MelanA, HMB-45 stains of biopsy
Liver lesions predominant (CK7−, CK20−)	Serum AFP	Hepar1 stain of biopsy; albumin IHS
Any histology without a single cancer site or tissue of origin predicted by IHC or small amount of biopsy		Molecular cancer classifier assay of biopsy; Comprehensive molecular profiling for determination of NTRK, microsatellite, tumor mutation burden, and other potentially actionable genetic alterations; liquid biopsies

- Biopsy samples should be generous if possible; avoiding fine needle aspirations since several tests may be necessary. The first

goal is confirming the diagnosis of cancer and second goal the specific type of cancer.

- Standard pathologic examination including immunohistochemical (IHC) staining is routinely done on CUP biopsies.
- Table 31.2 lists some of the useful IHC staining patterns, but the selection of stains is often based on the light microscopic histopathological appearance of the biopsy and clinical features; there are false positives and negatives with all the stains which can lead to erroneously diagnoses. Obtaining multiple stains indiscriminately exhausts the biopsy specimen and rarely improves the diagnostic ability.
- Additional evaluation recommended based on the initial findings is outlined in Table 31.3.
- The lineage of the cancer (carcinoma, sarcoma, melanoma, lymphoma) is usually diagnosed by light microscopic appearance and if necessary IHC staining.
- Molecular cancer classifier assays have been developed based on gene expression profile patterns and are a major advance in the diagnosis of the cancer type in CUP patients. Currently, in the United States, there is one commercially available assay (BioTheranostics, Inc Cancer TYPE ID), a 92 gene RT-PCR assay, that provides a molecular classification of 50 cancer types/subtypes with an overall 87% accuracy. A newer DNA-based epigenetic assay (EPICUP) developed in Spain also appears to have about a 90% accuracy but does not appear to be commercially available. Recently, next generation sequencing/comprehensive molecular profiling platforms have reported some data on determining the cancer type in CUP, but these have thus far not had adequate validation.
- Data are accumulating to more definitively define specific cancer types within the CUP syndrome, response to site-specific therapy, and outcome compared to metastatic cancers of known primary site.
- The diagnostic ability of the combination of IHC and molecular cancer classifiers often provides critical information to plan

appropriate treatment for each patient.

HISTOLOGIC/MORPHOLOGIC CELL TYPES

- The light microscopic classification of CUP includes several recognized histologic types including adenocarcinoma (60%), poorly differentiated carcinoma with some features of adenocarcinoma (30%), squamous cell carcinoma (5%), neuroendocrine carcinomas (3%), and poorly differentiated neoplasm with confusing or undefined lineage (2%). Occasionally, melanoma or sarcoma present as CUP and generally are treated with site-specific therapies and not further discussed in this brief review.
- Segregation of the above histologic types is important since various favorable subsets could be more easily recognized. Over the past 4 decades, several favorable subsets (15% of all CUP patients) are now treated with site-specific therapy based on their presumed tissue of origin (discussed later).
- The majority of CUP patients (85%) are not included in any of the favorable subsets, and there does not appear to be any prognostic significance of the light microscopic histology.
- Nonspecific empiric chemotherapy regimens were developed in large part from 1995 through 2006, and the 85% of CUP patients with unfavorable prognostic features were usually treated; the cancer type could not be determined in most patients and the same empiric chemotherapy regimens were used for all patients assuming all CUP cancers were biologically similar. Although these empiric regimens helped a minority of patients, the overall median survival in larger series (greater than 100 patients each) has been only about 9 months.

FAVORABLE SUBSETS OF CUP PATIENTS

Clinical features including gender, metastatic sites, and histologic classification of these cancers and more recently IHC and molecular cancer classifier assays have provided the basis to presume a specific primary tumor or cancer type for selected patients. Treatment based upon these presumptive diagnoses have generally improved the overall outcome of these patient subsets (see Table 31.4.) Recent data reveal the cancer types of many of the favorable CUP subsets reported several years ago are as expected based on IHC staining and/or molecular cancer classifier assays.

TABLE 31.4
Favorable Subsets of CUP

Subset	Therapy
A. Young men (rarely women) retroperitoneal and/or mediastinal masses; serum B-HCG and/or AFP may be positive	Treat as germ cell carcinoma
B. Squamous cell carcinoma in cervical/neck nodes	Treat as head/neck carcinoma
C. Squamous cell carcinoma in inguinal/iliac nodes	Treat as anal, cervical, or vulvar carcinoma
D. Women (rarely men) with axillary carcinoma	Treat as breast carcinoma
E. Women (rarely men) with peritoneal carcinoma (usually serous adenocarcinoma)	Treat as ovarian carcinoma
F. Neuroendocrine tumors	
Well differentiated	Treat like carcinoid
Poorly differentiated	Treat like small cell lung carcinoma
G. Men with osteoblastic bone metastasis-PSA+	Treat like prostate carcinoma
H. CUP colorectal subset (IHC and/or molecular cancer classifier assay diagnosis of colorectal)	Treat like colorectal carcinoma
I. Single small site of metastasis	Treat with surgery and/or RT; chemotherapy
J. Poorly differentiated neoplasms (lineage unknown)	Many responsive neoplasms (further evaluation critical)
K. Isolated pleural effusion with carcinoma	Many responsive carcinomas (further evaluation critical)
L. Gestational carcinoma—serum B-HCG elevated	Treat as gestational choriocarcinoma

AFP, alphafetoprotien; CUP, cancer of unknown primary; IHC, immunohistochemical; PSA, prostate-specific antigen; RT, radiation therapy.

A. Extragonadal germ cell cancer syndrome

- These patients represent a rare, but important subset, since they have very treatable and potentially curable advanced cancers if recognized and treated appropriately.
- Most commonly, these tumors are not only found in young men but also even more rarely in women. These carcinomas usually involve the midline location (mediastinum and/or retroperitoneum) and/or multiple lung nodules.
- The histology of the biopsy is usually a poorly differentiated carcinoma or poorly differentiated neoplasm.
- Elevated serum levels of beta HCG and/or alpha-fetoprotein are commonly seen.
- IHC staining for germ cell tumors and/or a molecular cancer classifier assay or fluorescence in situ hybridization testing for an isochromosome of 12 may be diagnostic.
- Therapy for germ cell carcinomas is indicated even if the histology is atypical which is characteristic in these patients.

B. Axillary carcinoma in women and rarely men

- Most of these patients have occult breast carcinoma.
- IHC stains are usually positive for breast markers, but some are triple negative; molecular classifiers assays usually predict breast carcinoma.
- Mammography is negative; breast magnetic resonance imaging and positron emission tomography (PET) scans detect some small primaries.
- If mastectomy is done, about 60% have documented small invasive primary breast carcinomas. It is possible that many others also have a very small primary but are missed as it may take hundreds of tissue sections to find a very small clinically occult invasive primary.
- Treatment guidelines should be similar to stage II or III breast carcinoma; primary radiotherapy of the ipsilateral breast is an acceptable alternative to surgery; neoadjuvant or adjuvant chemotherapy and/or hormone therapy as per breast cancer guidelines is indicated.
- The prognosis of these patients appear similar to women with known stage II or III breast cancer when they are treated appropriately.
- In patients with an axillary mass and other metastasis, the suspicion of occult breast cancer should remain high.

C. Squamous cell carcinoma in upper cervical/neck nodes

- Highly suggests an occult head and neck carcinoma.
- PET scanning is indicated in this subset and reveals the primary site in more than one-third of these patients despite the inability to find it by any other testing.
- Human papillomavirus (HPV) association is common.
- Treatment can be curative with combined modality chemotherapy and radiotherapy as per known head and neck squamous carcinoma and outcomes similar.

D. Squamous cell carcinoma in inguinal or pelvic lymph nodes

- Most likely arising from an occult primary from the uterine cervix, anal canal, or more rarely the vulva or skin. HPV association is seen with both cervical and anal cell carcinomas.
- Potentially curable cancers with combined modality therapy.

E. Peritoneal carcinoma in women and rarely men

- They usually have serous adenocarcinoma but may be poorly differentiated carcinoma; these tumors are more common in BRCA1/2 germ line mutation patients.
- IHC staining and/or molecular classifier assays usually consistent with ovarian, fallopian tube, or primary peritoneal carcinoma.
- Serum CA125 often elevated but not specific.
- Treatment should be similar to stage III ovarian carcinoma and the outcomes are similar.

F. Neuroendocrine tumors

- An important distinction is the grade of the tumor—well differentiated or poorly differentiated; some poorly differentiated carcinomas are not recognized as neuroendocrine unless specific IHC stains and/or a molecular cancer classifier assay are obtained.
- Well-differentiated tumors have a similar biology to well-differentiated carcinoid or islet cell tumors.
- Treatment for well-differentiated tumors is similar to advanced carcinoid tumors; overall prognosis fair to good in part due to the indolent nature of these cancers and the evolving improving therapies.
- Treatment for high grade or poorly differentiated neuroendocrine tumor should be similar to small cell lung cancer or extrapulmonary small cell carcinomas with cisplatin- or carboplatin-based chemotherapy; radiotherapy should be added in those with local regional involvement.
- A small percentage (about 10%) of patients with poorly differentiated neuroendocrine carcinomas have long-term survival following combination chemotherapy including etoposide and platinum (most other patients have responses to chemotherapy with improvement in the quality and quantity of life).

G. Men with elevated prostate-specific antigen or osteoblastic metastasis

- Hormonal therapy for prostate carcinoma should be administered when the serum prostate-specific antigen (PSA) is elevated (serum PSA recommended for all men with CUP) or tumor PSA stain is positive. Men with osteoblastic metastasis warrant a trial of hormone therapy in selected clinical settings regardless of the PSA level. A molecular cancer classifier assay may also help with the diagnosis.

H. Single-small site of metastasis

- Local therapy with surgical resection and/or radiotherapy.
- Site-specific therapy should be considered depending on the determination of the cancer type by immunostaining and/or a molecular cancer classifier assay.

I. Poorly differentiated neoplasms

- About 2% of all CUP patients have a poorly differentiated neoplasm without a definitive lineage by light microscopic examination; after IHC staining, only a small minority of these cancers remain undefined; in this group, a molecular cancer classifier has been proven to be useful in the majority of patients.
- Precise diagnosis in these patients is important by the appropriate use of IHC staining panels, and if necessary, a molecular cancer classifier assay (several of these patients have highly treatable neoplasms including germ cell tumors, lymphoma, melanomas, and others).

J. CUP colorectal subset

- A subset of CUP patients with IHC stains and/or a molecular cancer classifier assay diagnostic of a lower GI primary have improved outcomes with median survivals about 24 months similar to known colorectal adenocarcinomas when treated with colorectal site-specific regimens.
- These patients do not have their primary sites found at colonoscopy and most have metastasis typical for colorectal primaries (liver, peritoneal cavity, retroperitoneal nodes).
- These CUP patients should be treated in a similar fashion as known metastatic colorectal adenocarcinoma since their outcome is improved.

K. Amelanotic melanoma

- Melanoma has been known for decades by pathologists as the "great imitator"; the histology can be confusing, particularly when no melanin pigment is identified in the cancer cells; melanoma may appear as a poorly differentiated carcinoma or the lineage may not be recognized.
- Appropriate IHC stains usually are diagnostic, but if there is a doubt, a molecular cancer classifier assay is usually helpful.
- Treatment implications are obvious since BRAF inhibitors and immune checkpoint inhibitors often provide useful therapy.

L. Isolated pleural effusion

- This subset is recognized with an overall better prognosis than those with multiple metastasis.
- A small peripheral lung carcinoma obscured by fluid should be suspected but occult breast cancer, ovarian cancer, and other occult primaries may present with metastasis and isolated pleural effusion; nonspecific empiric chemotherapy has been useful for some of these patients in the past, but specialized pathology with appropriate IHC stains, and if necessary, a molecular cancer classifier assay is indicated to direct site-specific therapy for these patients.

M. Unrecognized gestational choriocarcinoma

- CUP in a young woman with poorly differentiated carcinoma or neoplasm particularly during pregnancy or in the postpartum period or after spontaneous abortion should be suspected of harboring gestational choriocarcinoma; examination of the placenta or other tissue is usually diagnostic.
- A serum beta HCG is always elevated and chemotherapy for choriocarcinoma is usually curative; in the gestational setting, choriocarcinoma is most likely but an elevated serum beta HCG may also be from a germ cell carcinoma.

GENERAL PRINCIPLES, EVALUATION, AND TREATMENT OF CUP PATIENTS

- The goal in any patient with metastatic cancer is to determine the primary site or cancer type.
- Therapy is based upon an accurate identification of the precise cancer type.
- In patients with CUP, an anatomical primary site is not clinically identified after a reasonable evaluation; determination of the cancer type depends on considering all clinicopathological data, but particularly IHC staining panels and if necessary, a molecular cancer classifier assay is performed on a biopsy of a metastatic lesion. Next generation sequencing/comprehensive molecular profile may be very useful particularly after identification of the tissue of origin. There are many potentially treatable/actionable genetic alterations which may have an impact on appropriate therapy.
- Molecular cancer classifier assays have been proven to diagnose the cancer type in CUP in about 95% of patients.
- Data from several prospective and retrospective studies now support the use of molecular cancer classifier assays in the majority of patients (about 66%) who are not diagnosed with a single cancer type by IHC staining panels.
- Once the cancer type in CUP is diagnosed, comprehensive molecular profiling may be indicated as well as site-specific therapy for that cancer.
- Only one large phase 3 randomized prospective study is available comparing site-specific therapy based upon a molecular cancer classifier assay diagnosis versus empiric therapy. This study was designed more than a decade ago before most targeted therapies and immunotherapy was available for patients with specific diagnoses. Results of this trial did not reveal any progression-free survival benefit for site-specific treatment in all patients. However, in the minority of patients with molecular diagnoses of more treatable cancer

types, there was a notable improvement in survival at 2 years but was not statistically significant due to the small numbers. Additional randomized studies with the use of targeted therapy and immunotherapy as indicated are eagerly awaited.

- Precision or personalized therapy is now indicated for CUP patients based on the recognition of the cancer. CUP is not a single cancer and each patient has a specific cancer and therapy is indicated for their cancer type. For some cancer types (including breast, lung, colorectal, melanoma, ovary, renal, and others), several site-specific therapies, in some instances used sequentially, improve patient survival; the effectiveness and outcomes is variable and better for patients with cancers known to be responsive to therapies; the presence of genetic alterations which are successfully targeted by various drugs now also have proven survival benefit for some patients with lung, melanoma, breast, gastroesophageal junction/gastric, colorectal, and other cancers. The recognition of the usefulness of immune checkpoint inhibitors in several patients with a number of advanced cancers also makes the precise diagnosis of the cancer type important.
- CUP patients have a large range of cancer types arising from many occult anatomically undetectable primaries and some, particularly with the more responsive cancers, may be treated effectively if recognized.
- A small minority of CUP patients (about 5%) cannot have their precise cancer type identified despite the use of appropriate IHC panels and molecular cancer classifier assays; nonspecific empiric chemotherapy is appropriate in these patients.
- Examples of four frequently used empiric regimens for CUP including high-grade neuroendocrine carcinoma are illustrated in Table 31.5.

TABLE 31.5

Empiric Chemotherapy Commonly Used in the Past for Carcinoma of Unknown Primary

Adenocarcinoma or poorly differentiated carcinoma	
Paclitaxel	200 mg/m^2 IV day 1
Carboplatin	AUC 6 IV day 1
	Repeat cycle 3 wk
	six cycles
Gemcitibine,	1250 mg/m^2 IV days 1,8
Cisplatin	80-100 mg/m^2 day 1Repeat cycle 3 wk
	six cycles
High-grade neuroendocrine carcinoma	
Etoposide	100 mg/m^2 IV day 1,2,3
Carboplatin	AUC 5 IV day 1
	Repeat cycle 3 wk
	four-six cycles
Etoposide	100 mg/m^2 IV day 1,2,3
Cisplatin	80-100 mg/m^2 IV day 1
	Repeat cycle 3-4 wk
	four-six cycles

- The suggested algorithm for the management of a possible CUP patient is illustrated in Figure 31.1.

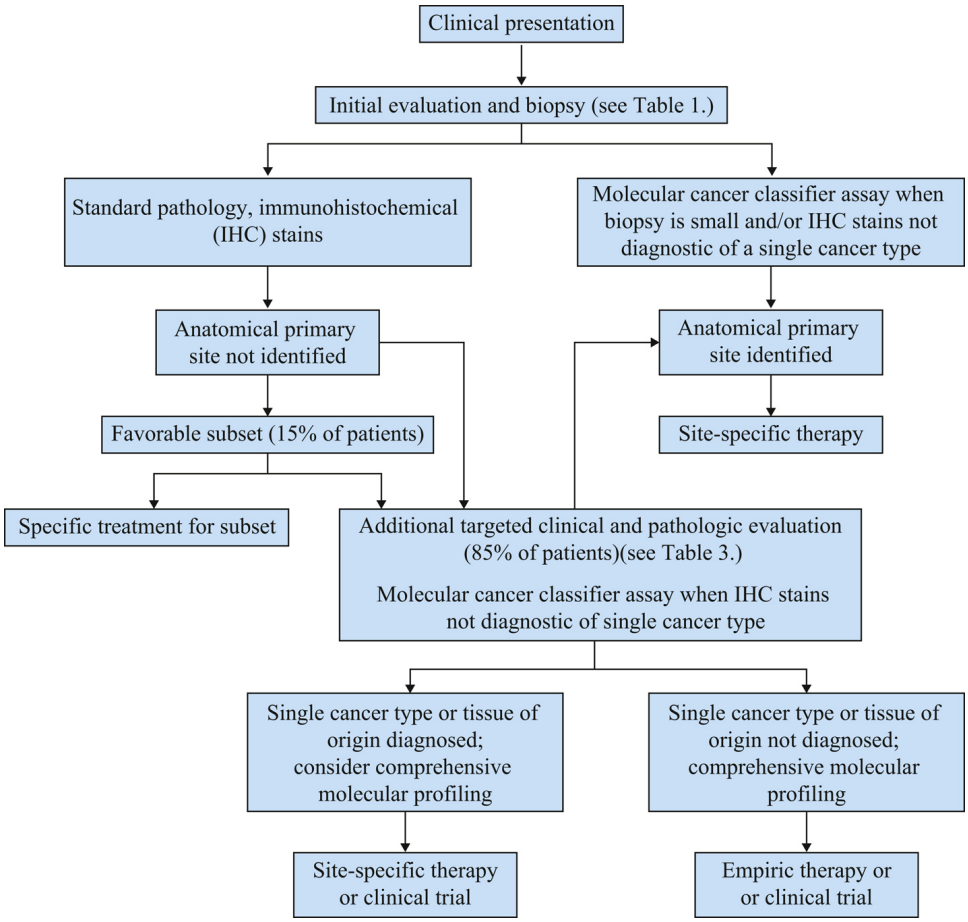

FIGURE 31.1 Suggested evaluation of a possible cancer of unkown primary patient.

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32

Central Nervous System Tumors

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INTRODUCTION

Tumors of the central nervous system (CNS) can be divided into two main groups: primary tumors and metastatic lesions. Primary CNS tumors can be further subdivided into benign and malignant cancers. While primary CNS tumors arise directly from the brain, spinal cord, or associated tissues, metastatic lesions originate from a distal cancer, most commonly from the lung, breast, skin, or colon. This chapter will discuss both primary CNS tumors and metastatic brain cancers with emphasis on the former to provide a schematic and practical approach to their evolving classification and management.

Intracranial tumors (including benign and malignant cancers) account for approximately 85% to 90% of all primary CNS tumors. The incidence rate of intracranial tumors increases with age. Brain tumors are more common in adults compared to children, but children are more likely to have a malignant brain cancer than a benign lesion. An increase of brain cancer incidence rate was reported in the literature at the end of the 20th century. Although the exact reason of this change is still unknown, it can be, at least partially, contributed to longer life expectancy and greater availability of imaging techniques. Most recently, the overall incidence rates of primary brain tumors are static. Certain tumor subtypes may show changes in incidence rates which are likely

attributable to the paradigm shifts occurring over the last decade in tumor classifications.

Most adult primary brain tumors are sporadic. However, about 5% of primary brain tumors have known hereditary factors and related to a genetic syndrome, such as Lynch syndrome, neurofibromatosis type I and II, Li-Fraumeni syndrome, tuberous sclerosis, von Hippel-Lindau disease, Turcot disease, familial adenomatous polyposis. Recognition of these syndromes is vital to provide appropriate medical care, targeted tumor screening, and genetic consultation for family members.

Brain tumors are often morphologically heterogeneous and many of them do transform over time, becoming more malignant due to the accumulation of genetic alterations, resulting in changes in the tumor biology. Although the initial differential diagnosis can be postulated by a combination of signs and symptoms (such as radiological findings, tumor location, patient's age, presence of seizures at diagnosis), the definitive diagnosis of CNS tumors requires tissue sampling and pathology testing, including histological as well as molecular analysis. Although the precision of diagnosis has markedly improved with the integration of histology and genetic markers, further research is needed to better define prognostic and predictive biomarkers that can guide individualized treatment and lead to improved patient outcome.

Metastatic brain tumors are more frequent than primary brain tumors. The incidence of metastatic brain lesions is rising due to a combination of factors, including advanced screening and longer survival after initial cancer diagnosis due to new therapeutics with good systemic effect but limited blood-brain barrier penetration. It has been estimated that up to one-fourth of patients with a diagnosis of cancer develop brain metastases.

Molecular Diagnosis of Primary Brain and CNS Tumors

Molecular diagnostics is a powerful tool that has been changing the landscape of neuro-oncology. In 2016, the World Health

Organization (WHO) formulated a major reconstruction of CNS tumor diagnoses by combining histological features and molecular parameters. The role of molecular diagnostics is being further solidified in the 2021 fifth edition of WHO classification, which echoes the recommendations of the 2019 cIMPACT-NOW Utrecht meeting. This comprehensive pathogenetic classification improves diagnostics by grouping tumors that share similar prognostic markers and increasingly guides patient management by enabling the use of targeted therapies. In the past, the histological features of a tumor determined the grade and so categorized the level of its aggressiveness. With recent advances in molecular diagnostics, the clinical relevance of frequently occurring genetic markers has been uncovered. To underline the powerful prognostic value of genetic mutations, the 2021 WHO classification recommends changing the grade level based on concerning molecular features even if the histology is suggestive of a lower grade tumor. In general, the malignancy grade divides tumors from one to four where the lower numbers represent low-grade tumors and the higher numbers assigned to more aggressive tumors.

Clinical Diagnosis and Considerations

Brain tumors cause symptoms and signs through a combination of mechanisms. Clinical manifestations depend on location, size, and tumor growth rate. Direct effects of the tumor are related to invasion and compression of the tumor on the brain parenchyma. Secondary effects are mostly related to vasogenic edema. Symptoms may be focal, reflecting the location of the tumor (eg, hemiparesis); generalized, which are nonlocalizing (eg, headache); or false localizing, which are caused by raised intracranial pressure (eg, tinnitus) (Table 32.1). The most common symptoms are new onset and progressively worsening headaches, seizures, mental status changes, behavioral changes, and unilateral weakness (paresis). Often, there could be involvement of cranial nerves, optic discs, and visual fields. Between 30% and 90% of patients with brain tumors experience seizures either at presentation or at some time during the

disease trajectory, often with progression. Secondary epilepsy is always focal in origin although seizures can secondarily generalize. Seizures are more common in primary tumors than metastases and more often associated with slow-growing/low-grade tumors. In children, most frequently occurring symptoms and signs of a brain tumor are related to increased intracranial pressure and ataxia. The time between the onset of symptoms and diagnosis varies, and there seems to be an inverse relationship between delayed diagnosis and poor outcome. This may be explained by the less-specific symptomatology that slower growing tumors are more likely to have in comparison with more severe and localizing symptoms earlier in the disease course of more aggressive tumors.

TABLE 32.1

Brain Tumors: Symptoms and Signs

Localizing	Seizures, hemiparesis, diplopia, aphasia, vertigo, incoordination, sensory abnormalities, and dysphagia
Generalized	Headache, nausea, vomiting, dizziness, mental status changes, visual obscurations, and seizures
False-localizing	Tinnitus, diplopia, hearing and visual loss

Acute Complications

Acute neurological complications in a brain cancer patient may be related to the growing cancer, to the cancer treatment, or to underlying medical problems. The most frequently seen serious medical problems include ischemic or hemorrhagic strokes, seizures, elevated intracranial pressure, and herniation. Acute stroke can develop due to the patient's comorbidities, paracrine effect of the cancer, or as a side effect of cancer treatment. Differential diagnosis of stroke includes disease progression, seizures, increased cerebral edema, and stroke-like migraine attacks after radiation therapy (SMART) syndrome. Mass occupying brain tumors and related cerebral edema may cause increased intracranial pressure after exhausting compensatory mechanisms. Morning headaches, nausea,

vomiting, and diplopia can be the signs of increased intracranial pressure. In more advanced cases, somnolence and cognitive impairment may develop. Uncontrolled cerebral edema may lead to herniation when the brain tissue is displaced from one cranial compartment to another in the direction of less resistance. Five common herniation syndromes can occur, either alone or in combination: subfalcine modification (cingulate), uncal (transtentorial), central, upward, and downward cerebellar (tonsillar) herniation (Figure 32.1). Clinical symptoms and findings depend on the type of herniation.

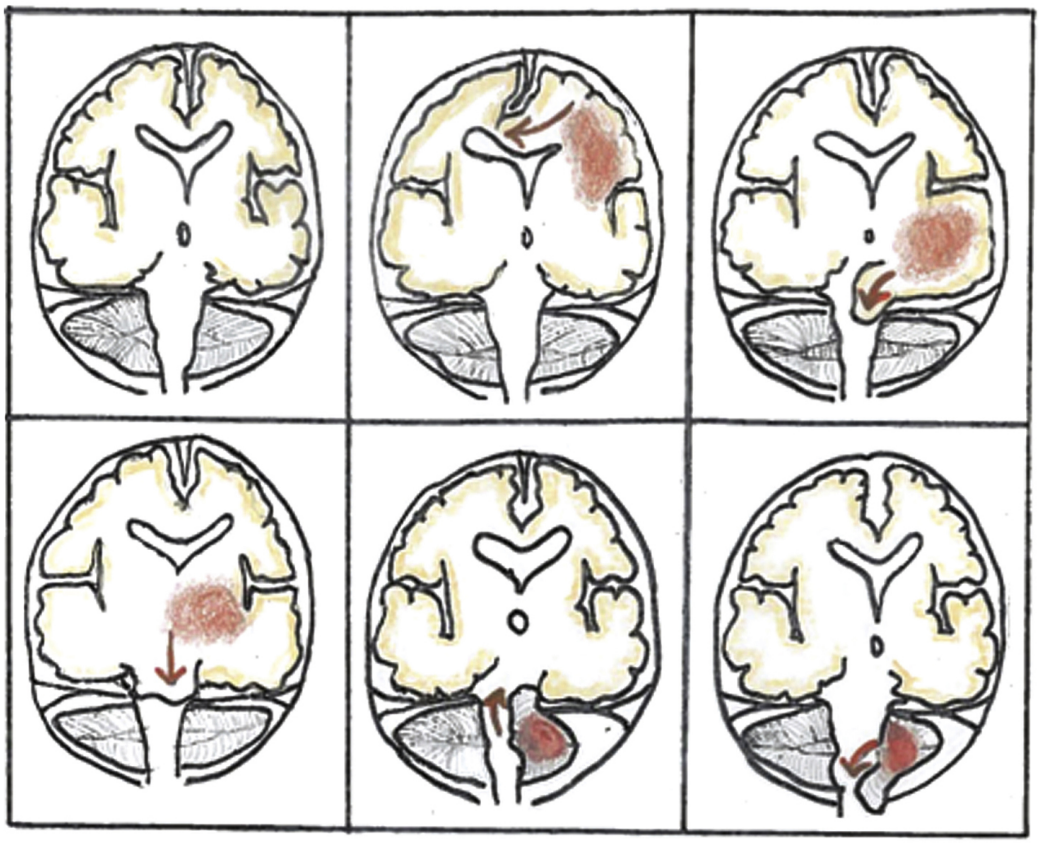

FIGURE 32.1 Herniation syndromes.Legend: top row, from left to right: normal brain, subfalcine herniation, uncal herniation. Bottom row, from left to right: central herniation, upward cerebellar, downward cerebellar.(Edited from a figure courtesy of Heidi Maj.)

TREATMENT CONSIDERATIONS

Therapeutic regimens typically encompass multiple treatment modalities at some point in the course of the disease. To select the best treatment option, careful consideration needs to be done by assessing the individual patient's comorbidities, functional status, genetic markers, expected side effects of the offered treatment, and goals of care. Optimal treatment should balance the quality of life of patients with the goal of prolonging survival.

Surgery

Surgery is the initial component of the management of many CNS tumors. Although occasionally resection can be curative in grade 1 tumors, for higher grade tumors it frequently does not achieve complete tumor removal due to the diffusely infiltrative nature of the disease. Surgery is usually aimed at maximal safe debulking of the tumor burden, where the limit is often set by the vicinity of eloquent brain areas and the related surgical risk of neurologic deficits. Surgery helps in the management of acute symptoms, relieving deficits caused by mass effect, and maximizing the benefits of other therapies by providing less tumor burden to be treated and potentially reducing toxicity risks from increased intracranial pressure and improving seizure control in selected patients. In addition to direct damage to the surrounding normal brain tissue, surgery does carry other risks, such as infection and wound breakdown. Stereotactic biopsy is a minimally invasive procedure for diagnostic purposes with very limited morbidity and mortality estimated to be 4% and 0.9%, respectively. However, biopsy may not provide a diagnosis in up to 5% of cases and it has limited diagnostic accuracy due to the limited sampling. In one study, the diagnosis was changed in 38% of cases when tumor tissue from biopsy was compared to tumor obtained by surgical resection. This discrepancy in pathological diagnosis has significant repercussions in clinical practice, affecting treatment decisions and outcome. In addition, comprehensive molecular diagnosis and clinical trial participation

may be compromised by the small amount of tissue from a brain biopsy.

Radiation Toxicity

The tolerance of normal brain parenchyma to radiation treatment is based on the total dose, the dose per fraction, and the volume of brain treated. Neurotoxicity due to radiation therapy (RT) can be acute, subacute, or delayed and late onset. Acute toxicity occurs during or soon after the treatment. It is self-limiting and thought to be due to edema and demyelination. The clinical syndrome most commonly manifest as fatigue, excessive somnolence, and encephalopathy. Subacute or delayed toxicity is most seen with the first imaging study after completion of radiotherapy but can manifest up to 3 to 6 months later. The imaging findings of this toxicity resemble those of tumor progression and so it cause diagnostic challenges to clinicians. Late effects may occur months to years after the treatment and are often referred to as radiation-induced necrosis. These chronic complications are thought to be due to damage to the normal cellular component of brain parenchyma and alterations in the function and integrity of the cerebral vasculature. There are a wide range of clinical manifestations, including seizures and cognitive dysfunction potentially leading to dementia. In children with an incompletely developed nervous system, radiation treatment can impair growth and development. A unique delayed radiation toxicity has recently been described as SMART syndrome. The disorder is characterized by complex migraine attacks associated with focal neurological deficits resembling stroke. Although no vascular occlusion or hemorrhage is seen, magnetic resonance imaging (MRI) usually reveals gyral enhancement, mild mass effect, and cortical thickening with or without diffusion restriction over the area of radiation field. These imaging changes will appear 2 to 7 days after symptom occurrence. Exposure to ionizing radiation can also lead to other late side effects, such as meningiomas and vascular abnormalities (eg, cavernomas).

Chemotherapy Toxicity

Chemotherapy agents used for brain tumor treatment are typically administered systemically either by oral or intravenous routes. Therefore, typical systemic toxicities occur as with other cancer patients. However, in addition, patients with CNS cancers are at increased risk of neurologic effects, likely the consequence of disease and treatment-induced brain injury. Seizures, neurocognitive impairment, and worsening of focal neurologic function can follow both systemic as well as locally delivered treatment. For example, chemotherapy-induced cognitive changes may represent the effect of DNA damage, telomere shortening, cytokine deregulation, genetic predisposition to increased chemotherapy vulnerability, as well as potentiating effects on cognitive decline from other concomitant treatments.

Targeted Treatments

Treatments targeting molecular signaling pathways that are essential to tumor growth may also impact neurologic function as well as impair the ability of the brain to repair after injury therefore impacting functional recovery. Most of the long-term side effects of the new treatments are unknown; therefore, it is crucial to systematically assess outcomes that aimed to establish the impact of treatments on neurological functions both in the short- and long-term.

FOLLOW-UP AND MONITORING CHALLENGES

The evaluation and assessment of patients with brain tumors to determine treatment response, progression, and treatment side effects can be very challenging. The notion of treatment-induced changes in imaging characteristics complicates the interpretation of imaging studies. For example, treatment-induced inflammatory changes, often called pseudoprogression, will appear as a contrast

enhancing mass with extensive edema. Conversely, some treatments, particularly antiangiogenic therapies, will decrease diffusion of contrast material leading to an improved imaging study but not necessarily indicating a decrease in tumor burden (pseudoresponse). Radiation can also cause damage to the healthy brain tissue, in particular, the white matter, leading to change in appearances even years after treatment. This damage, referred to as radiation necrosis, can continue to increase further mimicking tumor progression, thus increasing the challenges of disease evaluation for the clinician.

In general, postsurgery MRIs should be performed within 48 hours and not later than 72 hours to better detect residual tumor and minimizing postoperative changes that may mimic residual tumor.

New baseline imaging should be done approximately 4 weeks after the completion of radiation treatment. At this time point, increases in MRI contrast enhancement are frequently seen. These changes can be the result of a variety of processes, including treatment-related inflammation, postsurgical changes and ischemia, radiation necrosis, and subacute radiation effects that are difficult to differentiate from true tumor progression. In the first few months after radiation treatment, pseudoprogression is a recognized event. Overall, it is present in up to 25% of patients and more common in patients treated with concomitant chemoradiation compared to those who received radiation treatments alone. Also, patients with methylguanine-DNA-methyltransferase (MGMT)-methylated tumors are thought to be in higher risks for pseudoprogression. Although the pathogenesis is not entirely understood, it is thought to reflect a transient and local reaction characterized by inflammatory response, demyelination, and abnormal vessel permeability due to increased sensitivity to radiation of oligodendrocytes and endothelial cells.

The neuroimaging of pseudoprogression is characterized by increased enhancement on T1 postcontrast sequences (caused by abnormal vessel permeability due to breakdown of the blood-brain barrier) and increased T2 and fluid-attenuated inversion recovery

(FLAIR)-weighted signal (due to edema). Sometimes, but not always, these changes are also accompanied by the absence of increased perfusion. Certain imaging characteristics patterns are also more suggestive for pseudoprogression. Among these, linear pattern of enhancement and periventricular white matter changes can reflect local side effects of radiation treatment or signal active tumor growth. In most patients, the evolution of radiation-related MRI abnormalities is clinically asymptomatic. When symptoms arise, they usually affect general cognitive functioning or preexisting symptoms. Pseudoprogression usually response well to corticosteroid treatment, likely due to its anti-inflammatory effect and stabilization of the blood-brain barrier, but this cannot be reliably used to distinguish this from true tumor progression.

Later, in the disease trajectory, radiation necrosis is a known complication that usually occurs 18 to 24 months after radiotherapy (ranges between 2 months and 5 years). The incidence reports vary but has been reported to occur in 3% to 24% of brain tumors. The pathophysiology is thought to be the consequence of vascular change, edema, and fibrinoid exudate. On imaging studies, radiation necrosis appears as space-occupying lesion with mass effect therefore very difficult to be distinguished from tumor recurrence. It often affects the area of maximum radiation dose and periventricular white matter appearing with an enhancing “soap bubble” appearance. Metabolic studies may be difficult to interpret due to inflammatory activity. MR spectroscopy may help in differentiating from tumor recurrence by showing increased lactate/creatine, decreased choline/creatine, and lack of the 2-hydroxyglutarate (2HG) in isocitrate dehydrogenase (IDH)-mutated tumors. The sensitivity and specificity of MR spectroscopy remains too low to use this methodology as the exclusive means of differentiating tumor from necrosis.

Radiation necrosis can cause symptoms and decline in neurological function. In clinically symptomatic patients, management options include surgery that will confirm the underlying diagnosis and resolve the mass-related complications

and symptoms. Further options include addition of anti-vascular endothelial growth factor (VEGF) treatment to reverse the effect of increased VEGF expression in the white matter following RT that correlates with BBB breakdown and brain edema. This treatment has been proven in a randomized, placebo-controlled clinical trial. A variety of other treatments have been tried (including hyperbaric oxygen therapy, oral vitamin E administration, and laser interstitial thermal therapy) without convincing evidence of benefit.

Conversely, pseudoresponse is a phenomenon that describes imaging changes of signal reduction that are possibly due to "normalization" of the blood-brain barrier and are often associated with anti-VEGF therapies.

PRIMARY BRAIN AND CNS TUMORS

There are more than 130 types of primary brain and CNS tumors. The section will focus on the most common and those of particular scientific interest. The cellular origin for most brain tumors is unknown, and there are no recognized precursor lesions that define a premalignant status. Primary brain tumors are grouped accordingly to their histological appearances (that most closely resemble normal CNS cell constituents) and by their molecular markers. Neuroepithelial cells are thought to give rise to gliomas, pineal tumors, embryonal tumors (such as medulloblastoma), meninges, choroid plexus, germ cells, and sella origin (including pituitary tumors and craniopharyngiomas). Brain tumors are thought to arise from neural stem, progenitor cells, or dedifferentiated mature neural cells that undergo malignant transformation. Glial tumors account for approximately two-thirds of all intracranial tumors with age-related incidence by defined molecular and histological subtypes. Childhood tumors have different incidence, localization preference (ie, posterior fossa with main involvement of the cerebellum), and molecular profiles compared to adult tumors.

Epidemiology

- Primary CNS tumors are relatively rare, accounting for 1.8% of all cancers
- US incidence rate for brain and CNS tumors in adults (>40 years old) is 42.85 cases per 100,000, and 5.83 cases per 100,000 in the pediatric population (0–14 years old)
- The population subgroups at higher risk for brain cancer are elderly, Caucasians, and men
- Incidence rate follows a bimodal distribution, with a small peak in early childhood and more pronounced peak in late middle age
- The higher incidence for older individuals suggests a possible role for bioaccumulation from environmental toxic exposure
- Established environmental causal factors for brain tumors are ionizing radiation and possibly prolonged exposure to hydrocarbons
- Possible protective factors for glioma risk are allergy-related immune responses, elevated IgE, and previous history of chickenpox and/or positive VZV IgG
- According to the Central Brain Tumor Registry of the United States, an estimated 83,830 new cases of primary malignant and nonmalignant brain and other CNS tumors are expected to be diagnosed in the United States in 2020 (24,970 primary malignant and 58,860 primary nonmalignant tumors)
- Five-year survival rates after diagnosis of primary brain tumor progressively decrease with age
- Meningiomas make up 38.3% of all primary brain tumors and are more prevalent in women
- One-third of tumors are malignant, with the most frequent being glioblastoma (GBM) (14.5% of all tumors and 48.6% of malignant tumors)
- Brain and other CNS tumors are the most common form of solid tumors in children (age between 0 and 19 years old)
- Embryonal or primitive neuroectodermal tumors as well as astrocytic lineage tumors are the most frequent before the age of

20 years

Gliomas

Gliomas encompass a heterogeneous group of tumors that affect patients of different ages with often substantial differences in molecular profiles and behavior. Most gliomas in adults diffusely infiltrate the adjacent brain tissue and therefore are often referred as "diffuse gliomas" that encompass grade 2 to 4. Per the 2021 WHO classification, there are three main groups of adult-type diffuse gliomas, categorized as: (1) astrocytoma, IDH-mutant, (2) oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, and (3) GBM, IDH-wildtype (Table 32.2).

TABLE 32.2
Main Groupings of 2021 WHO Classification of CNS Tumors

Name	Grade	*Main Molecular Marker*/Molecular Profile
Adult-type diffuse gliomas		
Oligodendroglioma	2 or 3	*IDH 1 or 2-mutant; 1p/19q codeleted,* TERT promoter mutation, CIC, FUBP1, NOTCH1
Astrocytoma	2, 3, or 4	*IDH 1 or 2-mutant*, ATRX, TP53, CDKN2A/B
Glioblastoma	4	*IDH-wildtype*, TERT promoter, chromosome −7/+10, EGFR
Circumscribed astrocytic glioma		
Pilocytic astrocytoma	1	KIAA 1549-BRAF, BRAF, NF1
Ependymal tumors		
Supratentorial	2 or 3	ZFTA, RELA, YAP1, MAML2
Supratentorial, ZFTA fusion-positive	2 or 3	*ZFTA fusion-positive*
Supratentorial, YAP1-fusion positive	2 or 3	*YAP1 fusion-positive*
Posterior fossa	2 or 3	H3 K27me3, EZHIP (methylome)
Posterior fossa, group PFA	2 or 3	
Posterior fossa, group PFB	2 or 3	
Spinal	2 or 3	NF2, MYNC
Spinal, MYCN-amplified	2 or 3	*MYCN-amplified*
Myxopapillary	2	
Subependymoma	1	
Meningiomas		

Name	Grade	*Main Molecular Marker*/Molecular Profile
Meningioma	1, 2, or 3	NF2, AKT1, TRAF7, SMO, PIK3CA, KLF4, SMARCE1, BAP1 in subtypes, H3K27me3, TERT promoter, CDKN2A/B in grade 3
Embryonal tumors **Medulloblastoma**		
Medulloblastomas, molecularly defined		
Medulloblastoma, WNT activated	4	CTNNB1, APC
Medulloblastoma, SHH activated, and TP53-wildtype	4	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
Medulloblastoma, SHH activated, and TP53-mutant	4	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
Medulloblastoma, non-WNT/non-SHH	4	MYC, MYCN, PRDM6, KDM6A (methylome)
Hematolymphoid tumors **Lymphomas**		
CNS lymphomas		
Primary diffuse large B-cell lymphoma of the CNS		BCL6 gene rearrangement, (14;18) translocation, MYC
Pineal tumors		
Pineocytoma	1	
Pineal parenchymal tumor of intermediate differentiation	2 or 3	
Pineoblastoma	4	RB1, MYC
Papillary tumor of the pineal region	2 or 3	loss of chromosomes 10, 3, and 22q and gains of 8p and 12, PTEN
Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant		
Metastasis to the CNS		
Metastasis to the brain and spinal cord	NA	
Metastasis to the meninges	NA	

Diagnostic Approach and Clinicogenetic Considerations

Genomic alterations driving gliomagenesis pathways have been in the center of attention for a long time. For example, IDH1 or IDH2 mutations have been established as a common initiating event of carcinogenesis in lower-grade gliomas. Progression to more

aggressive tumors is associated with additional genetic changes and more complex chromosomal and genetic alterations.

Specific molecular signatures are now recognized as of crucial biological importance and underpin a new diagnostic approach with significant clinical repercussions and practical relevance in patient's management (Table 32.2). The major distinction for adult gliomas is based on IDH1 or IDH2 mutations as well as 1p/19q codeletion. Compared to IDH-wildtype tumors, IDH-mutant tumors have distinctive biology and clinical behavior that ultimately translates into better treatment response and patient outcomes. Moreover, IDH-mutated tumors, with loss of chromosome arms 1p and 19q (1p/19q codeletion), are associated with longer median overall survival (OS) compared to similar tumors without chromosome loss. On the other hand, there is a very small subgroup of low-grade tumors (6%) that do not harbor an IDH mutation but have some characteristics of pilocytic astrocytoma (BRAF mutation) that have a very low mortality rate. Therefore, the new WHO classification system emphasizes the importance of molecular testing as it has critical clinical relevance in treatment and prognosis.

New Classification: Histopathological and Genetic Considerations

While traditionally the CNS tumor-grading system was based on histological features, the revised WHO classification published in 2016 used molecular parameters for the first time in addition to histology to categorize tumor tissues. For example, it defined oligodendrogliomas by requiring the demonstration of IDH mutation along with 1p/19q codeletion. The role of molecular diagnostics in CNS tumor classification is being further solidified in the 2021 WHO classification. Most importantly, adult-type gliomas that are not oligodendrogliomas are now divided based on IDH status to IDH-mutant astrocytoma and IDH-wildtype GBM.

The list of biomarkers with diagnostic and risk stratification implications has been growing. They provide predictive information

that guide therapeutic decisions for clinicians. In particular:

- O^6-MGMT promoter methylation
- 1p/19q codeletion
- IDH mutation
- BRAF duplication/fusion

Diffuse gliomas in adult and pediatric patients, although with similar histopathologic appearance, are molecularly distinct. Pediatric gliomas rarely have IDH mutations or 1p/19q codeletions. Instead, BRAF and H3K27M mutations are more common, particularly for low-grade and midline tumors, respectively. These findings suggest a different pathogenesis and biology for pediatric brain tumors, mandating different treatment considerations, approaches, and eventually different outcomes.

Imaging: Advanced Techniques and Genetic Implications

Neuroimaging, an evolving area of medicine, is the basis of CNS tumor management. Brain computed tomography (CT) and MRI, as well as structural and functional techniques, provide information regarding the differential diagnoses (abscess, demyelinating plaques, stroke) of a CNS lesion. Certain techniques and sequences are helpful in predicting the grading of a tumor and used for evaluation, treatment planning, monitoring of treatment response, and side effects of therapy (radiation necrosis and pseudoprogression). Advanced neuroimaging is an exciting area of research that aims to find imaging markers related to the genetic profile of a tumor.

Important aspects of imaging studies include:

- CT imaging has a role in the detection of hemorrhage (eg, postoperative), herniation, and hydrocephalus.
- CT imaging is valuable to detect calcifications within the mass, suggesting brain tumor types as oligodendrogliomas or meningiomas.

- Contrast enhancement correlates with local breakdown of the blood-brain barrier and is a key feature of high-grade tumor although there are some exceptions, including some low-grade tumor such as pilocytic astrocytomas in children that do enhance.
- T2/FLAIR signal abnormalities around the mass lesion correlate with peritumoral edema.
- Oligodendroglial tumors typically have a heterogeneous image by contrast-enhanced MRI.
- MR spectroscopy is often used to help differentiate tumor from inflammation or radiation-induced injury although the sensitivity and specificity are low. MR spectroscopy shows peaks of N-acetylaspartate (NAA) decrement (due to processes that destroy or replace normal neurons) and increased peak of choline (due to increased cell turnover).

MR spectroscopy can detect accumulation of 2HG within the tumor in IDH-mutated glioma.

- Perfusion MRI can help differentiating treatment-related changes from tumor recurrence and a helpful tool in planning tumor sampling when contemplating a biopsy.
- MRI with diffusion-weighted imaging can help distinguish a primary CNS lymphoma; an important consideration to avoid profound tumor reduction with corticosteroids leading to a nondiagnostic neurosurgical procedure.

Malignant Gliomas

Malignant gliomas (MG) account for more than 75% of newly diagnosed malignant primary brain tumors in adults and carry a disproportionately high rate of morbidity and mortality despite treatment advances. GBM, grade 4 by WHO criteria, is the most aggressive tumor subtype and accounts for almost half of MG. The 2021 WHO classification now defines GBMs as IDH wildtype. Astrocytoma, WHO grades 2 to 4, typically affects a younger adult population and tend to progress from lower grade to more

malignant cancer over the years. Sometimes, the progression is clinically documented, but other times, patients get diagnosed with grade 4 astrocytoma. All non-GBM malignant astrocytomas are IDH-mutant per the 2021 WHO classification. Although they tend to respond to therapy initially, they eventually develop treatment resistance and lead to death. The only established risk factors for MG are exposure to ionizing radiation and rare familial syndromes, such as Lynch syndrome and Li-Fraumeni syndrome. Approximately 5% of patients with MG have a family history of gliomas. Clinically, patients may present with a combination of generalized and localizing symptoms and signs. Patients often complain of headache that resembling tension-type headache, which is resistant to treatment and progressively getting worse. They sometimes note to have worse headache in the morning with or without nausea and vomiting. This headache is manifestation of increased intracranial pressure due to a mass lesion. Another presenting symptom frequently experienced by brain tumor patient is a new-onset seizure. Imaging studies, most commonly MRI, reveals an irregular, enhancing mass with associated edema and mass effect. Metabolic imaging using fluorodeoxyglucose positron emission tomography (FDG PET) reveals increased glucose uptake, evidence of hypermetabolism. Evaluation of blood flow and tumor blood volume using either MRI with perfusion sequences or single-photon emission computed tomography demonstrates an increase compared to the contralateral uninvolved brain parenchyma.

Patients with MG present with a variety of neurological complications. These include the following:

- Seizures. These are typically focal with possible secondary generalization. Treatment is required and preferably utilizing the newer antiepileptic drugs (eg, levetiracetam, lamotrigine, gabapentin, cenobamate) that do not affect the hepatic cytochrome P450 system, thereby avoiding altering the metabolism and clearance of many systemic cancer treatments.

- Nonlocalized signs such as confusion and mental status alteration. These are often due to peritumoral edema and increased intracranial pressure although seizures may precipitate similar findings. Treatment is typically with corticosteroids, although in some situations, hyperosmotic agents such as mannitol or emergency tumor debulking may be required. Postictal confusion should be on the differential diagnosis and treated as appropriate.
- Localized signs such as hemiparesis, language dysfunction, and visual field loss. The neurologic dysfunction is typically directly related to the location of the tumor. For example, involvement of the dominant cerebral hemisphere, particularly the posterior frontal lobe and temporal lobe may cause aphasia, whereas involvement of the occipital lobe may result in contralateral hemianopia (visual field loss).

Standard treatment for newly diagnosed MG is maximal surgical resection despite the infiltrative nature of gliomas. Advantages are as follows:

- Defining diagnosis that helps prognostication and drives further treatment options.
- Improvement of symptoms resulting from mass effect.
- Studies have demonstrated that the extent of resection correlates with outcome. This is particularly important for medulloblastoma and ependymoma.

Specific considerations for GBM and anaplastic gliomas follow.

Glioblastoma

- The median age at diagnosis with GBM is 65 years, although it can occur at any age.
- Diagnosis with GBM at younger age should raise suspicion for a genetic syndrome.

- In adults, most current series have reported a median survival of 12 to 18 months with standard of care treatment.
- GBMs occur de novo, meaning that patients are diagnosed with this grade 4 malignancy without clinically detecting the transitioning from a lower grade tumor to higher grade.

Molecular Pathogenesis

- GBM presents with a genetic profile of IDH wildtype. Their characteristic molecular genetic profile includes epidermal growth factor receptor (EGFR) gene amplifications, TERT promoter mutation, +7/−10 chromosome copy number changes, PTEN mutation.
- MGMT methylation state is a determination that the gene promoter region is methylated. This is present in 35% to 40% of GBMs and portends increased chemotherapy sensitivity to alkylating agents such as temozolomide. Additionally, some studies suggest that tumors with MGMT methylation may be more prone to develop "pseudoprogression" after treatment with radiation and chemotherapy.

Imaging

- GBM characteristically enhance after contrast administration on both MRI and CT, often have a central necrotic cavity and more peritumoral edema, and are more likely to cross the corpus callosum.

Treatment

Standard of care since 2005 EORTC-NCIC study for newly diagnosed GBM following resection is radiotherapy (RT 60Gy) with concomitant and adjuvant temozolomide. During the concomitant phase, temozolomide is administered at 75 mg/m^2/d 7 days a week for 6 weeks or while radiation lasts. Following chemoradiation, patients get a 4-week-long treatment holiday before they start adjuvant temozolomide at mg/m^2/d for 5 days in a 28-day long cycle.

If the patient tolerates treatment well and there are no major toxicities, the dose of temozolomide can be increased to 200 mg/m^2/d for 5 days in the following cycles. Usually, six cycles of adjuvant treatment are recommended, although other clinical trials and practice have given up to 12 cycles of adjuvant therapy. Even though GBM is a disease of the elderly, there are very few studies designed to assess optimal treatment regimen for patients above 65 years old. This is an important question as elderly patients tend to have more comorbidities and develop more toxicities from cancer treatment compared to younger patients. A recent study addressed this gap in knowledge and showed that a short course of radiation treatment (a total of 40.5 Gy in 15 fractions over 3 weeks) with or without temozolomide was well tolerated in elderly patients. The median number of adjuvant cycles was five. The OS rate has increased from 7.6 months (of the radiation treatment alone arm) to 9.3 months with the combination treatment. The benefit of chemotherapy was even greater in patients with MGMT-methylated GBM.

Although concurrent radiation and temozolomide chemotherapy followed by maintenance temozolomide improves survival, tumor recurrence is inevitable. A variety of second-line therapies are used, although none have clearly demonstrated a survival benefit. They include:

- Implantation of carmustine-containing wafers.
- Cytotoxic chemotherapy agents such as lomustine, procarbazine, irinotecan, carboplatin.
- Bevacizumab, a monoclonal antibody against circulating VEGF, has been reported to improve progression-free survival (PFS), but it does not lead to survival benefit.
- Targeted molecular therapies against regulatory signaling pathways, such as EGFR, PDGF, and mammalian target of rapamycin have been tested; however, none have demonstrated clinical efficacy.
- Immunotherapies are under evaluation for GBM. These treatments include checkpoint inhibitors, peptide and dendritic

cell vaccines, and tumor injections with oncolytic virus.

Prognosis

- Established prognostic factors for GBM include patient age, performance status, extent of tumor resection, and tumor MGMT methylation status.
- Median survival with standard treatment in GBMs is 15 to 18 months with a 2-year survival of 26.5% to 35%.
- Prognosis is improved for patients with MGMT-methylated GBM that have median survival of 21 to 23 months and 2-year survival rate of 40% to 50%.
- Up to 10% of patients with GBM may live 5 years or longer.
- Children with high-grade tumors (grade 3-4) tend to do better than adults, with 5-year survival of 25%.
- Diffuse midline glioma, H3-K27M–mutant was first recognized as a separate entity in the 2016 WHO classification. GBMs harboring this mutation have a different molecular profile and unfavorable outcome.

Astrocytoma

- Astrocytoma affects younger people than GBM.
- Astrocytoma grade ranges from 2 to 4.
- Per the 2021 WHO classification, all astrocytoma harbors IDH-mutation.
- Additional mutations may be found in ATRX, TP53, CDKN2A/B.
- Patients with low-grade astrocytoma have a median survival of 8 to 10 years.
- The optimal treatment of astrocytoma remains under active investigation. Treatment options include maximum safe resection, concomitant chemoradiation followed by adjuvant temozolomide, and targeted therapy. Early results from the CATNON study demonstrated that radiation plus adjuvant temozolomide was superior to radiation alone in grade 3

astrocytoma. The second interim analysis of the study revealed no clinical benefit from concomitant temozolomide but showed clinical benefit from adjuvant temozolomide (for 12 months). Another exciting treatment option for patients with astrocytoma is IDH-targeting agents, such as ivosidenib and vorasidenib, which have shown clinical benefit in patients with hematologic malignancies. In a phase I study, ivosidenib improved the median PFS benefit in nonenhancing gliomas (considered to be low-grade gliomas [LGG]) but not in enhancing gliomas (considered to be high-grade gliomas). Additional targeted treatment options, like poly(ADP-ribose) polymerase (PARP) inhibitors, also show increasing evidence of efficacy in the treatment of astrocytoma.

Oligodendroglioma

- Oligodendroglioma tumors represent 5% to 20% of all glial tumors, with typical age peak at 40 to 60 years and anaplastic tumors preferring older age of onset.
- Per the 2021 WHO classification, oligodendroglioma must harbor an IDH-mutation along with 1p/19q-codeletion.
- Additional mutations may be found in TERT promoter, CIC, FUBP1, NOTCH1.
- Combined loss of 1p and 19q is associated with IDH mutation. Lack of IDH mutation may indicate partial loss of 1p and 19q and should prompt further testing for GBM markers.
- Survival time is prolonged and striking different compared to other gliomas highlighting the different biologic entities and stress the importance of genetic profiling to individualize treatment.
- Oligodendrogliomas are labeled as either grade 2 or grade 3.
- Oligodendrogliomas are more sensitive to chemotherapy than other gliomas. The relative 5-year survival rate for oligodendroglioma is 74.1%.

Low-Grade Gliomas

LGG encompass a heterogeneous group of tumors with astrocytic or oligodendroglial features that usually affects younger patient population and have longer survival. Because the prognosis is better, the long-term consequences of treatment are a critical aspect of determining optimal therapy.

Clinical presentation:

- Seizures are the presenting sign in over 50% cases and more than 80% of patients have a seizure during the disease trajectory. Radiotherapy may transiently decrease the seizure threshold during active treatment but ultimately this treatment leads to improve seizure control in general.
- Other presenting symptoms related to the location of the tumor and may include gradual loss of motor, sensory, language function or visual field loss.

Grade 1 Pilocytic Astrocytoma

Although the designation of low-grade astrocytoma encompasses both grade 1 (pilocytic astrocytomas) and grade 2 diffuse astrocytomas, they are biologically very different and must be considered separately. Most pilocytic astrocytomas develop before the age of 20 years with peak of age around the end of the first decade, and often occur as midline posterior fossa lesion involving the cerebellum, although could manifest in the optic-hypothalamic region and in the brainstem as dorsally exophytic lesions. Surgery is the primary treatment and can be curative. Characteristically, these tumors:

- Are cystic and well demarcated.
- Almost always enhance on MRI with brightly enhancing mural nodule appearance.
- Rosenthal fibers are the pathologic hallmark of pilocytic astrocytoma.
- They often have a tandem duplication of chromosome 7q34 which is associated with BRAF-KIAA fusion gene or the BRAF

V600E mutation.
- Complete surgical excision is typically curative accounting for the excellent prognosis with a 10-year survival rate of 95%.
- Malignant transformation is uncommon but may be associated with radiation treatment.

Grade 2 Diffuse Low-Grade Astrocytoma

Diffuse low-grade astrocytomas are classified as WHO grade 2. These tumors are typically slow-growing but local infiltration of surrounding brain parenchyma prevents cure with surgical resection alone. These tumors commonly occur in young-middle aged adults with median age at diagnosis at 35 to 45 years.

Molecular Pathogenesis

- All grade 2 gliomas have an IDH mutation without 1p19q codeletion.
- Additional genetic testing should include ATRX, TP53, CDKN2A/B and findings may alter grading.

Imaging

- T2/FLAIR hyperintense signal that follows the white matter distribution on MRI.
- Typically, the tumor is nonenhancing on postcontrast T1-weighted MRI sequences. When enhancement is seen, it may indicate that there has been malignant transformation to a higher grade.

Treatment

Maximum safe tumor resection is often pursued as this has important diagnostic and prognostic impact. These tumors may harbor regions demonstrating more malignant cells, thereby altering the diagnosis, prognosis, and treatment. Additionally, there is increasing evidence that extent of resection impacts survival.

There are a wide variety of treatment options, ranging from observation to aggressive combined treatment with radiotherapy and chemotherapy. Following surgery where a gross total resection has been achieved, observation might be a reasonable approach for young (below 40 years of age) and neurologically intact patients with a molecularly confirmed grade 2 astrocytoma. It has been shown that delaying RT does not have an adverse effect on OS but does increase quality that would be otherwise compromised by radiation side effects.

When further therapy is warranted, grade 2 astrocytomas are being treated with radiation followed by chemotherapy with either temozolomide or the PCV (procarbazine; CCNU/lomustine, vincristine) combination regimen. The compared radiation with radiation followed by PCV demonstrated an almost doubling of survival with the combination regimen. Temozolomide for 12 cycles is an appealing choice due to better tolerability and less side effects compared to PCV, but a trial comparing PCV with temozolomide in this patient population has not been completed. Increasing body of evidence support the use of targeted treatment, such as IDH mutation targeting agents or PARP inhibitors, in astrocytoma.

Prognosis

- Median survival of 10 to 12 years
- Potential to transform into higher grade, more aggressive tumors
- Size greater than 6 cm, crossing midline, presurgery neurological deficits, age > 40 years at disease onset are poor prognostic factors

Grade 2 Oligodendrogliomas

Low-grade oligodendrogliomas are three times more frequent than anaplastic tumors, accounting for 2% to 5% of primary brain tumors and up to 15% of all gliomas. They do occur more frequently in young adult males with a peak of incidence between 30 and 40 years,

and although not common, may present with intracerebral hemorrhage due to thin-walled capillary network. They have better prognosis than astrocytomas as they are more chemosensitive.

Molecular Pathogenesis

- Oligodendrogliomas are defined by 1p/19q codeletion and IDH mutation
- Neither ATRX nor TP53 is mutated

Imaging

- Occur more frequently commonly along the convexity in subcortical areas particularly in frontotemporal lobes.
- Appear as partially calcified mass lesions, easily detected as hyperintense on CT imaging particularly along the cortical ribbon as a gyriform pattern.
- On MRI, demonstrate a high signal on T2 and T2/FLAIR sequences.
- Contrast enhancement is not typical for grade 2 oligodendroglioma but could suggest a higher-grade tumor.
- Despite the grade 2 designation, leptomeningeal spread has been reported in 1% to 2% of cases.

Treatment

Optimal treatment remains controversial, centered around when to perform a surgical procedure and when to initiate therapy after surgical resection. Gross total resection may provide prolongation of PFS but the impact on OS has not been proven. Patients with gross total resection who are under the age of 40 years are often carefully monitored without additional treatment until progression. Patients over the age of 40 years or with residual tumor after surgery are typically treated. Results from RTOG 9802 suggest that radiation followed by chemotherapy may be better than radiation alone. Grade 2 oligodendroglioma are chemotherapy sensitive; therefore,

early use of chemotherapy to delay radiation treatment has been used, but this has not been proven to be a comparable approach.

Prognosis

- Median survival of 15 years
- Presence of contrast enhancement on MRI reduces the median survival, likely as this finding indicates a higher-grade tumor.

Ependymomas

Ependymomas range from grade 1 tumors (subependymoma) to grade 3. They are frequent in children especially below the age of 3 years, representing 10% of all intracranial tumors in pediatric population. Although ependymomas are rare in adults, they represent the most common adult tumor of the spinal cord.

- The most common location is the fourth ventricle in children.
- There is positive association with neurofibromatosis type II.
- On neuroimaging, they have typically heterogeneous appearances in all modalities due to areas of necrosis, calcification, cystic change, and hemorrhage.
- Symptoms at presentation depend on tumor localization. Supratentorial ependymomas frequently cause increased intracranial pressure symptoms, infratentorial location gives raise to cranial neuropathies, ataxia and hydrocephalus, and spinal ependymomas often manifest with back pain as well as radiculopathy.
- Incidence of spinal seeding ranges from 10% to 22% with higher rate from infratentorial tumors and from higher tumor grade. Notably, a recently identified subtype characterized by primary spine location and MYCN amplification has an almost 100% rate of cerebrospinal fluid (CSF) dissemination.

Molecular Pathogenesis

The molecular classification stratifies patient risks better than histopathological grading. According to the 2016 WHO

classification, ependymomas are classified based on a combination of histopathological and molecular features as well as the location of the tumor (supratentorial, posterior fossa, spinal compartments). Supratentorial tumors are further subdivided into two groups based on molecular characteristics, one having ZFTA fusion and the other one with YAP1 fusion. Posterior fossa ependymomas either belong to the PSA group or to the PSB group. Spinal ependymomas are categorized based on the presence or absence of MYCN amplification.

Treatment

Surgery is the standard treatment as a complete resection can be curative, particularly for grade 1 ependymomas.

Given the rarity of adult ependymomas, most data related to ependymoma treatment originate from the pediatric population. Current therapeutic strategy includes maximal safe surgical resection, followed by adjuvant radiotherapy. In selected cases, such as supratentorial tumors with no ventricular communication, gross total resection might be an option. Adjuvant chemotherapy has been pursued especially in young children in attempt to avoid or delay RT, but multiple clinical trials have failed to show a survival benefit.

In adults, surgery is the initial approach for low-grade ependymomas. This may be followed by radiation beam therapy depending on diagnostic findings, resection success, and determination of risk of recurrence. Clinical and neuroimaging monitoring including spine imaging are advised as follow-up. In case of recurrence, radiotherapy has been utilized using photon or proton radiation, with focal or craniospinal approach depending on individual risks, previous treatment and response, and dissemination findings. There are few established chemotherapy regimens although carboplatin, cisplatin, and temozolomide have reported responses. Recent combinations temozolomide with lapatinib and carboplatin with bevacizumab have shown activity in recent prospective clinical trials.

Prognosis

- The 10-year OS is about 64% in pediatric patients, with older patients doing better than younger ones. The 10-year OS in adults rages from 70% to 89%.
- Two molecular subgroups of ependymoma (posterior fossa EPN-A subgroup and supratentorial RELA-fusion) have been associated with poor outcome with 10-year OS of 50% and PFS of 20%.
- Recurrence rate is variable, usually occurring between 18 and 45 months, and traditionally with local relapses except for the MYCN-amplified tumors.

Non-Glial Tumors

Non-glial tumors of the brain are more commonly meningiomas and acoustic schwannomas, followed by embryonal tumors, pituitary tumors, primary CNS lymphoma, as well as tumors of the pineal gland and choroid plexus tumors. Rare tumors are slightly more common in men than in women, occurring across age ranges depending on tumor types and being characterized by longer survival rates than glial tumors. Detailed discussion of rare tumors is beyond the scope of this chapter. The following section will focus on the most common and those of relevance for specific age group or population subgroup.

Meningiomas

Meningiomas are extra-axial tumors that arise from arachnoid cap cells. They account for 33.8 % of all brain and CNS tumors and are the most common brain tumors diagnosed above the age of 34 years. Although they are usually benign, they can be associated with significant morbidity. Female sex, age, ionizing radiation exposure especially at childhood, and genetic condition (such as neurofibromatosis type II and MEN1) are recognized factor risks. Other possible predisposing factors are hormones, increased body index, and immunological factors. Meningiomas are classified as

benign (grade 1), atypical (grade 2), and anaplastic (grade 3). They have 15 subtypes based on distinct histological features. The 2016 WHO classification has defined brain invasion as criteria for the diagnosis of grade 2 atypical meningioma. The 2021 WHO classification emphasized the importance of molecular biomarkers and their prognostic value.

Molecular Pathogenesis

- Common feature in sporadic meningiomas is the deletion and inactivation of NF2 gene on chromosome 22.
- Additional genetic biomarkers include AKT1, TRAF7, SMO, PIK3CA, KLF4, SMARCE1, BAP1, H3K27me3, TERT promoter, CDKN2A/B.
- Malignant meningiomas have more genomic instability with multiple chromosomal copy number alterations, including loss of 1p, 10q, and 14q, and less frequently 6q and 18q.
- Familial meningiomas usually have germline defect in NF2 and other predisposing mutations.
- Research is undergoing to identify specific mutations that could serve as potential therapeutic targets (such as SMO and AKT).
- Epigenetic aberration as DNA methylation events may be predominant in meningioma biology.

Diagnosis

They are usually benign and slow-growing tumors with insidious onset. Most meningiomas are diagnosed incidentally in asymptomatic patients. In other cases, they present with focal neurological signs related to their location or due to mass effect. The most common locations in descending order are convexity, parasagittal, sphenoid, and middle cranial fossa.

Imaging

- Imaging hallmarks of meningiomas include broad dural base and dural tails.

- They are hypodense or isodense on T1 images and hyperdense or isodense on T2 sequences. On T1 postcontrast MRI, they show homogeneous enhancement.
- Calcification may predict decreased growth potential.
- X-ray and CT can display hyperostosis or lytic lesions by direct invasion or primary intraosseous meningiomas.
- Alanine peak, decreased NAA, and distinct peak of the chemical substance resonating at 3.8 ppm detected by MR spectroscopy are unique to meningiomas.
- Cerebral angiography and MR venogram to assess patency of dural-based blood sinuses are useful in planning treatment, particularly surgical morbidity and urgency of treatment intervention.

Medical Management

The treatment of meningiomas is specifically tailored for each patient after careful consideration of risks and benefits of clinically proven interventions, including neurosurgical intervention and RT. Incidentally found asymptomatic meningioma may only require observation. In symptomatic or rapidly growing meningiomas, surgical intervention is preferred if the tumor is accessible. It is preferred to surgically remove lesions before they compromise healthy tissue and cause irreversible damage in the surrounding area. Besides providing clinical improvement, the advantage of a surgical resection is to obtain tissue diagnosis with molecular characterization. Rapidly growing tumors or those with aggressive molecular features may require further treatment with radiotherapy. Observation with no treatment intervention may be pertinent in asymptomatic tumors in elderly as they are exposed to increased morbidity risks from treatment. Careful evaluation and consideration should be given to women of child-bearing potential with meningiomas because it may lead to tumor growth as a consequence of excessive hormone production during pregnancy. In addition, conflicting data have been published regarding the link between meningioma and hormonal replacement therapy (HRT) use

but larger studies seem to confirm this positive association raising questions regarding HRT use in women.

Treatment

- Treatment goal is complete surgical resection, as it has a main impact on preventing recurrence.
- Radiotherapy is typically performed on surgically not accessible lesions, for grade 3 meningiomas and incompletely resected grade 2 tumors. Radiation treatment for incompletely resected grade 1 and completely resected grade 2 meningiomas remains controversial.
- Chemotherapy is considered in recurrent meningiomas refractory to other treatment or when there are no other treatment options. Although no chemotherapy has been approved for the treatment of meningiomas yet, clinical trials are underway to assess the benefit of targeted therapy (for example hormonal therapy, somatostatin receptor agonists, and VEGF signaling pathway inhibitors).

Prognosis

- Approximately 80% of meningiomas are grade 1 meningioma.
- Recurrence rate varies from 5% to 20% within 10 years and increases with the length of follow-up.
- Deletion of 1p is associated with higher recurrence rate.
- Loss of 14q and loss of 9p with a specific CDKN2A impairment is associated with worse prognosis.

Medulloblastoma

Medulloblastomas are the most common malignant brain tumor of childhood, accounting for up to 25% of all pediatric CNS tumors and 40% of pediatric posterior fossa tumors. Around 80% of patients present between the age of 1 and 10 years. Most commonly, they present as midline masses in the roof of the fourth ventricle. In the adult population, where they account for 0.4% to 1% of brain

tumors, they present in the third or fourth decade in atypical location. Medulloblastomas are associated with a variety of genetic syndromes as Coffin-Siris, Cowden, Gardner, Gorlin, Li-Fraumeni, Turcot, and Rubinstein-Taybi syndromes.

Molecular Pathogenesis

Medulloblastoma classification has undergone major reconstruction in the 2016 WHO revision. The combination of four histological groups and four genetic variants stratifies the prognostic risks and outcome of patients from low-risk tumors (WNT-activated) to high-risk tumors (SHH-activated/TP53 mutant, and non-WNT/non-SHH).

- Up to 40% of medulloblastomas present abnormalities of chromosome 17.
- TP53 mutation has no prognostic implication on WNT subgroup, while it does affect prognosis on SHH subgroup almost doubling 5-year OS in the p53 wild-type tumors.

Diagnosis

Half of the patients have a short interval of 6 weeks prior to diagnosis while they experience progressively worsening symptoms related to intracranial hypertension and hydrocephalus (papilledema, headache, recurrent vomiting). They also often develop symptoms of cerebellar dysfunction, including ataxia, nystagmus, and appendicular dysmetria.

Imaging

Typically, CT and MRI reveal a contrast enhancing posterior fossa mass on the midline:

- 94% of pediatric medulloblastomas localize in the cerebellum and three quarter in the vermis.
- Adult medulloblastomas localize in the cerebellar hemispheres.
- Iso to hyperintense to gray matter in T2/FLAIR sequences with heterogeneous appearance due to cystic formation and presence of calcification and necrosis.

Treatment

Standard therapy consists of surgical resection followed by craniospinal irradiation (36 Gy or reduced 24 Gy in localized disease) with boost to the primary tumor site (32.4 Gy) and metastatic sites. Treatment in pediatric population with medulloblastoma is stratified on risk-adapted strategies, and studies are being carried out to evaluate the risk/benefit ratio of reducing further radiation dose to the neuraxis in children to 18 Gy. Radiotherapy in children below the age of 3 years is controversial because of the more severe neurodevelopmental effect of the treatment, and chemotherapy is often used to fill the interval gap before RT could be given with less long-term side effects burn.

- In average-risk patients with nondisseminated disease, reduced dose RT with adjuvant chemotherapy consisting in eight cycles of lomustine (CCNU), vincristine, and cisplatin regimen has been beneficial showing 3-year PFS rate of around 80%.
- In high-risk patients, chemotherapeutic agents typically used are cisplatin, carboplatin, cyclophosphamide, and vincristine.
- In recurrent disease, attempts with high-dose chemotherapy (cyclophosphamide) and with stem cell harvest for possible transplant have been tested, and treatments targeting molecular pathways such as SHH are under investigation.

There are few evidence-based guidelines for treatment in the adult population, and treatment considerations are modeled by data extrapolation from the pediatric experience. Surgery followed by craniospinal radiotherapy at 36 Gy with boost of 18.8 Gy to the origin tumor site in partial resection is the mainstream treatment approach. New therapies are evaluated in clinical trials based on subgroup molecular profiling of medulloblastomas.

Prognosis

- Disease-wide 5-year survival stands at 60% to 70%.
- 17p loss has been associated with poor outcome.

- MYC gene amplification and TP53 mutations are prognostic factors of poor outcome.
- Metastatic disease at diagnosis (seeding in one-third of patients at diagnosis), age < 3 years, and disease relapse are very poor prognostic factors.
- Staging evaluation is important and has been historically based on tumor size and extent of metastatic disease (spinal dissemination, bone marrow invasion) by Harisiadis and Chang in 1977.
- Despite 5-year survival rates with current therapies up to 80%, current treatment toxicity and long-term sequelae significantly impact the neurological and neurocognitive development of pediatric patients.

Primary CNS Lymphomas

Primary CNS Lymphomas (PCNSL) are extranodal high-grade non-Hodgkin B-cell lymphomas (NHL) arising in the CNS (brain, eyes, leptomeninges, spinal cord) that are diagnosed in the absence of systemic lymphomas and that typically remains in the brain. They account for 3% to 5% of all brain tumors and 1% of NHL. After a steady increase in incidence since the end of the 20th century, over the past decade, there has been a plateau or even a decrease in incidence of PCNSL among immunodeficient patients. This change is most likely linked to improved treatment and outcome of HIV/AIDS patients. Nonetheless, the incidence among immunocompetent elderly population remains high, with median age at diagnosis of 60 years.

Risk Factors

A prominent risk factor for the development of PCNSL is immunodeficiency due to congenital disorders, iatrogenic immunosuppression, and most notably, HIV that historically increased the risk of developing PCNSL by 3600-fold. It is also strongly associated with Epstein-Barr virus (EBV) infection in

immunosuppressed patients and immunocompetent elderly patients treated with mychophenolate mofetil, methotrexate, or azathioprine.

Diagnosis

CNS lymphoma usually presents with increased intracranial pressure and focal neurologic symptoms. Elderly patients more commonly present with change in behavior and personality. A profound steroid-induced response is classic but may prevent a tissue diagnosis; therefore, steroids should be withheld until tissue confirmation of diagnosis. CSF analysis highlights lymphomatous cells in 10% to 30% of patients. High suspicion is raised in HIV/AIDS patients with classic lesion on brain imaging and positive EBV DNA in the CSF. As systemic involvement is rare, staging is often achieved through neuroimaging, HIV testing, CSF analysis, ocular slit-lamp examination, and clinical assessment. In selected cases, body CT scan and bone marrow biopsy are pursued. For occult lymphoma, FDG body PET is required.

Imaging

- CNS lymphoma typically manifest on MRI or CT as homogeneously enhancing solitary (two-thirds of cases) or multiple lesions in the periventricular areas.
- Ring enhancement is more commonly seen in immunodeficient patients.
- Rapid leakage of contrast medium is reflected by distinct signal-time intensity curves.
- Significant elevation of lipid resonance at spectroscopy studies is detected.

Treatment

The treatment of primary brain lymphoma has made advances and increasing number of patients can achieve long-term remission. The standard of care for PCNSL is systemic chemotherapy with or without whole-brain radiotherapy (WBRT) or intrathecal chemotherapy. Traditionally, surgery has been discouraged apart

from diagnostic biopsy, but this paradigm has been challenged by a German PCNSL study group that showed increased PFS and OS in patients undergoing subtotal or gross total resection. WBRT usually at dosage of 40 to 50 Gy has several limitations including delayed neurotoxicity especially on neurocognitive functions, while low-dose radiation (23.4 Gy) in patients older than 60 years, the group most prone to late radiation effects does not seem to have comparable efficacy to the higher dose regimens. High-dose methotrexate has been used as induction chemotherapeutic regimen, and it is usually coupled with preventive measures to limit its side effects. High-dose chemotherapeutic consolidation has been investigated in a further attempt to decrease the need for radiation. Although several regimens are in use, most centers incorporate high-dose cytarabine and etoposide. For newly diagnosed PCNSL patients, a novel program has evaluated immunochemotherapy combination regimen (induction consisting of methotrexate, temozolomide, and rituximab followed by consolidative infusional etoposide plus high-dose cytarabine), with promising results. In recurrent disease, a key consideration is whether the lymphoma is methotrexate-sensitive, enabling retreatment. Other salvage treatments including autologous stem-cell transplantation are under study.

Prognosis

The significant advances in PCNSL treatment have led to improved outcomes so that between 40% and 50% of PCNSL patients will exhibit long-term survival and a significant proportion may be cured. Nonetheless, research stresses the importance of future developments as at least 40% to 50% of PCNSL patients will develop disease refractory to the current treatment agents.

Pineal Region Tumors

Most pineal region masses are malignant cell tumors. They usually occur in young male patients, the most frequent being germinoma. Given the location, these tumors can compress the aqueduct resulting in hydrocephalus. Symptoms are therefore related to

increased intracranial pressure with headache, nausea and vomiting, and cranial nerve palsies. When tumor compresses the superior colliculi, it leads to Parinaud syndrome characterized by impaired upgaze, convergence and retraction nystagmus, eyelid retraction, also called Collier sign, and pupillary light-near dissociation. Tumor markers such as α-fetoprotein, α-human chorionic gonadotropin, and placental alkaline phosphatase may be increased.

Pineal region masses give rise of a wide differential due to the variety of cell types in the region. Several characteristics may help differentiating them although biopsy is indicated for diagnosis confirmation:

- Germ cell tumors, half of which being germinoma, usually appear as homogeneous mass with signal intensity and attenuation similar to those of gray matter; engulfing a densely calcified pineal gland.
- Per the WHO 2021 classification, they include pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, papillary tumor of pineal region, desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant.
- Pineal parenchymal tumors demonstrate calcifications dispersed peripherally to the mass on neuroimaging.
- Pineal cysts often have a rim thin enhancement at contrast imaging.
- Tentorial meningioma tends to depress cerebral veins, while intrinsic pineal tumors tend to cause upward displacement of the internal cerebral veins.
- Tectal astrocytoma are slightly hyperintense on T2-weighted MRI images, can present cystic spaces and calcifications, and usually do not or minimally enhance on postcontrast T1 MRI images.

Diagnostic evaluation should include craniospinal MRI and CSF analysis. Molecular studies play an increasingly important role in the diagnosis. Biopsy should be pursued depending on the

suspected lesion. Stereotactic or endoscopic approach is preferred in germinoma or tectal glioma and microsurgical techniques for open biopsy in other cases. RT is first-line treatment for germinomas. Craniospinal radiotherapy associated with adjuvant chemotherapy is pursued when there is evidence of CSF seeding or malignant tumor.

Metastatic CNS Tumors

Tumor cells detaching from systemic tumors spread hematogenously into the CNS by producing and secreting angiogenic substances that enable them to open the blood-brain barrier locally. Different cancers show different intracranial compartment tropism.

Brain Metastases

Brain metastases occur in 15% to 40% of patients with systemic cancer. Although the true incidence of metastatic brain tumors remains unknown, it is following an increasing trend likely due to better control of systemic cancer and prolonged survival. Still, it remains undetected in 15% of patients. The most frequent primary tumor origin is lung, breast, melanoma, and colorectal. Hematological tumors constitute 10% of brain metastases and primarily affect the leptomeninges. Presentation is usually with focal neurologic deficits related to mass compression, edema, and increased intracranial pressure. From a neuroimaging point of view, lesions are characteristically localized at the gray/white matter junction and are surrounded by significant edema with higher edema/tumor size ratio. Most metastatic brain lesions are hypointense on T1-weighted images on MRI and hyperintense on T2-weighted images.

Medical management usually includes oral steroids to decrease the edema. Due to its optimal CNS distribution, dexamethasone is preferred at 4 to 8 mg/d or up to 16 mg/d for severe symptoms. One quarter of patients do present with seizure and antiepileptic

treatment is indicated. Prophylactic seizure prevention is not recommended for patients with known brain metastasis without history of seizures in general. The perioperative period is an exemption as many patients receive a 1- to 2-week-long course of antiepileptic drug treatment following brain surgery.

The treatment of brain metastases is individualized and tailored in the context of the primary tumor and the patient's overall systemic options. Depending on the primary tumor staging and grading, brain metastases treatment may encompass surgery, radiotherapy, and in certain cases, chemotherapy for chemosensitive tumors such as small cell lung carcinoma, germ cell tumors, and lymphoid neoplasms. To select the optimal chemotherapeutic agent for the treatment of brain metastasis, one must consider the chosen drug's blood-brain barrier permeability in addition to cancer's predicted drug sensitivity. The overall prognosis is often below a year of survival, but there is a wide heterogeneity that can be stratified depending on the status of the primary (systemic) disease, age of the patient (>65 years), functional status of the patients, Karnofsky performance score (KPS < 70), the number of metastatic lesions (single or multiple). Treatment effectiveness and neurotoxicity needs to be well balanced as the goal of therapy has shifted from short-term palliation to long-term survival and quality of life. Hence, WBRT is less preferable in situations where stereotactic radiosurgery and systemic agents are reasonable options. Surgical treatment with removal of brain parenchyma adjacent to the metastatic lesion confers better local control than gross total resection. The pathologic confirmation of tumor-free resection margins provides rate of local recurrence comparable to standard gross total resection and adjuvant radiotherapy.

Spinal Metastases

Metastases of the spine most frequently involve vertebral elements and epidural space. The most commonly seen source of spinal metastasis includes cancers of the lung, breast, liver, and prostate. Management includes tailored approach depending on the

localization of the metastasis, clinical symptomatology, and previous treatments. Treatment may include combination of steroids, surgery, radiation, and chemotherapies. Spinal cord compression due to tumor extension into the spinal canal is a true oncologic emergency and carries the risk of permanent neurologic deficits especially if the lesion compromises the vascular supply of the spinal cord. Depending on the location, spinal metastasis can be categorized as vertebral, leptomeningeal, intradural extramedullary and intramedullary metastases.

Neoplastic Meningitis

Meningeal involvement can occur by local infiltration or by dissemination of tumor cells by the cerebrospinal flow. Seeding of the leptomeninges by malignant cells may occur in primary brain tumor patients as well as in cancer patients for both hematological (more frequent) and solid (breast, lung, and melanoma) tumors in a percentage that is variable from 1% to 15%. Extensive investigations with contrast MRI of the brain and spine, as well as repeated high-volume lumbar punctures for CSF analysis are needed as CSF cytology may be negative in almost half of the patients. Neoplastic meningitis causes progressive neurological dysfunction. Treatment with focal radiation to areas of bulk disease may improve the clinical symptoms. In individual cases, intrathecal chemotherapy may be of benefit. More recently, selected chemotherapy agents have been systemically administered at high doses to generate therapeutic concentrations within the CSF. The optimal treatment of patients with leptomeningeal cancer is based on consideration of the primary cancer type, patient's performance status, CSF disease burden, and extent of systemic disease. Even with new therapies, neoplastic meningitis is associated with poor prognosis.

SUMMARY

Treatment of cancer in the CNS is complicated. Primary brain tumors, while rarely spreading outside of the CNS, are typically

invasive therefore not curable with surgery. Radiation and chemotherapy regimens have been developed for most primary brain tumors and are being increasing refined by tumor type and recently molecular subtypes, underscoring the importance of accurate histologic and molecular classification. Secondary CNS cancers (brain and leptomeningeal metastases) are often late complications of systemic cancer, and optimal treatment is based on the cancer type and stage or extent of the systemic disease. In all patients, realistic appraisal of treatment outcomes in the context of both short- and long-term toxicities highlights the need for systematic evaluation of patient outcomes to provide patients with cancer information necessary for informed decision-making.

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33

Endocrine Tumors

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INTRODUCTION

Endocrine tumors arise from hormone-secreting glands. They may be sporadic or part of a familial cancer syndrome (Table 33.1), the most common being the multiple endocrine neoplasia (MEN) syndromes. With the exception of thyroid cancer, endocrine tumors are often difficult to diagnose and treat effectively. They may cause morbidity and mortality through local and distant metastasis or through systemic effects caused by hormones produced by tumor cells. While relatively uncommon as a group, thyroid cancer has increased in incidence over the last decade more than any other malignancy. The most common endocrine tumors include the following:

TABLE 33.1

Hereditary Endocrine Cancer Syndromes

Familial Syndrome	Associated Malignancies	Gene Mutated
MEN 1 (Werner syndrome)	Pituitary adenomas Functioning pancreatic neuroendocrine tumors (insulinoma, gastrinoma) Nonfunctioning pancreatic neuroendocrine tumors Parathyroid hyperplasia/adenomas causing hyperparathyroidism Peptic ulcers (with Zollinger-Ellison syndrome) Bronchial, thymic, gastric carcinoid	*MEN 1*
MEN 2A (Sipple syndrome)	Medullary thyroid cancer Pheochromocytoma Primary hyperparathyroidism (parathyroid hyperplasia)	*RET*
MEN 2B	Medullary thyroid cancer Pheochromocytoma Marfanoid body habitus Multiple mucosal and digestive neurofibromas Megacolon	*RET*
Familial medullary thyroid cancer (MTC)	MTC in kindreds with 4-10 or more affected members	*RET*
Neurofibromatosis 1	Carcinoids Pheochromocytomas/paragangliomas Pancreatic neuroendocrine tumors Gastrointestinal stromal tumors	*NF1*

Familial Syndrome	Associated Malignancies	Gene Mutated
von Hippel-Lindau syndrome	Pheochromocytomas Pancreatic neuroendocrine tumors Hemangioblastomas Retinal angiomas Renal cell carcinomas Endolymphatic sac tumors Epididymal papillary cystadenomas	*VHL*
Li-Fraumeni syndrome	Adrenocortical cancer Breast cancer Sarcoma Leukemia Brain tumors	*TP53*
Beckwith-Wiedemann syndrome	Adrenocortical carcinoma Wilms tumor Rhabdomyosarcoma Neuroblastoma Hepatoblastoma	Multiple in the 11p15 region
Carney complex	Adrenocortical tumors Thyroid follicular neoplasms Pituitary adenomas Myxomas Schwannomas Sertoli cell tumors Leydig cell tumors	*PRKAR1A*
Familial polyposis coli	Thyroid carcinoma Sarcoma Hepatoblastoma Pancreatic carcinoma Medulloblastoma Adenomatous colon polyps	*APC*
Cowden syndrome	Follicular thyroid cancer Breast cancer Endometrial carcinoma	*PTEN*
Peutz-Jeghers syndrome	Thyroid cancer, benign ovarian sex cord tumors, calcifying Sertoli tumors of the testis, endometrial cancer, breast cancer, gastrointestinal cancer, pancreatic cancer, cervical cancer	*STK11/LKB1*
Hyperparathyroidism-jaw tumor	Parathyroid cancer, ossifying fibromas of the jaw, cystic and neoplastic renal lesions, uterine tumors	*HPRT2*

- Thyroid carcinoma
- Pheochromocytoma (PHEO) and paraganglioma (PGL)
- Carcinoid tumors
- Pancreatic neuroendocrine tumors (NETs)
- Adrenocortical carcinoma (ACC)
- Parathyroid carcinoma

THYROID CARCINOMA

General

Epidemiology

- Thyroid cancer is the most common endocrine malignancy and its incidence has been increasing over the last decade.
- The incidence of thyroid carcinoma is now about 9 per 100,000, with approximately 2.7 to 3.1 times as many women as men affected (in women at a rate >5% per year). The ratio of female to male patients is approximately 3:1.
- In 2021, the estimated new cases and death of thyroid cases in the United States is 44, 280 for new cases (2.3% of all new cancer cases) and 2200 deaths (0.4% of all cancer deaths).
- Mortality has also been rising for the past 2 decades. The precise reasons for the increase in incidence and mortality are unknown.

Risk Factors

- The best-established risk factor for thyroid cancer is head and neck radiation exposure during childhood for diseases such as Hodgkin lymphoma; hereditary factors, family history of thyroid cancer and with mutations in the *RE*arranged during *T*ransfection (*RET)* proto-oncogene; history of goiter or thyroid nodule; and/or preceding autoimmune thyroid disease.
- Autoimmune thyroid disease is more prevalent in women, and this may explain why thyroid cancer is more common in women that in men.
- Thyroid cancer has been observed to appear as early as 5 years and as late as 20 to 25 years after radiation exposure among atomic bomb survivors, and in some regions of Japan, the incidence of thyroid cancer in screened populations is as high as 0.1%—10-fold greater than expected based on US incidence rates.

Prognosis

- Prognosis varies by thyroid cancer subtype. Between 2011 and 2017, the overall 5-year relative survival is approximately 98.3%. This is because more than 80% of cases are papillary thyroid cancer (PTC), the subtype with the best survival.

Differentiated Thyroid Cancer: Papillary, Follicular, and Hürthle Cell

- More than 90% of all thyroid cancers are a subtype of differentiated thyroid cancer (DTC), with PTC being the most common subtype (80%-85%).
- PTC is generally unilateral, but may be multifocal within a lobe. Histologic subtypes of PTC that have a worse prognosis include tall cell variant, columnar cell variant, and diffuse sclerosing variant. A worse prognosis is also seen with highly invasive variants of follicular cancer, which is characterized by extensive vascular invasion and invasion into extrathyroidal

tissues or extensive tumor necrosis with many mitoses. PTC metastasizes primarily via lymphatic invasion; vascular invasion is uncommon.

- DTCs are derived from thyroglobulin (TG)-producing follicular cells (thyrocytes), often secrete TG, and are typically initially radioactive iodine (RAI) responsive. TG can be used as a tumor marker in anti-TG antibody–negative patients.
- Genetic alterations involved in the mitogen-activated protein kinase signaling pathway are found in at least 75% of PTC cases. *BRAF* ^{V600E} mutation is found in approximately 45% of PTCs, while *RET* is found in approximately 25%. Activating point mutations in the *RAS* oncogenes occur in approximately 10% of cases. RET rearrangements are found in approximately 25%, and upregulation of vascular endothelial growth factor (VEGF) signaling is also common in metastatic disease. NTRK1 fusions can be found in up to 12% in DTC.
- Follicular thyroid cancer (FTC) is the second most common type of thyroid carcinoma, comprising 10% to 15% of thyroid cancers. FTC typically disseminates hematogenously, with metastases to the bone and lung being most common in advanced disease.
- *RAS* point mutations and the *PAX8*/*PPARγ* translocation are the most common genetic alterations in FTC.
- Hürthle cell cancer is also referred to as oxyphilic or oncocytic thyroid cancer and represents approximately 5% of all DTCs. It is often considered a variant of FTC with less sensitivity to radioiodine and a more aggressive clinical course.

Clinical Presentation

- Most patients present with an asymptomatic thyroid nodule. Clinical symptoms may include the following:
  - Hoarseness caused by invasion of the recurrent laryngeal nerve or by direct compression of the larynx
  - Cervical lymphadenopathy
  - Dysphagia
  - Horner syndrome (miosis, partial ptosis, hemifacial anhidrosis)

Diagnosis

- Evaluation of any suspected thyroid nodule > 1 cm should include a serum thyroid-stimulating hormone (TSH) and thyroid ultrasound. Occasionally, thyroid nodules < 1 cm require evaluation because of suspicious ultrasound findings, associated with lymphadenopathy, head and neck irradiation, or a family history of thyroid cancer.
- If a nodule is seen on ultrasound
  - If TSH is normal or high, a fine-needle aspirate (FNA) should be done.

    - If the TSH is low, the nodule should be evaluated by radionuclide thyroid scan with either a ^{99m}Tc pertechnetate or ^{123}I to see if it is hyperfunctioning. Hyperfunctioning nodules are benign and patients with them should be treated for hyperthyroidism.
- Up to 30% of FNAs are indeterminate; therefore, a definitive diagnosis is often not made until the nodule is resected. A new gene expression classification assay was able to predict benign pathology when FNA cytology was indeterminate (eg, BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, PAX8-PPARγ) and may allow a more conservative approach for those who would otherwise undergo a diagnostic surgical procedure. If the cytology reading reports follicular neoplasm, a lobectomy or total thyroidectomy should be considered.
- Carcinoma is suggested by the following clinical findings: a history of head and neck radiation, family history of thyroid cancer, exposure to ionizing radiation, rapid growth of the nodule, hoarseness, vocal cord paralysis, and lymphadenopathy. There may also be specific features on ultrasound that are suggestive of possible malignancy.
- Staging for DTC incorporates age. For patients aged 45 years or younger, the most advanced they can be is stage II given their excellent prognosis.

Treatment

Surgery

- Total thyroidectomy is recommended for a DTC lesion >1 cm, a lesion that extends beyond the thyroid, or for patients with history of prior exposure to ionizing radiation to the head/neck.
- Unilateral lobectomy with en bloc resection of tumor may be considered for a DTC lesion < 1 cm or for follicular lesion with no evidence of multicentric disease.
- Total thyroidectomy with modified radical neck dissection should be done for regional lymph node metastases.
- Thyroidectomy should be performed in patients with distant metastases to permit treatment with radioiodine, which can still be curative.
- Mortality consequent to thyroidectomy in DTC is extremely low. Complications include recurrent laryngeal nerve damage in 2% of patients and hypoparathyroidism that is lifelong in 1% to 2% of patients.

TSH Suppression

- TSH suppression via administration of "supratherapeutic" levothyroxine is an essential component in the treatment of high-risk DTC, as residual cancer cells are usually initially responsive to TSH growth stimulation. Levothyroxine (T_4, usual dosage range 125-200 μg by mouth daily) is administered to keep the TSH level suppressed below 0.1 mIU/L in high-risk (macroscopic tumor

invasion, incomplete tumor resection, distant metastases) to intermediate-risk patients (microscopic invasion of tumor into the perithyroidal soft tissues, cervical lymph nodes metastases, tumor with aggressive histology, or vascular invasion).

- For low-risk patients, the goal is to maintain TSH below the lower limit of normal 0.1 to 0.5 mIU/L.
- Suppression of TSH below 0.1 mIU/L imposes long-term adverse effects on the bone and can negatively impact quality of life, sometimes producing symptoms of thyrotoxicosis.

Adjuvant Therapy

- Treatment with radioiodine (^{131}I, RAI) is used to ablate normal residual thyroid tissue, treat micrometastases, and decrease cancer-related death, tumor recurrence, and development of distant metastases. Table 33.2 outlines indications for iodine-131 treatment after surgery.

TABLE 33.2

Indications for Postsurgical Treatment With Iodine-131 in Patients With Thyroid Cancer

	Iodine-131	
Finding	**Indicated**	**Not Indicated**
Low risk of cancer-specific mortality or relapse		X
Incomplete excision of tumor	X	
Complete excision of tumor but high risk of mortality	X	
Complete excision of tumor but high risk of relapse due to	X	
Age (<16 y or >45 y)		
Histologic subtype (tall cell, columnar cell, diffuse sclerosing papillary variants; widely invasive or poorly differentiated follicular subtypes; Hürthle cell carcinomas)		
Extent of tumor (large tumor mass, extension beyond thyroid capsule, lymph node metastases)		
Distant metastases	X	
Elevated serum thyroglobulin >3 mo postsurgery	X	

- Adjuvant external beam radiotherapy is sometimes recommended for those patients with gross or microscopic residual disease or those with high-risk histology and visible extrathyroidal extension. Locally recurrent disease not amenable to surgery or radioiodine therapy can also be treated with external beam radiotherapy.

Targeted Therapy/Chemotherapy

- Several vascular endothelial growth factor receptor (VEGFR) inhibitors have been shown to have activity in well-differentiated thyroid cancers and two—sorafenib and lenvatinib—have received Food and Drug Administration

(FDA) approval on the basis of randomized phase III trials for patients with advanced disease that is refractory to iodine-131.

- Sorafenib is an inhibitor of several protein tyrosine kinases (VEGFR and PDGFR) and some intracellular serine/threonine kinases (eg, C-Raf, wild-type and mutant B-Raf). Safety and effectiveness were established in a randomized trial involving 417 participants with locally recurrent or metastatic, progressive DTC that had not responded to RAI treatment. The sorafenib dose was 400 mg twice a day. The median progression-free survival (PFS) was 10.8 months with sorafenib compared to 5.8 months with placebo ($P < .0001$). Partial responses were observed in 12.2% of patients receiving sorafenib compared with 0.5% in the placebo arm ($P < .0001$). The most common side effects with sorafenib were diarrhea, fatigue, alopecia, hand-foot skin reaction, rash, weight loss, anorexia, nausea, gastrointestinal and abdominal pains, and hypertension (Table 33.3).

TABLE 33.3

Systemic Therapy Regimens for Advanced or Metastatic Endocrine Cancers

Regimen	Malignancy
Sorafenib 400 mg orally twice daily	Radioactive iodine-refractory differentiated thyroid cancer
Lenvatinib 14 mg orally daily	Radioactive iodine-refractory differentiated thyroid cancer
Selpercatinib < 50 kg 120 mg orally twice daily >50 kg 160 mg orally twice daily	Radioactive iodine-refractory differentiated thyroid cancer (RET fusion)
Pralsetinib 400 mg orally once daily	Radioactive iodine-refractory differentiated thyroid cancer (RET fusion)
Larotrectinib 100 mg orally twice daily	Radioactive iodine-refractory differentiated thyroid cancer (NTRK1 fusion mutation)
Entrectinib Adults: 600 mg orally daily Pediatric body surface area (BSA) > 1.5 m^2: 600 mg orally daily Pediatric BSA 1.11-1.5 m^2: 500 mg orally daily Pediatric BSA 0.91-1.10 m^2: 400 mg orally daily	
Vandetanib 300 mg orally daily	Medullary thyroid cancer
Cabozantinib 140 mg orally daily	Medullary thyroid cancer
Selpercatinib < 50 kg 120 mg twice daily >50 kg 160 mg twice daily	Medullary thyroid cancer (RET mutant)
Pralsetinib 400 mg orally once daily	Medullary thyroid cancer (RET mutant)

Regimen	Malignancy
Cyclophosphamide 750 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, dacarbazine 600 mg/m^2 on day 1, and dacarbazine 600 mg/m^2 on day 2, every 21-28 d	Malignant pheochromocytoma [a]
High specific activity ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) <62.5 kg 296 MBq/kg/dose (8 mCi/kg/dose) IV × 2 doses > 90 days apart >62.5 kg 18,500 MBq (500 mCi) IV × 2 doses > 90 days apart	Malignant pheochromocytoma
^{177}Lu-DOTATATE 7.4 GBq (200 mCi) IV x 4 doses every 8 weeks	Pancreatic neuroendocrine tumors, carcinoid
Capecitabine 750 mg/m^2 twice daily on days 1-14 Temozolomide 200 mg/m^2 once daily on days 10-14 Every 28 days cycle	Pancreatic neuroendocrine tumors
Sunitinib 37.5 mg orally daily	Pancreatic neuroendocrine tumors, malignant pheochromocytoma [a]
Everolimus 10 mg orally daily	Pancreatic neuroendocrine tumors, carcinoid
Lanreotide 120 mg SC every 28 d	Pancreatic neuroendocrine tumors, carcinoid
Depot octreotide LAR 30 mg IM every 28 d	Pancreatic neuroendocrine tumors, carcinoid
Streptozocin 500 mg/m^2/d IV on days 1-5 and 5-fluorouracil 400 mg/m^2/d IV on days 1-5 every 6 weeks	Pancreatic neuroendocrine tumors, carcinoid [a]
Streptozocin 500 mg/m^2/d IV on days 1-5 and doxorubicin 50 mg/m^2 IV on days 1 and 22 every 6 weeks	Pancreatic neuroendocrine tumors, carcinoid [a]
Mitotane orally continuously (starting dose = 1-2 g/d, increase to mitotane level of 14-20 mg/L or toxicity)	Adrenocortical carcinoma
Mitotane orally continuously (starting dose = 1-2 g/d, increase to mitotane level of 14-20 mg/L or toxicity) and streptozotocin (1 g on days 1-5 in cycle 1; 2 g on day 1 in subsequent cycles every 3 weeks)	Adrenocortical carcinoma
Mitotane orally continuously (starting dose = 1-2 g/d, increase to mitotane level of 14-20 mg/L or toxicity) and etoposide (100 mg/m^2 IV on days 2, 3, and 4), doxorubicin (40 mg/m^2 IV on day 1), and cisplatin (40 mg/m^2 IV on days 3 and 4) every 4 weeks	Adrenocortical carcinoma

[a]Limited phase II data.

- Lenvatinib is an inhibitor of the vascular endothelial growth factor receptor 2 (VEGFR2). The approval of lenvatinib was based on a multicenter, double-blinded, placebo-controlled trial that enrolled 392 patients with locally recurrent or metastatic RAI-refractory DTC and radiographic evidence of progression within 12 months prior to randomization. Patients received lenvatinib 24 mg orally per day. Median PFS was 18.3 months in the lenvatinib arm and 3.6 months in the placebo arm (P < .0001). Objective response rates (ORRs) were 65% and 2% in the lenvatinib and placebo arms, respectively. No statistically significant difference in overall survival between the two arms

was demonstrated. The most common adverse reactions were hypertension, fatigue, diarrhea, arthralgia/myalgia, anorexia, weight loss, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. Adverse reactions led to dose reductions in 68% of patients receiving lenvatinib and 18% of patients discontinued lenvatinib for adverse reactions (Table 33.3).

- Patients whose tumors harbor genetic alterations can be treated with selective kinase inhibitors. DTC harboring *RET* fusions can be treated with either pralsetinib or selpercatinib, which are selective RET inhibitors. DTC harboring *NTRK* can be treated with either larotrectinib or entrectinib, which are NTRK inhibitors. BRAF and MEK inhibitors are not yet FDA-approved for *BRAF*-mutated DTC.
- Selpercatinib is a novel, ATP-competitive, highly selective small molecule inhibitor of RET kinase. Selpercatinib safety and efficacy was investigated in a phase I to II trial (LIBRETTO-001) in adolescent and adult patients with any solid tumor type harboring an activating *RET* alteration. Nineteen patients with RET fusion–positive radioiodine-refractory thyroid cancer were enrolled with at least one prior systemic therapy apart from RAI. Thirteen patients had PTC, three had poorly DTC, one had anaplastic thyroid cancer (ATC), and one had Hürthle cell thyroid cancer. Ninety-five percent of patients with RET fusion–positive thyroid cancer received the phase 2 dose of 160 mg twice daily. Seventy-nine percent of patients had an objective response (95% confidence interval [CI], 54-94). This was seen across multiple histologies. One-year PFS was 64%. Treatment-related adverse events (any grade) occurred in 94% of patients. In 28% of patients, grade 3 adverse events were observed and in 2% of patients grade 4. The most frequent adverse events of grade 3 or higher were hypertension (21%), increased alanine aminotransferase (ALT) level (11%), increased aspartate aminotransferase (AST) level (9%), hyponatremia (8%), and diarrhea (6%). Thirty percent had dose reductions due to treatment-related adverse events and 2% discontinued the drug due to adverse events. On May 8, 2020, the FDA granted accelerated approval to selpercatinib in adult and pediatric patients older than 12 years with advance or metastatic *RET* fusion–positive thyroid cancer in need of systemic therapy and are RAI refractory.
- Pralsetinib is a selective inhibitor of RET tyrosine kinase indicated for adult and pediatric patients aged 12 years and older with advanced or metastatic *RET* fusion–positive thyroid cancer who require systemic therapy and who are RAI refractory (if RAI is appropriate). The efficacy of pralsetinib was evaluated in *RET* fusion–positive metastatic thyroid cancer as part of an open-label, multicohort clinical trial. There were nine patients with PTC enrolled. The ORR was 89% with median duration of response (DOR) not reached, and DOR of at least 6 months was seen in 100% of patients. The dose of pralsetinib

is 400 mg by mouth once daily. The most common adverse reactions were constipation, hypertension, fatigue, musculoskeletal pain, and diarrhea.

- Larotrectinib is a potent and highly selective small molecule inhibitor of all three TRK proteins: TRKA, TRKB, and TRKC proteins. Larotrectinib safety and efficacy was investigated on a phase I to II (into three protocols: phase I study involving adults, phase I-II involving children, or a phase II study involving adolescents and adults) study in patients with TRK fusion–positive cancers. Fifty-five patients were enrolled, five of whom had thyroid cancer. The overall response rate was 75% (96% CI, 61-85). At 1 year, 71% of the responses were ongoing, and 55% of all patients remained progression free. Ninety-three percent of the treatment-related adverse events were grade 1 or 2. No adverse events of grade 4 or 5 were considered to be treatment related, and no treatment-related grade 3 events occurred in more than 5% of patients. The most frequent adverse events were increased ALT or AST level (38%), dizziness (25%), fatigue (16%), nausea (16%), constipation (16%), fatigue (11%), and increased body weight (11%).
- Entrectinib is a ROS1 and NTRK kinase inhibitor approved for adult and pediatric patients aged 12 years and older with solid tumors that have an *NTRK* gene fusion. Efficacy was assessed in the first 54 adult patients with solid tumors with an *NTRK* gene fusion enrolled. There were five patients with thyroid cancer. The response rate was 20%, with a DOR of 7.9 months. The most common adverse reactions were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorder.

Medullary Thyroid Cancer

- Medullary thyroid cancer (MTC) is an NET of the parafollicular or C cells of the thyroid gland. MTC accounts for approximately 4% of thyroid carcinomas. Its estimated incidence in the United States for 2010 is about 1300 to 2200 patients. Sporadic MTC accounts for about 80% of all cases of the disease. The typical age of presentation is in the fifth or sixth decade, and there may be a slight female preponderance.
- Hereditary MTC is caused by germline activating point mutations of the *RET* tyrosine kinase gene. It is divided into three distinct clinical subtypes. MEN 2A, or Sipple syndrome, is the most common subtype, accounting for approximately 70% to 80% of patients with hereditary MTC. MEN 2A is characterized by MTC in 100% of affected individuals, by PHEO in 50%, and by primary hyperparathyroidism in 20%. MTC is usually the first manifestation of the syndrome. Patients typically present with a thyroid nodule or neck mass by 15 to 20 years of age, but MTC can appear as early as

5 years of age. Sporadic tumors tend to be solitary, whereas familial tumors tend to be bilateral and multifocal.

- MEN 2B is less common than MEN 2A, accounting for approximately 5% of MTC cases. It is characterized by a clinically more aggressive form of MTC that is manifested at a younger age (second decade) and that occurs in 100% of affected individuals, by PHEO in 50%, and by characteristic dysmorphic features including distinctive mucosal neuromas on the tongue, lips, and subconjunctival areas, diffuse ganglioneuromas of the gastrointestinal tract, and marfanoid habitus. Hyperparathyroidism is not associated with MEN 2B (Table 33.1).
- Familial MTC is the third clinical subtype of inherited MTC. It accounts for 10% to 20% of hereditary MTC cases and is defined by the presence of MTC in kindreds with 4 to 10 or more affected members and with objective evidence of the absence of adrenal and parathyroid gland involvement. This form of hereditary MTC is less aggressive and has an older age at onset, usually between 20 and 40 years, compared to MEN 2A and 2B.

Clinical Presentation

- Patients typically present with an asymptomatic thyroid mass. Some may also have local symptoms such as dysphagia, dyspnea, or hoarseness.
- Approximately 10% will present with systemic symptoms usually consisting of bone pain, flushing, and/or diarrhea.
- Approximately 50% of patients present with regional lymphadenopathy.
- Distant metastases typically occur in late-stage disease and usually involve the lung, liver, bones, and adrenal glands.

Diagnosis

- Guidelines for evaluation of thyroid nodules should be followed as described for DTC.
- If the FNA is suggestive of MTC, further evaluation should consist of calcitonin and carcinoembryonic antigen measurement and genetic testing for germline *RET* mutations.

Treatment

- Total thyroidectomy with central lymph node dissection is the appropriate surgery.
- Surgery and/or external beam radiotherapy can be used for residual or recurrent disease treatment; however, the survival benefit for either modality is unclear.

- Metastatic MTC is the most common cause of death in patients with MEN 2A, MEN 2B, or familial medullary thyroid cancer, and the tumor is relatively unresponsive to conventional doses of radiation therapy and to standard cytotoxic chemotherapy. Recurrent/metastatic disease that is not surgically resectable can be treated with multikinase inhibitors vandetanib or cabozantinib (regardless of *RET* mutation status) or selective RET inhibitors selpercatinib or pralsetinib (if a *RET* mutation is present). No improvement in overall survival has been demonstrated in clinical trials for any of these drugs; therefore, patients with indolent disease should consider observation until their disease becomes necessary to treat.
- Vandetanib, an oral inhibitor of VEGFR, RET, and epidermal growth factor receptor, is approved for the treatment of advanced (metastatic or unresectable locally advanced) MTC based on an international randomized phase III trial. In a preliminary report of results (median follow-up of 24 months), median PFS was improved in patients randomly assigned to vandetanib versus placebo (hazard ratio [HR], 0.45; 95% CI, 0.30-0.69). The overall response rate was 45%. Objective responses were durable on the basis of the median DOR not being reached at 24 months of follow-up. The most common adverse reactions were diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infection, decreased appetite, and abdominal pain.
- Cabozantinib, a tyrosine kinase inhibitor (TKI) of hepatocyte growth factor receptor (MET), VEGFR2, and RET, demonstrated clinical efficacy in patients with MTC. A double-blinded, phase III trial comparing cabozantinib with placebo in 330 patients with documented radiographic progression of metastatic MTC was performed. The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR, 0.28; 95% CI, 0.19-0.40; $P < .001$). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and RET mutation status (hereditary or sporadic). The response rate was 28% for cabozantinib and 0% for placebo; responses were seen regardless of RET mutation status. Common cabozantinib-associated adverse events included diarrhea, PPE, decreased weight and appetite, nausea, and fatigue. See Table 33.3 for vandetanib and cabozantinib dosing.
- Selpercatinib is a novel, ATP-competitive, highly selective small molecule inhibitor of RET kinase. Selpercatinib safety and efficacy was investigated in a phase I to II trial (LIBRETTO-001) in adolescent and adult patients with any solid tumor type harboring an activating *RET* alteration. Fifty-five patients with *RET*-positive MTC were previously treated with vandetanib, cabozantinib, or both. The ORR was 69% (95% CI, 55-81). Nine percent had a complete response and 60% had a partial response. At 1 year, 86% of responses were ongoing (95% CI, 67-95) and 100% of patients were progression free. Moreover, 88 patients with *RET*-positive MTC were not

previously treated with vandetanib or cabozantinib. The ORR was 73% (95% CI, 62-82). Eleven percent had a complete response and 61% had a partial response. At 1 year, 91% of responses were ongoing (95% CI, 72-97) and 92% of patients were progression free. On May 8, 2020, the FDA granted accelerated approval to selpercatinib in adult and pediatric patients older than 12 years with advance or metastatic *RET*-positive MTC in need for systemic therapy.

- Pralsetinib is a selective inhibitor of RET tyrosine kinase indicated for adult and pediatric patients aged 12 years and older with advanced or metastatic *RET*-positive MTC who require systemic therapy. Efficacy was evaluated in 55 patients with RET-mutant metastatic MTC previously treated with cabozantinib or vandetanib (or both). The overall response rate was 60% with 2% CR (complete responses) and 58% PR (partial responses), with a median DOR not reached. DOR was at least 6 months in 79% of patients. Efficacy of pralsetinib was also evaluated in 29 patients with *RET*-mutant advanced MTC who were cabozantinib and vandetanib treatment naïve. The overall response rate was 65% with 10% CR and 55% PR, with a median DOR not reached. DOR was at least 6 months in 84% of patients. The most common adverse reactions were constipation, hypertension, fatigue, musculoskeletal pain, and diarrhea.

Anaplastic Thyroid Cancer

- ATC is a rare, high-grade, aggressive malignancy that accounts for 2% to 5% of all thyroid carcinomas. Up to 50% of patients have antecedent or concurrent history of DTC. Disease-specific mortality is nearly 100%.
- Patients typically present with a rapidly enlarging neck mass.
- Approximately 90% will have locoregional or distant metastases at the time of diagnosis.
- Treatment is primarily palliative and often aimed at preventing asphyxiation, the most common cause of death in these patients. It can consist of surgery, radiation, chemotherapy, or a combination of these modalities.
- Surgical resection does not improve local control or survival in patients. If surgery is performed, it should be followed by locoregional radiotherapy usually within 2 to 3 weeks after surgery. Local control is desirable in patients with ATC because of the likelihood of asphyxia from the rapidly enlarging tumor.
- Treatment with external beam radiotherapy with systemic therapy appears to achieve local control in two-thirds of patients with ATC; however, almost all subsequently die of distant metastases.
- A number of novel agents have been preliminarily studied in ATC such as fosbretabulin assessed in phase II trial with increased overall survival in some patients. TKIs such as sorafenib, axitinib, and gefitinib have been studied with

no evidence of RECIST response; however, a limited number of patients were reported to have stable disease.

- Twenty-five percent of ATC harbor an activating *BRAF* (V600E) mutation. A phase II trial of *BRAF* (dabrafenib) and *MEK* (trametinib) inhibitors included 16 patients with *BRAF* (V600E)-positive ATC. Sixty-nine percent confirmed overall response rate (95% CI, 41%-89%). Median DOR, PFS, and overall survival were not reached, with a 12-month estimate of 90%, 79%, and 80%, respectively. Common adverse events were fatigue (38%), pyrexia (37%), and nausea (35%). On May 4, 2018, the FDA approved dabrafenib and trametinib in combination for the treatment of patients with locally advanced or metastatic ATC with BRAF V600E mutation.

Other Thyroid Cancers

- Primary thyroid lymphoma
- Metastasis to the thyroid
- Thyroid sarcoma

PHEOCHROMOCYTOMA

Epidemiology

- PHEOs and PGLs are rare NETs that arise from chromaffin cells. PHEOs account for 90% of cases and arise in the adrenal glands, whereas PGLs, the extra-adrenal counterpart of PHEOs, arise from ganglia along the sympathetic and parasympathetic chain (eg, carotid body/skull base, urinary bladder, heart, organ of Zuckerkandl).
- Most PHEOs represent sporadic tumors and 15% of these are associated with somatic mutations. However, about 35% are familial in origin and patients are found to harbor germline mutations in susceptibility genes.
- The number of genes associated with susceptibility to PHEOs/PGLs was recently increased to 19 and includes the von Hippel-Lindau (*VHL*) tumor suppressor gene, the *RET* proto-oncogene, the neurofibromatosis type 1 (*NF1*) tumor suppressor gene, the genes encoding the four succinate dehydrogenase complex (*SDH*) subunits (*SDHA, SDHB, SDHC, SDHD*), and the gene encoding the enzyme responsible for flavination of the SDHA subunit (*SDHAF2*). Additionally, new susceptibility genes, transmembrane protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), and hypoxia-inducible factor 2α (*HIF2A*), have been identified. Others include the kinesin family member 1B, transcript variant β (*KIF1Bβ*), prolyl hydroxylase 1 and 2 (*PHD1/EGLN2* and *PHD2/EGLN1*), Harvey Ras sarcoma viral oncogene (*H-RAS*), Kirsten Ras sarcoma viral oncogene (*K-RAS*), isocitrate dehydrogenase 1

(IDH1), fumarate hydratase (*FH*), and *BRCA1*-associated protein 1 (*BAP1*). Finally, germline mutations in malate dehydrogenase 2 (*MDH2*) and somatic mutations in alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) genes were identified in PHEOs/PGLs (Table 33.5).

Clinical Presentation

- Clinical manifestations of PHEO/PGL are diverse, with similar symptoms occurring in other disease conditions. Most of the signs and symptoms are attributed to the direct actions of the over production of catecholamines. These include hypertension, headache, palpitations, and anxiety. Hypertension can be paroxysmal or sustained. Some patients may present with orthostatic hypotension. Biochemically silent tumors may be suspected from tumor mass effect or may be found incidentally on imaging studies (Table 33.4).

TABLE 33.4

Potential Clinical Manifestations of Pheochromocytomas

Mild labile hypertension to hypertensive crisis; sustained hypertension also common
Myocardial infarction
Cerebral infarction
Classic pattern of paroxysmal hypertension (30%-50% of cases)
Spells of paroxysmal headache
Pallor or flushing
Tremor
Apprehension
Palpitation
Orthostasis
Mild weight loss
Diaphoresis

TABLE 33.5

Clinical Characteristics of Genetic Mutations Associated With Pheochromocytoma (PHEO)/Paraganglioma (PGL)

Gene	Syndrome	Germline/Somatic	Common PHEO/PGL Sites	Malignancy	Other Associated clinical Characteristics/Tumors
SDHA		AD	Adrenal PHEOs or extra-adrenal PGLs	0%-14%	Homozygous patients: Leigh syndrome Renal cell carcinoma Gastrointestinal stromal tumors Pituitary adenomas

Gene	Syndrome	Germline/Somatic	Common PHEO/PGL Sites	Malignancy	Other Associated clinical Characteristics/Tumors
SDHB	PGL4	AD	Sympathetic PGLs (rarely adrenal PHEOs and head and neck PGLs)	31%-71%	Renal cell carcinoma Gastrointestinal stromal tumors Pituitary adenomas Possibly breast carcinoma Possible papillary thyroid carcinoma
SDHC	PGL3	AD	Head and neck PGLs, sometimes multiple (rarely sympathetic PGLs or adrenal PHEOs)	Rare	Renal cell carcinoma Gastrointestinal stromal tumors Pituitary adenomas
SDHD	PGL1	AD	Head and neck PGLs, commonly multiple (rarely extra-adrenal abdominal PGLs or adrenal PHEOs)	<5%	Renal cell carcinoma Gastrointestinal stromal tumors Pituitary adenomas
SDHAF2	PGL2	AD	Head and neck PGLs, sometimes multiple	Further study needed	
VHL	VHL	AD	Adrenal PHEOs (rarely sympathetic or head and neck PGLs)	<5%	Hemangioblastomas PHEO Renal cell carcinoma Pancreatic serous cystadenoma Endolymphatic sac tumor Pancreatic neuroendocrine tumors Epididymal papillary cystadenomas Retinal angiomas
NF1	NF1	AD	Adrenal PHEOs (rarely sympathetic PGLs)	~12%	Café-au-lait spots Neurofibromas Freckles Benign iris hamartomas Optic-nerve gliomas Sphenoid bone dysplasia/pseudoarthritis

Gene	Syndrome	Germline/Somatic	Common PHEO/PGL Sites	Malignancy	Other Associated clinical Characteristics/Tumors
RET	MEN 2	AD	Adrenal	Rare	MEN 2A: Medullary thyroid cancer, PHEO, hyperparathyroidism MEN 2B: Medullary thyroid cancer, PHEO, marfanoid habitus and mucosal ganglioneuromas
MAX		AD PI	Adrenal	20%-25%	
TMEM127		AD	Adrenal	<5%	Possibly linked to breast carcinoma Possibly linked to papillary thyroid carcinoma
HIF2A	Pacak-Zhuang	Somatic	Extra-adrenal PGLs, usually multiple PHEOs	None reported	Multiple somatostatinomas Polycythemia
KIF1β		Somatic	Further study needed	None reported	
PHD2	Yes	Germline	Multiple PGLs	None reported	
IDH		Somatic	Carotid PGL	None reported	Glioblastoma multiforme
FH		Germline	Adrenal PHEO		Polycythemia
H-RAS		Somatic	Both PHEO and PGL	None reported	

- The incidence of malignancy is about 10%, with metastases the only definite proof of malignancy, as there are no definitive histopathologic criteria for malignancy. Oncologists must read the literature carefully given that descriptions of benign and malignant are often combined.
- The overall 5-year survival rate for patients with malignant PHEO is 36% to 44%. About 50% or more of SDHB mutation carriers will develop malignant PGLs, and up to 60% of patients with a malignant PGL harbor a SDHB mutation.

Diagnosis

- Measurement of 24-hour urinary-fractionated metanephrines is the most specific tool for diagnosis of PHEO.
- Plasma-fractionated metanephrines measurement is the most sensitive test but has a high rate of false positives.

- Clonidine suppression test is recommended for indeterminate plasma catecholamine or metanephrine levels, both of which will not be suppressed in patients with PHEO.
- Computed tomography (CT) and magnetic resonance imaging (MRI) are equally sensitive diagnostic tools for PHEO. However, MRI is better for detection of liver metastasis.
- Iodine ^{123} metaiodobenzylguanidine (^{123}I-MIBG) has poor resolution and lower detection rate for metastasis when comparing with PET (positron emission tomography)/CT imaging modalities. PET/CT including ^{68}Ga-DOTATATE and ^{18}FDG has higher sensitivity to detect metastatic disease.
- In two prospective studies reporting a 98.6% lesion-based detection rate on ^{68}Ga-DOTATATE PET/CT and 86% lesion-based detection rate on ^{18}FDG-PET/CT in patients with SDHB-related metastatic PPGLs and in patients with sporadic metastatic PPGLs, the lesion-based detection rate with ^{68}Ga-DOTATATE PET/CT and ^{18}FDG-PET/CT was 97.6% and 49.2%, respectively. Given the high sensitivity of ^{68}Ga-DOTATATE PET/CT, when possible, it should be the first imaging modality to obtain to detect metastatic disease and in patients who may benefit from PRRT (peptide receptor radionuclide therapy) with ^{177}Lu-DOTATATE treatment as a part of a clinical trial. ^{123}I-MIBG is of utility to select patients for HS-^{131}I-MIBG therapy.

Treatment

Surgery

- Surgery remains the only curative treatment option with PHEO/PGL. Minimally invasive adrenalectomy is recommended for most adrenal PHEOs and open resection for large or invasive tumors to ensure complete resection and avoid local recurrence.
- Patients with hormone-secreting tumors should undergo preoperative blockade for 7 to 14 days with α-adrenergic receptor blockers such as phenoxybenzamine or doxazosin to prevent perioperative cardiovascular complications.
- Many patients require the addition of β-blockers, which are indicated for persistent tachycardia; however, to prevent hypertensive crisis secondary to unopposed vasoconstriction, β-blockers should not be given before α-antagonists. In patients in whom elevated blood pressure and arrhythmia cannot be controlled with α- and β-blockade, α-methyl-para-tyrosine (metyrosine, Demser), a competitive inhibitor of tyrosine hydroxylase, can be used.
- Importantly, normal postoperative biochemical test results do not exclude microscopic disease. Long-term periodic follow-up is recommended especially important if the tumors harbor mutations of disease-causing genes.

Radiation

- Radiation has a limited role in the treatment of PHEO but may be used for bone and soft-tissue metastases.
- Therapeutic doses of ^{131}I-MIBG in patients showing evidence of radiotracer uptake on MIBG scans have provided both radiographic and symptomatic responses.
- On July 30, 2018, the FDA-approved AZEDRA (a high specific activity ^{131}I-metaiodobenzylguanidine [^{131}I-MIBG]) for adult and pediatric patients (older than 12 years) with positive ^{123}I-MIBG in advanced, unresectable disease. The FDA approval was based on the results of the phase II open-label, multicenter trial that included 68 patients with PHEOs or PGLs. The primary end point was a >50% reduction of all antihypertensive medications lasting for at least 6 months. Twenty-five percent evaluable patients experienced a 50% or greater reduction of all antihypertensive medication for at least 6 months. Overall tumor response was achieved in 22% patients, and of those patients, 53% experienced durable tumor responses lasting 6 months or longer.
- PHEOs/PGLs often express somatostatin receptor types 2 (SSTR2) and 3 (SSTR3). A meta-analysis of studies involving advanced/metastatic PHEO/PGL patients treated with PRRT showed that 89.8% of pooled patients had achieved disease stabilization or a partial response; however, despite its approval in GEP NETs, it is currently not FDA-approved for metastatic PHEO/PGL. A prospective study is ongoing with ^{177}Lu-DOTATATE treatment for unresectable/metastatic disease (NCT03206060).

Chemotherapy/Targeted Therapy

- Combined chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has emerged as a standard option. Results of a nonrandomized, single-arm trial included 14 patients with confirmed malignant PHEO with metastatic disease and elevated urinary catecholamine secretion. After optimization of antihypertensive therapy, patients received cyclophosphamide, 750 mg/m^2 on day 1; vincristine, 1.4 mg/m^2 on day 1; and dacarbazine, 600 mg/m^2 on days 1 and 2, every 21 days. Combination chemotherapy with CVD produced a complete plus partial response rate of 57% (median duration, 21 months; range, 7 to more than 34). Complete and partial biochemical responses were seen in 79% of patients (median duration, more than 22 months; range, 6 to more than 35). All responding patients had objective improvement in performance status and blood pressure.
- A long-term follow-up study was conducted in 18 patients treated with CVD at the National Institutes of Health. Combination chemotherapy with CVD produced a complete response rate of 11% and a partial response rate of 44%. Median survival was 3.8 years for patients whose tumors responded to

therapy and 1.8 years for patients whose tumors did not respond (P = .65). All patients with tumors scored as responding reported improvement in their symptoms related to excessive catecholamine release and all had objective improvements in blood pressure. In this 22-year follow-up, there was no difference in OS between patients whose tumors objectively shrank and those with stable or progressive disease. However, patients reported improvement in symptoms, had objective improvements in blood pressure, and had tumor shrinkage that made surgical resection possible. CVD therapy is not indicated in every patient with metastatic PHEOs/PGLs, but should be considered in the management of patients with symptoms and where tumor shrinkage might be beneficial.

- Anecdotal reports suggest that the efficacy of chemotherapy may be high in patients with mutations in *SDHB*. Although the CVD regimen led to an overall response of approximately 50%, it is not clear if the administration of CVD impacts overall survival, as nearly all patients develop progressive and ultimately fatal disease.
- Temozolomide (TMZ) is the prodrug of dacarbazine and a retrospective study showed therapeutic benefit of TMZ in patients with metastatic PGL. Fifteen consecutive patients with metastatic PGL were enrolled; 10 (67%) carried a mutation in SDHB. The mean dose intensity of TMZ was 172 mg/m^2 daily for 5 days every 28 days. Median PFS was 13.3 months after a median follow-up of 35 months; 33% (5 patients) reported with partial response and 47% (7 patients) with stable disease and 20% with progressive disease.
- For patients not suitable for cytotoxic chemotherapy, a trial of octreotide is reasonable, though its benefit is unclear.
- Responses have also been reported with the targeted agent such as sunitinib, axitinib, and cabozantinib.
- See Table 33.3 for detailed chemotherapy regimens.

NEUROENDOCRINE TUMORS

NETs are cancers of the interface between the endocrine system and the nervous system. The updated WHO classifications of digestive tumors from July 2017 introduced significant changes to the previously published classifications from 2010. NETs are now classified into well-differentiated grade G1, G2, and G3 NETs and G3 neuroendocrine carcinomas (Table 33.6).

TABLE 33.6

Classification and Grading of Neuroendocrine Tumors (NETs) Gastrointestinal Tract and Hepatopancreatobiliary Organs

Terminology	Differentiation	Grade	Mitotic Rate	Ki67 Index (%)
NET, G1	Well differentiated	Low	<2	<3
NET, G2		Intermediate	2-20	3-20
NET, G3		High	>20	>20
NEC, small cell type	Poorly differentiated	High	>20	>20
NEC, large cell type			>20	>20

These rare tumors are distinguished from most other solid tumors by their ability to secrete biologically active molecules that can produce systemic syndromes. The most common types of NETs are carcinoid tumors and pancreatic NETs, both of which are typically well differentiated.

NETs Causing Carcinoid Syndrome

- Incidence in the United States is approximately 2 per 100,000 individuals.
- NETs producing carcinoid syndrome are slow-growing malignant tumors that arise from enterochromaffin cells of the aerodigestive tract.
- They are traditionally categorized by their embryonic origin and are most commonly found in the foregut (bronchial) and small intestine.
- The typical carcinoid syndrome consists of flushing and diarrhea and is seen most often with small intestine carcinoid tumors.
- Carcinoid syndrome is observed in 10% of patients, especially those with liver metastases, retroperitoneal disease, or disease outside of the GI tract where excessive hormones can bypass metabolism in the liver.
- Features of foregut, midgut, and hindgut carcinoids are outlined in Table 33.7.

TABLE 33.7
Carcinoid Features

Origin	Common Sites	Symptoms	Secretory Products
Foregut	Stomach, duodenum	Abdominal pain, anemia, bleeding, atypical carcinoid syndrome uncommon	5-HTP, histamine, tachykinins, other hormones, and peptides
	Bronchus	Pulmonary symptoms, atypical carcinoid syndrome uncommon	
Midgut	Small bowel	Abdominal pain, carcinoid syndrome with liver metastases	Serotonin, other hormones, and peptides
	Appendix	Asymptomatic, usually found incidentally, carcinoid syndrome with liver metastases	
Hindgut	Distal colon, rectum	Bowel habit changes, pain, obstruction, bleeding, carcinoid syndrome rare	Rare

Treatment

- Abdominal and rectal carcinoids tend to be small (2 cm). Surgery involves segmental resection with mesenteric lymphadenectomy.

- Appendiceal carcinoid is often discovered incidentally. If it is >2 cm or there is invasion or positive margins, right hemicolectomy is recommended. Right hemicolectomy is more controversial for tumors that are <2 cm and confined to the appendix.
- Liver metastases can be treated locally with surgical debulking, hepatic arterial embolization, chemoembolization, cryotherapy, or radiofrequency ablation.
- Patients with carcinoid syndrome should be treated with a somatostatin analog (SSA) such as octreotide. Octreotide has also demonstrated antitumor activity, potentially improving time to progression.
- The US FDA has recently approved telotristat ethyl (targets tryptophan hydroxylase, an enzyme that mediates the excess serotonin production within NET cells), an orally administered therapy for the treatment of carcinoid syndrome diarrhea in combination with SSA therapy (either octreotide LAR or lanreotide), in adults inadequately controlled by SSA therapy.
- On January 26, 2018, the FDA-approved ^{177}Lu-DOTATATE treatment for gastroenteropancreatic NET based on a randomized clinical trial of 229 patients with well-differentiated metastatic midgut NET. Patients received either ^{177}Lu-DOTATATE every 8 weeks plus best supportive care including long-acting octreotide or long-acting octreotide alone every 4 weeks. The estimated rate of PFS at month 20 was 65.2% (95% CI, 50.0-76.8) in the ^{177}Lu-DOTATATE group and 10.8% (95% CI, 3.5-23.0) in the control group. The response rate was 18% in the ^{177}Lu-DOTATATE group versus 3% in the control group ($P < .001$). Grade 3 or 4 neutropenia occurred in 1%, thrombocytopenia in 2%, and lymphopenia in 9% in patients receiving ^{177}Lu-DOTATATE comparing with the control group.
- Everolimus has been approved for advanced NET associated with carcinoid syndrome (RADIANT-2).
- Carcinoids are resistant to most chemotherapeutic agents. Active agents in NETs include 5-fluorouracil, capecitabine, streptozocin, doxorubicin, and interferon. Chemotherapy is typically reserved for patients who are progressing with no other treatment options. See Table 33.3 for detailed systemic therapy regimens.
- Radiation therapy is for palliation only.

Pancreatic NETs

Pancreatic NETs, also known as islet cell tumors, arise from the hormone-secreting cells of the pancreas. Up to 75% are nonfunctioning and not associated with clinical syndromes. The functioning pancreatic NETs and are categorized by the hormone and clinical syndrome they produce. Pancreatic NETs comprise approximately 3% of all pancreatic tumors, are generally well differentiated, and

are malignant. They are associated with familial syndromes in up to 25% of cases (Table 33.1).

Gastrinoma (Zollinger-Ellison Syndrome)

Gastrinoma is a tumor that secretes gastrin. Primary tumors predominate in the pancreatic head but may also develop in the small intestine or stomach.

Epidemiology

- Gastrinoma occurs in 0.1% to 1% of patients with peptic ulcer disease.
- They are usually diagnosed between the third and sixth decades but can occur at any age.
- Approximately 20% of gastrinomas are associated with the familial syndrome MEN 1%, and 80% are sporadic. Sporadic tumors often have somatic mutations in the *MEN 1* gene.
- Approximately one-third of patients with gastrinoma have metastatic disease at diagnosis.

Diagnosis and Clinical Presentation

- Patients typically present with severe, often refractory peptic ulcer disease accompanied by abdominal pain and diarrhea.
- Diagnosis is made by a fasting gastrin level: >1000 pg/mL with a gastric acid pH < 5.0 or gastrin level that increases by ≥200 pg/mL within 15 minutes of intravenous infusion of secretin.
- Other common diagnostic procedures include ultrasonography, CT scan, MRI, endoscopic ultrasonography, angiography, and octreotide scan.

Treatment

- Medical therapy is standard for gastrinoma associated with MEN 1, given that tumors are often multifocal and incurable. Some surgeons will offer resection with the intent of reducing future morbidity from metastatic disease.
- Surgical resection with exploratory laparotomy is curative in up to 50% of patients with sporadic gastrinoma without metastatic disease.
- The goal of medical therapy is to control gastrin secretion and acid production. Therapies include proton pump inhibitors, SSAs (eg, octreotide), and tumor embolization.

Insulinoma

Epidemiology

- Insulinoma is the most common type of functioning pancreatic NET.

- It occurs most commonly in the fifth decade of life, with a slight female predominance.
- Most insulinomas are solitary and approximately 10% are malignant, as defined by the presence of metastases.

Diagnosis and Clinical Presentation

- Three criteria, known as Whipple triad, suggest insulinoma:
  - Symptoms known or likely to be caused by hypoglycemia (confusion, personality change, palpitations, diaphoresis, tremulousness)
  - Hypoglycemia during symptoms
  - Relief of hypoglycemia symptoms when glucose is raised to normal
- An inappropriately high level of insulin during an episode of hypoglycemia establishes the presence of insulinoma.
- Asymptomatic patients may be diagnosed after prolonged fasting by testing levels of serum glucose, insulin, and C-peptide every 6 to 12 hours.

Treatment

- Surgery is the treatment of choice for insulinoma and is most often curative.
- Refractory hypoglycemia can be treated with oral diazoxide, which inhibits pancreatic secretion of insulin and stimulates release of catecholamine and glucose from the liver.

VIPoma (Verner-Morrison Syndrome)

- VIPoma is a rare NET that usually originates in the pancreas and produces vasoactive intestinal peptide (VIP).
- Elevated serum VIP establishes the presence of VIPoma.
- Patients present with watery diarrhea, hypokalemia, and hypo- or achlorhydria.
- Diarrhea may be treated effectively with SSAs, which decrease VIP secretion. Interferon-α can also be used.

Glucagonoma

- Glucagonoma is a rare tumor of the pancreas that results in overproduction of the hormone glucagon.
- Serum levels of glucagon > 500 pg/mL are diagnostic of glucagonoma.
- Glucagonoma leads to diabetes, weight loss, anemia, and increased risk of thromboembolism.
- Patients commonly present with necrolytic migratory erythema, which may be treated with zinc supplements and amino acid infusion.
- Surgery, SSAs, anticoagulants, and targeted therapy/chemotherapy (as described for the other pancreatic NETs) are therapeutic options for

glucagonomas.

Somatostatinoma

- Somatostatinoma is a tumor of the endocrine pancreas that secretes excess somatostatin. The tumor inhibits secretion of insulin, other pancreatic hormones, pancreatic enzymes, and gastric acid production.
- Surgery is the treatment of choice, but targeted therapy/chemotherapy (as described for the other pancreatic NETs) is indicated for unresectable disease.

Management of advanced/metastatic Pancreatic NETs

- Somatostatin analogues Octreotide LAR (PROMID trial) and lanreotide (CLARINET trial) demonstrated antitumor activity with PFS benefit. They are considered first-line treatment in well-differentiated gastroenteropancreatic (GEP) NETs with positive ^{68}Ga-DOTATATE scans.
- Patients with ^{68}Ga-DOTATATE positive scans who progress on somatostatin analogues can be treated with ^{177}Lu-DOTATATE. A clinical trial of 229 patients with well-differentiated metastatic midgut NET randomized patients to either ^{177}Lu-DOTATATE every 8 weeks plus best supportive care including long-acting octreotide or long-acting octreotide alone every 4 weeks. The estimated rate of PFS at month 20 was 65.2% (95% CI, 50.0-76.8) in the ^{177}Lu-DOTATATE group and 10.8% (95% CI, 3.5-23.0) in the control group. The response rate was 18% in the ^{177}Lu-DOTATATE group versus 3% in the control group ($P < .001$). Grade 3 or 4 neutropenia occurred in 1%, thrombocytopenia 2%, and lymphopenia 9% in patients receiving ^{177}Lu-DOTATATE comparing with the control group.
- Cytotoxic chemotherapy regimens such as TMZ and capecitabine are preferred when tumor response is needed for symptoms or large volume disease. In a retrospective study, 30 patients were treated with capecitabine and TMZ and 70% of patients achieved an objective radiographic response with a median PFS of 18-months. At 2 years, the rate of survival was 92%. Other active agents include streptozotocin, doxorubicin, 5-fluorouracil, and dacarbazine. See Table 33.3 for detailed chemotherapy regimens.
- Both sunitinib and everolimus (RADIANT-3) have been approved for the treatment of progressive, well-differentiated pancreatic NETs. Approval was based on improved PFS.
- Patients with recurrent disease that includes liver metastases or liver dominant metastatic disease can be treated with surgical resection (when possible) or liver-directed therapy such as chemoembolization or radiofrequency ablation.

ADRENOCORTICAL CARCINOMA

Epidemiology

- ACC is a rare malignancy arising from the adrenal cortex, with 1.5 to 2 cases per million population per year.
- It has a bimodal age distribution, with a first peak in children younger than 5 years and a second peak in adults in their fourth to fifth decade.
- ACC remains a difficult-to-treat disease, with a 5-year survival of 10% to 25% and an average survival from diagnosis of ≈14.5 months.
- Most cases are sporadic, but it can be a component of a hereditary syndrome (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, MEN 1) (Table 33.1).

Clinical Presentation

Symptoms may arise from the effects of local mass or distant metastases. Approximately 50% of patients present with evidence of hormonal excess consisting of:

- Hypercortisolism (Cushing syndrome)
- Virilization/feminization
- Mineralocorticoid excess

Diagnosis

- Imaging studies can usually distinguish benign adenomas from ACC. Because ACCs have lower lipid content than benign adenomas, they usually have higher density values on CT scans; while on MRI, they are usually isointense with the liver on T1 images and have intermediate to high intensity on T2 images.
- Biochemical evaluation (urinary steroids and suppression tests) should be conducted if clinically warranted.
- FNA cannot differentiate an adrenal adenoma from ACC and should only be done if the adrenal mass is suspected to be a metastasis from another malignancy.
- Diagnosis is often confirmed upon surgical resection; however, histologic differentiation of adrenocortical adenomas and carcinomas is challenging.
- Carcinomas tend to display mitotic activity, aneuploidy, and venous invasion. Carcinomas may also secrete abnormal amounts of androgens and 11-deoxysteroids.

Treatment

Surgery

- A tumor with local invasion and nodal involvement, tumor invading adjacent organs, or any tumor with distant metastases constitutes stage IV disease.
- En bloc resection is initially appropriate for stages I to III.
- Debulking of unresectable or stage IV disease should be considered, particularly for symptom relief from hormone-secreting tumors; local recurrence and metastatic disease require further resection when feasible.
- In general, adrenal tumors > 6 cm (or <6 cm but suspected of being malignant) should be resected via open adrenalectomy. Because surgery remains the only proven curative option for a patient with ACC, it must always be aggressively pursued at presentation and at relapse, and a laparoscopic approach should never be used.

Adjuvant Therapy

- Adjuvant mitotane may improve survival for patients with stage I to III disease who have undergone a complete resection.
- Several small and one large retrospective studies suggest mitotane given as an adjuvant therapy and continued indefinitely can at a minimum delay and possibly prevent a recurrence of disease.
- Replacement steroids can be started with the initiation of mitotane or when clinical and laboratory parameters indicate adrenal insufficiency. Both fludrocortisone and hydrocortisone should be given.
- An international prospective randomized trial comparing mitotane to placebo in this patient population is currently ongoing.

Advanced Disease

- For advanced disease, mitotane monotherapy induces hormonal response rates in up to 75% of patients with functional tumors, with no change in OS.
- Combination chemotherapy with mitotane plus etoposide, doxorubicin, and cisplatin (EDP) demonstrated better rates of response and disease-free survival than mitotane plus streptozotocin in patients with advanced disease based on the FIRM-ACT trial (**F**irst **I**nternational **R**andomized trial in locally advanced and **M**etastatic **A**drenocortical **C**arcinoma **T**reatment). The study found a significantly better response rate (23.2% vs 9.2%, $P < .001$) and PFS (5.0 vs 2.1 months; HR, 0.55; $P < .001$) with EDP plus mitotane than with streptozocin plus mitotane as first-line therapy, with similar rates of toxic events.
- Pembrolizumab is now FDA-approved for solid tumors with microsatellite-high and/or mismatch repair deficient status (MSI-H/MMR-D). A phase II clinical trial evaluated pembrolizumab in patients with ACC with a primary

end point of ORR. Thirty-nine patients were enrolled with a median follow-up time of 18.8 months. An ORR was reported to be 23% with a disease control rate of 52%; median PFS and OS were 2.1 and 24.9 months, respectively. Six patients in the study were noted to have MSI-H/MMR-D. Immune checkpoint inhibitors can be considered in patients with MSI-H/MMR-D tumors. The role of supraphysiological doses of circulating corticosteroids (related to hormonal excess) may limit the efficacy of these agents.

- Radiofrequency ablation may also be implemented for local control or metastases in patients with unresectable disease.
- See Table 33.4 for detailed chemotherapy regimens.

PARATHYROID CARCINOMA

Clinically, it is important to distinguish this disease from other benign disorders that cause hyperparathyroidism. Parathyroid carcinoma accounts for less than 1% of cases of hyperparathyroidism.

Epidemiology and Natural History

- Parathyroid carcinoma occurs in <1 per million individuals per year, predominantly diagnosed in the fifth or sixth decade of life.
- Germline or somatic mutations of the *HRPT2* tumor suppressor gene are detected in the majority of cases.
- Ten-year survival rate is approximately 70%; however, 40% to 60% will recur after initial surgery.
- Morbidity and mortality are usually related to hypercalcemia rather than complications of metastases.

Clinical Presentation

Patients typically present with the following:

- Symptoms of hypercalcemia, with calcium levels usually >14 mg/dL
- Elevated parathyroid hormone levels
- Palpable neck mass in up to 70%
- Metastases to the cervical lymph nodes, lungs bone, or liver in approximately 10%

Diagnosis

- Parathyroid carcinoma is difficult to diagnose preoperatively; differential includes parathyroid adenoma and hyperplasia.

- Most parathyroid carcinomas are diagnosed at surgery; however, some are not diagnosed until local recurrence or metastases. This is because there are no definitive histopathologic features to differentiate carcinoma from adenoma.
- FNA is inappropriate for diagnosis.

Treatment

Surgery

- Treatment consists of parathyroidectomy with en bloc resection of tumor and involved structures. This may include the ipsilateral lobe of thyroid. Radical lymph node dissection is not recommended.
- Recurrent tumor and oligometastases should also be resected.

Radiation

- Parathyroid tumors are generally not radiosensitive.
- Small retrospective studies suggest that there may be improved local control with postoperative radiotherapy for high-risk patients.
- Radiation may have palliative benefit.

Medical Therapy

- Chemotherapy efficacy is limited to case reports, and there is no standard regimen.
- Management of hypercalcemia is essential while treating parathyroid carcinoma.

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34

Hematopoietic Growth Factors

Philip M. Arlen

BACKGROUND

- Hematologic toxicity (leukopenia, anemia, and thrombocytopenia) is the most common side effect of chemotherapy and large-field radiotherapy. Further, cytopenia is inherent to stem cell transplantation. It can lead to serious complications, such as neutropenic fever, which may require hospitalization.
- Hematopoietic growth factors are the regulatory molecules that stimulate the proliferation, differentiation, and survival of hematopoietic progenitor and stem cells. They were originally called colony-stimulating factors (CSFs) because of their role in colony formation in bone marrow cell cultures.
- Several hematopoietic growth factors are currently available for clinical use and are synthesized mainly by DNA recombinant technology.
- Recommendations in this chapter come primarily from the evidence-based clinical practice guidelines of the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and the American Society of Hematology (ASH).

MYELOID GROWTH FACTORS

- Currently, two myeloid growth factors, filgrastim and pegfilgrastim, both of which are granulocyte–colony-stimulating factors (G-CSF), have been approved by the U.S. Food and Drug Administration (FDA) for use in prevention of chemotherapy-induced neutropenia. Filgrastim is specific for production of neutrophils but has immunomodulatory effects on lymphocytes, monocytes, and macrophages. Anti-inflammatory effects have also been described for G-CSF. Pegfilgrastim is a pegylated form of filgrastim and has a longer half-life ranging from 15 to 80 hours.
- Sargramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF) that stimulates the production of monocytes and eosinophils, in addition to neutrophils, and prolongs their half-lives. It also enhances their function through activation of chemotaxis, phagocytosis, oxidative activity, and antibody-dependent cellular cytotoxicity. The labeled clinical indication is for use to shorten the time to neutrophil recovery following induction chemotherapy in older adult patients with acute myelogenous leukemia and other various stem cell transplantation settings.

INDICATIONS

Primary Prophylaxis

CSFs are recommended for use with first- and subsequent-cycle chemotherapy to prevent febrile neutropenia (FN) when risk of FN is high (>20%). Primary prophylaxis is the administration of CSFs during the first cycle of myelosuppressive chemotherapy. This may reduce neutropenic complications throughout administration of chemotherapy cycles. Although no nomogram exists to calculate this risk, factors to consider determining a patient's risk of FN include type of chemotherapy regimen (dose-dense therapy, high-dose therapy, standard-dose therapy), goal of therapy (palliative or curative), and patient's risk factors including:

- Age above 65 years
- Poor performance status
- Extensive prior treatments, including large-port radiation
- Previous episodes of FN
- Cytopenia due to bone marrow involvement by tumor
- Advanced cancer
- Active infections or presence of open wounds
- Poor nutritional status
- Other serious comorbidities or renal or liver dysfunction

Several placebo-controlled randomized-controlled trials have shown that the prophylactic use of G-CSFs has been shown to reduce the incidence, length, and severity of chemotherapy-related neutropenia in various solid tumor types. Dose-dense chemotherapy regimens supported by G-CSF had shown superior clinical outcome compared to conventional chemotherapy in adjuvant treatment of node-positive breast cancer and in elderly patients with aggressive lymphoma. Cochrane meta-analyses of 2607 randomized lymphoma patients from 13 trials reported that G-CSF and GM-CSF as a prophylaxis reduced the risk of neutropenia, FN, and infection. However, there was no evidence that either G-CSF or GM-CSF provide a significant benefit in terms of tumor response, freedom from treatment failure, or overall survival. Finally, NCCN and ASCO guidelines during the COVID-19 pandemic have been updated lowering the threshold for the use of myeloid growth factors from those chemotherapy regimens which have a 20% or higher risk of FN to now include those regimens with a risk of 10% to 20%, including all of the intermediate-risk chemotherapy regimens.

Secondary Prophylaxis

The guidelines recommend administering CSFs to patients who experienced FN or dose-limiting neutropenic event in a prior cycle of chemotherapy when no CSFs were given and a repeat of which episode could impact the next planned dose of chemotherapy. Dose

reduction and treatment delay, however, are reasonable alternatives, especially in the palliative setting.

Neutropenic Fever

Routine adjunctive use of CSFs for FN is not recommended. CSFs should be considered in patients with FN who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include the following:

- Age above 65years
- Expected prolonged (more than 10 days)
- Profound (<100/μL) neutropenia
- Sepsis syndrome
- Being hospitalized at the time of the development of fever
- Pneumonia
- Invasive fungal infection
- Uncontrolled primary disease

A multicenter randomized trial demonstrated that therapeutic G-CSF shortens hospital stay (median, 5 vs 7 days; P = .015), antibiotic therapy (median, 5 vs 6 days; P = .013), duration of grade IV neutropenia (median, 2 vs 3 days; P = .0004), in 210 solid tumor patients with FN, and at least one high-risk feature. Cochrane meta-analysis of 1518 patients from 13 trials reported that therapeutic CSF was associated with shorter hospital stay, duration of neutropenia, but no improvement in overall survival.

Hematopoietic Stem Cell Transplantation

CSFs are used routinely to mobilize peripheral blood stem cell (PBSC) and to shorten the duration of neutropenia after cytoreduction and autologous PBSC transplantation. Post autotransplantation use of CSFs has been associated with shorter duration of neutropenia and hospitalization and reduced medical costs. In contrast, CSFs used after allogeneic transplantation have

been reported to increase the risk of severe graft-versus-host disease and to reduce survival.

For mobilization of stem cells before harvesting from the healthy donor or the patient before autologous stem cell transplant, different protocols exist.

Mobilizing stem cells typically involves daily injections of Filgrastim with the most common adverse events being bone pain and allergic reactions. While initially there was a concern about secondary leukemia in subjects having received G-CSF, large studies show no increase in incidence. Severe side effects are rare with less than 1% of donors experiencing such toxicity. In a review by the National Marrow Donor Program, among >23,000 subjects having donated peripheral stem cells, 4 fatalities were observed and 37 severe adverse events. The incidence of hematologic malignancies in follow-up (n = 12) did not exceed the expected incidence in the adjusted general population.

Leukemia and Myelodysplastic Syndromes

- In patients with acute myeloid leukemia (AML), CSFs can be used in two settings—(1) after completion of induction chemotherapy and (2) after completion of consolidation chemotherapy. Use of G-CSF shortly after completion of induction chemotherapy can lead to a modest decrease in neutropenia duration but has not shown to have favorable effect on remission rate, duration, or survival. Use of G-CSF after completion of consolidation chemotherapy seems to have a more profound beneficial effect on the duration of neutropenia and the rate of serious infections. However, no effect on complete response duration or overall survival can be observed. Indeed, a recent Cochrane meta-analysis including 5256 AML patients in 19 trials reported that the addition of CSFs did not alter all-cause mortality in the short- and long-term. In this meta-analysis, the administration of CSFs did not affect the occurrence of episodes of neutropenic fever, bacteremias, or

invasive fungal infections. Thus, currently, there are insufficient data to support the use of CSF for leukemia-priming effects. Likewise, insufficient data exist to support the use of long-acting CSF (pegfilgrastim) in AML.

- In myelodysplastic syndrome (MDS), intermittent use of CSFs may be considered in patients with severe neutropenia complicated by recurrent infections. There are no data on the safety of long-term use.
- In acute lymphoblastic leukemia (ALL), CSFs are recommended after the completion of the initial induction or first postremission chemotherapy course to shorten the duration of neutropenia. Their effect on duration of hospitalization and acquisition of serious infections are less consistent.

SIDE EFFECTS

Bone pain is frequently encountered with the use of myeloid growth factors. Rarely, splenic rupture and severe thrombocytopenia have been reported. CSFs may cause a transient acute respiratory distress syndrome or inflammatory pleuritis and pericarditis, which are thought to be secondary to neutrophil influx or capillary leak syndrome. In patients with sickle cell disease, use of CSFs has led to severe sickle cell crisis, resulting in death in some cases. Concurrent use of CSFs with chemotherapy and radiation therapy should be avoided because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy. In addition, CSFs should be avoided in patients receiving concomitant chemoradiotherapy, particularly involving the mediastinum. This is because of observation that patients receiving CSF support while being treated with concurrent chemoradiotherapy for lung cancers had more significant thrombocytopenia and increased pulmonary toxicities compared to patients in placebo arms. These findings suggested potential for an adverse interaction between mediastinal radiotherapy and CSF administration.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

- May cause flulike symptoms, fever, and rash.
- There is in vitro evidence that GM-CSF may stimulate HIV replication; however, clinical studies have not shown adverse effects on viral load among patients on antiretroviral therapy.
- The liquid form of sargramostim was withdrawn from the market in January 2008 because of increased reports of syncope, which was not seen with the lyophilized formulation.

GRANULOCYTE–COLONY-STIMULATING FACTOR

- In general, G-CSF is better tolerated than GM-CSF and is used more commonly.
- May rarely cause pathologic neutrophil infiltration (Sweet syndrome).
- Antibodies to growth factors have been detected with some preparations but are not neutralizing.
- Fragmentary evidence has raised concerns for increased risk of late monosomy 7–associated MDS and AML in patients with aplastic anemia treated with long-term G-CSF.

DOSING

- Recommended dosing of CSFs is listed in Table 34.1.

TABLE 34.1

Growth Factors for Transplant or Nonmyeloid Cancer Patients Only: FDA-Approved Dosing and Indications

Drug	Dosing	Indications

Drug	Dosing	Indications
Filgrastim (Neupogen)	5 μg/kg SC daily 24 h after completion of chemotherapy until ANC reaches 2000-3000/mm^3 10 μg/kg SC daily at least 4 d before the first leukapheresis; continue until the last leukapheresis	Myelosuppressive chemotherapy PBSC mobilization
Pegfilgrastim (Neulasta)	Single 6-mg fixed dose SC 24 h after completion of chemotherapy	Myelosuppressive chemotherapy
Sargramostim (Leukine)	250 μg/mm^2 IV daily until ANC reaches 1500/mm^3 for 3 consecutive days; reduce dose by 50% if ANC increases to >20,000/mm^3	Auto/allo BMT, after AML induction chemotherapy
Epoetin alfa (Epogen; Procrit)	Start at 150 U/kg SC TIW or 40,000 U SC weekly	Chemotherapy-induced anemia
	Escalate dose to 300 U/kg TIW or 60,000 U SC weekly if Hb rises <1 g/dL in 4 wk and remains below 10 g/dL, no reduction in transfusion requirements, or rise in Hb after 8 wk (for TIW dosing)	
	Reduce dose by 25% when Hb reaches level needed to avoid transfusion or Hb rises >1 g/dL in 2 wk	
	• Hold when Hb rises to a level where transfusions may be required; resume at 25% below previous dose when Hb reaches level where transfusion may be required	
Darbepoetin alfa (Aranesp)	Start at 2.25 μg/kg SC weekly or 500 μg SC Q3W Escalate dose to 4.5 μg/kg if Hb rises >1 g/dL after 6 wk Reduce dose by 40% of previous dose when Hb reaches level needed to avoid transfusion or Hb rises >1 g/dL in 2 wk Hold if Hb exceeds a level needed to avoid a blood transfusion. Resume at 40% below previous dose	Chemotherapy-induced anemia
Oprelvekin (Neumega)	50 μg/kg SC daily; start 6-24 h after completion of chemotherapy and continue until postnadir platelet count is >50,000/mm^3	Nonmyeloablative chemotherapy-induced thrombocytopenia

AML, acute myeloid leukemia; ANC, absolute neutrophil count; auto/allo BMT, autologous/allogeneic bone marrow transplant; d, days; ESA, erythropoiesis-stimulating agent; FDA, U.S. Food and Drug Administration; h, hours; Hb, hemoglobin; IV, intravenously; PBSC, peripheral blood stem cell; Q3W, every 3 weeks; SC, subcutaneously; TIW, three times per week; wk, weeks.

- In chemotherapy patients, transient increase in neutrophil count is typically observed in the first 1 to 2 days after initiation of CSFs. Treatment should continue until postnadir absolute neutrophil count (ANC) reaches 10,000/mm^3. Check complete blood count twice weekly.
- Pegfilgrastim should not be administered from 14 days before to 24 hours after myelosuppressive chemotherapy.
- Sargramostim is licensed for use after autologous or allogeneic bone marrow transplant and for AML.

ERYTHROPOIESIS-STIMULATING AGENTS

Erythropoiesis-stimulating agents (ESAs) are semisynthetic agents that simulate the effects of erythropoietin (EPO), an endogenous hormone produced by the kidneys. By binding to EPO receptors, ESAs stimulate the division and differentiation of committed erythroid progenitors in bone marrow. ESAs are manufactured by recombinant DNA technology and are available as epoetin alfa and darbepoetin alfa. Darbepoetin alfa has a half-life around three times longer than that of epoetin alfa; however, they are considered equivalent in terms of effectiveness and safety.

EFFECTS

- ESAs were first used to manage anemia in patients with chronic renal failure (CRF). Several randomized clinical trials have demonstrated that ESAs decrease blood transfusion requirements and improve quality of life in patients on hemodialysis.
- In cancer patients undergoing chemotherapy, ESAs have been shown to reduce the need for transfusions, but their effects on anemia symptoms and quality of life have not been proven.
- A growing body of evidence has raised serious concerns about the safety of ESAs.

Transfusion Requirements and Quality of Life

A recent systematic review summarized the results of 57 trials involving 9353 cancer patients randomly assigned to receive ESA plus RBC transfusion or transfusion alone. This meta-analysis included patients who did and patients who did not receive concurrent antineoplastic therapy. Results showed a 36% reduction in transfusion requirement in those receiving ESA. Although there was a positive overall effect on quality of life, the report could not draw definite conclusions because of the differing parameters used by the various studies.

Survival, Mortality, and Disease Control

- Observational studies have suggested that anemia in cancer patients is associated with shorter survival and that increasing hemoglobin (Hb) levels may improve survival and tumor response in some cancers. Because radiation and some chemotherapy agents are dependent on tissue oxygenation for their effect, it was speculated that improving oxygen delivery by increasing Hb levels may optimize the effects of antineoplastic treatments. Based on this hypothesis, several randomized trials in head and neck, breast, non-small cell lung, lymphoid, and cervical cancers were conducted to evaluate the effect of ESAs on survival and disease control. Most of these studies were terminated prematurely because of disease progression and increased mortality. A preliminary report of a study using ESAs in cancer patients not receiving chemotherapy showed no reduced need for blood transfusions; it did, however, show increased mortality. Based on this report, the FDA released a black-box safety alert in February 2007 warning against the use of ESAs for anemia in cancer patients not receiving chemotherapy. The FDA also recommended a minimum-effective dose of ESAs that would gradually increase Hb levels sufficient to avoid transfusion, but not to exceed 12 g/dL. Most of the ESA trials had set a goal of Hb > 12 g/dL; however, the

risks of shortened survival and thrombotic thrombocytopenic purpura (TTP) have persisted even when ESAs are dosed to achieve Hb levels >12 g/dL. An updated meta-analysis of 53 RCTs and 13,933 cancer patients looked for mortality as the primary end point and found ESAs to be associated with significantly greater overall on-study mortality. In those with chemotherapy-induced anemia (*n* = 10,441), a statistically significant mortality change could not be demonstrated. Poor outcomes could not be consistently attributed to a single mechanism.

- It has been suggested that shorter TTP could be attributed to EPO receptor-positive tumors. However, currently available assays to detect EPO receptors are nonspecific, and their validity has not been determined.
- In July 2007, the Centers for Medicare and Medicaid Services revised their national coverage guidelines to limit reimbursement of ESAs. Coverage of ESAs in cancer patients is now restricted to those receiving chemotherapy whose Hb level is 10 g/dL or lower prior to initiation of ESA treatment.
- Increased mortality and adverse events have also been observed in CRF patients, which have led to lower Hb targets in this patient population.

INDICATIONS

ASCO and ASH Guidelines

In nonmyeloid cancers, ESAs should be considered as one of the many options in patients receiving chemotherapy whose anemia is symptomatic and chemotherapy related. The goals are avoidance of blood transfusions and possible symptomatic benefit. ESAs can be initiated if Hb falls below 10. For Hb levels between 10 and 12, use of ESAs should only be based on symptoms, clinical circumstances, and patient preference. If there is no response after 6 to 8 weeks with appropriate dose modification, treatment should be discontinued.

Blood transfusion is a therapeutic option. In the most recent guidelines updated in 2019, the use of ESAs may be indicated in the setting of palliative chemotherapy, but they should not be used for patients whose treatment is for curative intent. This recommendation was made based on known risks, such as thromboembolic events, and the short-term mortality and decreased overall survival that have been observed across patient groups.

FDA-Approved Indications

ESAs are approved for chemotherapy-related anemia in nonmyeloid malignancies treated with palliative intent, CRF, HIV (zidovudine) therapy, and to reduce the need for blood transfusion in elective noncardiac and nonvascular surgeries.

Off-Label/Investigational Use

- There is evidence supporting the use of ESAs for anemia related to MDS. However, patients may require higher doses and response may be delayed. Predictors of response include low-risk MDS and low-EPO levels (_200 U/L). Combining ESAs and G-CSF in MDS patients has resulted in improved response rates.
- Other indications include multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, beta thalassemia, radiation therapy, rheumatoid arthritis, paroxysmal nocturnal hemoglobulinuria, Castleman disease, congestive heart failure, critical illnesses, hepatitis C (in patients treated with interferon-alfa and ribavirin), and blood-unit collection for autotransfusion.

DOSING

Recommended dosing and dose adjustments of ESAs in chemotherapy-induced anemia are listed in Table 34.1. After initiation or dose modification of ESAs, Hb should be monitored weekly until it stabilizes.

SIDE EFFECTS

- The most serious side effects of ESAs are thromboembolic events, defined as transient ischemic attack, stroke, pulmonary emboli, deep vein thrombosis, and myocardial infarction. A meta-analysis showed that thromboembolic events increased 67% in cancer patients; for a population with baseline risk of 20%, the number needed to harm would be 7.5 patients (95% CI, 3.1-15.6). There is evidence for increased risk of thromboembolic events in CRF and surgical patients, especially with higher Hb targets. Preliminary analysis of a trial in spinal surgery patients given ESAs to decrease postsurgery transfusion requirements showed increased incidence of thromboembolic events in the ESA arm. Notably, patients received no prophylactic anticoagulants postoperatively.
- ESAs are contraindicated in uncontrolled hypertension, more commonly seen in CRF patients who receive IV ESAs.
- Other side effects include headache, fatigue, fever, rash, pruritus, hypersensitivity reactions, arthralgia and myalgia, nausea, seizures, and pure red-cell aplasia due to neutralizing antibodies to native EPO.

OTHER CONSIDERATIONS

- Iron supplementation should be considered in patients receiving ESAs, especially those with borderline iron stores, because iron deficiency can develop soon after initiation of ESAs and can adversely affect response to ESAs. Data from multiple controlled trials have shown that IV iron can enhance ESA efficacy and can reduce the required dose in cancer patients.
- Measuring serum EPO levels may help to identify patients more likely to respond to ESAs. Patients with baseline EPO levels 100 U/L are more likely to respond to ESAs than those with levels 100 U/L.

PLATELET GROWTH FACTORS

- Thrombocytopenia can be a life-threatening consequence of antineoplastic treatments. Platelet transfusions are required to prevent or mitigate hemorrhagic complications. Due to the short life span of thrombocytes, transfusion necessity may arise as frequently as on a weekly basis. Patients at high risk for bleeding or who experience delays in receiving planned chemotherapy include the following:
  - Patients with poor bone marrow reserve or a history of bleeding
  - Patients on treatment regimens highly toxic to bone marrow
  - Patients with a potential bleeding site (eg, necrotic tumor)
- Fortunately, iatrogenic thrombocytopenia that requires platelet transfusion or causes major bleeding is relatively uncommon, although occurrence tends to increase with cumulative cycles of chemotherapy that are toxic to hematopoietic progenitor cells.
- Although several thrombopoietic agents are in clinical development, oprelvekin is the only thrombocytopoietic agent FDA-approved for clinical use in nonmyeloid malignancies with chemotherapy-induced anemia. Oprelvekin is a product of recombinant DNA technology and is nearly homologous with native IL-11. Oprelvekin stimulates megakaryocytopoiesis and thrombopoiesis and has been shown to modestly shorten the duration of thrombocytopenia and reduce the need for platelet transfusions in patients who develop platelet counts $<20 \times 10^3$ per μL after prior antineoplastic treatments. Oprelvekin is not indicated following myeloablative chemotherapy.

Major side effects include fluid retention and atrial arrhythmias. Hypersensitivity reactions, including anaphylaxis, have also been reported. Table 34.1 provides the recommended dose of oprelvekin.

A new generation of thrombopoietin (TPO) molecules have been developed; called the TPO (c-mpl ligand) family, based upon their common ability to bind and activate the TPO receptor, c-mpl. Ongoing clinical trials are studying TPO receptor agonists in chemotherapy-associated thrombocytopenia.

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CHAPTER 35

Infectious Complications in Oncology

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FEVER

- Fever is the most common sign of infection, and a common problem in patients with cancer.
- Fever is conventionally defined as one oral temperature greater than 38.3 °C or two oral temperatures greater than 38 °C measured 1 hour apart.
- Old age, malnutrition, and corticosteroids may blunt the febrile response. From the practical management standpoint, one must separate between fever in the neutropenic cancer patient ("neutropenic fever") and fever in the absence of neutropenia.
- Fever is a very common manifestation of cytokine release syndrome (CRS), which is frequently seen following many current forms of immunotherapy (cellular therapies, monoclonal antibodies like blinatumomab). Management of fever during immunotherapy may be particularly challenging, but the general rules of neutropenic fever should apply when the absolute neutrophil count (ANC) is <500/mm^3.

FEVER IN THE NEUTROPENIC CANCER PATIENT (NEUTROPENIC FEVER)

- Neutropenia, the most important risk factor for bacterial infection in cancer patients, is defined as an ANC <500/mm^3, or ANC ≤1000/mm^3, with a predicted decline to <500/mm^3 within 48 hours.
- Fever during neutropenia is always considered to be of infectious origin and managed accordingly.
- The risk of infection increases with the rapidity of onset, degree, and duration of neutropenia.
- Febrile neutropenic patients require immediate evaluation and prompt initiation of empirical broad-spectrum antibiotics with activity against *Pseudomonas aeruginosa* (Figure 35.1). Antibiotics are usually administered intravenously, but oral administration may be acceptable when patients are determined to be at low risk of severe morbidity and mortality based on biological features and access to care (see below).

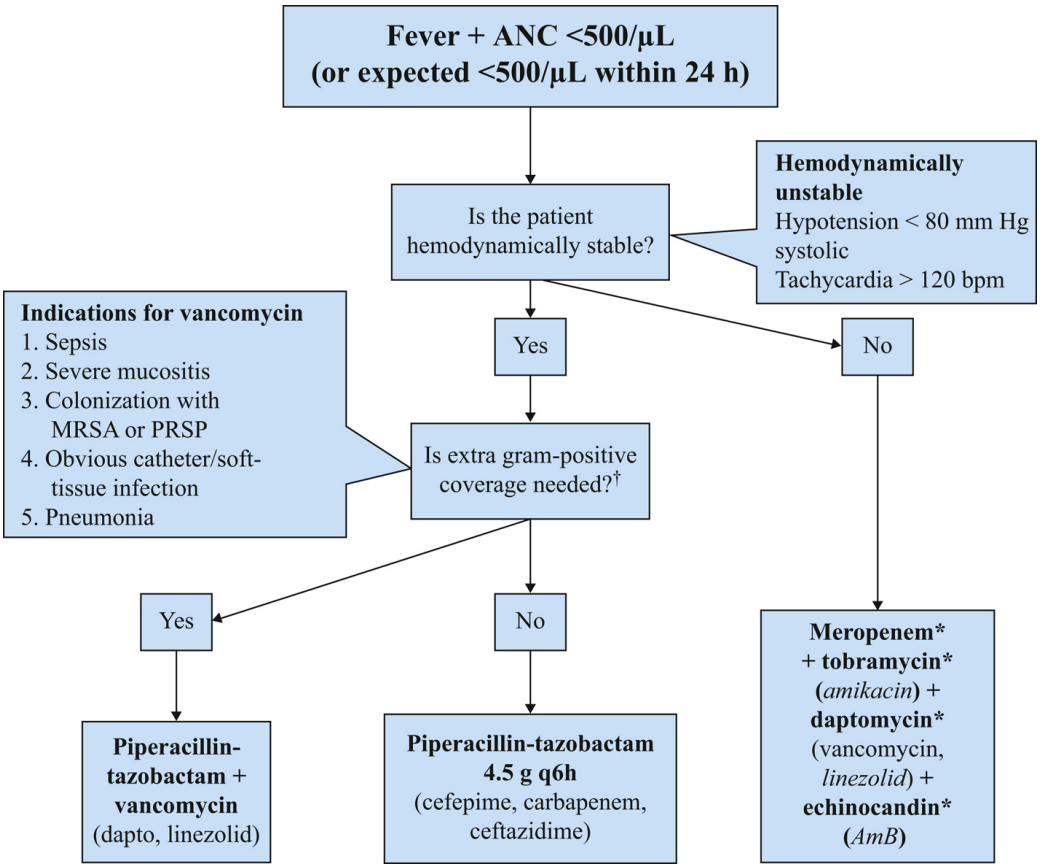

FIGURE 35.1 Approach to patients with fever and neutropenia without clinically or microbiologically documented infection.The choice between piperacillin-tazobactam (shown here emphasizing the higher dose required in neutropenic patients), cefepime, imipenem, meropenem, and ceftazidime will vary between institutions based on local resistance patterns. For specific infections, see the text and Table 35.1.* This antibacterial regimen for the neutropenic patient with sepsis will vary between institutions, depending on the local patterns of antibiotic resistance. Carbapenem + fluoroquinolone (or aminoglycoside or colistin) + vancomycin (or daptomycin or linezolid) + echinocandin is typical. We prefer meropenem and daptomycin because both can be "pushed" intravenously in a few minutes. The antifungal of choice will vary depending on previous antifungal prophylaxis.† The empirical gram-positive coverage should usually be discontinued after 48 to 72 hours if there is no bacteriologic documentation of a pathogen requiring its use, except in soft-tissue or tunnel infections. Linezolid or daptomycin may be substituted for vancomycin if there is suspicion or high endemicity of VRE. For a detailed discussion of antifungal therapy options, as well as for the role of oral antibiotics in low-risk patients, see the text. AmB, amphotericin B; MRSA, methicillin (oxacillin)-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*.

TABLE 35.1

Resistant Bacteria: What Everybody Should Know

	Resistant to	Treat With	Things to Remember
Gram positive			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Semisynthetic penicillins; first-, second-, and third-generation cephalosporins, carbapenems	Vancomycin, daptomycin, ceftaroline	Community-acquired MRSA is frequently susceptible to clindamycin, doxycycline, and trimethoprim/sulfamethoxazole (TMP/SMX)

	Resistant to	Treat With	Things to Remember
Vancomycin-resistant *Enterococcus* (VRE)	Vancomycin and all beta-lactams	Linezolid, daptomycin, quinupristin/dalfopristin May be tigecycline and oritavancin	Microbiological success is no higher than 40%; there is no clinical evidence to prefer one agent over another
Mycobacterium abscessus	Almost everything	*Infectious Diseases support required* Combination therapy required, usually with meropenem + amikacin + azithromycin ± linezolid	Respiratory colonizer AND potential pathogen, particularly in patients with abnormal airways/lungs
Gram negative			
SPICE Enterobacteriaceae (*Serratia*, *Pseudomonas*, indole-positive P*roteus*, *Citrobacter,* and *Enterobacter*)	They may seem susceptible, then become resistant to third-generation cephalosporins (like ceftriaxone and ceftazidime) during treatment	Carbapenems, fluoroquinolones (ciprofloxacin, levofloxacin), maybe cefepime	Your microbiology laboratory should add a note saying that **even if it looks susceptible by antibiogram**, the isolate may become resistant during treatment
ESBL (extended-spectrum beta-lactamase)-producing Enterobacteriaceae (most commonly *Escherichia coli* and *Klebsiella*)	All cephalosporins	Carbapenems	The antibiogram will show the resistance to third-generation cephalosporins
CRE (carbapenem-resistant Enterobacteriaceae) Any Enterobacteriaceae may carry a gene conferring resistance to carbapenems through carbapenemases like Klebsiella pneumoniae carbapenemase (KPC), metallo-betalactamases (MBLs), OXA betalactamases	All cephalosporins and carbapenems	*Infectious Diseases support required* Some may respond to ceftazidime-avibactam, some may respond to cefiderocol	It is important to be familiar with the methodology of the microbiology laboratory and ask for help interpreting the antibiogram. CRE produce carbapenemases, and these are of great epidemiological (as well as clinical) significance. Other mechanisms of resistance to carbapenems (eg, porin genes) are less severe
Multidrug-resistant (MDR) *Acinetobacter baumannii*	All commonly used antibiotics	*Infectious Diseases support required.* Cefiderocol seems promising	Inhaled colistin has been used in cases of MDR *Acinetobacter* or *Pseudomonas*, but its efficacy is far from clear
MDR *Pseudomonas aeruginosa*	All commonly used antibiotics	*Infectious Diseases support required.* Ceftazidime-avibactam and ceftolozane/tazobactam are effective sometimes, depending of the mechanism of resistance	
Stenotrophomonas maltophilia	Intrinsically resistant to carbapenems and aminoglycosides	TMP/SMX is the treatment of choice; levofloxacin and moxifloxacin and ceftazidime (if susceptible in vitro) are other options; tigecycline and colistin have been used with variable results	Think of it when a patient on meropenem develops breakthrough gram-negative bacteremia

- Three distinct syndromes of fever during neutropenia are of practical importance.

- **First fever:** In 20% to 25% of patients with fever and neutropenia, an infection is documented microbiologically (most commonly bacteremia). In 20% to 30% of patients, an infection is documented only clinically, without microbiologic confirmation (eg, typhlitis with negative blood cultures). In 50% of patients with fever and neutropenia, no infection is found. The response to empirical management with antibiotics is similarly favorable in these three subgroups. Gram-positive and gram-negative bacteria are isolated with roughly similar frequency. Treatment emphasizes coverage of gram-negative bacteria because these infections tend to progress faster and have higher mortality.
- **Persistent fever:** The average time to defervescence for the first episode of neutropenic fever is 3 to 4 days. When fever persists for 5 days or more (4-7, depending on the study), the frequency of invasive fungal infection is high enough that it is standard practice to add empirical antifungal therapy. *Candida* and *Aspergillus* species are the most common causes of fungal infections in neutropenic patients and increase in frequency with longer duration of neutropenia. The antifungal agent of choice may vary with the clinical situation and the preexistent use of antifungal prophylaxis. In the absence of antifungal prophylaxis, the most common fungal pathogen causing persistent fever is *Candida albicans.* If antifungal prophylaxis was being administered, *Aspergillus* and non-*albicans* species of Candida become more likely. Randomized controlled trials support the empirical addition of amphotericin B (deoxycholate or liposomal), voriconazole, and caspofungin for persistent fever. The choice varies based on what (whether) antifungal prophylaxis was being used and an estimate of the risk. It is appropriate to look for invasive fungal infection by blood cultures and computed tomography (CT) of the chest and possibly sinuses.
- **Recrudescent fever (new fever after resolution of the first episode):** This term refers to the reappearance of fever after the patient has been afebrile for more than 48 hours following the administration of broad-spectrum antibiotics for an episode of neutropenic fever. In this situation, an infectious cause is identified in most cases (as opposed to the initial fever, in which most frequently no cause is found) and both breakthrough bacterial and fungal infections are possible. Management includes changing (or adding, if antifungals were not part of the regimen) **both** antibiotics **and** antifungals plus diagnostic studies (CTs as outlined above). Drug-resistant bacteria are increasing (eg, extended-spectrum beta-lactamase [ESBL]–producing gram-negative bacilli, carbapenem-resistant Enterobacteriaceae [CRE], vancomycin-resistant *Enterococcus* [VRE]), so the antibiotic choice should be guided by local prevalence. In institutions where CRE are common, substitution of ceftazidime-avibactam may be appropriate. Conversely, in an institution with high frequency of ESBLs, early switch to imipenem or meropenem may be the best antibacterial strategy for recrudescent fever, when it happens during treatment with ceftazidime, cefepime, or piperacillin-tazobactam.

- The importance of fever during neutropenia is that it is a good surrogate marker for infection. It is not the only one, however, and other signs or symptoms suggestive of infection (eg, abdominal pain, erythema, hypotension, hypothermia) should be similarly treated empirically with antibiotics as well.

EVALUATION

- History and physical examination should be performed with special attention to potential sites of infection: skin, mouth, perianal region, and intravenous catheter exit site.
- Routine complete blood count with differential, chemistries, including liver enzymes and creatinine, urinalysis, and blood and urine cultures should be obtained. Evidence suggests a chest X-ray adds little information unless there are respiratory signs or symptoms, but we routinely recommend it as adding potentially useful baseline information.
- Blood cultures: Two sets of blood cultures are more sensitive than a single set for the diagnosis of bacteremia. There are data supporting the practice of drawing all cultures from the central line (sampling all lumens) in cancer patients to simply diagnose bacteremia. However, to determine if a bacteremic episode is related to the catheter, it is advisable to draw blood from the intravenous catheter and a peripheral vein simultaneously. A differential time to positivity of 2 hours or more (ie, the cultures obtained from the catheter become positive earlier than the peripheral stick) has good predictive value for catheter-related bacteremia.

- Any accessible sites of possible infection should be sampled for gram stain and culture (catheter site, sputum, etc).
- Ideally, blood cultures should be obtained prior to starting antibiotics, but failure to do so should not delay antibiotic administration.

EMPIRICAL ANTIBIOTIC THERAPY

- A summary of the initial management of the patient with fever and neutropenia and no localizing signs or symptoms is provided in Figure 35.1.
- The goal of treatment is to provide broad antibiotic coverage with minimal toxicity, *not* to initially cover any and all conceivable pathogens.
- Most bacterial infections during neutropenia are caused by microorganisms that colonize the oral mucosa, the bowel, and the skin of the patient. *P. aeruginosa* is particularly prevalent during neutropenia. Due to the potential for faster progression and higher morbidity, the emphasis is on coverage of gram-negative bacilli including *Pseudomonas.* This may be achieved by using single agents ("monotherapy") or by combining several antibiotics.

Monotherapy

- Monotherapy with selected broad-spectrum β-lactams with activity against *P. aeruginosa* is as effective as combination antibiotic regimens (β-lactam plus aminoglycoside) for empirical therapy of uncomplicated fever and neutropenia and has less toxicity. The following regimens are the options recommended by the 2011 guidelines from the Infectious Diseases Society of America (IDSA):
  - Cefepime, 2 g IV every 8 hours
  - Imipenem-cilastatin, 500 mg IV every 6 hours
  - Meropenem, 1 g IV every 8 hours
  - Piperacillin-tazobactam, 4.5 g IV every 6 hours
- The choice of one agent over another should be guided mainly by institutional susceptibilities, which may make one or more of these agents a poor choice. Some institutions may still find ceftazidime (which is not on the IDSA's list anymore), 2 g IV every 8 hours, perfectly adequate. By meta-analysis, all these agents seem to offer similar efficacy, but carbapenems may be associated with increased risk of *Clostridium difficile* colitis.

Combination Therapy With Expanded Gram-Negative Coverage

- Combination therapy aiming to broaden the anti–gram-negative activity may be used empirically in certain clinical circumstances, although **there are no definitive data showing clinical benefit.** Combination therapy should be used in cases of:
  - Severe sepsis or septic shock
  - High prevalence of multidrug-resistant gram-negative bacilli (Table 35.1)
- Effective antibiotic combinations include one of the β-lactams plus an aminoglycoside (choice based on local resistance) or colistin or polymyxin B. Ciprofloxacin could be used instead of an aminoglycoside if the prevalence of quinolone-resistant bacteria is low or in patients at high risk of aminoglycoside toxicity. Colistin and polymyxin B are being used more frequently with the increasing prevalence of CRE and multiresistant *Acinetobacter baumannii.*

Role of Vancomycin and Other Agents With Gram-Positive Coverage

Gram-positive coverage with vancomycin should be part of the **initial empirical regimen** only under the following circumstances:

- **Severe sepsis or septic shock** (to ensure coverage of methicillin-resistant *Staphylococcus aureus* [MRSA], penicillin-resistant *Streptococcus pneumoniae* [PRSP] and *Streptococcus mitis*)
- **Pneumonia** (consider it "health care–associated pneumonia")
- **Soft-tissue infection** (cellulitis, necrotizing fasciitis)
- **Clinically suspected catheter-related infections** (eg, because of tenderness or purulent drainage at the exit site; NOT the mere presence of an intravascular device)
- **Severe mucositis** or other risk factors for infection with ***S. mitis*** **(oral infection, use of prophylaxis with fluoroquinolones or trimethoprim/sulfamethoxazole (TMP/SMX), high-dose Ara-C, use of H_2 blockers)**
- **Known colonization** with MRSA or PRSP (this is important, and frequently forgotten)

Addition of vancomycin to the initial regimen:

- Persistent fever is NOT an indication for adding vancomycin because a randomized controlled trial showed that adding vancomycin in this setting was not better than adding placebo.
- Blood cultures that grow gram-positive bacteria are an indication for the addition of agents with gram-positive activity. Pending identification, the choice between vancomycin, linezolid, and daptomycin should be informed by the local prevalence of VRE and preliminary morphologic information from the gram stain as follows (Table 35.2):
  - Gram-positive cocci in clusters: usually *Staphylococcus* (it may be *S. aureus* or coagulase-negative *Staphylococcus*)—vancomycin provides adequate coverage. Rarely (typically in acute leukemia patients already on broad gram-negative coverage), it may mean *Rothia mucilaginosa* (previously *Stomatococcus mucilaginosus*), a dangerous cause of bacteremia and meningitis best treated by the combination vancomycin + meropenem.

TABLE 35.2

How to Interpret Preliminary Information From Blood Culture Reports

Micro Report	What It Means	What to Do	Caveats
Blood culture positive for gram-positive cocci in clusters	Coagulase-negative *Staphylococcus* *Staphylococcus aureus* (In a patient with acute leukemia and prolonged neutropenia, you may worry about *Rothia mucilaginosa*)	Repeat blood cultures from the line AND a peripheral stick (the peripheral is to check time to positivity and decide whether the line is the source of infection) and start vancomycin	Coagulase-negative *Staphylococcus* and *S. aureus* are very different: *S. aureus* can kill your patient in hours, but almost no one dies of coagulase-negative *Staphylococcus* bacteremia.
Blood culture positive for gram-positive cocci in pairs	*Enterococcus* (including VRE) *Streptococcus pneumoniae* Rarely, *Streptococcus agalactiae* (group B *Streptococcus*)	Repeat blood cultures and start either (1) vancomycin if *S. pneumoniae* is more likely or the prevalence of VRE is low OR (2) daptomycin if *Enterococcus* is more likely and there is high prevalence of VRE OR (3) linezolid if you cannot tell and are too tired to think	*Enterococcus* and pneumococcus may be indistinguishable by gram stain, but patients are usually very different (eg, a post allo-HCT with chronic GVHD and pneumonia is likely to have *S. pneumoniae*, whereas a neutropenic patient on cefepime with abdominal pain is likely to have *Enterococcus*). Daptomycin should not be used for pulmonary infections.

Micro Report	What It Means	What to Do	Caveats
Blood culture positive for gram-positive cocci in chains	*Streptococcus* If there is severe mucositis, think of *Streptococcus mitis*; if there are abscesses around, think of *Streptococcus anginosus*, group, also known as *Streptococcus milleri* Remember *Streptococcus pyogenes* (group A *Streptococcus*) and *S. agalactiae* (group B), particularly in patients with soft-tissue infection and at risk for infection with encapsulated bacteria (eg, multiple myeloma)	Add vancomycin	Two oncology scenarios worth remembering: *S. mitis* bacteremia in neutropenic patients with severe mucositis and other risk factors (it can cause ARDS and septic shock, *see* text) and *Streptococcus gallolyticus,* formerly *Streptococcus bovis*, in patients with colon cancer (sometimes not previously known).
Blood culture positive for gram-positive rods	Diphtheroids (skin contaminant) *Corynebacterium JK* (line infection) *Listeria monocytogenes* (bacteremia and meningitis in immunocompromised) *Clostridium* (typhlitis or metastatic gangrene with *Clostridium septicum*) *Bacillus* (catheter-related bacteremia) *Lactobacillus* *Propionibacterium acnes* (contaminant) Mycobacteria (line infection)	*Infectious Diseases support required* The possibilities are too many and with too different clinical implications	As you can see by the possible etiologies, there is no way to give a simple, straightforward recommendation. Vancomycin would be "the right answer" most of the time, but it does not cover *Listeria*, *Lactobacillus*, or mycobacteria and treatment is probably not needed for "diphtheroids" and *P. acnes*. Just call Infectious Diseases.
Blood culture positive for gram-negative rods, "enteric-like" or "lactose-fermenting"	Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella*, *Enterobacter*)	If your institution does not have CREs, imipenem or meropenem will cover 100% of these. If CREs are highly prevalent, switch to ceftazidime-avibactam	The important information from microbiology laboratory is that this SHOULD NOT BE *Pseudomonas*, *Acinetobacter*, or *Stenotrophomonas* (remember, preliminary means NOT definitive).
Blood culture positive for "*Pseudomonas*-like" gram-negative rods	*Pseudomonas aeruginosa*, much less likely *Stenotrophomonas maltophilia* or *Burkholderia*	Two antibiotics with activity against your institution's *P. aeruginosa* (eg, ceftazidime + tobramycin or colistin)	*P. aeruginosa* should be covered empirically with two antibiotics until final susceptibilities are known.
Blood culture positive for "nonfermenting gram-negative rods"	This includes *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia*, and a long list of not very pathogenic bacteria that commonly cause catheter infection in immunocompromised cancer patients (*Alcaligenes*, *Chryseobacterium, Comamonas*, *Sphingomonas, and Elizabethkingia,* among others)	*Infectious Diseases support required* The general concept is that you should consider empirical addition of TMP/SMX or levofloxacin (depending what antibiotic the patient was on), as some of the possibilities are resistant to beta-lactams	No easy answer. Meropenem is the treatment of choice for *Burkholderia*, and completely ineffective against *Stenotrophomonas*. Just call Infectious Diseases.
Blood culture positive for gram-negative coccobacilli	In the cancer patient, *Acinetobacter* should come to mind first	Institutional pattern of resistance dictates the choice	*Acinetobacter* may be difficult to identify on gram stain. "Coccobacilli" is a term that should be avoided.
Blood culture positive for gram-negative cocci	*Neisseria meningitidis* and *Neisseria gonorrhoeae* are uncommon in the cancer patient. *Moraxella* is a possibility. If it is the anaerobic bottle only *Veillonella* should be considered	A carbapenem is the easy answer, but this is uncommon, and it would be better to call Infectious Diseases	

ARDS, acute respiratory distress syndrome; CREs, carbapenem-resistant Enterobacteriaceae; GVHD, graft-versus-host disease; TMP/SMX, trimethoprim/sulfamethoxazole; VRE, vancomycin-resistant *Enterococcus*.

- Gram-positive cocci in pairs and short chains: This may be *Enterococcus* or *S. pneumoniae*—the clinical setting should support one or the other (hospitalized patient, neutropenic, on a third-generation cephalosporin: *Enterococcus*; outpatient with pneumonia at risk for encapsulated bacteria—eg, multiple myeloma—*S. pneumoniae*). In an institution with high frequency of VRE, daptomycin and linezolid are adequate first-line empirical agents here.
- Gram-positive cocci in long chains: *Streptococcus viridans*, it may be *S. mitis* associated with mucositis—vancomycin is appropriate.

- There is no good-quality evidence to suggest that patients known to be colonized with VRE should initially receive empirical coverage for it with linezolid or daptomycin.
- In the case of documented VRE infection, the choice between daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline is not based on clinical outcome data, but on theoretical considerations and local resistance patterns.
- Daptomycin is inactivated by surfactant in the lungs and should not be used to treat pneumonia. There is good evidence, however, that it is as effective as vancomycin or oxacillin to treat staphylococcal bacteremia.

Oral Therapy

- Empirical oral antibiotics may be acceptable for neutropenic patients who are not at high risk of severe morbidity or death.
- High-risk patients are those who received chemotherapy associated with prolonged and profound neutropenia (eg, acute myelogenous leukemia induction therapy), as well as patients with symptoms or signs of clinical instability, significant comorbidities (eg, chronic obstructive pulmonary disease, heart failure), or with expected prolonged neutropenia. Low-risk patients do not exhibit any high-risk factors and their neutropenia is expected to be short lived (<7 days). These patients may be considered for outpatient antibiotic treatment.
- A quantitative risk assessment, the Multinational Association for Supportive Care in Cancer scoring system, has been validated. Points are allocated for burden of illness (no or mild symptoms 5, severe symptoms 3), absence of hypotension (5), no COPD (4), solid tumor *or* no previous fungal infection (4), absence of dehydration (3), outpatient status (3), and age younger than 60 years (2) and the points are added up. Patients with a score of ≥21 points (of 26 possible) are at "low risk" and can be considered for oral therapy.
- The two recommended oral regimens are:
  - Ciprofloxacin, 750 mg PO every 12 hours, plus amoxicillin/clavulanate, 875 mg (amoxicillin component) PO every 12 hours
  - Ciprofloxacin, 750 mg PO every 12 hours, plus clindamycin 450 mg PO every 6 hours

We recommend starting oral antibiotics on an inpatient basis, and then consider discharge after 24 hours of observation and documentation that the blood cultures remain negative. Following discharge, patients should be seen daily and instructed to call or come into clinic for new or worsening symptoms or persistent high fever. Approximately 20% of patients will need readmission to the hospital (factors associated with need for admission: older than 70 years, poor performance, ANC < $100/mm^3$).

Low-risk patients with no documented infection who respond to empirical IV antibiotics can be switched to oral antibiotics until their neutropenia resolves based on clinical judgment. We recommend observing these patients on oral therapy as inpatients for at least 24 hours before discharge.

Modifications of the Initial Antibiotic Regimen

- After patients are started on empirical antibiotics for fever and neutropenia, their course must be monitored closely for the development of new signs or symptoms of infection; antibiotic therapy should be modified based on clinical findings.
- Therapy modification is necessary in 30% to 50% of cases during neutropenia.
- Specific modifications are dictated by specific clinical syndromes or by microbiologic isolates.
- Persistent fever with no other clinical findings is not an indication for modification of the antibacterial regimen.
- If there is no documented gram-positive infection, gram-positive coverage may be stopped after 48 hours if it had been initiated.
- After 4 to 7 days of persistent fever, it is accepted practice to start some antifungal agent.
- In the case of recrudescent fever, the antibacterial and antifungal agents should be changed and imaging studies performed.

Empirical Antifungal Therapy

Candida and *Aspergillus* infections are most common and increase in frequency with increased duration of neutropenia. An antifungal agent (Table 35.3) should be added empirically for neutropenic patients in the following circumstances:

TABLE 35.3
Basic Information About Commonly Used Systemic Antifungal Agents

Antifungal	Spectrum	Notable Resistant Fungi	When to Use	Special Concerns
Polyene				
Amphotericin B (deoxycholate and lipid formulations)	Most *Candida*, *Aspergillus*, and agents of mucormycosis	*Candida lusitaniae*, *Aspergillus terreus*, *Paecilomyces lilacinus*	Treatment of choice for mucormycosis. Treatment of choice for cryptococcosis. As effective as echinocandins for candidiasis. Effective in persistent fever. Inferior to voriconazole for aspergillosis.	Nephrotoxicity. Loss of glomerular filtration rate may be minimized by "salt loading," but tubulopathy with loss of Mg and K cannot be prevented.
Echinocandins Different trials have used different echinocandins in different settings, but they are considered essentially interchangeable for practical purposes	*Candida* and *Aspergillus*	Cryptococcus and all molds other than *Aspergillus*	Treatment of choice for candidiasis.	Poor penetration in eye, CSF, and urine.
Caspofungin			Good data for persistent fever. Weak (but some) data for aspergillosis.	
Micafungin			Good data for prophylaxis during neutropenia. Weak (but some) data for aspergillosis.	
Anidulafungin			Good data for combination therapy with voriconazole in aspergillosis.	
Azoles				All the azoles interfere with the hepatic metabolism of multiple drugs used in oncology (eg, corticosteroids, vincristine, cyclophosphamide, calcineurin inhibitors) and have the potential for significant drug interactions.
Fluconazole	*Candida albicans*	*Candida krusei* All molds	Best evidence for prophylaxis during neutropenia and for candidiasis, cryptococcosis, and coccidioidomycosis.	Hepatotoxicity.

Antifungal	Spectrum	Notable Resistant Fungi	When to Use	Special Concerns
Voriconazole	*Candida*, *Cryptococcus*, *Aspergillus*, most hyaline molds	Agents of mucormycosis *Paecilomyces variotii*	Treatment of choice for aspergillosis.	Significant individual variability on serum levels achieved makes therapeutic drug monitoring advisable. Hallucinations, visual disturbances, and hepatotoxicity. Photosensitivity and possibly fluorosis with long-term use.
Posaconazole	*Candida*, *Aspergillus*, most molds including some agents of mucormycosis		Best data for antifungal prophylaxis during prolonged neutropenia. As effective as voriconazole for aspergillosis. Active against some agents of mucormycosis.	Hepatotoxicity may be less than with voriconazole. It may cause hypokalemia and hypertension.
Isavuconazole	*Candida*, *Aspergillus*, most molds including some agents of mucormycosis		Equivalent to voriconazole for aspergillosis in a RCT. FDA-approved for mucormycosis based on comparison with registry controls.	Less variability in levels than voriconazole or posaconazole. Less hepatotoxicity than voriconazole. No prolongation of Q-T interval. Activity against mucormycosis still questionable.

CSF, cerebrospinal fluid; FDA, Food and Drug Administration; RCT, randomized controlled trial.

- Severe sepsis or septic shock: It may be caused by *Candida*; an echinocandin or amphotericin B should be added. Mold infections seldom cause septic shock.
- Persistent fever after 4 to 7 days of broad-spectrum antibiotic therapy.
- Recrudescent fever.
- *Candida* colonization: Candiduria, thrush.

Treatment options include:

- Amphotericin B deoxycholate, 0.6 to 1 mg/kg/d IV.
- A lipid formulation of amphotericin B such as liposomal amphotericin B (AmBisome) or amphotericin B lipid complex (Abelcet), 3 to 5 mg/kg/d IV.
- Voriconazole, 6 mg/kg IV every 12 hours for 24 hours followed by 4 mg/kg IV every 12 hours, aiming for a serum concentration >2 μg/mL.
- Caspofungin, 70 mg IV loading dose followed by 50 mg IV daily.
- Posaconazole, 300 mg IV every 12 hours twice loading dose followed by 300 mg IV daily (no data on empirical treatment as opposed to the treatment of documented infection).
- Isavuconazole, 200 mg IV every 8 hours for six doses loading followed by 200 mg IV daily (no data on empirical treatment as opposed to treatment of documented infection).

For persistent fever, amphotericin, caspofungin, and possibly voriconazole (not Food and Drug Administration [FDA]-approved for this indication) are well validated as empirical additions. Of note, an effort should be made to rule out the presence of active invasive fungal infection by performing a thorough physical examination and obtaining CT studies as clinically indicated (CT chest, possibly CT sinus, CT of abdomen and pelvis if there are signs of intra-abdominal infection or abnormal liver enzymes). A different approach suggests starting antifungal agents only when there is ancillary evidence of fungal infection besides

the fever (eg, positive serologic tests like galactomannan and/or β-D-glucan). The role of this so-called "preemptive" antifungal therapy as opposed to the traditional "empirical" addition of antifungal agents in persistent fever has not been clearly defined.

The IV formulation of posaconazole allows loading and obtaining therapeutic levels early, so it may be now considered another alternative for treatment of suspected or proven fungal infections (the previous oral formulation did not achieve therapeutic levels for 5-7 days). Posaconazole has shown to be noninferior to voriconazole for invasive aspergillosis. Isavuconazole has shown to be noninferior to voriconazole in a randomized controlled trial and similar to amphotericin for the treatment of mucormycosis in a case-control study.

For voriconazole, posaconazole, and isavuconazole, we recommend therapeutic drug monitoring, particularly when they are used for treatment of suspected fungal infection during neutropenia.

Duration of Antibiotic Therapy

The duration of antibiotic treatment is evolving, with evidence suggesting shorter regimens may be acceptable, particularly for neutropenic fever without documented infection. Of note, early antibiotic discontinuation may result in recrudescent fever and require quick reinitiating of antibiotics in a sizable minority of patients. This approach may result in better antibiotic stewardship, however.

- **Documented bacterial infection:** Traditionally, antibiotics were continued for the amount of time standard for that infection or until resolution of neutropenia, whichever was longer. Recommendations by the European Conference on Infections in Leukemia (ECIL-5) suggest antibiotic discontinuation after 7 days if the infection seems eradicated (negative culture), the symptoms resolve, and the patient is afebrile.
- **Uncomplicated fever and neutropenia of uncertain etiology:** The traditional recommendation was to continue antibiotics until the fever has resolved and the ANC is above 500 for 24 hours. Newer evidence suggests antibiotic discontinuation despite ANC < 500 if the patient is stable for more than 72 hours and afebrile for ≥48 hours.
- **After antibiotic discontinuation, it is acceptable to resume fluoroquinolone prophylaxis until marrow recovery, but mere observation may be adequate also**.
- If there is no documented fungal infection, antifungal agents can also be discontinued at the time of resolution of neutropenia.

FEVER IN THE NONNEUTROPENIC CANCER PATIENT

- Noninfectious causes of fever in cancer patients include, among others, the underlying malignancy, deep venous thrombosis and pulmonary embolism, medications, blood products, and, in allogeneic stem cell transplant, graft-versus-host disease.
- Infections, however, are common in patients with all types of malignancies in all stages of treatment. In addition to neutropenia, there are several other factors that contribute to increased susceptibility to infection and should be considered when trying to diagnose an episode of fever and formulate a treatment plan.
- Local factors: Breakdown of barriers (mucositis, surgery) that provide a portal of entry for bacteria; and obstruction (biliary, ureteral, bronchial) that facilitates local infection (cholangitis, pyelonephritis, postobstructive pneumonia).

- Intravascular devices, drainage tubes, or stents may become colonized and lead to local infection, bacteremia, or fungemia.
- Splenectomy increases susceptibility to infection due to *S. pneumoniae* and other encapsulated bacteria.
- Deficiencies of humoral immunity (multiple myeloma, chronic lymphocytic leukemia) lead to increased susceptibility to encapsulated organisms such as *S. pneumoniae* and *Haemophilus influenzae.*
- Defects in cell-mediated immunity (lymphoma; hairy cell leukemia; treatment with **steroids,** fludarabine, and other drugs; hematopoietic stem cell transplant [HSCT]) increase susceptibility to opportunistic infections caused by *Legionella pneumophila*, mycobacteria, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, cytomegalovirus (CMV), varicella zoster virus (VZV), and other pathogens.

Antibiotic Therapy in the Nonneutropenic Cancer Patient

- Antibiotics should be administered empirically in the setting of fever only when a bacterial infection is considered likely.
- Ideally one should formulate a "working hypothesis" as a fundamental basis on which to choose the appropriate regimen. For example, pneumonia, cholecystitis, and urinary tract infection would likely require different antibiotics.
- In the absence of localizing signs and symptoms, consider bacteremia, particularly in patients with intravascular devices. Many authorities recommend empirical antibiotics (levofloxacin, ceftriaxone) until bacteremia is ruled out.
- Clinically documented infections and sepsis should be treated with antibiotics as warranted by the clinical scenario.
- Whenever antibiotics are started, a plan with specific endpoints should be formulated to avoid unnecessary toxicity, superinfection, and the development of resistance.

SPECIFIC INFECTIOUS DISEASE SYNDROMES

If a patient presents with clinical signs and symptoms of a specific infection, with or without neutropenia, the workup and therapy are guided by the clinical suspicion (Table 35.4).

TABLE 35.4

Specific Infectious Disease Syndromes in Oncology Patients and Approach to Diagnosis and Management

Clinical Syndrome	Diagnostic Considerations	Management

Clinical Syndrome	Diagnostic Considerations	Management
Intravascular catheter–associated infections	Infections can be local involving the exit site or subcutaneous tunnel, or systemic causing bacteremia For local infections, check culture of exit site discharge as well as blood cultures	For tunnel and systemic infections, empirical therapy should include vancomycin as well as gram-negative coverage (eg, ceftazidime, cefepime, ciprofloxacin) Temporary intravascular catheters should always be removed. Permanent catheters should be removed in most cases, and we always remove them in the following situations: Tunnel infections Persistently positive blood cultures after 72 h of adequate therapy regardless of pathogen Specific pathogens: *Mycobacteria* spp., *Bacillus* spp., *Staphylococcus aureus*, fungi; case-by-case decision for *Corynebacterium jeikeium,* VRE, and gram-negative organisms Consider antibiotic lock if feasible
Skin/soft-tissue infections	Prompt biopsy with histologic staining and culture for bacteria, mycobacteria, viruses, and fungi Pathogens: *S. aureus*, *Streptococcus pyogenes*, gram-negative bacilli (eg, *Pseudomonas*), VZV, HSV, *Candida* For vesicular lesions, scrape base for DFA or PCR for VZV and HSV	Ecthyma gangrenosum: coverage of *Pseudomonas* (eg, ceftazidime, cefepime, ciprofloxacin) Infections with *S. pyogenes*: treat aggressively with penicillin G, clindamycin, IVIG, and surgical débridement Perianal cellulitis: broad-spectrum coverage including anaerobes (eg, imipenem) VZV, HSV: acyclovir
Sinusitis	Evaluate with CT scan and examination by otolaryngologist	Nonneutropenic: levofloxacin or amoxicillin/clavulanate
	Tissue should be biopsied if there is suspicion of fungal infection or no response to antibiotic therapy after 72 h	Neutropenic: broad-spectrum coverage including *Pseudomonas* (eg, carbapenem, cefepime) and MRSA and consider fungal coverage (eg, amphotericin B, voriconazole)
	Pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *S. aureus*, gram-negative bacilli (eg, *Pseudomonas*), fungi including agents of mucormycosis (Mucorales)	
Pulmonary infections	CT scan and BAL should be performed early Pneumonias in any cancer patient are often caused by gram-negative bacilli and *S. aureus* as well as community-acquired pneumonia pathogens: *S. pneumoniae*, *H. influenzae*, *Legionella* spp., and *Chlamydia pneumoniae*	For all patients, ensure adequate coverage of community-acquired pneumonia including *Legionella* (eg, levofloxacin)
		Neutropenic: coverage of *S. pneumoniae, S. aureus*, and *Pseudomonas* (eg, levofloxacin and ceftazidime and vancomycin); add antifungal coverage empirically (eg, amphotericin B, voriconazole) if pneumonia develops while on antibiotics. MRSA pneumonia is very unlikely if anares sample has a negative MRSA PCR
	Neutropenic patients are at risk for invasive fungal infections, particularly aspergillosis Patients with cell-mediated defects are at risk for infections with PCP, viruses (CMV, VZV, HSV), *Nocardia* spp., and *Legionella*	Cell-mediated immunodeficiency: consider coverage of *Pneumocystis* with TMP/SMX, CMV with ganciclovir, and *Nocardia* with TMP/SMX
	Mycobacteria should also be considered, particularly in patients with previous exposure	
Gastrointestinal tract infections	Lesions associated with mucositis can be superinfected with HSV or *Candida*	Mucositis or esophagitis: acyclovir and fluconazole
	Esophagitis can be caused by *Candida*, HSV, CMV	*Clostridium difficile*: fidaxomicin or vancomycin

Clinical Syndrome	Diagnostic Considerations	Management
	Diarrhea is most commonly caused by *C. difficile* (send toxin assay) but can also be caused by *Salmonella*, *Shigella*, *Aeromonas*, *Escherichia coli*, *Campylobacter*, viruses, parasites, etc	Neutropenic enterocolitis: broad-spectrum coverage including *Pseudomonas* and anaerobes (eg, carbapenem, piperacillin-tazobactam, cefepime + metronidazole)
	Enterocolitis in neutropenic patients is most commonly caused by a mix of organisms including *Clostridium* spp. and *Pseudomonas*	
Urinary tract infections	Pathogens: gram-negative bacilli, *Candida* Consider whether candiduria may represent disseminated candidiasis	Remove catheter to clear colonization Neutropenic patient: treat bacteriuria/candiduria regardless of symptoms Nonneutropenic patient: reserve treatment for symptomatic episodes Antibiotic treatment should be tailored to organism
CNS infections	Bacteria cause most cases of meningitis (*S. pneumoniae*, *Listeria*, *Neisseria meningitidis*) In patients with cell-mediated immunodeficiency, also consider *Listeria* or *Cryptococcus* Encephalitis is most commonly caused by HSV but consider other viruses (HHV-6, JC virus)	Bacterial meningitis: ceftriaxone, vancomycin, and ampicillin Cryptococcal meningitis: amphotericin B with flucytosine Encephalitis: treat *Listeria* and start ganciclovir, foscarnet, or both to cover both HSV and HHV-6
	Brain abscesses may be confused with tumor	

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; DFA, direct fluorescent antibody; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; VZV, varicella zoster virus.

Bacteremia/Fungemia

- A positive blood culture should prompt immediate initiation of appropriate antibiotics in a neutropenic patient or in a nonneutropenic patient who is febrile or clinically unstable.
- If the isolated organism is one that is commonly pathogenic, such as *S. aureus* or gram-negative bacilli, antibiotics should be started even if the patient is afebrile and clinically stable.
- If the isolate is a common contaminant, such as a coagulase-negative *Staphylococcus*, and the patient is afebrile, clinically stable, and nonneutropenic, it may be appropriate to repeat the cultures and observe before starting antibiotics.
- In every case of bacteremia, follow-up blood cultures should be obtained to document the effectiveness of therapy. The source of the infection should be sought.

Infections With Adoptive Cellular Therapy

- Adoptive cell therapy includes chimeric antigen receptor (CAR) T-cell therapies, tumor-infiltrating lymphocyte therapies, engineered T-cell receptor therapies, and natural killer cell therapies.
- CRS is a state of immune dysregulation that occurs when adoptive cell therapies initiate a cascade of immune activation leading to mobilization of bystander immune cells, production of cytokines, and enhanced vascular permeability.

- Data on infection incidence and risk of infections after adoptive cell therapy are based on multiple, small, retrospective studies mainly looking at the anti-CD19 CAR T-cell therapy.
- Infections can occur at any time from lymphocyte-depleting (LD) chemotherapy to after infusion of CAR T cells. However, patients may be at risk for different pathogens depending on the time that has elapsed after LD chemotherapy.
- The type of LD chemotherapy used may lead to neutropenia and lymphopenia. The duration of cytopenias will depend on multiple host factors including prior myelosuppressive therapy. Conditioning chemotherapies must be assessed for their specific infection risk; for example, patients who receive alemtuzumab as part of the conditioning regimen will likely have more profound, prolonged lymphopenia as compared to patients who receive a short-course of low-dose fludarabine and cyclophosphamide.
- Infections have been reported in roughly 25% to 40% of patients. Patients who have had more lines of prior therapy are more susceptible to infections. Underlying disease type can also affect risk of infection (patients with leukemia vs patients with lymphoma). The most common types of infection to occur in the first 30 days of CAR T-cell therapy are bacterial infections. This includes both bacteremias and bacterial site infections. Viral infections are also common, including respiratory viruses and herpes family infections. Most patients in retrospective studies received antiherpetic prophylaxis with acyclovir or valacyclovir.
- Patients who receive CAR T-cell therapy may be at high risk for opportunistic infections because of delayed $CD4^+$ T-cell recovery for greater than 1 year after therapy. As a result, many clinical trials and studies looking at CAR T-cell therapy administer *Pneumocystis* pneumonia (PCP) prophylaxis uniformly to patients with varying practices of the duration of prophylaxis.
- *C. difficile* may be an important pathogen that causes infection in patients after cell therapy; but more studies are needed to understand this phenomenon further.
- Fungal infections can occur but appear to generally be less common than bacterial and viral infections.
- Many patients who receive CD19-directed therapy develop B-cell aplasia that can last months and even years in some cases. Patients may benefit from scheduled infusions of intravenous immunoglobulin (IVIG) to mitigate infection risk in this patient population.
- More work is needed to delineate the response to vaccines post adoptive cell therapy and whether a revaccination schedule, similar to postautologous transplant, is warranted or beneficial.

Gram-Positive Bacteremia

Gram-Positive Cocci

- Coagulase-negative *Staphylococcus* species is the most common cause of bacteremia. The intravenous catheter is usually the source. In the setting of neutropenia or clinical instability, the patient should be treated with vancomycin.
- *S. aureus* bacteremia is associated with a high likelihood of metastatic complications if not treated adequately. Complicated *S. aureus* bacteremia (persistently positive blood cultures, prolonged fever, metastatic infection, and endocarditis) requires 4 to 6 weeks of

treatment. Many authorities recommend that transesophageal echocardiogram should be performed in every case of *S. aureus* bacteremia to rule out endocarditis.

- Cefazolin is the drug of choice for treating methicillin-susceptible *S. aureus*; vancomycin should be reserved for MRSA or the treatment of penicillin-allergic patients. Daptomycin may also be an alternative if there is no pulmonary involvement.
- Bacteremia with viridans group streptococci (*S. mitis*) may cause overwhelming infection with sepsis and acute respiratory distress syndrome in the neutropenic patient; vancomycin therapy should be used until susceptibility results are known (most, but not all, isolates are susceptible to ceftriaxone and carbapenems). Early information from the microbiology laboratory would likely be "gram-positive cocci in long chains."
- Risk factors for *S. mitis* bacteremia include severe mucositis (particularly following treatment with cytarabine), active oral infection, prophylaxis with TMP/SMX, or a fluoroquinolone and H_2 blockers.
- Enterococci (intrinsically resistant to all cephalosporins) often cause bacteremia in debilitated patients who have had prolonged hospitalization and have been on broad-spectrum antibiotics, particularly cephalosporins, which lack any antienterococcal activity.
- VRE is an increasingly common cause of bacteremia and should be treated with linezolid (600 mg every 12 hours IV), daptomycin (6 mg/kg every 12 hours IV), or quinupristin-dalfopristin (7.5 mg/kg every 8 hours IV). Tigecycline (100 mg IV loading followed by 50 mg IV every 12 hours) has also been used. The overall success rate of treatment for VRE bacteremia is only around 40%.

Gram-Positive Bacilli

- *Clostridium septicum* is associated with sepsis and metastatic myonecrosis during neutropenia. Treat with high-dose penicillin or a carbapenem.
- *Listeria monocytogenes* may cause bacteremia with or without encephalitis/meningitis in patients with defects in cell-mediated immunity. Ampicillin plus gentamicin is the treatment of choice. TMP/SMX can be used in penicillin-allergic patients.
- Other gram-positive bacilli such as *Bacillus*, *Corynebacterium*, and *Lactobacillus* species are common contaminants of blood cultures, but in the setting of neutropenia can cause true infection that is usually catheter related. *Cutibacterium* (formerly *Propionibacterium*) *acnes* is almost always a contaminant, but it can cause infection of Ommaya reservoirs and other neurosurgical devices.

Gram-Negative Bacteremia

- Gram-negative bacteria in the blood should never be considered contaminants and must be treated immediately.
- Depending on the preliminary result from the microbiology laboratory (variable from one laboratory to another), preliminary information may be nonexistent or may be specific enough (eg, "enteric-like" or "*Pseudomonas*-like" gram-negative bacillus) to guide antibiotic choice (Table 35.2). Depending on institutional patterns and preliminary information, it may be safer to initiate therapy with two antimicrobials to ensure adequate coverage until susceptibility results are available. Combination therapy offers no convincing benefit over single agent once susceptibilities are known.

- *Escherichia coli* and *Klebsiella* species are the most prevalent gram-negative pathogens in neutropenic patients; however, the use of prophylactic antibiotics such as ciprofloxacin or TMP/SMX may increase the prevalence of more resistant enteric organisms such as *Enterobacter*, *Citrobacter*, and *Serratia* species, some of which may carry an inducible β-lactamase (AmpC) that may result in treatment failure with third-generation cephalosporins like ceftazidime. Carbapenems, fluoroquinolones, and cefepime may be used in this setting.
- The prevalence of strains of *Klebsiella* and *E. coli* that produce ESBL is increasing; carbepenems are the drugs of choice for these organisms.
- *Klebsiella pneumoniae* carrying the KPC carbapenemase and other CRE are becoming more prevalent and have caused institutional outbreaks with high mortality. Some CRE may be successfully treated with ceftazidime-avibactam 2.5 g (ceftazidime 2 g and avibactam 0.5 g) every 8 hours IV. Other alternative agents for some CREs include imipenem-relebactam and meropenem-vaborbactam.
- *P. aeruginosa* is one of the most lethal agents of gram-negative bacteremia in the neutropenic patient. **Pending susceptibility results, combination therapy should be started to broaden the antimicrobial spectrum and ensure the patient is receiving at least one agent to which the isolate is susceptible.**
- *Stenotrophomonas maltophilia* causes infection in patients who have been on broad-spectrum antibiotics (frequently carbapenems) or who have intravascular catheters; TMP/SMX is the treatment of choice. For the allergic patient, ceftazidime, moxifloxacin, or levofloxacin may be effective. *S. maltophilia* may show in vitro susceptibility to tigecycline and colistin, but the clinical efficacy of these agents is unknown.
- *A. baumannii* bacteremia is frequently associated with infected intravascular catheters in cancer patients and is often resistant to multiple antibiotics, including imipenem-cilastatin. Ampicillin-sulbactam, tigecycline, or colistin may be effective, but consultation with an infectious disease specialist should be sought.

Fungemia

- *Candida* species cause most cases of fungemia in cancer patients. The frequency of non-*albicans* candidemia is increasing, probably because of the widespread use of fluconazole prophylaxis.
- The treatment of choice for candidemia is an echinocandin or amphotericin B.
- Fluconazole is reliably effective against *C. albicans.* **Non-*albicans* species are likely to be resistant to fluconazole and should be treated with caspofungin, anidulafungin, micafungin, amphotericin B, or a lipid formulation of amphotericin B.**
- Patients with candidemia should undergo ophthalmologic evaluation with fundoscopic examination. In most cases, intravascular catheters should be removed.
- Although *Candida* is the most common yeast found in blood cultures, other fungi with different susceptibility patterns may also cause fungemia: in patients with defects in cell-mediated immunity (eg, AIDS, alemtuzumab use), *C. neoformans*, which is resistant to echinocandins, should be considered. In neutropenic patients, *Fusarium, Scedosporium*, and *Trichosporon* species may also cause fungemia. Treatment for these relatively uncommon fungal isolates should be chosen in consultation with infectious diseases.

Intravascular Catheter-Associated Infections

Definitions

- Exit site infections are diagnosed clinically by the presence of erythema, induration, and tenderness within 2 cm of the catheter exit site.
- A tunnel infection is characterized by erythema along the subcutaneous tract of a tunneled catheter that extends 2 cm beyond the exit site.
- Catheter-associated bloodstream infection requires positive peripheral blood cultures (or a positive catheter tip culture) *and* evidence that the catheter is the source of the bacteremia. **The most readily available evidence is a differential time to positivity of ≥2 hours between the peripheral blood culture and the culture drawn through the catheter.** The blood drawn through the catheter grows faster because the bacterial inoculum in the blood drawn through the catheter (where the bacteria-colonized biofilm lays) is higher. **Of note, this definition makes necessary to draw blood cultures from the catheter as well as directly from a vein via a peripheral stick to make the diagnosis of catheter-related bacteremia.**

Management

- If a local infection is suspected, a swab of exit site discharge should be sent for culture, in addition to blood cultures.
- Uncomplicated catheter site infections (no signs of systemic infection or bacteremia) can be managed with local care and oral antibiotics such as dicloxacillin or cefalexin.
- If the patient has fever or there is significant cellulitis around the catheter site, vancomycin should be used empirically while awaiting culture results.
- Tunnel infections require IV antibiotics and removal of the catheter; empirical therapy should include vancomycin, as well as coverage of gram-negative bacilli such as ceftazidime, cefepime, or ciprofloxacin. Therapy can then be modified when an organism is identified.
- Septic thrombophlebitis also necessitates catheter removal, and anticoagulation should be considered. Surgical drainage or excision may be necessary, if antibiotics and anticoagulation fail to control symptoms and persistent bacteremia.
- Catheter-related bloodstream infections caused by coagulase-negative *Staphylococcus* or gram-negative bacilli are usually treated for 14 days with antibiotics. After the cultures are negative, therapy may be completed with oral antibiotics (linezolid or a fluoroquinolone) in stable nonneutropenic patients.

Indications for Removal of Intravascular Catheters

- Infected temporary catheters must be removed. Removal of permanent (eg, tunneled lines and implanted ports) catheters should always be considered, and we remove them in the following situations:
  - Tunnel (or pocket, in the case of implanted ports) infections.
  - Persistently positive blood cultures after 48 to 72 hours of appropriate therapy, regardless of the pathogen.
  - Septic thrombophlebitis.
  - Blood cultures positive for
    - *S. aureus*
    - *Bacillus* spp.
    - *Mycobacteria* spp.
    - *Candida* spp.
  - For other pathogens, including VRE, *Corynebacterium jeikeium*, and gram-negative pathogens like *Pseudomonas* and *Stenotrophomonas*, we occasionally attempt salvage therapy with systemic antibiotics and antibiotic lock.

This approach should be considered only when the global risk of removing the catheter (due for, for instance, refractory thrombocytopenia or paucity of IV access) is considered too high.

Skin and Soft-Tissue Infections

- Soft-tissue infections may represent local or disseminated infection.
- A biopsy for staining and culture for bacteria, mycobacteria, viruses, and fungi should be considered early in the evaluation of skin and soft-tissue infections, particularly in neutropenic or otherwise immunocompromised patients.
- Ecthyma gangrenosum often presents in neutropenic patients as a dark, necrotic lesion but can be quite variable in appearance. Typically a manifestation of *P. aeruginosa* bacteremia, it may also be caused by other gram-negative bacilli. Antibiotic therapy with coverage of *Pseudomonas* should be initiated and early surgical consultation for possible débridement is imperative.
- VZV and herpes simplex virus (HSV) generally present as vesicular lesions and may be indistinguishable. Scrapings from the base of vesicles should be sent for direct fluorescent antibody testing, viral culture, or polymerase chain reaction (PCR) to diagnose VZV or HSV. Treatment of VZV in the immunocompromised host is acyclovir 10 mg/kg IV every 8 hours, and for HSV, acyclovir 5 mg/kg IV every 8 hours. We prefer to use IV acyclovir in immunocompromised hosts. In immunocompetent patients, oral acyclovir, valacyclovir, and famciclovir have been used successfully.
- Cancer patients are at increased risk for streptococcal toxic shock syndrome and severe soft-tissue infections caused by *Streptococcus pyogenes.* Treatment is aggressive surgical débridement as needed and antibiotic therapy with penicillin G and clindamycin, as well as, in the case of shock, IVIG. The addition of clindamycin to penicillin G or ampicillin results in improved outcome, possibly because its action inhibits protein (hence toxin) synthesis.
- Perianal cellulitis may develop in neutropenic patients. Antibiotic therapy should include gram-negative and anaerobic coverage (eg, imipenem-cilastatin or meropenem or piperacillin-tazobactam as single agents or ceftazidime + metronidazole). A CT scan should be obtained to rule out a perirectal abscess. Incision and drainage may also be required in the setting of abscess or unremitting infection, but if possible, should be delayed until resolution of neutropenia.
- Rash, including skin breakdown, is a common side effect of many new targeted therapies. Patients should have a detailed skin examination at each visit to evaluate for superinfections of their rash, as well as dermatology consultation as needed. Drugs commonly implicated include mAb like cetuximab (head and neck cancer, colorectal cancer) and tyrosine kinase inhibitor like erlotinib (lung cancer) and sorafenib (renal cancer, hepatocellular carcinoma).
- Sweet syndrome can present with fever and cutaneous lesions that may resemble cellulitis and should be considered in the differential diagnosis of fever and rash, particularly in patients with myeloid malignancies.

Sinusitis

- In immunocompetent patients, acute sinusitis is usually caused by *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*, as well as *S. aureus.* Treatment is levofloxacin 500 mg daily or amoxicillin-clavulanate 875 mg twice daily.

- In immunocompromised hosts, sinusitis can also be caused by aerobic gram-negative bacilli, including *Pseudomonas*. Neutropenic patients are at high risk for fungal sinusitis.
- During neutropenia, sinusitis should be treated with broad-spectrum antibiotics, including coverage of *Pseudomonas*, and sinus CT scan and otolaryngology consult are appropriate. Biopsy should be obtained if there is any suspicion of fungal infection (eg, bony erosion on CT scan, necrotic eschar of nasal turbinates) or if there is no response to antibiotic therapy within 72 hours.
- *Aspergillus* is the most common cause of invasive fungal sinusitis, but other molds such as *Mucor* and *Rhizopus* (which are resistant to voriconazole) as well as *Fusarium* and, occasionally, dematiaceous molds like *Alternaria* are increasingly recognized. When patients have been receiving voriconazole prophylaxis, the relative frequency of mucormycosis increases.
- If invasive fungal sinusitis is confirmed, treatment is with surgical débridement and antifungal treatment, which should be started at maximum dosing:
  - Amphotericin B 1 to 1.5 mg/kg/d.
  - Lipid formulation of amphotericin B 5 to 7.5 mg/kg/d.
  - Voriconazole may be substituted only after it is certain that the infection is not caused by Zygomycetes (*Mucor*, *Rhizopus*), which are not susceptible to voriconazole.
  - Posaconazole or isavuconazole given IV, both with a very broad antifungal spectrum that covers most agents of fungal sinusitis, may be an alternative. If there is suspicion of mucormycosis, we consider amphotericin the treatment of choice.

Pneumonia

- Pulmonary infiltrates in the immunocompromised host can be due to infectious or noninfectious causes. It is important to obtain an etiologic diagnosis. We recommend early use of bronchoalveolar lavage (BAL) if a diagnostic sputum specimen cannot be obtained.

Pulmonary Infiltrates in the Neutropenic Patient

- Most cases of pneumonia during neutropenia are caused by gram-negative bacilli, including *P. aeruginosa.*
- The treatment should include the standard regimen for fever and neutropenia plus vancomycin for *S. aureus* and some antibiotic active against *Legionella* and other agents of community-acquired pneumonia (eg, newer generation fluoroquinolone like levofloxacin or moxifloxacin, or macrolide like azithromycin in addition to cefepime).
- CT scan and bronchoscopy for BAL should be performed early.
- If pulmonary infiltrates appear while the patient is on broad-spectrum antibiotic therapy, the likelihood of fungal pneumonia is high. Empirical antifungal coverage with voriconazole, liposomal amphotericin B, or amphotericin B should be started immediately. **Echinocandins should not be used for empirical fungal therapy for pulmonary infiltrates in neutropenic patients, as they have no activity against non-*Aspergillus* molds and their activity against *Aspergillus* is not known to be equivalent to voriconazole or amphotericin B.**

Fungal Pneumonia

- Fungal pneumonia is rare in the absence of neutropenia or corticosteroids.
- *Aspergillus* species are the most common disease-causing molds in cancer patients.

- Lack of systemic toxicity is characteristic. Clinical presentation includes the following:
  - Persistent or recurrent fever
  - Development of pulmonary infiltrates while on antibiotics
  - Chest pain, hemoptysis, or pleural rub
- In the setting of allogeneic HSCT, most cases of *Aspergillus* pneumonia occur after engraftment, when the patient is no longer neutropenic. The most important risk factors in this setting are graft-versus-host disease, corticosteroid use, and CMV disease.
- Demonstration of fungal elements in biopsy tissue is necessary for definitive diagnosis. When a biopsy is not possible, positive respiratory cultures (sputum or BAL fluid) are highly predictive of invasive disease in a high-risk patient.
- Galactomannan (*Aspergillus*) and β-D-glucan are serologic assays used to diagnose invasive fungal infections. **Galactomannan can also be determined in the BAL, where it has high sensitivity and specificity for aspergillosis in patients with hematologic malignancies.**
- There are molds that do not produce either galactomannan or β-D-glucan (eg, *Mucor*, *Rhizopus*). This means that a negative test *cannot* rule out invasive fungal infection.
- Positive serum galactomannan and β-D-glucan (usually defined as two consecutive rising values when the tests are obtained twice weekly or every other day) can be helpful to identify fungal infections early.
- The treatment of choice for invasive aspergillosis is voriconazole 6 mg/kg IV every 12 hours for 24 hours, then 4 mg/kg IV. Isavuconazole and Posaconazole have shown to be noninferior to voriconazole and may be used as alternatives. We routinely add an echinocandin to any azole until we document a therapeutic serum azole level, but some experts recommend monotherapy.
- Other options include the following:
  - High-dose lipid formulation of amphotericin B (5 mg/kg/d).
  - Amphotericin B (1-1.5 mg/kg/d).
  - Caspofungin (70 mg loading dose followed by 50 mg/d IV) has been approved for patients with invasive aspergillosis who are unresponsive to or intolerant of amphotericin B, but there have been no randomized controlled trials.
- Mucorales (previously known as zygomycetes) such as *Rhizopus*, *Mucor*, and *Cunninghamella* species are less common causes of pulmonary infection in neutropenic patients. They are resistant to voriconazole, but have variable susceptibility to posaconazole and isavuconazole. Treatment should include high-dose amphotericin B (deoxycholate or lipid formulation). Early consideration should be given to surgical excision where feasible.
- *Fusarium* is a less common cause of pulmonary infection in neutropenic patients. Voriconazole, isavuconazole, or high-dose amphotericin can be tried. Response is usually contingent on neutrophil recovery.
- Dematiaceous fungi such as *Scedosporium*, *Alternaria*, *Bipolaris*, *Cladosporium*, and *Wangiella* species are rare causes of pneumonia in neutropenic patients. The best treatment is not well established, and consultation with infectious diseases is strongly advised.

Pulmonary Infiltrates in Patients on High-Dose Corticosteroids or With Other Defects in Cell-Mediated Immunity

- In addition to the common bacterial causes of pneumonia, patients with defects in cell-mediated immunity are at risk for infections with *P. jirovecii*, *Nocardia* species, and viruses (see below), as well as *Legionella*, mycobacteria, and fungi.

- Bronchoscopy for BAL should be performed to aid in diagnosis.
- Empirical antibiotics should include newer generation fluoroquinolone for coverage of bacterial pathogens including *Legionella* and TMP/SMX for coverage of *Pneumocystis* and *Nocardia.* Consideration should also be given to antifungal and antiviral agents, depending on the clinical presentation.

Pneumocystis Pneumonia

- Patients with pneumonia from *P. jirovecii* usually present with rapid onset of dyspnea, nonproductive cough, hypoxemia, and fever. PCP may have a more indolent presentation in HIV-infected patients, stem cell transplant recipients, and patients on ibrutinib.
- Radiologic studies generally show diffuse bilateral interstitial infiltrates but can show focal infiltrates. The initial plain radiograph may be normal, but CT will almost always show characteristic ground-glass opacities. Pleural effusions are uncommon.
- Treatment should be started based on clinical suspicion: TMP/SMX 5 mg/kg IV every 8 hours. We recommend adding prednisone if the Po_2 is < 70 mm Hg or there is an A-a gradient > 35 mm Hg, but the role of steroids in HIV-negative patients with *Pneumocystis* is controversial.
- In TMP/SMX-allergic/intolerant patients, alternatives for serious disease include IV pentamidine, and for moderate disease dapsone-TMP, atovaquone, or clindamycin-primaquine. The combination clindamycin-primaquine may be the treatment of choice in cases of TMP/SMX failure.

Nocardia

- Pneumonia from *Nocardia* species can cause a dense lobar infiltrate or multiple pulmonary nodules with or without cavitation. Radiologically, it may be indistinguishable from aspergillosis.
- Diagnosis is made from material obtained at bronchoscopy, either by pathology or culture. Culture may take 4 to 7 days.
- Antibiotic susceptibility varies with the species, although most are susceptible to TMP/SMX. Imipenem-cilastatin or meropenem and amikacin are also effective against the majority of isolate. All *Nocardia* are susceptible to linezolid, but this agent may be associated with unacceptable toxicity (neuropathy and myelotoxicity) when used for the long period required for this infection. Treatment is usually given for 6 months to 1 year. Depending on the species, *Nocardia* frequently causes disseminated infection involving the central nervous system, which may be asymptomatic. We recommend obtaining MRI with gadolinium in any patient with nocardiosis.

Viral Pneumonia

- Pneumonia due to respiratory viruses (respiratory syncytial virus [RSV], influenza, parainfluenza, adenovirus, and metapneumovirus) is more common in patients with defects in cell-mediated immunity like stem cell transplant recipients. When upper respiratory infection progresses to pneumonia in immunocompromised patients, there is risk of progression to respiratory failure and death.

- The effect of antiviral treatment on the outcome of these viral respiratory infections is unclear, but it is generally recommended. Results seem to be better when treatment is initiated at the time of upper respiratory tract infection before progression to pneumonia.
- Influenza should be treated with neuraminidase inhibitors (most experience is with oral oseltamivir, 75 mg PO twice daily).
- RSV may be treated with aerosolized ribavirin 6 g daily delivered at a concentration of 20 mg/mL for 18 hours per day by a small particle aerosol generator unit via a face mask, ideally inside a scavenging tent to prevent environmental contamination or intermittently (2 g inhaled every 8 hours). The unproven efficacy and high cost of inhaled ribavirin have resulted in an increase of the use of oral ribavirin 600 to 800 mg PO bid for RSV infection. Some experts recommend adding IVIG or even the monoclonal antibody palivizumab, although there is no evidence that any of these interventions result in better outcome.
- Metapneumovirus and parainfluenza are also inhibited in vitro by ribavirin, but there is even less evidence than for RSV.
- Many strains of adenovirus are susceptible to cidofovir and some to ribavirin. Control of this infection, however, seems to be mainly related to the recovery of adenovirus-specific immunity.
- CMV pneumonia is a significant complication of allogeneic stem cell transplants that typically develops between 40 and 100 days posttransplant and presents with fever, dyspnea, hypoxemia, and diffuse interstitial infiltrates. Late CMV pneumonia (after day 100) should be considered in patients with a history of previous CMV infection.
- CMV infection and disease, typically restricted to allogeneic stem cell transplant recipients and AIDS patients, have also been rarely observed in patients with HTLV-I–associated adult T-cell leukemia/lymphoma and patients treated with alemtuzumab.
- After allogeneic stem cell transplant, the detection by culture of CMV in the BAL is considered sufficient to establish the diagnosis. In other settings, tissue is required. Of note, identifying CMV in the BAL by PCR only is not diagnostic of CMV pneumonia (the test is too sensitive; quantitative PCR may help).
- Treatment of CMV pneumonia is with ganciclovir 5 mg/kg IV every 12 hours. The addition of IVIG 500 mg/kg every 48 hours for 3 weeks may be considered, but there is little evidence IVIG helps. Foscarnet (90 mg/kg every 12 hours) may be substituted for ganciclovir.

COVID-19

- COVID-19 stands for COronaVIrus Disease 2019. It is caused by the newly identified coronavirus SARS-CoV-2. The disease was recognized in late 2019 as a cluster of atypical cases of pneumonia in Wuhan, China, and it has become the first pandemic of the 21st century, with more than 180 million cases as of this writing. Although it is mainly a respiratory illness (either upper respiratory tract or pneumonia), the virus may affect other organs including the nasal mucosa, GI tract, kidneys, and liver, and, through thrombotic and immunopathogenic effects, almost any organ system.
- After an incubation period of about 5 days (1-14), COVID-19 typically starts as an upper respiratory viral syndrome with cough, fever, shortness of breath, headache, and myalgias. Anosmia is a characteristic symptom. GI manifestations (diarrhea, nausea, and vomiting) may predominate in some patients. The proportion of asymptomatic cases has

been estimated around 15% (5), but presymptomatic and asymptomatic cases account for a disproportionate fraction (40%-60%) of the total transmissions. This is in part because the highest levels of virus are found in respiratory secretions in the day preceding onset of symptoms and the first few days of illness. In most affected individuals, the course is benign with complete resolution in 2 weeks, but at least 15% to 20% of patients develop pneumonia, typically bilateral, and require admission to the hospital for supplemental oxygen. There are several risk factors for severe disease: age, body mass index, and comorbidities like hypertension, diabetes, cardiovascular disease, chronic pulmonary disease, chronic kidney disease, and cancer.

- Published data on the relationship between cancer and COVID-19 are limited by a variety of methodological problems. It is not yet clear whether cancer patients are at higher risk of contracting COVID-19 or not, and it is not known whether the reported increased case fatality rate (CFR) reported by some investigators is real or artifactual. Currently the consensus is that COVID-19 should not be considered a reason to discontinue cancer treatment. It seems like age, uncontrolled cancer, and neutropenia are risk factors for poor outcome. Guidance from national and international cancer societies is updated frequently and should be obtained (https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19).
- Of all patients with COVID-19 admitted to the hospital, 15% to 20% may need intensive care unit care, typically for treatment of hypoxemic respiratory failure, and many of them require mechanical ventilation. The CFR varies significantly with age: less than 1% in people younger than 50 years and 20% to 30% after 70 years.
- Most transmission occurs by close person-to-person contact, mainly by respiratory droplets, but airborne transmission is possible and has been documented in poorly ventilated locales and when aerosol generation is increased. Transmission may be significantly decreased by physical distancing, use of masks, and meticulous hand hygiene.
- Treatment is evolving. At the time of this writing, effective interventions include the antiviral remdesivir, and the anti-inflammatory agents dexamethasone, baricitinib (a JAK inhibitor) and tocilizumab (an anti-interleukin 6 agent). Monoclonal antibodies, when used early after the onset of symptoms, significantly reduce the risk of hospitalization and death. Treatment guidelines are constantly updated by the National Institutes of Health (NIH) and professional societies.
- Vaccines, based on a diverse platforms (mRNA, replication-incompetent adenovirus, adjuvanted protein) are available and in development.
- This section will be outdated by the time it is printed, and the reader is urged to obtain current information from the websites of Centers for Disease Control and Prevention (cdc.gov https://www.cdc.gov/coronavirus/2019-nCoV/index.html), NIH (https://www.covid19treatmentguidelines.nih.gov/), and professional societies (https://www.asco.org)

Gastrointestinal Infections

Mucositis

- The shallow, painful ulcerations of the tongue and buccal mucosa caused by chemotherapy can become superinfected with HSV or *Candida.*

- If severe, HSV infection is treated with acyclovir 5 mg/kg IV every 8 hours for 7 days. Milder infection may be treated with valaciclovir 1000 mg PO every 12 hours or famciclovir 500 mg PO every 12 hours.
- Candidiasis can be treated locally with clotrimazole troches 10 mg dissolved in the mouth 5×/day, nystatin "swish and swallow," or systemically with fluconazole 200 mg PO/IV once, then 100 mg daily.
- Patients with fever and neutropenia with thrush should be covered empirically with systemic antifungals with activity against *Candida* species.

Esophagitis

- Odynophagia, dysphagia, and substernal chest discomfort can be a result of chemotherapy but may also be due to herpes or candidal infections.
- Endoscopy with biopsy should be performed when possible.
- If endoscopy and biopsy are not possible, empirical therapy with fluconazole for *Candida* and acyclovir for HSV is recommended. In neutropenic patients with fever and clinical symptoms of esophagitis, antibacterial therapy appropriate for upper GI flora should be added (eg, ceftazidime + vancomycin or piperacillin-tazobactam or imipenem or meropenem).
- CMV can also cause esophagitis.

Diarrhea

- *C. difficile* is the most common pathogen to cause diarrhea in cancer patients.
- Diagnosis can be made by detecting *C. difficile* toxin in the stool by immunoassay (EIA) or the toxin gene by PCR. Less commonly used tests include cytotoxicity assay and stool culture. It is important to be familiar with the diagnostic test used, as some toxin immunoassays are not sensitive enough to rule out the infection with certainty. Conversely, some tests like PCR are sensitive enough that repeating them is not associated with increased yield. In fact, PCR cannot differentiate between a patient colonized with *C. difficile* and diarrhea of another etiology and a patient with true *C. difficile*–associated disease (CDAD).
- Treatment of severe CDAD is with fidaxomicin 200 mg PO every 12 h or vancomycin 125 to 250 mg PO four times a day should be used. In fulminant cases, metronidazole 500 mg IV q 8 hours may be added. For mild/moderate cases, metronidazole 250 mg PO four times a day or 500 mg PO three times a day may be used. The antiparasitic agent nitazoxanide (500 mg PO twice a day) has also been used. In severe and/or refractory cases, fidaxomicin 200 mg PO twice daily is as effective as oral vancomycin and may be associated with less recurrences. Treatment is continued for 10 to 14 days. The stool should not be retested for *C. difficile* toxin, as many patients may remain asymptomatic carriers.
- Recalcitrant CDAD has been successfully treated by fecal microbiota transplantation.
- Bacteria such as *E. coli*, *Salmonella*, *Shigella*, *Aeromonas*, and *Campylobacter* species, as well as parasites like *Giardia* and *Cryptosporidium* and viruses like norovirus and rotavirus, are less common causes of diarrhea in cancer patients. Defects in cell-mediated immunity increase the likelihood of some of these pathogens. Stool should be sent for culture of bacterial pathogens. Stool should be sent for ova and parasites on three

consecutive days. Multiplex PCR in the stool is available and can detect more than 20 different pathogens.

Neutropenic Enterocolitis (Typhlitis)

- Typhlitis typically presents as abdominal pain, rebound tenderness, bloody diarrhea, and fever in the setting of neutropenia. The diagnosis should be entertained in every case of abdominal pain during neutropenia, although it is most common during prolonged, profound neutropenia during the treatment of acute leukemia.
- Characteristic CT scan findings include a fluid-filled, dilated, and distended cecum, often with diffuse cecal wall edema and possibly air in the bowel wall (pneumatosis intestinalis). However, the CT may be unremarkable in the early stages; it has a reported sensitivity of only 80%.
- Pathogens are typically mixed aerobic and anaerobic gram-negative bacilli (including *Pseudomonas*) and *Clostridium* species.
- Treatment is with broad-spectrum antibiotics including coverage of *Pseudomonas* and anaerobes (eg, imipenem or meropenem or the combination ceftazidime or cefepime plus metronidazole plus vancomycin).
- Patients should be monitored closely for complications that may require surgical intervention, such as bowel perforation, bowel necrosis, or abscess formation.

Perforations/Fistulas

- Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, has been associated with a gastrointestinal (GI) perforation/fistula rate of 1% to 5%.
- Patients with colon cancer and ovarian cancer have been found to be at greatest risk.
- Other risk factors may include prior abdominal/pelvic irradiation, bowel involvement by tumor, or unresected colon cancer.
- Any patient on bevacizumab with abdominal pain or new rectal bleeding should have prompt evaluation for perforation/fistula with imaging, as well as broad-spectrum antibiotic therapy covering gram-negative bacteria and anaerobes.

Hepatosplenic Candidiasis

- Hepatosplenic candidiasis typically presents as fever during neutropenia (sometimes after resolution of neutropenia) without localizing signs or symptoms.
- When neutropenia resolves, the patient may continue to have fever, develop right upper quadrant pain and hepatosplenomegaly, and have significant elevation in alkaline phosphatase.
- CT scan, ultrasound, or MRI will show hypoechoic and/or bulls eye lesions in the liver and spleen and sometimes the kidneys.
- Blood cultures are typically negative. A liver biopsy is recommended, since other fungal infections, tuberculosis, and lymphoma may show similar findings. The diagnosis will be established by pathology showing granulomatous inflammation and yeast, as biopsy culture results are usually negative.
- Treatment consists of a prolonged course of fluconazole 400 to 800 mg daily. Caspofungin has also been effective.

Hepatitis B

- Hepatitis B virus (HBV) reactivation can occur in chronic carriers who are undergoing cytotoxic chemotherapy, with lymphoma patients being at highest risk especially with rituximab administration.
- Risk factors include positive hepatitis B DNA, HBsAg, HBeAg, anti-HBc, and young age.
- Entecavir prophylaxis (0.5 mg/d) is recommended for patients with serological evidence consistent with past hepatitis B (eg, positive HbsAb without history of hepatitis B vaccination or those with anti-HBc antibody in the absence of other markers), including those with undetectable HBV DNA, beginning 1 week before chemotherapy and for several months after completion of treatment. Entecavir has shown to be superior to lamivudine in randomized trials.

Urinary Tract Infections

- In the presence of neutropenia, it is reasonable to treat bacteriuria even in the absence of symptoms. In the nonneutropenic patient, treatment should be reserved for symptomatic episodes.
- Patients with indwelling stents may have persistent microbial colonization and pyuria. Treatment should be initiated in neutropenic patients with pyuria even with a history of chronic asymptomatic pyuria.
- Candiduria may represent colonization in a patient with an indwelling urinary catheter, particularly in the setting of broad-spectrum antibiotics. Removal of the catheter is frequently sufficient to clear it.
- Persistent candiduria can occasionally cause infections such as pyelonephritis or disseminated candidiasis in immunocompromised patients. Additionally, candiduria can be indicative of disseminated candidiasis. However, treatment of asymptomatic candiduria with systemic antifungals has not been associated with improved outcomes overall.
- If a decision is made to treat, fluconazole 400 mg/d for 1 to 2 weeks is the treatment of choice. In the case of non-*albicans* candiduria, another azole or amphotericin should be used. Echinocandins are minimally present in the urine, but limited clinical experience suggests micafungin may successfully treat urinary tract infections.

Central Nervous System Infections

- Changes in mentation or level of consciousness, headache, double vision, or photophobia should be evaluated promptly with MRI and lumbar puncture.
- In addition to the usual bacterial causes of meningitis (*S. pneumoniae*, *Neisseria meningitidis*), *Listeria* and *Cryptococcus* should be considered, particularly when a defect in cell-mediated immunity is present.
- For *Listeria*, the treatment of choice is ampicillin 2 mg IV every 4 hours in combination with gentamicin.
- For *Cryptococcus*, treatment is with liposomal amphotericin B 3 mg/kg/d or amphotericin B 0.5 to 0.7 mg/kg/d in combination with flucytosine 37.5 mg/kg every 6 hours for 2 weeks. If the patient improves (afebrile, cultures negative), therapy can be subsequently changed to fluconazole 400 mg daily.

- Encephalitis in patients with cancer is most commonly caused by HSV. Diagnosis is made by the presence of viral DNA in cerebrospinal fluid, and it should be treated with acyclovir 10 mg/kg IV every 8 hours. Empirical HSV treatment may be considered in cases of altered mentation symptoms and focal changes on EEG or MRI, especially in the temporal lobes.
- VZV, CMV, and HHV-6 are other less common causes of encephalitis.
- Progressive multifocal leukoencephalopathy (PML), caused by JC virus, presents with multiple nonenhancing white matter lesions. This infection has been associated with rituximab and mycophenolate mofetil.
- Brain abscesses that develop during neutropenia are typically caused by fungi (most commonly *Aspergillus* and *Candida*). Bacterial abscesses may also be a local extension of infection (sinusitis, odontogenic infection), caused by mixed aerobic and anaerobic flora (streptococci, *Staphylococcus*, *Bacteroides*). Pending results from biopsy and cultures, we recommend empirical treatment with ceftazidime or cefepime plus vancomycin plus metronidazole plus voriconazole.
- Toxoplasmosis may present with multiple intracranial ring-enhancing lesions, frequently involving the basal ganglia. It is mainly an early complication of allogeneic stem cell transplant, but it has also been described after alemtuzumab.
- *Nocardia* (discussed above under pulmonary infections) may present as single of multiple brain abscess, usually on patients who are receiving corticosteroids.

Infectious Issues Secondary to Monoclonal Antibody Therapy

- The increased use of monoclonal antibodies, in particular those targeting leukocytes, has important implications for infectious disease.
- Alemtuzumab, an anti-CD52 antibody approved for chronic lymphocytic leukemia, results in profound depletion of cell-mediated immunity and places patients at risk for viral reactivation and infection with intracellular pathogens. *Pneumocystis*, HSV, and Epstein-Barr virus infection, as well as CMV reactivation, are being seen regularly.
- Rituximab, a monoclonal antibody against CD20 used in lymphoma and leukemia treatment, causes B-cell depletion from 6 to 9 months and can also result in prolonged hypogammaglobulinemia and reactivation of viral hepatitis.
- Perforation and fistula are rare but serious side effects of bevacizumab.
- Cetuximab (anti–epidermal growth factor receptor [EGFR]) is associated with acneiform rash and secondary bacterial infection.
- Brentuximab vedotin, an anti-CD30 monoclonal antibody conjugated to the toxin monomethyl auristatin E, has been associated with PML and CMV retinitis.
- Gemtuzumab ozogamicin is a monoclonal antibody conjugated to the toxin calicheamicin and directed against CD33. It causes profound, prolonged neutropenia.
- Inotuzumab targets CD22, but has been associated with neutropenia.
- Blinatumomab targets CD19 on malignant cells and CD3 on cytotoxic T cells, resulting in T-cell activation and lysis of the B cells. It has been associated with CRS.
- Daratumumab targets CD38 on the surface of myeloma cells. No opportunistic infections have been described with its use. Upper and lower respiratory tract infections have been described.
- Cetuximab and panitumumab target the EGFR and have been associated with febrile neutropenia.

PROPHYLAXIS

Antibacterial Prophylaxis

- Fluoroquinolones are the most commonly used antibiotics for prophylaxis against bacterial infections in neutropenic patients and can significantly reduce the frequency of gram-negative infections. However, they could conceivably result in the emergence of resistance among enteric gram-negative bacteria. Meta-analyses suggest fluoroquinolone prophylaxis may be associated with improved overall survival in patients with prolonged neutropenia. This approach is currently recommended for high-risk patients who are expected to remain neutropenic for more than 7 to 10 days. We start levofloxacin 500 mg PO the first day of neutropenia and continue until the ANC is ≥500/μL.

Antiviral Prophylaxis

HSV and VZV

- Prophylaxis against HSV should be considered in patients who are seropositive or have a history of herpetic stomatitis and are undergoing allogeneic stem cell transplant or highly immunosuppressive chemotherapy, including high-dose steroids and alemtuzumab. Patients treated with bortezomib are at high risk for VZV reactivation and should be considered for prophylaxis.
- In allogeneic transplant recipients, we institute acyclovir prophylaxis at the beginning of the conditioning chemotherapy prior to transplant and continue for 1 year. This approach is effective for VZV prophylaxis, although a significant fraction of patients will develop shingles in the first few months after discontinuing acyclovir. In general, it is not considered necessary to routinely administer prophylaxis for HSV beyond the immediate peritransplant period.
- The drugs of choice are acyclovir 250 mg/m^2 IV every 12 hours or 800 mg PO twice daily and valaciclovir 500 mg PO once or twice daily.

Cytomegalovirus

- Letermovir 480 mg/d for 100 days may be used for CMV prophylaxis in allogeneic stem cell transplant recipients who are CMV seropositive and have a negative CMV DNA in plasma.
- In CMV-seronegative recipients, monitoring for CMV infection by following CMV antigenemia or PCR weekly is recommended.
- When this preemptive approach is used, CMV infection should be treated with ganciclovir 5 mg/kg IV every 12 hours for 14 days followed by 5 mg/kg IV daily until CMV antigenemia or PCR results are negative 1 week apart.
- Alternative treatments include (1) foscarnet 60 to 90 mg/kg IV every 12 hours for 14 days followed by 90 mg/kg daily, (2) valganciclovir 900 mg IV every 12 hours for 14 days followed by 900 mg daily, or (3) cidofovir 5 mg/kg IV weekly for 2 weeks followed by 5 mg/kg IV every other week (very limited evidence is available regarding use of cidofovir for this indication).

P. jirovecii Pneumonia Prophylaxis

- Prophylaxis against *Pneumocystis* is generally administered to patients during the 6-month after stem cell transplant period or after being treated with alemtuzumab. Patients with a history of PCP or with brain tumors on high-dose steroids should also receive prophylaxis.
- The regimen of choice is 160 mg TMP/800 mg SMX PO daily 3 days a week.
- Alternative prophylaxis options include (1) dapsone 100 mg PO daily (rule out G6PDH deficiency before using dapsone and monitor for methemoglobinemia), (2) inhaled pentamidine 300 mg every 4 weeks, or (3) atovaquone 1500 mg daily with a fatty meal.

Antifungal Prophylaxis

- Fluconazole 400 mg PO/IV daily has been the regimen of choice. Of note, fluconazole has no activity against molds like *Aspergillus.*
- Posaconazole is the antifungal prophylactic agent of choice when the risk of mold infection is considered significant.
- Prophylaxis should be continued until 100 days posttransplant and until immunosuppressants have been discontinued.
- The use of fluconazole has led to increased frequency of fluconazole-resistant infections such as *Candida glabrata* and *Candida krusei*.

Suggested Readings

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Oncologic Emergencies and Paraneoplastic Syndromes

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INTRODUCTION

Earlier detection and vigorous screening programs have culminated in an increase in the number of new cancer diagnoses in recent years. However, therapeutic advances have resulted in consistent improvements in 5-year survival rates. Cancer patients are at increased risk of developing unique complications that can require emergent evaluation and treatment. Because of the expanding population of cancer survivors, it is pertinent that caregivers involved in their management including those in primary care or emergency medicine gain familiarity with the diagnosis of and initial treatment for common oncological emergencies. The most common emergencies we encounter can be classified into metabolic, hematologic, cardiovascular, neurologic, infectious, and chemotherapy or immunotherapy-related side effects. In this chapter, we will discuss the most common oncologic emergencies, initial diagnostic workup, and management.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava (SVC) syndrome occurs when blood flow through the SVC becomes obstructed due to external compression or internal occlusion by tumor invasion, fibrosis, or an intraluminal thrombus. This subsequently impairs venous drainage from the

head, neck, upper extremities, and thorax. Decreased venous return to the heart, in turn, causes decreased cardiac output, increased venous congestion, and edema.

Etiology

The causes of SVC syndrome can be classified into two main categories: malignant (>90% of cases) and benign. The most common malignancies associated with SVC syndrome include lung cancer (primarily small cell and squamous cell), lymphoma (primarily non-Hodgkin including diffuse large cell lymphoma or lymphoblastic lymphoma), and metastatic disease. Other mediastinal tumors, such as thymomas and germ cell tumors, account for <2% of cases. The most common benign etiology is an intravascular device (indwelling central venous catheter or pacemaker), and in these cases, the findings are predominantly unilateral. Other benign causes include retrosternal goiter, sarcoidosis, tuberculosis, fibrosing mediastinitis, and postradiation or idiopathic fibrosis.

Clinical Signs/Symptoms

The severity of symptoms (Table 36.1) depends on the acuity of the obstruction/occlusion and degree of compromise to the flow of the SVC. Gradual progression allows for the development of collateral circulation in the azygous venous system and thus a more benign presentation. However, sudden obstruction is a true emergency that can lead to airway compromise, increased intracranial pressure (ICP), and cerebral edema.

TABLE 36.1

Clinical Presentation of Superior Vena Cava Syndrome

Dyspnea	63%	Arm swelling	18%
Facial plethora	50%	Chest pain	15%
Cough	24%	Dysphagia	9%

Common symptoms include dyspnea (63%) and facial swelling/sensation of head fullness (50%). Cough, chest pain, and dysphagia are less frequently encountered. More severe cases may present with confusion, altered mental status from cerebral edema, visual changes from ocular edema, or stridor from laryngeal edema. Characteristic physical examination findings include venous distention of neck (66%), venous distention of chest wall (54%), and facial edema (46%). Other examination findings may include cyanosis, arm swelling, facial plethora, and edema of arms. Symptoms are generally exacerbated by bending forward, stooping, or lying down.

Diagnosis

Although SVC syndrome is a clinical diagnosis, imaging studies may be obtained for further confirmation. Superior mediastinal widening may be noted on chest X-ray. Computed tomography (CT) scan +/− venography, however, remains the most useful study for imaging the mediastinum, for identification of the site of obstruction, and, if warranted, to guide percutaneous biopsy. Based on imaging findings, more invasive methods such as bronchoscopy, thoracotomy, and mediastinoscopy may be pursued to obtain diagnostic tissue.

Treatment

The treatment and prognosis of SVC syndrome is driven by the underlying pathological process, and its management has shifted over the years from empiric radiotherapy to a more methodological and individualized approach. It has been shown that radiation prior to obtaining tissue diagnosis impedes accurate interpretation of the biopsy sample in >50% of cases. Exceptions to this rule, however, may include those with impending airway obstruction and/or a severe increase in ICP. In the presence of severe symptoms (significant cerebral edema, laryngeal edema with stridor, or significant hemodynamic compromise), a catheter-based venography may not only aid diagnosis but would also allow for

intravascular interventions such as thrombectomy or stenting. While radiation might be helpful for symptom control in such severe cases, it may obscure histologic diagnosis and if possible should be delayed until after a biopsy is obtained. In cases associated with a malignant compression or obstruction, histologic diagnosis should be pursued and treatment should be tailored accordingly. For chemotherapy-sensitive tumors such as small cell lung cancer (SCLC), systemic therapy should be initiated as soon as possible. Lymphomas and thymomas are typically steroid response and high doses of glucocorticoids may help alleviate symptoms before systemic therapy can be initiated.

Radiotherapy or chemotherapy can also be used in patients with non–small cell lung cancer (NSCLC); however, the percentage of patients who have been reported to have experienced relief were less than that of the SCLC population. The obstruction was also found to recur in approximately 20% of patients. Thus, the general recommendation for these patients consists primarily of radiation therapy, endovascular stenting, or a combination of both modalities. Some studies have shown that the presence of SVCS in patients with NSCLC foreshadows a shorter median survival of only 6 months as compared to 9 months in those without.

If SVC syndrome is detected early in patients with an indwelling venous catheter, fibrinolytic therapy can be used without removal of the catheter. Otherwise, these patients should have the catheter removed and be placed on anticoagulation to prevent embolization. The role for SVC bypass surgery in patients with SVC syndrome secondary to other benign causes (eg, mediastinal granuloma, fibrosing mediastinitis) has been one of the greatest debates. While the overall good prognosis of these patients sways physicians away from surgical methods, many have advocated surgical consideration in patients, where the syndrome develops suddenly or progresses/persists after 6 to 12 months of observation.

INCREASED ICP

The contents of our skull and dura can be divided into three main compartments: brain parenchyma (which occupies a volume of approximately 1.4 L), spinal fluid (52-160 mL), and blood (150 mL). An increase in any of these three compartments, as per the Monro-Kellie hypothesis, will occur at the expense of the remaining two. In addition, intracranial compliance has been noted to decrease with rising pressure, thus causing further compromise in cerebral perfusion. The normal range of ICP has been reported to be 5 to 15 mm Hg.

Etiology

In patients with cancer, volume changes in brain parenchyma can be the result of primary or secondary brain tumors +/− intratumoral hemorrhage, vasogenic (peritumoral) or cytotoxic (in the setting of cytotoxic chemotherapy) edema, extra-axial mass lesions (dural tumors, infection, or hemorrhage), or indirect neurologic complications. Brain metastases are, in fact, the most common cause of increased ICP in this population. Lung cancer and melanoma, specifically, are most commonly associated with central nervous system (CNS) metastasis.

An imbalance between cerebral spinal fluid (CSF) production and reabsorption may also contribute to increased ICP. Mass lesions located at or near "bottleneck regions" (foramen of Monro, cerebral aqueduct, medullary foramina, basilar subarachnoid cisterns) cause obstruction. Some examples of primary brain tumors that favor these locations include subependymal giant cell astrocytoma, lymphoma, choroid plexus papilloma, ependymoma, and meningioma. Carcinomatosis and meningitis impede CSF reabsorption at the arachnoid granulations. Fibrosis of arachnoid granulations can be seen in patients who have received whole brain or, less commonly, partial brain irradiation. Retinoic acid, an agent used for the treatment of promyelocytic leukemia, has also been associated with decreased CSF reabsorption. Increased production of CSF, however, is a rare cause of increased ICP. It can sometimes be seen in patients

with choroid plexus papilloma, especially if the disease is multifocal in nature.

The third and last compartment within the skull is blood. Cerebral perfusion pressures are normally maintained over a wide range (50-160 mm Hg); however, passive increases in ICP are seen when this autoregulatory mechanism fails. Venous outflow obstruction can be thrombotic or nonthrombotic. Patients receiving L-asparaginase therapy are at increased risk of developing dural venous sinus thrombosis. Nonthrombotic causes may include dural mass lesions such as meningioma, metastases from breast or prostate cancer, non-Hodgkin lymphoma, Ewing sarcoma, plasmacytoma, or neuroblastoma.

Intrathoracic pressure changes reflect on ICP as well, as demonstrated by coughing, sneezing, and straining. While these minimal fluctuations may not seem significant alone, patients with decreased compliance may experience transient decompensation.

Clinical Signs/Symptoms

The presentation of elevated ICP largely depends on the acuity of the underlying cause, with rapid progression often indicating hemorrhage. Slow, progressive changes may be accompanied by little to no symptoms, whereas dynamic changes can cause clinical deterioration. The Cushing response details the body's response to a rise in ICPs. First, the systolic blood pressure rises. In response, pulse pressure widens and bradycardia and irregular breathing ensue. Without correction, the heart rate will begin to rise, breathing will become shallow with episodes of apnea, and blood pressure will fall. With herniation and eventual cessation of brain stem activity, the patient goes into cardiac and respiratory arrest.

In the vast majority of patients with malignancy, the onset of symptoms occurs over days to weeks. Headache is the most common presenting symptom. Due to decreased venous drainage while in the supine position, patients generally report that their pain is most severe in the morning. Common analgesics rarely provide relief;

however, patients have been noted to experience immediate relief with emesis. Fundoscopic examination may be revealing; early findings include absence of venous pulsations in the center of the optic disc, while late findings are often papilledema with blurring of disc margins and/or small hemorrhages. Elevated ICP in the setting of mass effect can present with focal neurologic deficits based on the location of the mass. Patients with chronic disturbance of spinal fluid reabsorption can present with a triad of cognitive decline, incontinence, and ataxic gait. Hyponatremia may also be noted on laboratory testing as syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common metabolic complication seen with elevated ICP.

Diagnosis

A thorough history and physical examination followed by imaging to delineate the underlying etiology is the mainstay of diagnosis. CT scan with contrast is generally the initial preferred imaging study as it can identify the presence of CSF obstruction, herniation, hemorrhage, or neoplastic/infectious mass lesions. Magnetic resonance imaging (MRI) with gadolinium can further be used to differentiate between neoplastic, infectious, inflammatory, and ischemic process. Obstruction or infiltration of the dural venous sinuses is best visualized with magnetic resonance venography. If a lumbar puncture is being considered for diagnostic purposes, a CT of the head should be obtained prior to the procedure to rule out mass lesions of the posterior fossa as these would be a contraindication due to the risk of herniation.

Treatment

Few patients present emergently, such as those with obstructive hydrocephalus or mass effect from large intracranial tumors, and in these cases, immediate neurosurgical intervention will be necessary. In nonemergent cases, certain measures can be taken initially to help decrease ICP. These include elevation of the head of the bed above 30°, antipyretic use when the patient is febrile, and maintenance of

high normal serum osmolality with osmotic diuresis as needed. The most commonly used hyperosmolar agent used is 20% to 25% mannitol solution given at 0.75 to 1 g/kg body weight followed by 0.25 to 0.5 g/kg body weight every 3 to 6 hours. While moderate to high dose dexamethasone (6-10 mg every 6 hours up to 100 mg/d) can be effective in patients with vasogenic edema, they should be avoided in patients suspected to have CNS lymphoma prior to tissue diagnosis. Steroids are known to induce lymphocytic apoptosis and can therefore obscure the diagnosis. The most rapid, but transient, method to decreasing ICP is mechanical hyperventilation with goal Pco_2 of 25 to 30 mmHg. Antiepileptics may be indicated in the presence of clinical seizures or may be initiated prophylactically for high-risk lesions.

In addition to symptomatic management in these patients, it is crucial to treat the underlying disease process, whether that includes surgical resection/decompression, systemic/intrathecal chemotherapy, and/or whole brain irradiation.

SPINAL CORD COMPRESSION

Spinal cord compression (SCC) is a true oncologic emergency as delays in diagnosis can cause severe, irreversible neurologic compromise, decline in functional status, and impaired quality of life. SCC affects roughly 3% to 5% of all patients with cancer. The majority of cases result from spine metastases with extension into the epidural space. It is the second most frequent neurologic complication of cancer after brain metastases. The median overall survival of patients with SCC ranges from 3 to 16 months and most die of systemic tumor progression.

Etiology

Although all cancers capable of hematogenous spread can cause malignant SCC, the most common underlying cancer diagnoses

associated with this complication are breast, prostate, lung, multiple myeloma, and lymphoma.

Hematogenous seeding of tumor to the vertebral bodies is the most common cause of spinal metastases, followed by direct extension and cerebrospinal fluid spread. Nearly 66% of the cases with SCC have involvement of the thoracic spine and 20% have involvement of the lumbar spine. Colon and prostate malignancies more commonly spread to the lumbosacral spine, while lung and breast cancers frequently affect the thoracic spine. The cervical and sacral spines are rarely involved (less than 10% for each region).

The median time interval between cancer diagnosis and manifestation of SCC is approximately 6 to 12.5 months. Malignant SCC is rarely the primary manifestation of a malignancy.

Clinical Signs/Symptoms

The most common presenting symptom of malignant SCC is back pain. The complaint of back pain in a cancer patient, specifically with a malignancy that frequently seeds the spine, should be considered metastatic in origin until proven otherwise. The characteristic back pain that is described is often worst in the recumbent position, thus resulting in maximal intensity upon morning awakening. As time progresses, the back pain can become radicular in nature.

Other symptoms of malignant SCC are primarily dependent on the region of the spine that is affected.

Cervical spine involvement generally presents with headache, arm/shoulder/neck pain, breathing difficulties, loss of sensation, and weakness/paralysis in the upper extremities. Thoracic and lumbosacral spine involvement can present with pain in the back or chest, loss of sensation below the level of tumor, increased sensation above the level of tumor, positive Babinski sign, bladder/bowel retention, and/or sexual dysfunction.

A thorough physical examination should be performed including evaluation for motor and sensory deficits including pinprick testing, straight leg raise, and a rectal examination to assess sphincter tone.

The most important prognostic factor for regaining ambulatory function after treatment of SCC is pretreatment neurologic status, making the physical examination a vital component of overall prognosis. Generally speaking, the quicker the neurologic deficit evolves, the lower the chance of recovery after treatment.

Diagnosis

Despite the availability of diagnostic testing, there is often a lag between onset of symptoms and diagnosis (approximately 3 months). This delay can be primarily attributed to a delay in obtaining the diagnostic imaging by healthcare professionals. As back pain is a common complaint and the differential remains broad, having a high clinical suspicion is crucial. Red flags for SCC should include pain in the thoracic spine, persistence of symptoms despite conservative measures, and exacerbation of pain in the supine position.

MRI with contrast of the spine is the most sensitive diagnostic test. Its advantages include the ability to accurately identify the level of the metastatic lesion, define soft tissue from bone, and separate metastatic cord compression from other pathologic processes involving the axial skeleton, epi- or intradural space, and spinal cord. It avoids the need for lumbar or cervical puncture that is required with CT myelography and can be safely performed in most patients.

CT myelography after intrathecal injection of contrast was the study of choice in the pre-MRI era but is now used much less frequently. It remains useful, however, for patients in whom MRI is contraindicated.

Thorough investigations utilizing CT scans or PET/CT to determine the primary malignancy and obtain histologic diagnosis to help guide therapeutic decisions should be pursued. If the patient

does not have neurologic symptoms from the SCC and surgical intervention is not emergently warranted, performing a biopsy for purposes of diagnosis prior to treatment is prudent.

Treatment

Primary goals of treatment include pain control, preservation/recovery of neurologic function, and prevention of complications secondary to tumor growth.

Treatment with corticosteroids should be initiated immediately when SCC is suspected. This begins with an initial loading dose of 10 mg IV dexamethasone followed by 16 mg divided over the course of the day. Previous evidence suggests that higher doses are no more efficacious than standard dosing for dexamethasone and could potentially result in more prominent adverse effects. Corticosteroids facilitate pain management, reduce swelling around the cord, and may prevent additional spinal cord damage from decreased blood perfusion.

Immediate consultations to surgery and radiation oncology are required after diagnosis. Further therapy is then decided based on the clinical picture, availability of histologic diagnosis, spinal stability, and previous treatment. Patients with spinal instability, even in the absence of clinical signs/symptoms, should undergo surgery unless otherwise contraindicated.

At the time of diagnosis, 66% of patients receive radiation, 16% to 20% undergo surgical decompression, and the remainder are provided with comfort care measures. In a study of symptomatic patients with SCC with metastatic tumors other than lymphoma, debulking surgery followed by radiation resulted in four times longer duration of maintained ambulation after treatment and three times higher chance of regaining ambulation for nonambulatory patients than radiation alone. Combined-modality approaches help to achieve better pain control and bladder continence. This can also reduce steroid and narcotic use.

Radiation therapy is the most commonly used treatment modality. It is typically applied in asymptomatic individuals, in postoperative setting, or in symptomatic patients who are poor surgical candidates. Patients with radiosensitive tumors (breast, lymphoma, myeloma, prostate cancer) have a higher chance of regaining/preserving motor function than those with less radiosensitive tumors (NSCLC, melanoma, and renal cell carcinoma). Standard radiation doses consist of 3000 to 4000 cGy in 5 to 10 fractions. It can also be used for palliative purposes with one fraction of 8 Gy. Stereotactic radiation therapy is becoming a more frequent modality for spine metastases. It provides the ability to deliver a higher radiation dose without exceeding the tolerance of the spinal cord.

Systemic chemotherapy is most appropriate as a primary treatment modality only for patients with SCC caused by highly chemosensitive tumors such as Hodgkin and non-Hodgkin lymphoma, SCLC, breast cancers, and prostate cancers. It can also be used in those who are not candidates for radiation or surgery.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) refers to a constellation of metabolic imbalances that occur when malignant cells rapidly undergo lysis and empty their intracellular contents into the bloodstream at a rate that far exceeds the kidney's clearance capacity. The overwhelming release of nucleic acid products results in hyperuricemia, which can then contribute to crystallization and subsequent obstruction within the renal tubules. Hyperkalemia and hyperphosphatemia with secondary hypocalcemia can also be seen in these patients. Without appropriate time-sensitive treatment (Table 36.2), TLS can lead to lactic acidosis, acute renal failure, and even death.

TABLE 36.2

Management of Electrolyte Abnormalities in Tumor Lysis Syndrome

Metabolic Derangement	Severity	Treatment
Hyperkalemia	Moderate (≥6 mmol/L) and asymptomatic	• Limit intake • ECG/telemetry • Sodium polystyrene sulfonate 15-30 g PO
	Severe (>7 mmol/L) and/or symptomatic	• As above, plus any of the following: • If ECG changes present, calcium gluconate 1 g slow infusion • Regular insulin 10U IV + 100 mL D50 IV • Sodium bicarbonate 45-50 mEq slow IV infusion over 5-10 min • Albuterol 10-20 in 4 mL nebulized saline over 20 min • Dialysis
Hypocalcemia (≤7 mg/dL)	Asymptomatic	No treatment necessary
	Symptomatic	• Hyperphosphatemia should be corrected first, if present, unless the patient develops tetany or an arrhythmia • Calcium gluconate 1 g, administered slowly with ECG monitoring
Hyperphosphatemia	Moderate (≥6.5 mg/dL)	• Limit intake • Phosphate binders (calcium acetate, calcium carbonate, sevelamer, lanthanum carbonate, or aluminum hydroxide)
	Severe	• Hemodialysis
Hyperuricemia (≥8 mg/dL)	Low risk	• IV normal saline 150-200 mL/h • +/−Allopurinol 300 mg PO daily (100 mg/m^2 every 8 h)
	Intermediate risk	IV normal saline 150-200 mL/h Allopurinol 300 mg PO daily (100 mg/m^2 every 8 h) +/−Rasburicase 0.15 mg/kg IV daily for 5-7 d

Metabolic Derangement	Severity	Treatment
	High risk	• IV normal saline 150-200 mL/h • Rasburicase 0.2 mg/kg IV daily for 5-7 d • +/−Dialysis

Etiology

While TLS is most commonly seen in patients with high-grade lymphomas (particularly Burkitt lymphoma) or acute forms of leukemia, it can also be seen in those with kinetically active solid tumors and, at times, may even occur spontaneously. Factors that increase the risk of TLS include high baseline urate levels, large tumor burden (white blood cell count >50 × 10^9/L, high low-density lipoprotein, large tumor size), and chemosensitive disease. Generally speaking, many of the patients who develop TLS are patients who have recently started chemotherapy. TLS most commonly occurs within hours to 3 days following chemotherapy. TLS has also been reported, albeit rarely following other treatment modalities including ionizing radiation, embolization, radiofrequency ablation, monoclonal antibody therapy, glucocorticoids, interferon, and hematopoietic stem cell transplantation.

Clinical Signs/Symptoms

The presentation of patients with TLS can be fairly nonspecific and depends on the electrolyte abnormalities that are present. Although symptoms may precede initiation of chemotherapy, they are most often noted within 12 to 72 hours after initiation of cytoreductive treatment. Hyperkalemia can manifest with arrhythmias, muscle cramps, weakness, paresthesia, nausea/vomiting, and diarrhea. Hyperphosphatemia and hyperuricemia contribute to acute renal failure, which is evidenced by decreased urine output (UOP) and/or volume overload. Hyperphosphatemia also leads to secondary hypocalcemia. Hypocalcemic signs include muscle twitches, cramps, carpopedal spasm, paresthesia, tetany, mental status changes, nephrocalcinosis, and, rarely, seizures.

Diagnosis

Of all the metabolic abnormalities seen with TLS, hyperkalemia poses the most immediate threat and is often the first sign of the disease. Hyperuricemia, however, is the most common laboratory abnormality noted in these patients. Additional laboratory tests may be notable for elevated phosphorus, elevated lactate dehydrogenase, and low calcium levels. Clinical and laboratory TLS is defined by the Cairo and Bishop classification and grading system. Laboratory TLS is diagnosed when levels of two or more serum values of urate, potassium, phosphate, or calcium are abnormal at presentation or if there is a 25% change within 3 days before or 7 days after the initiation of treatment. Clinical TLS is diagnosed when laboratory TLS is present and one or more of the following complications are present: renal insufficiency, cardiac arrhythmias/sudden death, and seizures. Laboratory TLS is either present or absent based on available laboratory data, whereas clinical TLS is graded on a scale of 0 to 5 based on the severity of the clinical manifestation.

Treatment

Prevention is key in the management of TLS. Patients at low risk can be closely monitored, while patients at intermediate or high risk should be treated prophylactically to reduce incidence of TLS. The recommended prophylactic treatment for intermediate-risk patients is allopurinol (100 mg/m^2 every 8 hours) for 2 to 3 days prior to administration of chemotherapy and continued for 3 to 7 days afterward until normalization of serum urate levels. Severe cutaneous adverse events have been reported with allopurinol in patients with inheritance of the HLA-B*58:01 allele; screening is advised in high-risk patients (Han Chinese, Thai, Korean populations). Patients should also undergo aggressive hydration (in order to maintain UOP of atleast 100 $mL/m^2/h$) and be given oral phosphate binders. Metabolites should be vigilantly monitored in intervals of 3 to 4 hours after initiation of treatment.

Uric acid levels are generally not expected to decrease until 48 to 72 hours of treatment as the mechanism of allopurinol is through the inhibition of xanthine oxidase. The medication, therefore, only affects further uric acid synthesis and not preexisting uric acid. Rasburicase can be considered in patients at intermediate or high risk of TLS and with preexisting hyperuricemia (≥ 7.5 mg/dL) and should be administered within 4 hours of presentation. This medication, in contrast, acts on the degradation of uric acid. There has only been one phase III clinical trial to compare allopurinol with rasburicase in adults. While rasburicase was proven superior in time to control serum uric acid levels, there was a lack of evidence to determine whether clinical outcomes were improved. At this time, the evidence remains stronger for rasburicase use in children with high-risk conditions than in adults; however, the medication has been approved for use in both populations, with the recommended dose of 0.2 mg/kg/d for 5 to 7 days. In patients at intermediate risk, a single dose of 0.15 mg/kg may be sufficient and can minimize cost. In a retrospective study utilizing patient data from over 400 US hospitals from 2005 to 2009, it was noted that rasburicase administration compared to allopurinol was associated with a significant reduction in uric acid levels, ICU length of stay (LOS), overall LOS, and overall cost. In patients receiving single-dose rasburicase, it is recommended that they receive allopurinol following the rasburicase treatment. G6PD deficiency is a contraindication for rasburicase treatment because hydrogen peroxide can cause severe hemolysis; therefore, patients should undergo screening prior to use.

In patients in whom allopurinol and rasburicase are not an option, febuxostat can be cautiously considered as an alternative. Febuxostat was compared with allopurinol in the FLORENCE trial. The decrease in mean serum urate levels observed with febuxostat did not translate to improvement in laboratory or clinical TLS following chemotherapy. In addition, the arm that received febuxostat was noted to have a higher incidence of liver dysfunction, nausea, joint pain, and rash.

Patients diagnosed with TLS require hospitalization for further monitoring and treatment. An ECG should be obtained in these patients to evaluate for serious arrhythmias and conduction abnormalities. Hyperkalemia can be treated with any combination of calcium gluconate, sodium bicarbonate, insulin with hypertonic dextrose, loop diuretics, and kayexalate (sodium polystyrene sulfonate). Patients may require hemodialysis depending on the severity of the hyperkalemia, renal dysfunction, and volume status. With the exception of hyperkalemia management, calcium administration is generally avoided as it can promote metastatic calcifications. Hyperphosphatemia is treated with phosphate binders (ie, aluminum hydroxide) or hypertonic dextrose with insulin. As hypocalcemia resolves with management of the underlying hyperphosphatemia, treatment with calcium gluconate is only needed if the patient is symptomatic. Urine alkalinization is no longer common practice as there is a lack of data to demonstrate its efficacy and it poses the risk of calcium phosphate deposition in the kidneys, heart, and other organs.

HYPONATREMIA

Patients with cancer may develop hyponatremia due to imbalances in water and sodium homeostasis. The reported incidence is 3.7%.

Etiology

The differential for hyponatremia is quite extensive, including pulmonary infections, intracranial lesions, recent radiation therapy, gastrointestinal (GI) losses, heart failure, hypothyroidism, diabetes, and offending medications. In cancer patients specifically, the leading causes remain dehydration, GI or renal losses, and SIADH. SIADH generally occurs as either a paraneoplastic syndrome or as a complication of chemotherapy. The excess production of antidiuretic hormone (ADH) may originate from the hypothalamus or be ectopic, arising from cancer cells. Ectopic ADH is most commonly associated with SCLC, indicating a poor prognosis. Other associated

malignancies include head and neck carcinomas, hematological malignancies, and NSCLC. Chemotherapy agents that can cause SIADH include cyclophosphamide, ifosfamide, vincristine, vinblastine, vinorelbine, bortezomib, carboplatin, and cisplatin.

Ectopic production of a peptide similar to ADH, known as atrial natriuretic peptide (ANP), has also been described in patients with SCLC. ANP is released from atrial myocytes and works by increasing renal sodium excretion and possibly by suppressing an aldosterone response.

"Pseudohyponatremia" is a condition frequently seen in patients with multiple myeloma and hyperproteinemia as a way for the body to preserve electrical neutrality. Lastly, hyponatremia can also occur with cerebral salt wasting syndrome (CSWS) in patients with cerebral malignancies or metastases.

Clinical Signs/Symptoms

The clinical manifestations of hyponatremia largely depend on the severity. If the imbalance develops over a prolonged time period and/or the hyponatremia is not significant, patients may be asymptomatic. The most common symptoms reported in patients with mild hyponatremia have been nausea and weakness. Other symptoms may include anorexia, constipation, myalgia, polyuria, and polydipsia. With severe hyponatremia, patients may experience altered mentation, seizures, and even coma or death from the resultant cerebral edema and increased ICP. Physical examination findings, if present, may be notable for papilledema and hypoactive reflexes.

Diagnosis

Hyponatremia is defined as serum sodium level less than 130 mEq/L. The essential features for diagnosis of SIADH, in particular, include decreased effective osmolality, urine osmolality >100 mOsm/kg of water, clinical euvolemia, urine sodium >40 mmol/L in the setting of normal salt intake, normal thyroid and adrenal

function, and no recent diuretic use. The major criteria for CSWS include the presence of a cerebral lesion and high urinary excretion of sodium and chloride in a patient with contraction of extracellular fluid volume.

Treatment

The initial step in the treatment of hyponatremia should be to determine the underlying cause. Any offending medications should immediately be stopped. The cornerstone of therapy consists of free water restriction (500-1000 mL/d) and furosemide. As a general rule, the rapidity of correction of serum sodium is determined by its acuity, so as to prevent patients from developing an osmotic demyelination syndrome. Patients with acute presentations are likely to be more symptomatic and can tolerate more rapid correction. For asymptomatic patients who developed hyponatremia over weeks with serum sodium level less than 125 mmol/L, the goal should be to increase serum sodium level by 0.5 to 2 mmol/L/h. For symptomatic patients or patients with a serum sodium level below 115 mmol/L, sodium should be increased by 2 mmol/L/h, with the initial use of hypertonic saline. If the hyponatremia does not improve or worsen after 72 to 96 hours of free water restriction, IV fluids, and lasix, plasma levels of arginine vasopressin and ANP should be measured to evaluate for SIADH and syndrome of inappropriate secretion of atrial natriuretic peptide (SIANP). Patients with SIADH should be treated with demeclocycline 300 to 600 mg twice daily and ADH receptor antagonists such as IV conivaptan or oral tolvaptan may also be considered. Patients with SIANP will continue to have worsening hyponatremia, despite free water restriction, if they do not increase their salt intake. Management of cerebral salt wasting includes aggressive fluid and electrolyte replacement as well as mineralocorticoid supplementation with fludrocortisone 100 to 400 mg/d.

HYPERCALCEMIA

Of all paraneoplastic syndromes, hypercalcemia is the most common, seen in 10% to 30% of cancer patients at some time during their disease. Severe hypercalcemia, especially if combined with elevated parathyroid hormone–related protein (PTHrP), indicates a poor prognosis. Survival is often less than 6 months following diagnosis of hypercalcemia.

Etiology

The etiology of hypercalcemia in cancer patients can be divided into two distinct groups: the first being a humoral paraneoplastic syndrome (most common cause of hypercalcemia in cancer patients) and second, the result of bone destruction. Humoral hypercalcemia is most frequently seen with malignancies of the breast, lung, kidney, and head and neck, whereas hypercalcemia in the setting of osteolytic metastases is most frequently seen with multiple myeloma. In the latter group, tumor cells have been found to release local factors such as cytokines and growth factors that activate osteoclasts, either directly or indirectly via osteoblast-related upregulation of osteoclast-activating factors. In the former group, tumor cells release systemic factors that affect bone resorption and calcium reabsorption at the level of the kidney. PTHrP is the most commonly secreted systemic factor, found in about 80% of hypercalcemic cancer patients. PTHrP further exacerbates hypercalcemia via its synergistic activity with local factors such as interleukin 1, interleukin 6, and tumor necrosis factor alpha. As a third mechanism, some lymphomas cause hypercalcemia by releasing 1,25-dihydroxyvitamin D, which then promotes intestinal calcium absorption and bone resorption.

Clinical Signs/Symptoms

Patients will generally present with nonspecific findings such as nausea, vomiting, constipation, polyuria, dehydration, and/or confusion. These patients are also at high risk for bradycardia, arrhythmias, shortened QT interval, prolonged PR interval, and cardiac arrest.

Diagnosis

The diagnosis of hypercalcemia is determined by measuring the serum ionized calcium level. If total serum calcium is obtained, it must be appropriately adjusted for albumin levels. Corrected calcium = measured total calcium + (0.8 × [4 − serum albumin concentration]). A low chloride level should raise suspicion for malignancy-related hypercalcemia.

Treatment

Patients who are asymptomatic with calcium levels less than 13 mg/dL only require conservative management with hydration. Symptomatic patients with calcium levels greater than 13 mg/dL require hydration in addition to more aggressive treatment. Hemodialysis should be considered when calcium levels exceed 18 to 20 mg/dL and/or the patient develops neurological symptoms. Once adequate hydration has been attained, small doses of furosemide can be utilized to enhance calcium excretion. Bisphosphonates remain the most effective treatment for malignancy-related hypercalcemia, with zoledronate being the current best choice. Pamidronate may also be used. Normalization of serum calcium levels is achieved in 4 to 10 days and the effects last for about 4 to 6 weeks in 90% of patients. Bisphosphonates have a complex mechanism of action that ultimately leads to a decrease in bone resorption. As they have no effect on humoral mediated calcium reabsorption, they are less effective in patients with humoral-mediated hypercalcemia. Osteonecrosis of the jaw may be a potentially devastating adverse effect of bisphosphonate use, with myeloma patients at higher risk. Depending on the clinical urgency of bisphosphonate use, patients should undergo dental evaluation prior, if able, as poor dentition also places patients at increased risk.

Novel agents in the pipeline include osteoprotegerin (OPG), a decoy receptor that acts to inhibit bone resorption. The cytokine system of which OPG is a part of also consists of the receptor RANK and its ligand RANKL. When RANKL binds to RANK, osteoclast

formation is increased and osteoclast apoptosis is inhibited. This process is counterbalanced by OPG. Denosumab is a monoclonal antibody with high affinity for RANKL and has been approved for treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy as well as for treatment of bone metastases. In three randomized, phase III clinical trials, denosumab has proven to be superior than zoledronic acid by a median of 8.21 months for prevention of skeletal-related events in patients with bone metastases from advanced disease. Denosumab also does not require the close monitoring and renal dosing that is needed with zoledronic acid.

Hypercalcemia that is refractory to bisphosphonates may be treated with gallium nitrate, plicamycin, or calcitonin. Calcitonin can quickly lower calcium levels; however, the effect is often transient. Plicamycin and gallium nitrate are associated with serious adverse effects and therefore are infrequently used. Glucocorticoids are effective in hypercalcemia secondary to elevated levels of vitamin D and can also be useful for relief of other symptoms related to metastatic disease. Long-term treatment and prevention of recurrence will ultimately require treatment of the underlying malignancy. Comfort care should be considered for truly refractory cases.

FEBRILE NEUTROPENIA

Infection can be a significant source of morbidity and mortality in cancer patients, especially in patients who are immunosuppressed from chemotherapy or who have low neutrophil counts secondary to their disease.

Etiology

While febrile neutropenia most frequently occurs in patients undergoing chemotherapy, it can also be seen in patients with acute leukemia, myelodysplastic syndrome, or in other diseases with

leukopenias. In general, patients' neutrophil counts tend to be at their lowest 510 days following the last dose of chemotherapy with recovery of counts within 5 days of this nadir. Common pathogens that cause febrile neutropenia include gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*), gram-positive bacteria (*Staphylococcus* species, *Streptococcus* species, and *Enterococcus* species), or polymicrobial infections. In about 75% to 80% of cases, however, no organism is able to be identified.

Clinical Signs/Symptoms

Fever is commonly the only symptom that these patients present with as other typical signs of infection can be masked in the setting of neutropenia. Other possible symptoms may include chills, diarrhea, rash, nausea, vomiting, cough, and shortness of breath. A thorough physical examination, including inspection of the oral cavity and perianal region, should be performed on these patients.

Diagnosis

Neutropenia is defined as an absolute neutrophil count (ANC) less than 1500 cells/μL, and severe neutropenia is defined as an ANC less than 500 cells/μL or an ANC that is expected to decrease to less than 500 cells/μL in the next 48 hours. Risk of infection is higher in patients with severe neutropenia, especially when the neutropenia is prolonged (>7 days). Fever is defined as a temperature greater than 100.4 °F that is sustained for more than an hour or a single temperature greater than 101.3 °F. All patients who have received chemotherapy within 6 weeks of presentation and meet criteria for a systemic inflammatory response syndrome are assumed to have a neutropenic sepsis syndrome, unless proven otherwise.

Treatment

Febrile neutropenic patients should initially be stratified based on the MASCC (Multinational Association for Supportive Care in Cancer) risk index score to identify those who can be treated in an outpatient setting (Figure 36.1). The MASCC score takes into account

burden of illness, presence or absence of hypotension, history of chronic obstructive pulmonary disease, the type of tumor (solid vs liquid), history of fungal infections, volume status, and age. A total score of 21 or greater indicates low risk of serious infection. These patients can be monitored in the emergency department for at least 4 hours after antibiotic initiation and should have all cultures drawn prior to discharge. They can be further treated as an outpatient with ciprofloxacin 750 mg twice daily in addition to amoxicillin/clavulanate 500 to 125 mg every 8 hours or alternatively with moxifloxacin monotherapy. Patients already on prophylactic fluoroquinolone therapy should not receive fluoroquinolone therapy for empiric treatment. For these patients, it would be reasonable to treat with an IV antibiotic regimen on an outpatient basis. Daily evaluation by a healthcare provider is recommended for the first 3 days of treatment. Outpatient therapy is continued for 7 days or until the patient has been afebrile for 4 to 5 days.

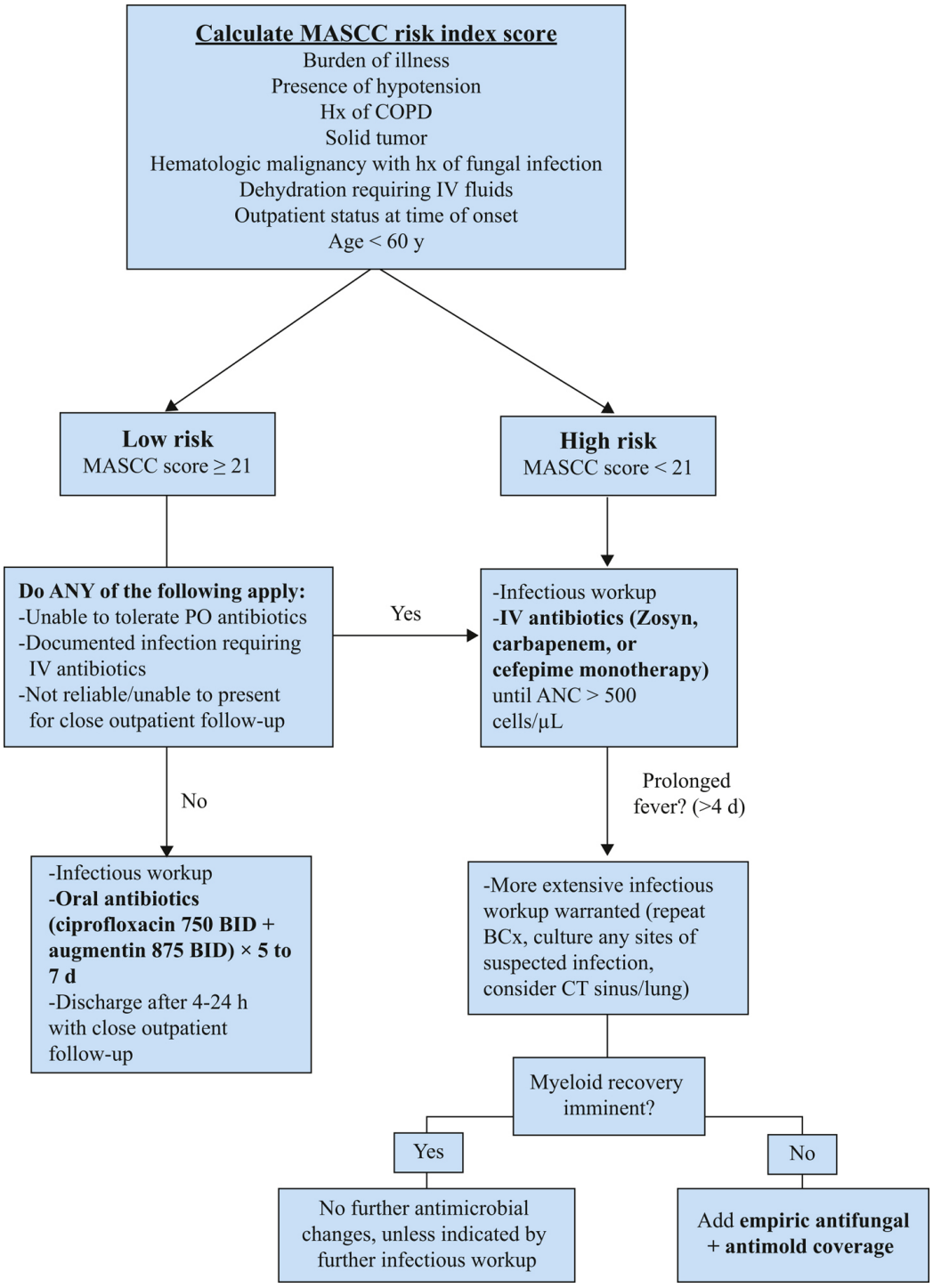

FIGURE 36.1 Treatment algorithm for febrile neutropenia.ANC, absolute neutrophil count; COPD, chronic obstructive pulmonary disease; MASCC, Multinational Association for Supportive Care in Cancer.

Patients with a MASCC score of less than 21 are stratified as high risk and should be admitted to the hospital for IV antibiotics and

closer monitoring. Blood cultures, with one sample drawn from a peripheral vein and one from a central line, if available, should be drawn upon presentation. The remainder of the infectious workup may include urine culture, sputum culture (if available), stool studies, CSF analysis, chest X-ray +/− high-resolution CT of the chest. Once the diagnosis has been established and cultures have been collected, patients should be started on empiric antibiotic therapy (ideally within an hour of triage). Common agents used as monotherapy include cefepime, meropenem, imipenem-cilastatin, ceftazidime, and Zosyn. Dual therapy agents include an aminoglycoside in addition to either piperacillin, cefepime, ceftazidime, or a carbapenem. Patients at high risk of gram-positive bacteremia should be started on an additional antibiotic with appropriate coverage, usually vancomycin. This group includes patients with gram-positive colonization, catheter-related infections, and severe sepsis +/− hypotension. UOP should be maintained at >0.5 mL/kg/h. Fevers, on average, are expected to defervesce within 2 to 5 days of treatment. If the patient remains febrile on empiric antibiotics (>4 days) and is hemodynamically stable, the ANC should be evaluated. If myeloid recovery appears imminent, no change in antibiotics is needed. If myeloid recovery does not appear to be imminent, consideration should be given to obtaining a CT scan of the sinuses and lungs. It may also be beneficial to add antifungal +/− antimold coverage. If there is a documented infection and the patient is not responsive to targeted antibiotics, consider reimaging, culture/biopsy/drain sites of worsening infection, and the addition of empiric antifungal therapy.

IMMUNE-RELATED ADVERSE EFFECTS

Over the last decade, the field of immuno-oncology has grown in leaps and bounds. Immune checkpoint inhibitors (ICIs) that harness patient's own immune system have demonstrated efficacy across a wide range of solid tumors resulting in significant improvement in survival outcomes. Since immune checkpoints are crucial in the

physiologic pathways that mediate immune homeostasis, predictably inhibiting these pathways can result in adverse effects that resemble autoimmune diseases. The immune-related adverse effects (irAEs) can occur at any point after the initiation of ICIs and may even occur several months after discontinuation of treatment. While the entire spectrum of irAEs is quite broad and beyond the scope of this chapter, we will discuss select common toxicities that can be life threatening if they are not identified and treated in a timely manner.

Pneumonitis

Pneumonitis is an uncommon but potentially life-threatening irAE seen in approximately 5% of patients treated with ICI monotherapy. Worsening dyspnea, cough, decreasing exercise tolerance, and hypoxia in a patient receiving immunotherapy should prompt urgent evaluation including a physical examination, pulse oximetry, and a CT of the chest, preferably with contrast (PE protocol) to rule pulmonary embolism, which can have a similar clinical presentation. A workup for infectious etiologies should be performed and a bronchoscopy with BAL ± biopsy may be considered for diagnostic purposes. If pneumonitis is suspected, ICI therapy should be held and may even need to be discontinued permanently for severe or life-threatening symptoms (grade 3 or higher toxicity). Prednisone 1 to 2 mg/kg/d should be initiated without delay and empiric antibiotics should be considered. In severe cases or if there is life-threatening respiratory compromise, solumedrol 1 to 2 mg/kg/d should be started along with empiric antibiotics. There is no consensus on second-line agents that can be used in patients with refractory pneumonitis but IV immunoglobulin, mycophenolate mofetil, and cyclophosphamide have all been used with some success. Steroids should be tapered slowly over 4 to 6 weeks.

Colitis

Colitis is more frequently seen in patients receiving CTLA4 inhibitors than PD-1/PD-L1 inhibitors and appears to be dose

dependent. If not treated in a timely manner, it could result in bowel perforation necessitating a colectomy. Median time to onset is 6 to 8 weeks. Patients often present with diarrhea, abdominal pain, nausea, cramping, blood or mucus in stool, or changes in bowel habits. Initial workup should include stool testing to rule out infectious etiologies and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. Fecal lactoferrin could help identify patients who might need urgent endoscopy. Fecal calprotectin can be useful to monitor disease activity with treatment. A CT of the abdomen pelvis could be considered for severe symptoms to identify patients who are high risk for having steroid refractory disease. For toxicity above grade 2, ICI should be held and steroids (prednisone 1-2 mg/kg/d) should be initiated after ruling out infectious etiologies such as clostridium difficile. For symptoms refractory to oral steroids for 3 days, an endoscopy should be strongly considered and IV steroids or an alternate agent such as infliximab should be administered.

Endocrine irAEs

Adrenal insufficiency, hypophysitis, and ICI-induced diabetes mellitus are the endocrine irAEs that are most likely to require urgent management. Patients with autoimmune diabetes secondary to ICIs often present with diabetic ketoacidosis. The workup and management of these endocrine toxicities mimic their non-irAE counterparts.

Hepatitis

The median time to onset of hepatotoxicity is 8 to 12 weeks. The incidence of hepatotoxicity is much higher with the combination of PD-1 and CTLA4 inhibitors, to the tune of 20%. Ruling out alternate etiologies by performing serologies for hepatitis, liver vascular ultrasound, and CT abdomen to rule out metastatic disease to the liver is essential. If suspicion for primary autoimmune hepatitis is high, one can consider checking for antinuclear antibodies, anti-smooth muscle antibodies, and antineutrophil cytoplasmic

antibodies. For patients with hepatitis refractory to initial management, a liver biopsy may be useful. For transaminases that are elevated up to five times of upper limit of normal, ICI should be held and treatment with prednisone at 1 mg/kg/d should be initiated. For more severe elevation of liver enzymes, higher doses of steroids—1 to 2 mg/kg/d of methylprednisolone—should be initiated. If liver enzymes do not improve after 3 days, other agents such as mycophenolate mofetil or azathioprine should be considered. Since infliximab has been associated with liver failure, it is often not used for this indication. Steroids should be tapered over 4 to 6 weeks.

Neurologic irAEs

The manifestations of neurologic irAEs can be quite varied but the more life threatening ones include myasthenia gravis, Guillain-Barré syndrome, transverse myelitis, and encephalitis. These are usually investigated and managed in a similar fashion to their non-irAE counterparts.

Cardiovascular irAEs

Cardiovascular toxicities of immunotherapy while rare tend to be one of the more fatal toxicities of these agents. Manifestations range from myocarditis, pericarditis, and cardiomyopathy to vasculitis. High-dose steroids, including pulse steroids, should be considered for the initial management of these toxicities. Other agents that have been used in refractory cases include CellCept, infliximab, or antithymocyte globulin (Figure 36.2).

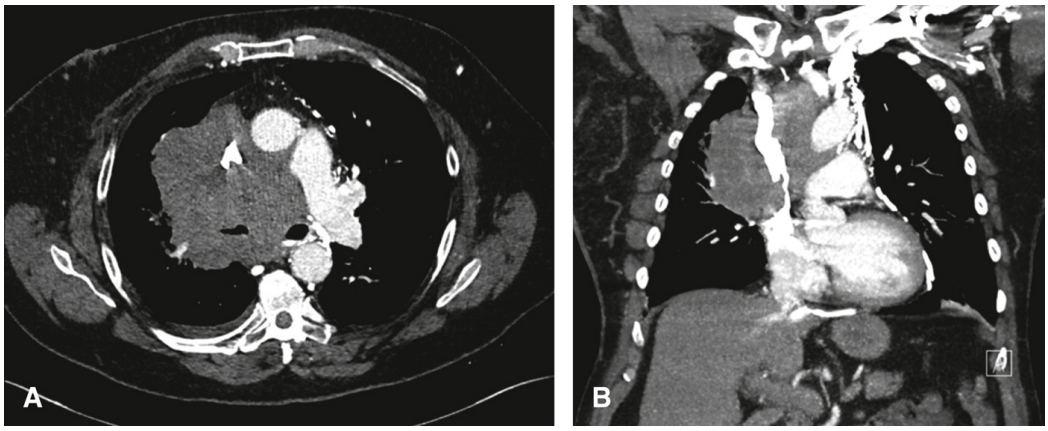

FIGURE 36.2 (A) Axial and (B) coronal images from a CT chest of a patient with superior vena cava syndrome.

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Psychopharmacologic Management in Oncology

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INTRODUCTION

It is commonly accepted that the etiology of psychiatric symptoms is multifactorial, with contributions from biological, psychological, and complex social factors influencing how people view and interact with the world around them. As we learn more about the interplay between mental health and our physical well-being, it has become clear that there are overlaps in the pathology between cancer and depression and anxiety, including the involvement of inflammation, oxidative stress, decreased immune surveillance, and dysfunction of the hypothalamic-pituitary-adrenal axis. This might provide some insight into why patients with cancer are considerably more likely to experience psychiatric symptoms, predominantly depression and anxiety, when compared to their peers.

Prevalence rates for depressive and anxiety disorders vary depending on multiple cancer-related factors, such as cancer type and stage, time since diagnosis, current treatment modalities, and physical symptom burden. This has made it challenging to fully appreciate the impact that mental health has on cancer outcomes. However, there is evidence that shows associations between depression and a number of concerning outcomes. This includes higher rates of pain and fatigue, nonadherence with aspects of cancer care, substance misuse, lower rates of engagement in preventative medicine and health screenings, lower patient

satisfaction with care, higher healthcare utilization and costs, and even increased mortality. Patients with cancer also have higher rates of suicidal thoughts and actions. This has led to a greater focus on mental health as an aspect of routine oncology care in recent years.

COMMON PSYCHIATRIC SYNDROMES IN THE ONCOLOGY SETTING

Medical Causes of Neuropsychiatric Syndromes

Psychiatric symptoms are often manifestations of an underlying medical disorder or complications of its treatment. For example, cancer can have direct effects on the central nervous system (CNS) due to primary brain disease, metastatic lesions, leptomeningeal involvement, and paraneoplastic processes. Chemotherapy has been linked to cancer-related cognitive dysfunctions including impairments in short-term memory, attention and concentration, processing speed, and ability to multitask successfully. Hormonal therapies, corticosteroids, and cytokines such as interleukin-2 and interferon alpha have been implicated in the onset of various cognitive, emotional, and behavioral disturbances. The use of immunotherapy agents can lead to endocrinopathies, including impact on thyroid and reproductive hormones that are clear factors in mood regulation. Radiation therapy, particularly cranial therapy and whole-brain radiation therapy, is also associated with cognitive deficits and fatigue.

Delirium, a generally reversible neuropsychiatric syndrome linked to higher morbidity and mortality, is a common comorbidity in patients with cancer. With prevalence rates varying widely and as high as nearly 90% in patients with cancer at the end of life, delirium should be considered in the differential diagnosis of all patients presenting for psychiatric evaluation. Delirium is a waxing and waning of mental status that can include disorientation, impairments in attention and concentration, disorganization of thought and

behavior, and fluctuations in the level of consciousness. Hyperactive delirium is most frequently identified as it can present with disinhibition, agitation, and hallucinations. This is often distressing to caregivers and patients alike. Hypoactive delirium can be confused with depression as it can present with social withdrawal, selective mutism, psychomotor retardation, and less engagement in treatment.

Patients with cancer can be particularly prone to many of the common causes of delirium, including metabolic derangements, nutritional deficiencies, dehydration, and infection. Oncology treatment regimens also often include medications that can precipitate or exacerbate delirium, including corticosteroids, opioids, benzodiazepines, anticholinergics, and antihistamines. Chimeric antigen receptor T-cell therapy and the resultant cytokine release syndrome can lead to encephalopathy known as immune effector cell–associated neurotoxicity syndrome. Management is focused on addressing the underlying etiologies, avoiding polypharmacy when possible, regulating the day-night cycle, assessing regularly for safety issues, and helping connect the patient to their environment. Antipsychotic medications might be considered in patients with distressing hallucinations, paranoia impacting care, agitation, or other behaviors posing a safety concern.

Depressive Disorders

It is important to note that feelings of sadness can be a normal response to difficult circumstances, such as the diagnosis of cancer in oneself or a loved one. Unfortunately, depressive symptoms can also interfere with one's functioning in daily life or even ability to participate in health care and warrant close monitoring and intervention. The *Diagnostic and Statistical Manual of Mental Disorders*, currently in its fifth edition (DSM-5), is the most commonly accepted source for diagnostic criteria to help differentiate psychiatric syndromes in order to guide care.

Adjustment disorders describe emotional or behavioral symptoms that begin in the context of a significant stressor, like the diagnosis of cancer, and resolve within 6 months of the stressor's resolution. These symptoms must cause more distress than would be expected in the circumstances or lead to impairment in daily functioning. Adjustment disorders can feature a number of symptom clusters, referred to as "specifiers" in the DSM-5, that include depressed mood, anxiety, and disturbances in emotion and/or conduct. Adjustment disorders are common in patients with cancer and warrant close monitoring and treatment using strategies similar to those used for major depressive disorder (MDD).

MDD is the diagnosis that captures the symptoms most people consider when thinking about "depression." This includes at least 2 weeks of impairing symptoms that can include depressed mood or irritability, anhedonia, changes in weight, changes in sleep, psychomotor agitation or retardation, low energy, feelings of worthlessness or guilt, impairments in attention and concentration, and recurrent thoughts of death or suicidal ideation. The diagnosis of MDD can be a challenge when working with patients with significant medical illness, and a frequent diagnostic task in the oncology setting is differentiating symptoms of MDD that are caused by the underlying cancer itself or its treatment. Patients with cancer, especially those with advanced disease and those who are undergoing systemic treatments, are more likely to experience fatigue, changes in appetite and sense of taste, weight loss, and changes in sleep, regardless of whether depression is present. During an assessment, increased focus on the quality and range of mood, from where one finds meaning and hope in life, and exploration of the nature of thoughts of death can be helpful in identifying depressive symptoms that are likely to respond to depression treatments. Other factors like a personal or family history of depression, excessive guilt, or concurrent anxiety might also help point one toward treatment. As the number of well-tolerated, safe, and effective antidepressants has grown, the threshold for treating depressive symptoms in the oncology setting has lowered.

Demoralization, the experience of hopelessness with loss of meaning and purpose, can occur in patients with depression and those without. It is important to differentiate this from the depressive disorders above because the evidence-based treatment differs. Largely studied as an end-of-life syndrome, one that is linked to important phenomenon like desire for hastened death, demoralization can be seen in a wide range of patients. In the oncology setting, this often can be seen in patients whose physical symptoms have impacted their ability to do the things that give purpose and meaning in daily life, within a family structure, or within the greater community. Patients who experience demoralization respond most robustly to therapeutic interventions and less so to pharmacologic options. If there are other symptoms of depression present, it would be wise to encourage both medication management and engagement in therapy.

Anxiety Disorders

Anxiety is a natural response to a perceived threat and can be adaptive, driving us to prepare for challenges or react to danger. However, anxiety can also be problematic when it is persistent, out of proportion to the threat, or interfering with one's abilities. Anxiety disorders are the most common psychiatric disorders in the general population, and the same is true in the oncology setting. Clinically significant anxiety is estimated to be present in around 19% of cancer patients across all disease types with additional patients describing bothersome anxiety that does not meet the criteria for a formal diagnosis. Anxiety prevalence rates vary with risk factors, including female gender, younger than 50 years, disfiguring or stigmatized disease, personal and family history of anxiety, prior traumatic experiences, poor social supports, and caregiver anxiety. Although anxiety is common at the time of diagnosis, particularly in those with lung, gynecologic, and hematologic cancers, the course can vary with exacerbations at times of transition such as disease progression/recurrence, changes in treatment, and even completion of aspects of the treatment course.

Anxiety, commonly related to fear of recurrence, can persist well beyond active treatment, with long-term survivors continuing to describe impairing anxiety at rates higher than the general population. Given the high prevalence of anxiety and the impact on quality of life and cancer-related outcomes, screening and treatment are high-yield parts of overall cancer treatment.

As with depression, it is important to consider a wide differential diagnosis for anxiety in patients with cancer and rule out potential medical and pharmacological causes of anxiety symptoms. It is common for patients with anxiety to struggle with the uncertainty of disease course, loss of control, impact on independence and need to rely on others, guilt about how illness impacts those around them, and existential themes like fear of death and finding meaning. Adjustment disorders, discussed above, commonly include an anxiety component.

Acute stress disorder (ASD), posttraumatic stress disorder (PTSD), and the less clearly defined cancer-related posttraumatic stress are of particular importance in oncology. Accurate estimates of the prevalence for ASD and PTSD in cancer have been elusive, but there is consensus that they are more common in patients with cancer than the general population. ASD, with quick onset but lasting less than 1 month, and PTSD, which can emerge later and have a prolonged course, are characterized by persistence of hyperarousal from a perceived lethal or near-lethal threat. This can include a specific experience within the cancer course or be linked to an overall sense of trauma over the course of treatment. These disorders can manifest differently for different people but might include increased irritability, emotional dysregulation, intense and intrusive thoughts of the traumatic experience, frequent nightmares about the event, hopelessness or loss of future-oriented thinking, and avoidance of reminders of the event. In the oncology setting, patients might avoid clinical settings or phone calls, experience increased physical symptoms prior to appointments, or be triggered by specific sounds or smells associated with traumatic aspects of their cancer care.

Generalized anxiety disorder (GAD) is the most common anxiety disorder in the general population and, by extension, affects a large number of patients with cancer. GAD is characterized by the presence of prototypical anxiety symptoms, including persistent and difficult-to-control worry over many things, irritability, difficulty relaxing, restlessness, sleep problems, catastrophic thinking, and fatigue. Patients may report physical symptoms like palpitations, shortness of breath, or nausea in general or in the context of a panic attack. GAD is chronic and, in the oncology context, will predate the cancer diagnosis in most cases. Increasing stressors can precipitate worsened symptoms or relapse to problematic anxiety that warrants treatment modification, so patients with GAD should be monitored closely during cancer care.

MANAGEMENT STRATEGIES

Nonpharmacologic Interventions

Many nonpharmacologic approaches to emotional distress in patients with cancer have been investigated and found to offer benefit. Programs targeting communication and education efforts that aim to provide greater understanding of disease physiology, prognosis, medication use/safety, decision-making, and symptom management have proven beneficial. Improvements in quality of life, physical functioning, and several neuropsychiatric symptoms have been demonstrated through collaborative approaches to care utilizing multidisciplinary teams with a focus on nutrition, physical activity, and quality sleep hygiene. Psychotherapy is outside of the typical scope of practice for oncologists, but an awareness of the available treatment options is important in utilizing the resources in one's community.

Cognitive behavior therapy (CBT) is a structured, pragmatic psychotherapy that focuses on identifying patterns in immediate, maladaptive thoughts, assessing how those thoughts impact one's emotional responses and behaviors, and then working to change this

pattern with the guidance of a skilled therapist. In broad terms, CBT-based interventions have the most evidence in improving quality of life and symptom burden. Specific modes of CBT exist to address different symptoms that impact patients with cancer, including chronic pain, sleep, uncontrolled emotional expression, trauma, depression, and anxiety.

Mindfulness-based interventions aim to improve awareness of one's thoughts, emotions, and physical sensations in a nonjudgmental state such that a greater sense of control and connection is achieved. Two specific and well-known modalities include mindfulness-based stress reduction and mindfulness-based cancer recovery. Other techniques include body scanning (focusing awareness on parts of one's body to improve accuracy of sensation), controlled breathing, progressive relaxation, and intentionally utilizing distraction. These techniques show promise in reducing overall distress and are increasingly being incorporated into many practices, especially with the increasing popularity of yoga in the United States.

Several therapy modalities have been developed specifically for patients facing life-limiting illness with the goal of finding meaning in one's experiences. This includes existential psychotherapy, individual and group meaning-centered psychotherapy, dignity therapy and other narrative-based interventions, supportive-expressive therapy, CALM (managing cancer and living meaningfully), and others.

Medication Strategies

Prescribing Pearls

When prescribing psychotropics in the medically ill, one should make attempts to use medications that can target more than one symptom at a time whenever possible. For example, many patients struggle with neuropathic pain caused by chemotherapy and benefit from an agent that has this indication as well. Close attention must

be paid to possible drug-drug interactions. It is always best to start at a low dose and titrate slowly. This helps mitigate potential side effects like headache and nausea. Although some side effects can happen quickly, most medications used to treat depression and anxiety take 1 to 2 weeks to begin working and 4 to 6 weeks for their full benefit at a given dose. If there is a partial response to a medication, it is generally advisable to maximize one medication before adding a second or switching to an alternate agent to minimize side effect risks with polypharmacy. If you have reached a moderate dose for at least 1 month without any benefit, a cross-titration to a different agent might be indicated. There are limited data to guide the decision of how long a person should stay on a medication. In general, if someone has had one depressive episode, they should remain on the medication for 6 to 9 months after recovery. If someone has had multiple episodes, this increases to at least 2 years. There are limited data on duration of treatment in the cancer population, but it is important to engage the patient in this decision.

Of note, there have historically been limited data on the use of psychotropics in patients with cancer as these patients often met exclusion criteria from large studies. The discussion and tables referenced in this chapter include many off-label indications and uses of medications. Given these factors and the complexity of care in this patient population, there are likely to be times when it is important to engage a mental health specialist in the care of a patient.

Examples of when to refer to a psychiatrist:

Anytime you are not comfortable with the management

Hopelessness or suicidality

Concern for bipolar illness or psychotic disorder

History of self-injury, suicide attempt, or psychiatric hospitalization

Past or current comorbid eating disorder

Comorbid substance misuse

Comorbid kidney or liver disease

Pregnancy, desire for pregnancy, or breastfeeding

Past or upcoming surgery involving the upper gastrointestinal (GI) tract

Concurrent use of tamoxifen, linezolid, procarbazine, or other possible interactions

A Review by Drug Class

Selective serotonin reuptake inhibitors (SSRIs) remain the gold standard for first-line medication treatment of depression and anxiety. These medications work by inhibiting the reuptake of serotonin from the postsynaptic cleft, thereby increasing the amount of serotonin available. About 50% to 65% of people respond to the first medication trial. There is a warning for the class due to increased cases of suicidal thoughts in people aged 24 years and younger. The most common side effects are listed in the table below (Table 37.1). Rare, but more serious side effects do exist and can include the syndrome of inappropriate antidiuretic hormone secretion, GI bleeding through an impact on platelet adhesion when combined with nonsteroidal anti-inflammatory drugs or blood thinners, higher rates of bone fractures, and QT prolongation. The use of an antidepressant without a mood stabilizer in a patient with bipolar illness can precipitate mania, which is a psychiatric emergency. All patients should be screened for a bipolar illness prior to initiating antidepressant medications.

TABLE 37.1

Antidepressants by Class

Drug Class	Indications and Benefits	Cautions
SSRIs	Gold standard for depression and anxiety	GI upset, headache, weight gain or loss, sexual dysfunction, insomnia or sedation, emotional blunting

Drug Class	Indications and Benefits	Cautions
citalopram (Celexa)	Few DDIs	Linked to QT prolongation
escitalopram (Lexapro)	Few DDIs	
fluoxetine (Prozac)	Long $t_{1/2}$	Watch DDIs
fluvoxamine (Luvox)	Historically used for OCD	Watch DDIs
paroxetine (Paxil)		Watch DDIs, teratogenic
sertraline (Zoloft)	Few DDIs	Most GI distress
SNRIs	Depression, anxiety, hot flashes, neuropathic pain, fibromyalgia	Same as above
desvenlafaxine (Pristiq)		
duloxetine (Cymbalta)	Evidence in neuropathic pain	No IR formulation
venlafaxine (Effexor)	Management of hot flashes	Risk of abstinence syndrome
TCAs	Depression, anxiety, hot flashes, neuropathic pain, fibromyalgia, IBS, IBD, migraines	Sedation, weight gain, orthostasis, tachycardia, arrhythmias, sexual dysfunction, dry mouth, constipation, urinary retention Class warning: Fatal in overdose
amitriptyline (Elavil)		
clomipramine (Anafranil)		
desipramine (Norpramin)		
doxepin (Sinequan)	FDA approved for insomnia	
imipramine (Tofranil)		
nortriptyline (Pamelor)		
mirtazapine (Remeron)	Depression, anxiety, insomnia, low appetite/weight loss Less sexual dysfunction Available as dissolvable tablet	Dry mouth, sedation, constipation, increased appetite and weight gain

Drug Class	Indications and Benefits	Cautions
bupropion (Wellbutrin, Forfivo, Zyban)	Depression, SAD, smoking cessation, weight loss, ADHD Least likely to cause weight gain or sexual dysfunction Least likely to induce mania	HTN, appetite suppression, exacerbation of anxiety, restlessness, insomnia Lowers seizure threshold at higher doses
trazodone (Desyrel)	Depression Most commonly used off-label for insomnia	Morning fatigue, orthostasis

ADHD, attention deficit hyperactivity disorder; DDIs, drug-drug interactions; FDA, Food and Drug Administration; GI, gastrointestinal; HTN, hypertension; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IR, immediate release; OCD, obsessive-compulsive disorder; SAD, seasonal affective disorder; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; $t_{1/2}$, half-life; TCAs, tricyclic antidepressants.

This includes the most commonly used medications and brand names. This is not an exhaustive list.

The above includes many off-label indications for medications.

Serotonin and norepinephrine reuptake inhibitors (SNRIs) block the reuptake of both serotonin and norepinephrine from the postsynaptic cleft. For some patients, this added action has benefits in managing depression and anxiety. This drug class also has more evidence in the treatment of several physical symptoms that impact patients with cancer including neuropathic pain, fibromyalgia, and hot flashes. There is a greater risk for uncomfortable withdrawal symptoms when compared to SSRIs. Some patients even report experiencing this after just one missed dose.

Tricyclic antidepressants (TCAs) have been used less since the development of newer, well-tolerated agents. However, there are times when a TCA might be an appropriate choice. The use of TCAs is an evidence-based approach to management of depression and anxiety, often used when trials of SSRIs and SNRIs have not had the desired effect. Like SNRIs, members of this drug class have also been shown to be beneficial in the management of several physical symptoms including neuropathic pain, fibromyalgia, diarrhea-predominant irritable bowel syndrome, inflammatory bowel disease,

and migraine prophylaxis. They exert their effect similarly to SNRIs but also have stronger antihistamine, antimuscarinic, and anti-α_1 properties that contribute to the majority of side effects. TCAs are typically fatal in overdose due to cardiotoxicity, so all patients should have routine safety screening and consideration for smaller supplies of medications should be made.

Mirtazapine has a unique mechanism of action, leaving it in a drug class of its own. It has benefits for depression and anxiety but is often chosen over other agents in the cancer population due to its potential benefits in targeting sleep and appetite. Its antagonism at the 5-HT3 receptor can have mild antiemetic properties. In addition, it is available as a dissolvable tablet, which can have benefits for patients who struggle with dysphagia or painful mucositis/esophagitis. It is gastrically absorbed, so it does need to be swallowed in order to work. Mirtazapine may also be used as an augmentation agent for depression treatment in conjunction with other antidepressants.

Bupropion similarly has a unique mechanism of action, inhibiting reuptake of norepinephrine and dopamine from the postsynaptic cleft. This medication has been approved for the management of depression, seasonal affective disorder, and smoking cessation. It has been shown to potentially lower appetite and is approved for weight loss in a combined product with naltrexone. It must be used with caution in patients who are struggling to maintain their PO intake. Bupropion at a daily dose of ≥400 mg is linked to an increased risk of seizures and should be used with caution in patients with other risk factors for seizures.

Trazodone is Food and Drug Administration (FDA) approved for depression but often is not tolerated due to sedation. It is commonly used off-label at lower doses for insomnia and seems to be particularly helpful in the management of sleep impaired by ruminating worry. There is a generally dose-dependent risk of orthostasis. There is some evidence for the short-term use of stimulant medications in the management of depression. This

approach is most commonly used in patients near the end of life, given the only transient improvement in mood. Stimulants are best managed with input from palliative medicine or psychiatry in the oncology setting.

Table 37.2 summarizes selected additional strategies in the management of anxiety. SSRIs are considered the gold standard for initial medication management (Table 37.1). Again, it is wise to make medication selections with the goal of managing multiple symptoms whenever possible. Benzodiazepines are the most frequently used medication class for the short-term treatment of anxiety. Through binding to the γ-aminobutyric acid receptor type A ($GABA_A$) chloride channel, these medications enhance the impact of the inhibitory neurotransmitter, GABA. Side effects can include sedation, dizziness, and cognitive impairments. Caution should be used in the medically ill, who often are more sensitive to these side effects and more likely to experience a paradoxical reaction. In oncology, it is important to be aware of the increased risk for respiratory depression when combined with other CNS depressants, like opioids or gabapentin, which are a common part of an oncology treatment plan. Although benzodiazepines are the treatment of choice for delirium caused by alcohol or sedative-hypnotic withdrawal, they can exacerbate or precipitate delirium with other etiologies. In addition, regular use of benzodiazepines can lead to tolerance and dependence, making withdrawal with discontinuation a risk. In general, use of this class of medications should be limited to a short-term course, as a bridge while other treatment options are being started (ie, therapy, other medication options), or for patients who have infrequent anxiety. For example, a one-time dose of a benzodiazepine prior to radiation or an MRI can aid many patients in participating in care with less distress.

TABLE 37.2

Additional Medications Used to Manage Anxiety in Oncology

	Indications and Benefits	Cautions

	Indications and Benefits	Cautions
Benzodiazepines	Quick acting, varying $t_{1/2}$	Sedation, fatigue, dizziness, cognitive impairments Class warning: Respiratory depression when combined with other CNS depressants Risk for tolerance and withdrawal
clonazepam (Klonopin)	Intermediate onset, long acting	
lorazepam (Ativan)	Fast onset, requires more frequent dosing, safe in liver disease	
buspirone (Buspar)	Well tolerated, less sedating Often use as an augmentation strategy for anxiety	Takes 1-2 weeks to start working Some patients find less helpful than benzodiazepines
Alpha-1 blockers prazosin (Minipress)	Reduces frequency and severity of nightmares in PTSD	Hypotension, dizziness, headache
Second-generation antipsychotics chlorpromazine (Thorazine) haloperidol (Haldol) olanzapine (Zyprexa) quetiapine (Seroquel)	Typically for end-of-life care Most often used for agitated delirium, multiple routes of administration Best for nausea, can help with sleep and increase appetite Off-label for steroid-related sleep impairments	Sedation Higher rates of EPS in PO and QT prolongation in IV Sedating, constipation, dry mouth Sedating, dizziness, more frequent dosing

CNS, central nervous system; EPS, extrapyramidal symptom; PTSD, posttraumatic stress disorder

Clonazepam 0.25 mg is equivalent to lorazepam 1 mg.

There are multiple other medication strategies used for the management of anxiety. Buspirone, a partial agonist at the $5HT_{1A}$ receptor, is most commonly used as an augmentation strategy for anxiety. Like antidepressants, this medication takes 1 to 2 weeks to start working and is generally less helpful in managing panic attacks in the moment. However, it should be noted that there are some patients who find it helpful in this off-label application, likely due to a placebo effect. Alpha-1 adrenergic blockers, like prazosin, have been shown through limited evidence to lower the frequency and severity of trauma-related nightmares in patients diagnosed with PTSD. Some patients experience an improvement in autonomic hyperactivity in general. One must monitor blood pressure closely.

Gabapentin, often a component of oncology care given its benefits for neuropathic pain, has anxiolytic properties, but its need for frequent dosing, high rates of sedation, and potential for misuse in the community make this less ideal for the management of anxiety.

Atypical or second-generation antipsychotics are often used at low doses for off-label applications in patients with cancer. This can include severe anxiety, corticosteroid-related anxiety and insomnia, nausea/vomiting, delirium, and agitation. They primarily work through antagonism of dopamine and serotonin receptors but also have antimuscarinic, antiadrenergic, and antihistaminergic properties that can contribute to side effects and occasionally be taken advantage of for therapeutic benefits.

Drug-Drug Interactions

Potential interactions between psychotropics and cancer therapeutics should be considered. The most commonly discussed interaction in this area is that of tamoxifen with multiple psychotropics through their inhibition of the cytochrome P450 2D6. As tamoxifen is a prodrug and its action is primarily through its active metabolites, the concurrent use of an inhibitor would theoretically decrease its efficacy. Of interest, studies on the clinical application of this interaction have been limited. The most comprehensive study to date has led to less concern about the concurrent use of psychotropics and tamoxifen and a more nuanced approach to mediation management in patients requiring tamoxifen as part of their treatment regimen (Table 37.3).

TABLE 37.3

Antidepressant Inhibitors of CYP2D6

Degree of Inhibition	Medication
Strong	bupropion, fluoxetine, paroxetine
Moderate	duloxetine, fluvoxamine, sertraline
Weak	citalopram, escitalopram, mirtazapine, venlafaxine

Additionally, it is important to note the overlapping actions of many medications that are commonly used in the management of patients with cancer. For example, dopamine-blocking antiemetics can potentially lead to extrapyramidal symptoms, especially if used in combination or taken concurrently with antipsychotic medications. Serotonin syndrome classically includes altered mental status, autonomic instability, GI distress, and hyperreflexia and clonus. Many medications can potentially increase serotonin, including antidepressants and second-generation antipsychotics, but also triptans, opioids, and tramadol to name a few. Patients are often on multiple agents with anticholinergic effects, which increases the likelihood and severity of bothersome symptoms like dry mouth and constipation.

SPECIAL CONSIDERATIONS IN CARING FOR CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

As with adults, the diagnosis of cancer and subsequent treatment course is often associated with high levels of distress and higher levels of mood disturbance and anxiety than the general population. This younger population is similarly impacted by physical symptoms that can contribute to or mimic depression, including fatigue, sleep disruption, cognitive impairments, and nutritional deficits. Pain is clearly linked to depression and anxiety symptoms and can be more challenging to assess in children. Assessments generally rely more on collateral information from family members or other caregivers and observation of behaviors in the very young. It is important to engage a multidisciplinary team that can work together to develop a multimodal treatment plan. This often involves the use of therapeutic supports for the patient and caregivers as well as medications if necessary.

Psychotropic medications targeted at specific symptoms may be indicated, particularly when symptoms cause distress or functional

impairment. While the only FDA-approved SSRIs for depression in this population are fluoxetine (ages 8+ years) and escitalopram (ages 12+ years), sertraline and citalopram are commonly used off-label. Amitriptyline, a TCA, is approved for depression (ages 12+ years), and duloxetine, an SNRI, is approved for GAD (ages 7+ years). Duloxetine might have additional benefits in treating pain and is FDA-approved for treating fibromyalgia in children (ages 12+ years). Of note, SSRIs and other serotonergic medications have an FDA warning for suicidal thinking in children and young adults through 24 years of age. This possibility warrants careful monitoring of suicidality in all children treated with antidepressants.

The use of non–FDA-approved psychopharmacologic agents in children with cancer may be considered when standard psychotropics are not effective, in cases of severe and prolonged distress, or when there is risk of treatment being compromised due to psychiatric disturbance. In addition, children and adolescents who cannot tolerate antidepressants may benefit from stimulants, such as methylphenidate, for depression and apathy. Psychostimulants are generally well tolerated in this age group and have a rapid onset of action. Although there is a dearth of research in pediatric cancer psychopharmacology, child psychiatry consultation may considerably improve the quality of life for children undergoing cancer treatment and coping with cancer survival. Routine psychological screening of children with cancer and survivors can detect ongoing distress.

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38

Management of Emesis

Lisa M. Cordes

INTRODUCTION

Prior to the development of modern antiemetics starting in the 1990s, radiation- and chemotherapy-associated emesis had a detrimental impact on the quality of life of patients with cancer. Nausea and vomiting were consistently reported as the most distressing side effects of chemotherapy. However, as new antiemetic agents have become available, the incidence of emesis has sharply declined allowing patients a greater opportunity to remain on effective treatments longer with limited disruption to their everyday lives. In a survey conducted by the American Society of Clinical Oncology (ASCO), antiemetics were selected as one of the "Top 5 Advances in 50 Years of Modern Oncology."

CLASSIFICATION AND PATHOPHYSIOLOGY

For the purposes of this chapter, the term "chemotherapy" is used synonymously with anticancer medications and encompasses cytotoxic chemotherapy, targeted therapy, and immunotherapy. Treatment-associated emetic symptoms are labeled as "acute" or "delayed" by their temporal relationship with the start of emetogenic medications. Although the terms are useful for describing clinical events and approaches to symptom management, the assignment of symptom onset/duration to fixed periods predated identification of principal neural mechanisms that elicit acute- and delayed-phase symptoms and remain an oversimplification of physiological events. Three main neurotransmitters are implicated in the pathophysiology of chemotherapy-induced nausea and vomiting (CINV): serotonin, dopamine, and substance P (Figure 38.1).

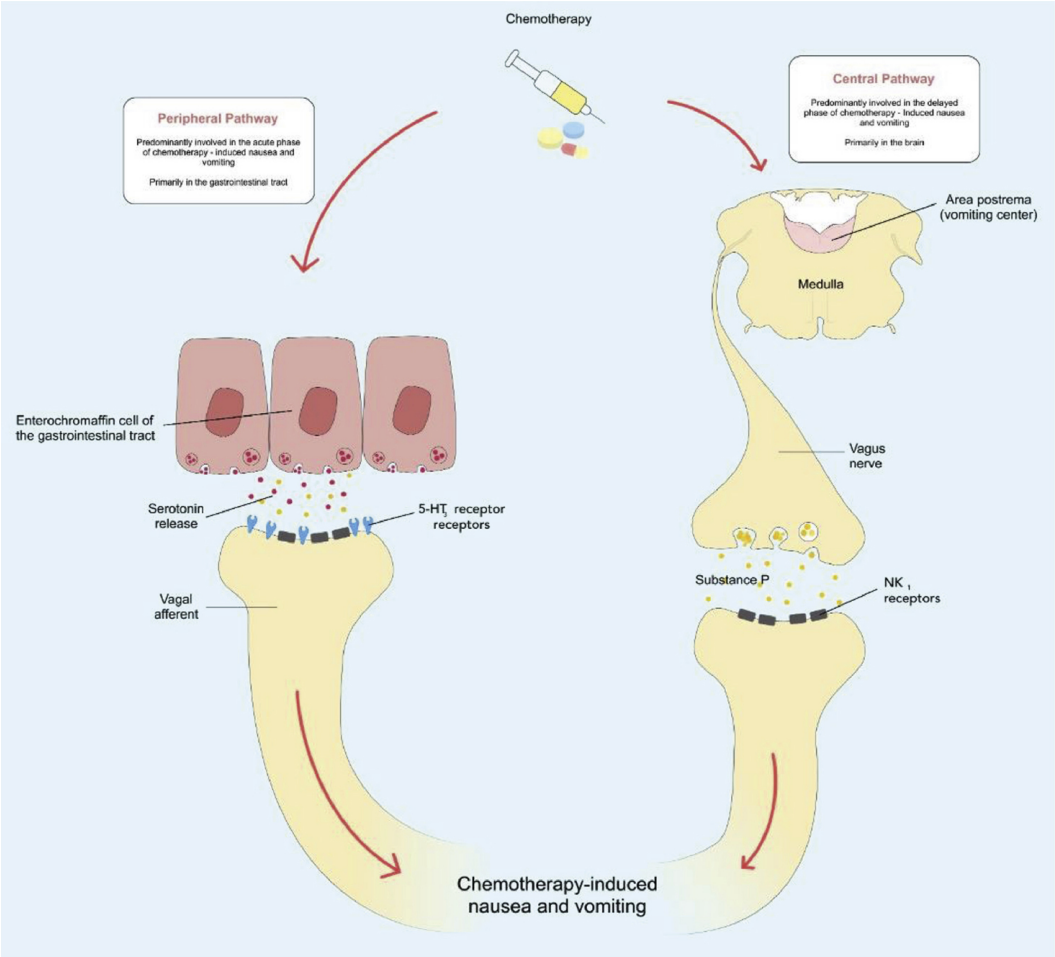

FIGURE 38.1 The role of 5-hydroxytryptamine type 3 and neurokinin-1 in the pathophysiology of chemotherapy-induced nausea and vomiting.(Reprinted from Gupta K, Walton R, Kataria SP. Chemotherapy-induced nausea and vomiting: Pathogenesis, recommendations, and new trends. *Cancer Treat Res Commun*. 2021;26:100278. Copyright © 2020 Elsevier. With permission.)

Acute-Phase Symptoms

Emetic symptoms that occur within 24 hours after treatment are identified as acute-phase symptoms. Acute-phase symptoms have been shown to correlate with serotonin (5-hydroxytryptamine, 5-HT) release from enterochromaffin cells. Emetic signals are propagated at local serotonin (5-HT_3 subtype) receptors and transmitted along afferent vagus nerve fibers. They activate a diffuse series of effector nuclei in the medulla oblongata (the so-called "vomiting center"), which integrates afferent emetic signals and subsequently activates and coordinates motor

nuclei that produce the physiologic changes associated with vomiting. In general, the greatest incidence of acute symptoms occurs within 2 to 6 hours after treatment. Notable exceptions include the following: mechlorethamine (nitrogen mustard), which generally induces rapid symptom onset (≤1 h); cyclophosphamide (after intravenous [IV] administration); and carboplatin, all of which have long latency periods before acute-phase onset, and symptoms may persist or intermittently recur for ≥12 hours after treatment.

Delayed-Phase Symptoms

Delayed-phase symptoms are defined as those that occur >24 hours after treatment and are primarily associated with central activation of neurokinin type 1 (NK_1) receptors, for which substance P is the natural ligand. Drugs with high emetogenic potential and, in many cases, drugs with moderate emetic risk may cause delayed-phase symptoms. Symptoms may commence as early as 16 to 18 hours after emetogenic treatment, with a period of greatest incidence between 24 and 96 hours after treatment. Delayed emesis may occur in patients who do not experience symptoms acutely, but incidence characteristically decreases in patients who achieve complete emetic control during the acute phase. Although emesis is typically less severe during the delayed phase than during the acute phase, the reported severity of nausea is similar during both phases.

Anticipatory Events

Anticipatory nausea or vomiting describes emetic symptoms occurring before repeated exposure to emetogenic treatment that develop as an aversive conditioned response as a consequence of poor emetic control during prior therapy. Nausea is reported to occur more commonly than anticipatory vomiting. The risk of developing anticipatory symptoms has been shown to increase with repeated courses of emetogenic treatment, particularly in patients who experience incomplete emetic control during treatments they previously received. Emetic symptoms during pregnancy and motion sickness have also been identified as contributing risk factors. Although anxiolytic amnestic drugs (eg, benzodiazepines) are helpful in preventing and delaying anticipatory symptoms, complete emesis control throughout all antineoplastic treatments is the best preventive strategy.

Behavioral therapies such as relaxation techniques and systematic desensitization may be useful if symptoms occur. After symptoms develop, medical interventions for anticipatory symptoms during subsequent emetogenic treatment are limited to preventing the reinforcement of conditioned stimuli, which may exacerbate symptoms.

PATIENT RISK FACTORS

Patients at greatest risk for emetic symptoms include the following:

- Female sex, particularly women with a history of persistent and/or severe emetic symptoms during pregnancy
- Children and young adults
- Patients with a history of acute- and/or delayed-phase emetic symptoms during prior treatments are at great risk for poor emetic control during subsequent treatments
- Patients with low performance status and a predisposition to motion sickness
- Nondrinkers are at greater risk than patients with a history of chronic alcohol consumption (>100 g ethanol daily for several years)
- Patients with intercurrent pathologies, such as gastrointestinal (GI) inflammation, compromised GI motility or obstruction, constipation, brain metastases, metabolic abnormalities (hypovolemia, hypercalcemia, hypoadrenalism, uremia), visceral organs invaded by tumor, and concurrent medical treatment (opioids, bronchodilators, aspirin, nonsteroidal anti-inflammatory drugs), may predispose and exacerbate emetic symptoms during treatment and complicate good emetic control

EMETOGENIC (EMETIC) POTENTIAL

In addition to patient-specific risk factors, the chemotherapy regimen (including dose, schedule, and route of administration) and radiation therapy techniques influence the emetic risk potential and symptom patterns. Assignment to emetic risk categorizes (eg, *high, moderate, low, minimal*) follows guidelines published by oncology professional organizations. The primary recommendations that help guide emetic risk

classification and subsequent treatment discussions include the following: ASCO Antiemetic Guidelines; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis; and the MASCC/ESMO (Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology) Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting Guidelines. Emetic potential of chemotherapy agents is estimated from data provided in the literature and product labeling for the drug. Categorization of emetic risk reported in guidelines or product labeling may be inconsistent because the data from which it is derived may represent:

- Inconsistent characterization and selective reporting or underreported emetic symptoms during antineoplastic drug development.
- Inconsistent methods for reporting adverse drug events (eg, events reported after a single dose of an emetogenic drug, after repeated doses within a cycle, after repeated cycles).
- Unregulated antiemetic use during emetogenic drug development prior to establishing an agent's emetogenic risk.
- A predisposition for developing emetic symptoms due to personal risk factors and/or history of poor emetic control during previously administered emetogenic treatment among subjects who received the emetogenic drug during its clinical development.

Parenteral Chemotherapy

Intrinsic emetogenicity is an antineoplastic drug's propensity for causing emetic symptoms. The emetogenicity classification for parenteral chemotherapy is based on the Hesketh classification and is the basis of the risk levels incorporated into national and international guidelines. Parenteral anticancer agents are divided into four risk categories based on the incidence of acute emesis without prophylaxis: high emetic risk is defined as > 90% emesis; moderate emetic risk is >30% to 90% emesis; low emetic risk is 10% to 30% emesis; and minimal emetic risk is <10% emesis (Table 38.1). Drug dose and formulation are also significant factors affecting emetogenic potential and the duration for which symptoms persist.

TABLE 38.1
Emetic Potential of Parenteral Anticancer Agents

Parenteral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)			
AC (anthracycline + cyclophosphamide)	High	High	High
Ado-trastuzumab emtansine	Low	Low	
Aldesleukin >12-15 million IU/m^2	Moderate		
Aldesleukin ≤12 million IU/m^2	Low		
Alemtuzumab	Minimal	Moderate	Moderate
Amivantamab-vmjw	Moderate		
Arsenic trioxide	Low	Moderate	Moderate
Asparaginase	Minimal		Low
Atezolizumab	Minimal	Minimal	
Avelumab	Minimal	Minimal	
Axicabtagene ciloleucel	Low	Low	
Azacitidine	Moderate	Moderate	Moderate
Belantamab mafodotin-blmf	Minimal		
Belinostat	Low	Low	Low
Bendamustine	Moderate	Moderate	Moderate
Bevacizumab	Minimal	Minimal	Minimal
Bleomycin	Minimal	Minimal	Minimal
Blinatumomab	Minimal	Low	Low
Bortezomib	Minimal	Low	Low
Brexucabtagene autoleucel	Low		
Brentuximab vedotin	Low	Low	Low
Busulfan	Moderate	Moderate	Minimal
Cabazitaxel	Low	Low	Low
Carboplatin AUC ≥ 4	High	Moderate	Moderate
Carboplatin AUC < 4	Moderate [d]		
Carfilzomib	Low	Low	
Carmustine > 250 mg/m^2	High	High	High
Carmustine ≤ 250 mg/m^2	Moderate [d]		
Cetuximab	Minimal	Low	Low
Cemiplimab-rwlc	Minimal	Minimal	
Cisplatin	High	High	High
Cladribine	Minimal	Minimal	Minimal
Clofarabine	Moderate	Moderate	Moderate
Copanlisib	Low	Low	
Cyclophosphamide > 1500 mg/m^2	High	High	High
Cyclophosphamide ≤ 1500 mg/m^2	Moderate [d]	Moderate	Moderate
Cytarabine > 1000 mg/m^2	Moderate	Moderate	Moderate
Cytarabine > 200-1000 mg/m^2	Moderate	Low	Low
Cytarabine (low dose) 100-200 mg/m^2	Low		
Cytarabine < 100 mg/m^2	Minimal		
Cytarabine + daunorubicin liposomal formulation	Moderate	Moderate	

Parenteral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)			
Dacarbazine	High	High	High
Dactinomycin	Moderate [d]		Low
Daratumumab	Minimal	Minimal	
Daratumumab and hyaluronidase-fihj	Minimal		
Daunorubicin	Moderate [d]	Moderate	Moderate
Decitabine	Minimal	Low	
Dinutuximab	Moderate		
Docetaxel	Low	Low	Low
Dostarlimab-gxly	Minimal		
Doxorubicin ≥ 60 mg/m^2	High	Moderate	Moderate
Doxorubicin < 60 mg/m^2	Moderate [d]		
Doxorubicin (liposomal)	Low	Low	Low
Durvalumab	Minimal	Minimal	
Elotuzumab	Minimal	Low	
Enfortumab vedotin-ejfv	Low	Low	
Eribulin	Low	Low	Low
Epirubicin > 90 mg/m^2	High	Moderate	Moderate
Epirubicin ≤ 90 mg/m^2	Moderate [d]		
Etoposide	Low	Low	Low
Fam-trastuzumab deruxtecan-nxki	Moderate [d]	Moderate	
5-Fluorouracil (5-FU)	Low	Low	Low
Floxuridine	Low		
Fludarabine	Minimal	Minimal	Minimal
Gemcitabine	Low	Low	Low
Gemtuzumab ozogamicin	Low	Low	
Idarubicin	Moderate [d]	Moderate	Moderate
Idecabtagene vicleucel	Low		
Ifosfamide ≥ 2 g/m^2 per dose	High	Moderate	Moderate
Ifosfamide < 2 g/m^2	Moderate [d]		
Inotuzumab ozogamicin	Low	Low	
Interferon-α			Moderate
Ipilimumab	Minimal	Minimal	Low
Irinotecan	Moderate [d]	Moderate	Moderate
Irinotecan (liposomal)	Moderate	Moderate	
Isatuximab-irfc	Low		
Ixabepilone	Low	Low	
Lisocabtagene maraleucel	Low		
Loncastuximab tesirine-lpyl	Low		
Lurbinectedin	Moderate		
Luspatercept-aamt	Minimal		
Margetuximab-cmkb	Minimal		
Mechlorethamine	High	High	High
Melphalan ≥ 140 mg/m^2	High		
Melphalan < 140 mg/m^2	Moderate		
Methotrexate ≥ 250 mg/m^2	Moderate [d]	Low	Low
Methotrexate > 50 to < 250 mg/m^2	Low		

Parenteral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)			
Methotrexate ≤ 50 mg/m^2	Minimal		
Mitomycin	Low	Low	Low
Mitomycin pyelocalyceal solution	Low		
Mitoxantrone	Low	Low	
Mogamulizumab-kpkc	Low		
Moxetumomab pasudotox-tdfk	Low	Low	
Naxitamab-gqgk	Moderate		
Necitumumab	Low	Low	
Nelarabine	Minimal	Low	
Nivolumab	Minimal	Minimal	Minimal
Obinutuzumab	Minimal	Minimal	
Ofatumumab	Minimal	Minimal	
Omacetaxine	Low		
Oxaliplatin	Moderate [d]	Moderate	Moderate
Paclitaxel	Low	Low	Low
Paclitaxel—albumin bound	Low	Low	Low
Panitumumab	Minimal	Low	Low
Pembrolizumab	Minimal	Minimal	Minimal
Pemetrexed	Low	Low	Low
Pentostatin	Low		
Pertuzumab	Minimal	Low	Low
Pertuzumab/trastuzumab and hyaluronidase-zzxf	Minimal		
Polatuzumab vedotin-piig	Low	Minimal	
Pralatrexate	Low	Minimal	
Ramucirumab	Minimal	Minimal	
Rituximab	Minimal	Minimal	Minimal
Rituximab and hyaluronidase	Minimal		
Romidepsin	Moderate	Moderate	Moderate
Sacituzumab govitecan-hziy	High		
Siltuximab	Minimal		
Streptozocin	High	High	High
Tafasitamab-cxix	Low		
Tagraxofusp-erzg	Low	Low	
Talimogene laherparepvec	Low		
Temozolomide	Moderate	Moderate	Moderate
Temsirolimus	Minimal	Low	
Thiotepa	Low	Moderate	Moderate
Tisagenlecleucel	Low	Low	
Tisotumab vedotin-tftv	Low		
Topotecan	Low	Low	Low
Trabectedin	Moderate [d]	Moderate	Moderate
Trastuzumab	Minimal	Minimal	Minimal
Trastuzumab and hyaluronidase-oysk	Minimal		
Valrubicin	Minimal		
Vinblastine	Minimal	Minimal	Minimal
Vincristine	Minimal	Minimal	Minimal

Parenteral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)			
Vincristine (liposomal)	Minimal		
Vinorelbine	Minimal	Minimal	Minimal
Ziv-aflibercept	Low	Low	Low

Amifostine, which may be administered in combination with chemotherapy, is categorized as an agent with moderate emetic risk (doses > 300 mg/m2) or low emetic risk (doses ≤ 300 mg/m2) in the NCCN guidelines.

Dexrazoxane, which may be administered in combination with chemotherapy, is categorized as an agent with minimal emetic risk in the NCCN guidelines.

ASCO, American Society of Clinical Oncology; AUC, area under the curve; ESMO, European Society of Medical Oncology; IU, international unit; m, meter; MASCC, Multinational Association of Supportive Care in Cancer; mg, milligram; National Comprehensive Cancer Network® (NCCN®).

[a]Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [January 2022]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

[b]Adapted from Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. *J Clin Oncol*. 2020;38(24):2782-2797. Reprinted with permission. Copyright © 2020 American Society of Clinical Oncology. All rights reserved.

[c]Adapted from Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133. Copyright © 2016 European Society for Medical Oncology. With permission.

[d]These agents may be highly emetogenic in certain patients.

Oral Chemotherapy

Unlike parenteral antineoplastics that are classified into four emetic risk levels, there is no international consensus on the optimal stratification method for oral agents. The NCCN Guidelines® and ASCO guidelines recommend a two-tiered approach based on risk of emesis without prophylaxis: moderate to high emetic risk is defined as ≥30% frequency of emesis and minimal to low risk is defined as <30% frequency of emesis (Table 38.2). Of note, the ASCO guidelines only recently changed their risk classification strategy citing the challenges with inconsistent reporting of emesis outcomes in trials with oral agents. However, the MASCC/ESMO guidelines continue to use the four-tiered approach similar to that described with parenteral chemotherapy. Many oral chemotherapy agents are given on a continuous (eg, once daily) schedule,

so long-term toxicities of the antiemetic must be taken into consideration when selecting the regimen.

TABLE 38.2
Emetogenic Potential of Oral Anticancer Agents

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)	
Abemaciclib	Minimal–low	Moderate–high	
Acalabrutinib	Minimal–low	Minimal–low	
Afatinib	Minimal–low	Minimal–low	Low
Alectinib	Minimal–low	Minimal–low	
Alpelisib	Minimal–low	Minimal–low	
Altretamine (hexamethylmelamine)	Moderate–high	Moderate–high	High
Asciminib	Minimal–Low		
Avapritinib	Moderate–high	Moderate–high	
Axitinib	Minimal–low	Minimal–low	Low
Azacytidine	Moderate–high		
Belzutifan	Minimal–Low		
Bexarotene	Minimal–low	Minimal–low	
Binimetinib	Moderate–high		
Brigatinib	Minimal–low	Minimal–low	
Bosutinib > 400 mg/d	Moderate–high	Moderate–high	Moderate
Bosutinib ≤ 400 mg/d	Minimal–low		
Busulfan ≥ 4 mg/d	Moderate–high		
Busulfan < 4 mg/d	Minimal–low		

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		**High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)**	
Cabozantinib	Moderate–High	Moderate–high	
Capecitabine	Minimal–low	Minimal–low	Low
Capmatinib	Minimal–Low		
Ceritinib	Moderate–high	Moderate–high	Moderate
Chlorambucil	Minimal–low	Minimal–low	Minimal
Cobimetinib	Minimal–low	Minimal–low	
Crizotinib	Moderate–high	Moderate–high	Moderate
Cyclophosphamide ≥ 100 mg/m^2/d	Moderate–high	Moderate–high	Moderate
Cyclophosphamide < 100 mg/m^2/d	Minimal–low		
Dabrafenib	Moderate–high	Minimal–low	Low
Dacomitinib	Minimal–low	Minimal–low	
Dasatinib	Minimal–low	Minimal–low	Low
Decitabine and cedazuridine	Minimal–low		
Duvelisib	Minimal–low	Minimal–low	
Enasidenib	Moderate–high	Moderate–high	
Encorafenib	Moderate–high	Minimal–low	
Entrectinib	Minimal–low	Minimal–low	
Erdafitinib	Minimal–low	Minimal–low	
Erlotinib	Minimal–low	Minimal–low	Minimal
Estramustine	Moderate–high	Minimal–low	
Etoposide	Moderate–high	Minimal–low	Low
Everolimus	Minimal–low	Minimal–low	Low

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		**High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)**	
Fedratinib	Moderate–high	Moderate–high	
Fludarabine	Minimal–low	Minimal–low	Low
Gefitinib	Minimal–low	Minimal–low	Minimal
Gilteritinib	Minimal–low	Minimal–low	
Glasdegib	Minimal–low	Minimal–low	
Hydroxyurea	Minimal–low	Minimal–low	Minimal
Ibrutinib	Minimal–low	Minimal–low	Low
Idelalisib	Minimal–low	Minimal–low	Low
Imatinib > 400 mg/d	Moderate–high	Moderate–high	Moderate
Imatinib ≤ 400 mg/d	Minimal–low		
Infigratinib	Minimal–Low		
Ivosidenib	Minimal–low	Minimal–low	
Ixazomib	Minimal–low	Minimal–low	
Lapatinib	Minimal–low	Minimal–low	Low
Larotrectinib	Minimal–low	Minimal–low	
Lenalidomide	Minimal–low	Minimal–low	Low
Lenvatinib > 12 mg/d	Moderate–high	Moderate–high	
Lenvatinib ≤ 12 mg/d	Minimal–low		
Lomustine	Moderate–high	Moderate–high	
Lorlatinib	Minimal–low	Minimal–low	
Melphalan	Minimal–low	Minimal–low	Minimal
Mercaptopurine	Minimal–low		

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)	
Methotrexate	Minimal–low	Minimal–low	Minimal
Midostaurin	Moderate–high	Moderate–high	
Mitotane	Moderate–high		
Mobocertinib	Moderate–high		
Neratinib	Minimal–low	Minimal–low	
Nilotinib	Minimal–low	Minimal–low	Low
Niraparib	Moderate–high	Moderate–high	
Olaparib	Moderate–high	Minimal–low	Low
Osimertinib	Minimal–low	Minimal–low	
Palbociclib	Minimal–low	Minimal–low	
Pazopanib	Minimal–low	Minimal–low	Low
Pemigatinib	Minimal–low		
Pexidartinib	Minimal–low	Minimal–low	
Pomalidomide	Minimal–low	Minimal–low	Minimal
Ponatinib	Minimal–low	Minimal–low	Low
Pralsetinib	Minimal–low		
Procarbazine	Moderate–high	Moderate–high	High
Regorafenib	Minimal–low	Minimal–low	Low
Ribociclib	Minimal–low	Moderate–high	
Ripretinib	Minimal–low		
Rucaparib	Moderate–high	Moderate–high	
Ruxolitinib	Minimal–low	Minimal–low	Minimal

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		**High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)**	
Selinexor	Moderate–high	Moderate–high	
Selpercatinib	Minimal–low		
Sonidegib	Minimal–low	Minimal–low	
Sorafenib	Minimal–low	Minimal–low	Minimal
Sotorasib	Minimal–low		
Sunitinib	Minimal–low	Minimal–low	Low
Talazoparib tosylate	Minimal–low	Minimal–low	
Tazemetostat	Minimal–low	Minimal–low	
Temozolomide > 75 mg/m^2/d	Moderate–high	Moderate–high	Moderate
Temozolomide ≤ 75 mg/m^2/d	Minimal–lowd		
Tepotinib	Minimal–low		
Thalidomide	Minimal–low	Minimal–low	Low
Thioguanine	Minimal–low	Minimal–low	Minimal
Tivozanib	Minimal–low		
Topotecan	Minimal–low	Minimal–low	
Trametinib	Minimal–low	Minimal–low	
Tretinoin	Minimal–low		
Trifluridine/tipiracil	Minimal–low	Moderate–high	
Tucatinib	Minimal–low		
Umbralisib	Minimal–low		
Vandetanib	Minimal–low	Minimal–low	Low
Vemurafenib	Minimal–low	Minimal–low	Minimal

Oral Anticancer Agent	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
Moderate–High (≥30%), Minimal–Low (<30%)		High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)	
Venetoclax	Minimal–low	Minimal–low	
Vismodegib	Minimal–low	Minimal–low	Minimal
Vorinostat	Minimal–low	Minimal–low	Low
Zanubrutinib	Minimal–low	Minimal–low	

ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; m, meter; MASCC, Multinational Association of Supportive Care in Cancer; mg, milligram; National Comprehensive Cancer Network® (NCCN®).

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[c]Adapted from Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133. Copyright © 2016 European Society for Medical Oncology. With permission.

[d]Temozolomide ≤ 75 mg/m2/d should be considered moderately emetogenic with concurrent radiotherapy.

Radiation Therapy

The emetic potential of ionizing radiation correlates directly with the location of the irradiated site (eg, upper abdomen) and the field size, where a field size >400 cm^2 indicates a greater risk of emesis. The patient-related risk factor that closely correlates with radiation-induced nausea and vomiting (RINV) is previous treatment with chemotherapy. Overall, the guidelines have taken a similar risk stratification strategy for RINV (Table 38.3). Other considerations for the emetic risk potential should include the concurrent administration of chemotherapy. In those cases, the antiemetic regimen should be appropriate for the chemotherapy risk level unless the radiation risk level is higher.

TABLE 38.3
Emetogenic Potential of Radiation Therapy

Site of Radiation Therapy	NCCN [a]	ASCO [b]	MASCC/ESMO [c]
High (>90%), Moderate (30%-90%)	High (>90%), Moderate (>30%-90%), Low (10%-30%), Minimal (<10%)		
Total body irradiation	High	High	High
Upper abdomen	Moderate	Moderate	Moderate
Craniospinal irradiation		Moderate	Moderate
Brain, head and neck, thorax, pelvis		Low	Low
Extremities, breast		Minimal	Minimal

ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; National Comprehensive Cancer Network® (NCCN®).

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[c]Adapted from Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133. Copyright © 2016 European Society for Medical Oncology. With permission.

ANTIEMETIC DRUGS

An antiemetic regimen is developed based on the chemotherapy or radiation emetic risk level along with patient-specific factors. The goal is the prevention of nausea and vomiting.

Serotonin (5-HT_3 Subtype) Receptor Antagonists

Among 5-HT_3 receptor antagonists (RAs) that have received US Food and Drug Administration (FDA) approval for commercial use, granisetron and ondansetron comprise the first-generation agents, whereas

palonosetron is a second-generation agent. Postmarketing surveillance of dolasetron, also a first-generation 5-HT_3 RA, revealed a risk of torsade de pointes, and the injection and tablet formulations have since been discontinued by the manufacturer.

Pharmacologic Considerations

- 5-HT_3 RAs are generally safer and more effective against acute-phase symptoms compared to other pharmacological classes of medications with clinically useful antiemetic activity.
- Administering 5-HT_3 RAs at doses greater than those shown to be maximally effective does not substantially improve emetic control but increases the risk of toxicity.
- Single-dose prophylaxis is preferred for acute-phase symptoms.
    - After administration of a single maximally effective dose, additional doses of 5-HT_3 RAs within the first 24 hours after emetogenic treatment have not been shown to improve emetic control.
- Granisetron, ondansetron, and palonosetron have excellent oral bioavailability, and when given at appropriate doses and intervals, each agent provides equivalent antiemetic protection whether given orally or parenterally.
- Palonosetron has the longest half-life among 5-HT_3 RAs currently marketed in the United States and has additional pharmacological characteristics not shared by first-generation 5-HT_3 RAs.
- Granisetron is available as a subcutaneous injection and a transdermal patch, which allows for extended coverage during the delayed phase.

Adverse Reactions Reported with the Class of 5-HT_3 RAs

- Headache
- Constipation
- Transient effects on cardiac electrophysiology, decreased cardiac rate, and cardiovascular adverse effects (see drug-specific comments below)
- Serotonin syndrome, most often associated with concomitant use of drugs that affect serotonin neurotransmission and/or reuptake

Pharmacogenomic Considerations

- Pharmacogenomic evaluation may help to identify patients at risk for suboptimal and adverse responses to 5-HT_3 RAs that are substrates for catabolism by cytochrome P450 (CYP) enzymes.
- CYP2D6 is polymorphically expressed among human populations.
  - Persons with >2 functionally competent (wild type) *CYP2D6* alleles may have increased metabolic capacity (characterized as ultrarapid metabolizers), which has been associated with diminished emetic control in patients who received 5-HT_3 RAs for which CYP2D6 metabolism predominates.
  - Patients who lack one or both *CYP2D6* alleles or express one or more variant alleles with reduced function generally have altered functional capacity for CYP2D6 substrates (poor and intermediate metabolizers) and may have high concentrations and attenuated elimination of 5-HT_3 RA substrates for which CYP2D6 metabolism predominates.
- Patients who express genetic polymorphism for 5-HT_3 receptors or the ABCB1 (P-glycoprotein [P-gp], MDR1) transporter may experience suboptimal antiemetic responses with 5-HT_3 RAs.

Select pharmacokinetic considerations for 5-HT_3 RAs, as well as other common antiemetics, are provided in Table 38.4.

TABLE 38.4
Pharmacokinetic Characteristics of Select Antiemetics

Antiemetic	Route of Administration [a]	Half-Life [b]	Plasma Protein Binding	Metabolism/Transport Effects [c]		
Substrate	**Inhibitor**	**Inducer**				
5-HT 3 RA						
Granisetron	PO, IV, subq, patch	PO: 6 h IV: 5-9 h Subq: 24 h	~65%	CYP3A4		
Ondansetron	PO, IV, IM	3-6 h	~70%-76%	CYP1A2, CYP2C9, CYP2D6, CYP2E1, CYP3A4, P-gp		
Palonosetron	IV	40 h	~62%	CYP1A2, CYP2D6, CYP3A4		

Antiemetic	Route of Administration [a]	Half-Life [b]	Plasma Protein Binding	Metabolism/Transport Effects [c]		
Substrate	**Inhibitor**	**Inducer**				
NK_1 RA						
Aprepitant	PO, IV	9-13 h	>95%	CYP1A2, CYP2C19, CYP3A4	CYP3A4	CYP2C9
Fosaprepitant	IV					
Netupitant	PO	80 ± 29 h	>99%	CYP3A4, CYP2C9, CYP2D6		
Rolapitant	PO	7 d	>99%	CYP3A4	BCRP, CYP2B6, CYP2D6, P-gp	
Glucocorticoids						
Dexamethasone	PO, IV	PO: 4 h IV: 1-5 h		CYP3A4, P-gp		CYP3A4
Olanzapine						
Olanzapine	PO	30 h	~93%	CYP1A2, CYP2D6, UGT1A4		
Dopamine RA						
Promethazine	PO	4-34 h	~93%	CYP2B6, CYP2D6		
Prochlorperazine	PO, IV	6-10 h				
Haloperidol	PO	14-37 h	88%-93%	CYP1A2, CYP2D6, CYP3A4		
Metoclopramide	PO, IV	5-6 h	~30%	CYP1A2, CYP2D6		

5-HT_3, 5-hydroxytryptamine type 3; BCRP, breast cancer resistance protein; CYP, cytochrome P450; h, hour; IM, intramuscular; IV, intravenous; NK_1, neurokinin type 1; P-gp, P-glycoprotein; PO, by mouth; RA, receptor antagonist; subq, subcutaneous; UGT, uridine 5′-diphospho-glucuronosyltransferase.

[a]Route of administration commonly used for CINV or RINV.

[b]Estimated terminal half-life of the parent compound in adults with normal organ function.

[c]See prescribing information regarding the significance of the metabolism or the extent of the induction/inhibition.

Granisetron

- Granisetron is available in multiple formulations (oral tablet, IV solution, subcutaneous extended-release injection, transdermal

patch) and is recommended by the guidelines for the prevention of CINV and RINV. Additionally, the oral, IV, or patch formulations may be considered for the treatment of breakthrough nausea/vomiting.

- Granisetron IV solution has received FDA approval for use in patients aged 2 years or older.
    - Some injectable products may contain benzyl alcohol, which has been associated with serious adverse reactions, including death in neonates. Avoid dosage forms containing benzyl alcohol in neonates.
- The tablet formulation has not received FDA approval for use in pediatric patients. Safety and efficacy of the transdermal patch or subcutaneous formulation in patients younger than 18 years have also not been established.

- ECG abnormalities are rare with granisetron when used at FDA-approved dosages and schedules.
- Granisetron transdermal patch (Sancuso) is an adhesive-backed patch that contains 34.3 mg of granisetron and delivers an average daily dose of 3.1 mg granisetron for up to 7 days.
    - The patch is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days.
    - A patch is applied to clean, dry, intact skin on the outer upper arm a minimum of 24 hours (up to 48 h) before emetogenic chemotherapy administration and remains in place ≥24 hours after chemotherapy is completed.
    - The duration of application should not exceed 7 days.
    - Granisetron may degrade with exposure to natural or artificial sunlight (eg, sun lamps, tanning beds) and results of an in vitro study suggested a potential for photogenotoxicity. Patients must be instructed to keep the transdermal patch covered with clothing at all times, and to keep the application site protected from light exposure during wear and for 10 days after removal.
    - Heating pads and other heat sources should not be applied over or near a site where a granisetron transdermal patch is applied as increased granisetron plasma concentrations have been reported.
    - Adverse effects unique to the route of administration include the following:
        - Patch nonadhesion
        - Erythema
        - Irritation, pain
        - Hypersensitivity reactions (erythematous macular or papular rashes, pruritis, urticaria)
        - Vesicle formation, burn
- Granisetron extended-release injection for subcutaneous use (SUSTOL) is available as a prefilled syringe that contains 10 mg granisetron incorporated in an extended-release polymer vehicle.
    - It is indicated in combination with other antiemetics for prophylaxis against acute and delayed emetic symptoms during initial and repeated courses of moderately emetogenic cancer therapies or anthracycline + cyclophosphamide-containing regimens.
    - Dosing and administration:
        - SUSTOL is intended ONLY for subcutaneous injection administered by a healthcare provider in the upper arm or skin of the abdomen. See prescribing information for preparation and administration details.
        - Each dose continuously delivers granisetron for an extended period of time. Measurable granisetron levels can be detected in serum for up to 7 days after administration.

- Initial and repeated administration is constrained by renal function:
  - Not more frequently than every 7 days in patients whose creatinine clearance (Clcr) is ≥60 mL/min
  - Not more frequently than every 14 days in patients with Clcr of 30 to 59 mL/min
  - AVOID use in patients with Clcr <30 mL/min

- Adverse effects unique to the route of administration include the following:
  - Infections at the injection site
  - Bleeding at the injection site
  - Bruising/hematomas at the injection site with median onset of 2 days; delayed onset ≥5 days in 15% of patients
  - Pain and tenderness at the injection site with median duration of 5 days, but persisting for >7 days in 6% of patients
  - Nodule formation at the injection site that may persist for >3 weeks after administration

Ondansetron

- Ondansetron is recommended by the guidelines for the prevention of CINV and RINV and for the treatment of breakthrough emesis.
  - Ondansetron injection has received FDA approval for use in patients ≥6 months of age for the prevention of emetic symptoms associated with highly emetogenic chemotherapy.
  - Oral formulations (tablets, orally disintegrating tablets, film, and solution) have received FDA approval for use in patients aged 4 years and older receiving moderately emetogenic chemotherapy.
- The risk of adverse effects is low at FDA-approved dosages and schedules.
  - Ondansetron prolongs the cardiac QT interval in a dose-dependent manner potentially resulting in fatal ventricular tachyarrhythmias such as torsades de pointes.
    - A comparison between single IV doses of ondansetron 32 and 8 mg revealed the maximum mean difference in QTcF (the QT interval measurement corrected by the Fridericia formula) from placebo after baseline correction was 20 and 6 ms, respectively. Consequently, the product labeling was amended to state no single IV dose should exceed 16 mg.
  - Risk factors for developing QT prolongation with ondansetron include the following:
    - Underlying heart conditions, such as congenital long QT syndrome, congestive heart failure, or bradyarrhythmias
    - Hypokalemia and hypomagnesemia
    - Concomitant use of medications that are also associated with QT prolongation
  - Patients should be advised to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while they are taking ondansetron.

Palonosetron

- Palonosetron is a second-generation 5-HT_3 RA with a substantially longer elimination half-life than the IV formulations of granisetron or ondansetron. Additional characteristics of palonosetron that suggest a pharmacological advantage over first-generation 5-HT_3 RAs include the following:

- Allosteric binding that produces a conformational change in 5-HT_3 receptors with increased binding affinity between the receptor and palonosetron, which may be the result of at least one more molecule binding to the same receptor (suggests positive cooperativity).
    - In contrast, granisetron and ondansetron exhibit simple competitive binding with 5-HT_3 receptors.
- Binding to 5-HT_3 receptor that results in receptor internalization, and consequently, a persistent inhibition of receptor function.
- Evidence indicating palonosetron bound to internalized NK_1 receptors diminishes signaling (cross talk) between NK_1 and substance P receptors.

- Palonosetron is currently available in the following formulations: an IV solution (single agent); an IV solution in combination with the NK_1 RA fosnetupitant; and as an oral capsule in combination with the NK_1 RA netupitant.
    - Palonosetron injection received FDA approval for use in adult patients as antiemetic prophylaxis for
        - Acute and delayed nausea and vomiting in initial and repeat courses of moderately emetogenic chemotherapy.
        - Acute nausea and vomiting in initial and repeat courses of highly emetogenic chemotherapy.
    - Palonosetron injection also received FDA approval for use in pediatric patients from 1 month to 17 years of age as antiemetic prophylaxis for initial and repeat courses of emetogenic chemotherapy including highly emetogenic chemotherapy.
    - Palonosetron/fosnetupitant (Akynzeo IV) and palonosetron/netupitant (Akynzeo oral) are approved in combination with dexamethasone for the prevention of acute and delayed nausea and vomiting in initial and repeat courses of highly emetogenic chemotherapy.
- There is a low risk of adverse effects at currently approved dosages and schedules.
    - The risk of ECG abnormalities associated with palonosetron use, including QT prolongation, is lower than the risk associated with ondansetron.
        - FDA-approved product labeling indicates single doses of palonosetron 0.25, 0.75, or 2.25 mg in healthy adult men and women demonstrated no significant effect on any ECG interval including QT interval duration.

Neurokinin (NK_1 Subtype) RAs

- NK_1 RAs have demonstrated activity against acute-phase emetic symptoms but are more effective against delayed-phase emesis than other pharmacological classes of antiemetics currently available.
- Currently, three NK_1 RAs are available as oral formulations including aprepitant, rolapitant, and netupitant. Additionally, aprepitant, fosaprepitant (a prodrug of aprepitant), and fosnetupitant (a prodrug of netupitant) are available for IV administration.
- All NK_1 RAs are indicated only for the prevention of CINV but should not be used for the treatment of breakthrough emesis.

Furthermore, these agents are yet to be extensively studied for the prevention of radiation-associated emesis and are therefore not recommended in the RINV guidelines at this time.

- Safe use of NK_1 RAs with other medications prudently requires healthcare providers to recognize the potential for drug-drug interactions during concomitant use.
    - Data indicating clinically significant drug-drug interactions between antiemetics and anticancer agents are yet to emerge. However, healthcare providers should be cognizant of the potential for interaction and evaluate the risks and benefits on a case-by-case basis.
    - See Table 38.4 for pharmacokinetic characteristics that should be considered when NK_1 RAs are used concomitantly with other medications.

Aprepitant and Fosaprepitant

- Aprepitant and fosaprepitant are currently FDA approved for use in preventing acute and delayed nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic chemotherapy.
- Commercially available products include the following:
    - Aprepitant oral capsules (Emend) for patients aged 12 years and older. Generic capsules are only approved for use in adults.
    - Aprepitant oral suspension (Emend) for patients aged 6 months and older (≥6 kg) who are not able to swallow capsules.
    - Aprepitant IV emulsion (Cinvanti) for patients aged 18 years and older. Safety and effectiveness have not been established in pediatric patients.
    - Fosaprepitant IV solution (Emend or generic) for patients aged 6 months or older (≥6 kg).
- Approval was based on studies with chemotherapy given on a single day with the exception of aprepitant IV, which is approved for use with 3-day moderately emetic chemotherapy.
- Potential drug interactions with aprepitant and fosaprepitant:
    - Aprepitant is a substrate and moderate inhibitor of CYP3A4, and a moderate inducer of CYP3A4 and CYP2C9. Inhibition may occur after a single dose; induction occurs after repeated doses. Since fosaprepitant is the prodrug of aprepitant, drug interactions must also be considered.
    - Aprepitant inhibits CYP3A4 in the gut and liver.
    - The potential for interaction with many CYP3A4 substrates is unknown.
    - Aprepitant increases the bioavailability of concomitantly administered dexamethasone and methylprednisolone.
    - When used in combination with aprepitant, fosaprepitant, or netupitant, dexamethasone should not exceed a 12 mg dose when given for antiemetic prophylaxis.
        - Do NOT modify the doses of steroids used as components of a chemotherapy regimen.

        - Aprepitant metabolism and elimination may be adversely affected by drugs that inhibit or induce CYP3A4.
- Common side effects of aprepitant in combination with a 5-HT_3 RA and high-potency glucocorticoids include the following:
    - Abdominal pain, epigastric discomfort
    - Dyspepsia
    - Hiccups
    - Anorexia
    - Dizziness
    - Fatigue, asthenia

Netupitant and Fosnetupitant

- Netupitant received FDA approval for commercial use, but only in combination with palonosetron in an oral capsule formulation, as described above. Fosnetupitant is also available in combination with palonosetron for IV administration.
- Potential drug interactions with netupitant:
    - Netupitant is a substrate for metabolism and a moderate inhibitor of CYP3A4.
        - Avoid concomitant use of CYP3A4 substrates for 1 week, if feasible. If concomitant use of CYP3A4 substrates during 7 days after Akynzeo use is not avoidable, consider reducing the doses of CYP3A4 substrates.
        - The potential for interaction with many CYP3A4 substrates is unknown.
    - When used in combination with fosnetupitant or netupitant, dexamethasone should not exceed a 12 mg dose when given for antiemetic prophylaxis.
        - Do NOT modify the doses of steroids used as components of a chemotherapy regimen.
- Adverse reactions associated with the use of netupitant/palonosetron and fosnetupitant/palonosetron include the following:
    - Headache
    - Asthenia
    - Fatigue
    - Dyspepsia
    - Constipation

Rolapitant

- Rolapitant is indicated in patients aged 18 years and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
- Rolapitant is administered orally within 2 hours prior to emetogenic chemotherapy.
- Potential drug interactions with rolapitant:
    - There is no drug interaction between rolapitant and dexamethasone. No dose adjustment for dexamethasone is required when used concomitantly with rolapitant.

    - After a single dose of rolapitant, CYP2D6 inhibition lasts at least 7 days and may last longer.
        - Avoid concomitant use of rolapitant and pimozide (CYP2D6 substrate) due to risk of QT prolongation.
        - Monitor for adverse reactions if rolapitant use concomitant with other CYP2D6 substrates with a low or narrow therapeutic index cannot be avoided.
        - Rolapitant had no significant effects on the pharmacokinetics of ondansetron, a CYP2D6 substrate.
    - Rolapitant inhibits intracellular efflux transport of substrates of the breast cancer resistance protein (BCRP, ABCG2, MXR1) transporter.
        - Be wary of concomitant use of rolapitant and BCRP substrates that have a low or narrow therapeutic index (eg, daunorubicin, doxorubicin, epirubicin, irinotecan, methotrexate, mitoxantrone, rosuvastatin, topotecan).
        - Monitor for adverse reactions related to BCRP substrates if concomitant use with rolapitant cannot be avoided.
        - Use the lowest effective dose of rosuvastatin if used concomitantly with rolapitant.
    - Rolapitant inhibits intracellular efflux transport of P-gp substrates.
        - Monitor for adverse reactions related to P-gp substrates if concomitant use with rolapitant cannot be avoided.
- Adverse reactions associated with the use of rolapitant in combination with dexamethasone and a 5-HT_3 RA include the following:
    - Fatigue
    - Constipation
    - Headache
    - Hiccups
    - Abdominal pain
    - Dizziness
    - Dyspepsia

Glucocorticoids

- High-potency glucocorticoids such as dexamethasone and methylprednisolone are effective as single agents against both acute- and delayed-phase emesis symptoms.
    - At clinically useful doses, dexamethasone and methylprednisolone are equally effective after either IV or oral administration.
    - Both dexamethasone and methylprednisolone enhance the antiemetic effectiveness of 5-HT_3 and NK_1 RAs when used concomitantly.
- The glucocorticoid dose and schedule are dependent on concurrently administered antiemetics and the emetic potential and schedule of the chemotherapy regimen.
    - There is no evidence that single doses of dexamethasone >20 mg improve antiemetic response.
- Potential for adverse effects after a single dose or a short course is generally low and limited to GI upset and activating psychogenic effects such as anxiety, insomnia, and sleep disturbances.
    - Coadministration with drugs that decrease gastric acid production (histamine H_2 RAs or proton pump inhibitors) should be considered in select patients to prevent GI irritation.

    - Administering steroids early in a patient's waking cycle may minimize adverse effects on sleep.
- Adrenocortical suppression is generally not a concern when high-potency glucocorticoids are used for brief periods.
- Glycemic control should be monitored in patients with incipient or frank diabetes.

Olanzapine

- Olanzapine, an atypical neuroleptic or antipsychotic, is a potent antagonist at multiple neurotransmitter receptors, including muscarinic ($m_1 > m_{2-4}$), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6), alpha adrenergic (α_1), dopaminergic (D_1, D_2, D_4), and histaminergic receptors (H_1).
- The addition of olanzapine to a triplet antiemetic regimen (NK_1 RA, 5-HT_3 RA, and dexamethasone) resulted in better control of nausea than the triplet regimen alone in patients receiving highly emetic chemotherapy.
    - As a result, the ASCO and NCCN Guidelines prefer the four-drug regimen prior to highly emetic chemotherapy.
    - Only the olanzapine oral tablets are recommended for CINV. Other formulations (eg, intramuscular suspension) should not be administered for this indication.
- Olanzapine has also been studied for the treatment of breakthrough CINV and is recommended as a preferred antiemetic from the NCCN Guidelines when not used as part of the preventative regimen.
- Pharmacokinetic considerations:
    - Olanzapine is a substrate for direct glucuronidation catalyzed by uridine diphosphate glucuronosyltransferase (UGT) enzymes, UGT1A4 and UGT2B10, and for oxidation catalyzed primarily by CYP1A2 and flavin-containing monooxygenase 3, and to a lesser extent by CYP2D6 and CYP3A4.
        - Olanzapine's pharmacokinetic behavior is susceptible to drugs and substances that induce and inhibit CYP1A2 (eg, carbamazepine, fluvoxamine, tobacco).
    - Olanzapine is a substrate with moderate affinity for P-gp and has been shown to inhibit P-gp at concentrations achieved during therapeutic use.
- The following adverse effects have been reported with olanzapine:
    - Sedation
        - Consider a lower dose in elderly patients
        - Unless given as a premedication, bedtime administration is recommended
    - Postural hypotension
    - Anticholinergic effects
    - Fatigue
    - Dystonic reactions
    - QT prolongation

- Nervousness, agitation, cognitive impairment
- Headache
- Adverse events primarily seen with prolonged use: weight gain, new-onset diabetes, hyperlipidemia, and increased serum alanine aminotransferase
- Increased mortality in elderly patients with dementia-related psychosis (see US labeling boxed warning)

Dopamine RAs

Until the 1970s, antiemetics that inhibit the dopamine receptor, such as prochlorperazine, metoclopramide, and haloperidol, were the mainstay of CINV antiemetic regimens. However, the use of these agents has waned over time due to the development of more effective and better tolerated antiemetics. Today, the use of dopamine RAs is primarily limited to the treatment of breakthrough emesis.

Phenothiazines

- Prochlorperazine and promethazine are phenothiazine derivatives that block postsynaptic mesolimbic dopaminergic receptors in the brain. A muscarinic-blocking effect may also contribute to their efficacy.
- Compared to prochlorperazine, promethazine has a significantly higher affinity to the H_1 receptor and is therefore associated with significant sedation. As a result, prochlorperazine is generally the preferred phenothiazine for breakthrough CINV.
- Adverse effects correlate with dose and frequency of administration and include the following:
  - CNS depression
  - Extrapyramidal symptoms (dystonia, akathisia, dyskinesia)
  - Anticholinergic effects
  - Hypotension, particularly with parenteral administration or high doses
  - Serious tissue injury with promethazine injection; subcutaneous administration is contraindicated
- Available products:
  - Oral tablet (promethazine, prochlorperazine)
  - Oral solution (promethazine)
  - Injectable solution (promethazine, prochlorperazine; however, the Institute for Safe Medication Practices does not recommend injectable promethazine due to the risk of severe tissue damage)
  - Rectal suppository (promethazine, prochlorperazine; however, this route of administration should be avoided in patients receiving chemotherapy who are at risk for developing neutropenia or mucositis)

Haloperidol

- As a first-generation antipsychotic, haloperidol exerts its antiemetic effect by blocking postsynaptic D_2 receptors in the brain.
- Lower doses of haloperidol are required for an antiemetic effect compared to an antipsychotic effect.
- Given the safety profile and efficacy of the newer generation antiemetics, the use of haloperidol is primarily historical, but it is still considered an option in the NCCN Guidelines for breakthrough CINV.

Metoclopramide

- Metoclopramide has affinity for several neurotransmitter receptors associated with antiemetic activity but is often categorized among D_2 RAs. At high doses, metoclopramide becomes a competitive antagonist at vagal and central 5-HT_3 receptors.
- Although the use of metoclopramide for CINV has been largely replaced by other antiemetics with better tolerability and efficacy, patients with intercurrent GI motility disorders (eg, gastroparesis) may particularly benefit from its prokinetic effects.
- Long-term use has been associated with dyskinesias; tardive dyskinesia may be irreversible. Use should be limited to <12 weeks.

Benzodiazepines

- Benzodiazepines are important adjuncts to antiemetics for their anxiolytic and anterograde amnestic effects.
    - Irrespective of its cause, anxiety may be a factor in developing or exacerbating emetic symptoms prior to, during, and after completing emetogenic treatments.
    - In addition to nonpharmacologic therapies, benzodiazepines should be considered for the prevention of anticipatory nausea/vomiting.
    - Benzodiazepines are clinically useful for mitigating akathisias associated with D_2 RAs.
- Available products:
    - Lorazepam, midazolam, and diazepam are available in oral and injectable formulations.
        - Lorazepam and alprazolam tablets are rapidly absorbed after sublingual administration.
- Primary liability is dose-related sedation.
- Pharmacodynamic effects are exaggerated in elderly patients.

Cannabinoids

- Commercially available synthetic cannabinoids are agonists at endocannabinoid (CB_1 subtype) receptors.
  - Dronabinol is an oral formulation of Δ9-tetrahydrocannabinol (Δ9-THC) and is classified as a controlled substance (Schedule III) in the United States. It is available as both a capsule and oral solution, which are not bioequivalent.
  - The FDA-approved indication for dronabinol is CINV in patients who have failed to adequately respond to conventional antiemetics.
  - Dronabinol may be particularly advantageous in patients who would also benefit from appetite stimulation associated with its use.
  - To minimize adverse effects, start with lower doses and titrate.
- Cannabis is a natural product derived from the plant *Cannabis sativa*, which is thought to contain two pharmacologically active components: THC and cannabidiol.
  - Evidence for the prevention or treatment of CINV is lacking and cannabis is not endorsed by the NCCN Guidelines, ASCO, or MASCC/ESMO guidelines for this indication.
  - In addition to the adverse effects associated with cannabinoids described below, fungal pulmonary toxicities related to inhaled cannabis are of particular concern in this patient population. Hyperemesis syndrome has also been reported.
- Adverse effects of synthetic cannabinoids occur within the range of clinically useful doses; incidence and severity vary with dose and correlate inversely with the interval between successive doses. Potential adverse effects include the following:
  - Sedation
  - Confusion/decreased cognition
  - Dizziness
  - Short-term memory loss
  - Euphoria/dysphoria
  - Ataxia
  - Dry mouth
  - Orthostatic hypotension ± increased heart rate

Anticholinergic (Antimuscarinic) Agents and Histamine (H_1) RAs

- The utility of using anticholinergic or H_1 RAs in preventing or treating emetic symptoms is not defined.
- Anticholinergics may be most effective when used for prophylaxis; less effective after emetic symptoms develop.
- Anticholinergics (eg, scopolamine) are useful in prophylaxis and treatment for patients whose emetic symptoms are referable to

movement, positional changes, or excessive secretions.

- Individual agents have different affinities for histaminic and cholinergic neuronal receptors, and, in some cases, agonistic and antagonistic activities at adrenergic, dopaminergic, and other neuroreceptors.
- Adverse effects correlate directly with dose and frequency of administration, and include the following:
  - Sedation
  - Dry mouth
  - Loss of visual accommodation/blurred vision
  - Deceased GI motility with constipation or diarrhea
  - Urinary retention or frequency
  - Mydriasis ± photophobia
  - Increased heart rate

PRIMARY ANTIEMETIC PROPHYLAXIS

When developing an antiemetic regimen for primary prophylaxis, the two principal considerations are the emetic potential of the chemotherapy or radiation therapy and patient-specific factors. As described above, chemotherapy agents are classified according to their emetic risk. Therefore, to determine the initial antiemetic selection for a specific patient initiating chemotherapy, determine the emetic potential of each chemotherapy agent in the regimen. Consider factors such as the chemotherapy dose, schedule, and route of administration. The chemotherapy agent with the highest emetic risk should be used as the basis of the antiemetic regimen. Next, review the antiemetic regimen options suggested in the guidelines based on the determined emetic risk. To finalize the regimen, consider patient-specific factors including drug-drug interactions and drug-disease concerns. An as-needed medication for breakthrough nausea/vomiting should be offered to all patients regardless of the chemotherapy emetic potential. Antiemetics should be administered at the lowest effective dose. Although National Comprehensive Cancer Network® (NCCN®), ASCO, and MASCC/ESMO offer evidence-based recommendations to optimize antiemetic selections, these suggestions may not be appropriate in all patients or clinical circumstances. Healthcare providers must exercise clinical judgment.

Multiday chemotherapy requires special consideration as patients may be at risk for both acute and delayed emesis on any given day of

treatment. Therefore, when designing an antiemetic regimen for multiday chemotherapy, numerous factors must be evaluated. In general, antiemetics should be given prior to chemotherapy that are appropriate for the emetic risk of the chemotherapy on that specific day. The ASCO guidelines recommend that antiemetics for multiday chemotherapy be continued for 2 days after the completion of the chemotherapy.

Patients' responses to antiemetic prophylaxis and treatment should be serially monitored and documented with standardized validated tools.

- Healthcare providers historically underestimate the incidence and severity of emetic symptoms associated with chemotherapy and radiation therapy, particularly nausea.
- Patient input is essential to capture information about
    - Events that healthcare providers cannot observe due to patient location and the subjective nature of nausea.
    - Conditions and interventions that modulate a patient's emetic symptoms.
    - Changes in a patient's response to antiemetic prophylaxis through a succession of treatment cycles or courses.
- The MASCC has developed a standardized eight-item questionnaire that can be used to document the number of vomiting episodes and the number and severity of episodes of nausea both acutely and within the 4 days (24-120 h) following the day on which emetogenic treatment was given.
    - The MASCC Antiemesis Tool (MAT), a guide for using the tool, and Patient Outcomes Score Sheets are available in multiple languages in digital formats for downloading, and in an application for handheld devices.
    - Nonprofit entities may use the MAT without incurring charges. Commercial companies are required to obtain written approval from MASCC and will incur a nominal fee prior to using the MAT.
    - Information about the MAT is available online at http://www.mascc.org/index.php?option=com_content&view=article&id=352:MAT&catid=24:guidelines-and-assessment-tools (accessed June 13, 2021).

Antiemetic Regimens for Parenteral Chemotherapy

- Options for acute and delayed emesis prevention with parenteral chemotherapy in adult patients are provided in Table 38.5. The antiemetic regimens are compiled from the NCCN Guidelines, ASCO, and MASCC/ESMO guidelines.

TABLE 15.5

Select Antiemetic Options for the Prevention of Acute and Delayed Emesis Associated With Parenteral Chemotherapy in Adults [a]

High Emetic Risk		
Day 1 (Prechemotherapy)	**Days 2, 3, 4**	**Notes**
Olanzapine + NK_1 RA + Dexamethasone + $5\text{-}HT_3$ RA	Olanzapine days 2, 3, 4 + Aprepitant days 2, 3 (if aprepitant used day 1) + Dexamethasone days 2, 3, 4	Four-drug regimen preferred by NCCN and ASCO
NK_1 RA + Dexamethasone + $5\text{-}HT_3$ RA	Aprepitant days 2, 3 (if aprepitant used day 1) + Dexamethasone days 2, 3, 4	
Olanzapine + Palonosetron + Dexamethasone	Olanzapine days 2, 3, 4	NCCN-specific recommendation
Moderate Emetic Risk		
Day 1 (Prechemotherapy)	**Days 2, 3**	**Notes**
Dexamethasone + $5\text{-}HT_3$ RA	Dexamethasone days 2, 3 OR $5\text{-}HT_3$ RA monotherapy days 2, 3 (no additional $5\text{-}HT_3$ required with palonosetron or granisetron subq or patch)	Long-acting $5\text{-}HT_3$ RA (ie, granisetron subq or palonosetron) preferred by NCCN
NK_1 RA + Dexamethasone + $5\text{-}HT_3$ RA	Aprepitant days 2, 3 (if aprepitant used day 1) ± Dexamethasone days 2, 3	Three-drug regimen recommended by ASCO for carboplatin AUC ≥4; recommended by NCCN for select patients with additional patient-related risk factors or previous treatment failure with a corticosteroid + 5-HT3 RA alone.
Olanzapine + Palonosetron + Dexamethasone	Olanzapine days 2, 3	NCCN-specific recommendation for select patients with additional patient-related risk factors or previous treatment failure with a corticosteroid + 5-HT3 RA alone.
Low Emetic Risk		
Day 1 (Prechemotherapy)	**Days after chemotherapy**	**Notes**
Dexamethasone OR $5\text{-}HT_3$ RA	No routine prophylaxis required	NCCN and MASCC/ESMO also provide a dopamine RA as an option on day 1
Minimal Emetic Risk		
Day 1 (Prechemotherapy)	**Days after chemotherapy**	**Notes**

High Emetic Risk		
Day 1 (Prechemotherapy)	**Days 2, 3, 4**	**Notes**
No routine prophylaxis required		

5-HT_3, 5-hydroxytryptamine type 3; ASCO, American Society of Clinical Oncology; AUC, area under the curve; ESMO, European Society of Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; National Comprehensive Cancer Network® (NCCN®); NK_1, neurokinin type 1; RA, receptor antagonist; subq, subcutaneous.

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- Drug selection and utilization should be tempered by professional judgment, including an assessment of patient-specific risk factors and circumstances, and recognition of available resources.
- The premedication selection and the duration of antiemetic prophylaxis are dependent on the emetic potential of the chemotherapy regimen.
  - High emetic risk
    - A minimum of three antiemetics are given prior to chemotherapy
    - The addition of olanzapine to the three-drug regimen (therefore a four-drug regimen) is preferred by the NCCN Guidelines and ASCO guidelines
    - Prophylaxis is given on days 2 to 4 to prevent delayed emesis
  - Moderate emetic risk
    - A minimum of two antiemetics are given prior to chemotherapy
    - Prophylaxis is given on days 2 to 3 to prevent delayed emesis
  - Low emetic risk
    - A minimum of one antiemetic is given prior to chemotherapy and should be repeated daily for multiday doses of anticancer therapy
    - No prophylaxis is given in the days following chemotherapy
  - Minimal emetic risk
    - No routine prophylaxis required
- Patients should be provided an as-needed medication for breakthrough nausea and/or vomiting.
- The ASCO guidelines for primary prophylaxis specific to pediatric patients receiving parenteral chemotherapy are summarized below. The MASCC/ESMO guidelines provide similar recommendations.
  - High emetic risk (pediatric recommendations)
    - A $5HT_3$ RA + dexamethasone + aprepitant/fosaprepitant
    - Patients unable to receive aprepitant or fosaprepitant should be offered a $5HT_3$ RA + dexamethasone
    - Patients unable to receive dexamethasone should be offered palonosetron + aprepitant/fosaprepitant

- Moderate emetic risk (pediatric recommendations)
  - A $5HT_3$ RA + dexamethasone
  - Patients unable to receive dexamethasone should be offered a $5HT_3$ RA + aprepitant/fosaprepitant
- Low emetic risk (pediatric recommendations)
  - Ondansetron or granisetron
- Minimal emetic risk (pediatric recommendations)
  - No routine prophylaxis required

Antiemetic Regimens for Oral Chemotherapy

- Emesis prophylaxis options for oral chemotherapy are provided in Table 38.6. Given the emetogenic classification of oral anticancer agents is different in the ESMO guidelines, the recommendations provided in this section are based on the ASCO and NCCN Guidelines.
  - High to moderate emetic risk
    - A single antiemetic is recommended for prophylaxis starting prior to treatment and continued daily

TABLE 38.6

Select Antiemetic Options for the Prevention of Emesis Associated With Oral Chemotherapy in Adults [a]

High-Moderate Emetic Risk
Prechemotherapy and continued daily
5-HT_3 RA (choose one) Granisetron 1-2 mg (total dose) PO daily or transdermal patch every 7 days Ondansetron 8-16 mg (total dose) PO daily Dolasetron 100 mg PO daily
Low-Minimal Emetic Risk
Prechemotherapy and continued daily
No routine prophylaxis required; however, metoclopramide, prochlorperazine, or 5-HT3 RA should be given on an as needed basis

5-HT_3, 5-hydroxytryptamine type 3; mg, milligram; PO, by mouth; RA, receptor antagonist.

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  - Low to minimal emetic risk
    - No routine prophylaxis required; however, metoclopramide, prochlorperazine, or 5-HT3 RA should be given on an as needed basis

Antiemetic Regimens for Radiation Therapy

- Recommendations for antiemetic prophylaxis for patients receiving radiation therapy are provided in Table 38.7. For patients who receive chemotherapy and radiation concomitantly, antiemetic prophylaxis is selected based on the chemotherapy component that presents the greatest emetogenic potential, *unless* the emetic risk from radiation is greater. $5HT_3$ RAs and dexamethasone are the backbone of antiemetic regimens for RINV. As described above, the role of NK_1 RAs has yet to be defined in this population.

TABLE 38.7

Select Antiemetic Options for the Prevention of Emesis Associated With Radiation Therapy in Adults [a]

Regimen	Schedule	Notes
High Emetic Risk		
5-HT_3 RA + Dexamethasone	Prior to each day of radiation then on the day after each radiation therapy (if no radiation planned)	MASCC/ESMO and ASCO
5-HT_3 RA (granisetron or ondansetron) ± Dexamethasone		NCCN recommends this pretreatment regimen for each day of total body irradiation
Moderate Emetic Risk		
5-HT_3 RA + Dexamethasone	5-HT_3 RA prior to each day of radiation; dexamethasone prior to each day of radiation for five fractions	ASCO
5-HT_3 RA (granisetron or-ondansetron) ± Dexamethasone	Prior to each day of radiation	NCCN recommends this for radiation therapy of upper abdomen/localized sites and MASCC/ESMO
Minimal–Low Emetic Risk		
No routine prophylaxis required		Dexamethasone preferred if needed for brain

5-HT_3, 5-hydroxytryptamine type 3; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; National Comprehensive Cancer Network® (NCCN®); RA, receptor antagonist.

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BREAKTHROUGH SYMPTOMS

Primary antiemetic prophylaxis recommended by oncology specialty organizations' guidelines are associated with complete control (no emesis) during the acute phase in ≥80% of patients who receive highly emetogenic treatments and even greater complete control rates in the

setting of moderately emetogenic treatment. However, patients may still experience delayed or breakthrough nausea or emesis. In general, it is more difficult to arrest emetic symptoms after they develop than it is to prevent them from occurring. Breakthrough symptoms require rapid intervention. All patients who receive moderately or highly emetogenic treatment should have access to antiemetic medications for treating breakthrough symptoms, whether through a visit or admission to a healthcare facility, or for outpatients, a supply of antiemetic medication and clear instructions for use. If needed and once begun, breakthrough treatment should be administered at scheduled intervals and continued at least until after emetogenic treatment is completed and symptoms abate. In general, nausea may still occur and often is more prevalent than vomiting in patients who achieve overall good or better control of emesis during the acute and delayed symptoms phases.

Suboptimal Control

Clinicians may expect to encounter a minority of patients who do not respond to appropriate antiemetic prophylaxis recommended by the guidelines. Suboptimal antiemetic prophylaxis places patients at risk for breakthrough and refractory emetic symptoms and debilitating morbidity, which may adversely affect patient safety, comfort, and quality of life, and complicate their care.

For patients who respond suboptimally to initial antiemetic prophylaxis, reevaluate factors that may cause or contribute to emetic symptoms, and those that may compromise the effectiveness of pharmacological prophylaxis, including the following:

- The emetogenic risk associated with treatment.
    - The appropriateness of initial antiemetic prophylaxis for the emetogenic challenge presented by treatment.
        - Selection of drugs, doses, administration routes, and schedules for use.
- Healthcare provider adherence in prescribing and patient compliance in using planned antiemetic prophylaxis.
- Disease status.
- Comorbid conditions (electrolyte abnormalities, renal failure, sepsis, constipation, tumor infiltrating or obstructing the GI tract, intracranial disease, vestibular dysfunction).

- Whether concomitantly administered medications may potentially compromise antiemetic effectiveness:
    - Using medications with intrinsic emetogenic potential unrelated to antineoplastic treatment that nevertheless increase the cumulative emetogenic burden.
    - By altering the pharmacokinetics of emetogenic drugs that result in exposures greater in magnitude or duration than would otherwise occur.
    - By altering the pharmacokinetics of agents used in antiemetic prophylaxis or treatment.

Empiric secondary prophylaxis and treatment for patients who demonstrate suboptimal antiemetic control should follow a rational approach. In general, pharmacological interventions typically include drugs presumed to mediate antiemetic effects through an interaction with one or more neurotransmitter receptors implicated in either provoking or mitigating emesis and through mechanisms not exploited by antiemetics already in use. Unfortunately, drugs used empirically are often less tolerable at effective or clinically useful doses and schedules (eg, dopaminergic and cannabinoid RAs) than agents recommended for primary prophylaxis. Whether used adjunctively or as replacement for initial prophylaxis, second-line alternatives may increase treatment costs and the risk of overtreatment and adverse effects.

Suboptimal control of emetic symptoms with antiemetic prophylaxis raises the following questions:

- Was the prophylactic strategy given an adequate trial (time of initiation relative to the start of emetogenic treatment and duration of use)?
- Were the antiemetics selected and the doses and administration schedules prescribed appropriate for the emetogenic challenge?
- Did the patient understand and comply with instructions for antiemetic use?
- Would increased doses or shorter administration intervals improve antiemetic effectiveness without causing or exacerbating adverse effects associated with the antiemetics utilized?

Rescue Interventions

If it becomes necessary to “rescue” a patient from a suboptimal response,

- Assess a symptomatic patient's state of hydration and serum/plasma electrolytes for abnormal results.
  - Replace fluids and electrolytes as needed.
- Add antiemetic agents that act through mechanisms different from antiemetics already in use.
  - It may be necessary to use more than one additional drug to establish antiemetic control.
- Give scheduled doses *around-the-clock* at least until emetogenic treatment is completed, and at doses and on a schedule appropriate for the medication.
  - Do not rely on *as-needed* administration to achieve or maintain control of emetic symptoms.
- Consider replacing ineffective drugs with a more potent or longer-acting agent from the same pharmacologic class.
- Consider replacing an antiemetic medication that requires ingestion and absorption from the GI tract or percutaneous absorption with the same or a different drug given by a different administration route (eg, disintegrating tablets and soluble films for oral administration, injectable formulations).
  - Emetic symptoms may impair GI motility and drug absorption from the gut.
  - Some patients may be too ill to swallow and retain oral medications.
- Sustained- and extended-release formulations (oral, transdermal patches, and injectable sustained- or extended-release products) should not be used to initially bring ongoing symptoms under control.
- Replace drugs associated with unacceptable adverse effects with one or more drugs from the same or a different pharmacologic class without a potential for the same toxicity, or for which particular adverse effects are less likely to occur.

These strategies may be utilized during cyclical treatment or to intervene when response to prophylaxis is unsatisfactory.

Secondary Antiemetic Prophylaxis

When antiemetic treatment is needed for breakthrough symptoms, reevaluate the prophylactic regimen that failed to provide adequate antiemetic control before repeating cycles of emetogenic treatment. Consider alternative antiemetic prophylaxis strategies during subsequent emetogenic treatments, including the following:

- Consider escalating antiemetic prophylaxis to a regimen appropriate for the next greater level of emetic risk.
- Add additional scheduled antiemetics at appropriate doses and administration intervals.
  - Consider drugs that previously proved of value in controlling breakthrough symptoms or another drug that acts through the same pharmacological mechanism.
- For regimens that included a 5-HT_3 RA, consider switching to a different 5-HT_3 RA.
  - Not all patients achieve the same measure of antiemetic control with every 5-HT_3 RA.
- Consider adding an anxiolytic drug to the patient's regimen.
- Consider adding a NK_1 RA to antiemetic prophylaxis if its potential for pharmacokinetic interactions will not adversely affect concomitantly administered medications.
- If alternative treatment for a patient's neoplastic disease exists, consider a different regimen with which similar therapeutic benefit may be achieved without greater adverse outcomes.
  - Perhaps worth considering only if the goal of treatment is not curative.

NONPHARMACOLOGICAL INTERVENTIONS

- Guidance for patients who may preserve nutritional status and alleviate emetic symptoms, include the following
  - Eat small frequent meals low in fat content, especially for patients with anorexia or early satiety.
  - Choose healthful foods.
  - Eat soft, bland, easily digested foods served at room temperature.
    - Eat dry foods; for example, crackers, toasted bread, and dry cereals.
    - Avoid foods and beverages known or found to produce nausea.
    - Advise patients to avoid favorite foods to prevent developing conditioned aversions to those foods, particularly at times when emetic symptoms are anticipated to occur.
    - Avoid sweet, fatty, highly salted and spicy foods, dairy products, and foods with strong odors.
  - For patients who are nauseated by the smell of food:
    - Let someone else do the cooking. Leave areas when and where cooking smells are present.
    - Avoid foods and beverages that provoke nausea.
      - Patients may experience sensitivities to food odors, appearance, taste, textures ("mouth feel").
      - Greasy and fried foods and brewing coffee may provoke symptoms.
  - Suggest prepared foods that can be warmed at a low temperature or a meal that does not need to be cooked.
- Acupressure or acupuncture
  - Stimulation of the ventral side of the wrist where the median nerve is closest to the surface of the skin, an acupuncture point referred to as pericardium-6 (P-6) or Neiguan point may be of benefit in some patients.

Suggested Readings

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39

Nutrition

Sarah Henke

INTRODUCTION

While only effective cancer treatment can reverse the symptoms of cancer cachexia, nutritional deficits and weight loss in patients with cancer can be minimized with timely nutritional intervention and pharmacologic management.

INCIDENCE AND IMPACT OF MALNUTRITION

- More than 40% of oncology patients develop signs of malnutrition during treatment. The risk of malnutrition varies depending on the type of cancer, with patients diagnosed with pancreas and gastric cancers being at especially high risk.
- Malnourished patients incur higher costs for their care and have impaired responses to treatment, greater risk of drug toxicity, and increased rates of morbidity and mortality compared to patients with normal nutritional status.
- As many as 20% of oncology patients die from nutritional complications rather than from their primary diagnosis.
- When malnutrition is identified, diagnosed, and treated, reimbursement to cover the increased cost of care can also be increased—if the physician includes the diagnosis and degree of malnutrition in their documentation, using the currently accepted criteria for diagnosing adult malnutrition (Table 39.1).

TABLE 39.1

Clinical Characteristics to Support a Diagnosis of Malnutrition in Adults

Clinical Characteristics	Related to Acute Illness/Injury	Related to Chronic Illness	Related to Social or Environmental Circumstance
Moderate Protein-Calorie Malnutrition ICD-10 Code: E44.0			
Weight loss	1%-2% in 1 wk 5% in 1 mo 7.5% in 3 mo	5% in 1 mo 7.5% in 3 mo 10% in 6 mo 20% in 12 mo	5% in 1 mo 7.5% in 3 mo 10% in 6 mo 20% in 12 mo
Energy intake (* per registered dietitian assessment)	<75% of estimated needs* for >7 days	<75% of estimated needs* for ≥1 mo	<75% of estimated needs* for ≥3 mo
Physical findings: Mild fat and muscle loss, mild fluid accumulation			
Severe Protein-Calorie Malnutrition ICD-10 Code: E43.0			
Weight loss	>2% in 1 wk >5% in 1 mo >7.5% in 3 mo	>5% in 1 mo >7.5% in 3 mo >10% in 6 mo >20% in 12 mo	>5% in 1 mo > 7.5% in 3 mo >10% in 6 mo >20% in 12 mo
Energy intake	≤50% of estimated needs for ≥5 d	<75% for ≥1 mo	≤50% for ≥1 mo
Fat loss (eg, of orbital fat pads, triceps, biceps, ribs, lower back)	Moderate depletion (eg, iliac crest prominent)	Severe depletion (eg, loss of orbital fat pads)	Severe depletion (eg, depression between ribs very apparent)
Muscle mass loss (eg, of the temporalis, clavicle, scapular and patella region, dorsal hand, posterior calf)	Moderate depletion (eg, visible clavicle bone in male; clavicle protruding in female)	Severe depletion (eg, wasting of the temporalis muscle)	Severe depletion (eg, flattening of interosseous muscle between thumb and forefinger)
Fluid accumulation	Moderate to severe (eg, slight swelling of extremity)	Severe (eg, 3+ edema)	Severe (eg, deep pitting)
Functional	Grip strength has	Grip	Grip strength below

assessment	decreased	strength below normative values	normative values

Adapted from White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. 2012;36(3):275-283.

CANCER CACHEXIA

- Nearly two-thirds of patients with cancer develop cancer cachexia characterized by systemic inflammation, anorexia, immunosuppression, and metabolic derangements. These can lead to unintentional weight loss and failure to preserve muscle and fat mass.
- There is no consistent relationship between tumor type, tumor burden, anatomic site of involvement, and cancer cachexia.
- Hypermetabolism is not uniformly present.
- Tumor-induced changes in host production of pro-inflammatory cytokines (tumor necrosis factor, interleukin [IL]-1, IL-6, and interferon) can lead to hypermetabolism and anorexia due to changes in ghrelin, serotonin, and leptin production. Tumor production of proteolysis-inducing factor and lipid-mobilizing factor contributes to loss of muscle and fat mass—even in the presence of adequate nutrition intake. Inefficient energy metabolism and insulin resistance lead to further depletion of lean body mass.
- Identification of patients with muscle loss has become increasingly difficult as 40% to 60% of patients with cancer are overweight or obese, with fat mass masking muscle loss. This is considered sarcopenic obesity.
- Overfeeding is likely to worsen metabolic dysregulation and will not result in weight gain.

SCREENING FOR NUTRITIONAL RISK

- Nutritional deterioration can be minimized if patients are screened at each visit, so that problems can be identified and interventions provided when they can have the most impact. The Joint Commission on Accreditation of Healthcare Organizations standards state that inpatients are to be screened for nutritional risk within 1 day of admission. Screening is often conducted by nursing staff, but in some facilities the registered dietitian nutritionist (RD or RDN) will perform this role.
- Validated screening tools such as the Subjective Global Assessment form (https://www.accc-cancer.org/oncology_issues/supplements/Scored-Patient-Generated-Subjective-Global-Assessment-PG-SGA.pdf) may be especially helpful in the outpatient setting. Parameters include weight change, symptoms impacting nutrition, changes in diet, functional status, and changes in metabolism and in muscle, fat, and fluid status. The use of the form also serves to demonstrate to the patient that nutrition is a priority of the medical team.

The Pediatric Subjective Global Nutrition Assessment rating form has been validated for use in children. The tool combines clinical judgment and objective criteria to determine a global rating of nutritional status and for identifying those at higher risk of nutrition-related complications (https://www.ncbi.nlm.nih.gov/pubmed/22717202). Parameters include appropriateness of current height for age (stunting), current weight for height (wasting), unintentional changes in body weight, adequacy of dietary intake, gastrointestinal symptoms, functional capacity and metabolic stress of disease, loss of subcutaneous fat, muscle wasting, and nutrition-related edema.

NUTRITIONAL ASSESSMENT

- RDs use anthropometric data, biochemical indices, nutrition-focused physical assessment, functional assessment, diet, and medical histories to assess the nutritional status of patients and to determine appropriate intervention. See Table 39.2 for RD referral information and suggestions for addressing nutrition and dietary supplement questions from patients.

TABLE 39.2

To Address Patients' Questions About Nutrition or Dietary Supplements

Refer to a registered dietitian nutritionist (RD or RDN) for individualized nutrition counseling	The registered dietitian nutritionist is the only professional with standardized education, clinical training, continuing education, and national credentialing necessary to be directly reimbursed as a provider of nutrition therapy. RD requirements include a bachelor's degree or higher (>40% have a master's or doctoral degree), 1200-h supervised internship, a national credentialing examination, and continuing education. Other nutrition credentials, degrees, or titles do not meet these standards (http://www.eatright.org/find-an-expert).
For free, responsible nutrition/cancer guidelines	"Heal Well" from the American Institute for Cancer Research, LIVESTRONG, and Meals to Heal address common nutrition concerns and myths such as "Does sugar feed cancer?" (http://www.aicr.org/assets/docs/pdf/education/heal-well-guide.pdf). "Eating Hints" from the National Cancer Institute provides nutrition suggestions for patients undergoing treatment (https://www.cancer.gov/publications/patient-education/eatinghints.pdf).
For vitamin and other dietary supplement information	The National Institutes of Health Office of Dietary Supplements provides evidence-based, responsible professional and consumer level handouts (https://ods.od.nih.gov/factsheets/list-all/).The Natural Medicines Comprehensive Database (published by the Therapeutic Research Faculty) provides thorough, frequently updated, well-referenced information including potential drug interactions and has consumer level information available (http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=cepda&s=ND).

BODY COMPOSITION

- Obtaining baseline measurements of body composition and comparing these measurements over time can be helpful for monitoring nutritional status.
- Body composition is an important predictor of anticancer drug efficacy and toxicity. The use of body surface area (BSA) for dosing chemotherapy is being questioned as cytotoxic drugs are largely metabolized and excreted by the liver and kidney, which does not correlate with BSA. There is literature to suggest that lean body mass or fat-free mass may be a better basis for normalizing drug dosages in patients with cancer, especially for hydrophilic drugs.
- The recommended measurement for diagnosing sarcopenia (muscle loss) is by direct measurement of lean body mass by either DXA (dual-energy x-ray absorptiometry) or computed tomography (CT). The DXA, however, does not distinguish between lean and adipose tissue subcompartments.
- The third lumbar vertebra has been validated as the standard landmark for body composition analysis (via CT) because in this region, the percentage of skeletal muscle and adipose tissue has been found to accurately reflect the percentage of skeletal muscle and fat in the entire body.
- Especially as patients with cancer frequently have routine CT monitoring, the use of the third lumbar CT slice to monitor changes in body composition may become routine in the future.
- Measures of muscle mass can include the use of skin calipers to measure mid-arm circumference and mid-arm muscle circumference. Triceps skinfold measurements can be used to estimate fat stores. There is evidence that ultrasound may also become a useful tool for monitoring muscle mass (eg, used at bedside to measure the quadriceps).
- Body mass index (BMI) correlates well with body fat, morbidity, and mortality. However, BMI could incorrectly categorize highly muscled patients or those with edema or ascites as having excess fat stores. The BMI is a reasonable means of estimating recommended weights (Table 39.3).

TABLE 39.3

IBW and BMI

IBW (ideal body weight)	IBW men (metric) = 48 kg for first 152.4 cm of height + 1.1 kg for each additional cm IBW men (US) = 106 lb for first 5 ft of height + 6 lb for each additional inch IBW women (metric) = 45 kg for first 152.4 cm of height + 0.9 kg for each additional cm IBW women (US) = 100 lb for first 5 ft of height + 5 lb for each additional inch Derived from 1943 standard height/weight insurance tables—IBW included a component of frame size and height was measured while wearing 1″ heels. IBW came to represent fat-free mass—useful for pharmaceutical and other equations. IBW is not recommended for setting target weight goals as it does not represent current standards for height or weight.	
BMI (body mass index)	BMI = Weight (kg)/height (meter)^2 BMI < 18.5 kg/m^2 = Underweight BMI 18.5-24.9 kg/m^2 = Reference range BMI 25-29.9 kg/m^2 = Overweight BMI 30-34.9 kg/m^2 = Obesity 1 BMI 35-39.9 kg/m^2 = Obesity II BMI > 40 kg/m^2 = Obesity III	BMI may overestimate body fat in taller individuals, athletes, or those with muscular builds. BMI may underestimate body fat in those who are shorter or have low muscle mass.
Maximum recommended weight	Maximum recommended weight (BMI = 24.9 kg/m^2) To find corresponding weight: Weight = 24.9 × height (meter)^2 Example—for a patient 160 cm tall: Recommended maximum weight = Height (meter)^2 × 24.9 Recommended maximum weight = (1.60 m)^2 × 24.9 = 63.7 kg	
Minimum recommended weight	Minimum recommended weight (BMI = 18.5 kg/m^2) To find corresponding weight: Weight (kg) = 18.5 × height (meter)^2 Example—for a patient 160 cm tall: Recommended minimum weight = Height (meter)^2 × 18.5 Recommended minimum weight = (1.60 m)^2 × 18.5 = 47.4 kg	

- Ideal body weight is not appropriate for setting weight goals as it does not reflect standard heights and weights.

PROTEIN

- If energy intake is inadequate, catabolism of protein will occur, especially as tumors preferentially metabolize protein. Limiting protein intake has not been shown to interfere with tumor growth and may lead to protein malnutrition and impaired immunity.
- Protein turnover in patients with cancer is similar to that of patients with infection or injury; their protein requirements are 50% above those of healthy individuals.
- Transport proteins (such as albumin and thyroxin-binding prealbumin) are negative acute-phase proteins that decrease in the presence of inflammation, regardless of a patient's protein status. Earlier studies incorrectly correlated these proteins with nutritional status, not accounting for their role as inflammatory markers. Dietary history and nitrogen balance measurements are more reliable measures of protein adequacy.
- The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (ASPEN) published guidelines for nutrition support of the critically ill patient in 2016, which includes the recommendation that visceral proteins (such as prealbumin and albumin) not be used as markers of nutrition status.

NUTRITIONAL REQUIREMENTS

- Indirect calorimetry, the preferred method for estimating resting energy expenditure, measures O_2 consumed (VO_2) and volume of carbon dioxide produced (VCO_2) to determine respiratory quotient. This can be done with a portable metabolic

cart operated by a respiratory therapist or by a handheld device recently approved by the Food and Drug Administration.

- There are a variety of recommended calculations for estimating energy, fluid, and protein requirements (Tables 39.4-39.6). However, formulas that rely on stress and activity factors, or calculations such as >45 kcal/kg "for stress," have been shown to overestimate requirements. It is important not to overfeed patients with cancer. Overfeeding can increase risk of infection and induce respiratory distress, hyperglycemia, and fatty liver.

TABLE 39.4

Estimates of Energy Requirements

Patient/Condition	Kilocalories/kg [a]
Acutely ill; obese (BMI 30-50 kg/m^2)	11-14 (use actual weight)
Cancer	25-30
Hypermetabolism; malabsorption	35
Stem cell transplant	30-35

[a]Fever increases energy needs by ~14%/°F.

TABLE 39.5

Mifflin-St. Jeor Formula for Estimating Resting Energy Expenditure

Males	REE = 10W + 6.25H − 5A + 5
Females	REE = 10W + 6.25H − 5A − 161

A, age (y); H, height (cm); REE, resting energy expenditure; W, weight (kg).

TABLE 39.6

Recommended Protein Intake for Adults

Disease State	Grams of Protein per Kilogram Body Weight
Cancer	1-1.2
Cancer cachexia	1.2-1.5
Hematopoietic stem cell transplant	1.5
Renal disease	
Obese patient	2-2.5 (using ideal body weight)
Predialysis GFR 26-55 mL/min	0.8

Disease State	Grams of Protein per Kilogram Body Weight
GFR 10-25 mL/min	0.6
Hemodialysis	1.1-1.4
Peritoneal dialysis	1.2-1.5
CVVHD	1.5-2
Liver disease	1-1.5
Hepatitis chronic or acute	
Encephalopathy grade 1 or 2	0.5-1.2
Encephalopathy grade 3 or 4	0.5

CVVHD, continuous venovenous hemodialysis; GFR, glomerular filtration rate.

NUTRITIONAL INTERVENTION

- Nutritional counseling by an RD is associated with improvement in the quality of life scores and nutritional parameters, and with success of oral nutritional intervention for oncology patients. Continual reassessment, pharmacologic management, and nutritional counseling can often help avoid costly, risky nutritional support options. See Table 39.7 for nutrition recommendations appropriate for patients who are able to tolerate oral or enteral feedings.

TABLE 39.7

Oral Nutrition Recommendations for Patients (by Condition)

Condition	Recommendations
Diabetes/hyperglycemia	Begin by familiarizing patients with the carbohydrate content of foods. Most men need 45-75 g of carbohydrate per meal; most women need 45-60 g per meal. For a snack, 15-30 g of carbohydrate is usually recommended. (One ounce of bread product, ½ cup cooked starch, ½ cup fruit or juice, and 8 oz milk each provide ~15 g of carbohydrate.)
Diarrhea	↓ Lactose, ↓ fat, ↓ insoluble fiber (wheat bran, skin, and seeds of produce), ↑ soluble fiber (peeled fruit, oat bran, guar gum products). Cheese has insignificant carbohydrate/lactose content (<2/100 g of cheese) and yogurt is naturally low in lactose.

Condition	Recommendations
Early satiety	Calorically dense foods/nutrition products (eg, medical nutrition beverages with >1.5 kcal/mL); foods such as nuts, cheese, seeds, modular kcal, or protein supplements that can be added to foods without significantly altering the flavor or volume of foods.
Fat malabsorption	↓ Fat diet and medium-chain triglyceride (MCT)–oil fortified foods/products. A diet with <30% of kcal from fat or <40 g of fat/d may be unrealistic over the long term. A trial of pancreatic enzymes and bile acid sequestrants may significantly improve symptoms.
Hypercalcemia of malignancy	Does not respond to low-calcium diet. Often, crucial sources of protein and kcal are limited by such a diet.
Magnesium and potassium status	Refractory hypokalemia is often related to limited Mg stores, even when serum Mg levels are within normal range. Repletion of Mg may help normalize K levels. Increased intake of dietary Mg, K, and P can reduce reliance on supplements without the gastrointestinal side effects associated with supplementation.
Malabsorption	Semi-elemental palatable products, trials of pancreatic enzymes, bile acid sequestrants, and MCT may reduce symptoms.
Neutropenia	Many hematopoietic transplant centers emphasize prevention of food-borne illness (verifying temperatures of cooked foods/meats with a thermometer, avoiding unpasteurized dairy products and juices, etc) rather than strict diets that limit fresh produce, have poor compliance rates, and have no proven benefit in reducing infection rates.
Poor appetite/fatigue	Recommend >5 scheduled feedings/day to lessen dependence on appetite, with use of nutritious liquids for high % of kcal (milk, lactose-treated milk, soup, soy milk, fruit smoothies made with nut butter, or meal replacement beverages). Discourage patients from relying on water alone to meet fluid requirement, as nutritious beverages such as milk contain >90% water and could provide significant nutrition; excess water intake may blunt appetite.
Diet advancement	Based on expert consensus, clear liquids are not required as the first meal postoperatively. Patients should be allowed solid foods as tolerated.

NUTRITIONAL SUPPORT

Although tumor growth is stimulated by a variety of nutrients, limiting the nutrients preferred by tumors can be detrimental to the patient. If patients have moderate to severe malnutrition and are unable to meet their nutritional needs with oral intake alone, specialized nutrition support such as parenteral or enteral nutrition (EN) is indicated (Figure 39.1). Sample parenteral nutrition (PN) recommendations are shown in Table 39.8.

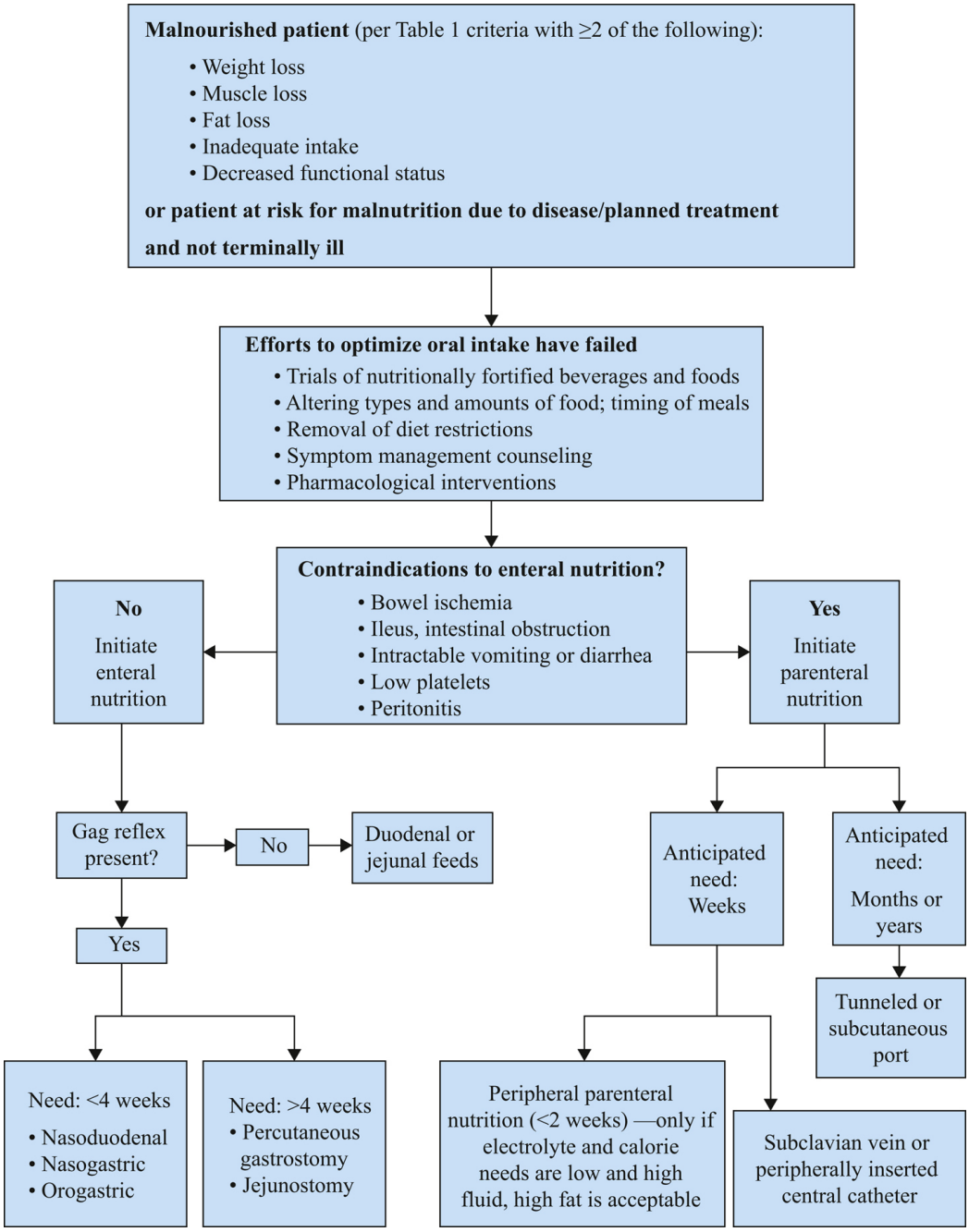

FIGURE 39.1 Nutrition support algorithm.

TABLE 39.8
Sample Parenteral Nutrition Recommendations

	Infants/Children (3-30 kg)	Adolescents (≥30 kg)	Adults

	Infants/Children (3-30 kg)	Adolescents (≥30 kg)	Adults
Water	1500-1800 mL/m^2/d, 1500 mL/kg for first 20 kg and 25 mL/kg for remaining weight	1500 mL/m^2/d	1500 mL/m^2/d, 35 mL/kg or 1 mL/kcal
Energy	70-110 kcal/kg/d	40-60 kcal/kg/d	20-35 kcal/kg/d
Dextrose (3.4 kcal/g for the hydrated form)			
Initial	5%-10% (50-100 g/L)	5%-10% (50-100 g/L)	10%-15% (100-150 g/L)
Advance	5% (50 g/L)	5% (50 g/L)	5%-10% (50-100 g/L)
Maximum dextrose oxidation rate	12-15 mg/kg/min	5-13 mg/kg/min	4-5 mg/kg/min
Maximum dextrose concentration	20%-35% (200-350 g/L)	20%-35% (200-350 g/L)	20%-35% (200-350 g/L) for central access; 10% for peripheral
Protein			
Initial	1 g/kg/d	1 g/kg/d	At goal
Advance	0.5-1 g/kg/d	1 g/kg/d	—
Maximum	2-3 g/kg/d	1.5-2 g/kg/d	2 g/kg/d
Intravenous Fat Emulsion	20% lipid provides 2 kcal/mL. Due to glycerol in fat emulsions, 1 g of fat in 20% emulsions = 10 kcal; ~1 g of fat per 5 mL of 20% IV fat emulsion		
Initial	1 g/kg/d	1 g/kg/d	At goal; usually ≥250 mL 20% IV fat emulsion for ~30% of total kcal
Advance	1 g/kg/d	1 g/kg/d	—
Maximum	2-3 g/kg/d	2 g/kg/d	2 g/kg/d (60% of total kcal)
Minerals			
Sodium	2-4 mEq/kg/d	2-3 mEq/kg/d	1-2 mEq/kg, 60-150 mEq/d max, 155 mEq/L

	Infants/Children (3-30 kg)	Adolescents (≥30 kg)	Adults
Potassium	2-3 mEq/kg/d	1.5-3 mEq/kg/d	1-2 mEq/kg, 40-240 mEq/d max, 80 mEq/L
Magnesium	0.3-0.5 mEq/kg/d	0.2-0.3 mEq/kg/d	8-24 mEq/d
Calcium	0.5-2.5 mEq/kg/d	0.5-1 mEq/kg/d	10-40 mEq/d max, 30 mEq/L
Phosphorus	0.5-2 mM/kg/d	0.5-1.3 mM/kg/d	20-40 mM/d max, 30 mM/L
Selenium	2 µg/kg/d (40 µg/max)	2 µg/kg/d (40 µg/max)	40 µg
Trace metals and multivitamins	Daily	Daily	Daily

Enteral Nutrition

- Reviews of nutritional support practices indicate that PN is often instituted even when safer, more physiologic EN support could have been provided. The benefits of EN over PN have been well demonstrated, including fewer infections, decreased catabolic hormones, improved wound healing, shorter hospital stay, and maintenance of gut integrity. In other words, if the gut works, use it.
- To be successful, EN should be implemented as soon as possible. Surgeons may approve of enteral feeding within 4 hours of placement of gastrostomy tubes and immediately after jejunostomy (because bowel sounds are not needed). Prophylactic placement of gastrointestinal tubes can considerably reduce weight loss during radiotherapy and may reduce the need for hospitalization due to dehydration, weight loss, or other complications of mucositis.
- Many long-accepted practices for initiating and monitoring EN and PN have been overturned recently. See with the 2016 Society of Critical Care Medicine and ASPEN guidelines for the

nutrition support of critically ill patients for the most current recommendations.

Parenteral Nutrition

- PN can be beneficial to cancer patients when response to treatment is good but associated nutritional morbidity is high and when the GI tract is unavailable to support nutrition. Perioperative PN should be limited to patients who are severely malnourished, with surgery expected to prevent oral intake for more than 10 days after surgery.
- For the families of cancer patients, feeding is often synonymous with caring. However, end-stage patients who are encouraged to eat and drink as desired may have better quality of life than if specialized nutrition support is provided (which could contribute to incontinence, fluid imbalance, and respiratory compromise). The risks and benefits of PN must be addressed individually and evaluated for each case with patient and family input. In general, PN is not usually indicated in patients with an expected survival of less than 3 months.

COMPLICATIONS OF NUTRITIONAL SUPPORT

Refeeding Syndrome

- Feeding after starvation is associated with increased intravascular volume, cardiopulmonary compromise, and plummeting levels of phosphorus, magnesium, and potassium due to the intracellular movement of electrolytes during anabolism. Malnourished individuals with severe weight loss, negligible intake for >7 days, a history of alcoholism, recent surgery, electrolyte losses due to diarrhea, high-output fistulas,

issues with malabsorption, recent bowel resection, or vomiting are especially vulnerable.

- In patients at high risk of refeeding syndrome, the recommendation is to initiate nutrition support with 100 to 150 g of dextrose or 10 to 20 kcal/kg during the first 24 hours with slow advancement to goal depending on patient's tolerance. Phosphorus, magnesium, and potassium should all be monitored daily while feeding is advanced to the goal.
- Thiamine, an important coenzyme for carbohydrate metabolism, should be supplemented at 100 mg for at least 5 to 7 days after initiating nutrition support. Folic acid and a multivitamin are also commonly added for patients at high risk of refeeding syndrome.

Hypertriglyceridemia

For individuals receiving PN who have preexisting hyperlipidemia and obesity, or for those taking sirolimus, cyclosporine, and other medications associated with increased triglyceride (TG) levels, the goal is to keep TG < 400 mg/dL. Ensure that blood is drawn 4 hours after lipid infusion or before lipids are hung, to avoid falsely elevated TG. Lipid dose should be reduced if TG is between 300 mg/dL and 400 mg/dL; however, stopping lipids altogether may worsen liver dysfunction. Five hundred milliliters per week of 20% IV fat emulsion can prevent essential fatty acid deficiency in adults.

PN-Associated Liver Disease

Hepatic fat accumulation is most common in adults and usually resolves within 2 weeks, even if PN continues. It typically presents within 2 weeks of PN with moderate elevations in serum aminotransferase concentrations. PN-associated liver disease is usually a complication of overfeeding; it has become less common in the past 10 years, since calories provided via PN have become more appropriate.

PN-Associated Cholestasis

- PN-associated cholestasis (PNAC) is primarily a result of excess calories in PN. Overfeeding contributes to fat deposition in the liver by stimulating insulin release, which promotes lipogenesis and inhibits fatty acid oxidation. PNAC occurs most often in children. It is associated with elevated serum conjugated bilirubin (>2 mg/dL) and may progress to cirrhosis and liver failure. Factors unrelated to PN that have been misattributed to PNAC include bacterial and fungal infections.
- Fat-free PN formulations have also been implicated in the development of fatty liver, since a high percentage of calories from carbohydrates can lead to fat deposition in the liver. Providing a balance of calories from dextrose and fat seems to decrease the incidence of steatosis, possibly by decreasing hepatic TG uptake and promoting fatty oxidation.

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Pain and Palliative Care

Daniel Fischer, Rita Manfredi

WHAT IS PALLIATIVE CARE?

- Palliative care is the critical discipline of alleviating symptoms and all types of distress in people suffering from serious illnesses with a focus on both patients and their families.
- Palliative care treatment modalities are aimed at addressing not only physical elements of patients' distress but their psychological, social, and spiritual needs as well.
- The robust palliative care team consists of physicians, advance practice providers, nurses, social workers, and chaplains to address the complex needs of the oncologic patient.
- Palliative care can be complementary to disease-directed therapy (DDT) and should supplement traditional oncologic care.
- The provision of palliative care is provided in multiple settings: outpatient clinic, inpatient facility, and home environments.
- A referral to palliative care occurs for symptom management and goals of care conversations and should not be confused with a referral to hospice which focuses on end-of-life care. Palliative care and hospice are not synonymous.

OBJECTIVES OF PALLIATIVE CARE

- A palliative care consultation provides an additional layer of support to not only the patient and their family but the oncologist and their team as well.

- The ENABLE II (2009) and Temel et al (2010) studies found that patients with advanced cancer who were assigned to palliative care intervention had higher quality of life (QOL), lower depressed mood, and improved survival versus those patients assigned to usual care.
- Palliative care improves symptom control and reduces the cost of care in patients receiving DDT.
- According to current American Society of Clinical Oncology guidelines, a referral to palliative care should be made as early as possible for all patients with a malignancy diagnosis alongside active cancer treatment to ascertain the patient's goals.
- An early referral will encourage the patient to gain some insight into their own belief and value system, which can help dictate what QOL they may or may not find acceptable in the future. Such an insight may help the patient and oncologist collaborate to determine a tailored treatment plan.
- The interdisciplinary palliative care team is committed to addressing spiritual and existential distress that may appear during the patient's disease course, involving chaplaincy services as needed.
- With goals of care elucidated and symptoms addressed by the palliative care team, the oncologist can devote maximal time and effort to treating the patient's cancer.

PAIN ASSESSMENT AND MANAGEMENT

Definitions

- Pain is a common referral for palliative care consultation. It is subjective and may be influenced by emotional, psychological, social, and spiritual factors, as well as financial concerns and fear of death. This constellation of factors is known as "total pain" and is best treated with an interdisciplinary approach to address all areas of suffering for patients and family.
- Acute pain is the predictable physiologic response to an adverse chemical, thermal, or mechanical stimulus. It is normally

associated with surgery, trauma, and acute illness. It is generally time limited and responsive to a variety of pharmacologic and nonpharmacologic therapies.
- When acute pain persists overtime, it is classified as chronic pain. Oncologic pain may present acutely but often persists as chronic pain.

Epidemiology

- Most cancer patients experience some degree of pain, especially in the advanced or metastatic phases of disease. In advanced cancer, the prevalence of pain is about 70% but varies with the type and stage of disease.
- There are several published guidelines for cancer pain management recommended by the World Health Organization, and effective treatments are available for 70% to 90% of cases.

An estimated 40% of cancer patients remain undertreated for reasons related to the health care provider, the patient, and family, or cultural mores. Most frequently, the cause of undertreatment surrounds misconceptions about opioid use.

Pain Assessment

- Proper pain assessment fosters an optimal physician/patient relationship, guides the therapeutic regimen, improves pain management, maximizes patient comfort and function, and increases patient and family satisfaction with therapy. Failure to fully assess pain in the cancer patient may result in adverse pain outcomes, regardless of the amount or type of analgesia and adjuvants used.
- Patients' self-reports should be the main source of pain assessment. For infants and the cognitively impaired, practitioners can utilize nonverbal pain scales (eg, FPS-R, FLACC) (Periyakoil et al, 2019).
- Patients should be reassessed frequently to determine pain relief after each dose or treatment. A consistent disparity between

patients' self-report of pain and their ability to function necessitates further assessment to ascertain the reason for the disparity.

- When addressing total pain, it is important to look at other forms of suffering and appropriate treatments in addition to physical suffering to ensure that medication management such as opioids are not over- or underutilized in the oncologic patient (Figure 40.1).

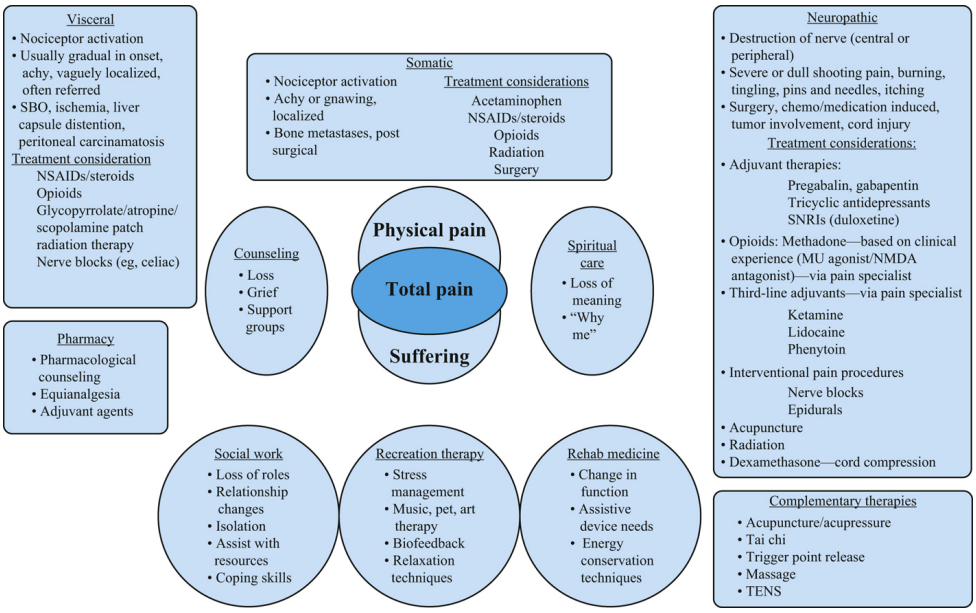

FIGURE 40.1 Total pain in oncology patient.

Treatment of Pain

- Treatment of physical pain should be tailored to each patient, based on the type and expected duration of pain (somatic, visceral, neuropathic, and acute vs chronic).
- Use of an interdisciplinary team to assist with suffering improves management of the patient's total pain (ie, social work, chaplain, recreation therapist, physical therapist, pharmacist), thus limiting the use of prescription medications for nonphysical pain.
- No maximal therapeutic dose for analgesia has been established for opioids. Immediate-release opioids (mu receptor agonists) are

short-acting and may be appropriate for acute incidental pain, breakthrough pain, or to initiate and titrate opioid therapy. Long-acting opioids are used around the clock for baseline pain and to maintain analgesia once an adequate regimen has been established.

- Titration of opioids: Start at lower doses and titrate as tolerance to side effects develops. If pain persists, titration upward by dose increments of 30% to 50% may be necessary to achieve adequate analgesia. For severe uncontrolled pain (extremis), increase the dose by 100% and reassess at peak effect. Additionally, adjust dose based on kidney function when titrating opioids, and stop escalation at adequate pain control or dose-limiting side effects (Table 40.1).

TABLE 40.1

Opioid Doses Equianalgesic to Morphine 10 mg Parenteral (IV/IM) for Treatment of Chronic Pain in Cancer Patients (Derby et al, 1998 and McPherson, 2018) [a]

Drug	mg Oral	mg IV/IM	Duration (h)	Considerations
Morphine	25	10	2-4 (IV) 2-4 (IR) 8-24 (SR/CR)	Most toxic metabolites in renal failure should be avoided Various formulations of long-acting agents with different duration
Oxycodone	20	—	3-4 (IR) 8-12 (SR)	As with all SR/CR tablets, do not crush IR opioids can be crushed
Hydromorphone	5	2	2-4(IV) 2-4 (IR)	Use cautiously in renal failure
Methadone	—	—	—	Complex pharmacodynamics and highly recommend management per pain or palliative care specialists Based on clinical experience, helpful with somatic and neuropathic pain Can prolong QTc interval and requires monitor with ECG with use Can be used in renal dysfunction
Oxymorphone	10	—	2-4	

Drug	mg Oral	mg IV/IM	Duration (h)	Considerations
Fentanyl	—	0.15 (150 µg)	30-60 min	Can be administered as continuous IV or SC infusion; based on clinical experience, 10 µg IV = 1 mg IV morphine Can be used in renal dysfunction, cautious use in liver dysfunction
Fentanyl Transdermal	—	—	48-72	Based on clinical experience, 25 µg/h is roughly equianalgesic to morphine 50 mg PO per day Adequate adipose tissue required for absorption would not recommend in cachexia Fevers and diaphoresis can affect absorption

CR, controlled release; IR, immediate release; SR, sustained release.

[a]Adapted by permission from Springer: Derby S, Chin J, Portenoy RK. Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. *CNS Drugs*. 1998;9(2):99-109. Copyright © 2012 Springer Nature; Reprinted with permission from McPherson ML. *Demystifying opioid conversion calculations: A guide for effective dosing*. American Society of Health-System Pharmacists; 2018.

- Common adverse effects of opioids include constipation, sedation, nausea/vomiting, pruritus, sweating, dry mouth, and weakness.
- Except for constipation, tolerance often develops rapidly to most of the common opioid-related adverse effects. Unless contraindicated, a bowel regimen is required to prevent constipation and must be maintained in patients receiving opioid therapy.
- Uncommon adverse effects of opioids include dyspnea, urinary retention, confusion, hallucinations, nightmares, myoclonus, dizziness, dysphoria, and hypersensitivity/anaphylaxis.
- Except for methadone, most opioids may not treat neuropathic pain adequately. Alternative agents, such as duloxetine or gabapentinoids, may be better suited for this purpose.
- Nonpharmacological therapies, such as acupuncture and acupressure, have been significantly associated with reduced cancer pain and decreased use of analgesics.

Safe and Responsible Prescribing

- Physicians have an ethical and regulatory duty to inform the patient of the risks and benefits of long-term opioid use, particularly when initiating treatment in patients at high risk for misuse of opioids (utilize random urine drug tests, referrals to pain management physicians, and pain contracts in high-risk patients).
- Opioid therapy should be tailored to each patient, based on the type and expected duration of pain, as it is difficult to predict which patients will achieve adequate analgesia or develop intolerable adverse effects from a given opioid.
- Certain factors, such as personal or family history of substance abuse, risk of diversion of opioids, or lack of compliance, dictate a multidisciplinary approach, including involvement of a pain specialist.
- Long-term use of opioids should always be supported by maximizing nonopioid coanalgesics and adjuvants, psychological therapy, spiritual counseling, and appropriate follow-up.
- The Centers for Disease Control and Prevention has published guidelines for the management of chronic pain to minimize the harms associated with opioids including overdose and opioid use disorders. These guidelines focus on effective treatments available for chronic pain such as adjuvants and nonpharmacological approaches to pain control.
- Key recommendations include the following:
    - Nonopioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
    - When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
    - Providers should always exercise caution when prescribing opioids and monitor all patients closely.

Risks of Long-Term Opioid Use

- Addiction: Extremely rare in cancer patients but all patients should be assessed for risk factors and continuously reassessed.
    - Risk factors: Personal and family history of substance abuse; age; history of preadolescent sexual abuse; certain psychiatric disorders: attention deficit disorder, obsessive-compulsive disorder, bipolar, schizophrenia, and depression (Webster & Webster, 2005).

- Physical dependence: Manifested by withdrawal syndrome at cessation or dose reduction.
- Tolerance: Diminution of one or more of the opioid's effects over time often related to disease progression in the oncology patient.
- Pseudoaddiction: Iatrogenic syndrome that develops in response to poorly treated pain where the patient demonstrates behaviors (grimacing, moaning, watching the clock) wrongly interpreted by clinicians as indicators of addiction. Index case was oncologic patient in 1989.

COMMON NONPAIN SYMPTOMS

- Nausea is an extremely frequent symptom experienced by patients with malignancy and should be treated based on etiology (Table 40.2).

TABLE 40.2

Antinausea Medication Classifications

Class of Drugs	Receptors Affected	Neuroanatomical Sites	Examples of Drugs	Indication Based on Nausea Etiology
Dopamine antagonist	D2	CTZ	Haloperidol Prochlorperazine	Medication-induced
Serotonin antagonist	5-HT3	CTZ Mechanoreceptors and chemoreceptors in GI tract	Ondansetron Granisetron	CINV
Antihistamine	H1	Vestibular system	Diphenhydramine Meclizine	Labyrinthine disorders Motion sickness
Gastroprokinetic agent	D2, 5-HT3, Achm	GI tract, CTZ, VC	Metoclopramide	Delayed gastric emptying
Atypical antipsychotic	D2, Achm, 5-HT3, H1	GI tract, CTZ, VC	Olanzapine	Multifactorial Intractable nausea

Class of Drugs	Receptors Affected	Neuroanatomical Sites	Examples of Drugs	Indication Based on Nausea Etiology
NK1 receptor antagonist	NK1	GI tract, CTZ	Aprepitant	CINV
Corticosteroid	Inhibits neutrophil migration	Reduces peritumoral inflammation	Dexamethasone	Elevated intracranial pressure GI malignancies

5-HT3, 5-hydroxytryptamine type 3 receptor; CINV, chemotherapy-induced nausea and vomiting; CTZ, chemoreceptor trigger zone; GI, gastrointestinal; NK, neurokinin 1; VC, vomiting center.

- While constipation is frequently an expected adverse effect from routine opioid use, other etiologies, such as stool impaction or bowel obstruction, should be ruled out if suspected.
- Constipation is the most frequently cited reason patients avoid or discontinue opioids. For opioid-induced constipation, regular use of stimulant laxatives, such as senna or bisacodyl, should be implemented. Osmotic laxatives, such as polyethylene glycol, can be added as well, provided the patient does not have evidence of bowel obstruction.
- Managing delirium, whether hyperactive or hypoactive, includes identifying and treating the underlying cause, initially with nonpharmacological interventions, followed by pharmacological use. Psychoactive medications, including benzodiazepines and dopamine antagonists, should be used sparingly in the patient with delirium, in favor of nonpharmacologic interventions. Terminal delirium is common during the end of life and should be treated more aggressively.
- Dyspnea can be common even in malignancies without lung involvement. Opioids are generally the mainstay of treatment for the feeling of breathlessness and should be titrated in a manner similar to treating pain. Therapeutic air, such as a fan blowing near the face, has shown benefit for cancer and chronic obstructive pulmonary disease patients.

HOSPICE

- Hospice is a model of care that provides compassionate support and treatment for patients with a life-limiting illness, regardless of age, religion, race, or illness. Hospice insurance benefits are covered by Medicare, Medicaid, private insurance, or managed care organizations. Services are provided for patients approaching end-of-life, designed to provide optimal comfort to a person in their home or other place of residence (such as a nursing facility or inpatient hospice unit).
- Hospice services are generally reserved for patients with advanced serious illness or malignancy with a life expectancy of 6 months or less who are no longer eligible for or decline any further DDT.
- Concurrent DDT along with hospice can be provided to the following classes of people: children up to the age of 18 years, US veterans, and patients with select private insurance companies.
- Core hospice benefits include the following:
    - Physician-directed treatment plans
    - Nursing visits for education, specialized medication administration, and wound care
    - Durable medical equipment
    - Medications
    - Social work and chaplain services, including bereavement for family and caregivers
    - Availability of a nutritionist for consultation
    - 24/7 provider availability via telephone for emergent concerns

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Central Venous Access Device

Abraham Levitin, Hannah W. Hazard-Jenkins

INTRODUCTION

Once the diagnosis of cancer has been made and the patient has undergone full evaluation, including staging resulting in the development of a plan of care for the newly diagnosed or recurrent cancer, it is prudent to assess the need for venous access. This should be undertaken early in treatment planning to avoid any delays. Most systemic treatments are administered intravenously. Factors to consider include, but are not limited to, nature of the chemotherapy medication (vesicant chemotherapy requires central venous access); length of infusion (continuous infusion requires central venous access); expected treatment duration; need for multiple simultaneous infusions; compatibility of different medications; need for apheresis; patient preference; status of patient's peripheral veins; renal function; etc. Chemotherapy administration for the cancer patient may be delivered over a more prolonged schedule with the placement of a long-term, central venous access device (CVAD). Moreover, these devices have facilitated the implementation of increasingly complex treatment regimens at home.

The rationale for placing CVADs is derived from the caustic properties of chemotherapeutic agents and the consequences of repeated venipuncture on the peripheral veins. The innermost layer of a vein is known as the tunica intima. It is this layer that becomes damaged with the repeated trauma associated with peripheral venipuncture. This damaged endothelium results in exposure of the

underlying thrombogenic layer, the tunica media, which results in platelet aggregation and subsequent thrombosis. Implanted venous access devices are either placed through a peripheral, extremity vein or into a central vein. In both circumstances, repetitive trauma to the peripheral veins is reduced. The instillation of vesicant substances is more tolerable in the central veins, as they are much less likely to infiltrate and have a much larger volume of blood flow and thicker vein walls. Once the decision has been made to place a CVAD, various factors must be taken into consideration in choosing the most appropriate site and device. These factors may include specific patient characteristics and preferences, patient history and associated comorbidities, and specific infusion needs. The many options for venous access can then be considered in a collaborative fashion.

The initial interaction with the patient should be used to evaluate the level of care they and/or their significant others will be capable of providing for whichever vascular device is ultimately selected. Moreover, lifestyle, habits, and activities should be taken into account during the selection process. Patients may prefer to have devices placed on their nondominant side to facilitate care. Devices implanted in the chest may be positioned strategically to assist in hiding them under garments and to provide for easy visualization without the need of a mirror. Consideration should be given in females to the position of bra straps and modifying placement accordingly. Additionally, patients who partake in certain recreational activities such as firearm shooting may prefer to have an implanted port positioned away from the shoulder in which the firearm rests.

A history of previous venous device placement must also be assessed as this could modify the potential available sites of catheter insertion. Preoperative ultrasound evaluation of the upper extremities, jugular, and central veins may be beneficial in patients with a history of multiple prior central venous accesses. Moreover, any prior or anticipated surgical interventions or presence of other devices such as automated implantable cardioverter defibrillators

and pacemakers should be noted. The presence of inferior vena cava (IVC) filter devices should also be noted, as this may require the use of an alternate type of access wire (ie, straight wires instead of J-curved wires). Patient allergies need to be documented to ensure compatibility of the device and procedural equipment. Finally, the physical examination is also a key part of the preoperative patient assessment. The skin at the insertion and final placement sites should be assessed for adequacy. Patients with underlying skin conditions or prior surgical sites may dictate location of implantable device. Moreover, evidence of dilated superficial veins may herald an undisclosed central venous stenosis that may complicate catheter placement and initiate further evaluation before operative intervention. Body habitus may need to be considered as well in choosing the most appropriate device. Peripheral access is to be avoided in patients with renal failure to preserve extremity veins in case of future need for hemodialysis access.

Ultimately, the type of infusion agent and the frequency needed may dictate the type of access device used. Patients in need of chronic and continuous infusion may best benefit from tunneled devices, whereas subcutaneous ports are ideal devices for patients who will only need accessed intermittently. The type of infusates used and their relative compatibilities may also be a consideration in deciding the number of lumens that may be needed in a particular device. As a general rule, the number of lumens should be limited to minimum necessary for treatment, as each additional lumen increases the risk of device thrombosis and/or infection.

INDICATIONS

Indications for venous access placement in the oncology patient are guided by complex factors that evolve during the transition from diagnosis to treatment and finally into remission. Consideration is given to the composition of the infusates being administered, the frequency of treatment (monthly, weekly, and daily), the size or number of lumens required, the patient's and family's ability to

provide care of the device, and patient's preference (which may be influenced by vanity, an appropriate consideration in the decision-making process). Additional factors to consider are the potential for daily maintenance needs such as flushing and dressing changes that may or may not be covered by insurance and patients may not be able to do on their own. For example, a bone marrow transplant patient may require a large-bore multichannel catheter for stem cell collection initially but will also need a long-term catheter for the remainder of the transplant process.

CONTRAINDICATIONS

The placement of various CVADs is associated with very few contraindications. Patients with uncontrolled coagulopathy are at risk for developing hematomas at sites of soft tissue dissection (port pocket, subcutaneous tunnel, cephalic vein cutdown), venotomy site, and around the catheter exit sites. The 2019 SIR Consensus Guidelines consider tunneled venous catheter including port-placement low risk and are safe to place with INR corrected to ≤2.0 to 3.0 and platelets ≥20 × 10^9/L. Additionally, according to the guidelines, there is no need to discontinue direct oral anticoagulant treatment prior to port or tunneled central venous catheter (CVC) insertion or removal. Every effort should be made to correct significant coagulopathy before a CVAD is placed. It is also important to realize that the subclavian vein is essentially noncompressible due to the overlying clavicle and direct pressure may not work to control catheter site bleeding. Additionally, due to the high incidence of subclavian vein stenosis and potential risk of pinched-off syndrome, subclavian vein access has fallen out of favor. The internal jugular vein is currently the preferred access for centrally inserted central venous access. Attempted access in specific vessels with known thrombosis, diagnosed by ultrasound or contrast imaging, is a contraindication and only patent vessels should be attempted to be accessed. A bloodstream infection, as demonstrated by positive blood cultures, is also a contraindication for long-term

CVADs due to the high-colonization rates and thus requiring subsequent removal. The CVAD may be placed once the infection has been adequately treated and negative blood cultures are documented for 48 hours.

Certain CVADs requiring the positioning of a device in the subcutaneous tissue of the chest may not be an appropriate option in some situations or certain types of tumors. Moreover, certain patients, such as those with cystic fibrosis, may require constant chest percussive therapy making a secondary site of placement a more viable option. These sites include the upper arm or a part of the abdomen. In addition to port placement, it is also necessary to understand the position of the catheter. For instance, in patients with head and neck cancer, presence of an internal jugular catheter may interfere with radiation and future surgical exploration. For these patients, contralateral internal jugular or arm access may be more appropriate. Similarly, for patients with breast cancer following surgery, especially axillary node dissection, access is preferable on the contralateral side.

INFUSION DEVICES

Venous access devices can be categorized into five groups based on the mechanism of insertion and catheter dwell potentials. These categories include peripherally inserted central catheters (PICCs) or midline catheters, percutaneous nontunneled central catheters, tunneled CVCs, and implanted ports. Each category is then further defined by device-specific characteristics such as flow rates, lumen size, catheter tip location, catheter tip design, and dwell time. In utilizing this process, it is easier to identify which catheter meets the specific needs of the patient in Table 41.1.

TABLE 41.1

Venous Access Devices

Type of Catheter	Indications	Limitations
Peripheral angiocatheters	Hydration, PPN, short-term access	Frequent infiltration/phlebitis, easily dislodged, short dwell time (up to 72 h) cannot be used for solutions with extreme pH or osmolarity, not for at-home patients
Midline catheters	Hydration, PPN, short-term access	Less frequent infiltration/phlebitis than angiocatheters, 2-4 wk dwell time, cannot be used for solutions with extreme pH or osmolarity, not for at-home patients
Peripherally inserted central catheters (PICCs)	Hydration, antibiotic, blood transfusions, venous sampling, chemotherapy, medication administration	Requires weekly dressing change and flushing, must keep dry at all times, limited flow rates, visible, potential for easily dislodgement, higher occlusion rate, avoid placement if potential dialysis in future, up to 12 mo dwell time
Nontunneled central venous catheters: a. Central lines b. Temporary dialysis or pheresis catheters	a. Acute care medication, larger bore, hydration, all IV medication, CVP measurements b. Hemodialysis, stem cell collection and transplant, plasmapheresis treatment	Short dwell time: 7-14 d for central lines, 1-4 wk for pheresis catheters, higher risk of infection than tunneled catheter, increased risk of dislodgement, highly visible, risk for pneumothorax, not typically used for at-home patients
Tunneled central venous catheters: a. Traditional tunneled catheter b. Tunneled dialysis catheters c. Hybrid triple-lumen tunneled catheters	a. Long-term IV medication, hydration, chemotherapy b. Hemodialysis, plasmapheresis, stem cell collection/double-lumen c. Stem cell collection, transplantation requiring triple lumen	Requires routine dressing changes and flushing, must keep site dry at all times, may be visible to others, lower risk of infection than nontunneled catheters

Type of Catheter	Indications	Limitations
Implantable ports a. Chest ports b. Arm ports	Intermittent IV access, chemotherapy, hydration, antibiotics, laboratory draws	Requires needlestick to access, difficult to access in obese patients, port may rotate and become difficult to access

CVP, central venous pressure; PPN, partial parenteral nutrition.

The use of a predictive tool such as the A-DIVA Scale (Adult Difficult Intra Venous Access Scale) may be useful to direct patients with difficult peripheral access to more advanced options. Therapeutic agents with extremes of pH (normal pH = 7.35-7.45) or osmolarity (normal 280-295 mOsm/L) should not be administered through peripheral access as the concentration of material infused can lead to patient discomfort, infiltration, clotting, and infection. One exception is peripheral parenteral nutrition in which dextrose contents are under 10%.

While not a CVAD, it is worth mentioning the peripheral intravenous angiocatheter (PIVC), as it is the simplest access to utilize. The angiocatheters are relatively easy to insert and remove; specialized training or certification is not required for insertions and most practitioners are qualified to place a PIVC. These catheters come in a variety of gauges and lengths to accommodate patients as well as large-bore peripheral catheters preferred for rapid infusion of large volumes such as venous contrast or blood products. Intermittent nonvesicant chemotherapy can be administered via peripheral access. However, reliability of obtaining access during each treatment session may be unpredictable and, if unsuccessful, may delay treatment.

Limitations of PIVCs include short dwell time (3-4 days), high thrombophlebitis rates, inadvertent dislodgement, thrombosis and shear of the vessel, infiltration into the surrounding tissue, cellulitis, and pain with infusions. As a result of these limitations, PIVCs are

reserved primarily for hospital/clinic use and management by healthcare professionals.

One subclass of peripheral angiocatheters is the *midline catheter*. With the guidance of a handheld ultrasound device, these catheters are usually inserted in the upper arm veins. The catheter is approximately 20 cm in length and is typically placed with the tip near or in the axillary vein. In this position, the catheter is not considered central and should be treated as a peripheral angiocatheter with regard to infusates. However, since the catheter tip is in a larger vessel with increased blood flow, the risk of phlebitis and infiltration is decreased as compared to peripheral angiocatheters. Typical dwell time for midline catheters is 2 to 4 weeks with careful monitoring for complications. In addition to extended dwell time, the midline catheter, unlike the PICC, does not need radiographic verification for tip placement, since it is not advanced centrally. As a result, this is a less costly means of access and simplifies positioning. Midlines are particularly beneficial in patients who would otherwise require serial placements of short PIVCs and do not need the long-term access or a PICC line.

Midline catheters do have limitations. First, their tips do not reside centrally so infusates are limited to those that are safe for PIVCs. Since the axillary vein lies deep in the axillary region, it may be difficult to identify early phlebitis, infiltration, or infection. Frequently, a blood return is not achieved for confirmation of vascular patency or specimen collection. The short intravenous catheter length compared to the external component yields increased risk of dislodgement. Midline catheters require daily flushing to maintain patency and dressing changes at least weekly, which may require home health services. Moreover, catheter-related bloodstream infection rates are similar to those of PICCs, and thrombosis rates would be expected to be higher than those of PICCs as the tip is in a smaller vein.

Peripherally Inserted Central Catheters

Hoshal first described the peripherally inserted CVC in 1975. In a case series, he described threading 61 cm silicone catheters into the superior vena cava (SVC) through the basilic or cephalic veins. Thirty of 36 catheters lasted the entire duration of treatment (up to 56 days) of total parenteral nutrition and thus successful application of the concept of central access. In current practice, a PICC is a long, flexible catheter inserted into a peripheral vein and advanced into the central circulation, typically placed into a vein of the upper arm. Alternative, off-label, access sites can include the internal or external jugular veins, the long or short saphenous veins, the temporal vein, or the posterior auricular veins. The saphenous, temporal, and posterior auricular veins are typically reserved for pediatric patients. Once the vein is cannulated, the catheter is advanced until its distal tip resides in the SVC or the IVC, depending on originating vein. The tip location of the PICC is desired in the lower third of the SVC, preferably at the junction of the right atrium with either the SVC or the IVC. The external component is secured to skin, preferably with a removable locking device or sutures. One advantage of a PICC line is that there is minimal risk to chest organs as compared to catheters placed directly in the central venous system.

PICCs come in single, dual, or triple lumens and a variety of luminal sizes. The catheters have a small outer diameter allowing for initial insertion into smaller vessels prior to advancement centrally and are radio-opaque for visualization of catheter tip placement on chest radiograph. The length of these devices can be modified to accommodate different patient body habitus.

PICCs are used for patients with poor venous access that need infusions of solutions with extreme pH or osmolarity, extended intravenous medications use (1 week to several months in duration), intermittent blood sampling, and as a respite from long-term catheters. For these purposes, PICCs are associated with greater ease and safety with insertion when compared with conventional CVCs. Moreover, PICCs also help minimize the pain associated with repeated venipuncture whether for replacement IVs or laboratory draws. Power-injectable PICCs may be utilized in patients for whom

frequent contrasted imaging studies are likely. Certified nurses can perform insertions at the bedside during inpatient hospitalization or in outpatient settings. In the past, catheter tip position needed confirmation with fluoroscopy or chest x-ray (CXR); currently, PICCs can be placed accurately with the use of intracavitary electrocardiogram without the need for fluoroscopic or CXR confirmation of catheter tip position.

There are a few potentially negative factors to take into consideration when contemplating the placement of a PICC line. PICC lines have relatively small lumen(s) and the long length of the catheter results in decreased flow rates. This is especially so with infusions of viscous solutions such as blood products and intravenous nutrition therapy. PICC lines often cannot be used for gravity-driven infusions as is frequently used in home settings. Frequent flushing of the catheter with normal saline and/or heparin lock and dressing changes weekly or more frequently may be challenging for some patients. In addition, careful attention is required to protect the exposed catheter exit site from contamination or damage, and a patient's modesty may be compromised due to visibility of the external component. There are activity limitations with PICCs that include, but are not limited to, any straining maneuvers such as heavy lifting or straining that could elevate the intrathoracic pressure leading to catheter tip migration. Migration can even occur with physiologic pressure changes during cough or forceful emesis. Submersion of the extremity in water when bathing in pools or hot tubs is forbidden secondary to increased infection risks. Patients may not be candidates for PICCs if they have had surgical alteration of vascular anatomy, lymphedema, ipsilateral radiation to the chest or arm, axillary lymph node dissection, loss of skin integrity at the anticipated insertion site, or anticipate future dialysis access needs (low glomerular filtration rate).

However, minimal PICC-related complications should be recognized. These include infection, phlebitis, vein thrombosis, catheter occlusion, catheter fracture and leak, and inadvertent removal prior to completion of therapy (Table 41.2). At baseline,

oncology patients are at increased risk for venous thrombus formation secondary to their malignancy, treatment regimen, and the trauma of catheter insertion. Various studies have shown PICCs have equivalent to higher incidence of venous thrombosis as tunneled catheters and a higher rate of vein thrombosis than ports. PICCs have a higher incidence of catheter occlusion than tunneled catheters and ports.

TABLE 41.2

Complication of Central Venous Access Devices

Complication	PICC	Nontunneled Catheter	Tunneled Catheter	Implantable Port
Arterial puncture	Rare	IJV: ~6% SCV: 0.5%-4% Without US: up to 8.4% With US: ~1%	IJV: ~6% SCV: 0.5%-4% Without US: up to 8.4% With US: ~1%	IJV: ~6% SCV: 0.5%-4% Without US: up to 8.4% With US: ~1%
Malposition	10%	Right IJV: 4.3% Left IJV: 12% Right SCV: 9.3% Left SCV: 7.3%	Right IJ: 4.3% Left IJ: 12% Right SCV: 9.3% Left SCV: 7.3%	Right IJV: 4.3% Left IJV: 12% Right SCV: 9.3% Left SCV: 7.3%
Pneumothorax	NA	IJV: 0.1%-0.2% SCV:1.5%-3.1%	IJV: 0.1%-0.2% SCV: 1.5%-3.1%	IJV: 0.1%-0.2% SCV: 1.5%-3.1%
Bacteremia	2.1/1000 catheter days	2.7/1000 catheter days	1.6/1000 catheter days	0.1/1000 catheter days
Pocket infection	NA	NA	NA	0.7%
References	26, 35, 37	26, 30, 33, 36	26, 30, 33	26, 27, 30, 33

IJV, internal jugular vein; SCV, subclavian vein; US, ultrasound.

Percutaneous CVCs

Aubaniac was the first to describe cannulation of a central vein (the subclavian) for venous access. These CVCs, either the thin flexible or the larger rigid variety, are inserted directly into the central circulation via the subclavian vein, the external jugular vein, the internal jugular vein, or the femoral vein. Catheters included in this

category include the standard CVC or temporary hemodialysis/apheresis catheters. CVCs are typically used for rapid infusion, when multiple infusates are needed simultaneously and/or for hemodynamic monitoring (central venous pressure measurement). Thus, CVCs are for use in hospitalized patients in acute care settings with typical dwell times of up to 7 days.

The nontunneled, central hemodialysis catheters are larger bore, have two lumens, and are typically used for acute hemodialysis, access after removal of an infected tunneled dialysis catheter, stem cell collection for autologous transplant, healthy donor collection, or for therapeutic apheresis. There is a hybrid nontunneled variety, Trialysis catheter, with an extra lumen for central venous access. Certified nurse practitioners, physician assistants, or physicians can place these catheters at the bedside, in a surgical suite, or in interventional radiology. Catheter exchange at the same venous site can maintain the use of a single-access site, which may be limited in hemodialysis patients or oncology patients due to prior access and thrombosis of other central access points; however, this practice should be reserved for the patient with truly limited central venous access.

Complications related to these devices include infection, bleeding, inadvertent arterial access, air embolism, pneumothorax, hemothorax, cardiac perforation with tamponade, and cardiac dysrhythmia. The cancer patient with cachexia is at increased risk for insertion complications as are patients with large body habitus or coagulopathies. Utilization of image-guided placement with ultrasound technology for venipuncture and modified Seldinger approach helps to minimize these risks. While the catheter is in place, infections, thrombosis of the accessed vein, loss of catheter lumen patency, and dislodgment can occur and consideration should be made for removal of the device if this occurs. Frequent assessment of the catheter for integrity, dislodgment, and site evaluation is required. Flushing of each catheter lumen is performed frequently for patency. The catheter exit site must be kept dry with an intact occlusive dressing and changed biweekly to minimize

infection risks. Normal saline lock is the current standard to maintain patency of CVCs as studies have shown no benefit to the use of heparin. Sodium citrate 4% or heparin lock is typically used for dialysis catheters. Accidental dislodgment of nontunneled CVCs can occur even though sutures are placed; unrecognized dislodgement can lead to life-threatening hemorrhage. Usage of these catheters and dressing changes are typically reserved for certified technicians or nurses to provide consistent management.

Tunneled Catheters

A tunneled catheter is a larger bore catheter inserted into the central circulation followed by tunneling through the subcutaneous tissue to an exit site remote from the venous access site. After tunneling, the catheter is advanced into the central circulation via the jugular vein, subclavian vein, femoral vein, or percutaneous translumbar IVC access (only in vein-compromised patients). Very rarely extreme measures such as percutaneous transhepatic, percutaneous transrenal, or direct right atrial (open surgical) access are necessary. The tip of the catheter should terminate in the SVC/right atrial junction or IVC/right atrial junction, depending on venous access origin. For optimal, long-term function, dialysis catheters should terminate in the right atrium. A retention cuff, which causes inflammation and ingrowth into the cuff, is integrated on the catheter and is positioned within the tunnel approximately 1 to 2 cm from the catheter exit site. The cuff serves as a barrier to bacteria migration along the tract into the central circulation. Additionally, the cuff helps prevent inadvertent catheter dislodgement.

Tunneled catheters can be further divided into several types: small-bore tunneled catheters such as the Hohn (Bard), traditional tunneled catheters, dialysis catheters, and hybrid tunneled catheters. Small-bore tunneled catheters are essentially PICC lines designed with a cuff and meant to be placed directly into a central vein and tunneled subcutaneously with the cuff within 1 to 2 cm of the exit site, similar to traditional tunneled central lines, except that they are of small caliber (5-6 French, come in 1-2 lumens, and are not meant

for longer than several months' use). The traditional tunneled catheters are available in single, double, or triple lumen; the best known are the Hickman (Bard), Broviac (Bard), or Groshong (Bard) catheters. These are intended for patients requiring long-term central venous access use in instances such as total parenteral nutrition, chemotherapy, chronic medication administration, transfusions, and blood sampling. The second are the dialysis catheters. These come with two lumens and are typically used for hemodialysis, but they are also utilized for stem cell collection and plasmapheresis. The final catheter type, the hybrid tunneled catheters (two lumens for apheresis and the third, smaller lumen, for central venous access, such as the trifusion [Bard] catheter) are most often used in transplant patients for stem cell collection, transplant access, or photophoresis treatments in graft-versus-host disease. These catheters are available in a variety of catheter lengths and different lumen sizes, based upon intended use. As would be expected, these catheters have lower infection rates as compared to nontunneled catheters.

Management of tunneled catheters requires flushing protocols, weekly dressing changes, and protection from inadvertent dislodgment. In addition, the patient is restricted from submersion of the catheter during bathing or swimming. The traditional tunneled catheters are flushed with normal saline and the dialysis catheters with high-dose heparin lock solution or sodium citrate 4% requiring removal of the lock prior to catheter use to prevent inadvertent systemic injection.

Complications of tunneled catheters include those associated with the insertion procedure (ie, bleeding, air embolus, pneumothorax, hemothorax, and cardiac dysrhythmia) as well as long-term issues (ie, infection, migration, thrombosis, and catheter shear). Most medical centers will stock catheter repair kits that allow for the salvage of cracked or leaking catheters; however, if prolonged continued need for access is anticipated, over-the-wire exchange may be a better long-term option. Extrusion of the cuff from the

subcutaneous position is an indication for exchange, replacement, or removal of the tunneled catheter.

Implanted Ports

The first reported fully implantable vascular access device was reported in 1982 by Gyves J et al. Since then, the use of these devices has expanded exponentially. Totally implanted ports are CVCs attached to a reservoir with a self-sealing septum, which can be repetitively accessed with a specialized needle. The reservoir is implanted into a subcutaneous pocket typically in the infraclavicular/prepectoral anterior chest wall; the attached catheter is tunneled subcutaneously and advanced into the central venous circulation. The implanted port is ideal for patients undergoing long-term intermittent or cyclic therapy. Ports are also very well suited to chemotherapy administration or venous access for laboratory draws in vein-compromised patients requiring chronic venous access. Early identification of patients who will need ports helps to facilitate placement prior to the anticipated neutropenia, weakness, and wound healing difficulties often associated with chemotherapy. Most current models of implanted ports allow power injections of contrast material for radiologic imaging (power ports). Medical device companies also promote ports with differing flow patterns or characteristics within the reservoir chamber (ie, “the port”) that claim to improve infusion, blood draws, and lower thrombosis rates. In particular, the Vortex port (angiodynamics) and the Sport/Tidal port (Norfolk Medical) tout particular design features which minimize sludging and occlusions and allow for the higher flow rates of apheresis. Compared to tunneled catheters, studies have also demonstrated up to a 10-fold advantage in long-term infection rates due to the completely implanted nature of the catheter. Nevertheless, continuous access of the port will certainly defeat this advantage. Ports provide patients with improved modesty as it is not visible, especially if the port pocket is located in a discrete location. In addition, active patients may find more freedom during deaccessed periods. These catheters have an extended dwell time of

several years or longer depending on the needs of the patient. Consideration should be given to retaining the port for a period of time after completion of therapy for use in surveillance blood testing purposes.

Patients with uncontrolled coagulopathy, bacteremia, or sepsis should have those conditions addressed prior to the placement of a new indwelling device, as with other CVADs. Some individuals with severe malnutrition or cachexia may have an extremely poor healing capacity and may be at undue risk for port erosion through the skin. These patients should undergo therapy with a PICC or other alternative until such a time when a port may be better tolerated or consider the use of a low-profile port.

As mentioned previously, the port is placed in a subcutaneous pocket most commonly in a location on the anterior chest wall, the arm, or thigh with the catheter advanced into the corresponding vein. Use of the port requires sterile preparation of the site and access with a noncoring, Huber needle to prevent damage to the reservoir. As the entire system is subcutaneous, the patient may feel a needlestick as the port is being accessed but applying topical anesthetics to the skin over the port prior to the needlestick may minimize the discomfort. While the port is accessed, it requires daily flushing and it must be flushed after each use as well. When the port is not actively being used, periodic flushes (saline flush every 3 months for valved [Groshong] ported catheters and monthly heparin flush for end hole, nonvalved ports) are required to help maintain patency. Complications associated with ports are rare and are divided into early and late events. Early complications in oncology patients include hematoma, catheter malposition, and iatrogenic pneumothorax. The incidence of these complications have been minimized with the use of ultrasound and fluoroscopic guidance during placement. Late complications are dominated by catheter thrombosis and infection; however, catheter fracture and embolization can also occur.

SPECIAL CONSIDERATIONS

Power Injection Catheters

Traditional catheters have been studied in the past for safety when power injections are done for radiographic studies with mixed results. The studies found efficacy depends on the gauge, length, and material of the catheter. Incidence of inadequate flow rates and catheter rupture due to limited pounds per square inch (PSI) restrictions outlined by the manufacturers limits the use of many catheters for power injection. However, more recent products overcome these limitations. In fact, most ports, PICCs, some traditional tunneled CVCs, and tunneled central venous Hohn catheters are now power injector compatible. One should consider power injection catheters for patients anticipated to have recurring contrast medium injection studies. Special equipment (ie, access needle) may be required for accessing power injection ports so as to prevent rupture or extravasation. One must check the hub of the catheter for which lumen is compatible with power injection, the patient's wallet card, and manufacturer's website to determine if a device is power injector compatible and at what injector rate and PSI. Some power ports are designed with a particular shape or bumps or radiopaque marker indicating power injector compatibility.

Before using standard central access devices for power injection, manufacturer's instructions should be reviewed and institutional policies should be in place to address the practice, as there may be additional training required for the staff prior to utilizing such devices to minimize complications.

Valve Technology

Ongoing clinical presentation of heparin allergies, specifically heparin-induced thrombocytopenia, has led to the development of catheters with valve technology. The valve remains closed unless acted upon by negative (aspiration) or positive (infusion) pressure.

By opposing central venous pressure and preventing the reflux of blood into the catheter tip during the cardiac cycle or changes in intrathoracic pressure that naturally occurs in everyday life, valvular technology is designed to improve patency and minimizes exposure and/or need for regular flushing of the device. Additionally, removal of a syringe after flushing or deaccessing the port can facilitate negative pressure drawing blood into the catheter. Without blood in the catheter tip, the risk of catheter occlusion related to internal clotting is thought to be eliminated. PASV (Boston Scientific Corporation, Natick, Mass.) valved implanted port and Groshong (Bard Access System, Salt Lake City, Utah) are examples of valved ports. Valve technology has been incorporated into some catheters at the distal tip or in the proximal end piece. A saline-only flush is recommended every 3 months, when the catheter is otherwise not in use.

The "Difficult Access" Patient

There is a population of patients requiring long-term access who develop venous occlusions and are left with limited options for central venous access. For these patients, it is of utmost importance to consult with a vascular access specialist, such as an interventional radiologist, prior to catheter removal for malfunction, or even non–life-threatening infection to develop a plan for maintaining long-term central venous access. If the central line is in the last available central vein, it may be more appropriate to exchange, rather than remove the catheter, or even exchange for a nontunneled line while undergoing antibiotic therapy, and then converting back to a tunneled central line, once the infection clears. Such decisions should be made in a multidisciplinary fashion with the referring oncologist, vascular access specialist, and infectious disease expert. As mentioned above, alternative central venous access routes, such as collateral venous channels, femoral, translumbar, and transhepatic routes may need to be considered for these patients.

CONCLUSION

The diagnosis of a malignancy and the subsequent rigorous treatment regime(s) are overwhelming for most patients. If venous access for administration of treatment becomes difficult, it adds to a patient's stress and anxiety during an already difficult time of their life. CVADs can and often do minimize that one aspect of a patient's care. However, care must be taken to ensure the device selected and placed is optimal for the type of treatment regime selected. Treatment factors to consider (but not limited to) include frequency of therapy administration, pH and osmolality of the medication, location of treatment (home vs hospital), and duration of therapy. Patient characteristics to take into account include comorbidities, prior line placement, history of thrombosis or thrombophlebitis, and the ability and resources to care for a device. Finally, and most importantly, the patient should be able to help select the device that is most appropriate for them based on their lifestyle and personal preferences. When selected and used appropriately, central venous devices are extremely useful to the patient and the provider, as they allow for adherence to treatment regimes while minimizing patient discomfort.

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42

Procedures in Medical Oncology

Kerry Ryan, George Carter

INTRODUCTION

Procedures performed in oncology patients may serve both diagnosis and treatment. This chapter describes common procedures performed in medical oncology, along with special considerations and techniques to assist in performing them rapidly and confidently and to keep the patient comfortable and well informed.

INFORMED CONSENT AND UNIVERSAL PROTOCOL

Written informed consent, or a legally sufficient substitute, must be obtained before every procedure described here and filed in the patient's medical record. Review patient's history and current medications to ensure there is no contraindication to the planned procedure. If appropriate for the planned procedure, mark the procedure side and perform a "time-out" to verify correct patient, correct site, and correct procedure.

ANESTHESIA

All procedures typically can be performed under local anesthesia. Lidocaine (1% mixed in a 3:1 or 5:1 ratio with $NaHCO_3$ to prevent the usual lidocaine sting) or alternative anesthetic will ensure proper anesthetic effect. For certain patients and procedures, conscious

sedation with a narcotic (fentanyl) and a benzodiazepine (midazolam) or alternatively monitored anesthesia care should be considered.

INSTRUMENTS

Most medical facilities are equipped with sterile trays or self-contained disposable kits specific to each procedure. Additional instruments may be used at the operator's discretion or preference.

PROCEDURES

Bone Marrow Aspiration and Biopsy

Indications

- Diagnosis
- Analysis of abnormal blood cell production
- Staging of hematologic and nonhematologic malignancies

Contraindications

- Only absolute contraindication is the presence of hemophilia, severe disseminated intravascular coagulopathy, or other severe bleeding disorder.
- Severe thrombocytopenia is not a contraindication. However, depending on the circumstances may transfuse for platelets <20,000.
- Skin infection at proposed site of biopsy; consider alternative site.
- Biopsy at previously radiated site may cause fibrosis; consider alternative site.
- Avoid sternal aspirate in patients younger than 12 years, with thoracic aortic aneurysm or with lytic bone disease of ribs or

sternum.

- Determine if the patient is taking an anticoagulation agent or clopidogrel. If the patient is on these medications, consider stopping them if the risk of bleeding outweighs the risk of thrombosis in the patient. Bone marrow biopsy is considered a low risk for bleeding.

Anatomy

- Sternal aspiration (not recommended as a site of biopsy due to the risk of fatal hemorrhage; if it is a chosen site, then a skilled and experienced clinician should perform the procedure):
  - Patient is supine; head is not elevated.
  - Landmarks: Sternal angle of Louis and lateral borders of sternum in second intercostal space.
- Posterior superior iliac spine aspiration and biopsy (Figure 42.1) (this is the preferred site of biopsy and aspiration):
  - Patient is prone or in lateral decubitus position.

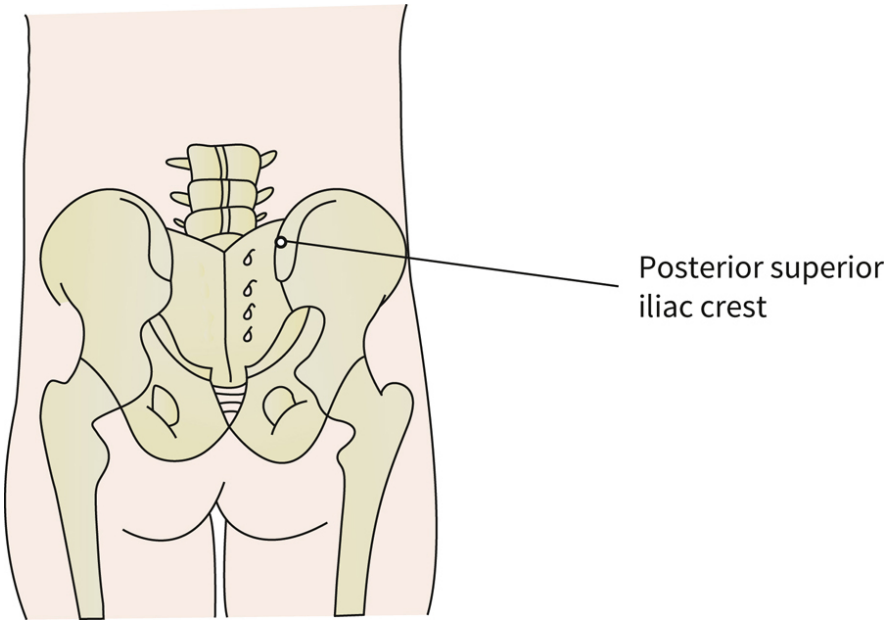

FIGURE 42.1 Biopsy site in the posterior superior iliac spine.The needle should be directed toward the anterior superior iliac spine.

- Anterior iliac crest aspiration and biopsy (consider for patients with history of radiation to pelvis or extremely obese patients):
  - Patient is supine.

Imaging Guidance

Some institutions have started performing bone marrow biopsy and aspiration of the posterior iliac crest with the use of CT guidance. Imaging guidance should be considered, particularly in obese patients, where surface anatomical landmarks may prove unreliable.

Procedure

- Posterior superior iliac spine aspiration and biopsy:
    1. The technique described here is for the Jamshidi bone marrow needle. Other available needles, such as the HS Trap System Set, Goldenberg Snarecoil, T-Lok bone marrow biopsy system, are variations of the Jamshidi with their own specific instructions. Also available is the OnControl Bone Marrow Biopsy System that utilizes a battery-powered drill to insert the needle into the iliac bone.
    2. The patient may be prone, but the lateral decubitus position is more comfortable for the patient and better for identifying anatomic sites. These positions are suitable for all but the most obese patients. For extremely obese patients or for those who have had radiation to the pelvis, aspirate and biopsy may be taken from the anterior iliac crest.
    3. Once the site has been prepared and anesthetized, make a small incision at the site of insertion, and advance the needle into the bone cortex until it is fixed. Attempt to aspirate 0.2 to 0.5 mL of marrow contents. If unsuccessful, advance the needle slightly and try again. Failure to obtain aspirate, known as a "dry tap," is often due to alterations within the marrow associated with myeloproliferative or leukemic disorders and less commonly due to faulty technique. In such case, a touch preparation of the biopsy often provides sufficient cellular material for diagnostic evaluation.
    4. Biopsy can be performed directly after aspiration without repositioning to a different site on the posterior iliac crest. Advance the needle using a twisting motion, without the obturator in place, to obtain the recommended 1.5 to 2 cm biopsy specimen. To ensure successful specimen collection, rotate the needle briskly in one direction and then the other, then gently rock the needle in four directions by exerting pressure perpendicular to the shaft with the needle capped. Gently remove the needle while rotating it in a corkscrew manner. Remove the specimen from the needle by pushing it up through the hub with a stylet, taking care to avoid needle-stick injuries. Jamshidi needle kits include a small, clear plastic guide to facilitate this process.

Aftercare

- Place a pressure dressing over the site and apply direct external pressure for 5 to 10 minutes to avoid prolonged bleeding and

hematoma formation.
- The pressure dressing should remain in place for 24 hours.
- The patient may shower after the pressure dressing is removed, but should avoid immersion in water for 1 week after the procedure to avoid infection.

Complications

Infection and hematoma are the most common complications of bone marrow biopsy and aspiration. Careful technique during and after the procedure can minimize these effects.

Lumbar Puncture

Indications

- Analysis of cerebrospinal fluid (CSF), including pressure measurement, for diagnosis and to assess adequacy of treatment
- Administration of intrathecal chemotherapy

Contraindications

- Increased intracranial pressure.
- Coagulopathy or thrombocytopenia. There are not significant data regarding the optimum platelet count at which a lumbar puncture (LP) can be performed. American National Red Cross transfusion guidelines suggested a minimum of 40,000.
- Infection near planned site of LP.
- Anticoagulation agents and clopidogrel should be discontinued before procedure and may be resumed after hemostasis is achieved.

Anatomy

- Avoid interspaces above L3 (Figure 42.2), as the conus medullaris rarely ends below L3 (L1-L2 in adults, L2-L3 in

children).

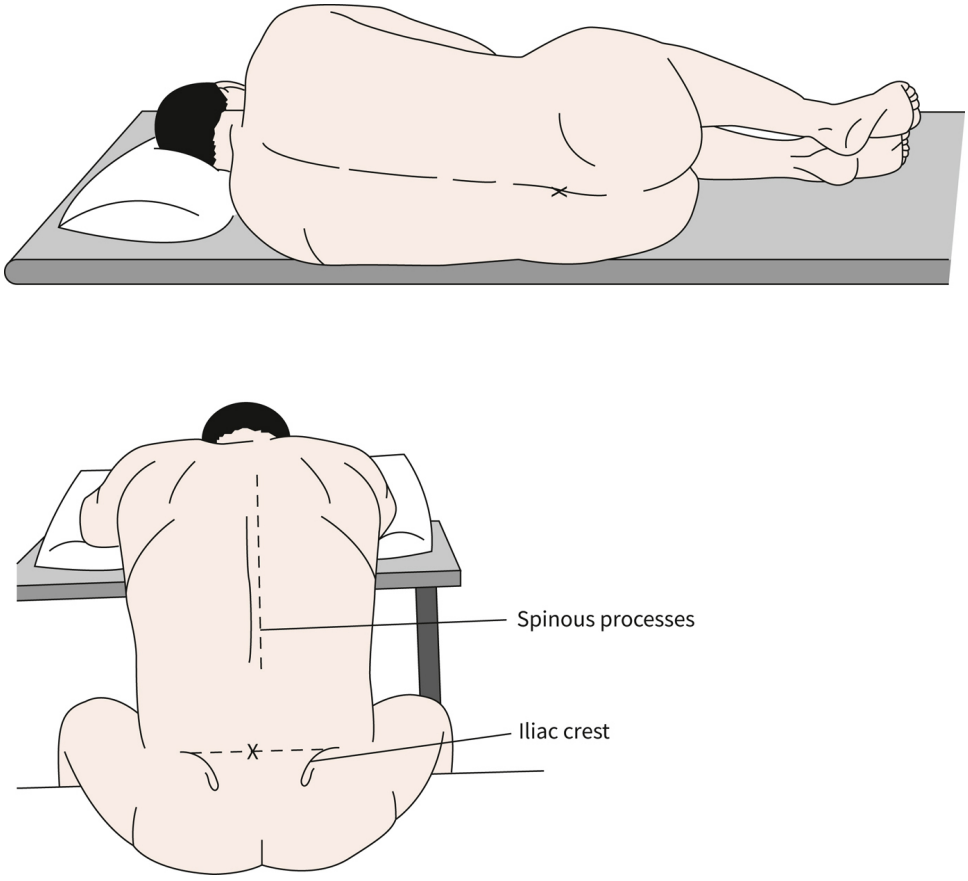

FIGURE 42.2 Anatomy of the lumbar spine.Ideal needle insertion is between L3 and L4 interspace, which can be found where the line joining the superior iliac crests intersects the spinous process of L4. Positioning of patient for lumbar puncture: in lateral decubitus or sitting positon.(Reprinted with permission from Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures*. Lippincott Williams & Wilkins; 1994:13.)

- The L4 spinous process or L4 to L5 interspace lies in the center of the supracristal plane (a line drawn between the posterior and superior iliac crests).
- There are eight layers from the skin to the subarachnoid space: skin, supraspinous ligament, interspinous ligament, ligamentum flava, epidural space, dura, subarachnoid membrane, and subarachnoid space.

Imaging Guidance

- Fluoroscopy: The fluoroscopic guidance for a LP should be considered if multiple attempts without imaging were performed and were unsuccessful. Also, it could be considered if the patient is obese or has a difficult anatomy due to prior surgery.
- Ultrasound: Ultrasound is another imaging guidance technique that can be considered for patients with difficult anatomy, particularly obesity.

Procedure

1. Describe the procedure to the patient, with assurances that you will explain what you are about to do before you do it.
2. Patient should be in a lateral decubitus or sitting position. The prone position is usually used for LPs performed under fluoroscopic guidance and will not be discussed here. The lateral decubitus position is preferable for obtaining opening pressures. The seated position may be used if the patient is obese or has difficulty remaining in the lateral decubitus position. Either seated or lying on one side, the patient should curl into a fetal position with the spine flexed to widen the gap between spinous processes (Figure 42.2).
3. Identify anatomic landmarks and the interspace to be used for the procedure. Ultrasound can be used to help identify proper landmarks; however, there are mixed data to demonstrate benefit and will not be discussed here.
4. Using sterile technique, prepare the area and one interspace above or below it with povidone-iodine solution. Drape the patient, establishing a sterile field.
5. Using 1% lidocaine/bicarbonate mixture, anesthetize the skin and deeper tissues, carefully avoiding epidural or spinal anesthesia.
6. Insert the spinal needle through the skin into the spinous ligament, keeping the needle parallel to the bed or table. Immediately angle the needle 30° to 45° cephalad. The bevel of the spinal needle should be positioned facing the patient's flank,

allowing the needle to spread rather than cut the dural sac. Advance the needle through the eight layers in small increments. With practice, an experienced operator can identify the "pop" as the needle penetrates the dura into the subarachnoid space. Even so, it is wise to remove the stylet to check for CSF before each advance of the needle.

7. When the presence of CSF is confirmed, attach a manometer (either traditional manometer or digital pressure transducer device) to the hub of the needle to measure opening pressure. Collect the minimum amount of CSF required to perform the tests being ordered, typically 8 to 15 mL of CSF is required. If special studies are required, up to 40 mL of CSF may be safely removed. Confirm with your laboratory the order of the tests that should be done on each tube, as different laboratories have different preferences.
8. Replace the stylet, withdraw the needle, observe the site for CSF leak or hemorrhage, and bandage appropriately.
9. Ease the patient into a recumbent position. Bed rest is often still done for a period of time following an LP; however, it has been established that bed rest does not decrease the incidence of headache after LP.

Complications

- Spinal headache occurs in approximately 20% of patients after LP. Incidence appears to be related to needle size and CSF leak and not to postprocedure positioning. There is no evidence that increased fluid intake prevents spinal headache. It is characterized by pounding pain in the occipital region when the patient is upright. Incidence is highest in female patients, younger patients (peak 20-40), and patients with a history of headache prior to LP. Patients should remain recumbent if possible and take over-the-counter analgesics. For severe and/or persistent spinal headache, stronger medication, caffeine, or an epidural blood patch may be indicated. Data indicate that a

Sprotte ("pencil-tipped") needle reduces the risk of post-LP headache.

- Nerve root trauma is possible but rare. A low interspace entry site reduces the risk of this complication.
- Cerebellar or medullar herniation occurs rarely in patients with increased intracranial pressure. If recognized early, this process can be reversed.
- Infection, including meningitis.
- Bleeding: A small number of red blood cells in the CSF is common. In approximately 1% to 2% of patients, serious bleeding can result in neurologic compromise from spinal hematoma. Risk is highest in patients with thrombocytopenia or serious bleeding disorders, or patients given anticoagulants immediately before or after LP.

Paracentesis

Indications

- To confirm diagnosis or assess diagnostic markers
- As treatment for ascites resulting from tumor metastasis or obstruction

Contraindications

- The complication rate for this procedure is about 1%.
- The potential benefit of therapeutic paracentesis outweighs the risk of coagulopathy. However, they should be avoided in patients with disseminated intravascular coagulation.
- Perform with caution in patients who have organomegaly, bowel obstruction, distended bladder, or intra-abdominal adhesions. Consider ultrasound guidance in these patients. Also, a nasogastric tube should be placed first in patients with bowel obstruction and a urinary catheter should be inserted in patients with urinary retention.

- Modify site location to avoid surgical scars. Surgical scars have been associated with tethering of the bowel to the abdominal wall.

Anatomy

- Identify the area of greatest abdominal dullness by percussion, or mark the area of ascites via ultrasound. Take care to avoid abdominal vasculature and viscera.

Procedure

1. Place the patient in a comfortable supine position at the edge of a bed or table.
2. Identify the area of the abdomen to be accessed (Figure 42.3). Ultrasound can be used to confirm the presence of fluid and the absence of bowel or spleen in the selected site.

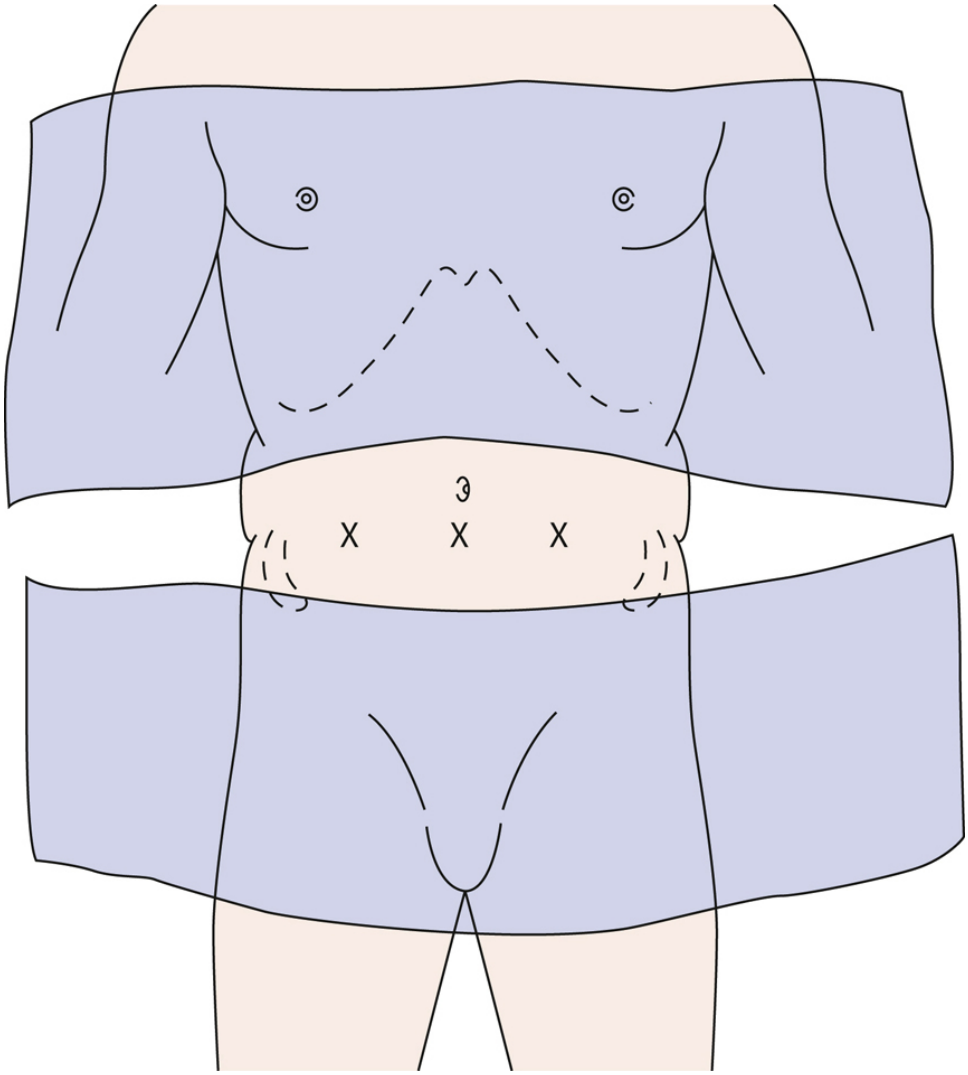

FIGURE 42.3 Sites for diagnostic paracentesis.(Reprinted with permission from Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures*. Lippincott Williams & Wilkins; 1994:46.)

3. Prepare the area with povidone-iodine solution and establish a sterile field by draping the patient.
4. Anesthetize the area with a 1% lidocaine/bicarbonate mixture.
5. For diagnostic paracentesis, insert a 22- to 25-gauge needle attached to a sterile syringe into the skin, then pull the skin laterally and advance the needle into the abdomen. Release the tension on the skin and withdraw an appropriate amount of fluid for testing. This skin retraction method creates a "Z"-track into the peritoneal cavity, which minimizes the risk of ascitic leak after the procedure (Figure 42.4).

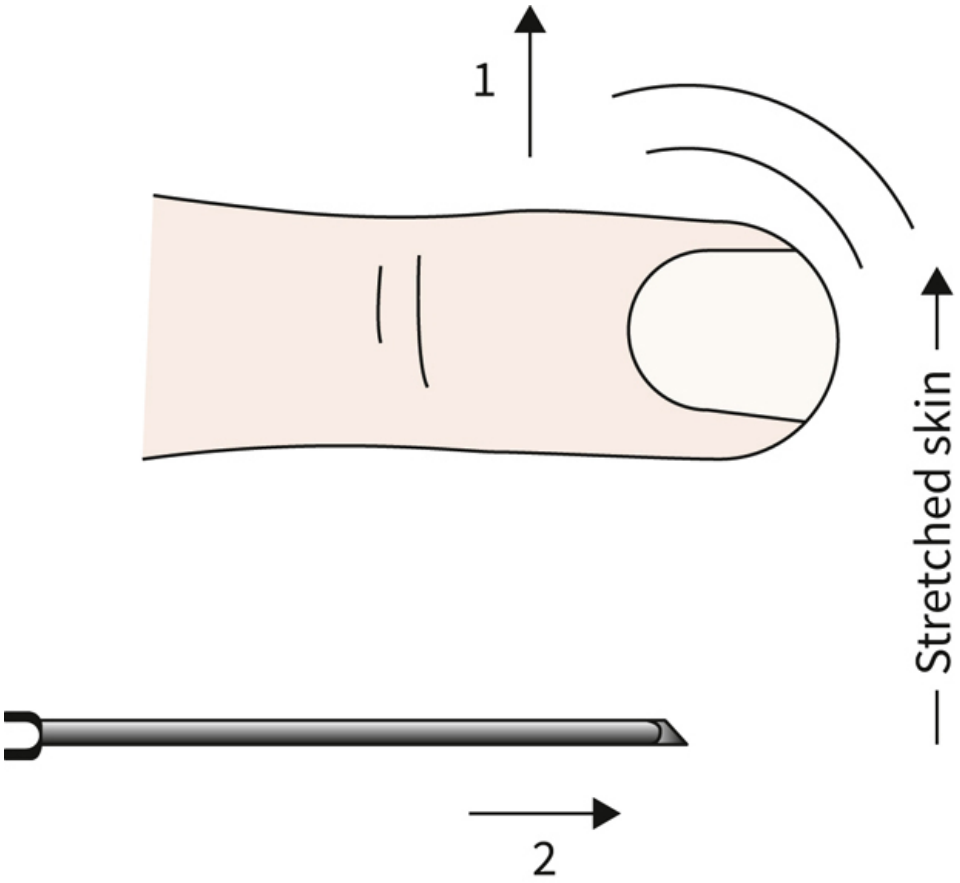

FIGURE 42.4 "Z"-track technique for inserting a needle into the peritoneal cavity.(Reprinted with permission from Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures*. Lippincott Williams & Wilkins; 1994:47.)

6. For therapeutic paracentesis, use the Z-track method with a multiple-port flexible catheter over a guide needle. When the catheter is in place, the ascites may be evacuated into multiple containers. Make sure that the patient remains hemodynamically stable while removing large amounts of ascites.
7. When the procedure is completed, withdraw the needle or catheter and, if there is no bleeding or ascitic leakage, place a pressure bandage over the site.
8. Following therapeutic paracentesis, the patient should remain supine until all vital signs are stable. Offer the patient assistance getting down from the bed or table.

9. If necessary, standard medical procedures should be used to reverse orthostasis. The patient should be hemodynamically stable before being allowed to leave the operating area.

Complications

- Hemorrhage, ascitic leak, infection, and perforated abdominal viscus have been reported. Properly siting paracentesis virtually eliminates these complications.

Thoracentesis

Indications

- Diagnostic or therapeutic removal of pleural fluid.

Contraindications

There are no absolute contraindications to diagnostic thoracentesis. Relative contraindications include the following:

- Coagulopathy and thrombocytopenia (platelets less than 50,000/μL). A decision to reverse the coagulopathy or correct the thrombocytopenia needs to be individualized, weighing the risks and benefits, as a thoracentesis is considered a low-risk bleeding procedure.
- Bullous emphysema (increased risk of pneumothorax).
- Pleural effusion less than 1 cm at its maximum depth adjacent to the parietal pleura (when ultrasound guidance is used).
- Patients on mechanical ventilation with positive end-expiratory pressure have no greater risk of developing a pneumothorax than nonventilated patients. However, mechanically ventilated patients are at greater risk of developing tension physiology or persistent air leak if a pneumothorax does occur.
- Patients unable to cooperate.
- Cellulitis, if thoracentesis would require penetrating the inflamed tissue.

Imaging Guidance

Ultrasound-guided thoracentesis has become a standard of practice in most institutions for performing a thoracentesis, as it decreases the risk of pneumothorax and has a higher sensitivity for identifying pleural effusions. An ultrasound should be used to identify the puncture site either while the procedure is being done or before the procedure is done to mark the site. If a pleural effusion is complex or loculated, CT imaging may be required.

Anatomy

- Place the patient in a seated position facing a table, arms resting on a raised pillow. Have the patient lean forward 10° to 15° to create intercostal spaces. The lateral recumbent position (with the side of the pleural effusion up) can be used if the patient is unable to sit up.
- Perform thoracentesis through the seventh or eighth intercostal space, along the posterior axillary line. With guidance of ultrasound, the procedure may be performed below the fifth rib anteriorly, the seventh rib laterally, or the ninth rib posteriorly. Without radiographic guidance, underlying organs may be injured.
- If ultrasound is not available, the extent of pleural effusion is indicated by decreased tactile fremitus and dullness to percussion. Begin percussion at the top of the chest and move downward, listening for a change in sound. When a change is noted, compare to the percussive sound in the same interspace and location on the opposite side. This will denote the upper extent of pleural effusion.

Procedure

1. After the appropriate site has been identified either by ultrasound or physical examination, position the patient and clean the site with antiseptic. Initially, infiltrate the epidermis

using a 25-gauge needle and 1% or 2% lidocaine. Next, with a syringe attached to a 22-gauge needle, advance toward the rib and then "walk" over the superior edge of the rib (Figure 42.5). This decreases the risk of injury to the neurovascular bundle. Aspirate frequently to ensure that no vessel has been pierced and to determine the distance from the skin to the pleural fluid. When pleural fluid is aspirated, remove the anesthesia needle and note the depth of penetration.

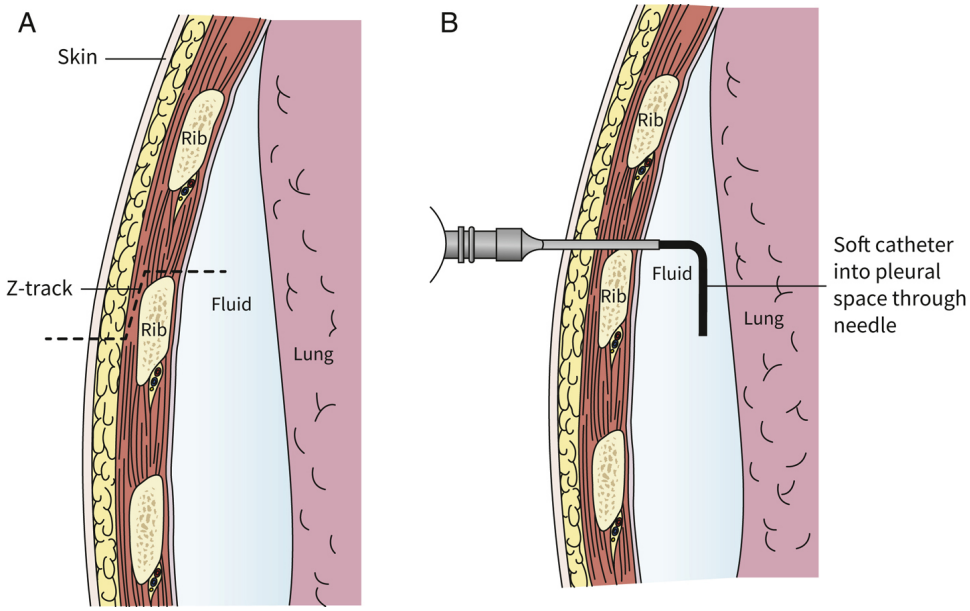

FIGURE 42.5 Thoracentesis. **A,** "Z"-track technique for anesthetizing to prevent injury to neurovascular bundle. **B,** Advancement of soft plastic catheter through the needle into pleural space.(Reprinted with permission from Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures*. Lippincott Williams & Wilkins; 1994:26, 27.)

2. A small incision may be needed to pass a larger gauge thoracentesis needle into the pleural space. Generally, a 16- to 19-gauge needle with intracath is inserted just far enough to obtain pleural fluid. Fluid that is bloody or different in appearance from the fluid obtained with the anesthesia needle may be an indication of vessel injury. In this case, the procedure must be stopped. If there is no apparent change in the pleural fluid aspirated, advance the flexible intracath and withdraw the

needle to avoid puncturing the lung as the fluid is drained. Using a flexible intracath with a three-way stopcock allows for removal of a large volume of fluid with less risk of pneumothorax. If only a small sample of pleural fluid is needed, a 22-gauge needle connected to an airtight three-way stopcock is sufficient. Attach tubing to the three-way stopcock and drain fluid manually or using a Vacutainer. Withdrawing more than 1000 mL per procedure requires careful monitoring of the patient's hemodynamic status. As the needle is withdrawn, have the patient hum or do the Valsalva maneuver to increase intrathoracic pressure and lower the risk of pneumothorax.

3. After the procedure, obtain a chest radiograph to determine the amount of remaining fluid, to assess lung parenchyma, and to check for pneumothorax. Small pneumothoraces do not require treatment, whereas pneumothoraces involving >50% lung collapse do.

Complications

- Pneumothorax
- Air embolism (rare)
- Infection
- Pain at puncture site
- Bleeding
- Splenic or liver puncture

Suggested Readings

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Basic Principles of Radiation Oncology

Crystal Seldon, Chirag Shah

INTRODUCTION

Radiation therapy represents an essential modality in the treatment of patients with malignancy and differs significantly from other commonly used modalities such as surgery and systemic therapy in its delivery and mechanism of action. It can be used as definitive therapy alone (eg, prostate cancer), in conjunction with chemotherapy (eg, lung cancer), prior to or as adjuvant therapy with surgery (eg, esophageal and breast cancer), for benign disease (eg, keloids), or for palliation (eg, bone and brain metastases). The purpose of this chapter is to provide a review of the basics of radiation oncology, including an introduction to radiation biology and radiation physics, a summary of patient workflow and treatment delivery, and finally, an evaluation of alternative radiation techniques beyond conventional external beam radiation therapy.

RADIATION BIOLOGY AND PHYSICS

Radiation therapy is primarily delivered using external beam radiation therapy via a linear accelerator with the predominant treatment method being high-energy photons or x-rays (MV energy). These photons represent ionizing radiation and are part of the electromagnetic spectrum. Alternatives to photons exist including electrons and to a lesser degree protons and neutrons. Photon-based

radiation therapy is considered indirectly ionizing in that it does not produce damage directly, for the most part, but instead has its energy transferred to secondary particles (usually electrons) which produce DNA damage. This primarily occurs through the Compton process for photons. Heavy charged particles, though rarely used in therapeutic radiation centers at this time, are directly ionizing and can cause damage without secondary particles. Radiation therapy causes biologic effects through DNA damage, in particular double-stranded DNA breaks. DNA damage occurs through interactions between particles and DNA, which can occur directly or indirectly. Direct action occurs when the photon transfers energy to an electron, which subsequently interacts with the DNA. Indirect action occurs when the secondary electron interacts to produce free radicals, which can then damage DNA. Photon-based radiation therapy works primarily through indirect action, while heavy charged particles work primarily through direct action.

Radiation therapy is typically delivered via fractionation, with multiple small radiation doses delivered, allowing for a higher total dose, which increases tumor control probability while reducing the risk of significant toxicity by allowing for repair of normal cells. It should be noted that with improvements in treatment planning, treatment delivery, and image guidance, there is a renewed interest in hypofractionation (larger doses per fraction). Further, the development of stereotactic body radiotherapy (SBRT) allows for the delivery of radiation therapy in 5 fractions or less using large doses per fraction with smaller targets and less dose to normal tissues.

The four fundamental radiobiologic principles guiding standard fractionation and clinical radiation oncology are (1) Repair, (2) Reassortment, (3) Repopulation, and (4) Reoxygenation. Repair is essential and one of the key reasons for fractionation. After receiving photon-based radiation therapy, normal tissue cells are able to repair sublethal damage, limiting toxicity, while cancer cells are limited in their abilities to repair sublethal damage, allowing for an improvement in the therapeutic ratio with fractionation. Reassortment is important because cancer cells have varying degrees

of radiosensitivity based on the stage of the cell cycle they are in, with the G2-M phase being the most radiosensitive and S phase being the least sensitive. As such, fractionation allows for reassortment of cells into more radiosensitive phases of the cell cycle, enhancing cell kill. Repopulation is important for two reasons. Repopulation with fractionation allows for normal tissues to recover if an adequate time interval is introduced. More importantly, some malignancies have been shown to clinically demonstrate repopulation (eg, head and neck cancer, cervical cancer) during treatment requiring clinicians to complete treatment within a certain duration of time or risk suboptimal local control and outcome. Finally, reoxygenation represents a key principle of radiation sensitivity and damage. As most radiation is delivered with photons, the primary mechanism of DNA damage is indirect action via free radicals. The presence of oxygen allows "fixation" of the DNA damage caused by free radicals enhancing the impact of the radiation. Fractionation enhances reoxygenation, increasing radiation sensitivity of tumors.

TREATMENT WORKFLOW AND DELIVERY

Regardless of treatment location, radiation oncology workflows are consistent. Patients are initially seen in consultation to discuss the role of radiation therapy and inform patients regarding the potential benefits of treatment as well as acute, subacute, and chronic toxicities associated with treatment to allow for informed decision-making. This is followed by the process of radiation therapy planning which proceeds with a simulation or planning scan. The simulation typically consists of some form of imaging. Traditionally, this was done with two-dimensional films or fluoroscopy but has been replaced primarily with a computed tomography (CT) simulator and CT scan. At this time, immobilization is created to achieve reproducible patient positioning, depending on location (eg, mask for central nervous system [CNS] and head and neck cases). Immobilization can also be dependent on the type of treatment; for

example, more rigid immobilization may be used when high-dose treatments (eg, SBRT) are performed. At the time of simulation, contrast can be used to enhance assessment of vasculature and lymph nodes. Four-dimensional (4D) scans are performed to assess the impact of respiratory motion on target and organ at risk volumes. The patient is scanned and an isocenter is placed. Additionally, tattoos are commonly placed to facilitate patient setup daily. There has been growing utilization of magnetic resonance imaging (MRI) simulation where the patient undergoes a CT scan and an MRI in the treatment position to assist with target delineation. There remain some radiation indications where a "clinical" simulation is performed on the treatment machine, but these are limited.

Once simulation is complete, the images obtained are transferred to a treatment planning program. The physician will then draw in contours or volumes for the target including the gross tumor volume, the clinical target volume, and the planning target volume based on physical examination, imaging, and any other procedures (eg, colonoscopy, esophagogastroduodenoscopy, nasopharyngoscopy). Additionally, if a 4D scan is performed, an internal target volume can be created to assess for variations in organ motion and position. Contours are also made for all critical normal tissue structures in the treatment field. A radiation plan is then created by a dosimetrist and reviewed by the physician. Once approved by the physician, a medical physicist reviews the treatment plan, and it undergoes quality assurance checks based on the radiation technique utilized.

Modern radiation therapy is typically delivered with a linear accelerator. A linear accelerator generates high-energy photons by accelerating electrons and having them approach a metal target. The x-rays/photons are primarily produced when the electrons are deflected (Bremsstrahlung radiation). Additionally, electrons can be used as the therapeutic particle when the metal target is removed. Electrons are commonly utilized for superficial lesions (eg, skin cancers) or shallow targets (eg, tumor bed boost in breast cancer).

Inside the head of the linear accelerator are several structures designed to allow for safe and efficient treatment delivery. In patients treated with photons, beyond the x-ray target is a flattening filter, which creates a more uniform radiation field, ion chambers, which measure radiation dose, and subsequently jaws, which can shape the beam. There is a light-field system to visualize the treatment field as well as an optical distance indicator used to measure the source to surface distance. Modern linear accelerators also include a multileaf collimator, which can be used to shape the beam. A similar set of structures is noted for electron treatments with the exception of the target being removed and the use of scattering foils rather than flattening filters. Radiation therapists perform treatment delivery; treatment plans created in the treatment planning system are sent to information systems that communicate with the linear accelerator while also serving as an electronic medical record to document daily treatment.

Multiple treatment techniques can be utilized to deliver external beam radiation therapy. Modern radiation therapy primarily utilizes a CT simulator for treatment planning and therefore a three-dimensional (3D) approach. Beams can then be shaped using the jaws in the linear accelerator or with leaves within a multileaf collimator. Such approaches are known as 3D conformal radiotherapy (3D-CRT). Over the past 2 decades, an alternative technique to 3D-CRT has emerged known as intensity-modulated radiation therapy (IMRT). IMRT allows for the modulation of the intensity of the beam, providing clinicians with the ability to preferentially give dose to one area while sparing another. This is accomplished through inverse treatment planning algorithms where the treatment planning system is provided dose constraints for the target and normal tissue structures (with weighting for each objective provided), as well as beam angles. IMRT is routinely performed in the treatment of many different malignancies including CNS malignancies, head and neck cancers, cancers of the thorax and abdomen, sarcomas, genitourinary, and gynecologic malignancies.

External beam radiation therapy can be utilized in many different scenarios. Definitive radiation therapy can be utilized in the management of some CNS tumors, lymphomas, early-stage lung cancers, and prostate cancers. Definitive radiation in conjunction with chemotherapy can also be utilized in the treatment of some CNS malignancies, head and neck cancers, inoperable advanced lung cancers, esophageal cancers, pancreas cancers, gynecologic malignancies, and bladder cancers, allowing for organ preservation and the potential for improved toxicity and quality of life. Radiation therapy can also be delivered pre- or postoperatively for patients at high risk for recurrence or residual microscopic disease before or after surgery. As adjuvant therapy, this is most commonly seen in breast cancers but is also used in CNS malignancies, head and neck cancers, pancreatic cancer, sarcomas, genitourinary, and gynecologic malignancies.

Radiation therapy can also be utilized for palliation, most commonly for bone metastases, brain metastases, lung masses, and bleeding. Common oncologic emergencies where radiation therapy is utilized include spinal cord compression, airway compromise, superior vena cava syndrome, and symptomatic brain metastases not amenable to surgery. Radiosensitizers can be used with radiation therapy to increase the response to treatment. Clinically, this is most commonly performed with the addition of concurrent chemotherapy. However, alternatives have been studied including halogenated pyrimidines and hypoxic radiosensitizers though both are used sparingly in the clinic at this time. Radioprotectors, compounds that protect the body from radiation, have also been explored. At this time, the only clinically utilized radioprotector is amifostine, which is utilized to prevent xerostomia with data demonstrating no difference in clinical oncologic outcomes when using the compound in head and neck cancers.

Radiation therapy can be associated with acute, subacute, and chronic toxicities. The most common toxicities noted during treatment are fatigue and skin erythema/irritation. Additional acute toxicities are typically dependent on the area of the body being

irradiated. Common acute and subacute side effects are listed based on treatment site: CNS (headache, nausea, alopecia, tinnitus), head and neck (mucositis, xerostomia, altered tasted, dysphagia), thorax (esophagitis, pneumonitis), gastrointestinal (nausea, vomiting, diarrhea), genitourinary/gynecologic (urinary frequency/urgency, dysuria, diarrhea, vaginal irritation). Acute and subacute side effects tend to resolve within weeks to months of the completion of treatment. Chronic toxicities can be long-lasting; however, the use of normal tissue toxicity constraints can limit the risk of chronic toxicities based on treatment site.

ADDITIONAL TECHNIQUES

As noted above, stereotactic radiation therapy is a technique that allows for the delivery of highly conformal radiation, allowing for large doses per fraction. With respect to terminology, stereotactic radiosurgery (SRS) is usually associated with a single fraction while stereotactic body radiation therapy (SBRT) typically is more than one fraction and usually up to 5 fractions. SRS is best known for its use in the CNS and can be performed with a linear accelerator or more specialized treatment machine (eg, Gamma Knife). While most commonly associated with the treatment of brain metastases, SRS can also be used for pituitary adenomas, trigeminal neuralgia, acoustic neuromas, meningiomas, and arteriovenous malformations as well. More recently, SRS has been incorporated into the management of spine metastases as well, replacing standard radiation therapy in some cases, and offering the potential for improved local control and pain control.

SBRT is most commonly associated with treatment of inoperable early-stage non–small cell lung cancers. Promising initial data from Indiana University led to a multi-institutional study, which confirmed excellent rates of local control and an acceptable toxicity profile. Moving forward, current trials are evaluating optimal dose and fractionation schemes for peripheral and central tumors as well as comparing SBRT to surgery in operable patients. SBRT is also

being utilized in the management of prostate cancer with studies demonstrating the safety and efficacy of the approach as compared to external beam and brachytherapy. More recently, SBRT has been utilized to treat liver metastases and hepatocellular carcinoma with encouraging preliminary outcomes with respect to local control and liver toxicity as well as pancreatic cancers. Additionally, SBRT is being evaluated in a number of treatment sites for recurrences including soft tissue sarcoma and head and neck cancers.

Brachytherapy is a radiation therapy technique where radioactive sources are implanted on or inside a patient. Brachytherapy can be performed with low-dose rate (LDR) implants typically associated with prostate seed implants, or high-dose rate (HDR) implants typically associated with temporary gynecologic or breast implants. Brachytherapy is a commonly utilized treatment in the management of prostate cancer. As noted above, many are familiar with LDR brachytherapy for prostate cancer with excellent clinical outcomes and toxicity profiles reported. Additionally, increasing data are available supporting HDR brachytherapy in prostate cancer, which unlike LDR allows for modulation of dose, once catheters are in place and the potential for improved toxicity profiles. While treatment with brachytherapy in prostate cancer is primarily monotherapy, data are available on the use of brachytherapy boost in patients with higher risk prostate cancer.

Brachytherapy has also emerged as a standard of care treatment option in appropriately selected women with early stage breast cancer via accelerated partial breast irradiation (APBI), which treats the lumpectomy cavity with a margin. Initial studies evaluated that APBI used multicatheter interstitial HDR; however, more recent studies have evaluated single-entry applicators, increasing the ability for patients to receive this treatment. At this time, multiple randomized trials comparing brachytherapy with standard whole breast irradiation have been performed, with no difference in local recurrence noted. Intraoperative radiation therapy represents a form of partial breast irradiation different from APBI and can be delivered with multiple techniques at the time of surgery; however, two

randomized trials evaluating the technique have demonstrated increased rates of local recurrence compared with whole breast irradiation, and as such, this technique should not be considered off-protocol at this time. Brachytherapy remains an essential component in the management of gynecologic cancers. In patients with endometrial cancer, postoperative vaginal cylinder brachytherapy is routinely used based on clinical and pathologic factors, while brachytherapy remains essential in the management of cervical cancers. Brachytherapy can also be utilized in head and neck cancers, as well as soft tissue sarcomas.

Traditionally, radiation therapy was delivered with photons (high energy x-rays) or electrons for superficial treatments. Photons, which are the most commonly utilized form of radiation therapy, are uncharged and are known for characteristics including the need for a buildup region and dose deposition over several centimeters. Protons, on the other hand, are different than photons in that the majority of dose is deposited within a small range (few millimeters) known as the Bragg peak, which can be modulated by changing the energy of the protons. It should be noted, however, this range is typically too small for a true Bragg peak, and as such, a spread-out Bragg peak is used. The biology of protons is considered similar to photons with the advantage being primarily improved dose distribution rather than greater biologic effect as seen with neutrons for example. While previously limited to a few centers throughout the United States, a significant expansion in the number of proton centers has occurred. One of the challenges associated with proton therapy is the amount of resources required to deliver treatment and therefore, the cost of treatment. However, proton therapy is particularly attractive for pediatric malignancies with data available supporting the utilization of protons in pediatric cancers, particularly CNS malignancies.

With respect to other malignancies, much has been made of the role of protons in the management of prostate cancer. However, at this time, the data do not support the utilization of this technology in the management of prostate cancer and should be only performed

on-protocol. Similarly, there are limited data supporting the role of protons in breast cancer with data demonstrating increased acute toxicities and no difference in outcomes. There are data which suggest that protons can be used for APBI and may be cost-effective; however, the limited number of patients treated with this technique mandates further study before patients are routinely treated off-protocol. Moving forward, further technological advances including intensity-modulated proton therapy and advanced image guidance may allow for further improvement in outcomes with proton therapy. In light of the limited data suggesting comparable or improved outcomes and the lack of data demonstrating cost-effectiveness, outside of accepted indications (eg, pediatric cancers), proton therapy should be limited to use on-protocol primarily.

OLIGOMETASTATIC DISEASE

There is widespread heterogeneity in the definition of oligometastatic disease (OMD); however, it is known as the intermediate phase between local disease and widespread metastatic disease. OMD can be further subdivided into synchronous, de novo presentation of a primary cancer with limited metastases, or metachronous, new metastatic lesions after prior detection of a primary tumor. With the advancement of pharmacotherapy, surgical techniques, and radiation modalities, treatment of this state has gained increasing significance as studies have demonstrated improved outcomes in multiple cancer types. Given the increasing interest in curative intent therapy in this setting, the European Society for Therapeutic Radiology and Oncology and the American Society of Clinical Oncology formed a consensus on how to define OMD. Per these guidelines, OMD that is amenable to curative radiation therapy can be defined as one to five metastatic lesions, in which all metastatic sites can be safely treated with or without a controlled primary.

SBRT is increasingly utilized in the treatment of OMD. Several studies have demonstrated that SBRT increases survival and

progression-free survival in numerous cancer types and is also a safe treatment to receive. Future studies are underway, such as NRG-LU002 and NRG-BR002, which will shed light on curative intent radiation therapy for OMD as well as develop prognostic and predictive biomarkers to aid in forming treatment decisions.

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Clinical Genetics

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INTRODUCTION

Clinical genetics is the specialty that oversees the diagnosis and management of hereditary disorders. For the oncology healthcare provider, recognition of these syndromes is critical in order to provide proper care related to cancer therapy decisions, to identify other risks for that patient, and to counsel family members about risks and options. Hereditary cancers are important to detect because the age of onset is early, multiple primary cancers can develop, and cancer predisposition may be inherited. Hereditary syndromes account for only a minority of cases of cancer, but those who are affected have extremely high risks. Patients at increased risk may benefit from enhanced surveillance, chemopreventive strategies, or risk-reducing surgeries.

If a hereditary cancer syndrome is suspected (Table 44.1), a focused examination should be performed that is specific to the syndrome (ie, dermatologic and head circumference for *PTEN*-hamartoma tumor syndrome), to include genetic counseling with an expanded pedigree detailing the types of cancer, bilaterality, age at diagnosis, ethnicity, and medical record documentation as needed (ie, pathology reports of primary cancers or carcinogen exposure). Prior to genetic testing, patients must give informed consent with an understanding of the benefits, risks, and limitations of testing as well as the goals for cancer family risk assessment in alignment with the American Society of Clinical Oncology policy statement on genetic

testing. Options for family planning include preimplantation genetic testing and prenatal diagnosis. Patients should be made aware of the Genetic Information Nondiscrimination Act of 2008, which prohibits employment and health insurance discrimination based on genetic information.

TABLE 44.1
The Most Common Hereditary Cancer Syndromes

Syndrome	Gene	Associated Cancers/Tumors
Birt-Hogg-Dube	*FLCN*	RCC
Familial adenomatous polyposis	*APC*	Colon, gastric, small bowel, thyroid, brain
Familial medullary thyroid cancer	*RET*	Medullary thyroid
Familial papillary renal cancer	*MET*	Type 1 papillary RCC
Fanconi anemia	Multiple genes including biallelic *BRCA2* mutations; diagnosis is made by increased chromosomal breakage in lymphocytes cultured in the presence of DNA cross-linking agents	AML, MDS, solid tumor especially squamous cell carcinoma of the head and neck or vulva. Breast cancer if associated with biallelic *BRCA2* mutations
Gorlin syndrome	*PTCH*	Basal cell, medulloblastoma
Hereditary breast and ovarian cancer syndrome	*BRCA1*	Breast, ovarian (prostate, pancreatic, male breast)
	BRCA2	Breast, ovarian, prostate, pancreatic, melanoma, male breast
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric cancer, lobular breast cancer
Hereditary leiomyomatosis	*FH*	Type 2 papillary RCC
Hereditary melanoma	*CDKN2A, CDK4*	Melanoma, pancreas

Syndrome	Gene	Associated Cancers/Tumors
Juvenile polyposis syndrome	*BMPR1A, SMAD4*	Juvenile/hamartomatous gastrointestinal polyposis, colorectal, gastric, hereditary hemorrhagic telangiectasia (*SMAD4* only)
Li–Fraumeni syndrome	*TP53*	Breast, sarcoma, leukemia, brain tumors, adrenocortical carcinoma, lung bronchoalveolar
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Colon, endometrial, ovarian, gastric, small bowel, biliary, pancreatic, upper urinary tract, skin, brain
Multiple endocrine neoplasia type 1	*MEN1*	Parathyroid, pituitary, pancreatic, or extrapancreatic
Multiple endocrine neoplasia type 2A	*RET*	Medullary thyroid, pheochromocytoma, parathyroid
Multiple endocrine neoplasia type 2B	*RET*	Medullary thyroid, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas
MUTYH-associated polyposis	*MUTYH*	Similar to FAP
PALB2	*PALB2*	Breast, pancreatic, ovary, male breast
Peutz-Jeghers syndrome	*STK11*	Colon/rectum, breast, stomach, small bowel, pancreas, lung, cervix, ovaries, testicles
PTEN-hamartoma tumor syndrome	*PTEN*	Breast, endometrial, thyroid, kidney, melanoma, and colorectal
Von Hippel–Lindau disease	*VHL*	Clear cell RCC, pheochromocytomas, neuroendocrine

Genetic counseling approaches are used to identify hereditary cancer syndromes. A detailed, four-generation family tree is elicited, and this information, together with the personal history of the

patient, determines whether the presentation is most suggestive of sporadic, familial, or hereditary cancer. This comprehensive risk assessment ensures that the correct genetic testing is offered to the most appropriate patients, with personalized interpretation of results and provision of future management recommendations. Guidelines are available for management of many syndromes.

In this chapter, we will review the most commonly seen and tested hereditary cancer syndromes in adults.

HEREDITARY BREAST CANCER SYNDROMES

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast cancer accounts for 5% to 10% of all breast cancers. The most common hereditary breast cancer syndrome involves pathogenic variants in the *BRCA1/2* genes, two tumor suppressor genes that play a role in double-stranded DNA repair. These mutations account for 65% of hereditary breast cancers and demonstrate an autosomal dominant pattern of inheritance. The incidence is 1 in 280 for the general population but 1 in 40 in the Ashkenazi Jewish population.

Pathogenic variants in these genes are associated with significantly elevated risks of both breast cancer (up to 70%) and ovarian cancer (up to 44%), as well as earlier age of onset of both cancers. The *BRCA1* gene is frequently associated with triple-negative breast cancer histology and both genes are associated with serous ovarian cancer. The risk of other cancers is higher, particularly in patients with *BRCA2* gene mutations. Per guidelines set forth by the National Comprehensive Cancer Network (NCCN), *BRCA1/2* testing is recommended in individuals:

- from a family with a known pathogenic variant in *BRCA1* or *BRCA2*;

- with interest in multigene panel testing and who meet the criteria listed below but whose previous limited testing was negative;
- with a personal history of breast cancer and either:
    - diagnosed at the age of 45 years or younger; or
    - diagnosed between the age of 46 and 50 years with:
        - unknown family history
        - a second breast cancer diagnosed at any age; or
        - at least one blood relative with breast, ovarian, pancreatic, or prostate cancer at any age; or
    - with triple negative breast cancer at any age
    - diagnosed with breast cancer at any age with:
        - associated Ashkenazi ancestry
        - one or more close blood relatives with breast cancer diagnosed at the age of 50 years or younger; or male breast cancer
        - ovarian, pancreatic, metastatic, intraductal or cribriform histology, or high- or very-high-risk prostate cancer at any age; or
    - two or more close blood relatives with either breast or prostate cancer at any age
    - with breast cancer diagnoses in three or more close blood relatives, including the patient; or
- Diagnosed at any age with male breast cancer; or
- With epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; or
- With exocrine pancreatic cancer at any age; or
- With prostate cancer at any age and associated:
    - metastatic disease, intraductal/cribriform histology, or at high to very-high risk; or
    - close relatives (one or more) with breast cancer at the age of 50 years or younger; or
    - relatives with ovarian, pancreatic, or metastatic or intraductal/cribriform prostate cancer at any age; or
    - two or more close relatives with either breast or prostate cancer (any grade) at any age;
- a mutation identified on genomic testing of the tumor that has critical implications if also identified in the genome; or
- an individual who meets Li-Fraumeni syndrome (LFS) or Cowden/PTEN hamartoma tumor syndrome testing criteria to aid decision-making for systemic therapies for HER-2 negative metastatic breast cancer, among other diagnostic and potentially therapeutic scenarios.
- Testing is also recommended:
    - to aid in systemic treatment decisions using PARP inhibitors in the metastatic setting;

- to aid in adjuvant treatment decisions with olaparib for high-risk, HER-2 negative breast cancer;
- lobular breast cancer with a personal or family history of diffuse gastric cancer.

As with all hereditary syndromes, testing of unaffected individuals should be considered only when an affected family member is unavailable or unwilling to test, and the family history identifies a first- or second-degree relative who meets the above criteria. In this circumstance, the significant limitations of interpreting results must be addressed prior to testing as negative test results in an unaffected individual will be categorized as uninformative.

When a *BRCA* pathogenic variant is found, options for risk management include enhanced surveillance, chemoprevention, and sometimes risk-reducing surgery. Breast self-awareness is recommended starting at the age of 18 years. Women should be familiar with their breasts and report changes to their healthcare provider. Periodic, consistent breast self-examination (BSE) may facilitate breast self-awareness. Clinical breast examination is recommended every 6 to 12 months starting at the age of 25 years. Annual magnetic resonance imaging (MRI) screening is recommended from the age of 25 years until the age of 75 years, and annual screening mammograms should begin at 30. MRI has been shown to be more sensitive for cancer detection in this population. Risk-reducing mastectomy (RRM) can reduce the risk of breast cancer by >90%. Counseling should include discussions about the degree of protection, reconstructive options, and surgical risks. The data on use of tamoxifen for prevention in this population are limited, but they do suggest a possible reduction of ER+ disease in patients with a *BRCA2* mutation but the numbers were small and did not reach statistical significance.

Given the elevated risk for ovarian cancer and the lack of effective screening, and given the fact that it may reduce breast cancer risk by 50% to 55%, risk-reducing salpingoophorectomy (RRSO) is recommended between the ages of 35 and 40 years for *BRCA1*, or upon completion of childbearing. This has been the only

intervention thus far shown to reduce overall mortality. Because ovarian cancers occur in patients with *BRCA2* mutations an average of 8 to 10 years later than in patients with *BRCA1* mutations, it is reasonable to delay RRSO until the age of 40 to 45 years in patients with *BRCA2* mutations. Counseling includes discussions of reproduction preferences, tolerance of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone therapy to the time of natural menopause, and related medical issues. Though the majority of serous ovarian cancers are felt to originate in the fallopian tubes, and clinical trials are ongoing, salpingectomy alone (with or without delayed oophorectomy) is not currently standard of care for risk reduction. In addition, it is important to note that in premenopausal women, oophorectomy reduces the risk of developing breast cancer in *BRCA* carriers by 50% to 55% depending upon the patient's age at the time of the procedure. For those patients who elect not to undergo RRSO, data do not support routine ovarian screening and can lead to a false sense of reassurance for both patients and providers. Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific to support a positive recommendation but may be considered at the clinician's discretion starting at the age of 30 to 35 years. Serum CA125 may also be offered with caveats similar to those of transvaginal ultrasounds.

The risk of breast cancer for men with BRCA1 is ~1%, with a higher risk (~7%) in male *BRCA2* carriers. Annual clinical breast examination in this population should start at the age of 35 years. Consideration of annual screening mammography is recommended either at the age of 50 or 10 years earlier than the first affected male breast cancer in the family. Prostate cancer screening is recommended for *BRCA2* carriers starting at the age of 40 years and should be considered for *BRCA1* carriers at the age of 40 years. No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized depending on cancers observed in the family.

Pancreatic cancer screening is most commonly offered to patients with a known pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*) and a family history of pancreatic cancer in a first-degree relative. Pancreatic cancer screening can be offered to patients with *STK11* or *CDKN2A* even without family history. No specific guidelines exist for melanoma.

PTEN-Hamartoma Tumor Syndrome

PTEN-hamartoma tumor syndrome (PHTS) is a genetic diagnosis that encompasses two conditions: Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. An autosomal dominant syndrome with an incidence of 1 in 200,000, it is caused by a loss of function in the *PTEN* tumor suppressor gene and is associated with multiple hamartomas in a variety of tissues; characteristic dermatologic manifestations; and an increased risk of breast, endometrial, thyroid, kidney, and colorectal cancers, and melanoma. The lifetime risk of breast cancer may be as high as 85% in patients with a documented pathogenic variant in the *PTEN* gene. Thyroid cancer, typically follicular and rarely papillary, develops in two-thirds of carriers and can occur in childhood. Renal cell carcinoma can be seen in 13% to 34% of carriers. The prevalence of colon polyps is 66% to 93%. While hamartomatous polyps appear predominantly, patients with PHTS often develop a mix of ganglioneuromas and hamartomatous, adenomatous, serrated, and inflammatory polyps. The lifetime risk of colorectal cancer is as high as 16%. Neurologic manifestations may include dysplastic gangliocytoma of the cerebellar cortex, macrocephaly, intellectual disability, and autism. Women commonly have benign abnormalities such as significant fibrocystic breast changes, breast hamartomas, uterine fibroids, and ovarian cysts. Men often have lipomatosis of the testes. Both men and women frequently have benign thyroid lesions, such as adenomas and multinodular goiter. Benign glycogenic acanthosis and lipomas can also be seen.

Genetic testing criteria are divided into major and minor. Major criteria include macrocephaly, breast cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, epithelial endometrial cancer, macular pigmentation of the penis, Lhermitte-Duclos disease (adult), and characteristic mucocutaneous lesions (such as trichilemmomas, acral keratosis, mucocutaneous neuromas, oral papillomas). Minor criteria include autism spectrum disorders, colon cancer, esophageal glycogenic acanthi, lipomas, intellectual disability, papillary thyroid cancer (papillary or follicular), structural thyroid lesions (adenoma or multinodular goiter), renal cell carcinoma, single gastrointestinal hamartomas or ganglioneuromas, testicular lipomatosis, and vascular anomalies. PTEN testing should be offered to individuals with the following:

- Macrocephaly plus at least one additional major criterion;
- three major criteria, without macrocephaly;
- one major plus three or more minor criteria;
- four or more minor criteria;
- adult Lhermitte-Duclos disease;
- autism spectrum disorder plus macrocephaly;
- two or more biopsy-proven trichilemmomas.

Genetic testing should be offered to any individual with a single major or two minor criteria and a family member with a clinical diagnosis of Cowden syndrome or PHTS. Clinical diagnostic Cowden syndrome criteria, which vary slightly from the testing criteria, have been established by the NCCN and International Consortium Cowden Consortium. The estimated lifetime risk of breast cancer in a patient with clinical Cowden syndrome is felt to be 25% to 50%. *PTEN* testing includes sequencing of the entire coding region plus deletion/duplication analysis. Pathogenic variants have also been reported in the *PTEN* promoter region. Other candidate genes for Cowden syndrome are actively being investigated. De novo mutations are not uncommon.

The NCCN management guidelines for women with PHTS include BSE training and education starting at the age of 18 years, clinical breast examination every 6 to 12 months starting at the age of 25 years, and annual mammography and breast MRI starting at the age of 35 years. These guidelines are individualized based on the earliest age of onset in family and MRI continues until at least the age of 75 years, depending on comorbidities. The option of RRM should be discussed in women with pathogenic or likely-pathogenic variants. For those with clinical Cowden syndrome/PTHS, consideration of RRM should be based on family history. Patients should be encouraged to report abnormal uterine bleeding which must be evaluated. Consideration can be given to screening endometrial biopsy every 1-2 years. For endometrial cancer screening, consideration can be given to annual endometrial biopsies beginning at the age of 30 to 35 years. Hysterectomy can be considered. Men and women should have an annual physical examination starting at the age of 18 years or 5 years prior to the youngest age of diagnosis of cancer in their family, with emphasis on thyroid examination. A baseline thyroid ultrasound should be done at the time of diagnosis (as early as age 7) and annually thereafter. Screening colonoscopies should begin at the age of 40 years with follow-up every 5 years. Consider renal ultrasound every 1 to 2 years beginning at the age of 40 years.

Li-Fraumeni Syndrome

LFS is a hereditary syndrome associated with a wide range of cancers that appear at an unusually young age. LFS exhibits an autosomal dominant pattern of inheritance and is associated with pathogenic variants in the *TP53* tumor suppressor gene, which plays a major role in DNA repair. The lifetime risk of cancer is nearly 100%, with 90% of individuals diagnosed with cancer by the age of 60 years. The classic tumors seen in this syndrome are sarcoma, breast cancer, leukemia, brain tumors, and adrenal gland cancers.

Classic Li-Fraumeni criteria include a proband with both sarcoma before the age of 45 years, AND a first-degree relative with cancer

before the age of 45 years, AND an additional first- or second-degree relative with cancer before the age of 45 years, or sarcoma at any age. Chompret criteria include one of the following:

- A proband with a tumor in the LFS spectrum (sarcoma, premenopausal breast cancer, brain tumor, adrenocorticoid tumor, leukemia, or lung bronchoalveolar cancer) before the age of 46 years *plus* at least one first- or second-degree relative with a tumor in the LFS spectrum before the age of 56 years, or with multiple LFS-related tumors.
- A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS spectrum and the first of which occurred before the age of 46 years.
- A proband diagnosed with adrenocortical tumor or choroid plexus tumor regardless of age and irrespective of family history.

Testing is recommended for individuals who meet these criteria as well as women with breast cancer before the age of 35 years who have tested negative for the *BRCA1/2* variants. De novo mutations occur in 7% to 20% of patients. *TP53* is included with most multigene cancer panels.

The management guidelines for women with LFS include BSE training and education starting at the age of 18 years and clinical breast examination every 6 to 12 months starting at the age of 20 years. In the 20s, annual breast MRI is recommended or mammogram, if MRI is not available. Beginning at the age of 30 years, annual breast MRI alternating with low-dose digital mammography is recommended. RRMs should be offered as an option. All carriers should have an annual physical examination, including dermatologic and neurologic examinations. Colonoscopy screening should be considered starting at the age of 25 years with follow-up every 2 to 5 years. Other screening options that should be discussed with the patient include annual dermatology examinations beginning at the age of 18 years, whole-body MRI,

brain MRI, and pancreatic cancer screening for those with a family history. Additional targeted surveillance should be based on family history. Therapeutic radiation should be avoided if possible.

HEREDITARY GASTROINTESTINAL SYNDROMES

Lynch Syndrome

Lynch syndrome is an autosomal dominant disorder characterized by germline pathogenic variants in the DNA mismatch repair (MMR) genes or *EPCAM*. Lynch syndrome accounts for 2% to 3% of all colorectal cancers and is associated with an 8.7% to 61% lifetime risk of colorectal cancer. The lifetime risk of colorectal cancer can be further stratified by gender and MMR gene, with male *MLH1* carriers at the highest risk. As compared with sporadic colorectal cancers, Lynch-syndrome–associated colorectal cancers are usually diagnosed earlier (ages 44-61 vs age 69 in the general population) and more commonly consist of poorly differentiated, mucinous tumors in the right colon. Despite these aggressive histologic features, affected patients have better 5-year survival rates than those with common sporadic colorectal cancers. For those diagnosed with one colorectal cancer and treated with limited resection, the risk of developing another colorectal cancer 10 years after an initial diagnosis is 16% to 19%, with the risk rising to 41% to 47% over the ensuing 20 years.

Endometrial carcinoma is the most common extracolonic tumor in Lynch syndrome, accounting for about 2% of all endometrial cancers, and with a lifetime risk ranging from 13% to 57% in female carriers. As with colorectal cancer, women with Lynch syndrome are typically younger at diagnosis (age 50 vs age 65 in the general population). Other organs at increased risk of cancer include the ovaries (≤1%-38% lifetime risk), stomach (≤1%-7%), small bowel (≤1%-11%), pancreas/hepatobiliary tract (≤1%-6.2%), upper urinary

tract (≤1%-28%), skin (≤1%-9%), and brain (≤1%-7.7%). Breast and/or prostate cancers are seen in many families though risk has not been clearly defined.

Defects in the MMR system, which identifies base-pair mismatches and repairs them, are the hallmark characteristic of Lynch syndrome. The MMR genes affected in Lynch syndrome include *MLH1*, *MSH2*, *MSH6*, and *PMS2*. A germline deletion in *EPCAM*, which inactivates *MSH2*, has also been associated with Lynch syndrome. MMR and *EPCAM* pathogenic variants are inherited in an autosomal dominant manner. For an individual with Lynch syndrome once the second (formerly intact) allele is inactivated, whether by acquired somatic mutation, loss of heterozygosity, or promoter hypermethylation, for example, the consequent loss of ability to repair DNA mismatches results in an increased rate of mutations and associated genomic instability.

DNA mismatches tend to occur in areas of repeated nucleotides, particularly mono- and di-nucleotides. These sequences are called microsatellites. An accumulation of mismatched nucleotides in these regions leads to expansion or contraction of the microsatellites and is termed microsatellite instability (MSI). Approximately 90% to 95% of Lynch syndrome–associated colorectal cancers display high levels of MSI (MSI-H). Approximately 88% of Lynch syndrome–associated colorectal cancers demonstrate MMR deficiency through immunohistochemical (IHC) staining of the MMR proteins.

Biallelic inheritance of mutations in an MMR gene causes constitutional MMR-deficiency syndrome (CMMRD) and is associated with the development of Lynch syndrome–associated cancers as well as childhood cancers, hematologic malignancies, polyposis, brain tumors, and neurofibromatosis features such as café-au-lait spots.

Patients with colorectal or endometrial cancer who are suspected of having Lynch syndrome can be screened for MSI by polymerase chain reaction (PCR) or IHC. PCR detects MSI by identifying expansion or contraction of the microsatellite regions. If 30% or more

of the microsatellites show instability, then the tumor is considered to have MSI-H, which suggests a defect in a DNA MMR gene. IHC testing detects MMR proteins by an antibody assay. Unlike MSI testing, IHC has the advantage of being able to identify the missing protein product and, by proxy, to implicate the potentially mutated gene. Confirmation of Lynch syndrome requires germline testing of the MMR gene(s).

MSI is sensitive but not specific for Lynch syndrome. MSI-H is found in up to 15% of sporadic colorectal cancers, most commonly due to the loss of *MLH1* via hypermethylation of the *MLH1* promoter region. Approximately 50% of colorectal cancers with *MLH1* promoter hypermethylation will have the somatic *BRAF* V600E variant, which is rarely seen in Lynch syndrome tumors. Endometrial cancers with *MLH1* promoter hypermethylation do not display somatic *BRAF* mutations, so *BRAF* testing is not a useful tool for screening endometrial cancers. In patients who have MSI-H colorectal tumors with loss of *MLH1,* testing for the *BRAF* V600E mutation (colorectal cancer only) or *MLH1* promoter hypermethylation (colorectal or endometrial cancers) should be done to rule out sporadic cases. If this testing is negative, then patients should be offered germline *MLH1* testing. Patients with an absence of other MMR proteins and a diagnosis of colorectal or endometrial cancer should proceed to MMR gene testing and genetic counseling. An estimated 40% to 50% of individuals with abnormal MSI/IHC results will have a germline MMR pathogenic variant and thus confirmation of a diagnosis of Lynch syndrome. Approximately 40% to 50% of patients with abnormal MSI/IHC results will have acquired somatic MMR pathogenic variants, which is ***not*** consistent with a diagnosis of Lynch syndrome. If an MMR pathogenic variant is not detected on germline testing, consideration should be given to MMR gene testing of the tumor DNA.

Identification of Lynch syndrome patients remains challenging. The Amsterdam I criteria were originally developed to identify individuals appropriate for hereditary colorectal cancer research. The Amsterdam II Criteria were later broadened to include other

cancers observed in these families. The Amsterdam Criteria are useful for identifying patients appropriate for genetic counseling and testing. Those families that meet the Amsterdam Criteria are given a clinical diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC). An estimated 50% of families with HNPCC will actually have Lynch syndrome. The Revised Bethesda guidelines were created to help identify colorectal cancers appropriate for MSI/IHC testing.

Amsterdam II Criteria

1. Three or more relatives with HNPCC-associated cancers (colorectal, endometrial, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two.
2. Two or more generations with the above cancer(s).
3. At least one individual with the above cancer(s) in the family diagnosed before the age of 50 years.
4. The family does not have a different inherited colorectal cancer genetic condition called "familial adenomatous polyposis (FAP)."

Revised Bethesda Guidelines:

- Colorectal cancer in a patient younger than 50 years.
- Colorectal cancer with MSI-H histology in a patient younger than 60 years.
- Presence of synchronous or metachronous colorectal or other HNPCC-associated tumors, regardless of age.
- A patient with colorectal cancer who has one or more first-degree relatives with an HNPCC-associated tumor, with one of the cancers diagnosed under the age of 50 years.
- A patient with colorectal cancer who has two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

Given the reduced sensitivity and specificity of the Amsterdam Criteria and Bethesda Guidelines, in 2009 the Evaluation of Genomic

Application in Practice and Prevention (EGAPP) endorsed universal MSI and/or IHC screening in all newly diagnosed colorectal cancers.

For patients with Lynch Syndrome due to germline variants in *MLH1* or *MSH2*/*EPCAM*, colorectal cancer surveillance with colonoscopies should begin at the age of 20 to 25 years, with follow-up every 1 to 2 years. Among *MSH6* and *PMS2* carriers, colonoscopy surveillance can begin between ages 30 to 35 years, with follow-up every 1 to 2 years. Patients must be made aware that dysfunctional uterine bleeding warrants evaluation. There is no clear evidence to support screening Lynch syndrome patients for endometrial cancer. However, annual office endometrial sampling can be considered beginning at the age of 30 to 35 years. While there may be circumstances where clinicians find screening helpful, the data do not support routine ovarian screening for Lynch syndrome. Controversy exists surrounding the screening of other extracolonic cancers, and, with the exception of annual skin surveillance, no firm recommendations have been established. Upper endoscopy with visualization of the duodenum can be considered every 3 to 5 years starting at the age of 30 to 35 years. Primary prophylactic colectomy is generally not recommended. An annual urinalysis can be considered starting at the age of 30 to 35 years, particularly among MSH2 carriers. Although not shown to reduce mortality, hysterectomy with bilateral salpingoophorectomy has been associated with a reduced incidence of cancer and can be considered on an individual basis after the age of 35 years, once childbearing is complete.

Familial Adenomatous Polyposis

FAP is an autosomal dominant disorder characterized by the presence of colorectal adenomatous polyposis. FAP is caused by germline pathogenic variants in the tumor suppressor adenomatous polyposis coli (*APC*) gene located on chromosome 5. Unlike colorectal cancer, for which it has near-complete penetrance, FAP has a number of associated extracolonic carcinomas, with variable penetrance.

FAP accounts for less than 1% of all colorectal cancers. Seventy-five percent of FAP cases inherit a germline *APC* mutation, with the remaining 25% of cases occurring de novo. *APC* pathogenic variants are identified in 80% of patients with more than 1000 adenomas. The mutation detection rate drops as a function of total number of adenomas, with a 56% rate associated with 100 to 999 colorectal adenomas, 10% with 20 to 99 adenomas, and 5% with 10 to 19 adenomas.

Based on the colorectal adenoma burden, two classes of FAP have been described: (1) classic/profuse FAP, and (2) attenuated FAP (AFAP). Patients with classic or profuse FAP have greater than 100 adenomatous polyps. Adenomas typically begin to develop around puberty, and without surgical intervention, the risk of colorectal cancer is 100%. On average, the colorectal cancer diagnosis is made in the third decade of life. AFAP is characterized by less than 100 adenomas, which typically begin to develop in the late teenage years or early 20s. A lower, yet still significant, risk of colorectal cancer development is seen (up to 80%) with a later age of cancer diagnosis, often in the fifth decade of life.

Patients with FAP can also develop upper gastrointestinal tract polyps. Fundic gland polyps and gastric adenomas develop in 12% to 84% of patients. The gastric cancer risk is low though increased relative to the general population. Duodenal adenomas develop in 50% to 90% of patients. The risk of duodenal cancer ranges from 4% to 12% and is based on the Spigelman stage.

Extraintestinal manifestations, both malignant and benign, are observed in individuals with FAP. Malignant extraintestinal tumors are rare and include papillary thyroid cancer, pancreatic cancer, childhood hepatoblastoma, and central nervous system (CNS) tumors. Benign findings include desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, fibromas, dental abnormalities, adrenal adenomas, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Turcot syndrome was previously employed to refer to the association of familial colon cancer with

CNS tumors, including the medulloblastomas observed in FAP kindred. Gardner syndrome refers to families with FAP who also have osteomas and soft tissue tumors. Both Turcot syndrome associated with adenomatous polyposis and Gardner syndrome are forms of FAP caused by *APC* variants.

FAP should be suspected in any patient with 10 or more colorectal adenomas, and genetic counseling and testing for germline mutation of the *APC* gene should be offered to these patients. Testing for *MUTYH*-associated polyposis (MAP) (see below) and other rare polyposis syndromes should be considered as well in those who test negative for a pathogenic variant in the *APC* gene. Unlike most other hereditary cancer syndromes, genetic counseling and predictive genetic testing should be offered to children in a classic FAP kindred by the ages of 8 to 10 years. In families with AFAP, genetic counseling and predictive testing can be delayed until the late teenage years.

Per the NCCN guidelines, screening flexible sigmoidoscopy or full colonoscopy should begin around puberty for classic/profuse type FAP annually. Patients with AFAP should begin screening colonoscopy in the late teenage years, with follow-up every 2 to 3 years. Patients found to have profuse polyposis, multiple large (greater than 1 cm) adenomas, or adenomas with villous histology or high-grade dysplasia should be treated with colectomy followed by routine surveillance of the ileal pouch. AFAP patients with less disease burden can undergo polypectomy followed by continued annual surveillance. Upper endoscopy with visualization of the ampulla should begin at the ages of 20 to 25 years. Those with no duodenal polyposis should repeat endoscopy in 4 years. Individuals with Spigelman stage I (minimal polyposis; 1-4 tubular adenomas, size 1-4 mm) need repeat endoscopy in 2 to 3 years; those with stage II (mild polyposis; 5-19 tubular adenomas, size 5-9 mm) require follow-up every 1 to 3 years; and those with stage III (moderate polyposis; 20 more lesions, or size 1 cm or greater) require follow-up every 6 to 12 months. Patients with stage IV duodenal disease (dense polyposis or high-grade dysplasia) should have surveillance every 3

to 6 months and be sent for surgical evaluation to consider mucosectomy, duodenectomy, or a Whipple procedure. Annual examination of the thyroid should commence in the late teenage years; thyroid ultrasound can be considered. For families with desmoid tumors, abdominal MRI or CT may be considered 1 to 3 years postcolectomy and every 5 to 10 years thereafter. Data are presently insufficient to support any additional screening or surveillance.

MUTYH-Associated Polyposis

MAP is an autosomal recessive hereditary cancer syndrome characterized by adenomatous polyposis and early onset colorectal cancer. *MUTYH* is a base excision repair protein that plays a major role in correcting G:C > T:A transversions in the DNA. Among those of northern European ancestry, two common pathogenic variants c.536A > G (p.Tyr179Cys) and c.1187G > A (p.Gly396Asp) have been reported to account for up to 80% of *MUTYH* pathogenic variants. An estimated 1% to 2% of individuals of northern European ancestry carry one of these mutations. Other founder mutations have been reported in individuals of Dutch, Italian, British Indian, Pakistani, Spanish, Portuguese, Tunisian, Brazilian, French, Japanese, and Korean ancestry.

The majority of MAP patients develop ten to hundreds of colorectal adenomas; profuse polyposis is typically not observed. Some individuals will also develop serrated polyps (hyperplastic polyps, sessile serrated adenomas/polyps, and serrated adenomas). The average age of diagnosis is 50 years. A rare subset of patients will present with early onset colorectal cancer in the absence of polyposis. The lifetime risk of developing colorectal cancer for individuals with MAP ranges from 43% to 100%.

Patients with MAP also develop upper gastrointestinal tract neoplasms. Approximately 10% to 15% of patients will develop fundic gland polyps and/or gastric adenomas. It is unclear whether MAP is associated with an increased risk of gastric cancer.

Approximately 17% to 25% of patients will develop duodenal adenomas, with an estimated 4% lifetime risk of developing duodenal cancer.

Other cancers, including thyroid, skin, endometrial, ovarian, breast, and bladder, have been reported at an increased incidence in MAP patients. Additional reported diagnoses include benign thyroid disease, dermatologic findings, dental abnormalities, and CHRPE.

There is speculation that *MUTYH* carriers may have an increased risk of developing colorectal cancer. Odd ratios among carriers have been reported between 1.1 to 1.2 and 2 to 3.

The NCCN recommends beginning colonoscopy at the age of 25 to 30 years for those with biallelic *MUTYH* mutations. If negative, the examination should be repeated every 2 to 3 years. If polyps are identified, colonoscopy and polypectomy should be repeated every 1 to 2 years. Colectomy should be considered: (1) when the polyp burden is >20 on a single examination; (2) when polyps have been previously ablated; (3) when some polyps reach >1 cm; or (4) when advanced histology is encountered. The adenoma distribution and polyp burden should inform the extent of colectomy. Upper endoscopy with visualization of the ampulla could be considered beginning at the age of 30 to 35 years. Follow-up is based on Spigelman score, as discussed in the section Familial Adenomatous Polyposis. In monoallelic *MUTYH* carriers, the NCCN currently endorses beginning colonoscopy screening at the age of 40 years, with follow-up at least every 5 years in those individuals with a first-degree relative with colorectal cancer. General population colorectal cancer screening recommendations are advised for *MUTYH* carriers with either no family history of colon cancer or no closer than a second-degree relative with colorectal cancer.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (DGC) is an autosomal dominant disorder caused by germline pathogenic variants in the *CDH1* gene.

CDH1 codes for E-cadherin, a cell-adhesion protein that affects cell-to-cell interaction and plays a critical role in cell development, differentiation, and architecture. Individuals who harbor these germline mutations have a 67% to 83% lifetime risk of developing DGC by the age of 80 years with a median age of onset of 37. More recent clinical laboratory-based studies have shown lifetime risk estimates of 33% to 42%. These gastric cancers form beneath an intact mucosal surface, causing gastric wall thickening rather than the formation of a discrete mass. Because they become visible only late in the disease process, early detection is extremely challenging. Therefore, screening of high-risk individuals via EGD with random biopsies should begin in the late teenage years. Prophylactic gastrectomy should be offered to all *CDH1* mutation carriers between the ages of 18 and 40 years.

Like DGC, the absence of E-cadherin expression is also the key underlying defect in lobular breast carcinoma. Female carriers therefore have a 39% to 55% lifetime risk of developing lobular breast carcinoma by the age of 80 years. Given this considerable risk, the addition of annual MRI screening to annual screening mammography is recommended beginning at the age of 30 years or 10 years earlier than the first affected relative. RRM should be discussed as an option.

According to expert opinion, genetic testing criteria for HDGC are as follows:

- Lobular breast cancer with a personal or family history of diffuse gastric cancer
- At least two cases of gastric cancer regardless of age, with at least one confirmed DGC; or
- DGC diagnosed under the age of 50 years without family history, or
- Personal or family history of DGC and invasive lobular cancer, with one diagnosed before the age of 70 years, or
- At least two cases of lobular breast cancer prior to the age of 50 years; or

- DGC at any age in individuals of Maori ancestry; or with a personal or family history of cleft lip/palate, or
- Bilateral lobular breast cancer before the age of 70 years

Any individual meeting the above criteria should be offered *CDH1* testing. If *CDH1* is negative, then *CTNNA1* testing should be offered. *CDH1* mutation detection rates in those who met clinical criteria were previously reported to be 25% to 50%. With the expansion of the above testing criteria, the mutation detection rate has decreased to 10% to 18%.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant disorder characterized by multiple gastrointestinal hamartomatous polyps, mucocutaneous pigmentation, and an increased risk of malignancies. Approximately 88% of patients with PJS will develop Peutz-Jeghers polyps. Peutz-Jeghers polyps are characterized by a cerebriform appearance due to smooth muscle arborization within the polyps. These polyps often begin to develop in the first decade of life and are most common in the small bowel but can also be observed in the colon, rectum, and stomach. An estimated 50% of patients will present with intussusception by the age of 20 years. PJS is often recognized by characteristic mucocutaneous pigmentation. The lesions are small (1-5 mm), flat, blue-gray to brown spots, and are commonly found around the mouth and nose, in the buccal mucosa, and on the hands and feet, perianal areas, and genitals. Over time, this pigmentation can fade. Malignancies are also commonly seen in PJS, and affected patients carry up to an 80% to 90% lifetime risk of developing cancer. The most common malignancies occur in the colon and rectum, but there is also an increased risk of breast, stomach, small bowel, pancreatic, lung, cervical, ovarian, and testicular cancers.

The World Health Organization (WHO) established the following clinical criteria for PJS:

- three or more histologically confirmed Peutz-Jeghers polyps;
- any number of Peutz-Jeghers polyps and a family history of PJS;
- characteristic mucocutaneous pigmentation and a family history of PJS; or
- any number of Peutz-Jeghers polyps in an individual with characteristic mucocutaneous pigmentation.

PJS is caused by germline mutations in *STK11*. *STK11* mutations are found in 60% to 99% of patients who meet the WHO criteria. Annual screening breast MRI is recommended to begin at the age of 25 years with the addition of annual screening mammography beginning at the age of 30 years. Individuals with PJS should undergo colonoscopy screening every 2 to 3 years, beginning in the late teens. Additional guidelines for screening of the stomach, small bowel, pancreas, uterus, ovaries, and testes are outlined in NCCN guidelines.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is caused by mutations in the genes *BMPR1A* and *SMAD4*. This syndrome is characterized by gastrointestinal hamartomatous polyps and an increased risk of malignancy. The term "juvenile" is a reference to the hamartomatous polyps observed in this syndrome. Polyps often begin to develop in the teenage years and are most common in the colon and rectum. Patients with *SMAD4* pathogenic variants can also develop massive gastric polyposis, which are less commonly observed in those with *BMPR1A* pathogenic variants. Small bowel polyps have been reported but are rare. The lifetime risk of developing cancer ranges from 17% to 68%, with a 50% lifetime risk of developing colorectal cancer. The risk of gastric or duodenal cancer is 15% to 21%. Germline *SMAD4* mutations have also been associated with hereditary hemorrhagic telangiectasia (HHT) and aortopathy. These clinical criteria have been established for JPS:

- more than three to five juvenile polyps of the colon or rectum;
- juvenile polyps throughout the gastrointestinal tract; or

- any number of juvenile polyps and a positive family history of JPS

Among those individuals who meet clinical criteria, *SMAD4* and *BMPR1A* mutations are identified in approximately 40% to 50% of patients.

Colonoscopy and upper endoscopy should begin around the age of 15 years, with follow-up every 1 to 3 years. Colectomy and/or gastrectomy may be considered in cases where the polyp burden is endoscopically unmanageable. Individuals with *SMAD4* mutations should undergo screening for HHT.

SPECIAL CONSIDERATIONS

In some cases, a genetic test result that identifies a *TP53* mutation may not actually be a true germline mutation of the type associated with LFS. Possible explanations for this type of result are (1) the presence of tumor cells circulating in the blood (somatic mosaicism) or (2) clonal hematopoiesis, which is a form of mosaicism that is wholly restricted to the hematopoietic compartment. In as much as a diagnosis of LFS has profound implications for breast cancer patients and their relatives, further testing, to include a skin biopsy, is often indicated to further assess for true germline LFS.

As systemic therapies become increasingly linked to pathogenic variants in specific somatic- or tumor-related genes (ie, targeted therapies), tumor-genetic testing will expand. However, tumor-specific testing alone will not indicate whether a variant has been inherited through the germline. Either *paired somatic and germline* or *follow-up germline* testing is recommended to assess for both treatment indications as well as potential medical and psychological impacts of becoming aware of pathogenic hereditary variants For these reasons, informed consent is essential.

The timing of when to test children also requires consideration. As most genes associated with breast cancer susceptibility do not have

corresponding pediatric/adolescent health risks, the traditional consensus has been to preserve the child's autonomy and, therefore, to defer testing until the child is able to give adequate consent. However, where the results impact medical management, or reproductive decision-making, a few genes related to breast cancer susceptibility also have health risks relevant to individuals under the age of 18 years. In those cases, the testing of minors should be discussed with their family. Relevant examples include *TP53* (pediatric cancer risks) and *PTEN* (autism and thyroid disease including early-onset cancers). Additionally, given the potential for early onset of gastric cancer, consideration should be given to testing adolescents for *CDH1*.

PRACTICAL BREAST MANAGEMENT IN HIGH-RISK GENE CARRIERS

Genetic testing for hereditary breast cancer susceptibility can be an important consideration in surgical decision-making for newly diagnosed cancer patients. *BRCA* mutation carriers have been shown to have high rates of contralateral breast cancer (CBC) development, so that those who choose bilateral over unilateral mastectomy are less likely to die from breast cancer. Other genes have been shown to have a lower, but still elevated, CBC risk. In one study, *PALB2* was associated with a 10% 5-year cumulative risk of CBC in comparison to a 17% 5-year risk with *BRCA1*. *CHEK2* is associated with a 10-year risk of CBC of 12% to 29%. The option of contralateral prophylactic mastectomy (CPM) is frequently discussed if a patient has a *BRCA1* or *BRCA2* mutation but is also often reasonable in the setting of pathogenic variants in *TP53, PTEN, PALB2,* or *CHEK2 1100delC,* given the high risk of a second primary or risk of contralateral disease. Treatment of breast cancers with lumpectomy plus radiation is often an appropriate treatment option, though not in the case of *TP53*, however, where radiation therapy is contraindicated. Of course, given compelling family history or young age at diagnosis, CPM is often chosen, particularly in the United States.

In *BRCA* carriers, not only is RRSO associated with a 77% reduction in all-cause mortality, but specifically following a diagnosis of an ER-negative breast cancer in a patient with a *BRCA1* mutation, has been associated with a 62% reduction in breast cancer-specific mortality. The RRSO has therefore been shown to be an important early intervention in this patient population. More recently, similar data have emerged showing a benefit of early oophorectomy as well in patients with *BRCA2* mutations who have been diagnosed with breast cancer. *BRCA1* and *BRCA2* associated tumors are also particularly sensitive to PARP Inhibitors, a topic that is discussed elsewhere in this *Handbook.*

Testing Considerations

Testing for hereditary predisposition to breast cancer is rapidly expanding in parallel with the emerging field of molecular genetics. A myriad of associated implications exist regarding screening, risk reduction, and cancer therapeutics in identified gene mutation carriers. Given the advent of next generation sequencing technology, which provides the ability to sequence multiple genes simultaneously at lower cost, coupled with the genetic heterogeneity of breast and ovarian cancer susceptibility, multigene panel testing has now become commonplace.

Breast screening of women with highly penetrant gene mutations (*BRCA1, BRCA2, PALB2, CDH1, PTEN, and TP53*) is driven largely by published guidelines. Given clear estimations of penetrance, recommendations and age at which screening should commence are provided by the NCCN and are based on large bodies of evidence. Management of patients with pathogenic variants in moderate-risk genes presents unique challenges. The lifetime risk for breast cancer in patients with *ATM* and *CHEK2* mutations is approximately 30%. In these patients, breast screening consists of an annual mammogram (with consideration of tomosynthesis) and consideration of breast MRI beginning at the age of 40 years, with potential modification of recommendations depending on family history; screening will typically begin 5 to 10 years prior to the age

(at diagnosis) of the youngest affected relative. Risk-reducing surgery is a consideration in some women with compelling family history.

To whom should genetic testing be offered? While guidelines have been available for many years, concerns have been raised regarding the possibility that existing guidelines may miss significant numbers of breast cancer patients with a hereditary cancer syndrome. For example, Beitsch et al reported a mutation rate of 7.9% in a study of 959 breast cancer patients (P = .4241), who did not meet the 2.2017 NCCN guidelines for genetic testing in contrast to a mutation rate of 9.3% in those who did meet those guidelines. Based partly on this research, the American Society of Breast Surgeons issued new guidelines in February 2019 stating that "genetic testing should be made available to all patients with a personal history of breast cancer." Critics of this guideline, however, have called into question both its practicality and the extent of its application. To date, these guidelines have not been broadly incorporated as standard of care. For now, the debate continues regarding guideline-based versus more generalized testing.

With multiple genes being tested and a myriad of possible results and implications, genetic counseling is of paramount importance for both patients and providers in promoting an understanding of risk and options for risk management. Guidelines have been developed to facilitate a multidisciplinary approach to management of individuals at increased risk, and an appreciation of the need for flexibility is essential as these guidelines are applied to individual patients and their families.

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Basic Principles of Immuno-Oncology

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INTRODUCTION

The concept of immunotherapy has existed for centuries, with discoveries from early investigations of the complex interplay between infection and immune response setting the stage for how we understand the role of immunity in cancer treatment today. In the past decade, a plethora of immune-based therapies have exploded onto the scene; the past 5 years, alone, have seen approvals for an extraordinary number of indications for the use of immune checkpoint inhibitors in solid tumor treatment, as well as the emergence of multiple chimeric antigen receptor (CAR) T cell therapies for the treatment of hematologic malignancies. On May 23, 2017, the U.S. Food and Drug Administration (FDA) issued its first tissue/site-agnostic approval for the use of the programmed cell death protein-1 (PD-1)–blocking antibody pembrolizumab in the treatment of patients with unresectable or metastatic solid tumors exhibiting deficient mismatch repair (dMMR) or high levels of microsatellite instability (MSI-H) who have received prior therapy. This unique approval is monumental in that it not only critically shapes the manner in which cancer is defined but also raises awareness of the potential significance of biomarker analyses, as well as impacts the regulatory processes through which agents are evaluated for approval as therapies.

This chapter provides an updated overview of the cytokines, therapeutic cancer vaccines, immune checkpoint inhibitors, and

adoptive cell therapies currently approved for use in the treatment of malignant diseases (Table 45.1). All approvals discussed herein apply to adult patients and to indications specifically associated with malignant diseases. All approvals denoting the prerequisites of programmed death-ligand 1 (PD-L1) expression, specific tumor proportion scores (TPS), combined positive scores (CPS), or tumor mutational burden (TMB) should be understood as requiring the use of FDA-approved diagnostic tests or methodologies in the determination of these criteria. All mention of radiographic assessments of response should be interpreted as having been performed in accordance with RECIST or RECIST 1.1 criteria (or modified RECIST [mRECIST] criteria, where further specified). The information provided is intended as brief synopses of agents and should not replace official prescribing information (as referenced under "Suggested Readings"). Please refer to official prescribing information regarding dosage and administration of agents and for further details of clinical studies contributing to FDA approvals.

TABLE 45.1

FDA-Approved Immunotherapy Agents Used in Cancer Treatment

Cytokine therapies	Aldesleukin (rhIL-2) (PROLEUKIN)
	Interferon alfa-2b (INTRON A)
	Peginterferon alfa-2b (SYLATRON)
Therapeutic cancer vaccines	Bacillus Calmette-Guerin (BCG) (TICE)
	Sipuleucel-T (PROVENGE)
Oncolytic viruses	Talimogene laherparepvec (T-VEC) (IMLYGIC)
Immune checkpoint inhibitors	Ipilimumab (YERVOY)
	Nivolumab (OPDIVO)
	Pembrolizumab (KEYTRUDA)
	Atezolizumab (TECENTRIQ)
	Durvalumab (IMFINZI)
	Avelumab (BAVENCIO)
	Cemiplimab (LIBTAYO)
	Dostarlimab (JEMPERLI)
Adoptive cell transfer therapies	Tisagenlecleucel (KYMRIAH)
	Axicabtagene ciloleucel (YESCARTA)
	Lisocabtagene maraleucel (BREYANZI)

	Brexucabtagene autoleucel (TECARTUS)
	Idecabtagene vicleucel (ABECMA)
Bispecific antibodies	Blinatumomab (BLINCYTO)

FDA-APPROVED IMMUNOTHERAPIES

Cytokine Therapies

Aldesleukin (Interleukin [IL]-2; High-Dose IL-2; PROLEUKIN)

- It is FDA-approved for the treatment of patients with metastatic melanoma, as well as metastatic renal cell carcinoma (RCC).
- In eight clinical trials, 270 patients with metastatic melanoma were treated with single-agent aldesleukin. Of the 270 patients, 43 (16%) had an objective response, with 17 (6%) achieving complete response (CR) and 26 (10%) demonstrating partial response (PR). In addition, in 7 clinical trials, 255 patients with metastatic RCC were treated with single-agent aldesleukin. Of the 255 patients, 37 (15%) had an objective response with 17 (7%) achieving CR and 20 (8%) having PR. It should also be noted that patients achieving CR with this therapy have a near 90% 10-year disease-free survival (DFS).
- Aldesleukin has been associated with capillary leak syndrome, severe hypotension, reduced organ perfusion, and increased risk of disseminated infection. It can also cause cardiac arrhythmias, angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes. Treatment should be withheld in patients developing moderate to severe lethargy or somnolence, as continued administration may result in coma or toxic psychosis.

Interferon Alfa-2b (INTRON A)

- Interferon alfa-2b is FDA-approved for the following indications:
  - Hairy cell leukemia.
  - Adjuvant treatment of malignant melanoma in patients who are disease free and at high risk for systemic recurrence within 56 days of surgery.
  - Aggressive, follicular non-Hodgkin lymphoma (NHL) in conjunction with an anthracycline-containing combination chemotherapy regimen.
  - AIDS-related Kaposi sarcoma.
- Hairy cell leukemia
  - In clinical trials, 75% of patients with hairy cell leukemia treated with interferon alfa-2b achieved substantial and sustained improvements in granulocyte, platelet, and hemoglobin counts following transient depressions in hematopoiesis. At least, some response (or "minor response") was evident in 90% of patients, overall. Treatment also resulted in decreased bone marrow hypercellularity and hairy cell infiltrates. Analyses of results, however, indicated that prolonged treatment with interferon alfa-2b might be necessary to achieve maximal reduction in marrow tumor cell infiltrates. Thus, 126 patients who had responded to initial therapy were randomized to receive an additional 6 months of treatment or undergo observation. During these 6 months, 3% of patients receiving prolonged treatment with interferon alfa-2b–treated were found to relapse compared to 18% of patients under observation.
- Malignant melanoma
  - The safety and efficacy of interferon alfa-2b as adjuvant therapy in the treatment of patients with melanoma who have undergone resection but who remain at high risk for recurrence were evaluated in a randomized, controlled trial of 280 patients. Within 56 days of surgery, 143 patients began treatment with interferon alfa-2b at 20 million IU/m^2 IV five times per week for 4 weeks during an induction phase, followed by 10 million IU/m^2 subcutaneously (SC) three times per week for 48 weeks as maintenance therapy. A second group comprised of 137 patients were postoperatively observed. Patients who had received adjuvant interferon alfa-2b demonstrated a significant increase in both relapse-free survival (RFS) and overall survival (OS). Median times to relapse for the interferon alfa-2b–treated patients and patients who had been under observation were 1.72 and 0.98 years, respectively ($P < .01$). The estimated 5-year RFS rates were 37% for treated patients and 26% for observed patients. Median OS was 3.82 years for treated patients and 2.78 years for observed patients ($P = .047$) and estimated 5-year OS rates were 46% and 37%, respectively.
- Aggressive follicular NHL
  - In a randomized, controlled trial evaluating the safety and efficacy of first-line treatment with interferon alfa-2b in patients with clinically aggressive, large tumor burden, stage III/IV follicular NHL, patients were randomized to receive chemotherapy (cyclophosphamide, doxorubicin, teniposide, and prednisone) with or without interferon alfa-2b over 18 months. Compared with patients receiving chemotherapy alone, the group receiving the combination of chemotherapy and interferon alfa-2b were shown to have a significantly longer

progression-free survival (PFS) (2.9 vs 1.5 years, *P* = .0001). After a median follow-up of 6.1 years, median survival for patients treated with chemotherapy alone was 5.5 years, while the median survival for patients treated with the combination of treatment had not been reached (*P* = .004).

- AIDS-related Kaposi sarcoma
  - In one study, 144 patients with AIDS-related Kaposi sarcoma received interferon alfa-2b (30 million IU/m^2 SC three times per week, adjusted for patient tolerance). With a median time to response of 2 months, 44% of asymptomatic patients exhibited response. In contrast, only 7% of symptomatic patients showed response, with a median time to response of 1 month. The median duration of response (DoR) was approximately 3 months and 1 month for asymptomatic and symptomatic patients, respectively. Interestingly, the median survival time was longer in patients with CD4 counts greater than 200 than in patients with CD4 less than or equal to 200 (30.7 vs 8.9 months, respectively). Among responders, the median survival time was 22.6 versus 9.7 months in nonresponders.
- The use of alpha interferons may potentially induce or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders, as well as serious depression, with suicidal ideation and completed suicides having been observed with use.

Peginterferon Alfa-2b (SYLATRON)

- Peginterferon alfa-2b is approved for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection, including complete lymphadenectomy.
- This approval is based upon a phase III study which randomized 1256 patients with surgically resected stage III melanoma to peginterferon alfa-2b or observation. Based on 696 RFS events, an improvement in RFS was seen for those receiving interferon (hazard ratio [HR] 0.82; 95% CI: 0.71, 0.96; *P* = .011). The estimated median RFS was 34.8 months with peginterferon alfa-2b as compared to 25.5 months with observation. Of note, no difference in OS between those receiving peginterferon and patients in the observation arm was appreciated (HR 0.98; 95% CI: 0.82, 1.16).

- Cardiac adverse reactions, including myocardial infarction, bundle-branch block, ventricular tachycardia, supraventricular arrhythmia, and cardiomyopathy, have been observed to occur with use. Peginterferon alfa-2b should be permanently discontinued if new onset of ventricular arrhythmia or cardiovascular decompensation occurs.
- Peginterferon alfa-2b can cause serious ocular changes resulting in decreased visual acuity or blindness due to retinopathy. A complete eye examination should be performed in patients with preexisting retinopathy at baseline and in patients who develop new or worsening retinopathy while on treatment.
- Peginterferon alfa-2b increases the risk of hepatic decompensation and death in patients with cirrhosis; thus, serum bilirubin, alkaline phosphatase, lactate dehydrogenase, and transaminase levels should be monitored.
- Peginterferon alfa-2b can cause new onset or worsening of hypothyroidism, hyperthyroidism, and diabetes mellitus. Thyroid function should be monitored.
- As with alpha interferons, in general, peginterferon alfa-2b can increase the risk of serious depression, with suicidal and homicidal ideation, completed suicides, relapse of recovering drug addicts, and other serious neuropsychiatric disorders.
- Peginterferon alfa-2b should be permanently discontinued in patients with persistently severe or worsening signs or symptoms of depression, psychoses, or encephalopathy. Based on postmarketing experience, neuropsychiatric adverse reactions such as aggressive behavior, psychoses, hallucinations, bipolar disorders, mania, and encephalopathy were reported up to 6 months after discontinuation of use.

Therapeutic Cancer Vaccines

Bacillus Calmette-Guerin (BCG; TICE BCG)

- Intravesical BCG therapy is FDA-approved for the treatment and prophylaxis of carcinoma in situ (CIS) of the urinary

bladder and for the prophylaxis of primary or recurrent state Ta and/or T1 papillary tumors following transurethral resection.

- The approval for TICE BCG for the treatment of CIS was based on data derived from six uncontrolled phase II trials. Initial overall response rate (ORR) based on a 2-year follow-up was 75.6%. After a median duration of follow-up of 47 months, overall long-term response was 38%.
- The efficacy of intravesical TICE BCG in preventing the recurrence of a Ta or T1 tumor after complete transurethral resection was evaluated in two open-label, randomized phase III studies. In the SWOG trial, patients were randomized to receive TICE BCG or mitomycin C for 1 year. At 2 years, no statistically significant differences were shown between the groups for time to tumor progression, tumor invasion, or OS; however, estimated DFS was 57% (95% CI: 0.50, 0.65) for patients in the BCG arm and 45% (95% CI: 0.38, 0.53) for individuals who had received mitomycin C. In the Nijmegen Netherlands study, 437 patients who received intravesical instillations of TICE BCG, BCG-RIVM, or mitomycin C were evaluated. At a median follow-up of 32 months (range 12, 56), there were no significant differences for the three arms for the presence of papillary tumors (P = .08) nor CIS (P = .20).
- Physicians using this product should be familiar with the literature on prevention, diagnosis, and treatment of BCG-related complications; when appropriate, a specialist with experience in the diagnosis and treatment of mycobacterial infections should be consulted.

Sipuleucel-T

- Sipuleucel-T is an autologous dendritic cell-based vaccine platform that is FDA-approved for the treatment of patients with minimally symptomatic mCRPC.
- This approval is based on results of the IMPACT trial, a phase III double-blind placebo-controlled trial in which 512 patients with minimally symptomatic mCRPC were randomized to

receive sipuleucel-T every 2 weeks for a total of three doses or placebo. Patients receiving sipuleucel-T had a 4.1-month improvement in median OS (25.8 vs 21.7 months; HR 0.78; 95% CI: 0.61, 0.98; *P* = .03).

- Retrospective analysis suggests patients with relatively lower prostate-specific antigen values (likely a marker for less tumor volume) benefit most from the vaccine.

Oncolytic Viruses

Talimogene Laherparepvec (T-VEC; IMLYGIC)

- T-VEC is a genetically modified oncolytic viral therapy derived from herpes simplex virus, type 1 (HSV-1) that is FDA-approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma who have recurrent disease after initial surgery.
- FDA approval was based on a phase III trial, which randomized 436 patients with unresected stage IIIB, IIIC, or IV melanoma 2:1 to receive T-VEC or control therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF). The objective response rate for T-VEC was 26% with 11% CR, versus 6% with 1% CR in those receiving GM-CSF. The durable response rate (lasting more >6 months) for T-VEC was 16% versus 2% with GM-CSF ($P < .0001$). In addition, a final planned survival analysis showed a trend in favor of T-VEC. Median OS for T-VEC was 23.3 versus 18.9 months for GM-CSF (HR 0.80; 95% CI: 0.62, 1.01; *P* = .06).
- It is recommended that health care providers and close contacts should avoid direct contact with injected lesions, dressings, or body fluids of patients to minimize the risk of transmission of T-VEC and herpetic infection. Health care providers who are immunocompromised and pregnant women are recommended against administering T-VEC.

Immune Checkpoint Inhibitors

Ipilimumab (YERVOY)

- Ipilimumab is a monoclonal antibody and inhibitor of cytotoxic T-lymphocyte antigen 4 that is FDA-approved for the treatment of subgroups of patients with melanoma, RCC, colorectal cancer (CRC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), and mesothelioma.
- Only two indications are approved for ipilimumab use as monotherapy; both are indications for the treatment of melanoma. As the other indications for ipilimumab require nivolumab to be given in combination, their supporting studies will be discussed in the following section, under indications for nivolumab use.
- Melanoma
  - Ipilimumab is approved to treat unresectable or metastatic melanoma. A phase III trial randomized (3:1:1) 676 patients with unresectable stage III or IV melanoma to receive ipilimumab plus gp100 (a peptide-based vaccine against glycoprotein 100), ipilimumab alone, or gp100 alone. Median OS of ipilimumab was significantly improved when compared to gp100 alone (10.1 vs 6.4 months; HR 0.66; $P = .003$). The combination of gp100 and ipilimumab did not show any added survival benefit compared to ipilimumab alone (10 vs 10.1 months; HR 1.04; $P = .76$).
  - Ipilimumab is also approved as adjuvant therapy in patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm and who have undergone complete resection, including total lymphadenectomy. Approval was based on results from the phase III EORTC 18,071 trial, in which 951 patients with stage III resected cutaneous melanoma were randomized to receive adjuvant ipilimumab versus placebo. At a median follow-up of 2.74 years, the median RFS for adjuvant ipilimumab was 26.1 months as compared to 17.1 months with placebo (HR 0.75; 95% CI: 0.64, 0.90; $P = .0013$).

Nivolumab (OPDIVO)

- Nivolumab is a monoclonal antibody and inhibitor of PD-1 that is FDA approved for several indications, including the following:

- As a single agent or in combination with ipilimumab for unresectable or metastatic melanoma (BRAF V600 mutant or BRAF wild-type).
- As adjuvant treatment in patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection.
- In combination with ipilimumab and two cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
- In combination with ipilimumab as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 (≥1%), with no EGFR or ALK genomic tumor aberrations.
- Metastatic NSCLC following previous platinum-based chemotherapy and following EGFR- or ALK-targeted therapy when EGFR- or ALK-sensitizing genomic alterations exist.
- In combination with ipilimumab as first-line treatment for unresectable malignant pleural mesothelioma.
- Advanced RCC following previous antiangiogenic therapy.
- Intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab.
- In combination with cabozantinib as first-line treatment for advanced RCC.
- Locally advanced or metastatic urothelial carcinoma progressing on or following platinum-containing chemotherapy or progressing within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.
- Recurrent or metastatic squamous cell carcinoma (SCC) of the head and neck (HNSCC) with disease progression on or after a platinum-based therapy.
- Classical Hodgkin lymphoma following autologous hematopoietic stem cell transplantation (HSCT) and posttransplant brentuximab vedotin or following progression of three or more lines of systemic therapy, including autologous HSCT.
- As single agent or in combination with ipilimumab for MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- As single agent or in combination with ipilimumab for HCC previously treated with sorafenib.
- Progression of unresectable advanced, recurrent, or metastatic esophageal SCC following treatment with fluoropyrimidine- and platinum-based chemotherapy.
- In combination with chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

- Melanoma
  - In a randomized phase III trial, nivolumab was compared to dacarbazine or carboplatin, standard second-line chemotherapy options, in patients with metastatic melanoma that had been previously treated with ipilimumab and, if tumors expressed BRAF V600 mutation, a BRAF inhibitor, as well. After 167 patients were followed for at least 6 months, the median ORR was 32% for nivolumab compared to 11% for chemotherapy. After a median 8.4 months of

follow-up, the median DoR for nivolumab was not reached, with 95% of nivolumab-treated patients still responding, compared to 80% in the chemotherapy-treated group.

- A phase III trial in patients with previously untreated melanoma without BRAF mutation showed that nivolumab produced an ORR of 40% versus 13.9% for dacarbazine (HR 4.06; $P < .001$). At 1 year of follow-up, OS was 72.9% in the nivolumab group versus 42.1% in the dacarbazine group (HR 0.42; 99.8% CI: 0.25, 0.73; $P < .001$).
- The approval of nivolumab in combination with ipilimumab was based upon a phase III trial in previously untreated advanced melanoma (CheckMate 067), which randomized 945 patients to receive ipilimumab, nivolumab, or a combination of the two agents. PFS was 11.5 months (95% CI: 8.9, 16.7) for the combination regimen compared to 2.9 months (95% CI: 2.8, 3.4; $P < .001$) for ipilimumab alone and 6.9 months (95% CI: 4.3, 9.5; $P < .001$) for nivolumab alone.
- Approval of nivolumab as adjuvant therapy in patients with advanced melanoma who have undergone complete resection was based on improvement in RFS in the CheckMate 238 trial, a randomized, double-blind trial evaluating nivolumab versus ipilimumab treatment in the postoperative setting for 1 year. Patients in the nivolumab arm experienced fewer recurrences/deaths (34%) compared with patients in the ipilimumab arm (45.5%) (HR 0.65; 95% CI: 0.53, 0.80; $P < .0001$).

- NSCLC
  - FDA approval for nivolumab monotherapy in NSCLC is based on two key trials, one in squamous NSCLC and one in nonsquamous NSCLC. Approval for nivolumab as first-line therapy in patients with NSCLC whose tumors exhibit no EGFR or ALK genomic aberrations occurred subsequently and is contingent on the concurrent use of ipilimumab, either as a chemotherapy-sparing regimen for PD-L1 expressing tumors or in conjunction with platinum-doublet chemotherapy.
  - Approval for the combination of nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations, was based on results from the CheckMate 9LA trial, in which previously untreated patients with metastatic or recurrent NSCLC were randomized (1:1) to receive either the combination of nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy ($n = 361$) or platinum-doublet chemotherapy for four cycles ($n = 358$). Statistically significant benefits in OS, PFS, and ORR were demonstrated for patients receiving nivolumab, ipilimumab, and platinum therapy compared to those receiving platinum-doublet therapy alone. Median OS was 14.1 months (95% CI: 13.2, 16.2) for the combination arm versus 10.7 months (95% CI: 9.5, 12.5) (HR 0.69; 96.71% CI: 0.55, 0.87) for the platinum-only arm. Median PFS was 6.8 months (95% CI: 5.6, 7.7) in the nivolumab plus ipilimumab and chemotherapy arm and 5 months (95% CI: 4.3, 5.6) in the chemotherapy arm (HR 0.70; 95% CI: 0.57, 0.86). Confirmed ORR was 38% (95% CI: 33, 43) and 25% (95% CI: 21, 30), respectively, with a median DoR of 10 months in the

nivolumab plus ipilimumab and chemotherapy arm and 5.1 months in the chemotherapy arm.

- Improved OS for patients with tumors exhibiting PD-L1 tumor expression ≥1% and with no EGFR mutations or known ALK translocations sensitive to targeted therapy was shown for individuals receiving nivolumab plus ipilimumab compared to patients treated with platinum-doublet chemotherapy in the CheckMate 227 trial. Median OS was 17.1 months (95% CI: 15, 20.1) versus 14.9 months (95% CI: 12.7, 16.7) (HR 0.79; 95% CI: 0.67, 0.94; *P* = .007). OS rates at 1 year and 2 years with nivolumab plus ipilimumab were 62.6% and 40.0%, respectively; OS rates with chemotherapy were 56.2% and 32.8%, respectively. Objective response rates were 35.9% (95% CI: 31.1, 40.8) with nivolumab plus ipilimumab versus 30.0% (95% CI: 25.5, 34.7) with chemotherapy. Median DoR was 23.2 months (95% CI: 15.2, 32.2) with nivolumab plus ipilimumab and 6.2 months (95% CI: 5.6, 7.4) with chemotherapy.
- A phase III trial comparing nivolumab to docetaxel in patients with metastatic squamous NSCLC who had failed at least two prior regimens showed a median OS of 9.2 months for nivolumab versus 6.0 months for docetaxel (HR 0.59; 95% CI: 0.44, 0.79; *P* = .00025). The ORR in the nivolumab group was a modest 20%, but, notably, these patients developed durable responses, with a median DoR still not reached after a median 11 months of follow-up.
- A similar phase III trial evaluated nivolumab versus docetaxel in patients with nonsquamous NSCLC who had failed standard platinum-based doublet chemotherapy. In this study, nivolumab produced a median OS of 12.2 versus 9.4 months with docetaxel (HR 0.73; 96% CI: 0.59, 0.89; *P* = .00155).

- Mesothelioma
  - The combination of nivolumab and ipilimumab was granted FDA approval for the first-line treatment of unresectable malignant pleural mesothelioma based on the results of the CheckMate 743. This trial randomized (1:1) previously untreated patients with unresectable disease to either the combination of nivolumab and ipilimumab or combination chemotherapy with cisplatin or carboplatin plus pemetrexed. OS was shown to be significantly improved for patients treated with nivolumab plus ipilimumab compared with those who received chemotherapy, with a median OS of 18.1 months (95% CI: 16.8, 21.5) for the immune checkpoint inhibitor arm versus 14.1 months (95% CI: 12.5, 16.2) for the chemotherapy arm (HR 0.74; 95% CI: 0.61, 0.89; *P* = .002). Median PFS was 6.8 months (95% CI: 5.6, 7.4) and 7.2 months (95% CI: 6.9, 8.1) in the checkpoint inhibitor and chemotherapy arms, respectively (HR 1.0; 95% CI 0.82, 1.21). Confirmed ORR was 40% (95% CI: 34, 45) and 43% (95% CI: 37, 49), respectively, with a median DoR of 11.0 months in patients receiving nivolumab plus ipilimumab and 6.7 months in the chemotherapy arm.
- RCC
  - Nivolumab was approved for the treatment of advanced RCC after progression on antiangiogenic therapy based on a phase III trial which found that such patients treated with nivolumab had a median OS of 25.0 months compared to a median 19.6 months with standard second-line everolimus (HR 0.73; 98.5% CI: 0.57, 0.93; *P* = .002).

- The CheckMate 214 trial demonstrated higher OS and OR rates with the combination of nivolumab and ipilimumab compared with sunitinib among intermediate- and poor-risk patients with previously untreated advanced RCC. Estimated median OS was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (HR 0.63; 95% CI: 0.44, 0.89; $P < .001$). Objective response rates were 42% with combination treatment versus 27% ($P < .001$) with sunitinib (among which CR rates were 9% vs 1%, respectively).
- Approval for nivolumab, in combination with cabozantinib, as first-line treatment for advanced RCC was based on findings from the CheckMate 9ER trial, in which the combination resulted in improved PFS, OS, and ORR for previously untreated patients compared with those who had received sunitinib alone. Median PFS was 16.6 versus 8.3 months; HR 0.51 (95% CI: 0.41, 0.64). Median OS was not reached in either arm; HR 0.60 (95% CI: 0.40, 0.89). Confirmed ORR was 55.7% and 27.1% in the nivolumab plus cabozantinib and sunitinib arms, respectively.

- Urothelial carcinoma
  - Nivolumab was granted FDA approval for locally advanced or metastatic urothelial carcinoma progressing on or following platinum-containing chemotherapy or progressing within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy based on a phase II trial ($n = 270$), which found that such patients treated with nivolumab had an ORR of 19.6%.
- HNSCC
  - Nivolumab was granted FDA approval for recurrent or metastatic HNSCC with disease progression on or after a platinum-based therapy based on a randomized phase III trial ($n = 361$), which found that such patients treated with nivolumab had a median OS of 7.5 months compared to a median 5.1 months with standard second-line therapy (HR 0.70; 97.73% CI: 0.51, 0.96; $P = .01$).
- Classical Hodgkin lymphoma
  - Nivolumab received FDA approval for the treatment of refractory classical Hodgkin lymphoma based on data in a small cohort of 23 patients showing an ORR of 87%, including 17% with CR and 70% with PR.
- CRC
  - Nivolumab's approval to be administered as a single agent in the treatment of MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan was granted based on outcomes revealed in the CheckMate 142 trial. The ORR in previously treated patients with MSI-H or dMMR disease receiving nivolumab monotherapy was 28% (95% CI: 17, 42), with responses lasting ≥6 months in 67% of responding patients (95% CI: 38, 88).
  - Approval for the combination of nivolumab and ipilimumab as second-line treatment for MSI-H/dMMR metastatic CRC also stemmed from CheckMate 142 findings. Among 82 previously treated patients, 46% (95% CI: 35, 58) responded to the combination of nivolumab and ipilimumab. Among all responders, the median DoR was not reached (range: 1.9, 23.2+ months); 89%

had responses of 6 months or longer and 21% had responses of 12 months or longer.

- HCC
  - CheckMate 040 was a multicenter, open-label trial investigating nivolumab with or without ipilimumab in patients with HCC and Child-Pugh class A cirrhosis. In patients refractory or intolerant to sorafenib who received nivolumab monotherapy, the ORR was 14.3% (95% CI: 9.2, 20.8), with 91% of responders exhibiting responses lasting 6 months or longer and 55% with responses lasting 12 months or longer.
  - Cohort 4 of CheckMate 040 was comprised of patients who had progressed on or were intolerant to sorafenib who were treated with the combination regimen of nivolumab plus ipilimumab. The ORR for patients in this cohort was 33% (95% CI: 20, 48), with 4 CRs and 12 PRs in the 16 responding patients. Response duration ranged from 4.6 to over 30 months, with 31% of responses lasting at least 24 months.
- SCC of the esophagus
  - The efficacy of nivolumab monotherapy in the treatment of patients with unresectable advanced, recurrent, or metastatic esophageal SCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen was evaluated in the ATTRACTION-3 trial. This study found a statistically significant improvement in OS in patients receiving nivolumab compared with those receiving investigator's choice of taxane-based therapy (10.9 months [95% CI: 9.2, 13.3] vs 8.4 months [95% CI: 7.2, 9.9]) (HR: 0.77; 95% CI: 0.62, 0.96; $P = .019$), regardless of tumor PD-L1 expression level. The ORR was 19.3% (95% CI: 13.7, 26) in the nivolumab arm versus 21.5% (95% CI: 15.4, 28.8) in the chemotherapy arm; median response durations were 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2), respectively.
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma
  - Approval for the first-line use of nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma was granted based on the CheckMate 649 trial. The CheckMate 649 trial randomized (1:1) 1581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma to receive either nivolumab in combination with chemotherapy or chemotherapy alone. Two chemotherapy regimens were used with or without nivolumab—mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin). PD-L1 CPS was determined for all patients. Statistically significant improvements in PFS and OS were demonstrated for patients with PD-L1 CPS ≥ 5 who had received the combination of nivolumab and chemotherapy; median PFS was 7.7 months (95% CI: 7.0, 9.2) in the nivolumab plus chemotherapy arm versus 6.0 months (95% CI: 5.6, 6.9) in patients who had received chemotherapy alone (HR 0.68; 95% CI: 0.58, 0.79; $P < .0001$). Median OS was 14.4 months (95% CI: 13.1, 16.2) in the nivolumab plus chemotherapy arm versus 11.1 months (95% CI: 10.0, 12.1)

in patients who had received chemotherapy alone arm (HR 0.71; 95% CI: 0.61, 0.83; *P* < .0001). OS was also shown to be significantly improved for all patients who received the combination of chemotherapy and nivolumab, irrespective of PD-L1 CPS; median OS was 13.8 months (95% CI: 12.6, 14.6) in patients receiving combination therapy versus 11.6 months (95% CI: 10.9, 12.5) in the chemotherapy alone arm (HR 0.80; 95% CI: 0.71, 0.90; *P* = .0002).

Pembrolizumab (KEYTRUDA)

- Pembrolizumab is a humanized monoclonal IgG4 antibody and inhibitor of PD-1.
- On May 23, 2017, pembrolizumab became the first FDA-approved tissue-agnostic drug for cancer treatment, gaining accelerated approval for use in previously treated patients with unresectable or metastatic solid tumors determined to be MSI-H or dMMR and who have no satisfactory alternative treatment options.
- FDA approval exists for disease-specific indications, as well, including:
    - As treatment of patients with unresectable or metastatic melanoma.
    - As adjuvant treatment of patients with melanoma with nodal involvement who have undergone complete resection.
    - In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
    - In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
    - As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 and no EGFR or ALK genomic tumor aberrations and is either metastatic or stage III where patients are not candidates for surgical resection or definitive chemoradiation.
    - As a single agent for the treatment of patients with metastatic NSCLC expressing PD-L1 who have had disease progression on or after platinum-containing chemotherapy (and for those who also have disease known to harbor EGFR or ALK genomic tumor aberrations and are refractory to FDA-approved therapy for these aberrations).
    - In combination with platinum and 5-fluorouracil for the first-line treatment of patients with metastatic or unresectable, recurrent HNSCC.
    - As a single agent for first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1.
    - As a single agent for the treatment of patients with recurrent or metastatic HNSCC refractory to platinum-based chemotherapy.

- For the treatment of patients with refractory classical Hodgkin lymphoma who have relapsed after three or more prior lines of therapy.
- For the treatment of patients with refractory primary mediastinal large B-cell lymphoma (PMBCL) or who have relapsed after two or more prior lines of therapy (in the absence of need for urgent cytoreductive therapy).
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are ineligible for any platinum-containing chemotherapy, regardless of PD-L1 status.
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease have progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- For the treatment of patients with BCG-unresponsive, high-risk, non–muscle invasive bladder cancer (NMIBC) with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- For the treatment of patients with MSI-H or dMMR solid tumors who have progressed on prior treatment and who have no satisfactory alternative treatment options.
- For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC.
- For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 who have had disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy (and if appropriate, HER2/neu-targeted therapy).
- For the treatment of patients with recurrent locally advanced or metastatic SCC of the esophagus whose tumors express PD-L1 and with disease progression after one or more prior lines of systemic therapy.
- In combination with platinum- and fluoropyrimidine-based chemotherapy as first-line treatment of patients with metastatic or locally advanced esophageal carcinoma or gastroesophageal carcinoma with tumor epicenter 1 to 5 cm above the gastroesophageal junction who are not candidates for surgical resection or definitive chemoradiation who are not candidates for surgical resection or definitive chemoradiation.
- In the treatment of patients with recurrent or metastatic cervical cancer expressing PD-L1 whose disease have progressed on or after chemotherapy.
- For the treatment of patients with HCC previously treated with sorafenib.
- For treatment of patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).
- In combination with axitinib for the first-line treatment of patients with advanced RCC.
- In combination with lenvatinib for the treatment of patients with advanced endometrial carcinoma that is *not* MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
- For the treatment of unresectable or metastatic tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) solid tumors that have

progressed following prior treatment in patients who have no satisfactory alternative treatment options.
- As treatment for patients with recurrent or metastatic cutaneous SCC not curable by surgery or radiation.
- In combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1.

- Melanoma
  - Pembrolizumab's initial FDA approval for metastatic melanoma was based on two trials, one evaluating pembrolizumab in ipilimumab-naïve melanoma and one evaluating pembrolizumab in ipilimumab-refractory melanoma. Subsequent approval for adjuvant therapy was based on a randomized, double-blind trial evaluating patients with completely resected stage III melanoma, with enrollment requirements of complete resection with negative margins, lymph node dissection, and completion of radiotherapy, if indicated, within 13 weeks prior to starting treatment.
  - In an open label, multicenter, active controlled trial, 834 patients with ipilimumab-naïve metastatic melanoma were randomized 1:1:1 to pembrolizumab at 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks or ipilimumab 3 mg/kg every 3 weeks for a total of 4 doses. Patients with BRAF V600-mutated melanoma were not required to have received prior BRAF inhibitor therapy. Objective responses were found in 34% and 33% of those treated with pembrolizumab at 2 and 3 weeks, respectively, as compared to 12% in those treated with ipilimumab. In addition, OS was significantly longer in patients treated with pembrolizumab at 2 weeks (HR 0.69; 95% CI: 0.52, 0.90; $P = .004$) and 3 weeks (HR 0.63; 95% CI: 0.47, 0.83; $P < .001$), compared to those treated with ipilimumab.
  - A multicenter controlled trial randomized 540 patients with ipilimumab refractory metastatic melanoma 1:1:1 to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks or investigator's choice chemotherapy. Objective responses were found in 21% and 25% of those treated with pembrolizumab at 2 mg/kg and 10 mg/kg, respectively, as compared to 4% in those treated with chemotherapy. In addition, PFS was significantly longer in patients treated with pembrolizumab at 2 mg/kg (HR 0.57; 95% CI: 0.45, 0.73; $P < .001$) and 10 mg/kg (HR 0.50; 95% CI: 0.39, 0.64; $P < .001$) as compared to those treated with chemotherapy.
  - Approval as adjuvant therapy was based on results from the placebo-controlled EORTC1325/KEYNOTE-054 trial. Patients receiving pembrolizumab experienced fewer recurrences/deaths (26%), compared with 43% on the placebo arm (HR 0.57; 95% CI: 0.46, 0.70; $P < .001$). The RFS benefit for pembrolizumab compared with placebo was observed regardless of tumor PD-L1 expression. Median RFS was 20.4 months in the placebo arm and not reached for those receiving pembrolizumab.
- NSCLC
  - Accelerated FDA approval for pembrolizumab in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations, was

granted in May 2017 based on results of the KEYNOTE-021 study, which showed improvements in ORR and PFS for patients receiving pembrolizumab with pemetrexed and carboplatin, compared to pemetrexed and carboplatin alone. Regular approval was granted after the KEYNOTE-189 trial confirmed a statistically significant improvement in OS for patients randomized to pembrolizumab and chemotherapy (HR 0.49; 95% CI: 0.38, 0.64; $P < .001$), compared to individuals who had received placebo in combination with pemetrexed and investigator's choice of either cisplatin or carboplatin.

- Approval for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line therapy for metastatic squamous NSCLC was based on results from the KEYNOTE-407 trial, which demonstrated statistically significant improvements in OS, PFS, and ORR for patients receiving pembrolizumab in combination with chemotherapy compared with those who had received placebo plus chemotherapy. Median OS was 15.9 and 11.3 months for the pembrolizumab-chemotherapy and placebo-chemotherapy arms, respectively (HR 0.64; 95% CI: 0.49, 0.85; $P = .0017$). Median PFS was 6.4 and 4.8 months for the pembrolizumab-chemotherapy and placebo-chemotherapy arms, respectively (HR 0.56; 95% CI: 0.45, 0.70; $P < .0001$). The analysis of ORR was limited to the initial 204 patients randomized; ORR was 58% in the pembrolizumab-chemotherapy arm and 35% in the placebo-containing arm (difference of 23.6%; 95% CI: 9.9, 36.4; $P = .0008$). Estimated median response durations were 7.2 and 4.9 months, respectively.
- FDA approval for pembrolizumab as first-line treatment of patients with PD-L1–expressing stage III NSCLC with metastatic disease or who are not candidates for resection or definitive chemoradiation, with either population having no tumor EGFR or ALK genomic aberrations, resulted from findings from the KEYNOTE-042 trial. Patients had not received prior systemic treatment for metastatic NSCLC and had tumors expressing PD-L1 (TPS ≥ 1%). Statistically, significant OS improvements were shown for patients with tumors with TPS ≥ 1%, TPS ≥ 20%, and TPS ≥ 50% who were randomized to pembrolizumab compared with those who had received chemotherapy in all three populations. Median OS in the TPS ≥ 1% population was 16.7 and 12.1 months for the pembrolizumab and chemotherapy arms, respectively (HR 0.81; 95% CI: 0.71, 0.93; $P = .0036$); median OS for the TPS ≥ 20% subgroup was 17.7 and 13.0 months, respectively (HR 0.77; 95% CI: 0.64, 0.92; $P = .004$); estimated median OS for the TPS ≥ 50% subgroup was 20 and 12.2 months for those receiving pembrolizumab and chemotherapy, respectively (HR 0.69; 95% CI: 0.56, 0.85; $P = .0006$).
- Approval for pembrolizumab in NSCLC as first-line therapy was also influenced by the results of KEYNOTE-024, a phase III trial which randomized 305 patients with previously untreated advanced NSCLC with PD-L1 expression in at least 50% of tumor cells to pembrolizumab or platinum-based chemotherapy. PFS was significantly longer for pembrolizumab as compared to platinum-based chemotherapy (10.3 vs 6.0 months; HR 0.50; 95% CI: 0.37, 0.68; $P < .001$).
- FDA approval for pembrolizumab in NSCLC as second-line therapy is based upon an open-label, phase II/III study, KEYNOTE-010, which randomized 1034 patients with previously treated advanced NSCLC with PD-L1 expression in at

least 1% of tumor cells 1:1:1 to pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 every 3 weeks. OS was significantly longer for pembrolizumab 10 mg/kg versus docetaxel (12.7 vs 8.5 months; HR 0.71; 95% CI: 0.58, 0.88; P = .0008) and for pembrolizumab 2 mg/kg versus docetaxel (10.4 vs 8.5; HR 0.61; 95% CI: 0.49, 0.75; P < .0001).

- HNSCC
  - First-line treatment of metastatic or unresectable, recurrent HNSCC as a single agent and in combination with platinum and 5-fluorouracil chemotherapy was investigated in KEYNOTE-048, a multicenter, open-label, active-controlled trial in which patients who were treatment-naïve patients or who had recurrent disease considered incurable by local therapies were randomized (1:1:1) to receive one of the following regimens: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and 5-fluorouracil; or cetuximab, carboplatin or cisplatin, and 5-fluorouracil. Randomization was stratified by tumor PD-L1 expression (TPS ≥ 50% or <50%) and HPV status according to p16 IHC (positive or negative), in addition to ECOG PS (0 vs 1). A statistically significant improvement was demonstrated in OS in the overall population for patients randomized to pembrolizumab plus chemotherapy (median OS of 13.0 months) compared with cetuximab plus chemotherapy (10.7 months; HR 0.77; 95% CI: 0.63, 0.93; P = .0067), with similar results in the CPS ≥ 20 subgroup (HR 0.69; 95% CI: 0.51, 0.94) and CPS ≥ 1 subgroup (HR 0.71; 95% CI: 0.57, 0.88). Statistically significant improvements in OS were also shown for the subgroups of patients with PD-L1 CPS ≥ 1 and PD-L1 CPS ≥ 20 randomized to pembrolizumab monotherapy compared with cetuximab plus chemotherapy: in the CPS ≥ 1 subgroup, median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab plus chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; P = .0171). For the CPS ≥1 subgroup, median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab plus chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; P = .0171). For the CPS ≥ 20 subgroup, the median OS was 14.9 and 10.7 months for the pembrolizumab arm and the cetuximab plus chemotherapy arm, respectively (HR 0.61; 95% CI: 0.45, 0.83; P = .0015). A significant difference in OS was not demonstrated between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the overall population at the time of interim analysis.
  - Pembrolizumab received FDA approval for second-line treatment in HNSCC based upon KEYNOTE-012, a multicenter, nonrandomized, open-label phase Ib trial that enrolled 192 patients with recurrent or metastatic HNSCC with disease progression following platinum-containing chemotherapy. Patients received pembrolizumab at 10 mg/kg every 2 weeks (n = 53) or 200 mg every 3 weeks (n = 121). The ORR was 17.7%. Among responding patients, the median DoR had not been reached after a median 12.5 months of follow-up. ORR was 21.9% in HPV$^+$ patients and 15.9% in HPV$^-$ patients.
  - Approval was based on KEYNOTE-204 (NCT02684292), a phase III, randomized, open-label trial in 304 adult patients with relapsed or refractory cHL who had received prior treatment with at least one multiagent regimen. Patients were randomized (1:1) to receive either pembrolizumab or brentuximab vedotin for up to 2 years. PFS was statistically significantly longer

for patients in the pembrolizumab arm, at 13.2 months (95% CI: 10.9, 19.4), versus 8.3 months (95% CI: 5.7, 8.8) for patients receiving brentuximab vedotin (HR of 0.65; 95% CI: 0.48, 0.88; *P* = .0027).

- Classical Hodgkin lymphoma
  - Approval was based on KEYNOTE-204 (NCT02684292), a phase III, randomized, open-label trial in 304 adult patients with relapsed or refractory cHL who had received prior treatment with at least one multiagent regimen. Patients were randomized (1:1) to receive either pembrolizumab or brentuximab vedotin for up to 2 years. PFS was statistically significantly longer for patients in the pembrolizumab arm, at 13.2 months (95% CI: 10.9, 19.4), versus 8.3 months (95% CI: 5.7, 8.8) for patients receiving brentuximab vedotin (HR of 0.65; 95% CI: 0.48, 0.88; *P* = .0027).
- PMBCL
  - Accelerated approval for the treatment of patients with refractory PMBCL or who have relapsed after two or more prior lines of therapy was based on data from the multicenter, open-label, single-arm trial known as KEYNOTE-170. Patients were treated with pembrolizumab until unacceptable toxicity or documented disease progression or for up to 24 months for patients who did not progress. ORR was 45% (95% CI: 32, 60), with median DoR not reached within the follow-up period (median 9.7 months).
  - Pembrolizumab should not be used in the treatment of patients with PMBCL who require urgent cytoreductive therapy.
- Urothelial carcinoma
  - Results from the KEYNOTE-052, -045, and -057 trials led to the approval of pembrolizumab for use in the treatment of patients with urothelial carcinoma who are cisplatin ineligible, who have disease progression following platinum-based therapy, or who exhibit BCG-unresponsive high-risk NMIBC.
  - Approval for first-line treatment was based on data from a single-arm, open-label trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed ineligible to receive cisplatin-containing chemotherapy. Initial results revealed an ORR of 28.6% (95% CI: 24, 34). A median DoR was not reached; observed response durations ranged from 1.4+ to 17.8+ months. Responses were observed regardless of PD-L1 status, with a confirmed ORR of 21% (95% CI: 16%-26%) in patients with CPS < 10 or unknown and 47% (95% CI: 38%, 57%) in those with CPS ≥ 10. Median DoR was not reached in either of these subgroups. At the time of data cutoff, responses were ongoing for at least 6 months in 52% of responders and for at least 12 months in 7% of responding patients.
  - In June 2018, the FDA added PD-L1 status to the label for pembrolizumab for the frontline approval for use in platinum-ineligible patients with urothelial carcinoma, limiting the indication to treatment of patients with locally advanced or metastatic urothelial carcinoma who cisplatin-ineligible and whose tumors express PD-L1 (CPS ≥ 10) or in patients who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 status. This limitation was based on the lower OS rates shown with the PD-1 inhibitor compared with OS rates shown with platinum-based chemotherapy for patients with metastatic PD-L1-low-expressing platinum-eligible urothelial carcinoma. In patients who

are already receiving pembrolizumab and who are responding to treatment and are cisplatin-ineligible, continuation of treatment can be considered, regardless of PD-L1 status.

- Approval for the second-line indication of treatment for locally advanced or metastatic disease was based on data from the KEYNOTE-045 study, a multicenter, randomized, active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Statistically significant improvements in OS and ORR were demonstrated for patients assigned to pembrolizumab as compared to chemotherapy. Median OS was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR 0.73; 95% CI: 0.59, 0.91, *P* = .004). ORR was 21% for those receiving pembrolizumab and 11% for the chemotherapy arm (*P* = .002). No statistically significant difference in PFS between the two arms was observed.
- The efficacy of pembrolizumab in the treatment of patients with BCG-unresponsive high-risk NMIBC was shown in a multicenter, single-arm trial in which patients received pembrolizumab monotherapy 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression. CR rate was 41% (95% CI: 31, 51); median response duration was 16.2 months (0.0+, 30.4+). Forty-six percent of responding patients experienced CR lasting at least 12 months.

- MSI-H cancer and MSI-H/dMMR CRC
  - Accelerated FDA approval was based on data from patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multicohort, multicenter, single-arm clinical trials. Ninety of the 149 collectively enrolled patients had CRC; 59 patients had one of fourteen other cancer types. Patients received pembrolizumab for either every 2 weeks or every 3 weeks until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered. The ORR was 39.6% (95% CI: 31.7, 47.9), with responses lasting 6 months or more for 78% percent of responders. The ORR for patients with CRC was 36%; the ORR for patients with other cancer types was 46%.
  - Regular approval for first-line treatment of unresectable or metastatic MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan was based on the KEYNOTE-177 trial. In this trial, patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC were randomized (1:1) to receive either pembrolizumab or investigator's choice of mFOLFOX6/FOLFIRI ± bevacizumab or cetuximab. Patients randomized to chemotherapy were offered pembrolizumab at the time of disease progression. Median PFS was 16.5 months (95% CI: 5.4, 32.4) in the pembrolizumab arm and 8.2 months (95% CI: 6.1, 10.2) in the chemotherapy arm (HR 0.60, 95% CI 0.45, 0.80; two-sided *P*-value = .0004). At the time of the PFS analysis, the OS data were not mature.
- Gastric, gastroesophageal, and esophageal cancer

- Pembrolizumab's accelerated approval for the treatment of previously treated patients with PD-L1–expressing (CPS ≥ 1) recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma of which 55% had tumors expressing PD-L1 stemmed from the results of an open-label, multicenter, noncomparative, multicohort trial of 259 patients, 55% of whom had tumors expressing PD-L1 and either MSS, or undetermined MSI or MMR status. For this subgroup of patients, ORR was 13% (95% CI: 8.2, 20.0); response duration ranged from 2.8+ to 19.4+ months, with 58% of responders having response durations of 6 months or longer and 26% having response durations of 12 months or longer. ORR for the subgroup of patients determined to have MSI-H tumors (3% of the overall population) was 57%, with response duration ranging from 5.3+ to 14.1+ months.
- Pembrolizumab is indicated for the treatment of patients with recurrent, locally advanced or metastatic SCC of the esophagus whose tumors express PD-L1 (CPS ≥ 10) and who have had disease progression after one or more prior lines of systemic therapy. Approval was based on two studies, one evaluating patients who had progressed on or after one prior line of systemic treatment for advanced or metastatic disease and the other evaluating those who progressed on or after at least two prior systemic treatments for advanced disease. Both studies randomized patients to either pembrolizumab monotherapy or investigator's choice of paclitaxel, docetaxel, or irinotecan. The HR for OS in patients treated with one or more prior regimens whose tumors expressed PD-L1 CPS ≥ 10 was 0.64 (95% CI: 0.46, 0.90). Median OS was 10.3 months (95% CI: 7.0, 13.5) and 6.7 months (95% CI: 4.8, 8.6) in the pembrolizumab and control arms, respectively. In those whose tumors expressed PD-L1 (CPS ≥ 10) and had progressed on or after at least two prior systemic treatments, ORR was 20% (95% CI: 8, 37) with DoR ranging from 4.2 to 25.1+ months. Seventy-one percent of these responders had responses of 6 months or longer and 57% demonstrated responses of 12 months or longer.
- Approval for pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy for the first-line treatment of patients with metastatic or locally advanced esophageal carcinoma or gastroesophageal carcinoma with tumor epicenter 1 to 5 cm above the gastroesophageal junction (Siewert type 1) who are not candidates for surgical resection or definitive chemoradiation was based on the KEYNOTE-590 trial. The KEYNOTE-590 trial randomized (1:1) 749 patients with previously untreated advanced/unresectable or metastatic esophageal adenocarcinoma, esophageal SCC, or gastroesophageal junction adenocarcinoma to receive either pembrolizumab in combination with cisplatin and fluorouracil or placebo with cisplatin and fluorouracil until unacceptable toxicity or disease progression. Statistically significant improvements in OS and PFS were demonstrated for patients randomized to pembrolizumab with chemotherapy, with a median OS of 12.4 months (95% CI: 10.5, 14.0) for patients receiving pembrolizumab and chemotherapy versus 9.8 months (95% CI: 8.8, 10.8) for those receiving placebo and chemotherapy (HR 0.73; 95% CI: 0.62, 0.86; $P < .0001$). Median PFS was 6.3 (95% CI: 6.2, 6.9) and 5.8 months (95% CI: 5.0, 6.0), respectively (HR 0.65; 95% CI: 0.55, 0.76; $P < .0001$). Objective response rates were 45.0% in individuals who had received pembrolizumab and 29.3% in those who had not received the

immune checkpoint inhibitor ($P < .0001$). PD-L1 status was determined for all patients. Among patients with CPS ≥ 10, the median OS was 13.5 months with the combination of pembrolizumab and chemotherapy versus 9.4 months with chemotherapy alone (HR 0.62; $P < .0001$); the median PFS was 7.5 and 5.5 months, respectively (HR 0.51; $P < .0001$.

- Cervical cancer
  - Pembrolizumab's indication for the second-line treatment of patients with PD-L1–expressing (CPS ≥ 1) cervical cancer was based on a multicenter, nonrandomized, open-label, multicohort trial that demonstrated an ORR of 14.3% (95% CI: 7.4, 24.1) in patients with PD-L1–expressing tumors who had received at least one line of chemotherapy for metastatic disease. A median DoR was not reached (range 4.1, 18.6+ months); 91% of responders had a response duration ≥6 months. No responses were observed in patients whose tumors did not have PD-L1 expression (CPS < 1).
- HCC
  - Accelerated approval for the treatment of sorafenib-treated patients with HCC was based on KEYNOTE-224, a single-arm, multicenter trial enrolling 104 patients with HCC that demonstrated an ORR of 17% (95% CI: 11, 26) for patients treated with pembrolizumab monotherapy. Durations of response ranged from 3.1 to 16.7 months; 89% of responders had response durations of ≥6 months and 56% had response durations of ≥12 months.
- MCC
  - Findings from the KEYNOTE-017 study provided the basis for accelerated approval for the use of pembrolizumab for the treatment of patients with MCC. Treatment-naïve patients with recurrent locally advanced or metastatic MCC enrolled in the nonrandomized, open-label KEYNOTE-017 trial demonstrated an ORR of 56% (95% CI: 41, 70), with a CR rate of 24%, following treatment with pembrolizumab monotherapy. Ninety-six percent had response durations of greater than 6 months; 54% had response durations of greater than 12 months.
- RCC
  - FDA approval for pembrolizumab in combination with axitinib for the first-line treatment of patients with advanced RCC was based on findings from the KEYNOTE-426 trial, a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC, regardless of PD-L1 tumor expression status. Treatment with the combination of pembrolizumab and axitinib resulted in a statistically significant improvement in OS (HR 0.53; 95% CI: 0.38, 0.74; $P < .0001$) compared to treatment with sunitinib. Twelve month OS rate was 90% in the combination arm and 78% for those treated with sunitinib. An improvement in PFS was also demonstrated for patients receiving pembrolizumab plus axitinib (HR 0.69; 95% CI: 0.57, 0.84; $P = .0001$). The median PFS was 15.1 and 11.1 months for those receiving pembrolizumab plus axitinib versus sunitinib, respectively.
- Endometrial carcinoma
  - Accelerated approval for the combination of pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not MSI-

H or dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation was based on findings from Study 111/KEYNOTE-146. This trial was a single-arm, multicenter, open-label, multicohort trial that enrolled 108 patients with metastatic endometrial carcinoma who had disease progression following prior systemic therapy. The ORR in the 94 patients whose tumors were not MSI-H or dMMR was 38.3% (95% CI: 29, 49) with 10 CRs (10.6%) and 26 PRs (27.7%). Twenty-five patients (69%) had response durations ≥6 months. Median DoR was not reached at the time of data cutoff.

- Breast cancer
  - Accelerated approval for pembrolizumab to be used in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) resulted from findings generated from the KEYNOTE-355 trial. KEYNOTE-355 was a multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy of pembrolizumab or placebo in combination with different chemotherapy treatments (paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin) in previously untreated patients with locally recurrent unresectable or metastatic TNBC. Median PFS in patients with CPS ≥ 10 receiving the combination of pembrolizumab and chemotherapy was 9.7 months (95% CI: 7.6, 11.3) and 5.6 months (95% CI: 5.3, 7.5) in the placebo arm (HR 0.65; 95% CI: 0.49, 0.86; one-sided *P*-value = .0012).
- Cutaneous SCC
  - The KEYNOTE-629 trial was the trial upon which FDA approval was based for pembrolizumab for treatment of patients with recurrent or metastatic cutaneous SCC not curable by surgery or radiation. The trial demonstrated an ORR of 34% (95% CI: 24, 44) for those receiving pembrolizumab. Median DoR was not reached (range: 2.7, 13.1+ months).
- TMB-H solid tumors
  - Accelerated approval for pembrolizumab for the treatment of patients with unresectable or metastatic TMB-H (≥10 mutations/megabase [mut/Mb]) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options was based on the KEYNOTE-158 study, a prospectively planned retrospective analysis of 10 cohorts that included previously treated patients with various TMB-H solid tumors. Thirteen percent of these patients had tumors identified as TMB-H (defined as TMB ≥ 10 mut/Mb); the ORR for these patients who received at least one dose of pembrolizumab was 29% (95% CI: 21, 39), with 4% exhibiting CR and 25% demonstrating PR. The median DoR was not reached, with 57% of patients having response durations ≥ 12 months and 50% of patients having response durations ≥24 months.

Atezolizumab (TECENTRIQ)

- Atezolizumab is an anti–PD-L1 antibody that is FDA-approved as monotherapy in the treatment of urothelial carcinoma and certain subtypes of NSCLC; it is also approved to be used in combination with chemotherapy agents in the treatment of NSCLC, SCLC, and TNBC, as well as in combination with bevacizumab in the treatment of HCC and in combination with cobimetinib and vemurafenib to treat melanoma.
- Urothelial carcinoma
    - Atezolizumab is currently approved for the first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating ICs covering ≥5% of the tumor area) or for those who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status.
    - The IMvigor130 trial was a randomized phase III trial that compared atezolizumab with or without platinum-based chemotherapy versus placebo plus platinum-based chemotherapy in 1213 previously untreated patients with locally advanced or metastatic urothelial carcinoma. Patients were randomized to one of the following three groups: atezolizumab plus platinum-based chemotherapy, atezolizumab monotherapy, or placebo plus platinum-based chemotherapy. Patients receiving chemotherapy received gemcitabine plus either carboplatin or cisplatin. At a median follow-up of 11.8 months, the final median PFS in patients receiving combination atezolizumab and chemotherapy was 8.2 months (95% CI: 6.5, 8.3) compared with 6.3 months (95% CI: 6.2, 7.0) in patients receiving the combination of placebo and chemotherapy (HR 0.82, 95% CI: 0.70, 0.96; one-sided P = .007). At the interim analysis, a clinically meaningful improvement in OS for the combination arm versus chemotherapy was observed, with a median OS of 16.0 months (95% CI: 13.9, 18.9) and 13.4 months (95% CI: 12.0, 15·2) for patients receiving atezolizumab/chemotherapy and placebo/chemotherapy, respectively (HR 0.83; 95% CI: 0.69, 1.00; one-sided P = .027). Randomization was also stratified by PD-L1 immune cell expression status (IC0 [<1%] vs IC1 [≥1% and <5%] vs IC2/3 [≥5%]). An OS benefit was observed for patients with PD-L1-positive tumors (IC2/3) who were treated with atezolizumab monotherapy compared with patients treated with placebo/chemotherapy (HR, 0.68; 95% CI, 0.43-1.08). The median OS for patients receiving the PD-L1 inhibitor was not estimated; median OS was 17.8 months for patients receiving in the chemotherapy arm. In the PD-L1 IC0/1 subgroup, the median OS was 13.5 months with atezolizumab monotherapy versus 12.9 months with chemotherapy/placebo (HR 1.07; 95% CI: 0.86, 1.33).
- NSCLC
    - Atezolizumab is approved for treatment of patients with disease progression during or following platinum-based chemotherapy and in patients in whose tumors EGFR- or ALK-sensitizing genomic alterations exist who have had disease progression following treatment with EGFR or ALK tyrosine kinase

inhibitors. Approval was based on the phase III OAK trial in which 850 patients with previously treated metastatic NSCLC were randomized to atezolizumab or docetaxel. Median OS was improved with atezolizumab as compared with docetaxel (13.8 vs 9.6 months; HR 0.73; 95% CI: 0.62, 0.87; *P* = .0003).

- Approval for atezolizumab in combination with paclitaxel protein-bound and carboplatin as first-line treatment for patients with metastatic nonsquamous NSCLC with no EGFR or ALK aberrations based on the Impower130 trial. This trial randomized (2:1) patients with stage IV nonsquamous NSCLC who had received no prior chemotherapy for metastatic disease but could have received prior EGFR or ALK kinase inhibitor therapy, if appropriate, to receive atezolizumab, paclitaxel protein-bound, and carboplatin, followed by single-agent atezolizumab or to receive paclitaxel protein-bound and carboplatin, followed by maintenance pemetrexed at investigator's discretion. Median PFS in the subpopulation of patients documented to have no EGFR or ALK genomic tumor aberrations was 7.2 months (95% CI: 6.7, 8.3) for the atezolizumab arm compared to 6.5 months (95% CI: 5.6, 7.4) for the control arm (HR 0.75; 95% CI: 0.63, 0.91; *P* = .0024). Median OS in this subpopulation was 18.6 months (95% CI: 15.7, 21.1) for those receiving atezolizumab and chemotherapy and 13.9 months (95% CI: 12.0, 18.7) for patients receiving chemotherapy alone (HR 0.80; 95% CI: 0.64, 0.99; *P* = .0384).
- Atezolizumab is approved in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of adult patients with metastatic nonsquamous NSCLC with no EGFR or ALK aberrations. Approval was based on the IMpower150 trial, which randomized (1:1:1) 1202 chemotherapy-naïve patients with metastatic nonsquamous NSCLC (87% of whom harbored no EGFR or ALK tumor aberrations) to receive one of the following: atezolizumab, carboplatin, paclitaxel, and bevacizumab (four drug regimen); atezolizumab, carboplatin, and paclitaxel (three-drug regimen); or carboplatin, paclitaxel, and bevacizumab (control arm), followed by maintenance of bevacizumab and atezolizumab in the four-drug arm, maintenance of atezolizumab in the three-drug arm, and maintenance of bevacizumab in the control arm. Among patients without EGFR or ALK mutations, estimated median OS was 19.2 months for those receiving the four drug regimen and 14.7 months for those in the control arm (HR 0.78; 95% CI: 0.64, 0.96; *P* = .016). The estimated median PFS was 8.5 and 7.0 months for patients receiving the four-drug regimen and those in the control arm, respectively (HR 0.71; 95% CI: 0.59, 0.85; *P* = .0002). ORRs were 55% and 44% in the four-drug arm and control arm, respectively. No significant differences in interim OS or final PFS were observed between the three-drug arm and the control arm.
- Atezolizumab was granted approval for use in the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1–stained ≥50% of tumor cells or PD-L1–stained tumor-infiltrating ICs covering ≥10% of the tumor area), with no EGFR or ALK genomic tumor aberrations. The IMpower110 trial randomized (1:1) treatment-naïve patients with stage IV, PD-L1–expressing (TC ≥ 1% or IC ≥ 1%) NSCLC to receive either atezolizumab- or platinum-based therapy. A statistically significant improvement in OS was demonstrated for patients whose tumors had high PD-L1 expression who received atezolizumab (median OS of 20.2 months; 95% CI:

16.5, ÑE) compared to those with high PD-L1-expressing tumors treated with platinum-based chemotherapy (13.1 months; 95% CI: 7.4, 16.5) (HR 0.59; 95% CI: 0.40, 0.89; *P* = .0106). There was no statistically significant difference in OS for patients with tumors with lower levels of PD-L1 expression (TC ≥ 5% or IC ≥ 5%; and TC ≥ 1% or IC ≥ 1%). Median PFS was 8.1 months (95% CI: 6.8, 11.0) in patients receiving atezolizumab and 5.0 months (95% CI: 4.2, 5.7) in those receiving the platinum-based therapy (HR 0.63; 95% CI: 0.45, 0.88). Confirmed ORR was 38% (95% CI: 29, 48) and 29% (95% CI: 20, 39), respectively.

- TNBC
  - Atezolizumab is approved in combination with paclitaxel protein-bound for treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (≥1%). Approval for this indication was based on results from the IMpassion130 trial that randomized (1:1) 902 treatment-naïve patients with unresectable locally advanced or metastatic TNBC to receive either atezolizumab or placebo infusions on days 1 and 15 of every 28-day cycle, plus paclitaxel protein-bound on days 1, 8, and 15 of every 28-day cycle. Median PFS in patients whose tumors expressed PD-L1 was 7.4 months (6.6, 9.2) for patients receiving atezolizumab with paclitaxel protein-bound and 4.8 months (3.8, 5.5) for those receiving placebo with paclitaxel protein-bound (stratified HR 0.60; 95% CI: 0.48, 0.77; *P* < .0001). The ORR was 53% for the atezolizumab arm and 33% for the placebo-containing arm. OS data were immature with 43% deaths in the intent-to-treat population.
  - Atezolizumab is not indicated for use in combination with paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC.
- SCLC
  - Atezolizumab is approved in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage SCLC (ES-SCLC). Approval was based on the IMpower133 study, a trial that randomized (1:1) previously untreated patients with ES-SCLC to receive atezolizumab, carboplatin, and etoposide for a maximum of four cycles, followed by atezolizumab or to receive placebo, carboplatin, and etoposide for a maximum of four cycles, followed by placebo. ORRs did not significantly differ; however, both PFS and OS were significantly improved in patients receiving atezolizumab with carboplatin and etoposide compared to patients in the placebo arm. Median OS was 12.3 months (10.8, 15.9) for patients receiving atezolizumab with chemotherapy and 10.3 months (9.3, 11.3) for those receiving placebo with chemotherapy (HR 0.70; 95% CI: 0.54, 0.91; *P* = .0069). Median PFS was 5.2 months (4.4, 5.6) compared with 4.3 months (4.2, 4.5) in the atezolizumab and placebo arms, respectively (HR 0.77; 95% CI: 0.62, 0.96; *P* = .0170).
- HCC
  - Atezolizumab is approved in combination with bevacizumab for first-line treatment of patients with unresectable or metastatic HCC. Approval was based on findings generated by the IMbrave150 trial, which randomized (2:1) previously untreated patients with unresectable or metastatic HCC to receive

either atezolizumab and bevacizumab or sorafenib. Median OS was not reached in patients who received atezolizumab plus bevacizumab; median OS was 13.2 months (95% CI: 10.4, NE) in the patients who received sorafenib (HR 0.58; 95% CI: 0.42, 0.79; *P* = .0006). The estimated median PFS was 6.8 months (95% CI: 5.8, 8.3) in the combination therapy arm versus 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm (HR 0.59; 95% CI: 0.47, 0.76; *P* < .0001). Both RECIST and mRECIST assessment for HCC criteria were utilized in analyses of response; ORR per RECIST 1.1 was 28% (95% CI: 23, 33) in those receiving dual-agent treatment compared with 12% (95% CI: 7, 17) in the sorafenib group (*P* < .0001). The ORR per mRECIST was 33% (95% CI: 28, 39) versus 13% (95% CI: 8, 19), respectively (*P* < .0001).

- Melanoma
  - Atezolizumab is approved in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Approval for treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma was based on the IMspire150 study, which randomized (1:1) patients to either atezolizumab, cobimetinib, and vemurafenib or placebo, cobimetinib, and vemurafenib following a 28-day cycle of treatment of patients in both arms with cobimetinib and vemurafenib. Median PFS was 15.1 months (95% CI: 11.4, 18.4) and 10.6 months (95% CI: 9.3, 12.7) in the atezolizumab arm and the placebo arm, respectively (HR 0.78; 95% CI: 0.63, 0.97; *P* = .0249). No significant differences in OS, ORR, and DoR were demonstrated between the groups.

Durvalumab (IMFINZI)

- Durvalumab is a PD-L1–blocking antibody that is indicated for the treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy and in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with ES-SCLC.
- NSCLC
  - Durvalumab's indication for use in patients with NSCLC was based on a planned interim analysis of PFS from the PACIFIC trial, a randomized double-blind, placebo-controlled trial evaluating durvalumab versus placebo in patients who had completed concurrent platinum-based chemotherapy and radiation within 42 days prior to study drug initiation. A statistically significant improvement in PFS for durvalumab compared to placebo was demonstrated (HR 0.52; 95% CI: 0.42, 0.65; *P* = .00010).
- SCLC
  - Approval for use in ES-SCLC was based on the CASPIAN trial, a randomized trial evaluating previously untreated patients receiving either durvalumab in combination with chemotherapy or chemotherapy alone. Median OS was

13.0 months (95% CI: 11.5, 14.8) in the durvalumab plus chemotherapy arm compared with 10.3 months (95% CI: 9.3, 11.2) in the chemotherapy alone arm (HR 0.73; 95% CI: 0.59, 0.91; *P* = .0047). Median PFS in the durvalumab plus chemotherapy arm was 5.1 months (95% CI: 4.7, 6.2) and 5.4 months (95% CI: 4.8, 6.2) in patients receiving chemotherapy alone (HR 0.78; 95% CI: 0.65, 0.94). ORRs were 68% (95% CI: 62, 73) in the durvalumab plus chemotherapy arm and 58% (95% CI: 52, 63) in the chemotherapy alone arm.

Avelumab (BAVENCIO)

- Avelumab is an anti–PD-L1 antibody that holds FDA approval for use in MCC, urothelial carcinoma, and RCC.
- MCC
  - Avelumab was granted accelerated approval by the FDA for treatment of metastatic MCC in March 2017. Approval of avelumab for MCC was based upon data from the phase I multicenter JAVELIN Merkel 200 trial, demonstrating an ORR of 33% (95% CI: 23.3, 43.8). The CR rate was 22% and PR rate was 11%, with 86% of responses durable at 6 months. No correlation between tumor PD-L1 status and responses was observed.
- Urothelial carcinoma
  - Avelumab received accelerated approved for treatment of locally advanced or metastatic urothelial carcinoma that has progressed on or following platinum-based chemotherapy or has progressed within 12 months of adjuvant/neoadjuvant platinum-based therapy. It is also approved as maintenance therapy in patients with locally advanced or metastatic urothelial carcinoma who have not progressed with first-line platinum-containing chemotherapy.
  - Approval for urothelial carcinoma was based upon findings from the urothelial cohorts (*n* = 242) in the multicenter JAVELIN phase I, single arm trial in solid tumors. Data reported in March 2016 from 153 patients with 6 months follow-up demonstrated an ORR of 17.7% (95% CI: 12.0, 24.6) with 9 CRs and 18 PRs. The 24-week response rate was 92% (95% CI: 71.6, 97.9), and the median was not reached. The median OS was 7 months (95% CI: 5.6, 11.2). Of evaluable tumors, 56 patients' tumors were PD-L1+ (based on 5% PD-L1 staining) and 75 were PD-L1-negative. ORR was 25% (95% CI: 14.4, 38.4) and 14.7% (95% CI: 7.6, 24.7; *P* = .178), respectively, suggesting that PD-L1 tumor status by this method is not a predictor of response.
  - Avelumab is also approved for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. Approval was based on the JAVELIN Bladder 100 trial, in which patients were randomized (1:1) to receive either avelumab plus best supportive care (BSC) or BSC alone following last chemotherapy dose. Median OS in all patients (regardless of PD-L1 expression) was 21.4 months in those receiving avelumab compared to 14.3 months in those receiving BSC alone arm (HR: 0.69; 95% CI: 0.56, 0.86; *P* = .001). Among patients

with PD-L1–expressing tumors (51%), the HR for OS was 0.56 (95% CI: 0.40, 0.79; $P < .001$). In an exploratory analysis of patients with PD-L1–negative tumors (39%), the OS HR was 0.85 (95% CI: 0.62, 1.18).

- RCC
  - Avelumab is approved to be given in combination with axitinib for the first-line treatment of patients with advanced RCC. Approval for the use of avelumab plus axitinib to treat patients with RCC was based on the JAVELIN Renal 101 trial, which randomized previously untreated patients with advanced RCC to receive either avelumab in combination with axitinib or sunitinib monotherapy. Statistically significant improvements in PFS were demonstrated in the total population (HR 0.69; 95% CI: 0.56, 0.84; $P = .0002$), as well as in patients with PD-L1–expressing tumors (HR 0.61; 95% CI: 0.48, 0.79; $P = .0001$). Median PFS was 13.8 months for patients on the avelumab plus axitinib arm and 8.4 months for patients who received sunitinib. OS data were immature with 27% deaths in the intent-to-treat population (median OS follow-up was 19 months).

Cemiplimab (LIBTAYO)

- Cemiplimab is a PD-1–blocking antibody that is indicated for the treatment of subgroups of patients with locally advanced or metastatic cutaneous SCC or basal cell carcinoma (BCC), as well as for the first-line treatment of patients with advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation whose tumors have high PD-L1 expression with no EGFR, ALK, or ROS1 aberrations.
- Cutaneous SCC
  - Cemiplimab was first approved for the treatment of patients with metastatic cutaneous SCC or locally advanced cutaneous SCC who are ineligible for curative surgery or radiation. Approval was based on the R2810-ONC-1423 and R2810-ONC-1540 trials. Among all patients with locally advanced and metastatic cutaneous SCC combined who had received cemiplimab, ORR was 47.2% (95% CI: 38, 57), with 4% of responders exhibiting CR and 44% demonstrating PR. Median DoR was not reached (range: 1.0-15.2+ months); 61% of responses were durable for 6 months or longer.
- BCC
  - Findings from Study 1620, a multicenter, nonrandomized trial evaluating the effects of cemiplimab on ORR and DOR in patients with advanced BCC who had previously been treated with a hedgehog pathway inhibitor (HHI) or for whom a HHI was not appropriate, provided the basis for approval of the use of the PD-1 inhibitor in this patient population.
  - Study 1620 demonstrated an ORR of 29% (95% CI: 19, 40) for the 84 patients with locally advanced BCC receiving cemiplimab with a median DoR not reached (range: 2.1-21.4+ months); 79% of these responders maintained their

responses for at least 6 months. Among the 28 patients with metastatic BCC receiving cemiplimab, the ORR was 21% (95% CI: 8, 41) with a median DoR not reached (range: 9-23.0+ months); all responders maintained responses for 6 months or longer.

- NSCLC
  - Approval for cemiplimab to be used as first-line treatment of patients with advanced NSCLC was granted based on results of Study 1624, a multicenter, randomized trial evaluating OS and PFS in 710 treatment-naïve patients with locally advanced or metastatic NSCLC receiving either cemiplimab or platinum-based chemotherapy. Only patients whose tumors had high PD-L1 expression (TPS ≥ 50%) were eligible. Patients with EGFR, ALK, or ROS1 genomic tumor aberrations were ineligible. Statistically significant improvements in OS and PFS were demonstrated for patients receiving cemiplimab compared to those treated with platinum-based chemotherapy. Median OS was 22.1 months (95% CI: 17.7, NE) for patients in the cemiplimab arm compared with 14.3 months (95% CI: 11.7, 19.2) in the chemotherapy arm (HR 0.68; 95% CI: 0.53, 0.87, P = .0022). Median PFS was 6.2 months (4.5, 8.3) in the cemiplimab arm and 5.6 months (4.5, 6.1) in the chemotherapy arm (HR 0.59; 95% CI: 0.49, 0.72, P < .0001). ORRs were 37% (95% CI: 32, 42) and 21% (95% CI: 17, 25) in the cemiplimab and chemotherapy arms, respectively.

Dostarlimab (JEMPERLI)

- Dostarlimab is a PD-1–blocking antibody that is indicated for the treatment of patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.
- Approval for this indication was based on findings from the GARNET trial, a multicenter, multicohort, open-label trial conducted in patients with advanced solid tumors, of which cohort A1 was comprised of 71 previously treated patients with dMMR recurrent or advanced endometrial cancer who progressed on or following a platinum-containing regimen. ORR was 42.3 % (95% CI: 30.6; 54.6), with 12.7% of patients achieving CR and 29.6% demonstrating PR. The median DoR was not reached (range 2.6-22.4+ months); 93.3% of responders had a DoR of ≥ 6 months.

Adoptive Cell Transfer Therapies

- Only CAR T cell therapy is currently FDA-approved for use in the United States, although other types of therapies, such as TCR therapy, TIL therapy, and NK cell therapy, are being investigated in clinical trials. Five CAR T cell therapies are FDA-approved for use. Their indications are for the treatment of hematological malignancies; no therapy has been granted approval for use in the treatment of solid malignancies, thus far.
- CAR T cell therapy typically requires lymphodepletion with fludarabine and cyclophosphamide prior to cell delivery, which may place patients at risk for serious infection.
- Neutropenia, leukopenia, lymphopenia, thrombocytopenia, anemia, and hypogammaglobulinemia can often occur with CAR T cell therapy.
- Potential adverse effects that can occur with these therapies are cytokine release syndrome (CRS) and neurological toxicity, both of which can be fatal or life-threatening. Availability of tocilizumab should be confirmed prior to treatment and patients should be closely monitored for neurological events.
- Individuals treated with these therapies are also at risk for the development of secondary malignancies and must undergo life-long monitoring.
- Tisagenlecleucel (KYMRIAH)
    - Tisagenlecleucel was the first cell-based gene therapy to be approved by the FDA; it is approved for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and young adults up to age 25 with relapsed or refractory acute lymphoblastic leukemia (ALL).
    - Efficacy and safety of tisagenlecleucel treatment in adult patients were evaluated in the JULIET trial, an open-label, multicenter, single-arm trial that demonstrated CR in 22 of an efficacy-evaluable population of 68 patients who had previously been treated with rituximab and anthracycline or who relapsed following autologous HSCT. The median time to first response (CR or PR) was 0.9 months (range: 0.7-3.3 months). The median DoR was not reached. Response durations were longer in patients who achieved CR, as compared to patients with best response of PR. Of the 22 patients who experienced CR, 9 achieved this response by 1 month, 12 more patients by month 3, and the last patient by month 6 following cell delivery.
    - Efficacy in pediatric and young adults with relapsed or refractory B-cell precursor ALL was evaluated in an open-label single-arm trial known as the ELIANA trial. Among 63 infused patients, 52 (83%) achieved CR or complete remission with incomplete count recovery (CRi), all of which were minimum

residual disease (MRD)-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2-14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders.

- Axicabtagene ciloleucel (YESCARTA)
  - Axicabtagene ciloleucel is FDA-approved for the use of treatment of individuals with the following conditions that have either not responded to or have relapsed following two or more lines of systemic therapy:
    - DLBCL
    - PMBCL
    - High-grade B-cell lymphoma
    - DLBCL that results from follicular lymphoma (FL)
    - Relapsed or refractory FL
  - A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of axicabtagene ciloleucel in adult patients with relapsed or refractory aggressive B-cell NHL. Of 101 patients receiving axicabtagene ciloleucel, 76% had DLBCL, 16% had transformed FL, and 8% had PMBCL. Fifty-two patients achieved CR, with 14 initially having stable disease (7 patients) or PR (7 patients). The median time to response was 0.9 months (range: 0.8-6.2 months). Median time to improvement was 2.1 months (range: 1.6-5.3 months). Response durations were longer in the patients who achieved CR, as compared to patients with PR as best response.
  - The ZUMA-5 study evaluated axicabtagene ciloleucel in adult patients with relapsed or refractory FL after two or more lines of therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Among 81 efficacy-evaluable patients in the primary analysis, the ORR was 91% (95% CI: 83, 96) with 60% of responders achieving CR; median time to response was 1 month. The median DoR was not reached, and the 1 year rate of continued remission was 76.2% (95% CI: 63.9, 84.7). For all leukapheresed patients (n = 123), the ORR was 89% (95% CI: 83, 94) with 62% of responding patients achieving CR.
- Lisocabtagene maraleucel (BREYANZI)
  - Lisocabtagene maraleucel is indicated for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including:
    - DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma)
    - High-grade B-cell lymphoma
    - PMBCL
    - FL, grade 3B
  - The efficacy of lisocabtagene maraleucel in adult patients with relapsed or refractory large B-cell NHL after at least two lines of therapy was evaluated in an open-label, multicenter, single-arm trial known as the TRANSCEND trial. Diagnoses of the 192 patients in the main efficacy population included de novo DLBCL (53%), DLBCL transformed from indolent lymphoma (25%), high-grade B-cell lymphoma (14%), PMBCL (7%), and FL, grade 3B (1.0%). The ORR was 73%, with 104 patients achieving CR and 37 patients achieving PR. The median time to first CR was 1.0 month (range 0.8, 12.5). Of the 104 patients who achieved CR, 23 initially had stable disease (6 patients) or PR (17 patients), with a median time to improvement of 2.2 months (range: 0.7-11.6 months).

Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR. Of the 104 patients who achieved CR, 68 (65%) had remission lasting at least 6 months and 64 (62%) had remission lasting at least 9 months.

- Brexucabtagene autoleucel (TECARTUS)
  - Brexucabtagene autoleucel is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
  - Efficacy and safety of brexucabtagene autoleucel in adult patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib) were investigated in the ZUMA-2 study. Of 60 efficacy-evaluable patients, 52 (87%) (95% CI: 75, 94) exhibited response, among whom 37 (62%) (95% CI: 48, 74) had CR and 15 (25%) (95% CI: 5, 38) achieved PR. Median duration of CR was not reached (range 1.9+, 29.2+). Median time to response was 28 days (range: 24-92 days), with a median DoR of 8.6 months.
- Idecabtagene vicleucel (ABECMA)
  - Idecabtagene vicleucel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
  - The efficacy of idecabtagene vicleucel was evaluated in the KarMMa study, a single-arm, multicenter study of 127 adult patients with relapsed and refractory multiple myeloma who had received at least three prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (the median number of prior lines of therapy was 6, with 88% of patients having received four or more prior lines of therapies). Of 100 efficacy-evaluable patients, the ORR was 72% (95% CI: 62, 81), with a CR of 28% (95% CI: 19, 38). Median DoR was longer for patients who achieved CR (19.0 months) than those with PR or very good partial response (4.0 and 11.1 months, respectively). Of complete responders, 65% (95% CI: 42, 81) remained in remission for ≥12 months.
  - In addition to CRS and neurological toxicities that can potentially occur with any CAR T cell therapy, life-threatening hemophagocytic lymphohistiocytosis/macrophage activation syndrome has also been reported to occur in patients treated with idecabtagene vicleucel.

Bispecific Antibodies

Blinatumomab (BLINCYTO)

- Blinatumomab is indicated for the treatment of:
  - CD19-positive B-cell precursor ALL in first or second complete remission with MRD ≥ 0.1%.
  - Relapsed or refractory CD19-positive B-cell precursor ALL.

- MRD-positive B-cell precursor ALL
  - Approval for use in the treatment of MRD-positive B-cell precursor ALL was based on the results of the BLAST trial, an open label, multicenter, single-arm trial that included 86 patients who had received at least three chemotherapy blocks of standard ALL therapy and who were in complete hematologic remission (defined as 1 Gi/L, platelets > 100 Gi/L), with MRD at a level ≥0.1%. Following up to four cycles of blinatumomab, 74% patients in CR1 and 56% patients in CR2 underwent allogeneic HSCT in continuous hematologic CR. Efficacy was based on the achievement of undetectable MRD within one cycle of blinatumomab treatment and hematological RFS. Overall, undetectable MRD was achieved by 70 patients (81.4%) (95% CI: 71.6, 89.0); undetectable MRD was achieved by 85% of patients in CR1 (95% CI: 74, 93) and 72% of patients in CR2 (95% CI: 51, 88). Overall, the median hematological RFS was 22.3 months, with a median estimated hematological RFS of 35.2 (range 0.4, 53.5) months for patients in CR1 and 12.3 (range 0.7, 42.3) months for patients in CR2.
- Relapsed or refractory CD19-positive B-cell precursor ALL
  - Approval was granted based on four studies: the TOWER, MT103-211, ALCANTARA, and MT103-205 trials.
  - The TOWER trial randomized 405 patients with relapsed or refractory B-cell precursor ALL to blinatumomab or standard-of-care chemotherapy. A statistically significant improvement was shown in OS for patients treated with blinatumomab compared to those treated with chemotherapy (HR 0.71; 95% CI: 0.55, 0.93; *P* = .012). Estimated median OS was 7.7 months in the blinatumomab arm (95% CI: 5.6, 9.6) and 4.0 months in the chemotherapy arm (95% CI: 2.9, 5.3). An early termination of study for efficacy was recommended by an independent monitoring committee based on these results.
  - Study MT103-211 was a single-arm study that evaluated individuals with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic HSCT and had ≥10% blasts in bone marrow). Efficacy-evaluable patients included 185 patients who received at least one infusion of blinatumomab (the median number of treatment cycles was 2 [range 1-5]). Among the treated patients, 63 (34.1%) had undergone HSCT prior to receiving blinatumomab, and 32 (17.3%) had received more than two prior salvage therapies. Seventy-seven (41.6%) patients achieved a CR with complete or partial hematological recovery within two cycles of treatment with blinatumomab (95% CI: 34.4, 49.1). Median DoR/RFS for those achieving CR was 5.9 (0.13-16.5) months. The HSCT rate among those who achieved CR was 39% (30 out of 77).
  - The single-arm ALCANTARA study enrolled 45 patients with Philadelphia chromosome-positive ALL who either had disease resistant to second-generation tyrosine kinase inhibitors or who were intolerant to second-generation tyrosine kinase inhibitors and had disease resistant to imatinib. Patients received at least one infusion of blinatumomab (median number of treatment cycles was 2 [range 1-5]). Thirty-six percent of patients achieved CR

with complete or partial hematological recovery. The median DoR/RFS was 6.7 months (range 3.6, 12).

- Study MT103-205 was a single-arm study in pediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments, and had >25% blasts in bone marrow). Among the 70 treated patients, 40 (57.1%) had undergone allogeneic HSCT prior to receiving blinatumomab and 39 (55.7%) had refractory disease. The median number of treatment cycles was 1 (range 1-5). Twenty-three of 70 (32.9%) patients achieved CR with complete or partial hematological recovery within two cycles of treatment with blinatumomab, with 17 out of 23 (73.9%) occurring within the first cycle of treatment. The median DoR/RFS was 6.0 months (range 0.5, 6.4). The HSCT rate among those who achieved CR was 48%.

- As potentially occurring with CAR T cell therapy, CRS and neurological toxicity may occur and can be life-threatening or fatal. Availability of tocilizumab should be confirmed prior to treatment and patients should be closely monitored for neurological events.

Management of Immune Checkpoint Inhibitor-Associated Immune-Related Adverse Events

- Although occurring rarely, a number of serious immune-related adverse events (irAEs) have been reported with the use of immune checkpoint inhibitors, including colitis, nephritis, pneumonitis, endocrinopathies (hypothyroidism, type 1 diabetes mellitus, adrenal insufficiency, hypopituitarism), myasthenia gravis, Guillain-Barré, meningoencephalitis, pericarditis, uveitis, iritis, nerve palsies, hemolytic anemia, pancreatitis, hepatitis leading to hepatotoxicity, and hyperacute GVHD following allogeneic HSCT.
- Because of these risks, it is recommended that liver function tests, adrenocorticotropic hormone, and thyroid function be routinely monitored in addition to routine bloodwork, such as complete blood cell counts and chemistry panels.
- In the event of severe irAEs, treatment should be permanently discontinued and systemic high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent) should be administered. Patients should continue corticosteroids until symptoms

improve, at which time a steroid taper lasting over a month should be initiated. While patients may be concerned about corticosteroids abrogating the effects of therapy, at least one small trial evaluating ipilimumab in 139 patients with advanced melanoma suggests that corticosteroids given for irAEs do not affect duration of objective responses (P = .23).

- If patients do not respond to corticosteroids within 3 to 5 days, treatment with infliximab 5 mg/kg IV with or without continuation of corticosteroids should be considered after confirming the absence of bowel perforation or sepsis. A second dose of infliximab 5 mg/kg IV may be given 2 weeks after the first dose if severe symptoms persist.
- For moderate irAEs, it is recommended that treatment be held until side effects have resolved or improved to at least grade 1. Depending on the specific immune checkpoint inhibitor, treatment may be recommended to be held until the patient is receiving <7.5 mg prednisone or equivalent per day.
- Prophylactic antibiotics should be administered to patients on long-term immune suppression, particularly to prevent pneumocystis pneumonia.
- Infusion reactions have also been described. For severe and life-threatening infusion reactions, infusions should be stopped and treatment discontinued. For mild or moderate reactions, interruption or slowing the rate of infusion should be considered.
- There should be a low threshold for concern and potential early intervention regarding patients with diarrhea or dyspnea as colitis and pneumonitis, respectively, can be lethal toxicities if not addressed expeditiously.

CHALLENGES TO THE EVALUATION OF IMMUNOTHERAPY EFFICACY

Delayed Responses

- Effective antitumor immune activation by immunotherapy may take weeks to months to occur, leading to delayed responses. This phenomenon is more commonly seen with vaccine and oncolytic virus–based therapies (see T-VEC study data, above), however, may occasionally occur with immune checkpoint inhibitors (see studies supporting immune checkpoint inhibitor approvals, above). Specifically, with regard to checkpoint inhibitors, the median time to response of 2 months demonstrated in multiple studies may partly underlie the reason for the specification of 2 months as the time point for first radiographic reassessment frequently seen in clinical trials assessing the efficacy of immune checkpoint inhibition. Objective responses achieved with immunotherapy are usually durable. Although durable responses have been seen with agents representing all classes of immunotherapy, the responses elicited by pembrolizumab in studies evaluating its efficacy in patients with dMMR/MSI-H malignancies are particularly striking (see data summarized in pembrolizumab section, above).

Pseudoprogression

- Tumor-infiltrating lymphocytes play a critical role in facilitating immune-induced antitumor activity, and their enrichment of the tumor microenvironment (TME) is thought to heavily influence immune checkpoint inhibitor efficacy. In a small population of patients, however, an initial increase in tumor burden or the appearance of one or more new lesions may be perceived on radiographic assessment following the initiation of treatment with immune checkpoint inhibition. This phenomenon, known as pseudoprogression, reflects an infiltration of ICs into the tumor and the associated edema that may occur with activation of the immune response, rather than the increase in tumor cell proliferation seen with true progression of disease. Pseudoprogression is characterized by regression and

subsequent response following this apparent increase in tumor size.

- The radiographic distinction between pseudoprogression and true disease progression can be challenging and may require the adaptation of conventional criteria used in the radiographic assessment of tumor response. The observation of unique tumor response patterns associated immune checkpoint inhibition has led to the development of newer immune-related response criteria designed to reduce the occurrences of premature treatment discontinuation due to the erroneous supposition that disease has progressed. Among other changes to traditional response criteria (ie, RECIST), these newer criteria introduce the concept of confirmation of progression on follow-up scans. Based on this approach, it is generally recommended that patients who are receiving immune checkpoint inhibition have confirmatory scans approximately 4 weeks after first radiographic progression to confirm true disease progression.
- However, while this is the general rule, it should be noted that pseudoprogression is a relatively uncommon occurrence, having been reported in only 2% to 10% of patients receiving immune checkpoint inhibitors. Upon the retrospective evaluation of 356 patients afflicted by various types of solid tumors who were treated with immune checkpoint inhibitors, the investigators of one study found that only 6% of patients had exhibited pseudoprogression by immune-related response criteria.
- In summary, the decision to continue with treatment while awaiting confirmation of disease progression should not be reflexive, as pseudoprogression occurs only in a minority (<10%) of patients. Clinical assessment and factors such as patient preferences, rate of tumor growth, and changes in levels of tumor markers should be considered in decision-making regarding continuing, changing, or discontinuing treatment.

PREDICTIVE BIOMARKERS FOR IMMUNOTHERAPY RESPONSE

PD-L1 Expression

- Data from studies across many types of solid malignancies suggest that response rates to anti–PD-1/PD-L1 treatment are substantially higher in patients who have biopsy-proven PD-L1 expression in the TME. The TPS is the ratio of the number of tumor cells with membranous PD-L1 expression to the number of all tumor cells. Tumors are considered to have PD-L1 expression if TPS ≥ 1% and high PD-L1 expression if TPS ≥ 50%. In contrast, the CPS considers PD-L1-expressing ICs and represents the number of all cells expressing PD-L1 divided by the total number of viable tumor cells, multiplied by 100. Interestingly, many studies have associated increased PD-L1 expression in the TME with an underlying baseline tumor immune response (eg, T cell infiltration in tumors). Tumors with a preexisting, underlying immune response are often referred to as "hot" tumors, whereas their counterparts without an underlying immune response are often referred to as "cold" tumors. Immune checkpoint inhibitors, especially anti–PD-1/PD-L1 therapies, do not create a tumor-specific immune response de novo but allow a baseline immune response to proceed unchecked. This may explain why "hot" tumors, which are associated with increased PD-L1 expression, seemingly respond better to anti–PD-1/PD-L1 therapy. Although beyond the scope of this chapter, a massive research effort is underway to convert "cold" tumors into "hot" tumors and thereby increase the percentage of patients who may benefit from immune checkpoint therapy.

Tumor Mutational Burden

- The tumor mutational load, or burden (TMB), refers to the frequency of nonsynonymous somatic mutations existing within a tumor. It is quantified by the total number of mutations per DNA megabase (Mb) in an interrogated genomic sequence and can be calculated via whole exome sequencing or by next-generation sequencing targeted panels. Tumors determined to express a high mutational load are considered TMB-high (TMB-H) and harbor ≥10 mutations/Megabase (mut/Mb). TMB is highly variable among different types of malignancies; however, it has been suggested to be a predictive factor for response to immunotherapy, with correlations demonstrated between high-TMB and durable objective responses, PFS and OS in patients with certain tumor types treated with immune checkpoint inhibitors. The 2020 tissue-agnostic accelerated approval for pembrolizumab reflects the significance of the potential impact of mutational burden on clinical outcomes in patients with cancer (study data supporting the approval are described in the above section on pembrolizumab).

Mismatch Repair Deficiency and MSI

- Tumor mutational load, MMR status, and MSI have become recognized as determinants of immune checkpoint inhibitor efficacy. Impaired MMR results in MSI, which then leads to an accumulation of frameshift mutation-derived peptides that are thought to behave as tumor-specific antigens. These tumor-specific antigens, or "neo-antigens," are thought to be highly immunogenic; tumors harboring high levels are thought to be particularly sensitive to immune checkpoint inhibition. Clinical data suggest that patients with tumors that are dMMR/MSI-H are more likely to respond and benefit from immune checkpoint inhibition. In a phase II study of pembrolizumab in patients with progressive metastatic carcinoma, 40% of patients with dMMR CRC had objective responses, while no patients with pMMR CRC exhibited response. Further, objective responses were observed in 71% patients with dMMR noncolorectal

tumors. In this study, whole exome sequencing of tumors showed significantly more mutations in dMMR tumors versus mismatch repair proficient (pMMR) tumors (mean of 1782 vs 73; *P* = .007). A high somatic mutational burden was also found to be significantly associated with longer PFS (*P* = .02). Multiple studies by the KEYNOTE and CheckMate investigators have clarified this link in patients with CRC, in particular, and have led to the approval of the use of immune checkpoint inhibitors in both first- and second-line treatment in select groups of patients. Numerous studies evaluating the impact of dMMR/MSI-H on the efficacy of checkpoint inhibition in multiple types of cancer are ongoing.

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Anticancer Agents

Lisa M. Cordes, Thomas E. Hughes

INTRODUCTION

Please note that all information has been obtained from current product labeling as of July 1, 2021. Doses listed are those from the package insert and apply when the agent is given alone, unless otherwise noted. Doses are expressed in accordance with nomenclature guidelines from Kohler et al.

ADVERSE REACTIONS

Adverse reactions to anticancer agents involve the following:

- Cardiovascular system (CV)
- Skin and integument system (DERM)
- Electrolyte abnormalities (ELECTRO)
- Endocrine system (ENDO)
- Gastrointestinal system (GI)
- Genitourinary system (GU)
- Hematopoietic system (HEMAT)
- Hepatic system (HEPAT)
- Infusion-related reactions (INFUS)
- Neurologic system, central and peripheral (NEURO)
- Ocular system
- Pulmonary system (PULM)
- Liver function
- Serum creatinine (Cr)

- Creatinine clearance (CrCl)
- Nausea and vomiting (N/V): classified on a four-level system for parenteral anticancer agents or on a two-level system for oral agents. Emetogenic potential is based on the incidence of acute emesis based on the classification by national chemotherapy-induced nausea and vomiting (CINV) guidelines. Parenteral agents: minimal, <10%; low, 10% to 30%; moderate, >30% to 90%; and high, >90%. Oral agents: moderate-high, ≥30%; and minimal-low, <30% (Chapter 38). When discrepancies existed among the guidelines regarding emetic risk, the authors classified the agent on personal opinion consistent with one of the available national CINV guidelines.

ABEMACICLIB (VERZENIO)

Mechanism of Action

- Inhibitor of cyclin-dependent kinase (CDK) 4 and 6, which results in the blockade of retinoblastoma protein phosphorylation, leading to arrest in the G1 phase of the cell cycle

FDA-Approved Indications

- Breast cancer:
  - In combination with an aromatase inhibitor as initial endocrine-based treatment of postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer (MBC)
  - In combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy
  - As monotherapy for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

FDA-Approved Dosage

- In combination with fulvestrant or an aromatase inhibitor: 150 mg orally twice daily.
- As monotherapy: 200 mg orally twice daily.
- Continue treatment until disease progression or unacceptable toxicity. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): yes
- Cytochrome P450 (CYP) 3A inhibitors (strong or moderate): yes
- Hematologic toxicities: yes
- Nonhematologic toxicities: yes

Adverse Reactions

- CV: venous thromboembolism (VTE)
- DERM: alopecia
- GI: diarrhea, N/V (minimal-low), abdominal pain, and decreased appetite
- HEMAT: neutropenia, anemia, leukopenia, and thrombocytopenia
- HEPAT: hepatotoxicity
- NEURO: headache
- PULM: interstitial lung disease (ILD)/pneumonitis
- OTHER: infections and fatigue

Comments

- Avoid concomitant use of strong and moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the abemaciclib dose. Avoid concomitant ketoconazole.
- Avoid concomitant use of strong and moderate CYP3A inducers.

- Embryo-fetal risk: abemaciclib may cause fetal harm when administered to a pregnant woman.

ABIRATERONE (ZYTIGA)

Mechanism of Action

- Androgen biosynthesis inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

FDA-Approved Indications

- Prostate cancer: in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and high-risk castration-sensitive prostate cancer.

FDA-Approved Dosage

- Metastatic castration-resistant prostate cancer: abiraterone 1000 mg (two 500 mg tablets or four 250 mg tablets) PO once daily in combination with prednisone 5 mg PO twice daily.
- High-risk castration-sensitive prostate cancer: abiraterone 1000 mg (two 500 mg tablets or four 250 mg tablets) PO once daily in combination with prednisone 5 mg PO once daily. Patients receiving abiraterone should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Abiraterone must be taken on an empty stomach, swallowed whole with water. No food should be consumed for at least 2 hours before the dose and for at least 1 hour after the dose of abiraterone.

Dose Modification Criteria

- Renal: no
- Hepatic (moderate, Child-Pugh class B): yes
- Hepatic (severe, Child-Pugh class C): avoid use

Adverse Reactions

- CV: hypertension
- ELECTRO: hypokalemia, hypernatremia, and hypophosphatemia
- ENDO: adrenal insufficiency, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia
- GI: constipation, diarrhea, and dyspepsia
- GU: hematuria and urinary tract infection
- HEMAT: anemia and lymphopenia
- HEPAT: elevated alkaline phosphatase, elevated bilirubin, and elevated liver function tests (LFTs)
- PULM: cough, dyspnea, nasopharyngitis, and upper respiratory tract infection
- OTHER: confusion, edema, fatigue, hot flush, insomnia, joint swelling/discomfort, and muscle discomfort

Comments

- Use abiraterone with caution in patients with a history of CV disease. The safety of abiraterone in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association (NYHA) class II to IV heart failure was not established in clinical studies. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure (BP), serum potassium, and symptoms of fluid retention at least monthly.
- Monitor for signs and symptoms of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during, and after stressful situations.
- Hepatotoxicity can be severe and fatal. Monitor liver function and modify, interrupt, or discontinue based on the

recommendations outlined in product labeling.

- Abiraterone is an inhibitor of CYP2D6. Avoid coadministration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (eg, thioridazine). Based on in vitro data, avoid or use with caution with strong CYP3A4 inhibitors or inducers.
- Abiraterone peak concentration (Cmax) and area under the concentration-time curve (AUC) exposure were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone was administered with a meal compared to a fasted state. Patients must be counseled to take abiraterone on an empty stomach.
- Severe hypoglycemia has been observed with abiraterone when administered to patients with preexisting diabetes receiving medications containing thiazolidinediones or repaglinide. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with abiraterone. Antidiabetic drug dosages may require adjustment.
- Abiraterone is not indicated for use in women. Embryo-fetal toxicity: abiraterone can cause fetal harm when administered to a pregnant woman.

ACALABRUTINIB (CALQUENCE)

Mechanism of Action

- Small molecule inhibitor of Bruton tyrosine kinase (BTK) leading to the inhibition of BTK enzymatic activity

FDA-Approved Indications

- Mantle cell lymphoma (MCL) following at least one prior therapy
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

FDA-Approved Dosage

- 100 mg orally twice daily, approximately every 12 hours, with or without food. Administer until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2 by Modification of Diet in Renal Disease [MDRD]): no significant effect on pharmacokinetics (PK)
- Renal (severe, eGFR < 30 mL/min/1.73 m^2 by MDRD): no data available
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): avoid use
- CYP3A inhibitors (moderate): yes
- CYP3A inducers (strong): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: atrial fibrillation and flutter
- GI: N/V (minimal-low) and diarrhea
- HEMAT: anemia, neutropenia, thrombocytopenia, and hemorrhage
- NEURO: headache
- OTHER: musculoskeletal pain, upper respiratory tract infection, serious and opportunistic infections, and second primary malignancies

Comments

- Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of patients in clinical trials. Skin

cancer was reported in 6% of patients; monitor and advise protection from sun exposure.
- Avoid concomitant use of strong CYP3A inhibitors. If the CYP3A inhibitor will be used for a short term (eg, anti-infective), interrupt acalabrutinib.
- If concomitant administration of a moderate CYP3A inhibitor is necessary, reduce the acalabrutinib dose frequency.
- Avoid concomitant use of strong CYP3A inducers. If coadministration cannot be avoided, increase the acalabrutinib dose.
- Avoid concomitant use of proton pump inhibitors (PPIs). Alternately, separate dosing with locally acting antacids by at least 2 hours or take acalabrutinib 2 hours before taking an H_2 antagonist.
- Embryo-fetal toxicity: acalabrutinib may cause fetal harm and dystocia when administered to a pregnant woman.

ADO-TRASTUZUMAB EMTANSINE (KADCYLA)

Mechanism of Action

- HER2-targeted antibody-drug conjugate (ADC) composed of the humanized anti-HER2 IgG1 antibody trastuzumab, and the small molecule cytotoxin DM1, which is a microtubule inhibitor. Once ado-trastuzumab emtansine binds to the HER2 receptor, receptor-mediated internalization occurs, leading to intracellular release of DM1.

FDA-Approved Indications

- Breast cancer:
  - HER2-positive metastatic breast cancer in patients who have previously received trastuzumab and a taxane, separately or in combination. Patient

should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.
- HER-2 positive early breast cancer in patients who have residual invasive disease after neoadjuvant taxane- and trastuzumab-based treatment.

FDA-Approved Dosage

- 3.6 mg/kg IV infusion every 3 weeks. Treatment duration for patients with metastatic breast cancer is until disease progression or unacceptable toxicity and for patients with early breast cancer treat for 14 cycles unless there is disease recurrence or unmanageable toxicity.

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): limited data available
- Hepatic (mild to moderate): no
- Hepatic (severe): not studied, use with caution
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: left ventricular dysfunction
- GI: diarrhea, constipation, and N/V (low)
- HEMAT: hemorrhage, thrombocytopenia, and anemia
- HEPAT: increased transaminases
- INFUS: flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia
- NEURO: peripheral neuropathy and headache
- PULM: dyspnea, cough, pulmonary infiltrates, and pneumonitis
- OTHER: arthralgia, myalgia, and fatigue

Comments

- Do not substitute ado-trastuzumab emtansine for or with trastuzumab.
- Do not administer as an intravenous (IV) push or bolus. Do not use dextrose 5% (D5W) solution.
- Hepatotoxicity and liver failure have occurred in patients treated with ado-trastuzumab emtansine. Monitor hepatic function prior to initiation of therapy and prior to each dose. Dose withholding or dose modification may be necessary.
- Ado-trastuzumab emtansine may lead to reductions in LVEF. Assess LVEF prior to initiation and at regular intervals during treatment and monitor for signs or symptoms of cardiac toxicity.
- Interstitial lung disease has been reported. Monitor and withhold for acute onset or worsening of pulmonary symptoms.
- Monitor for signs or symptoms of neurotoxicity. Temporarily discontinue for grade 3 or 4 peripheral neuropathy.
- Embryo-fetal toxicity: ado-trastuzumab may cause fetal harm when administered to a pregnant woman.

AFATINIB (GILOTRIF)

Mechanism of Action

- Covalently binds to the kinase domains of epidermal growth factor receptor (EGFR), HER2, and HER4 and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC):
  - First-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations as detected by an FDA-approved test
  - Metastatic, squamous NSCLC progressing after platinum-based chemotherapy

FDA-Approved Dosage

- 40 mg orally, once daily. Take at least 1 hour before or 2 hours after a meal.

Dose Modification Criteria

- Renal (mild or moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl 15-29 mL/min): yes
- Hepatic (mild or moderate): no
- Hepatic (severe, Child-Pugh class C): no data available, use with caution
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: bullous and exfoliative skin disorders, rash/acneiform dermatitis, dry skin, pruritus, and paronychia
- ELECTRO: decreased potassium
- GI: diarrhea, stomatitis, and N/V (minimal-low)
- GU: decreased CrCl, cystitis
- HEMAT: decreased lymphocytes
- HEPAT: increased alanine aminotransferase/aspartate aminotransferase (ALT/AST), increased alkaline phosphate, and increased bilirubin
- PULM: interstitial lung disease
- Ocular system: keratitis and conjunctivitis
- OTHER: pyrexia

Comments

- Diarrhea may result in dehydration and renal failure. Withhold afatinib for severe or prolonged diarrhea not responsive to antidiarrheal agents.
- Withhold afatinib for severe or prolonged cutaneous reactions.

- Afatinib may cause interstitial lung disease. Withhold afatinib for acute onset or worsening of pulmonary symptoms.
- Monitor LFTs periodically during therapy. Withhold afatinib for severe or worsening liver tests.
- GI perforation, including fatal cases, has occurred with afatinib. Risk factors may include concomitant corticosteroids; nonsteroidal anti-inflammatory drugs (NSAIDs) or antiangiogenic agents; older patients; or patients with a history of GI ulceration, diverticular disease, or bowel metastases.
- Afatinib may cause ulcerative keratitis. Withhold and evaluate for new symptoms of keratitis.
- Embryo-fetal toxicity: afatinib may cause fetal harm when administered to a pregnant woman.
- Coadministration of afatinib and P-glycoprotein (P-gp) inhibitors or inducers can lead to changes in afatinib exposure and may require dose modification. See product labeling for recommendations on dose modifications.

ALDESLEUKIN (PROLEUKIN)

Mechanism of Action

- Cellular immunity activation

FDA-Approved Indications

- Metastatic renal cell carcinoma (RCC)
- Metastatic melanoma

FDA-Approved Dosage

- 600,000 IU/kg IV over 15 minutes every 8 hours for a maximum of 14 doses
- May be repeated after 9 days of rest for a maximum of 28 doses per course

Dose Modification Criteria

- Withhold or interrupt a dose for toxicity

Adverse Reactions

- CV: hypotension, tachycardia, and arrhythmia
- DERM: rash and pruritus
- GI: diarrhea, N/V (low to moderate [dose dependent]), mucositis, and anorexia
- GU: oliguria and acute renal failure
- HEMAT: myelosuppression
- NEURO: confusion, somnolence, anxiety, and dizziness
- PULM: dyspnea and pulmonary edema
- OTHER: pain, fever, chills, and malaise

Comments

- Restrict use to patients with normal cardiac and pulmonary function.
- Monitor for capillary leak syndrome (CLS).
- Associated with impaired neutrophil function; consider antibiotic prophylaxis for patients with indwelling central lines.
- Withhold in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

ALECTINIB (ALECENSA)

Mechanism of Action

- Inhibitor of tyrosine kinases, including anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET) kinase

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): ALK-positive, metastatic NSCLC patients who have progressed on or are intolerant to crizotinib

FDA-Approved Dosage

- 600 mg orally twice daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data, use with caution
- Hepatic (mild): no
- Hepatic (moderate to severe): no data, use with caution
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: bradycardia
- DERM: rash
- ELECTRO: hypocalcemia, hypokalemia, hypophosphatemia, and hyponatremia
- ENDO: hyperglycemia
- GI: constipation, N/V (minimal-low), and diarrhea
- GU: increased creatinine
- HEMAT: anemia and lymphopenia
- HEPAT: ALT/AST elevations, and increased bilirubin
- NEURO: headache
- PULM: interstitial lung disease, pneumonitis, cough, and dyspnea
- OTHER: myalgia, creatine phosphokinase (CPK) elevation, fatigue, and edema (peripheral, generalized, eyelid, and periorbital)

Comments

- Hepatotoxicity: monitor LFTs every 2 weeks during the first 3 months of treatment, then once monthly and as clinically indicated.
- Alectinib may cause interstitial lung disease. Withhold alectinib for acute onset or worsening of pulmonary symptoms.
- Bradycardia: monitor heart rate and BP regularly and withhold and modify therapy if a patient becomes symptomatic from bradycardia.
- Myalgia and musculoskeletal pain are common toxicities. Monitor CPK every 2 weeks during the first month of treatment and in patients reporting musculoskeletal pain. Withholding therapy and dose modifications may be necessary.
- Embryo-fetal toxicity: alectinib may cause fetal harm when administered to a pregnant woman.

ALEMTUZUMAB (CAMPATH)

Mechanism of Action

- Humanized monoclonal antibody directed against the cell surface protein CD52. The CD52 antigen is expressed on the surface of normal and malignant B and T lymphocytes, natural killer (NK) cells, monocytes, macrophages, and a subpopulation of granulocytes. The proposed mechanism of action is antibody-dependent lysis of leukemic cells following cell surface binding.

FDA-Approved Indication

- B-cell chronic lymphocytic leukemia (CLL)

FDA-Approved Dosage

- Alemtuzumab is dose escalated in a stepwise format to a maintenance dose of 30 mg.

- The initial recommended dose is 3 mg IV over 2 hours daily. When this dose is tolerated (infusion-related toxicities ≤ grade 2), the daily dose should be escalated to 10 mg IV over 2 hours daily and continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of 30 mg may be initiated. The maintenance dose is 30 mg IV over 2 hours administered three times per week (ie, Monday, Wednesday, and Friday) for up to 12 weeks. In most patients, escalation to 30 mg can be accomplished in 3 to 7 days. If therapy is interrupted for 7 or more days, alemtuzumab should be reinitiated with gradual dose escalation.
- Single doses of Campath >30 mg or cumulative doses >90 mg/wk should not be administered because these doses are associated with a higher incidence of pancytopenia.
- Premedicate patients with an antihistamine (eg, diphenhydramine 50 mg oral or IV) and acetaminophen (650 mg oral) 30 minutes prior to alemtuzumab to ameliorate or avoid infusion-related toxicity. Antiemetics, meperidine, and corticosteroids have also been used to prevent or treat infusion-related toxicities.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- CV: hypotension and edema/peripheral edema
- DERM: rash, urticaria, and pruritus
- GI: N/V (minimal), diarrhea, anorexia, and mucositis/stomatitis
- HEMAT: myelosuppression and lymphopenia
- INFUS: rigors, fever, chills, N/V, hypotension, dyspnea, bronchospasm, headache, rash, and urticaria
- NEURO: headache, dysthesias, and dizziness
- PULM: dyspnea, cough, bronchitis, pneumonia, and bronchospasm

- OTHER: opportunistic infections, sepsis, fatigue, asthenia, and pain

Comments

- Alemtuzumab (Campath) was removed from the commercial market in September 2012. The Campath Distribution Program was developed to ensure continued access to alemtuzumab for appropriate patients. Drug supplies are provided free of charge, but in order to receive drug, the healthcare provider is required to document and comply with certain requirements. For additional information, contact Clinigen Direct (1877-768-4303).
- Alemtuzumab-treated patients are at risk for opportunistic infections due to profound lymphopenia. Anti-infective prophylaxis is recommended upon initiation of therapy and for a minimum of 2 months following the last dose of alemtuzumab or until the CD4 count is ≥200 cells/µL. Prophylaxis directed against *Pneumocystis* pneumonia (eg, trimethoprim/sulfamethoxazole) and herpesvirus infections (eg, famciclovir or equivalent) should be utilized.
- Do not administer as an IV push or bolus.
- Careful monitoring of BP and hypotension is recommended especially in patients with ischemic heart disease and in patients on antihypertensive medications.
- Patients who have recently received alemtuzumab should not be immunized with live viral vaccines.

ALPELISIB (PIQRAY)

Mechanism of Action

- Inhibitor of phosphatidylinositide 3-kinase (PI3K) alpha that prevents the phosphorylation of PI3K downstream targets, including Akt. Alpelisib has shown activity in cell lines harboring a PIK3CA mutation.

FDA-Approved Indications

- Breast cancer: in combination with fulvestrant for the treatment of postmenopausal women and men with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen

FDA-Approved Dosage

- 300 mg orally once daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to <90 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild to severe, Child-Pugh class A, B, or C): no significant effect on PK
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: creatinine increased
- DERM: rash, alopecia, and severe cutaneous adverse reactions
- ELECTRO: hypocalcemia
- ENDO: hyperglycemia and hypoglycemia
- GI: N/V (minimal-low), diarrhea, decreased appetite, stomatitis, lipase increased
- HEMAT: lymphopenia, anemia, and activated partial thromboplastin time prolongation
- HEPAT: increased gamma-glutamyltransferase (GGT) and increased ALT
- PULM: pneumonitis
- OTHER: fatigue, weight decreased, and severe hypersensitivity

Comments

- Alpelisib can cause severe hyperglycemia, including ketoacidosis. The safety of alpelisib in patients with type 1 or uncontrolled type 2 diabetes has not been established. Before starting alpelisib, test fasting plasma glucose, HbA1c, and optimize blood glucose then monitor closely during treatment.
- Avoid concomitant administration of CYP3A4 inducers.
- Avoid concomitant use of breast cancer resistance protein (BCRP) inhibitors. If coadministration is necessary, closely monitor for increased alpelisib adverse reactions.
- If concurrent administration with a CYP2C9 substrate is necessary, closely monitor the substrate if decreases in the plasma concentration may reduce activity.
- Embryo-fetal toxicity: alpelisib may cause fetal harm when administered to a pregnant woman.

AMIVANTAMAB (RYBREVANT)

Mechanism of Action

- As a bispecific antibody, amivantamab binds to the extracellular domains of EGFR and mesenchymal-epithelial transition (MET). The presence of EGFR and MET on tumor cell surfaces allows for targeted destruction through antibody-dependent cell-mediated cytotoxicity (ADCC) and trogocytosis.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation, as detected by an FDA-approved test, following progression on or after platinum-based chemotherapy

FDA-Approved Dosage

- Premedications:
  - Prior to all doses: diphenhydramine plus acetaminophen
  - Prior to week 1, days 1 and 2 (in addition to the above): glucocorticoid
- Dosage:
  - Baseline body weight <80 kg: 1050 mg
  - Baseline body weight ≥80 kg: 1400 mg
- Administer as an IV infusion weekly for 4 weeks (with the initial dose as a split infusion on day 1 and day 2) followed by every 2 weeks thereafter.
- Infusions during weeks 1 and 2 should be given via peripheral line due to the high incidence of infusion-related reactions during initial treatment. Subsequent doses may be administered via central line. See prescribing information for infusion rates.

Dose Modification Criteria

- Renal (mild or moderate, CrCl ≥ 29 mL/min): no significant effect on PK
- Renal (severe, CrCl < 29 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash (including acneiform dermatitis and toxic epidermal necrolysis [TEN]) and paronychia
- ELECTRO: hypophosphatemia, hypokalemia, and hyponatremia
- ENDO: hyperglycemia
- GI: N/V (not classified), stomatitis, and constipation
- HEMAT: lymphopenia
- HEPAT: increased alkaline phosphatase and increased GGT
- INFUS: infusion-related reactions
- Ocular system: dry eye, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis

- PULM: dyspnea, cough, and interstitial lung disease/pneumonitis
- OTHER: musculoskeletal pain, fatigue, edema, and hypoalbuminemia

Comments

- Embryo-fetal toxicity: amivantamab may cause fetal harm when administered to a pregnant woman.

ANASTROZOLE (ARIMIDEX)

Mechanism of Action

- Selective, nonsteroidal aromatase inhibitor

FDA-Approved Indications

- Breast cancer
  - Adjuvant treatment: postmenopausal women with HR-positive early breast cancer
  - First-line therapy: postmenopausal women with HR-positive or HR unknown locally advanced or metastatic breast cancer
  - Second-line therapy (after tamoxifen) in postmenopausal women with advanced breast cancer

FDA-Approved Dosage

- 1 mg orally daily (no requirement for glucocorticoid or mineralocorticoid replacement)

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate impairment): no
- Hepatic (severe impairment): unknown

Adverse Reactions

- CV: hot flashes/flushing
- GI: N/V (not classified) and diarrhea
- HEPAT: LFTs (in patients with liver metastases)
- NEURO: headache
- PULM: dyspnea
- OTHER: asthenia, pain, back pain, and vaginal bleeding

Comments

- Patients with estrogen receptor (ER)–negative disease and patients who do not respond to tamoxifen rarely respond to anastrozole.
- In women with preexisting ischemic heart disease, an increased incidence of ischemic cardiovascular events associated with anastrozole use compared to tamoxifen use has been demonstrated.
- Embryo-fetal toxicity: anastrozole may cause fetal harm when administered to a pregnant woman.
- Decreases in bone mineral density (BMD) and increases in total cholesterol may occur. Consider monitoring.

APALUTAMIDE (ERLEADA)

Mechanism of Action

- Androgen receptor inhibitor that binds directly to the ligand-binding domain, inhibits nuclear translocation, inhibits DNA binding, and impedes androgen receptor–mediated transcription

FDA-Approved Indications

- Metastatic castration-sensitive prostate cancer (mCSPC)

- Non-metastatic castration-resistant prostate cancer

FDA-Approved Dosage

- 240 mg orally once daily with or without food

Dose Modification Criteria

- Renal (mild or moderate, eGFR 30-89 mL/min/1.73 m^2 by MDRD): no significant effect on PK
- Renal (severe, eGFR <30 mL/min): no data available
- Hepatic (mild or moderate): no significant effect on PK
- Hepatic (severe): no data available
- Nonhematologic criteria: yes

Adverse Reactions

- CV: hypertension and cerebrovascular and ischemic cardiovascular events
- DERM: rash
- ENDO: hot flush
- GI: N/V (not classified), decreased appetite, and diarrhea
- NEURO: fall and seizures
- OTHER: fatigue, arthralgia, weight decreased, and fractures

Comments

- A GnRH analog should be administered concurrently, or the patient should have undergone a bilateral orchiectomy.
- Factures have been reported. Evaluate patients for risk and treat with bone-targeted agents according to established guidelines.
- Concomitant administration with medications that are sensitive substrates of the following enzymes and transporters may result in reduced activity of those medications: CYP3A4, CYP2C19, CYP2C9, uridine diphospho-glucuronosyltransferase (UGT), P-

gp, BCRP, and organic anion transporting polypeptide (OATP) 1B1.

- Embryo-fetal toxicity: apalutamide may be harmful to a developing fetus. Advise males of the following:
  - Use effective contraception during treatment and for 3 months after the last dose with female partners of reproductive potential.
  - Use a condom if having sex with a pregnant woman.
  - Apalutamide may impair fertility and patients should not donate sperm during therapy and for 3 months after the last dose.

ARSENIC TRIOXIDE (TRISENOX)

Mechanism of Action

- The mechanism is not completely defined.
- Induces apoptosis in NB4 human promyelocytic leukemia (PML) cells in vitro and causes damage or degradation of the fusion protein PML/retinoic acid receptor alpha (RARα).

FDA-Approved Indications

- Acute promyelocytic leukemia (APL) characterized by the presence of the t(15;17) translocation or PML/RARα gene expression.
  - Newly diagnosed adults with low-risk APL in combination with tretinoin.
  - Second-line treatment for the induction of remission and consolidation of APL patients who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy.

FDA-Approved Dosage

- Newly diagnosed low-risk APL:
  - Induction: 0.15 mg/kg IV over 1 to 2 hours daily in combination with tretinoin until bone marrow remission. Total induction dose should not exceed 60 doses.
  - Consolidation: 0.15 mg/kg IV over 1 to 2 hours daily for 5 days per week during weeks 1 to 4 of each 8-week cycle for a total of four cycles in combination with tretinoin. Omit tretinoin during weeks 5 to 6 of the fourth cycle of consolidation.

- Relapsed or refractory APL:
  - Induction: 0.15 mg/kg IV over 1 to 2 hours daily until bone marrow remission or up to a maximum of 60 days.
  - Consolidation: 0.15 mg/kg IV over 1 to 2 hours daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

Dose Modification Criteria

- Renal: no data, use with caution
- Hepatic: no data

Adverse Reactions

- CV: QT interval prolongation, complete atrioventricular block, torsades de pointes–type ventricular arrhythmia, atrial dysrhythmias, tachycardia, hypotension, and edema
- DERM: rash, dermatitis, dry skin, and pruritus
- ENDO: hyperglycemia, hypokalemia, and hypomagnesemia
- GI: N/V (low), diarrhea, abdominal pain, anorexia, and constipation
- HEMAT: leukocytosis and myelosuppression
- HEPAT: elevated LFTs
- NEURO: headache, dizziness, paresthesias, encephalopathy
- PULM: dyspnea and cough
- OTHER: fatigue, arthralgia, myalgia, pain, and APL differentiation (RA-APL) syndrome (RA-APL syndrome—fever, dyspnea, weight gain, radiographic pulmonary infiltrates, and pleural or pericardial effusion)

Comments

- The APL differentiation syndrome (RA-APL syndrome) has occurred in some patients treated with arsenic trioxide. Early recognition and high-dose corticosteroids (dexamethasone 10 mg IV every 12 hours × 3 days or until the resolution of symptoms) have been used for management.

- Prior to stating arsenic trioxide, a 12-lead electrocardiogram (ECG) should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; preexisting electrolyte abnormalities should be corrected. Avoid concomitant drugs that may prolong the QT interval. During therapy with arsenic trioxide, monitor and maintain normal potassium and magnesium concentrations (see package insert).
- Risk factors for QT prolongation and subsequent arrhythmias include other QT prolonging drugs, a history of torsades de pointes, preexisting QT prolongation, congestive heart failure (CHF), administration of potassium wasting diuretics, or other drugs or conditions that result in hypokalemia or hypomagnesemia.
- Hepatotoxicity: in the clinical trials for newly diagnosed, low-risk APL, 44% of patients treated with arsenic trioxide and tretinoin developed LFT abnormalities. These abnormalities usually resolve with temporary discontinuation of therapy, but long-term liver abnormalities can occur. Monitor LFTs at least twice weekly during induction therapy and at least once weekly during consolidation therapy.
- Encephalopathy, including Wernicke, has occurred with arsenic trioxide and may be a neurologic emergency. Consider testing for thiamine levels in patients at risk for thiamine deficiency and administer parenteral thiamine if indicated. Monitor patients for neurological symptoms and nutritional status during therapy.
- Carcinogenesis: arsenic trioxide is a carcinogen and may cause secondary malignancies.
- Embryo-fetal toxicity: arsenic trioxide may cause fetal harm when administered to a pregnant woman.

ASPARAGINASE (ERWINAZE)

Mechanism of Action

- Asparaginase depletes asparagine, an amino acid required by some leukemic cells.

FDA-Approved Indications

- Erwinaze (asparaginase derived from *Erwinia chrysanthemi*): acute lymphoblastic leukemia (ALL) induction therapy for patients who have developed hypersensitivity to *Escherichia coli*–derived asparaginase

FDA-Approved Dosage

- Consult current literature for doses.
- Erwinaze: ALL induction therapy—25,000 IU/m^2 intramuscularly or intravenously substituting for each planned dose of either pegaspargase or *E. coli*–derived asparaginase.

Dose Modification Criteria

- None available

Adverse Reactions

- DERM: skin rash
- ENDO: hyperglycemia
- GI: N/V (minimal) and pancreatitis
- GU: prerenal azotemia
- HEMAT: coagulopathy (thrombosis or hemorrhage)
- HEPAT: increased LFTs, hyperbilirubinemia, and decreased serum albumin
- NEURO: variety of mental status changes
- OTHER: hypersensitivity, anaphylactic reactions, and hyperthermia

Comments

- Contraindicated in patients with active pancreatitis or history of pancreatitis. Discontinue asparaginase if severe or hemorrhagic pancreatitis develops while on therapy. Hypersensitivity and anaphylactic reactions can occur. Discontinue with serious reactions.
- Glucose intolerance may be irreversible. Monitor and treat accordingly.
- Serious thrombotic or hemorrhagic events may occur and should lead to discontinuation of therapy.
- Intramuscular (IM) administration has a lower incidence of hypersensitivity reactions compared to IV administration.
- IV infusions of Erwinaze should be over 1 to 2 hours.
- The asparaginase formulation derived from *E. coli* (Elspar) was discontinued in December 2012.

ATEZOLIZUMAB (TECENTRIQ)

Mechanism of Action

- Humanized monoclonal antibody that binds to programmed death-ligand 1 (PD-L1) and blocks interactions with the programmed death 1 (PD-1) and B7-1 receptors

FDA-Approved Indications

- Urothelial carcinoma: locally advanced or metastatic urothelial carcinomas that (1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or (2) are not eligible for any cisplatin-containing chemotherapy regardless of PD-L1 status.
- Non–small cell lung cancer (NSCLC): adult patients with metastatic NSCLC as:
    - Single agent as first-line therapy in patients whose tumors have high PD-L1 expression.
    - Combination therapy as first-line therapy with bevacizumab, paclitaxel, and carboplatin in metastatic nonsquamous NSCLC with no EGFR or ALK genomic

aberrations.
    - Combination therapy as first-line therapy with protein-bound paclitaxel and carboplatin in metastatic nonsquamous NSCLC with no EGFR or ALK genomic aberrations.
    - Single agent after disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic aberrations should have disease progression after receiving FDA-approved therapy directed toward these aberrations.
- Triple-negative breast cancer (TNBC): patients with locally advanced or metastatic disease whose tumors express PD-L1.
- Small cell lung cancer (SCLC): first-line therapy in adult patients with extensive-stage disease in combination with carboplatin and etoposide.
- Hepatocellular carcinoma (HCC): first-line therapy in adult patients with unresectable or metastatic disease in combination with bevacizumab.
- Melanoma: patients with BRAF V600 mutation–positive unresectable or metastatic melanoma in combination with cobimetinib and vemurafenib.

FDA-Approved Dosage

- Dosing schedules utilized for both single-agent and combination therapy:
    - 840 mg IV every 2 weeks
    - 1200 mg IV every 3 weeks
    - 1680 mg IV every 4 weeks

See product labeling for sequencing in combination therapy. Continue therapy until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal: no
- Hepatic (mild): no
- Hepatic (moderate to severe): no data
- Nonhematologic toxicity: doses should be held, not reduced due to toxicities. See package insert for specific recommendations regarding holding doses and starting corticosteroids

Adverse Reactions

- DERM: rash and pruritus
- ELECTRO: hyponatremia
- ENDO: immune-related hypophysitis, thyroid disorders, adrenal insufficiency, and diabetes mellitus
- GI: immune-related colitis, immune-related pancreatitis, decreased appetite, constipation, diarrhea, and N/V (minimal)
- GU: urinary tract infection
- HEMAT: lymphopenia
- HEPAT: immune-related hepatitis
- INFUS: infusion reactions
- NEURO: immune-related myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, and meningoencephalitis
- Ocular system: ocular inflammatory toxicity
- PULM: immune-related pneumonitis or interstitial lung disease, dyspnea, and cough
- OTHER: fatigue, pyrexia, arthralgia, peripheral edema, and back/neck pain

Comments

- Infusion-related reactions can occur and may be severe and life-threatening. Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening reactions.
- Immune-mediated adverse reactions (IMAR), which may be severe or fatal, can occur in any organ system or tissue. Monitor patients closely for symptoms and signs that may be clinical manifestations of immune-mediated reactions. Withholding parameters for immune-related toxicities are provided in the product labeling.
- Complications of allogeneic hematopoietic stem cell transplant (HSCT) after PD-1/PD-L1 inhibitors: fatal or other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1 or PD-L1

blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly.
- Triple-negative breast cancer (TNBC) patients treated with the combination of atezolizumab and paclitaxel had an increase in mortality in one clinical trial compared to those treated with placebo and paclitaxel.
- Embryo-fetal toxicity: atezolizumab may cause fetal harm when administered to a pregnant woman.

AVAPRITINIB (AYVAKIT)

Mechanism of Action

- Kinase inhibitor that targets KIT D816V, platelet-derived growth factor receptor (PDGFR) A, and PDGFRA D842 mutants. As a result, avapritinib prevents the downstream signaling caused by certain PDGFRA and KIT mutations.

FDA-Approved Indications

- Unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations
- Advanced systemic mastocytosis with platelet counts of ≥50,000/μL

FDA-Approved Dosage

- GIST: 300 mg orally once daily.
- Advanced systemic mastocytosis: 200 mg orally once daily.
- All indications: administer on an empty stomach, at least 1 hour before or 2 hours after food. Continue treatment until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild or moderate): no
- Hepatic (severe): not established
- CYP3A inhibitors (strong or moderate): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: hair color changes and rash
- GI: N/V (moderate-high), decreased appetite, diarrhea, constipation, and abdominal pain
- NEURO: cognitive impairment, dizziness, and intracranial hemorrhage
- Ocular system: increased lacrimation
- OTHER: edema and fatigue/asthenia

Comments

- Avoid concomitant administration of strong or moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the avapritinib dose.
- Avoid concomitant administration of strong or moderate CYP3A inducers.
- Embryo-fetal toxicity: avapritinib may cause fetal harm when administered to a pregnant woman.

AVELUMAB (BAVENCIO)

Mechanism of Action

- Human monoclonal antibody that binds to PD-L1, blocking the interaction with its receptors. Avelumab has also been shown to induce ADCC.

FDA-Approved Indications

- Merkel cell carcinoma (MCC): adult and pediatric patients 12 years and older with metastatic MCC
- Urothelial carcinoma:
  - Maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy
  - Treatment of adult patients with locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
- Renal cell carcinoma (RCC): adult patients for the first-line treatment of advanced RCC in combination with axitinib

FDA-Approved Dosage

- Premedicate with an antihistamine and acetaminophen for the first four infusions and subsequently as needed
- 800 mg as an IV infusion over 60 minutes every 2 weeks

Dose Modification Criteria

- No dose reductions of avelumab are recommended. In general, withhold for toxicity.
- Renal (CrCl ≥ 15 mL/min): no significant effect on PK.
- Hepatic (mild or moderate): no significant effect on PK.
- Hepatic (severe): no data available.

Adverse Reactions

- DERM: rash
- GI: N/V (minimal), diarrhea, and decreased appetite
- GU: urinary tract infection
- INFUS: infusion-related reactions
- OTHER: fatigue, musculoskeletal pain, peripheral edema, and immune-mediated adverse reactions (any organ system)

Comments

- Fatal and other serious complications of allogeneic hematopoietic stem cell transplant (HSCT) after PD-1/PD-L1 inhibitors have been reported.
- Immune-mediated adverse reactions can occur in any organ system or tissue and include the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis, and immune-mediated dermatologic reactions. Monitor for signs and symptoms of immune-mediated adverse reactions and consult the prescribing information and established guidelines for management.
- Embryo-fetal toxicity: avelumab may cause fetal harm when administered to a pregnant woman.

AXICABTAGENE CILOLEUCEL (YESCARTA)

Mechanism of Action

- An autologous chimeric antigen receptor (CAR)–positive T-cell therapy targeting CD19-expressing cancer cells and normal B cells. Antigen-specific activation of axicabtagene ciloleucel results in T-cell activation, cytokine secretion, and subsequent cytolytic killing of CD19-expressing cells.

FDA-Approved Indications

- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)
- Relapsed or refractory FL after two or more lines of systemic therapy

FDA-Approved Dosage

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion.
- Premedicate with acetaminophen and an H_1 antagonist; avoid prophylactic corticosteroids.
- The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells administered as an IV infusion.

Dose Modification Criteria

- No dose modifications of axicabtagene ciloleucel are recommended.
- Hepatic and renal impairment studies were not conducted.

Adverse Reactions

- CV: hypotension, tachycardia, and arrhythmias
- GI: N/V (low), decreased appetite, diarrhea, and constipation
- HEMAT: prolonged cytopenias and febrile neutropenia
- INFUS: hypersensitivity reactions
- NEURO: severe or life-threatening neurologic toxicities, encephalopathy, headache, tremor, and dizziness
- PULM: cough and hypoxia
- OTHER: cytokine release syndrome (CRS), fever, chills, fatigue, infections, musculoskeletal pain, hypogammaglobulinemia, and secondary malignancies

Comments

- Axicabtagene ciloleucel is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and should only be administered at a certified healthcare facility.
- Axicabtagene ciloleucel is associated with boxed warnings for the following:

    - CRS, including fatal and life-threatening reactions. Confirm availability of tocilizumab prior to infusion and treat severe or life-threatening CRS with tocilizumab +/− corticosteroids.
    - Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.
- Axicabtagene ciloleucel may have effects on the ability to drive and use machines. Advise patients to refrain from operating heavy or dangerous machinery for at least 8 weeks after administration.

AXITINIB (INLYTA)

Mechanism of Action

- Inhibits receptor tyrosine kinases (RTKs) including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3

FDA-Approved Indications

- Renal cell carcinoma (RCC):
    - First-line therapy in advanced RCC in combination with avelumab OR pembrolizumab
    - Second-line therapy in advanced RCC as a single agent after failure of one prior systemic therapy

FDA-Approved Dosage

- 5 mg orally twice daily. Swallow whole with a glass of water. Administer axitinib doses approximately 12 hours apart with or without food. When combined with avelumab or pembrolizumab in first-line therapy, dose escalation above the initial 5 mg dose may be considered at intervals of 2 weeks (avelumab combination) or 6 weeks (pembrolizumab combination).

Dose Modification Criteria

- Renal (mild, moderate, and severe): no
- Renal (end-stage renal disease [ESRD]) (CrCl < 15 mL/min): use caution
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate, Child-Pugh class B): yes
- Hepatic (severe, Child-Pugh class C): not studied
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: creatinine increased
- CV: hypertension and cardiac failure
- DERM: dry skin, palmar-plantar erythrodysesthesia (PPE), and rash
- ELECTRO: decreased bicarbonate, hyperkalemia, hypernatremia, hypocalcemia, hyponatremia, and hypophosphatemia
- ENDO: hyperglycemia, hypoglycemia, and hypothyroidism
- GI: abdominal pain, anorexia, constipation, diarrhea, N/V (minimal-low), and stomatitis
- GU: proteinuria
- HEMAT: anemia, leukopenia, lymphopenia, and thrombocytopenia
- HEPAT: hypoalbuminemia, hyperbilirubinemia, increased alkaline phosphatase, and increased LFTs
- NEURO: headache and dysgeusia
- PULM: cough and dyspnea
- OTHER: asthenia, arterial and venous thromboembolic events, dysphonia, fatigue, hemorrhage, pain in extremity, and weight decreased

Comments

- BP should be well controlled prior to starting axitinib and should be monitored regularly during treatment.
- Cardiac failure has been observed and can be fatal. Monitor for signs of symptoms of cardiac failure. Major adverse cardiovascular events have been reported with the combination of axitinib in combination with avelumab, which may be severe or fatal.
- Use with caution in patients who are at an increased risk for arterial and venous thrombotic events, as these events have been observed.
- Hemorrhagic events have been reported. Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active GI bleeding and should not be used in these patients.
- GI perforation and fistula have occurred.
- Hypothyroidism requiring thyroid hormone replacement has been reported. Thyroid function should be monitored prior to and throughout treatment.
- Stop axitinib at least 24 hours prior to scheduled surgery. The decision to resume axitinib after surgery should be based on clinical judgment of adequate wound healing.
- Reversible posterior leukoencephalopathy syndrome (RPLS) has been observed. Permanently discontinue axitinib if signs or symptoms of RPLS, such as headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances, occur.
- Monitor for proteinuria before initiation of, and periodically throughout, treatment with axitinib.
- Hepatotoxicity can be seen with single-agent therapy and may occur at higher rate of frequency when used in combination therapy with avelumab or pembrolizumab. Monitor LFTs prior to initiation and throughout therapy.
- Concomitant use of strong CYP3A4/5 inhibitors should be avoided. If coadministration is necessary, decrease the axitinib dose by half.

- Embryo-fetal toxicity: axitinib may cause fetal harm when administered to a pregnant woman.

AZACITIDINE (VIDAZA, ONUREG)

Mechanism of Action

- Antimetabolite. A pyrimidine nucleoside analog of cytidine. Azacitidine causes hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow.

FDA-Approved Indications

Parenteral (SC or IV) Azacitidine (Vidaza)

- Myelodysplastic syndrome (MDS): the specific subtypes of MDS for which azacitidine is indicated include refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myeloid leukemia (CML).

Oral Azacitidine (Onureg)

- Acute myeloid leukemia (AML): patients in first complete remission (CR) or CR with incomplete blood recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy.

FDA-Approved Dosage

Parenteral (SC or IV) Azacitidine (Vidaza)

- First treatment cycle: the recommended starting dose for all patients regardless of baseline hematology laboratory values is 75 mg/m^2 SC or IV, daily for 7 days.
- Subsequent treatment cycles: a cycle should be repeated every 4 weeks. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after two treatment cycles and if no toxicity other than N/V has occurred.
- Duration: minimum duration of four treatment cycles is recommended; complete or partial response may take more than four treatment cycles; may be continued as long as the patient continues to benefit.

Oral Azacitidine (Onureg)

- 300 mg PO once daily with or without food on days 1 through 14 of each 28-day cycle. Continue oral azacitidine until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal: no data, use with caution (dose modify for renal toxicity)
- Hepatic: no data (use with caution)
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: injection site erythema or pain, ecchymosis, rash, and pruritus
- ELECTRO: renal tubular acidosis (alkaline urine, fall in serum bicarbonate, and hypokalemia)
- GI: N/V (IV: moderate, PO: moderate-high), diarrhea, constipation, anorexia, abdominal pain, and hepatotoxicity
- GU: increased Cr and blood urea nitrogen (BUN), renal failure, and renal tubular acidosis
- HEMAT: anemia, neutropenia, and thrombocytopenia

- NEURO: headache and dizziness
- PULM: cough and dyspnea
- OTHER: fever, rigors, fatigue, weakness, peripheral edema, and tumor lysis syndrome (TLS)

Comments

- Parenteral and oral azacitidine have different PK and have different dose and schedule recommendations as well as different indications. Do not interchange or substitute one for the other.
- Embryo-fetal toxicity: teratogenic, women of childbearing potential should be advised to avoid becoming pregnant while receiving azacitidine. Men should be advised to not father a child while receiving azacitidine.
- Use caution in patients with liver disease. Azacitidine is potentially hepatotoxic in patients with preexisting hepatic impairment.
- Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.
- Azacitidine and its metabolites are primarily cleared renally. Patients with renal impairment should be closely monitored for toxicity. Renal toxicity has been reported rarely with IV azacitidine in combination with other chemotherapeutic agents for non-MDS conditions.

BACILLUS CALMETTE-GUÉRIN (BCG) LIVE (INTRAVESICAL [TICE BCG])

Mechanism of Action

- Local inflammatory and immune response

FDA-Approved Indications

- Treatment and prophylaxis of carcinoma in situ (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent-stage Ta and/or T1 papillary tumors following transurethral resection

FDA-Approved Dosage

- Tice Bacillus Calmette-Guérin (BCG): vial contains 50 mg (wet weight) or 1 to 8 × 10^8 colony-forming units.
  - One reconstituted vial (50 mg/1 mL), diluted in a total volume of 50 mL preservative-free normal saline (0.9% sodium chloride injection, USP), instilled into bladder for as long as possible (up to 2 hours) once weekly for 6 weeks followed by once monthly for 6 to 12 months.

Dose Modification Criteria

- Withhold on any suspicion of systemic infection

Adverse Reactions

- GU: irritative bladder symptoms (eg, dysuria, typically beginning 4-6 hours after instillation and lasting for 24-72 hours)
- OTHER: malaise, fever, and chills; infectious complications (uncommon)

Comments

- May complicate tuberculin skin test interpretation.
- BCG live products contain live, attenuated mycobacteria. Because of the potential risk of transmission, it should be prepared, handled, and disposed of as a biohazard material.
- BCG live products are contraindicated in immunosuppressed patients or those with congenital or acquired immune deficiencies.

BELANTAMAB MAFODOTIN (BLENREP)

Mechanism of Action

- As a B-cell maturation antigen (BCMA)–directed ADC, belantamab mafodotin binds to BCMA on multiple myeloma (MM) cells, undergoes internalization, and then releases the cytotoxic payload monomethyl auristatin phenylalanine (a microtubule inhibitor) resulting in DNA damage and apoptotic cell death. Belantamab mafodotin also causes tumor cell lysis through ADCC and antibody-dependent cellular phagocytosis (ADCP).

FDA-Approved Indications

- Multiple myeloma (MM): relapsed or refractory MM following at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor (PI), and an immunomodulatory agent

FDA-Approved Dosage

- 2.5 mg/kg as an IV infusion over 30 minutes once every 3 weeks

Dose Modification Criteria

- Renal (mild or moderate, eGFR 30-89 mL/min/1.73 m^2 by MDRD): no
- Renal (severe, eGFR < 30 mL/min/1.73 m^2 by MDRD): not established
- Hepatic (mild): no
- Hepatic (moderate or severe): not established
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: creatinine increased

- GI: N/V (not classified)
- HEMAT: thrombocytopenia, lymphopenia, anemia, and neutropenia
- HEPAT: increased GGT
- INFUS: infusion-related reactions
- Ocular system: keratopathy (corneal epithelium changes on eye examination), decreased visual acuity, and blurred vision
- OTHER: pyrexia and fatigue

Comments

- Belantamab mafodotin is associated with a boxed warning for ocular toxicity and is only available through a REMS program. Changes in corneal epithelium resulting in vision changes, including severe vision loss and corneal ulcer, have been reported. Ophthalmic examinations must be conducted at baseline, prior to each dose, and promptly for worsening symptoms.
- Embryo-fetal toxicity: belantamab mafodotin may cause fetal harm when administered to a pregnant woman.

BELINOSTAT (BELEODAQ)

Mechanism of Action

- Histone deacetylase (HDAC) inhibitor

FDA-Approved Indications

- Relapsed or refractory peripheral T-cell lymphoma (PTCL)

FDA-Approved Dosage

- 1000 mg/m^2 IV on days 1 to 5 of a 21-day cycle until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to moderate, CrCl >39 mL/min): no
- Renal (severe, CrCl ≤39): no data available
- Hepatic (moderate to severe [total bilirubin >1.5 × ULN]): no data available
- Myelosuppression: yes
- Nonhematologic toxicity: yes
- Reduced UGT1A1 activity (homozygous for UGT1A1*28 allele): yes

Adverse Reactions

- CV: prolonged QT
- DERM: rash and pruritus
- GI: N/V (low), diarrhea, and constipation
- HEMAT: thrombocytopenia, neutropenia, lymphopenia, and anemia
- HEPAT: LFT abnormalities and hepatotoxicity
- INFUS: infusion site pain and phlebitis
- NEURO: headache
- PULM: dyspnea and cough
- OTHER: infection, fatigue, pyrexia, peripheral edema, chills, and tumor lysis syndrome

Comments

- Monitor LFTs before treatment and before each cycle. Interrupting therapy or dose modification may be necessary for hepatic toxicity.
- Monitor patients for tumor lysis syndrome particularly in patients with advanced-stage disease and/or high tumor burden.
- Infections: serious and sometimes fatal infections have occurred in patients while on belinostat. Do not administer belinostat in patients with an active infection.

- Avoid concomitant administration of strong UGT1A1 inhibitors.
- Embryo-fetal toxicity: belinostat may cause fetal harm when administered to a pregnant woman.

BENDAMUSTINE HYDROCHLORIDE (TREANDA)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL)
- Indolent B-cell non-Hodgkin Lymphoma (NHL): disease progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen

FDA-Approved Dosage

- CLL: 100 mg/m^2 IV over 10 minutes on days 1 and 2 of a 28-day cycle, up to six cycles
- NHL: 120 mg/m^2 IV over 10 minutes on days 1 and 2 of a 21-day cycle, up to eight cycles

Dose Modification Criteria

- Renal: no data; use with caution in patients with mild to moderate renal impairment, avoid in patients with CrCl <40 mL/min
- Hepatic: no data; use with caution in patients with mild hepatic impairment, avoid in patients with moderate to severe hepatic impairment
- Myelosuppression: yes

- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, pruritus, toxic skin reactions, bullous exanthema, and extravasation injuries
- GI: N/V (moderate), diarrhea, and mucositis
- HEMAT: myelosuppression
- HEPAT: increased LFTs, hepatotoxicity
- INFUS: fever, chills, pruritus, rash, anaphylaxis, or anaphylactoid reactions
- PULM: cough
- OTHER: tumor lysis syndrome, asthenia, and infections

Comments

- Infusion reactions occurred commonly in clinical trials. Monitor clinically and discontinue drug for severe reactions (grade 3 or worse). Measures to prevent severe reactions (eg, antihistamines, antipyretics, and corticosteroids) should be considered in subsequent cycles in patients who have previously experienced grade 1 or 2 infusion reactions.
- Monitor for tumor lysis syndrome, particularly with the first treatment cycle, and utilize prevention strategies during the first 1 to 2 weeks of therapy in patients at high risk. Allopurinol has been used during the beginning of bendamustine therapy but there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are used concomitantly.
- Severe skin reactions have been reported necessitating drug therapy to be withheld or discontinued.
- Hepatotoxicity, including serious and fatal cases, has been reported with bendamustine. Monitor LFTs prior to start and during therapy with bendamustine.
- Extravasation of bendamustine may cause local erythema, swelling and pain. Assure good venous access prior to starting drug infusion and monitor the infusion site.

- Bendamustine hydrochloride is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. Some metabolism via CYP1A2 occurs forming active metabolites; thus, potential drug interactions with CYP1A2 inhibitors or inducers should be considered.
- Embryo-fetal toxicity: bendamustine may cause fetal harm when administered to a pregnant woman.
- Do not use bendamustine solution for injection with devices that contain polycarbonate or acrylonitrile butadiene styrene including most closed system transfer devices.
- Concomitant CYP1A2 inducers or inhibitors have the potential to alter the exposure of bendamustine.

BEVACIZUMAB (AVASTIN)

Mechanism of Action

- Recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

FDA-Approved Indications

- Metastatic colorectal cancer (mCRC): first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum, in combination with IV 5-fluorouracil (5-FU)–based chemotherapy. Second-line treatment of metastatic colorectal carcinoma (in combination with fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based therapy) in patients who have progressed on a first-line bevacizumab-containing regimen.
- Nonsquamous, non–small cell lung cancer (NSCLC): first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC, in combination with carboplatin and paclitaxel.

- Glioblastoma: second-line single-agent therapy in patients with progressive disease following prior therapy.
- Metastatic renal cell cancer (RCC): in combination with interferon-α.
- Cervical cancer: persistent, recurrent, or metastatic disease in combination with paclitaxel and cisplatin or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer that is:
  - Stage III or IV disease following initial surgical resection in combination with carboplatin and paclitaxel followed by bevacizumab as a single agent.
  - Platinum-resistant, recurrent disease following no more than two prior chemotherapy regimens in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.
  - Platinum-sensitive, recurrent disease in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.
- Hepatocellular carcinoma (HCC): first-line therapy for unresectable or metastatic HCC in combination with atezolizumab.

FDA-Approved Dosage

- Metastatic colorectal cancer: 5 mg/kg IV every 2 weeks when used in combination with bolus IFL.
  - 10 mg/kg IV every 2 weeks when used in combination with FOLFOX4.
  - 5 mg/kg IV every 14 days or 7.5 mg/kg IV every 3 weeks when used in combination with a fluoropyrimidine-irinotecan–based or fluoropyrimidine-oxaliplatin–based chemotherapy regimen in patients who have progressed on a first-line bevacizumab-containing regimen.
- Nonsquamous NSCLC: 15 mg/kg IV every 3 weeks in combination with carboplatin and paclitaxel.
- Glioblastoma: 10 mg/kg IV every 2 weeks.
- Metastatic RCC: 10 mg/kg IV every 2 weeks in combination with interferon-α.
- Cervical cancer: 15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:

    - Stage III or IV disease following initial surgical resection: 15 mg/kg IV every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, then 15 mg/kg IV every 3 weeks as a single agent for up to 22 cycles or until disease progression.
    - Platinum-resistant recurrent disease: 10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week) OR 15 mg/kg IV every 3 weeks with topotecan given every 3 weeks.
    - Platinum-sensitive recurrent disease: 15 mg/kg IV every 3 weeks in combination with carboplatin/paclitaxel for 6 to 8 cycles, followed by 15 mg/kg IV every 3 weeks as a single agent, OR 15 mg/kg IV every 3 weeks in combination with carboplatin/gemcitabine for 6 to 10 cycles, followed by 15 mg/kg IV every 3 weeks as a single agent until disease progression.
- Hepatocellular carcinoma: 15 mg/kg IV after administration of 1200 mg of atezolizumab IV on the same day every 3 weeks until disease progression or unacceptable toxicity.
- Do not administer bevacizumab as an IV push or bolus. The initial bevacizumab dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Dose Modification Criteria

- Renal: no
- Hepatic: no
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, hypertensive crisis, and CHF
- DERM: dry skin and exfoliative dermatitis
- GI: N/V (minimal), taste alteration, diarrhea, abdominal pain, GI perforation, and wound dehiscence
- GU: proteinuria and nephrotic syndrome
- INFUS: fever, chills, wheezing, and stridor
- NEURO: headache
- PULM: dyspnea and wheezing stridor

- OTHER: rhinitis, back pain, epistaxis, and other mild to moderate hemorrhagic events; serious hemorrhagic events; wound healing complications; deep vein thrombosis or other thromboembolic events; and asthenia

Comments

- Bevacizumab can result in the development of GI perforation, fistulae and wound dehiscence, and other wound healing complications. The appropriate interval between termination of bevacizumab and subsequent elective surgery required to avoid the risks of wound healing/wound dehiscence has not been determined. Product labeling suggests that bevacizumab should not be initiated for at least 28 days following major surgery and the surgical incision should be fully healed.
- Bleeding complications secondary to bevacizumab occur in two distinct patterns: minor hemorrhage (most commonly grade 1 epistaxis) and serious, and in some cases, fatal hemorrhagic events. Patients with squamous cell NSCLC appear to be at higher risk for serious hemorrhagic events. There is a risk of CNS bleeding in patients with CNS metastases based on limited data (refer to product labeling). In patients with HCC, an evaluation for the presence of varices is recommended within 6 months of starting bevacizumab.
- BP monitoring should be conducted every 2 to 3 weeks during therapy and more frequently in patients who develop hypertension.
- Arterial and venous thromboembolic events have been associated with bevacizumab. Discontinue bevacizumab for severe or life-threatening thromboembolic events.
- Posterior reversible encephalopathy syndrome (PRES) associated with bevacizumab use has been reported rarely (<0.5%).
- Monitor urinalysis serially for proteinuria; patients with a 2+ or greater urine dipstick reading should undergo further assessment (eg, a 24-hour urine collection).

- Infusion-related reactions may occur. Reduce rate of infusion for mild reactions, interrupt infusion if clinically significant, and consider resuming at a slower rate upon resolution. Discontinue for severe reactions and administer appropriate therapy.
- Bevacizumab may increase the risk of ovarian failure in premenopausal females.
- Bevacizumab is not indicated for use with anthracycline-based chemotherapy due to an increased risk of congestive heart failure and decline in LVEF.
- Embryo-fetal toxicity: angiogenesis is critical to fetal development and bevacizumab has been shown to be teratogenic in rabbits.

BEXAROTENE (TARGRETIN)

Mechanism of Action

- A retinoid that selectively binds and activates retinoid X receptor subtypes.
- Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation.

FDA-Approved Indications

- Cutaneous T-cell lymphoma (CTCL): second-line treatment of the cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy (oral bexarotene)
- Topical treatment of cutaneous lesions in patients with CTCL (stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies (topical bexarotene 1% gel)

FDA-Approved Dosage

- 300 mg/m^2 orally daily with a meal
- Bexarotene 1% gel is applied to cutaneous lesions every other day for the first week and then the application frequency is increased at weekly intervals up to four times daily according to individual lesion tolerance

Dose Modification Criteria

- Renal: no (caution due to possible protein binding alterations)
- Hepatic: use with caution
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: peripheral edema
- DERM: dry skin, photosensitivity, rash, and pruritus
- ENDO: hypothyroidism and hypoglycemia (diabetic patients)
- GI: nausea (minimal-low), pancreatitis, and abdominal pain
- HEMAT: leukopenia and anemia
- HEPAT: elevated LFTs
- NEURO: headache
- Ocular system: cataracts
- OTHER: lipid abnormalities (elevated triglycerides, elevated total and low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol), asthenia, and infection

Comments

- Monitor fasting blood lipid tests prior to initiation of oral bexarotene and weekly until the lipid response is established (usually occurs within 2-4 weeks) and then at 8-week intervals thereafter.
- Monitor LFTs prior to initiation of oral bexarotene and then after 1, 2, and 4 weeks of treatment and, if stable, at least every 8 weeks thereafter during treatment.

- Monitor complete blood count (CBC) and thyroid function tests at baseline and periodically thereafter.
- Pancreatitis: interrupt oral bexarotene and evaluate if suspected.
- Minimize exposure to sunlight and artificial ultraviolet light during treatment with bexarotene.
- Embryo-fetal toxicity: bexarotene is a teratogen and may cause fetal harm when administered to a pregnant woman. Bexarotene must not be given to a pregnant woman or a woman who intends to become pregnant. A negative pregnancy test in female patients of childbearing potential should be obtained within 1 week prior to starting bexarotene therapy and then repeated at monthly intervals while the patient remains on therapy. Effective contraception (two reliable forms used simultaneously) must be used for 1 month prior to initiation of therapy, during therapy, and for at least 1 month following discontinuation of therapy. Bexarotene may induce the metabolism of hormonal contraceptives and reduce their effectiveness; thus, one form of contraception should be nonhormonal.

BICALUTAMIDE (CASODEX)

Mechanism of Action

- Antiandrogen

FDA-Approved Indications

- Prostate cancer: palliation of advanced prostate cancer (stage D2) in combination therapy with a luteinizing hormone-releasing hormone (LHRH) agonist

FDA-Approved Dosage

- 50 mg orally daily

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate impairment): no
- Hepatic (severe impairment): use with caution

Adverse Reactions

- ENDO: loss of libido, hot flashes, and gynecomastia
- GI: N/V (not classified), diarrhea, and constipation
- GU: impotence
- HEPAT: hepatitis

Comments

- Monitor LFTs prior to treatment, at regular intervals for the first 4 months, and periodically thereafter. Severe hepatic injuries including fatalities have been observed.
- R-bicalutamide is an inhibitor of CYP3A4; use caution when bicalutamide is used concurrently with CYP3A4 substrates.

BINIMETINIB (MEKTOVI)

Mechanism of Action

- Reversible inhibitor of MEK1 (mitogen-activated protein kinase/extracellular signal–regulated kinase) and MEK2 activity, which results in the inhibition of downstream signaling of the extracellular signal–regulated kinase (ERK) pathway

FDA-Approved Indications

- Metastatic melanoma: in combination with encorafenib for the treatment of unresectable or metastatic melanoma harboring a

BRAF V600E or V600K mutation, as detected by an FDA-approved test.

FDA-Approved Dosage

- 45 mg orally twice daily, approximately 12 hours apart, in combination with encorafenib until disease progression or unacceptable toxicity. May take without regard to food.

Dose Modification Criteria

- Renal (eGFR ≥ 30 mL/min): no
- Renal (eGFR < 30 mL/min): no significant effect on PK
- Hepatic (mild): no
- Hepatic (moderate or severe): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy and venous thromboembolism
- GI: N/V (moderate-high), diarrhea, and abdominal pain
- HEMAT: hemorrhage
- HEPAT: hepatotoxicity
- Ocular system: serous retinopathy, retinal vein occlusion, and uveitis
- PULM: interstitial lung disease
- OTHER: fatigue and rhabdomyolysis

Comments

- Assess LVEF before treatment, after 1 month of treatment, then every 2 to 3 months thereafter. Safety of binimetinib has not been established in patients with LVEF < 50%.
- Perform ophthalmologic evaluations at regular intervals and for any visual disturbances.

- Embryo-fetal toxicity: binimetinib may cause fetal harm when administered to a pregnant woman.

BLEOMYCIN (BLENOXANE)

Mechanism of Action

- Unknown, but may inhibit DNA and RNA synthesis

FDA-Approved Indications

- Squamous cell cancers, NHL, testicular cancer, Hodgkin disease, and malignant pleural effusions

FDA-Approved Dosage

- The product labeling recommends a test dose (two units or less) for the first two doses in lymphoma patients.
- From 0.25 to 0.50 units/kg (10-20 units/m^2) IV or IM or SC weekly or twice weekly.
- Malignant pleural effusions: 60 units as single intrapleural bolus dose.

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: erythema, rash, striae, vesiculation, hyperpigmentation, skin tenderness, alopecia, nail changes, pruritus, and stomatitis
- PULM: pulmonary fibrosis (increases at cumulative doses >400 units, but can happen at lower total doses) and pneumonitis
- OTHER: fever and chills; idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has

been reported in 1% of lymphoma patients; local pain with intrapleural administration

Comments

- Risk factors for bleomycin-induced pulmonary toxicity include age (older than 70 years old), underlying emphysema, prior thoracic radiotherapy (RT), high cumulative doses (eg, >450 units), and high single doses (>30 units).
- Patients who have received bleomycin may be at increased risk of respiratory failure during the postoperative recovery period after surgery. Use the minimal tolerated concentration of inspired oxygen and modest fluid replacement to prevent pulmonary edema.

BLINATUMOMAB (BLINCYTO)

Mechanism of Action

- CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. Blinatumomab activates endogenous T cells by connecting CD3 in the T-cell receptor complex with CD19 on benign and malignant B cells, leading to lysis of $CD19^+$ cells.

FDA-Approved Indications

- B-cell precursor acute lymphocytic leukemia (ALL), CD19-positive patients in the following categories:
  - First or second complete remission with MRD-positive disease (minimal residual disease greater than 0.1%) in adults and children
  - Relapsed or refractory disease in adults and children

FDA-Approved Dosage

- MRD-positive B-cell precursor ALL: a treatment course consists of a cycle of induction followed by up to three additional cycles for consolidation.
    - Premedicate with a glucocorticoid (see product labeling for dose suggestions) 1 hour prior to the first dose of each cycle, and when restarting an infusion after an interruption ≥4 hours.
    - For patients ≥45 kg:
        - Cycle 1 induction therapy: administer 28 μg/d via continuous IV infusion on days 1 to 28 followed by a 14-day treatment-free interval.
        - Cycles 2 to 4 consolidation therapy: administer 28 μg/d via continuous IV infusion on days 1 to 28 with a 14-day treatment-free interval after each cycle.
    - For patients <45 kg:
        - Cycle 1 induction therapy: administer 15 $\mu g/m^2/d$ (not to exceed 28 μg/d) via continuous IV infusion on days 1 to 28 followed by a 14-day treatment-free interval.
        - Cycles 2 to 4 consolidation therapy: administer 15 $\mu g/m^2/d$ (not to exceed 28 μg/d) via continuous IV infusion on days 1 to 28 followed by a 14-day treatment-free interval after each cycle.
- Relapsed or refractory B-cell precursor ALL: a treatment course consists of up to two cycles of induction therapy followed by three cycles of consolidation and up to four additional cycles of continued therapy.
    - Premedicate with a glucocorticoid (see product labeling for dose suggestions) 1 hour prior to the first dose of each cycle and when restarting an infusion after an interruption ≥4 hours.
    - For patients ≥45 kg:
        - Cycle 1 induction therapy: administer 9 μg/d via continuous IV infusion on days 1 to 7 followed by 28 μg/d via continuous IV infusion on days 8 to 28 followed by a 14-day treatment-free interval.
        - Cycle 2 (induction) and cycles 3 to 4 (consolidation) therapy: administer 28 μg/d via continuous IV infusion on days 1 to 28 with a 14-day treatment-free interval after each cycle.
        - Cycles 6 to 9 (continued therapy): administer 28 μg/d via continuous IV infusion on days 1 to 28 with a 56-day treatment-free interval after each cycle.
    - For patients <45 kg:
        - Cycle 1 induction therapy: administer 5 μg/kg (NTE 9 μg/d) via continuous IV infusion on days 1 to 7 followed by 15 $\mu g/m^2/d$ (not to exceed 28 μg/d) via continuous IV infusion on days 1 to 28 followed by a 14-day treatment-free interval.
        - Cycle 2 (induction) and cycles 3 to 4 (consolidation) therapy: administer 15 $\mu g/m^2/d$ (not to exceed 28 μg/d) via continuous IV infusion on days 1 to 28 followed by a 14-day treatment-free interval after each cycle.
        - Cycles 6 to 9 (continued therapy): administer 15 $\mu g/m^2/d$ (NTE 28 μg/d) via continuous IV infusion on days 1 to 28 with a 56-day treatment-free interval after each cycle.

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no (limited data)
- Renal (CrCl < 30 mL/min): no information available
- Hepatic: no information available
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash
- ELECTRO: hypokalemia
- GI: N/V (low), constipation, diarrhea, pancreatitis, and abdominal pain
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: increased ALT/AST
- INFUS: infusion reactions
- NEURO: encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, coordination and balance, seizures, headache, and tremor
- PULM: pneumonia, cough, and dyspnea
- OTHER: cytokine release syndrome, febrile neutropenia, tumor lysis syndrome, pyrexia, peripheral edema, fatigue, and chills

Comments

- Cytokine release syndrome and neurologic toxicity may be life-threatening or fatal. Patients should be closely monitored for signs and symptoms of these events. Guidance on criteria for interruption or discontinuation of blinatumomab is provided in the product labeling.
- Prepare according to the package insert to minimize errors.
- Do not flush infusion lines when changing bags or at the completion of infusion.
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Blinatumomab contains benzyl alcohol as a preservative. When prescribing for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources. Seven-day infusion bags containing bacteriostatic saline containing benzyl alcohol are not recommended for use in any patients weighing less than 22 kg.
- Advise patient to refrain from driving and engaging in hazardous occupations while blinatumomab is being

administered due to the potential for neurologic events.

BORTEZOMIB (VELCADE)

Mechanism of Action

- Bortezomib is a reversible inhibitor of the 26S proteosome, a large protein complex that degrades ubiquitinated proteins. Inhibition of the 26S proteosome prevents targeted proteolysis, which can effect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

FDA-Approved Indications

- Multiple myeloma
- Mantle cell lymphoma

FDA-Approved Dosage

- General dosing guidelines: the recommended starting dose for bortezomib is 1.3 mg/m^2. Bortezomib may be administered intravenously at a concentration of 1 mg/mL or subcutaneously at a concentration of 2.5 mg/mL. When administered intravenously, bortezomib is administered as a 3- to 5-second bolus IV injection.
- Multiple myeloma (first-line therapy in combination with melphalan and prednisone): 1.3 mg/m^2 IV or SC twice weekly on a 6-week treatment cycle on days 1, 4, 8, 11, 22, 25, 29, and 32 for cycles 1 to 4. In cycles 5 to 9, bortezomib is administered once weekly on days 1, 8, 22, and 29 of a 6-week treatment cycle (note that week 3 and week 6 of the cycle are rest periods).
- Mantle cell lymphoma (first-line therapy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone

[VcR-CAP]): 1.3 mg/m^2 IV twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period on days 12 to 21.

- Multiple myeloma (relapsed disease) and mantle cell lymphoma (relapsed disease): 1.3 mg/m^2 IV or SC administered twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). For extended therapy of more than eight cycles, bortezomib may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22) followed by a 13-day rest period (days 23-35). At least 72 hours should elapse between consecutive doses of bortezomib.
- Retreatment for multiple myeloma may be considered in patients who had previously responded to treatment and who have relapsed at least 6 months after completing prior therapy. Treatment may be started at the last tolerated dose.

Dose Modification Criteria

- Renal: no data (use caution)
- Hepatic (moderate or severe hepatic impairment): yes
- Myelosuppression: yes
- Nonhematologic toxicity (eg, neuropathy and neuropathic pain): yes

Adverse Reactions

- CV: hypotension (including orthostatic hypotension and syncope), edema, and heart failure
- DERM: rash
- GI: N/V (low), diarrhea, anorexia, and constipation
- HEMAT: myelosuppression (thrombocytopenia > anemia > neutropenia)
- HEPAT: hepatotoxicity
- NEURO: peripheral neuropathy, neuropathic pain, dizziness, headache, and posterior reversible encephalopathy syndrome (PRES)

- Ocular system: diplopia and blurred vision
- PULM: dyspnea and acute respiratory syndromes
- OTHER: asthenia, fatigue, fever, insomnia, arthralgia, thrombotic microangiopathy (TMA), and tumor lysis syndrome

Comments

- The reconstitution volume/concentration is different for the IV and subcutaneous routes. Use caution when calculating the volume to be administered.
- The incidence of peripheral neuropathy is lower when bortezomib is administered by the subcutaneous route of administration compared to the IV route. Starting bortezomib subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy.
- Use caution in treating patients with a history of syncope, who are on medications associated with hypotension, and in patients who are dehydrated.
- Embryo-fetal toxicity: bortezomib may cause fetal harm when administered to a pregnant woman.
- Bortezomib is a substrate of CYP3A4. Use caution in patients who are concomitantly receiving medications that are strong inhibitors or inducers of CYP3A4.

BOSUTINIB (BOSULIF)

Mechanism of Action

- Tyrosine kinase inhibitor (TKI) that inhibits the Bcr-Abl kinase that promotes CML; also an inhibitor of Src family kinases including Src, Lyn, and Hck.

FDA-Approved Indications

- Chronic myelogenous leukemia (CML):

- Newly diagnosed chronic phase (CP) Philadelphia chromosome–positive (Ph+) CML
- CP, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy

FDA-Approved Dosage

- Newly diagnosed CP Ph+ CML: 400 mg orally once daily with food
- CP, AP, BP Ph+ CML with resistance or intolerance to prior therapy: 500 mg orally once daily with food
- Dose escalation by 100 mg increments up to 600 mg orally once daily in patients may be considered in patients who did not achieve or maintain a hematologic, cytogenetic, or molecular response and who did not have grade 3 or higher adverse reactions at the recommended starting dosage

Dose Modification Criteria

- Renal (CrCl <50 mL/min): yes
- Hepatic (mild, moderate, and severe): yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiac failure, left ventricular dysfunction, cardiac ischemic events, and fluid retention
- DERM: pruritus and rash
- GI: abdominal pain, anorexia, diarrhea, and N/V (moderate-high [dose dependent])
- GU: renal toxicity (decline in glomerular filtration rate [GFR])
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- NEURO: dizziness and headache
- PULM: cough, nasopharyngitis, and respiratory tract infection
- OTHER: arthralgia, asthenia, back pain, fatigue, and pyrexia

Comments

- Avoid the concomitant use of strong or moderate CYP3A and/or P-gp inhibitors and inducers.
- Bosutinib may increase the plasma concentrations of drugs that are P-gp substrates, such as digoxin.
- PPIs may decrease bosutinib drug levels. Consider short-acting antacids or H_2 blockers in place of PPIs, and separate antacid or H_2 blocker dosing from bosutinib by more than 2 hours.
- Bosutinib did not inhibit the T315I and V299L mutant cells in mice.
- Monitor hepatic enzymes at least monthly for the first 3 months and as needed.
- Bosutinib can cause cardiovascular toxicity and may be more likely to occur in previously treated patients and in patients of advanced age or cardiac risk factors.
- Fluid retention may occur with bosutinib and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema.
- Monitor renal function at baseline and during therapy with bosutinib with particular attention to patients with preexisting renal impairment or risk factors for renal dysfunction.
- Embryo-fetal toxicity: bosutinib may cause fetal harm when administered to a pregnant woman.

BRENTUXIMAB VEDOTIN (ADCETRIS)

Mechanism of Action

- ADC consisting of a chimeric IgG1 directed against CD30 and monomethyl auristatin E (MMAE), a microtubule-disrupting agent that is covalently attached to the antibody via a linker. The ADC binds to CD30-expressing cells and is internalized, and, subsequently, MMAE is released via proteolytic cleavage.

Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis.

FDA-Approved Indications

- Classical Hodgkin lymphoma (cHL):
  - Previously untreated stage III or IV cHL in combination with doxorubicin, vinblastine, and dacarbazine
  - Consolidation therapy following auto-HSCT in adult patients at high risk of relapse or progression
  - Relapsed cHL after failure of auto-HSCT or after failure of at least two prior multiagent chemotherapy regimens in patients who are not auto-HSCT candidates
- Anaplastic large cell lymphoma (ALCL) or other CD30-expressing lymphomas:
  - Previously untreated systemic ALCL or other CD30-expressing peripheral T-cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone
  - Relapsed systemic ALCL after failure of at least one prior multiagent chemotherapy regimen
  - Relapsed primary cutaneous ALCL or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy

FDA-Approved Dosage

- Classical Hodgkin lymphoma (cHL):
  - Previously untreated stage III or IV cHL: 1.2 mg/kg IV in combination with chemotherapy every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity.
  - Consolidation therapy following auto-HSCT: 1.8 mg/kg IV every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.
  - Relapsed cHL: 1.8 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity.
- Anaplastic large cell lymphoma (ALCL) or other CD30-expressing lymphomas:
  - Previously untreated systemic ALCL or PTCL: 1.8 mg/kg IV in combination with chemotherapy every 3 weeks for six to eight doses.
  - Relapsed systemic ALCL: 1.8 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity.
  - Relapsed primary cutaneous ALCL or MF: 1.8 mg/kg IV every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

- Do not administer as an IV push or bolus. Administer as an IV infusion over 30 minutes.
- Continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity.
- The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg (maximum dose 180 mg).

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-80 mL/min): no
- Renal (severe, CrCl < 30 mL/min): avoid use
- Hepatic (mild, Child-Pugh class A): yes
- Hepatic (moderate to severe, Child-Pugh class B or C): avoid use
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Effects

- DERM: alopecia, night sweats, pruritus, rash, serious dermatologic reactions (eg, Stevens-Johnson syndrome [SJS] or toxic epidermal necrolysis)
- GI: abdominal pain, constipation, diarrhea, N/V (low), oropharyngeal pain, serious GI complications (eg, perforation)
- HEMAT: anemia, neutropenia, lymphadenopathy, and thrombocytopenia
- HEPAT: hepatotoxicity
- INFUS: anaphylaxis, breathing problems, chills, fever, and rash
- NEURO: dizziness, headache, and motor and sensory peripheral neuropathy
- PULM: cough, dyspnea, upper respiratory tract infection, and noninfectious pulmonary toxicity
- OTHER: arthralgia, back pain, chills, fatigue, insomnia, myalgia, pain in extremity, pyrexia, and tumor lysis syndrome

Comments

- JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death can occur. Consider the diagnosis of PML in any patient presenting with new onset signs and symptoms of central nervous system (CNS) abnormalities.
- Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity.
- Brentuximab vedotin–induced peripheral neuropathy is predominantly sensory and is cumulative.
- A higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.
- MMAE is primarily metabolized by CYP3A. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Coadministration of brentuximab vedotin with strong CYP3A4 inducers should be avoided.
- Embryo-fetal toxicity: brentuximab vedotin may cause fetal harm when administered to a pregnant woman.

BREXUCABTAGENE AUTOLEUCEL (TECARTUS)

Mechanism of Action

- An autologous CAR-positive T-cell therapy targeting CD19-expressing cancer cells and normal B cells. Antigen-specific activation of brexucabtagene autoleucel results in T-cell activation, cytokine secretion, and subsequent cytolytic killing of CD19-expressing cells.

FDA-Approved Indications

- Relapsed or refractory mantle cell lymphoma

FDA-Approved Dosage

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion
- Premedicate with acetaminophen and diphenhydramine; avoid prophylactic corticosteroids
- The dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells administered as an IV infusion

Dose Modification Criteria

- No dose modifications of brexucabtagene autoleucel are recommended.
- Hepatic and renal impairment studies were not conducted.

Adverse Reactions

- CV: hypotension, tachycardia, and arrhythmias
- DERM: rash
- GI: N/V (low), constipation, diarrhea, and decreased appetite
- HEMAT: prolonged cytopenias
- INFUS: hypersensitivity reactions
- NEURO: severe or life-threatening neurologic toxicities, encephalopathy, tremor, and headache
- PULM: hypoxia, cough, dyspnea, and pleural effusion
- OTHER: infections, hypogammaglobulinemia, secondary malignancies, pyrexia, chills, CRS, fatigue, musculoskeletal pain, edema, motor dysfunction, aphasia, and insomnia

Comments

- Brexucabtagene autoleucel is only available through a REMS program and should only be administered at a certified healthcare facility.

- Brexucabtagene autoleucel is associated with boxed warnings for the following:
  - CRS, including fatal and life-threatening reactions. Confirm availability of tocilizumab prior to infusion and treat severe or life-threatening CRS with tocilizumab +/− corticosteroids.
  - Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.
- Brexucabtagene autoleucel may have effects on the ability to drive and use machines. Advise patients to refrain from operating heavy or dangerous machinery for at least 8 weeks after administration.

BRIGATINIB (ALUNBRIG)

Mechanism of Action

- TKI with activity against ALK, ROS1, insulin-like growth factor 1 receptor, and FMS-like tyrosine kinase 3 (FLT-3) as well as EGFR deletion and point mutations

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): ALK-positive metastatic NSCLC, as detected by an FDA-approved test

FDA-Approved Dosage

- 90 mg orally once daily for the first 7 days, then increase to 180 mg once daily thereafter until disease progression or unacceptable toxicity. May take without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl 15-29 mL/min): yes

- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): yes
- CYP3A inhibitors (strong or moderate): yes
- CYP3A inducers (moderate): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension and bradycardia
- DERM: rash
- ENDO: hyperglycemia
- GI: N/V (minimal-low), diarrhea, and pancreatic enzyme elevation
- NEURO: headache
- Ocular system: visual disturbance
- PULM: cough, dyspnea, and interstitial lung disease/pneumonitis
- OTHER: fatigue, myalgia, and CPK elevation

Comments

- Dose titration recommended to reduce the incidence of early onset pulmonary toxicities.
- Avoid coadministration with strong or moderate CYP3A inhibitors. If coadministration of a strong or moderate CYP3A inhibitor is unavoidable, reduce the dose of brigatinib.
- Avoid coadministration with strong or moderate CYP3A inducers. If coadministration of a moderate inducer is unavoidable, increase the brigatinib dose.
- Embryo-fetal toxicity: brigatinib may cause fetal harm when administered to a pregnant woman.

BUSULFAN (MYLERAN); BUSULFAN INJECTION (BUSULFEX)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Oral busulfan: palliative treatment of CML
- Parenteral busulfan: conditioning regimen (in combination with cyclophosphamide) prior to allogeneic hematopoietic progenitor cell transplantation for CML

FDA-Approved Dosage

- Oral busulfan: induction, 4 to 8 mg orally daily; weight or body surface area (BSA) based: 60 μg/kg or 1.8 mg/m^2 orally daily; maintenance, 1 to 3 mg orally daily.
- Parenteral busulfan.
- Patients should receive phenytoin or an alternative antiseizure regimen prior to starting busulfan and continuing through the busulfan regimen.
- For nonobese patients, use ideal body weight (IBW) or actual body weight, whichever is lower.
- For obese or severely obese patients, use adjusted IBW (AIBW). AIBW should be calculated as follows: AIBW = IBW + 0.25 × (actual weight − IBW).
- 0.8 mg/kg IV over 2 hours every 6 hours × 16 doses (total course dose: 12.8 mg/kg) with cyclophosphamide.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: hyperpigmentation
- GI: N/V oral (<4 mg/kg/d): minimal-low, IV: moderate

- HEMAT: severe myelosuppression
- HEPAT: hepatic veno-occlusive disease (VOD)
- NEURO: seizures
- PULM: pulmonary fibrosis

Comments

- Therapeutic drug monitoring to determine AUC with the first administered dose is frequently done with high-dose parenteral busulfan.
- Alternative high-dose once daily parenteral dose regimens and multiple dose oral regimens have been utilized for conditioning regimens in the allogeneic blood and marrow transplant setting. Consult current literature for dosing regimens.
- Phenytoin reduces busulfan plasma AUC by 15%. Use of other anticonvulsants may result in higher busulfan plasma AUCs and potentially increased toxicity. Consult current literature in regard to the antiseizure regimen utilized within a regimen.
- Embryo-fetal toxicity: busulfan may cause fetal harm when administered to a pregnant woman.

CABAZITAXEL (JEVTANA)

Mechanism of Action

- Microtubule inhibitor that binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to stabilization of microtubules, which results in inhibition of mitotic and interphase cellular functions.

FDA-Approved Indication

- In combination with prednisone for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen

FDA-Approved Dosage

- 20 mg/m^2 as a 1-hour IV infusion every 3 weeks in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment. A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider (see comments).

Dose Modification Criteria

- Renal (CrCl ≥ 15 mL/min/1.73 m^2): no
- Renal (CrCl < 15 mL/min/1.73 m^2): use caution
- Hepatic (mild to moderate): yes
- Hepatic (severe): avoid use
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Effects

- DERM: alopecia
- GI: abdominal pain, anorexia, constipation, diarrhea, dyspepsia, and N/V (low)
- GU: hematuria, renal toxicity, cystitis, and recall radiation cystitis
- HEMAT: anemia, leukopenia, neutropenia, and thrombocytopenia
- INFUS: hypersensitivity reactions
- NEURO: peripheral neuropathy and dysgeusia
- PULM: cough and dyspnea and severe noninfectious respiratory disorders
- OTHER: arthralgia, asthenia, back pain, fatigue, and pyrexia

Comments

- Cabazitaxel should not be used in patients with neutrophil counts of ≤1500/mm^3.

- Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) should be considered in patients with high-risk clinical features (age older than 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Consider primary prophylaxis with G-CSF in all patients receiving 25 mg/m^2. Monitoring of CBCs is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed.
- Elderly patients (aged 65 years or older) may be more likely to experience certain adverse reactions. The incidence of neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection, and dehydration occurred at rates ≥ 5% higher in patients who were aged 65 years or older compared to younger patients.
- Since cabazitaxel is extensively metabolized in the liver, it should be dose modified in patients with mild to moderate impairment and not given to patients with severe hepatic impairment (see product labeling for definitions).
- Cabazitaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to other drugs formulated with polysorbate 80.
- Cabazitaxel requires two dilutions prior to administration, one with the supplied diluent (contains 5.7 mL of 13% w/w ethanol in water), followed by dilution in either 0.9% sodium chloride or 5% dextrose solution.
- Do not use polyvinyl chloride infusion containers and polyurethane infusion sets for preparation and administration. Use an in-line filter of 0.22 μm nominal pore size during administration.
- Cabazitaxel requires premedication with an antihistamine, corticosteroid, and H_2 antagonist, and patients should be observed closely for hypersensitivity reactions. Severe

hypersensitivity reactions can occur and require immediate discontinuation and administration of appropriate therapy.
- Diarrhea and electrolyte abnormalities may be severe and require intensive measures.
- Cystitis, recall radiation cystitis, and hematuria have been reported in patients treated with cabazitaxel who previously received pelvic radiation.
- Since cabazitaxel is primarily metabolized through CYP3A, concomitant administration of strong CYP3A inhibitors and inducers should be avoided. Patients should refrain from taking St. John's wort.
- Embryo-fetal toxicity: cabazitaxel may cause fetal harm when administered to a pregnant woman.

CABOZANTINIB (COMETRIQ, CABOMETYX)

Mechanism of Action

- Inhibits tyrosine activity of RET; MET; VEGFR-1, VEGFR-2, and VEGFR-3; KIT; TRKB; FLT-3; AXL; and TIE-2

FDA-Approved Indications

- Progressive, metastatic medullary thyroid cancer (Cometriq)
- Renal cell cancer (RCC):
  - RCC in advanced disease as a single agent (Cabometyx)
  - First-line therapy in advanced disease in combination with nivolumab (Cabometyx)
- Hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib (Cabometyx)

FDA-Approved Dosage

- Thyroid cancer: 140 mg orally once daily (Cometriq).

- RCC single agent in advanced disease: 60 mg orally once daily (Cabometyx).
- RCC in combination with nivolumab: 40 mg orally once daily (Cabometyx).
- HCC: 60 mg orally once daily (Cabometyx).
- Continue until disease progression or unacceptable toxicity.
- Do not eat for at least 2 hours before and at least 1 hour after taking cabozantinib.

Dose Modification Criteria

- Renal (mild or moderate): no
- Renal (severe): unknown
- Hepatic (mild or moderate): yes
- Hepatic (severe): use not recommended
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Effects

- CV: hypertension
- DERM: palmar-plantar erythrodysesthesia and wound complications
- ELECTRO: hypocalcemia and hypophosphatemia
- GI: N/V (minimal-low), abdominal pain, constipation, decreased appetite, diarrhea, oral pain, and stomatitis
- GU: proteinuria
- HEMAT: lymphopenia, neutropenia, and thrombocytopenia
- HEPAT: hyperbilirubinemia and transaminitis
- OTHER: decreased weight, dysgeusia, fatigue, hair color changes, hemorrhage, and thrombosis

Comments

- GI perforations and fistula formation have been reported. Severe, sometimes fatal, hemorrhage including hemoptysis and

GI hemorrhage has been reported. Monitor patients for signs and symptoms of bleeding, and do not administer cabozantinib to patients with a recent history of hemorrhage or hemoptysis.

- Cabozantinib treatment results in an increased incidence of thrombotic events.
- Withhold cabozantinib for wound dehiscence or complications requiring medical intervention. Stop treatment with cabozantinib at least 3 weeks prior to scheduled surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until adequate wound healing.
- Monitor BP and discontinue for hypertensive crisis.
- Treatment with cabozantinib can cause osteonecrosis of the jaw. Oral examination should be performed prior to initiation of cabozantinib and periodically during therapy. Patients should maintain good oral hygiene practices. For invasive dental procedures, therapy should be withheld for at least 3 weeks prior to scheduled surgery, if possible.
- Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function.
- Cabozantinib is a substrate of CYP3A4. For patients who require concomitant treatment with a strong CYP3A4 inhibitor or inducer, a dose modification of cabozantinib is necessary. Refer to product labeling for recommendations.
- Embryo-fetal toxicity: cabozantinib may cause fetal harm when administered to a pregnant woman. Effective contraception during treatment with cabozantinib and up to 4 months after completion of therapy is recommended.

CALASPARGASE PEGOL (ASPARLAS)

Mechanism of Action

- l-asparaginase is an enzyme that catalyzes the conversion of the amino acid l-asparagine into aspartic acid and ammonia. Calaspargase pegol depletes plasma l-asparagine resulting in the selective killing of leukemic cells that have a reduced ability to synthesize l-asparagine, thus depending on exogenous l-asparagine for survival.

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): a component of a multiagent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients aged 1 month to 21 years

FDA-Approved Dosage

- 2500 units/m^2 intravenously no more frequently than every 21 days

Dose Modification Criteria

- Renal: no data available
- Hepatic (mild or moderate): no data available
- Hepatic (severe): contraindicated
- Nonhematologic toxicities: yes

Adverse Reactions

- GI: N/V (not classified) and pancreatitis
- HEMAT: thrombosis, hemorrhage, and abnormal clotting studies
- HEPAT: hepatotoxicity, elevated transaminases, and bilirubin increased
- INFUS: hypersensitivity reactions

Comments

- Calaspargase pegol is contraindicated in the following patients:
  - Those with a history of serious hypersensitivity reactions to pegylated l-asparaginase
  - Those with a history of serious thrombosis during l-asparaginase therapy
  - Those with a history of serious pancreatitis related to previous l-asparaginase treatment
  - Those with a history of serious hemorrhagic events during previous l-asparaginase therapy
  - Those with severe hepatic impairment

CAPECITABINE (XELODA)

Mechanism of Action

- Antimetabolite that is enzymatically converted to FU in tumors

FDA-Approved Indications

- Colorectal cancer (CRC):
  - Adjuvant therapy: indicated as a single agent for adjuvant treatment in patients with Dukes C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred.
  - Metastatic disease: first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred.
- Breast cancer:
  - Combination therapy: capecitabine combined with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure with prior anthracycline-containing chemotherapy.
  - Breast cancer monotherapy: third-line therapy for metastatic breast cancer (after paclitaxel and an anthracycline-containing chemotherapy regimen) or second-line therapy (after paclitaxel) if anthracycline is not indicated.

FDA-Approved Dosage

- Give 1250 mg/m^2 orally twice daily (total daily dose: 2500 mg/m^2) at the end of a meal for 2 weeks, followed by a 1-week rest period, given as 3-week cycles. See product labeling for a dosing chart.

Dose Modification Criteria

- Renal (mild impairment, CrCl 51-80 mL/min): no
- Renal (moderate impairment, CrCl 30-50 mL/min): yes
- Renal (severe impairment, CrCl <30 mL/min): contraindicated
- Hepatic (mild to moderate impairment due to liver metastases): no; monitor closely
- Toxicity (grade 2 toxicity or higher): yes
- See product labeling for dose modification guidelines

Adverse Reactions

- DERM: hand and foot syndrome (palmar-plantar erythrodysesthesia) and dermatitis
- GI: N/V (minimal-low), diarrhea, mucositis, abdominal pain, anorexia
- HEMAT: myelosuppression
- HEPAT: hyperbilirubinemia
- NEURO: fatigue/weakness, paresthesia, and peripheral sensory neuropathy

Comments

- Altered coagulation parameters and/or bleeding have been reported in patients receiving concomitant capecitabine and oral coumarin-derived anticoagulation therapy. Anticoagulant response (international normalized ratio [INR] and prothrombin time [PT]) should be monitored frequently to adjust anticoagulant dose accordingly.
- Cardiotoxicity has been observed with capecitabine and is more common in patients with a history of coronary artery disease.
- Severe mucocutaneous reactions, Steven-Johnson syndrome, and toxic epidermal necrolysis have been reported with capecitabine. Discontinue therapy for severe mucocutaneous reactions or dermatologic toxicity.

- Patients with low or absent dihydropyridine dehydrogenase (DPD) activity are at increased risk of severe or fatal adverse reactions. In patients with evidence of acute early onset or unusually severe toxicity, withhold or permanently discontinue capecitabine as this might indicate low or absent DPD activity.
- Dehydration may occur secondary to GI toxicities and this has been observed to cause acute renal failure. Interrupt capecitabine therapy for grade 2 dehydration or greater until dehydration is corrected.
- Embryo-fetal toxicity: capecitabine may cause fetal harm when administered to a pregnant woman.
- Geriatric patients (older than 80 years) may experience a greater incidence of grade 3 and 4 adverse events.

CAPMATINIB (TABRECTA)

Mechanism of Action

- Kinase inhibitor that targets MET including the mutant variant produced by exon 14 skipping. As a result, capmatinib inhibits downstream signaling and ultimately survival of MET-dependent cancer cells.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): metastatic NSCLC that harbors a mutation leading to MET exon 14 skipping, as detected by an FDA-approved test

FDA-Approved Dosage

- 400 mg orally twice daily until disease progression or unacceptable toxicity. May take without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild or severe, Child-Pugh class A, B, or C): no significant effect on PK
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: photosensitivity
- GI: N/V (moderate-high) and decreased appetite
- HEPAT: hepatotoxicity
- PULM: interstitial lung disease/pneumonitis and dyspnea
- OTHER: peripheral edema and fatigue

Comments

- Avoid concomitant administration with strong and moderate CYP3A inducers.
- Embryo-fetal toxicity: capmatinib may cause fetal harm when administered to a pregnant woman.

CARBOPLATIN (PARAPLATIN)

Mechanism of Action

- Alkylating-like agent producing interstrand DNA cross-links

FDA-Approved Indications

- Advanced ovarian cancer:
  - First-line therapy (in combination with other agents)
  - Second-line therapy (including patients who have previously received cisplatin)

FDA-Approved Dosage

- With cyclophosphamide: 300 mg/m^2 IV × one dose on day 1 of the cycle; repeat cycles every 4 weeks × six cycles.
- Single agent: 360 mg/m^2 IV × one dose every 4 weeks.
- Formula dosing may be used as an alternative to BSA-based dosing.
- Calvert formula for carboplatin dosing:

  Total dose in milligrams = (target AUC) × (GFR + 25).
- The target AUC of 4 to 6 mg/mL/min using single-agent carboplatin appears to provide the most appropriate dose range in previously treated patients.
- The Calvert formula was based on studies where GFR was measured by ^{51}Cr-EDTA (ethylene diamine tetracetic acid) clearance. Alternatively, many clinicians commonly use estimated CrCl equations to determine GFR.

Dose Modification Criteria

- Renal: yes
- Myelosuppression: yes

Adverse Reactions

- GI: N/V (moderate to high [dose dependent])
- ELECTRO: Mg, Na, Ca, and K alterations
- GU: increased Cr and BUN
- HEMAT: myelosuppression (thrombocytopenia > leukopenia and anemia)
- HEPAT: increased LFTs
- NEURO: neuropathy
- OTHER: anaphylactic reactions, pain, and asthenia

Comments

- Do not confuse with cisplatin for dosing or during preparation.
- Use caution when estimating CrCl for use in formula (eg, Calvert equation) dosing. The current isotope dilution mass

spectrometry (IDMS) method to measure serum creatinine appears to underestimate serum creatinine values compared to older methods when the serum creatinine values are relatively low (eg, 0.7 mg/dL). Overestimating the GFR may result when using a serum creatinine measured by the IDMS method. The FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. The maximum dose recommended by the FDA is based on a GFR estimate that is capped at 125 mL to minute for patients with normal renal function.

CARFILZOMIB (KYPROLIS)

Mechanism of Action

- Tetrapeptide epoxyketone PI that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome and the proteolytic core particle within the 26S proteasome.

FDA-Approved Indications

- Multiple myeloma:
  - In combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab plus dexamethasone in patients with relapsed or refractory disease who have received one to three lines of therapy
  - As a single agent in patients with relapsed or refractory disease who have received one or more lines of therapy

FDA-Approved Dosage

- 20/27 mg/m^2 twice weekly regimen by 10-minute infusion: used in combination therapy with lenalidomide and dexamethasone or as monotherapy.
  - Recommended cycle 1 dose is 20 mg/m^2/d on days 1 and 2. If tolerated, increase on day 8 of cycle 1 dose and subsequent cycle doses to 27 mg/m^2/d.
  - For cycles 1 to 12, carfilzomib is administered intravenously over 10 minutes, on two consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16),

followed by a 12-day rest period (days 17-28). Each 28-day period is considered one treatment cycle. With cycle 13 and beyond, omit carfilzomib doses on days 8 and 9.

- 20/56 mg/m^2 twice weekly regimen by 30 minute infusion: used in combination with dexamethasone, daratumumab plus dexamethasone, or as monotherapy.
  - Recommended cycle 1 dose is 20 mg/m^2 on days 1 and 2. If tolerated, increase on day 8 of cycle 1 dose and subsequent cycle doses to 56 mg/m^2/d.
  - Carfilzomib is administered intravenously over 30 minutes on two consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17-28). Each 28-day period is considered one treatment cycle. With cycle 13 and beyond when used for monotherapy, omit carfilzomib doses on days 8 and 9 of the 28-day cycle.
  - 20/70 mg/m^2 once weekly regimen by 30-minute infusion: used in combination with dexamethasone and daratumumab plus dexamethasone
  - Recommended cycle 1 dose is 20 mg/m^2 on day 1. If tolerated, increase on day 8 of cycle 1 dose and subsequent cycle doses to 70 mg/m^2/d.
  - Carfilzomib is administered intravenously over 30 minutes on a once weekly regimen for 3 weeks (days 1, 8, 15) followed by a 13-day rest period (days 16-28). Each 28-day period is considered one treatment cycle.

Dose Modification Criteria

- Renal (for baseline impairment): no
- Hepatic (for baseline impairment): not studied
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiac toxicity, CHF, hypertension
- ELECTRO: hypokalemia
- GI: diarrhea and nausea (low)
- GU: acute renal failure and increased serum creatinine
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: increased bilirubin and increased LFTs
- INFUS: angina, arthralgia, chest tightness, chills, facial edema, facial flushing, fever, hypotension, myalgia, shortness of breath, syncope, vomiting, and weakness
- NEURO: headache and peripheral neuropathy

- PULM: cough, dyspnea, upper respiratory tract infection, pulmonary arterial hypertension (PAH)
- OTHER: back pain, edema, fatigue, pyrexia, muscle spasm, insomnia, and tumor lysis syndrome

Comments

- Dosing is capped at a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.
- Hydrate patients prior to and following administration of carfilzomib to prevent tumor lysis syndrome and renal toxicity. Consider hydration with both oral fluids (30 mL/kg at least 48 hours before cycle 1, day 1) and IV fluids (250-500 mL of IV normal saline or other appropriate IV fluid) prior to each dose in cycle 1. Give an additional 250 to 500 mL of IV fluids as needed following carfilzomib administration. Continue oral and/or IV hydration as needed in subsequent cycles.
- Premedicate with the recommended dose of dexamethasone for carfilzomib monotherapy (4 mg for 10-minute carfilzomib infusion regimen and 8 mg for 30-minute carfilzomib infusion regimen) or the recommended dexamethasone dose for combination therapy orally or intravenously prior to all cycle 1 doses, during the first cycle of dose escalation, and if infusion reaction symptoms develop or reappear. Administer at least 30 minutes and no more than 4 hours prior to carfilzomib. Infusion reactions can develop up to 24 hours after administration of carfilzomib.
- Monitor platelet counts frequently during treatment.
- Monitor serum potassium levels regularly during treatment.
- New onset or worsening of preexisting CHF with decreased left ventricular function or myocardial ischemia has occurred following administration of carfilzomib. Monitor for cardiac complications. Patients with NYHA class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not

eligible for the clinical trials; these patients may be at greater risk for cardiac complications.

- Monitor for and manage dyspnea immediately. Severe pulmonary toxicity and pulmonary hypertension have been observed.
- Venous thromboembolic events have been observed with carfilzomib. Thromboprophylaxis is recommended for patients treated with the combination of carfilzomib with dexamethasone, lenalidomide plus dexamethasone, or daratumumab plus dexamethasone.
- Cases of hepatic failure have been reported. Monitor liver enzymes and bilirubin frequently during treatment.
- Serious fatal cases of hemorrhage have been observed. Promptly evaluate signs and symptoms of bleeding or blood loss.
- Cases of thrombotic microangiopathy have been observed in patients receiving carfilzomib including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Monitor and discontinue drug therapy if suspected.
- Cases of posterior reversible encephalopathy syndrome (PRES) and progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving carfilzomib. Consider neuroradiological imaging and discontinue drug therapy if suspected.
- Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.
- Embryo-fetal toxicity: carfilzomib can cause fetal harm if administered to a pregnant woman.

CARMUSTINE (BICNU)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following: brain tumors, multiple myeloma, Hodgkin lymphoma, and NHL.

FDA-Approved Dosage

- Single agent in previously untreated patients: 150 to 200 mg/m^2 IV × one dose every 6 weeks *or* 75 to 100 mg/m^2 IV daily × two doses every 6 weeks

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- GI: N/V >250 mg/m^2 (high), ≤250 mg/m^2 (moderate)
- GU: nephrotoxicity with large cumulative doses
- HEMAT: myelosuppression (can be delayed)
- HEPAT: increased LFTs
- Ocular system: retinal hemorrhages
- PULM: pulmonary fibrosis (acute and delayed)

Comments

- Risk of pulmonary toxicity increases with cumulative total doses > 1400 mg/m^2 and in patients with a history of lung disease, radiation therapy, or concomitant bleomycin.
- Myelosuppression is delayed and blood counts should be monitored weekly for at least 6 weeks after a dose. Bone marrow toxicity is cumulative and dose adjustment must be considered based on nadir blood counts from the prior dose.

CEMIPLIMAB (LIBTAYO)

Mechanism of Action

- Human monoclonal antibody that binds to PD-1 receptors, blocking the binding of PD-1 ligand

FDA-Approved Indications

- Cutaneous squamous cell carcinoma (cSCC): metastatic or locally advanced cSCC in patients who are not candidates for curative surgery or curative radiation
- Basal cell carcinoma (BCC): metastatic or locally advanced BCC previously treated with a hedgehog pathway inhibitor or when a hedgehog pathway inhibitor is not appropriate
- Non–small cell lung cancer (NSCLC): first-line treatment of NSCLC with high PD-L1 expression (tumor proportion score [TPS] ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations in metastatic or locally advanced disease not amendable to surgical resection or definitive chemoradiation

FDA-Approved Dosage

- 350 mg as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity

Dose Modification Criteria

- No dose reductions of cemiplimab are recommended. In general, withhold for toxicity.
- Renal (CrCl ≥ 21 mL/min): no significant effect on PK.
- Hepatic (mild or moderate): no significant effect on PK.
- Hepatic (severe): no data available.

Adverse Reactions

- DERM: rash
- ELECTRO: hyponatremia, hypophosphatemia, and hyperkalemia
- GI: N/V (minimal) and diarrhea
- HEMAT: lymphopenia and anemia
- HEPAT: increased AST
- INFUS: infusion-related reactions
- OTHER: musculoskeletal pain, fatigue, and immune-mediated adverse reactions (any organ system)

Comments

- Fatal and other serious complications of allogeneic HSCT after PD-1/PD-L1 inhibitors have been reported.
- Immune-mediated adverse reactions can occur in any organ system or tissue and include the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis, and immune-mediated dermatologic reactions. Monitor for signs and symptoms of immune-mediated adverse reactions and consult the prescribing information and established guidelines for management.
- Embryo-fetal toxicity: cemiplimab may cause fetal harm when administered to a pregnant woman.

CERITINIB (ZYKADIA)

Mechanism of Action

- TKI of ALK

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): adult patients with metastatic NSCLC whose tumors are ALK positive

FDA-Approved Dosage

- 450 mg orally once daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no information
- Hepatic (mild to moderate): no
- Hepatic (severe): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation, bradycardia
- DERM: rash
- ENDO: hyperglycemia
- GI: diarrhea, N/V (moderate-high), abdominal pain, constipation, decreased appetite, and pancreatitis
- GU: creatinine increase
- HEMAT: decreased hemoglobin
- HEPAT: elevated ALT/AST and elevated total bilirubin
- PULM: interstitial lung disease/pneumonitis
- OTHER: fatigue

Comments

- GI adverse reactions with ceritinib were seen at a higher incidence and severity with the previously approved dose of 750 mg under fasted conditions. GI toxicity has been shown to be less common and less severe with the dose of 450 mg administered with food. Monitor and manage patients using

standard-of-care measures including antidiarrheals, antiemetics, or fluid replacement, as indicated. Severe or persistent GI toxicity may require withholding therapy and subsequent dose reduction of ceritinib.

- Ceritinib is a substrate of CYP3A4 and P-gp. Strong inhibitors of CYP3A4 or P-gp will increase ceritinib drug exposure and should be avoided or may require ceritinib dose reduction. Strong inducers of CYP3A4 should be avoided. Ceritinib may also affect the metabolism of other concomitant drugs; screen for potential drug interactions.
- Embryo-fetal toxicity: ceritinib may cause fetal harm when administered to a pregnant woman.

CETUXIMAB (ERBITUX)

Mechanism of Action

- Recombinant chimeric monoclonal antibody that binds to the extracellular domain of the human EGFR on both normal and tumor cells and competitively inhibits the binding of epidermal growth factor and other ligands, thus blocking phosphorylation and activation of receptor-associated kinases.

FDA-Approved Indications

- Head and neck cancer:
  - Locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation therapy
  - Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with FU
  - Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy as single-agent therapy
- Metastatic colorectal carcinoma (*K-Ras* mutation–negative [wild-type], EGFR-expressing metastatic disease):
  - Monotherapy: single-agent therapy in patients who have failed irinotecan- and oxaliplatin-based regimens or in patients who are intolerant of irinotecan-based chemotherapy

- Combination therapy: in combination therapy with FOLFIRI (irinotecan, 5-FU, leucovorin) for first-line treatment OR in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy

FDA-Approved Dosage

- Squamous cell carcinoma of the head and neck:
  - In combination with radiation therapy; 400 mg/m^2 IV infusion over 120 minutes administered 1 week prior to the first course of radiation therapy followed by subsequent doses of 250 mg/m^2 by IV infusion over 60 minutes once weekly for the duration of radiation therapy (6-7 weeks). Complete cetuximab administration 1 hour prior to radiation therapy.
  - Single agent or in combination with platinum-based therapy and FU:
    - Weekly dosage: initial dose of 400 mg/m^2 IV infusion over 120 minutes followed by subsequent doses of 250 mg/m^2 by IV infusion over 60 minutes once weekly.
    - Biweekly dosage: initial and subsequent doses of 500 mg/m^2 by IV infusion over 120 minutes every 2 weeks.
  - Complete cetuximab administration 1 hour prior to platinum-based therapy with FU. Continue until disease progression or unacceptable toxicity.
- Metastatic colorectal carcinoma (monotherapy or in combination with irinotecan or FOLFIRI):
  - Weekly dosage: initial dose of 400 mg/m^2 IV infusion over 120 minutes followed by subsequent doses of 250 mg/m^2 by IV infusion over 60 minutes once weekly.
  - Biweekly dosage: initial and subsequent doses of 500 mg/m^2 by IV infusion over 120 minutes every 2 weeks.
  - Complete cetuximab administration 1 hour prior to irinotecan or FOLFIRI.
  - Therapy is continued until disease progression or unacceptable toxicity.
- Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine intravenously 30-60 minutes prior to the first dose) is recommended. Premedication should be administered for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions.

Dose Modification Criteria

- Renal: no
- Hepatic: no
- Nonhematologic toxicity (dermatologic toxicity): yes

Adverse Reactions

- DERM: acneiform rash, skin drying and fissuring, and nail toxicity
- ELECTRO: Mg, Ca, and K alterations
- GI: N/V (low), constipation, and diarrhea
- INFUS: chills, fever, dyspnea, airway obstruction (bronchospasm, stridor, and hoarseness), urticaria, and hypotension
- PULM: interstitial lung disease
- OTHER: asthenia, malaise, and fever

Comments

- *K-Ras* mutation predicts for a lack of response to cetuximab. Determine *K-Ras* mutation and EGFR-expression status using FDA-approved tests prior to initiating treatment.
- Grade 1 and 2 infusion reactions (chills, fever, and dyspnea) are common (16% to 23%) usually on the first day of initial dosing. Severe infusion reactions have been observed in approximately 2% to 5% of patients and are characterized by a rapid onset of airway obstruction, urticaria, and/or hypotension. Severe infusion reactions require immediate interruption of the cetuximab infusion and permanent discontinuation from further treatment.
- Cardiopulmonary arrest and/or sudden death have been reported in patients with squamous cell carcinoma of the head and neck treated with radiation therapy and cetuximab.
- An acneiform rash is common (approximately 76% to 88% overall, 1% to 17% severe) with cetuximab therapy and is most commonly observed on the face, upper chest, and back. Skin drying and fissuring were common and can be associated with inflammatory or infections sequelae. Interruption of therapy and dose modification are recommended for severe dermatologic toxicity (see product labeling).
- Interstitial lung disease has been reported with cetuximab therapy rarely. In the event of acute onset or worsening

pulmonary symptoms, interrupt cetuximab therapy and promptly investigate symptoms.
- Hypomagnesemia and other electrolyte abnormalities are common and patients should be monitored closely during therapy and for at least 8 weeks following the completion of cetuximab.
- Embryo-fetal toxicity: no animal reproduction studies have been conducted and effects in pregnant women are unknown. However, EGFR has been implicated in the control of prenatal development and human IgG1 is known to cross the placental barrier.
- Do not administer as an IV push or bolus.

CHLORAMBUCIL (LEUKERAN)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Palliation of chronic lymphocytic leukemia (CLL), Hodgkin lymphoma, and NHL

FDA-Approved Dosage

- Initial and short courses of therapy: 0.1 to 0.2 mg/kg orally daily for 3 to 6 weeks as required. Usually the 0.1 mg/kg/d dose is used except for Hodgkin lymphoma, in which 0.2 mg/kg/d is used.
- Alternate regimen in CLL (intermittent, biweekly, or once monthly pulses). Initial single dose of 0.4 mg/kg orally × one dose. Increase dose by 0.1 mg/kg until control of lymphocytosis.
- Maintenance: not to exceed 0.1 mg/kg/d.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: rash and rare reports of progressive skin hypersensitivity reactions
- GI: N/V (minimal-low)
- HEMAT: myelosuppression and lymphopenia
- HEPAT: increased LFTs
- NEURO: seizures, confusion, twitching, and hallucinations
- PULM: pulmonary fibrosis
- OTHER: allergic reactions, secondary acute myelomonocytic leukemia (AML) (long-term therapy), and sterility

Comments

- Radiation and cytotoxic drugs render the bone marrow more vulnerable to damage; chlorambucil should be used with caution within 4 weeks of a full course of radiation therapy or chemotherapy.

CISPLATIN (PLATINOL)

Mechanism of Action

- Alkylating-like agent producing interstrand DNA cross-links

FDA-Approved Indications

- Metastatic testicular tumors (in combination with other agents) in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

- Metastatic ovarian tumors (in combination with other agents) in patients who have already received appropriate surgical and/or radiotherapeutic procedures.
- Metastatic ovarian tumors (as a single agent) as secondary therapy in patients who are refractory to standard chemotherapy and who have not previously received cisplatin.
- Advanced transitional cell bladder cancer, which is no longer amenable to local treatments such as surgery and/or RT.

FDA-Approved Dosage

- Metastatic testicular tumors: 20 mg/m^2 IV daily × 5 days every 4 weeks (in combination with other agents).
- Metastatic ovarian tumors: 75 to 100 mg/m^2 IV × one dose (in combination with cyclophosphamide) every 4 weeks, OR as single-agent therapy: 100 mg/m^2 IV × one dose every 4 weeks.
- Advanced bladder cancer: 50 to 70 mg/m^2 IV × one dose every 3 to 4 weeks (single-agent therapy).

Dose Modification Criteria

- Renal: no (consider delay in therapy for toxicity)
- Myelosuppression: no (consider delay in therapy based on nadir blood counts)

Adverse Reactions

- ELECTRO: Mg, Na, Ca, and K alterations
- GI: N/V (high)
- GU: increased Cr and BUN (cumulative)
- HEMAT: myelosuppression and anemia
- HEPAT: increased LFTs (especially AST and bilirubin)
- NEURO: neuropathy, paresthesia, and ototoxicity
- Ocular system: optic neuritis, papilledema, and cerebral blindness infrequently reported
- OTHER: anaphylactic reactions and rare vascular toxicities

Comments

- Check auditory acuity.
- Vigorous hydration recommended before and after cisplatin administration.
- Use other nephrotoxic agents (eg, aminoglycosides) concomitantly with caution.
- Exercise precaution to prevent inadvertent cisplatin overdose and confusion with carboplatin.

CLADRIBINE (LEUSTATIN)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Hairy cell leukemia (HCL)

FDA-Approved Dosage

- HCL: 0.09 mg/kg intravenously by continuous infusion over 24 hours daily × 7 days (a single course of therapy)

Dose Modification Criteria

- Renal: no data
- Hepatic: no data

Adverse Reactions

- CV: edema
- DERM: rash, pruritus, and diaphoresis

- GI: N/V (minimal), decreased appetite, diarrhea, constipation, and abdominal pain
- HEMAT: myelosuppression and lymphopenia
- NEURO: fatigue, headache, dizziness, and peripheral neuropathy
- PULM: cough
- OTHER: fever, chills, fatigue, asthenia, administration site reactions, infections, and TLS

Comments

- Immunosuppression (lymphopenia) is prolonged after cladribine therapy.
- Embryo-fetal toxicity: cladribine may cause fetal harm if administered to a pregnant woman.
- Cladribine is also FDA approved for the management of relapsing forms of multiple sclerosis for dosing orally with a 10 mg tablet formulation.

CLOFARABINE (CLOLAR)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- ALL: pediatric patients (age 1-21 years) with relapsed or refractory ALL after at least two prior regimens

FDA-Approved Dosage

- 52 mg/m^2 by IV infusion over 2 hours daily for 5 consecutive days.

- Treatment cycles are repeated following recovery or return to baseline organ function, approximately every 2 to 6 weeks.

Dose Modification Criteria

- Renal: yes
- Hepatic: no data, use with caution
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: tachycardia and hypotension
- DERM: dermatitis and palmar-plantar erythrodysesthesia syndrome
- GI: N/V (moderate), abdominal pain, diarrhea, gingival bleeding, and anorexia
- GU: elevated Cr
- HEMAT: myelosuppression
- HEPATIC: elevated LFTs, hyperbilirubinemia, hepatomegaly, and hepatic veno-occlusive disease
- INFUS: fever, chills, and rigors
- NEURO: headache and dizziness
- PULM: dyspnea, respiratory distress, and pleural effusion
- OTHER: tumor lysis syndrome, infections, fatigue, and asthenia

Comments

- Prophylaxis for tumor lysis syndrome (hydration, allopurinol) should be considered and patients should be closely monitored during therapy.
- Capillary leak syndrome or systemic inflammatory response syndrome (SIRS) has been reported and patients should be closely monitored. The use of prophylactic corticosteroids (eg, 100 mg/m^2 hydrocortisone on days 1 through 3) may be of benefit in preventing SIRS or capillary leak.

- Myelosuppression may be severe and prolonged. Severe hemorrhagic events have been observed often associated with thrombocytopenia.
- Hepatobiliary toxicities were frequently observed in clinical trials.
- Severe and fatal cases of enterocolitis have been observed with clofarabine therapy.
- Severe mucocutaneous dermatologic toxicity (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis) has been observed in patients treated with clofarabine.
- Dose adjustment is required in patients with renal impairment. Clofarabine may also cause nephrotoxicity; avoid concomitant nephrotoxic agents during therapy.
- Embryo-fetal toxicity: clofarabine may cause fetal harm when administered to a pregnant woman.

COBIMETINIB (COTELLIC)

Mechanism of Action

- Reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase 1 (MEK1) and MEK2. BRAF V600E and K mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2.

FDA-Approved Indications

- Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib

FDA-Approved Dosage

- 60 mg orally once daily for the first 21 days of a 28-day cycle until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no established recommendation
- Hepatic (mild to severe, Child-Pugh classes A-C): no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy
- DERM: new primary malignancies (cutaneous squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, and second primary melanoma), severe rash, and severe photosensitivity
- ELECTRO: hyponatremia and hypophosphatemia
- GI: diarrhea, N/V (minimal-low)
- GU: increased creatinine
- HEMAT: anemia, lymphopenia, thrombocytopenia, and hemorrhage
- HEPAT: increased ALT/AST and increased alkaline phosphatase
- Ocular system: retinopathy and retinal vein occlusion
- OTHER: rhabdomyolysis, CPK elevations, and pyrexia

Comments

- Cobimetinib is a substrate of CYP3A4. Avoid concomitant moderate or strong inhibitors or inducers of CYP3A4.
- New primary malignancies may occur following cobimetinib. Monitor prior to initiation of therapy, while on therapy, and for 6 months following the last dose of cobimetinib.
- Cardiomyopathy: evaluate LVEF prior to initiation of therapy, 1 month after initiation and then every 3 months during therapy with cobimetinib.
- Monitor for severe skin rashes and interrupt, reduce, or discontinue cobimetinib if necessary. Have patients avoid sun exposure due to photosensitivity.

- Ocular toxicity: perform an ophthalmological examination at regular intervals and for any visual disturbances.
- Embryo-fetal toxicity: cobimetinib may cause fetal harm when administered to a pregnant woman.

COPANLISIB (ALIQOPA)

Mechanism of Action

- Inhibitor of PI3Kα and PI3Kδ (expressed in malignant B cells), which prevents key cell signaling pathways and ultimately results in apoptosis of the tumor cell

FDA-Approved Indications

- Follicular lymphoma (FL): relapsed FL after at least two prior systemic therapies

FDA-Approved Dosage

- 60 mg IV infusion over 60 minutes on days 1, 8, and 15 of a 28-day cycle on an intermittent schedule (3 weeks on, 1 week off)

Dose Modification Criteria

- Renal (mild to severe, CrCl 15 to < 89 mL/min): no significant effect on PK
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate, Child-Pugh class B): yes
- Hepatic (severe, Child-Pugh class C): no data available
- CYP3A inhibitor (strong): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension
- DERM: severe cutaneous reactions
- ENDO: hyperglycemia
- GI: N/V (low) and diarrhea
- HEMAT: leukopenia, neutropenia, and thrombocytopenia
- PULM: lower respiratory tract infection and noninfectious pneumonitis
- OTHER: decreased strength and energy and infections

Comments

- Withhold treatment in patients until both the systolic BP is <150 mm Hg and the diastolic BP is <90 mm Hg.
- Avoid concomitant use with strong CYP3A inducers.
- Avoid concomitant use with strong CYP3A inhibitors. If coadministration is necessary, reduce the copanlisib dose.
- Embryo-fetal toxicity: copanlisib may cause fetal harm when administered to a pregnant woman.

CRIZOTINIB (XALKORI)

Mechanism of Action

- Inhibitor of RTKs including ALK, hepatocyte growth factor receptor (c-Met), ROS1 (c-ros), and recepteur d'origine nantais.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): metastatic NSCLC that is ALK positive as detected by an FDA-approved test.

FDA-Approved Dosage

- 250 mg orally twice daily with or without food.

Dose Modification Criteria

- Renal (mild, moderate): no
- Renal (severe, end-stage renal disease): yes
- Hepatic: not studied, use caution
- Myelosuppression: yes (except lymphopenia, unless associated with clinical events)
- Nonhematologic toxicity/tolerability: yes

Adverse Reactions

- CV: QT interval prolongation, bradycardia
- GI: abdominal pain, anorexia, constipation, diarrhea, esophageal disorder, N/V (moderate-high), and stomatitis
- HEMAT: lymphopenia
- HEPAT: increased LFTs
- NEURO: dizziness, headache, dysgeusia, and neuropathy
- Ocular system: vision disorder
- PULM: cough, dyspnea, interstitial lung disease/pneumonitis, and upper respiratory infection
- OTHER: arthralgia, back pain, chest pain, edema, fatigue, insomnia, and pyrexia

Comments

- Detection of ALK-positive NSCLC using an FDA-approved test is necessary for selection of patients for treatment with crizotinib.
- Avoid concurrent use of crizotinib with strong CYP3A inhibitors or inducers. Avoid grapefruit or grapefruit juice. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Avoid concurrent use of crizotinib with CYP3A substrates with narrow therapeutic indices.
- Monitor patients for pulmonary symptoms indicative of pneumonitis.

- Avoid crizotinib in patients with congenital long QT syndrome. Consider periodic monitoring with ECGs and electrolytes in patients with CHF, bradyarrhythmias, and electrolyte abnormalities or who are taking medications that are known to prolong the QT interval. Permanently discontinue crizotinib in patients who develop grade 4 QT prolongation, and in those who have recurrent grade 3 QT prolongation.
- Severe and fatal cases of hepatotoxicity have been observed with crizotinib. Monitor LFTs every 2 weeks during the first 2 months of therapy then once a month and as clinically indicated.
- Visual disorders generally start within 2 weeks of drug administration. Ophthalmologic evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could be signs of a retinal hole or pending retinal detachment. Advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder.
- Embryo-fetal toxicity: crizotinib may cause fetal harm when administered to a pregnant woman. Patients of childbearing potential should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

CYCLOPHOSPHAMIDE (CYTOXAN)

Mechanism of Action

- Activated by liver to alkylating agent

FDA-Approved Indications

- Lymphomas, leukemias, multiple myeloma, mycosis fungoides (advanced disease), neuroblastoma (disseminated disease), adenocarcinoma of the ovary, retinoblastoma, and breast cancer

FDA-Approved Dosage

- Parenteral (IV): many dosing regimens reported; consult current literature
- Oral: 1 to 5 mg/kg/d (many other regimens reported; consult current literature)

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: rash, skin and nail pigmentation, and alopecia
- GI: N/V (>1500 mg/m^2: high, ≤1500 mg/m^2: moderate), anorexia, and diarrhea
- GU: hemorrhagic cystitis and renal tubular necrosis
- HEMAT: myelosuppression (leukopenia > thrombocytopenia and anemia)
- NEURO: syndrome of inappropriate antidiuretic hormone (SIADH)
- PULM: pulmonary fibrosis
- OTHER: secondary malignancies; sterility, amenorrhea; anaphylactic reactions; cardiac toxicity with high-dose regimens

Comments

- Encourage forced fluid intake and frequent voiding to reduce the risk of hemorrhagic cystitis. Consider using vigorous IV hydration and mesna therapy with high-dose cyclophosphamide.

CYTARABINE (CYTOSAR AND OTHERS)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- In combination with other agents for induction therapy of acute nonlymphocytic leukemia (ANLL), acute lymphocytic leukemia (ALL), blast-phase chronic myeloid leukemia (CML), intrathecal prophylaxis, and treatment of meningeal leukemia

FDA-Approved Dosage

- ALL: consult current literature for doses.
- ANLL induction (in combination with other agents): 100 mg/m^2 IV by continuous infusion over 24 hours × 7 days *or* 100 mg/m^2 IV every 12 hours × 7 days. Consult current literature for alternative dosing regimens (eg, high-dose regimens such as ≥1 g/m^2/dose).
- Intrathecally: (use preservative-free diluents) 30 mg/m^2 (5-75 mg/m^2 dose range) intrathecally every 4 days until cerebrospinal fluid clear, and then one additional dose. Other doses and frequency of administration have been utilized.

Dose Modification Criteria

- Hepatic/renal: use with caution and at possibly reduced dose in patients with poor hepatic or renal function (no specific criteria)
- Nonhematologic toxicity (neurotoxicity): yes

Adverse Reactions

- DERM: rash and alopecia
- GI: N/V (>1 g/m^2: moderate; ≤200 mg/m^2: low), anorexia, diarrhea, mucositis, and pancreatitis (in patients who have previously received asparaginase)
- HEMAT: myelosuppression
- HEPAT: increased LFTs

- NEURO: cerebellar dysfunction, somnolence, coma (generally seen with high-dose regimens), and chemical arachnoiditis (intrathecal administration)
- Ocular system: conjunctivitis (generally seen with high-dose regimens)
- OTHER: cytarabine (Ara-C) syndrome (includes fever, myalgia, bone pain, rash, conjunctivitis, and malaise); acute respiratory distress syndrome reported with high-dose regimens

Comments

- Consider appropriate prophylaxis for tumor lysis syndrome when treating acute leukemias.
- Consider local corticosteroid eye drops to provide prophylaxis for conjunctivitis when employing high-dose regimens of cytarabine.
- Withhold therapy if acute CNS toxicity occurs with high-dose regimens.

DABRAFENIB (TAFINLAR)

Mechanism of Action

- Inhibitor of the mutated BRAF kinases V600E, V600K, and V600D

FDA-Approved Indications

- Metastatic melanoma:
  - As a single agent for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
  - In combination with trametinib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.
  - Adjuvant treatment, in combination with trametinib, of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-

approved test, and involvement of lymph node(s), following complete resection.

- Non–small cell lung cancer (NSCLC): treatment of patients with metastatic NSCLC, in combination with trametinib, with BRAF V600E mutation as detected by an FDA-approved test.
- Anaplastic thyroid cancer (ATC): treatment of patients with locally advanced or metastatic ATC, in combination with trametinib, with BRAF V600E mutation and with no satisfactory locoregional treatment options.

FDA-Approved Dosage

- 150 mg orally twice daily as a single or combination agent until disease progression or unacceptable toxicity. Take at least 1 hour before or 2 hours after a meal.

Dose Modification Criteria

- Renal: mild to moderate impairment: no; severe impairment: no data available
- Hepatic: mild impairment: no; moderate to severe impairment: no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy
- DERM: new primary malignancies (cutaneous squamous cell carcinoma, keratoacanthoma, and second primary melanoma), hyperkeratosis, palmar-plantar erythrodysesthesia syndrome, papilloma, alopecia, and rash
- GI: N/V (moderate-high)
- ENDO: hyperglycemia
- HEMAT: hemorrhage
- NEURO: headache
- Ocular system: uveitis

- OTHER: pyrexia, chills, and arthralgia

Comments

- Screen for drug interactions. Dabrafenib is metabolized through CYP3A4 and CYP2C8. Strong inhibitors or inducers of these enzymes will effect drug concentrations of dabrafenib. Dabrafenib is an inducer of CYP3A4 and CYP2C9, which may decrease the systemic exposure of other concomitant medications that are substrates of these enzymes.
- New primary malignancies may occur following dabrafenib. Monitor prior to initiation of therapy, while on therapy, and for 6 months following the last dose of dabrafenib.
- Cardiomyopathy: evaluate LVEF prior to initiation of therapy, 1 month after initiation, and then every 2 to 3 months during therapy with dabrafenib.
- Monitor for severe skin toxicity and interrupt or discontinue dabrafenib if necessary.
- Uveitis: monitor for visual signs or symptoms of uveitis (eg, change in vision, photophobia, and eye pain). Uveitis may require ocular therapy and interruption of discontinuation of dabrafenib.
- Serious febrile reactions may occur. The incidence of febrile reactions is higher when dabrafenib is used in combination with trametinib.
- Dabrafenib may cause hemolytic anemia in patients with G6PD deficiency.
- Embryo-fetal toxicity: dabrafenib may cause fetal harm when administered to a pregnant woman.

DACARBAZINE (DTIC-DOME)

Mechanism of Action

- Methylation of nucleic acids, direct DNA damage, and inhibition of purine synthesis

FDA-Approved Indications

- Metastatic malignant melanoma
- Hodgkin lymphoma (second-line therapy)

FDA-Approved Dosage

- Malignant melanoma: 2 to 4.5 mg/kg IV daily × 10 days; repeat every 4 weeks, *OR* 250 mg/m^2 IV daily × 5 days; repeat every 3 weeks
- Hodgkin lymphoma: 150 mg/m^2 IV daily × 5 days, repeat every 4 weeks (in combination with other agents), *OR* 375 mg/m^2 IV on day 1, repeat every 15 days (in combination with other agents)

Adverse Reactions

- DERM: alopecia, rash, facial flushing, and facial paresthesia
- GI: N/V (high), anorexia, and diarrhea
- HEPAT: increased LFTs and hepatic necrosis
- OTHER: pain and burning at infusion, anaphylaxis, fever, myalgias, and malaise

DACOMITINIB (VIZIMPRO)

Mechanism of Action

- Irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation)

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): first-line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations, as detected by an FDA-approved test

FDA-Approved Dosage

- 45 mg orally once daily until disease progression or unacceptable toxicity. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl <30 mL/min): not established
- Hepatic (mild to severe, Child-Pugh class A, B, or C): no
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, paronychia, dry skin, alopecia, and pruritus
- GI: diarrhea, stomatitis, and decreased appetite
- PULM: cough and interstitial lung disease
- OTHER: decreased weight

Comments

- Avoid concomitant use of PPIs. Alternately, use locally acting antacids or an H_2 antagonist. Administer dacomitinib at least 6 hours before or 10 hours after taking an H_2 antagonist.
- Avoid concomitant use of CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to significant toxicities.
- Embryo-fetal toxicity: dacomitinib may cause fetal harm when administered to a pregnant woman.

DACTINOMYCIN (COSMEGEN)

Mechanism of Action

- Intercalating agent

FDA-Approved Indications

- Indicated as part of a combination chemotherapy or multimodality treatment regimen for the following malignancies:
  - Wilms tumor (nephroblastoma)
  - Childhood rhabdomyosarcoma
  - Ewing sarcoma
  - Metastatic, nonseminomatous testicular cancer
  - Indicated as a single agent or as part of a combination regimen for gestational trophoblastic neoplasia
  - Indicated as a component of regional perfusion in the treatment of locally recurrent or locoregional solid malignancies

FDA-Approved Dosage

- For obese or edematous patients, dose should be based on BSA.
- Dose intensity should not exceed 15 μg/kg IV daily × 5 days *OR* 400 to 600 μg/m^2 IV daily × 5 days, repeated every 3 to 6 weeks.
- Consult with current literature for dosage regimens and guidelines.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: alopecia, erythema, skin eruptions, radiation recall, and tissue damage/necrosis with extravasation
- ELECTRO: hypocalcemia
- GI: N/V (moderate), mucositis, anorexia, and dysphagia

- HEMAT: myelosuppression
- HEPAT: increased LFTs and hepatotoxicity
- OTHER: fever, fatigue, myalgia, and secondary malignancies

Comments

- Vesicant

DARATUMUMAB (DARZALEX)

Mechanism of Action

- An immunoglobulin G1 kappa human monoclonal antibody that binds to CD38 and inhibits the growth of CD38-expressing tumor cells

FDA-Approved Indications

- Multiple myeloma:
  - In combination therapy with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant (ASCT) and in patients with relapsed or refractory disease who have received at least one prior therapy
  - In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for ASCT
  - In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for ASCT
  - In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
  - In combination with carfilzomib and dexamethasone in patients with relapsed or refractory disease who have received one to three prior lines of therapy
  - In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a PI
  - Monotherapy after at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent

FDA-Approved Dosage

- 16 mg/kg IV infusion (note exception for combination with carfilzomib and dexamethasone) according to the following schedule:
  - Monotherapy and in combination with lenalidomide and dexamethasone or pomalidomide and dexamethasone: weekly during weeks 1 to 8, every 2 weeks during weeks 9 to 24 and then every 4 weeks until disease progression
  - In combination with bortezomib, melphalan, and prednisone: weekly during weeks 1 to 6, every 2 weeks during weeks 7 to 54, and then every 4 weeks until disease progression
  - In combination with bortezomib, thalidomide, and dexamethasone: weekly during weeks 1 to 8, every 2 weeks during weeks 9 to 16 and then consolidation therapy postautologous stem cell therapy with dosing every 2 weeks for four doses
  - In combination with bortezomib and dexamethasone: weekly during weeks 1 to 9, every 3 weeks during weeks 10 to 24, and then every 4 weeks until disease progression
  - In combination with carfilzomib and dexamethasone: 8 mg/kg IV infusion on day 1 and 2 of week 1, then 16 mg/kg IV infusion weekly during weeks 2 to 8, every 2 weeks during weeks 9 to 24, and then every 4 weeks until disease progression
- See chart below for specific dilutions and infusion rates

	Dilution Volume	Initial Rate (First Hour)	Rate Increment	Maximum Rate
Single dose infusion week 1 (16 mg/kg)	1000 mL	50 mL/h	50 mL/h every hour	200 mL/h
Split dose infusion week 1 (8 mg/kg on days 1 and 2 for week 1 of regimen)	500 mL	50 mL/h		
Week 2 infusion (16 mg/kg)	500 mL	50 mL/h		
Subsequent infusions (16 mg/kg)	500 mL	100 mL/h		

- Premedicate with an IV corticosteroid (see product labeling for recommendation), oral antipyretics, and an oral or IV antihistamine
- Infusion should be completed within 15 hours
- Postinfusion medications: oral corticosteroid (see product labeling for recommendation) on the first and second day after all infusions for monotherapy and may be considered for combination therapy

Dose Modification Criteria

- Renal (CrCl > 15 mL/min): no
- Hepatic (mild to moderate) no
- Hepatic (severe): no data
- Myelosuppression: no (dose delays may be needed)

Adverse Reactions

- GI: N/V (minimal), diarrhea, constipation, and decreased appetite
- HEMAT: anemia, thrombocytopenia, neutropenia, and lymphopenia
- INFUS: infusion reactions (eg, bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema, pulmonary edema, respiratory symptoms, chills, and N/V)
- PULM: cough, nasal congestion, dyspnea, upper respiratory tract infection, and nasopharyngitis
- OTHER: fatigue, pyrexia, back pain, and arthralgia

Comments

- Daratumumab may cause severe infusion reactions. Approximately half of all patients experience a reaction, most during the first infusion. Administer in a setting with immediate access to emergency equipment and appropriate medical support to manage infusion reactions.
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab and continue for 3 months following treatment.
- Daratumumab binds to CD38 on red blood cells, resulting in a positive indirect antiglobulin test (Coombs test).
- Daratumumab may be detected on serum protein electrophoresis (SPEP) and immunofixation assays and interfere with clinical monitoring of endogenous M-protein.

DARATUMUMAB AND HYALURONIDASE (DARZALEX FASPRO)

Mechanism of Action

- Daratumumab: an immunoglobulin G1 kappa human monoclonal antibody that binds to CD38 and inhibits the proliferation of CD38-expressing tumor cells
- Hyaluronidase: degrades hyaluronan, an essential component of the extracellular matrix, resulting in a more permeable subcutaneous tissue thereby providing greater diffusion capacity and bioavailability

FDA-Approved Indications

- MM:
  - In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for ASCT
  - In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with relapsed or refractory MM who have received at least one prior therapy
  - In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for ASCT
  - In combination with bortezomib and dexamethasone following at least 1 prior therapy
  - Monotherapy, in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent
- Light chain amyloidosis: newly diagnosed patients with light chain amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone

FDA-Approved Dosage

- Premedicate with a corticosteroid, acetaminophen, and an H_1 antagonist.
- 1800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously into the abdomen over

approximately 3 to 5 minutes according to the schedule outlined in the prescribing information.
- Administer a corticosteroid for 2 days starting the day after daratumumab/hyaluronidase administration unless the background regimen contains a corticosteroid. May discontinue after the first four doses if no significant systemic administration-related reaction.

Dose Modification Criteria

- No dose reduction of daratumumab/hyaluronidase is recommended. Consider withholding for myelosuppression.
- Renal (CrCl 15-89 mL/min): no significant effect on PK.
- Hepatic (mild): no significant effect on PK.
- Hepatic (moderate to severe): no data available.

Adverse Reactions

- CV: cardiac toxicity (in patients with light chain amyloidosis)
- GI: N/V (minimal), constipation, and diarrhea
- HEMAT: neutropenia, thrombocytopenia, leukopenia, lymphopenia, and anemia
- INFUS: hypersensitivity reactions
- NEURO: peripheral sensory neuropathy
- PULM: cough, pneumonia, and dyspnea
- OTHER: upper respiratory tract infection, fatigue, pyrexia, insomnia, back pain, muscle spasms, and peripheral edema

Comments

- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab/hyaluronidase and continue for 3 months after treatment.
- Daratumumab binds to CD38 on red blood cells, resulting in a positive indirect antiglobulin test (Coombs test).

- Embryo-fetal toxicity: daratumumab/hyaluronidase may cause fetal harm when administered to a pregnant woman.

DAROLUTAMIDE (NUBEQA)

Mechanism of Action

- An androgen receptor inhibitor that competitively inhibits androgen binding, nuclear translocation, and androgen receptor–mediated transcription

FDA-Approved Indications

- Nonmetastatic castration-resistant prostate cancer

FDA-Approved Dosage

- 600 mg orally twice daily with food

Dose Modification Criteria

- Renal (mild or moderate, eGFR 30-89 mL/min/1.73 m^2): no
- Renal (severe, eGFR 15-29 mL/min/1.73 m^2): yes
- Hepatic (mild): no
- Hepatic (moderate): yes
- Hepatic (severe): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash
- OTHER: fatigue and pain in extremity

Comments

- A GnRH analog should be administered concurrently or the patient should have undergone a bilateral orchiectomy.
- Avoid concomitant use of dual P-gp and strong or moderate CYP3A inducers.
- When giving concurrently with dual P-gp and strong CYP3A inhibitors, monitor more frequently for daralutamide adverse reactions.
- Avoid concomitant use with BCRP substrates when possible. If coadministration cannot be avoided, monitor for adverse reactions and consider a dose reduction of the BCRP substrate.
- Concomitant use of OATP1B1 and OATP1B3 substrates may increase the plasma concentrations of these substrates. If coadministered, monitor more frequently for adverse reactions and consider a dose reduction of these drugs.
- Embryo-fetal toxicity: daralutamide can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose. Daralutamide may impair fertility in males of reproductive potential.

DASATINIB (SPRYCEL)

Mechanism of Action

- TKI (BCR-ABL, SRC family, c-KIT, EPHA-2, and PDGFRβ)

FDA-Approved Indications

- Chronic myeloid leukemia (CML):
  - Initial therapy in newly diagnosed adults and pediatric patients 1 year of age and older with Ph+ CML in CP
  - Chronic, accelerated, or myeloid or lymphoid BP CML in adults with resistance or intolerance to prior therapy including imatinib
- Acute lymphoblastic leukemia (ALL):
  - Adults with Ph+ ALL with resistance or intolerance to prior therapy

- Pediatric patients aged 1 year and older with newly diagnosed Ph+ ALL in combination with chemotherapy

FDA-Approved Dosage

- Adults:
  - CML, chronic phase: 100 mg orally once daily
  - CML, accelerated phase or myeloid or lymphoid blast phase: 140 mg orally once daily
  - ALL (Ph+): 140 mg orally once daily
- Pediatric patients with CML or ALL (recommended starting dose; see labeling for dose modifications)

Body Weight (kg)	Daily Dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
At least 45 kg	100 mg

Dose Modification Criteria

- Renal: no
- Hepatic: no (use with caution)
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: CHF, QT prolongation, left ventricular dysfunction, and myocardial infarction
- DERM: skin rash
- GI: N/V (minimal-low) and diarrhea
- HEMAT: myelosuppression and hemorrhage
- NEURO: headache
- PULM: pleural effusion, pulmonary edema, pericardial effusion, dyspnea, and pulmonary arterial hypertension
- OTHER: fluid retention (eg, edema), fatigue, musculoskeletal pain, and tumor lysis syndrome

Comments

- Myelosuppression may require dose interruption or reduction. Monitor closely.
- Severe bleeding-related events, mostly related to thrombocytopenia, have been reported. Use with caution in patients requiring medications that inhibit platelet function or anticoagulants.
- Dasatinib is metabolized through CYP3A4 isoenzyme. Screen for drug interactions with CYP3A4 inhibitors or inducers.
- Use with caution in patients who have or may develop QT prolongation. Correct hypokalemia or hypomagnesemia prior to starting therapy.
- Dasatinib may increase the risk of developing pulmonary arterial hypertension, which may occur any time after initiation and is reversible upon discontinuation.
- Severe mucocutaneous dermatologic toxicity (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis has been observed in patients treated with dasatinib.
- The bioavailability of dasatinib is pH dependent. Long-term suppression of gastric acid secretion by H_2 antagonists or PPIs is likely to reduce dasatinib exposure. Administration of antacids should be separated from dasatinib by a minimum of 2 hours.
- Dasatinib may have adverse effects on growth and development in pediatric patients. Monitor bone growth and development.
- Embryo-fetal toxicity: dasatinib may cause fetal harm when administered to a pregnant woman.

DAUNORUBICIN (CERUBIDINE)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- In combination with other agents for remission induction in adult and pediatric patients with acute nonlymphocytic leukemia (ANLL) or acute lymphoblastic leukemia (ALL)

FDA-Approved Dosage

- ANLL: in combination with cytarabine
  - Age younger than 60 years: (first course) 45 mg/m^2 IV daily × 3 days (days 1, 2, and 3); (subsequent course) 45 mg/m^2 IV daily × 2 days (days 1 and 2).
  - Age ≥60 years: (first course) 30 mg/m^2 IV daily × 3 days (days 1, 2, and 3); (subsequent course) 30 mg/m^2 IV daily × 2 days (days 1 and 2).
- ALL: (combined with vincristine, prednisone, l-asparaginase) 45 mg/m^2 IV daily × 3 days (days 1, 2, and 3).
- Pediatric ALL: (combined with vincristine, prednisone) 25 mg/m^2 IV × one dose weekly × 4 weeks initially. In children aged younger than 2 years or below 0.5 m^2 BSA, dosage should be based on weight (1 mg/kg) instead of BSA.

Dose Modification Criteria

- Renal: yes
- Hepatic: yes

Adverse Reactions

- CV: congestive heart failure (CHF) (risk of cardiotoxicity increases rapidly with total lifetime cumulative doses >400-550 mg/m^2 in adults or >300 mg/m^2 in children) and arrhythmias
- DERM: nail hyperpigmentation, rash, alopecia, and tissue damage/necrosis with extravasation
- GI: N/V (moderate) and mucositis
- HEMAT: myelosuppression
- OTHER: red-tinged urine, fever, chills, and secondary malignancies

Comments

- Consult current literature for dosing information. High-dose daunorubicin regimens (eg, 90 mg/m^2/dose) have been evaluated and shown to be superior to standard doses in younger patient populations.
- Vesicant.
- Consider appropriate prophylaxis for tumor lysis syndrome when treating acute leukemias.

DAUNORUBICIN AND CYTARABINE (VYXEOS)

Mechanism of Action

- Daunorubicin/cytarabine is a liposomal formulation of daunorubicin and cytarabine at a fixed 1:5 molar ratio
- Daunorubicin: an anthracycline that forms complexes with DNA, inhibiting topoisomerase II activity
- Cytarabine: antimetabolite that inhibits DNA polymerase

FDA-Approved Indications

- Acute myeloid leukemia (AML): newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults and pediatric patients 1 year and older

FDA-Approved Dosage

- Induction: daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome as an IV infusion over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed

- Consolidation: daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome as an IV infusion over 90 minutes on days 1 and 3

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (bilirubin ≤ 3 mg/dL): no
- Hepatic (bilirubin > 3 mg/dL): no data available

Adverse Reactions

- CV: impaired cardiac function and arrhythmia
- DERM: rash
- GI: N/V (moderate), mucositis, diarrhea, constipation, abdominal pain, and decreased appetite
- HEMAT: hemorrhage and febrile neutropenia
- INFUS: hypersensitivity reaction and tissue necrosis at the site of drug extravasation
- NEURO: headache
- PULM: dyspnea, cough, and pneumonia
- OTHER: edema, musculoskeletal pain, fatigue, bacteremia, chills, and sleep disorders

Comments

- Daunorubicin/cytarabine liposome for injection is associated with a boxed warning to advise against interchange with other daunorubicin and/or cytarabine-containing products.
- Vyxeos contains the anthracycline daunorubicin, which is associated with a known risk of cardiotoxicity. Treatment is not recommended in patients with cardiac function that is less than normal or in patients who have exceeded the maximum cumulative limit. Monitor cardiac function at baseline and throughout treatment.

- Embryo-fetal toxicity: daunorubicin/cytarabine may cause fetal harm when administered to a pregnant woman.

DECITABINE (DACOGEN)

Mechanism of Action

- Decitabine is an analog of the natural nucleoside 2′-deoxycytidine. Decitabine's mechanism of action is as a hypomethylating agent of DNA and also via direct incorporation into DNA.

FDA-Approved Indications

- Myelodysplastic syndromes (MDS): previously treated and untreated de novo and secondary MDS of all FAB subtypes and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups

FDA-Approved Dosage

There are two dosing regimens for decitabine. For either regimen, it is recommended that patients be treated for a minimum of four cycles; however, a complete or partial response may take longer than four cycles.

- 15 mg/m^2 by IV infusion over 3 hours repeated every 8 hours for 3 days. Cycles may be repeated every 6 weeks upon hematologic recovery.
- 20 mg/m^2 by IV infusion over 1 hour once daily for 5 days. Repeat cycles every 4 weeks upon hematologic recovery.

Dose Modification Criteria

- Renal: not studied (use with caution)
- Hepatic: not studied (use with caution)

- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: edema and peripheral edema
- DERM: rash, erythema, and ecchymosis
- ELECTRO: hypomagnesemia, hypokalemia, and hyponatremia
- ENDO: hyperglycemia
- GI: N/V (low), diarrhea, constipation, abdominal pain, stomatitis, and dyspepsia
- HEMAT: myelosuppression
- HEPAT: hyperbilirubinemia and increased LFTs
- NEURO: headache, dizziness, insomnia, and confusion
- PULM: cough and pharyngitis
- OTHER: fatigue, fever, rigors, arthralgia, and limb or back pain

Comments

- Embryo-fetal toxicity: decitabine may cause fetal harm if administered to a pregnant woman. Men should not father a child while receiving treatment with decitabine or for 2 months afterward.

DECITABINE AND CEDAZURIDINE (INQOVI)

Mechanism of Action

- Decitabine: an analog of the natural nucleoside 2′-deoxycytidine; acts as a hypomethylating agent of DNA and also via direct incorporation into DNA.
- Cedazuridine: a cytidine deaminase inhibitor.
- High levels of cytidine deaminase in the GI tract and liver degrade decitabine and limit its oral bioavailability.

Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

FDA-Approved Indications

- Myelodysplastic syndrome (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excessive blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System Groups

FDA-Approved Dosage

- One tablet (35 mg decitabine and 100 mg cedazuridine) taken on an empty stomach orally once daily on days 1 through 5 of each 28-day cycle

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl, 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available

Adverse Reactions

- DERM: rash
- GI: N/V (minimal-low), constipation, mucositis, diarrhea, and decreased appetite
- HEMAT: fatal/serious myelosuppression, hemorrhage, febrile neutropenia, leukopenia, thrombocytopenia, neutropenia, and anemia
- HEPAT: transaminase increased
- NEURO: dizziness and headache

- PULM: dyspnea, cough, and pneumonia
- OTHER: infections, fatigue, myalgia, arthralgia, and edema

Comments

- Embryo-fetal toxicity: decitabine/cedazuridine may cause fetal harm when administered to a pregnant woman. Based on findings in animals, decitabine/cedazuridine may impair male fertility.

DEGARELIX (FIRMAGON)

Mechanism of Action

- GnRH antagonist that binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone

FDA-Approved Indications

- Treatment of advanced prostate cancer

FDA-Approved Dosage

- Treatment is started with a dose of 240 mg given subcutaneously as two injections of 120 mg each.
- The starting dose is followed by maintenance doses of 80 mg administered as a single injection every 28 days. The first maintenance dose should be given 28 days after the starting dose.

Dose Modification Criteria

- Renal (CrCl 50-80 mL/min): no.
- Renal (CrCl < 50 mL/min): use with caution.

- Hepatic (mild, moderate): no testosterone concentrations should be monitored monthly until medical castration is achieved since hepatic impairment can lower degarelix exposure.
- Hepatic (severe): use with caution.

Adverse Reactions

- CV: hypertension and prolonged QT interval
- DERM: injection site reactions, including erythema, induration and nodule, pain, and swelling
- ENDO: hot flashes
- HEPAT: elevated LFTs and elevated GGT
- OTHER: back pain, chills, fatigue, and increased weight

Comments

- Long-term androgen deprivation therapy (ADT) prolongs the QT interval. The benefits of ADT should be weighed against the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or CHF and in patients taking class IA (eg, quinidine, procainamide) or class III (eg, amiodarone, sotalol) antiarrhythmic medications.
- Degarelix is administered as a subcutaneous injection in the abdominal region to areas that will not be exposed to pressure. The injection site should vary periodically. To minimize the risk of dermal exposure, impervious gloves should be worn when handling degarelix. If degarelix solution contacts the skin, immediately wash it thoroughly with soap and water. If degarelix contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.
- Following subcutaneous administration of 240 mg degarelix at a concentration of 40 mg/mL to prostate cancer patients, degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 53 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from depot formed at the injection site.

- The therapeutic effect of degarelix should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.
- Embryo-fetal toxicity: degarelix is not indicated for use in women. Degarelix can cause fetal harm when administered to a pregnant woman.

DINUTUXIMAB (UNITUXIN)

Mechanism of Action

- Binds to the glycolipid GD2, which is expressed on neuroblastoma cells and normal cells of neuroectodermal origin. The binding of dinutuximab to cell surface GD2 induces cell lysis through ADCC and complement-dependent cytotoxicity (CDC).

FDA-Approved Indications

- Neuroblastoma: high-risk neuroblastoma in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA) in pediatric patients who achieved at least a partial response to prior first-line multiagent, multimodality therapy.

FDA-Approved Dosage

- Prehydration: 0.9% sodium chloride 10 mL/kg IV over 1 hour just prior to initiating dinutuximab infusion
- Premedications:
  - Antihistamine IV 20 minutes prior to infusion and as tolerated every 4 to 6 hours during the infusion
  - Acetaminophen 20 minutes prior to each infusion and every 4 to 6 hours as needed for fever or pain. Administer ibuprofen every 6 hours as needed for control of persistent fever or pain

    - Morphine sulfate (50 μg/kg) IV immediately prior to initiation of dinutuximab followed by a morphine sulfate drip 20 to 50 μg/kg/h during and for 2 hours following completion of dinutuximab infusion
- 17.5 mg/m^2/d as an IV infusion over 10 to 20 hours for four consecutive days
- Initiate at an infusion rate of 0.875 mg/m^2/h for 30 minutes then increase as tolerated to a maximum rate of 1.75 mg/m^2/h
- Administer on days 4 to 7 of a 24-day cycle during cycles 1, 3, and 5 and on days 8 to 11 of a 32-day cycle during cycles 2 and 4

Dose Modification Criteria

- Renal: no data available
- Hepatic: no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: capillary leak syndrome and hypotension
- DERM: urticaria
- ELECTRO: hyponatremia, hypokalemia, and hypocalcemia
- GI: N/V (moderate) and diarrhea
- HEMAT: thrombocytopenia, anemia, neutropenia, and lymphopenia
- HEPAT: increased ALT/AST
- INFUS: facial and upper airway edema, dyspnea, bronchospasm, stridor, urticarial, and hypotension
- NEURO: pain during infusion (generalized pain, extremity pain, back pain, musculoskeletal chest pain, and arthralgia), peripheral neuropathy, transverse myelitis, and reversible posterior leukoencephalopathy syndrome
- Ocular system: neurological disorders of the eye
- OTHER: capillary leak syndrome, pyrexia, hypoalbuminemia, and atypical hemolytic uremic syndrome

Comments

- Infusion reactions: life-threatening infusion adverse reactions occur with dinutuximab infusions. Immediately interrupt for severe infusion reactions and permanently discontinue for anaphylaxis.
- Dinutuximab causes severe neuropathic pain. Administer IV opioid prior to, during, and for 2 hours following completion of the dinutuximab infusion. If morphine is not tolerated as a premedication, consider using fentanyl or hydromorphone.
- If pain is inadequately managed with opioids, consider use of gabapentin or lidocaine in conjunction with IV morphine.
- Capillary leak syndrome and hypotension may require interruption, infusion rate reduction, or permanent discontinuation.
- Neurological disorders of the eye: evaluate patients for visual disturbances. Dinutuximab has been reported to cause eye disorders characterized by blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema.
- Embryo-fetal toxicity: dinutuximab may cause fetal harm if administered to a pregnant woman.

DOCETAXEL (TAXOTERE)

Mechanism of Action

- Microtubule assembly stabilization

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC):
  - First-line therapy in combination with cisplatin for unresectable, locally advanced, or metastatic NSCLC
  - Second-line therapy as single agent after failure of prior platinum-based chemotherapy
- Breast cancer:

    - Locally advanced or metastatic breast cancer (after failure of prior chemotherapy)
    - For the adjuvant treatment of patients with operable node-positive breast cancer (in combination with doxorubicin and cyclophosphamide)
- Prostate cancer: castration-resistant (hormone-refractory) metastatic prostate cancer (in combination with prednisone)
- Gastric cancer: advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction (GEJ) (in combination with cisplatin and FU), and first-line therapy in advanced disease
- Head and neck cancer: induction treatment of locally advanced squamous cell carcinoma of the head and neck (in combination with cisplatin and FU)

FDA-Approved Dosage

- Premedication for hypersensitivity reactions and fluid retention: dexamethasone, 8 mg PO twice daily for 3 days starting 1 day before docetaxel administration. For metastatic castration resistant prostate cancer, given the concurrent use of prednisone, the recommended dexamethasone regimen is 8 mg orally at 12 hours, 3 hours, and 1 hour before the docetaxel infusion.
- NSCLC:
    - First-line therapy (combined with cisplatin): 75 mg/m^2 IV over 1 hour × one dose every 3 weeks (administered immediately prior to cisplatin).
    - Second-line therapy (single agent): 75 mg/m^2 IV over 1 hour × one dose every 3 weeks.
- Breast cancer:
    - Locally advanced or metastatic breast cancer: 60 to 100 mg/m^2 IV over 1 hour × one dose every 3 weeks.
    - In the adjuvant treatment setting: 75 mg/m^2 IV over 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles. Prophylactic filgrastim may be used.
- Prostate cancer: 75 mg/m^2 IV over 1 hour × one dose every 3 weeks; prednisone 5 mg orally twice daily is administered continuously.
- Gastric adenocarcinoma: 75 mg/m^2 IV over 1 hour on day 1 only every 3 weeks (in a combination regimen with cisplatin and FU).

- Head and neck cancer:
  - Induction chemotherapy followed by RT (TAX323): 75 mg/m^2 IV over 1 hour on day 1 only (in a combination regimen with cisplatin and FU), repeat cycle every 3 weeks for four cycles.
  - Induction chemotherapy followed by chemoradiotherapy (CRT) (TAX324): 75 mg/m^2 IV over 1 hour on day 1 only (in a combination regimen with cisplatin and FU), repeat cycle every 3 weeks for three cycles.
- All patients in the TAX323 and TAX324 docetaxel study arms received prophylactic antibiotics.

Dose Modification Criteria

- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes (consult with package labeling for dose modification guidelines)

Adverse Reactions

- DERM: rash with localized skin eruptions, erythema and pruritus, nail changes (pigmentation, onycholysis, and pain), and alopecia
- GI: N/V (low), diarrhea, mucositis, dysgeusia, anorexia, enterocolitis, neutropenic colitis
- HEMAT: myelosuppression
- HEPAT: increased LFTs
- INFUS: acute hypersensitivity-type reactions consist of hypotension and/or bronchospasm or generalized rash/erythema
- NEURO: peripheral neurosensory toxicity (paresthesia, dysesthesia, and pain)
- OTHER: severe fluid retention, myalgia, fever, asthenia, and tumor lysis syndrome

Comments

- Patients with preexisting hepatic dysfunction are at increased risk of severe toxicity.
- Patients with preexisting effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.
- Cystoid macular edema has been reported in patients treated with docetaxel. Patients who develop impaired vision should be evaluated promptly.
- Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with docetaxel alone and in combination with other chemotherapeutic agents. Caution in patients with neutropenia, particularly in those at risk for GI complications.
- Second primary malignancies (eg, AML, MDS, NHL, renal cancer) have been reported in patients treated with docetaxel-containing regimens.
- Alcohol content: cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. Patients should be counseled on the potential CNS effects and avoidance of driving or operating machinery. Lower dose, weekly dosage regimens are commonly utilized. Consult current literature for dose guidelines.
- Use non-di(2-ethylhexyl) phthalate (non-DEHP) plasticized solution containers and administration sets.
- Embryo-fetal toxicity: docetaxel may cause fetal harm when administered to a pregnant woman.

DOSTARLIMAB (JEMPERLI)

Mechanism of Action

- Humanized monoclonal antibody that binds to PD-1 receptors, blocking the binding of PD-1 ligands

FDA-Approved Indications

- Endometrial cancer: mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen

FDA-Approved Dosage

- Doses 1 through 4: 500 mg every 3 weeks.
- Subsequent doses (beginning 3 weeks after dose 4): 1000 mg every 6 weeks.
- Administer as an IV infusion over 30 minutes. Continue treatment until disease progression or unacceptable toxicity.

Dose Modification Criteria

- No dose reductions of dostarlimab are recommended. In general, withhold for toxicity.
- Renal (mild to severe): no significant effect on PK.
- Hepatic (mild to severe): no significant effect on PK.

Adverse Reactions

- GI: N/V (not classified), diarrhea, and constipation
- HEMAT: anemia
- INFUS: infusion-related reactions
- OTHER: fatigue/asthenia and immune-mediated adverse reactions (any organ system)

Comments

- Fatal and other serious complications of allogeneic HSCT after PD-1/PD-L1 inhibitors have been reported.
- Immune-mediated adverse reactions can occur in any organ system or tissue and include the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-

mediated nephritis, and immune-mediated dermatologic reactions. Monitor for signs and symptoms of immune-mediated adverse reactions and consult the prescribing information and established guidelines for management.
- Embryo-fetal toxicity: dostarlimab may cause fetal harm when administered to a pregnant woman.

DOXORUBICIN (ADRIAMYCIN AND OTHERS)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Breast cancer: as a component of multiagent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer
- Acute lymphoblastic leukemia; acute myeloblastic leukemia; Wilms tumor; neuroblastoma soft-tissue and bone sarcoma; breast, ovarian, thyroid, bronchiogenic, and gastric cancer; transitional cell bladder cancer; Hodgkin disease; and malignant lymphoma

FDA-Approved Dosage

- Many dosing regimens reported; consult current literature; common dose regimens listed below:
  - Single agent: 60 to 75 mg/m^2 IV × one dose repeated every 21 days
  - In combination with other agents: 40 to 75 mg/m^2 IV × one dose, repeated every 21 to 28 days

Dose Modification Criteria

- Hepatic: yes
- Myelosuppression: yes

Adverse Reactions

- CV: CHF (risk of cardiotoxicity increases rapidly with total lifetime cumulative doses >450 mg/m^2) and arrhythmias
- DERM: nail hyperpigmentation, onycholysis, alopecia, radiation recall, and tissue damage/necrosis with extravasation
- GI: N/V (moderate) and mucositis
- HEMAT: myelosuppression
- OTHER: red-tinged urine, fever, chills, and secondary malignancies

Comments

- Secondary malignancies: secondary acute myelogenous leukemia and myelodysplastic syndrome occur at a higher incidence in patients treated with anthracyclines.
- Radiation-induced toxicity can be increased by the administration of doxorubicin. Radiation recall can occur in patients who receive doxorubicin after prior RT.
- Embryo-fetal toxicity: doxorubicin may cause fetal harm when administered to a pregnant woman.
- Vesicant.

DOXORUBICIN HCL LIPOSOME INJECTION (DOXIL)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- AIDS-related Kaposi sarcoma (KS) (progressive disease after prior combination chemotherapy or in patients intolerant to

such therapy)
- Ovarian cancer (progressive or recurrent disease after platinum-based chemotherapy)
- Multiple myeloma: in combination with bortezomib for patients who have not received bortezomib and have received at least one prior therapy

FDA-Approved Dosage

- AIDS-related Kaposi sarcoma: 20 mg/m^2 IV over 30 minutes × one dose, repeated every 3 weeks.
- Ovarian cancer: 50 mg/m^2 IV over 60 minutes × one dose, repeated every 4 weeks.
- Multiple myeloma: 30 mg/m^2 IV over 60 minutes on day 4 only following bortezomib (bortezomib dose is 1.3 mg/m^2 IV bolus on days 1, 4, 8, and 11), every 3 weeks for up to eight cycles until disease progression or unacceptable toxicity.
- Note: infusion should start at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse events are observed, the rate of infusion can be increased to complete administration of the drug over 1 hour.

Dose Modification Criteria

- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity (palmar-plantar erythrodysesthesia, stomatitis): yes

Adverse Reactions

- CV: CHF and arrhythmias
- DERM: palmar-plantar erythrodysesthesia, alopecia, and rash
- GI: N/V (low) and mucositis/stomatitis
- HEMAT: myelosuppression

- INFUS: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in chest or throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and/or hypotension
- OTHER: asthenia and red-tinged urine

Comments

- Do not confuse with nonliposomal forms of doxorubicin.
- Liposomal formulations of the same drug may not be equivalent.
- Irritant.
- Mix only with D5W; do not use in-line filters.
- The majority of infusion-related events occur during the first infusion.
- Experience with large cumulative doses of doxorubicin HCl liposome injection is limited and cumulative dose limits based on cardiotoxicity risk have not been established. It is recommended by the manufacturer that cumulative dose limits established for conventional doxorubicin be followed for the liposomal product (eg, cumulative doses ≥ 400-550 mg/m^2 depending on risk factors).
- Embryo-fetal toxicity: doxorubicin HCl liposome may cause fetal harm when administered to a pregnant woman.

DURVALUMAB (IMFINZI)

Mechanism of Action

- Human monoclonal antibody that binds to PD-L1, blocking the interaction with its receptors.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): unresectable, stage III NSCLC in patients in whom the disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
- Small cell lung cancer (SCLC): in combination with etoposide and either carboplatin or cisplatin, as first-line treatment for extensive-stage SCLC

FDA-Approved Dosage

- Administered as an IV infusion over 60 minutes
- NSCLC:
  - Weight ≥ 30 kg: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks
  - Weight < 30 kg: 10 mg/kg every 2 weeks
- SCLC:
  - Weight ≥ 30 kg: 1500 mg every 3 weeks in combination with chemotherapy and then 1500 mg every 4 weeks as a single agent
  - Weight < 30 kg: 20 mg/kg every 3 weeks in combination with chemotherapy and then 10 mg/kg every 2 weeks as a single agent

Dose Modification Criteria

- No dose reductions of durvalumab are recommended. In general, withhold for toxicity.
- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK.
- Renal (severe, CrCl <30 mL/min): no data available.
- Hepatic (mild): no significant effect on PK.
- Hepatic (moderate or severe): no data available.

Adverse Reactions

- DERM: rash and alopecia
- GI: N/V (minimal)
- INFUS: infusion-related reactions
- PULM: cough
- OTHER: fatigue/asthenia, upper respiratory tract infections, dyspnea, and immune-mediated adverse reactions (any organ system)

Comments

- Fatal and other serious complications of allogeneic HSCT after PD-1/PD-L1 inhibitors have been reported.
- Immune-mediated adverse reactions can occur in any organ system or tissue and include the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis, and immune-mediated dermatologic reactions. Monitor for signs and symptoms of immune-mediated adverse reactions and consult the prescribing information and established guidelines for management.
- Embryo-fetal toxicity: durvalumab may cause fetal harm when administered to a pregnant woman.

DUVELISIB (COPIKTRA)

Mechanism of Action

- Inhibitor of PI3Kδ and PI3Kγ (expressed in malignant B cells), which prevents key cell signaling pathways and ultimately results in apoptosis of the tumor cell

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): relapsed or refractory CLL or SLL after at least two prior therapies
- Follicular lymphoma (FL): relapsed or refractory FL after at least two prior systemic therapies

FDA-Approved Dosage

- 25 mg orally twice daily with or without food

Dose Modification Criteria

- Renal (CrCl 23-80 mL/min): no significant effect on PK
- Hepatic (mild to severe, Child-Pugh class A, B, or C): no significant effect on PK
- CYP3A4 inhibitors (strong): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash and serious cutaneous reactions
- GI: N/V (minimal-low) and diarrhea/colitis
- HEMAT: neutropenia and anemia
- HEPAT: hepatotoxicity
- PULM: cough, pneumonia, and pneumonitis

- OTHER: fatigue, pyrexia, upper respiratory infection, serious infections, and musculoskeletal pain

Comments

- Duvelisib is associated with a boxed warning and REMS program related to the following fatal and serious toxicities: infections (31%), diarrhea or colitis (18%), cutaneous reactions (5%), and pneumonitis (5%).
- Administer prophylaxis for *Pneumocystis jirovecii* during and after treatment until the absolute $CD4^+$ T-cell count is >200 cells/μL. Consider prophylactic antivirals to prevent cytomegalovirus infection/reactivation.
- Avoid concomitant administration of CYP3A inducers.
- If strong or moderate CYP3A inhibitors are administered concurrently with duvelisib, monitor for duvelisib toxicities. Reduce the duvelisib dose when coadministered with strong CYP3A4 inhibitors.
- If concomitant administration with CYP3A substrates, monitor for signs of toxicities with sensitive CYP3A substrates.
- Embryo-fetal toxicity: duvelisib may cause fetal harm when administered to a pregnant woman.

ELOTUZUMAB (EMPLICITI)

Mechanism of Action

- Humanized IgG1 monoclonal antibody that targets the signaling lymphocytic activation molecule family member 7 (SLAMF7) protein expressed on myeloma cells and NK cells. The binding of elotuzumab to SLAMF7 facilitates the interaction between activated NK cells and myeloma cells leading to antibody-dependent cellular cytotoxicity (ADCC).

FDA-Approved Indications

- Multiple myeloma:
  - In combination with lenalidomide and dexamethasone for adult patients who have received one to three prior therapies.
  - In combination with pomalidomide and dexamethasone for adult patients who have received at least two prior therapies including lenalidomide and a PI.

FDA-Approved Dosage

- Multiple myeloma in combination with lenalidomide and dexamethasone:
  - Premedicate with dexamethasone 28 mg orally 3 to 24 hours before administration, and dexamethasone 8 mg IV, an H_1 antagonist, an H_2 antagonist, and acetaminophen 45 to 90 minutes before administration.
  - 10 mg/kg IV infusion every week for the first two cycles and every 2 weeks thereafter in combination with lenalidomide and dexamethasone. Cycle durations are 28 days.
- Multiple myeloma in combination with pomalidomide and dexamethasone:
  - Premedicate with dexamethasone 28 mg orally for patient younger than 75 years or 8 mg orally for patient older than 75 years at 3 to 24 hours before administration, and dexamethasone 8 mg IV, an H_1 antagonist, an H_2 antagonist, and acetaminophen 45 to 90 minutes before administration.
  - 10 mg/kg IV infusion every week for the first two cycles, then starting with cycle 3, 20 mg/kg IV infusion every 4 weeks in combination with pomalidomide and dexamethasone. Cycle durations are 28 days.
- Infusion rates are advanced in stepwise increments based on patient tolerance. For a 10 mg/kg dose, initiate cycle 1, dose 1 at 0.5 mL/min. Rate may be doubled in 30 minute intervals to a maximum rate of 2 mL/min. Cycle 1, dose 2 may be initiated at 3 mL/min and increased to 4 mL/min after 30 minutes. Subsequent 10 mg/kg doses may start at 5 mL/min. For a 20 mg/kg dose, initiate dose 1 at 3 mL/min and advance after 30 minutes to 4 mL/min. If tolerated, all subsequent doses may be infused at 5 mL/min.

Dose Modification Criteria

- Renal: no
- Hepatic (mild): no
- Hepatic (moderate to severe): no data

Adverse Reactions

- GI: diarrhea and constipation
- HEMAT: thrombocytopenia
- HEPAT: elevated ALT/AST and total bilirubin
- INFUS: fever, chills, and hypertension
- NEURO: peripheral neuropathy and headache
- PULM: pneumonia, cough, and nasopharyngitis
- OTHER: fatigue, pyrexia, and infections

Comments

- Elotuzumab can cause infusion reactions, which may be severe. Premedication is required and severe reactions may require dose interruption and rate reduction.
- Infection incidence in clinical trials was high. Monitor for fever and other signs and symptoms of infection and treat promptly.
- A higher incidence of second primary malignancies has been observed in patients treated with elotuzumab and patients should be monitored.
- Hepatotoxicity: monitor liver enzymes periodically during therapy. Stop therapy for grade 3 or greater elevation in liver enzymes. Resumption of therapy may be considered after return to baseline values.
- Elotuzumab may be detected in the SPEP and serum immunofixation assays of myeloma patients, interfering with correct response classification.

ENASIDENIB (IDHIFA)

Mechanism of Action

- Small molecule inhibitor of mutant isocitrate dehydrogenase (IDH2) variants that results in decreased d-2-hydroxyglutarate

(d-2-HG) levels, reduced blast counts, and increased percentages of mature myeloid cells

FDA-Approved Indications

- Acute myeloid leukemia (AML): relapsed or refractory AML harboring an IDH2 mutation, as detected by an FDA-approved test

FDA-Approved Dosage

- 100 mg orally once daily until disease progression or unacceptable toxicity. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl ≥30 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (moderate-high), diarrhea, and decreased appetite
- HEPAT: increased bilirubin
- OTHER: differentiation syndrome

Comments

- Enasidenib is associated with a boxed warning for differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid

therapy and hemodynamic monitoring until symptom resolution.
- When administered concurrently with substrates of OATP1B1, OATP1B3, BCRP, and P-gp, decrease the dosage of the substrate as recommended in its prescribing information and as clinically indicated.
- Embryo-fetal toxicity: enasidenib may cause fetal harm when administered to a pregnant woman.

ENCORAFENIB (BRAFTOVI)

Mechanism of Action

- Kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF

FDA-Approved Indications

- Metastatic melanoma: in combination with binimetinib for the treatment of unresectable or metastatic melanoma harboring a BRAF V600E or V600K mutation, as detected by an FDA-approved test
- Metastatic colorectal cancer (mCRC): in combination with cetuximab for the treatment of mCRC harboring a BRAF V600E mutation, as detected by an FDA-approved test, following prior therapy

FDA-Approved Dosage

- Metastatic melanoma: 450 mg orally once daily in combination with binimetinib until disease progression or unacceptable toxicity. May be taken without regard to food.
- mCRC: 300 mg orally once daily in combination with cetuximab until disease progression or unacceptable toxicity. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate or severe, Child-Pugh class B or C): not established
- CYP3A4 inhibitors (strong or moderate): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: dermatitis acneiform, rash, and new primary malignancies (cutaneous)
- GI: N/V (moderate-high), abdominal pain, diarrhea, and decreased appetite
- HEMAT: hemorrhage
- Ocular system: uveitis
- OTHER: fatigue, arthralgia, and new primary malignancies (noncutaneous)

Comments

- Encorafenib is not indicated for the treatment of patients with wild-type BRAF melanoma or CRC. Increased cell proliferation and tumor promotion in BRAF wild-type tumors can occur.
- Embryo-fetal toxicity: encorafenib may cause fetal harm when administered to a pregnant woman. Encorafenib may impair fertility in males of reproductive potential.

ENFORTUMAB VEDOTIN (PADCEV)

Mechanism of Action

- As a Nectin-4–directed ADC, enfortumab vedotin binds to Nectin-4 on tumor cells, undergoes internalization, and then releases the cytotoxic payload MMAE (a microtubule-disrupting agent) resulting in DNA damage and apoptotic cell death.

FDA-Approved Indications

- Urothelial cancer: locally advanced or metastatic urothelial cancer after previous treatment with a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting

FDA-Approved Dosage

- 1.25 mg/kg (maximum 125 mg) by IV infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate or severe, Child-Pugh class B or C): avoid use
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, alopecia, pruritus, dry skin, and severe cutaneous adverse reactions
- ENDO: hyperglycemia
- GI: N/V (low), decreased appetite, dysgeusia, and diarrhea
- INFUS: infusion site extravasation
- NEURO: peripheral neuropathy
- Ocular system: dry eye and ocular disorders of the cornea

- OTHER: fatigue

Comments

- Concomitant use of strong CYP3A4 inhibitors may increase exposure to MMAE.
- Embryo-fetal toxicity: enfortumab vedotin may cause fetal harm when administered to a pregnant woman.

ENTRECTINIB (ROZLYTREK)

Mechanism of Action

- Inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase (*NTRK*) genes). Also inhibits ROS1 and ALK. Entrectinib halts the hyperactivation of downstream signaling pathways that are driven by fusion proteins at TRK, ROS1, and ALK kinase domains.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): adult patients with ROS1-positive metastatic NSCLC
- Adult and pediatric patients aged 12 years and older with solid tumors that:
  - have an NTRK gene fusion without a known acquired resistance mutation
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have progressed following treatment or have no satisfactory alternate therapy.

FDA-Approved Dosage

- ROS1 NSCLC: 600 mg orally once daily
- Adults with NTRK gene fusion–positive tumors: 600 mg orally once daily

- Pediatric patients 12 years and older with NTRK gene fusion–positive tumors:
  - BSA >1.50 m^2 = 600 mg orally once daily
  - BSA 1.11 to 1.50 m^2 = 500 mg orally once daily
  - BSA 0.91 to 1.10 m^2 = 400 mg orally once daily
- For all indications, administer without regard to food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no
- Hepatic (moderate or severe): no data available
- CYP3A inhibitors (strong or moderate): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: congestive heart failure (CHF) and QT prolongation
- GI: N/V (minimal-low), constipation, diarrhea, and dysgeusia
- HEPAT: hepatotoxicity
- NEURO: dysesthesia and CNS effects (cognitive impairment, mood disorders, dizziness, and sleep disturbances)
- Ocular system: vision disorders
- PULM: dyspnea and cough
- OTHER: fatigue, edema, myalgia, increased weight, pyrexia, arthralgias, skeletal fractures, and hyperuricemia

Comments

- Assess LVEF prior to treatment initiation and monitor for signs and symptoms of CHF.
- Avoid concomitant administration of moderate and strong CYP3A inhibitors. If coadministration is required, reduce the entrectinib dose.

- Avoid concomitant administration of moderate and strong CYP3A inducers.
- Embryo-fetal toxicity: entrectinib may cause fetal harm when administered to a pregnant woman.

ENZALUTAMIDE (XTANDI)

Mechanism of Action

- Inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA.

FDA-Approved Indications

- Prostate cancer: patients with castration-resistant prostate cancer (CRPC) or metastatic castration-sensitive prostate cancer (mCSPC)

FDA-Approved Dosage

- 160 mg orally once daily with or without food

Dose Modification Criteria

- Hepatic (Child-Pugh class A, B, or C): no
- Renal (CrCl 30-89 mL/min): no
- Renal (<30 mL/min, end-stage renal disease): unknown
- Nonhematologic toxicity: yes

Adverse Effects

- CV: hypertension
- ENDO: hot flashes
- GI: diarrhea

- GU: hematuria
- HEMAT: neutropenia
- HEPAT: elevated LFTs
- PULM: lower respiratory infection
- NEURO: cauda equina syndrome, hallucinations, headache, paresthesia, seizure, and spinal cord compression
- OTHER: anxiety, arthralgia, asthenia, back pain, fatigue, muscular weakness, musculoskeletal pain, and peripheral edema

Comments

- The half-life of enzalutamide is 5.8 days. With daily dosing, enzalutamide steady state is achieved by day 28.
- Avoid strong CYP2C8 inhibitors (eg, gemfibrozil, ritonavir, and sorafenib). If coadministration is necessary, reduce the dose of enzalutamide to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, restart the original dose.
- Avoid strong CYP3A4 inducers. If coadministration is necessary, increase the dose of enzalutamide from 160 to 240 mg once daily. Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as enzalutamide may decrease the plasma exposure of these drugs.
- If enzalutamide is coadministered with warfarin, conduct additional INR monitoring.
- In the clinical trial, 0.9% patients treated with enzalutamide experienced a seizure. Seizures occurred from 31 to 603 days after initiation of therapy. The safety of enzalutamide in patients with predisposing factors for seizure is not known.
- Neurotoxicity: seizures and posterior reversible encephalopathy syndrome have been reported with enzalutamide.
- Embryo-fetal toxicity: enzalutamide is not indicated for use in women; enzalutamide can cause fetal harm when administered to a pregnant woman.

EPIRUBICIN (ELLENCE)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Breast cancer: adjuvant therapy of axillary node–positive breast cancer

FDA-Approved Dosage

- The following dosage regimens were used in the trials supporting use of epirubicin as a component of adjuvant therapy in patients with axillary node–positive breast cancer.
- CEF 120: 60 mg/m^2 IV × one dose on days 1 and 8 (120 mg/m^2 total dose each cycle), repeated every 28 days for six cycles (combined with cyclophosphamide and FU).
- FEC 100: 100 mg/m^2 IV × one dose on day 1 only, repeated every 21 days for six cycles (combined with cyclophosphamide and FU).

Dose Modification Criteria

- Renal: yes
- Hepatic: yes
- Myelosuppression: yes

Adverse Reactions

- CV: CHF (risk of cardiotoxicity increases rapidly with total lifetime cumulative doses >900 mg/m^2) and arrhythmias
- DERM: alopecia, rash, pruritus, radiation recall, and tissue damage/necrosis with extravasation
- GI: N/V (moderate), mucositis, and diarrhea

- HEMAT: myelosuppression
- Ocular system: conjunctivitis and keratitis
- OTHER: facial flushing, amenorrhea, lethargy, and secondary malignancies

Comments

- Embryo-fetal toxicity: epirubicin may cause fetal harm when administered to a pregnant woman.
- Vesicant.

ERDAFITINIB (BALVERSA)

Mechanism of Action

- Kinase inhibitor that binds to and inhibits fibroblast growth factor receptor (FGFR) 1, FGFR2, FGFR3, and FGFR4. Erdafitinib also binds RET, colony-stimulating factor 1 receptor (CSF1R), PDGFR, FLT4, KIT, and VEGFR.

FDA-Approved Indications

- Urothelial carcinoma: locally advanced or metastatic urothelial carcinoma harboring a susceptible FGFR3 or FGFR2 genetic alteration following progression on at least one line of prior platinum-containing chemotherapy

FDA-Approved Dosage

- 8 mg orally once daily with a dose increase to 9 mg once daily if criteria are met. May be taken without regard to food and treatment should continue until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, eGFR ≥ 30 mL/min/1.73 m^2 by MDRD): no significant effect on PK
- Renal (severe, eGFR < 30 mL/min/1.73 m^2 by MDRD): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- CYP2C9 or CYP3A4 inducers: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine
- DERM: onycholysis, dry skin, alopecia, and palmar-plantar erythrodysesthesia (PPE)
- ELECTRO: hyperphosphatemia, hypophosphatemia, hyponatremia, hypomagnesemia, and hypercalcemia
- GI: N/V (minimal-low), stomatitis, diarrhea, dry mouth, decreased appetite, dysgeusia, constipation, and abdominal pain
- HEMAT: anemia
- HEPAT: increased ALT, increased AST, and increased alkaline phosphatase
- Ocular system: dry eye and central serous retinopathy/retinal pigment epithelial detachment
- OTHER: fatigue, hypoalbuminemia, and musculoskeletal pain

Comments

- Hyperphosphatemia is a pharmacodynamic effect and a result of the inhibition of the FGFR pathway involved in a sodium-dependent phosphate cotransporter in the proximal tubule. Avoid concomitant use with agents that can alter serum phosphate levels before the initial dose modification period.
- Perform monthly ophthalmological examinations during the first 4 months of treatment then every 3 months thereafter.

- Avoid concomitant use with the following: moderate CYP2C9 or strong CYP3A4 inhibitors; strong CYP2C9 or strong CYP3A4 inducers; and CYP3A4 substrates with narrow therapeutic indices.
- When given with moderate CYP2C9 or CYP3A4 inducers, increase the erdafitinib dose.
- Avoid concomitant OCT substrates or consider reducing the dose of the OCT2 substrate based on tolerability.
- Administer erdafitinib at least 6 hours before or after the administration of P-gp substrates with narrow therapeutic indices.
- Embryo-fetal toxicity: erdafitinib may cause fetal harm when administered to a pregnant woman.

ERIBULIN (HALAVEN)

Mechanism of Action

- Inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin is a nontaxane microtubule dynamics inhibitor.

FDA-Approved Indications

- Breast cancer: metastatic breast cancer in patients who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
- Liposarcoma: patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

FDA-Approved Dosage

- 1.4 mg/m^2 IV over 2 to 5 minutes on days 1 and 8 of a 21-day cycle.

Dose Modification Criteria

- Renal (mild): no
- Renal (CrCl 15-49 mL/min): yes
- Renal (CrCl < 15 mL/min): not studied
- Hepatic (mild impairment, Child-Pugh class A): yes
- Hepatic (moderate impairment, Child-Pugh class B): yes
- Hepatic (Child-Pugh class C): not studied
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Effects

- DERM: alopecia
- CV: QT prolongation
- ELECTRO: hypokalemia, hypocalcemia, and hypophosphatemia
- GI: anorexia, constipation, diarrhea, abdominal pain, and N/V (low)
- GU: urinary tract infection
- HEMAT: anemia and neutropenia
- HEPAT: elevated LFTs
- NEURO: headache, peripheral motor, and sensory neuropathy
- PULM: cough and dyspnea
- OTHER: alopecia, arthralgia/myalgia, asthenia, back pain, bone pain, decreased weight, fatigue, pain in extremity, and pyrexia

Comments

- Do not mix with other drugs or administer with dextrose-containing solutions.
- Monitor for prolonged QT intervals in patients with CHF, bradyarrhythmias, drugs known to prolong the QT interval,

including classes IA and III antiarrhythmics, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome. Correct hypokalemia or hypomagnesemia prior to initiating eribulin and monitor electrolytes periodically during therapy.
- Patients should be monitored closely for signs of peripheral motor and sensory neuropathy.
- Embryo-fetal toxicity: eribulin is expected to cause fetal harm when administered to a pregnant woman. Women should use effective contraception during treatment.

ERLOTINIB (TARCEVA)

Mechanism of Action

- TKI (EGFR type I [EGFR/HER1])

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): treatment of patients with metastatic disease whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.
- Pancreatic cancer: first-line treatment in combination with gemcitabine in patients with locally advanced, unresectable, or metastatic pancreatic cancer.

FDA-Approved Dosage

- NSCLC: 150 mg orally daily (administer at least 1 hour before or 2 hours after the ingestion of food)
- Pancreatic cancer: 100 mg orally daily (administer at least 1 hour before or 2 hours after the ingestion of food) in combination

with gemcitabine

Dose Modification Criteria

- Renal: no
- Hepatic: use with caution
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, pruritus, dry skin, bullous, and exfoliative skin disorders
- GI: N/V (minimal-low), diarrhea, anorexia, and GI perforation
- GU: renal insufficiency, acute renal failure, and hepatorenal syndrome
- HEPAT: elevated LFTs, hepatic failure, and hepatorenal syndrome
- Ocular system: conjunctivitis, keratoconjunctivitis sicca, corneal perforation, or ulceration
- PULM: dyspnea, cough, and interstitial lung disease
- OTHER: fatigue

Comments

- KRAS mutation predicts for a lack of response to anti-EGFR agents like erlotinib. Consider evaluating for the KRAS mutation prior to initiating therapy.
- Interrupt therapy in patients who develop an acute onset of new or progressive pulmonary symptoms (eg, dyspnea, cough, or fever) for diagnostic evaluation. If interstitial lung disease is diagnosed, erlotinib should be discontinued.
- Diarrhea can usually be managed with loperamide. Interruption of therapy or dose reduction may be necessary in patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated.

- Monitor liver transaminases, bilirubin, and alkaline phosphatase during therapy with erlotinib. Therapy with erlotinib should be interrupted if changes in liver function are severe.
- The risk of myocardial infarction, cerebrovascular accidents, and microangiopathic hemolytic anemia is increased in patients with pancreatic cancer treated with erlotinib.
- Erlotinib is metabolized through CYP3A4 and 1A2 isoenzymes. Screen for drug interactions with CYP3A4 and 1A2 inhibitors or inducers. Other interactions include cigarette smoking (reduced erlotinib exposure), coumarin-derived anticoagulants (increased INR and bleeding events), and agents that reduced gastric pH (PPIs, H_2 antagonists, and antacids).
- Embryo-fetal toxicity: erlotinib may cause fetal harm when administered to a pregnant woman.

ESTRAMUSTINE (EMCYT)

Mechanism of Action

- Alkylating agent, estrogen, and microtubule instability

FDA-Approved Indications

- Prostate cancer: palliative treatment of metastatic and/or progressive carcinoma of the prostate

FDA-Approved Dosage

- 4.67 mg/kg orally three times daily *OR* 3.5 mg/kg orally four times daily (QID); total daily dose: 14 mg/kg.
- Administer with water 1 hour before or 2 hours after meals. Avoid the simultaneous administration of milk, milk products, and calcium-rich foods or drugs.

Dose Modification Criteria

- Hepatic: administer with caution, no specific dose modifications

Adverse Reactions

- CV: edema, fluid retention, venous thromboembolism, and hypertension
- ENDO: hyperglycemia, gynecomastia, and impotence
- GI: diarrhea and N/V (moderate-high)
- HEPAT: elevated LFTs (especially AST or LDH)
- PULM: dyspnea

ETOPOSIDE (VEPESID)

Mechanism of Action

- Topoisomerase II inhibition

FDA-Approved Indications

- Testicular cancer: in combination therapy for refractory disease
- Small cell lung cancer (SCLC): first-line therapy in combination with other agents

FDA-Approved Dosage

- Testicular cancer: 50 to 100 mg/m^2 IV over 30 to 60 minutes daily × 5 days (days 1-5), repeated every 3 to 4 weeks *OR* 100 mg/m^2 IV over 30 to 60 minutes on days 1, 3, and 5, repeated every 3 to 4 weeks (in combination with other approved agents). Consult current literature for dose recommendations.
- SCLC: 35 to 50 mg/m^2 IV over 30 to 60 minutes daily × 4 to 5 days, repeated every 3 to 4 weeks (in combination with other agents). Consult current literature for dose recommendations.

- Oral capsules: in SCLC, the recommended dose of etoposide capsules is two times the IV dose rounded to the nearest 50 mg.

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: alopecia, rash, urticaria, and pruritus
- GI: N/V (IV: low; oral: moderate-high), mucositis, and anorexia
- HEMAT: myelosuppression
- INFUS: hypotension (infusion rate–related) and anaphylactic-like reactions (characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension)
- OTHER: secondary malignancies

ETOPOSIDE PHOSPHATE (ETOPOPHOS)

Mechanism of Action

- Rapidly and completely converted to etoposide in plasma, leading to topoisomerase II inhibition

FDA-Approved Indications

- Testicular cancer: in combination therapy for refractory disease
- SCLC: first-line therapy in combination with other agents

FDA-Approved Dosage

- Testicular cancer: 50 to 100 mg/m^2 IV daily × 5 days (days 1-5), repeated every 3 to 4 weeks *OR* 100 mg/m^2 IV on days 1, 3, and 5, repeated every 3 to 4 weeks (in combination with other

approved agents). Consult current literature for dose recommendations.

- SCLC: 35 to 50 mg/m^2 IV daily × 4 to 5 days, repeated every 3 to 4 weeks (in combination with other agents). Consult current literature for dose recommendations.
- Higher rates of IV administration have been utilized and tolerated by patients with etoposide phosphate compared to etoposide. Etoposide phosphate can be administered at infusion rates from 5 to 210 minutes (generally infusion durations of 5-30 minutes have been utilized).

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: alopecia, rash, urticaria, and pruritus
- GI: N/V (low), mucositis, and anorexia
- HEMAT: myelosuppression
- INFUS: hypotension (infusion rate–related) and anaphylactic-like reactions (characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension)
- OTHER: secondary malignancies

Comments

- Etoposide phosphate is a water soluble ester of etoposide. The water solubility of etoposide phosphate lessens the potential for precipitation following dilution and during IV administration. Enhanced water solubility also allows for lower dilution volumes and more rapid IV administration compared to conventional etoposide.

EVEROLIMUS (AFINITOR, AFINITOR DISPERZ)

Mechanism of Action

- Inhibits mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 and thus inhibition of mTOR kinase activity.

FDA-Approved Indications

- Breast cancer: postmenopausal women with advanced HR-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- Progressive neuroendocrine tumors (pNETs) of pancreatic origin and progressive, well-differentiated, nonfunctional neuroendocrine tumors of GI or lung origin that are unresectable, locally advanced, or metastatic.
- Advanced renal cell cancer (RCC) after failure of treatment with sunitinib or sorafenib.
- Tuberous sclerosis complex (TSC):
  - Renal angiomyolipoma associated with TSC, not requiring immediate surgery.
  - Subependymal giant cell astrocytoma (SEGA) associated with TSC in adult and pediatric patients aged 1 year and older that requires therapeutic intervention but cannot be curatively resected.
  - Partial onset seizures associated with TSC as adjunctive treatment in adult and pediatric patients aged 2 years and older.

FDA-Approved Dosage

- Advanced HR+ BC, advanced NET, advanced RCC, or renal angiomyolipoma with TSC: 10 mg orally once daily with or without food
- SEGA associated with TSC: 4.5 mg/m^2 orally once daily

- Partial onset seizures associated with TSC: 5 mg/m^2 orally once daily

Dose Modification Criteria

- Renal: no
- Hepatic (Child-Pugh class A, B, or C): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine and renal failure
- CV: edema
- DERM: mouth ulcers and rash
- ELECTRO: hypophosphatemia
- ENDO: hypercholesterolemia, hyperglycemia, and hypertriglyceridemia
- GI: abdominal pain, decreased appetite, diarrhea, stomatitis (mucositis and mouth ulcers), N/V (minimal-low)
- GU: proteinuria
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- NEURO: headache
- PULM: cough, pneumonitis, and respiratory tract infection
- OTHER: asthenia, fatigue, fever, impaired wound healing, and infections

Comments

- Contraindicated in patients with hypersensitivity to everolimus, other rapamycin derivatives, or to any of the excipients. Afinitor Disperz contains mannitol.
- Available as tablets and tablets for oral suspension (Afinitor Disperz). Afinitor Disperz is recommended only for the treatment of patients with SEGA or partial onset seizures

associated with TSC and in conjunction with therapeutic drug monitoring. Maintain trough concentrations of 5 to 15 ng/mL.

- Avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines.
- Avoid the use of alcohol-, peroxide-, iodine-, or thyme-containing mouthwashes, since they may exacerbate mouth ulcers, oral mucositis, and stomatitis.
- Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of P-gp. Avoid the concomitant use of strong inhibitors or inducers of CYP3A4. Dose modifications are recommended when everolimus is used concomitantly with moderate inhibitors of CYP3A4 and/or P-gp or strong inducers of CYP3A4.
- Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, protozoal, or viral infections, including reactivation of hepatitis B.
- Noninfectious pneumonitis is a class effect of rapamycin derivatives. Patients should be monitored for hypoxia, pleural effusion, cough, or dyspnea.
- Radiation sensitization and recall have been reported in patients with treated with radiation prior to, during, or subsequent to everolimus treatment.
- Embryo-fetal toxicity: everolimus can cause fetal harm when administered to a pregnant woman.

EXEMESTANE (AROMASIN)

Mechanism of Action

- Irreversible steroidal aromatase inactivator

FDA-Approved Indications

- Breast cancer:

- Adjuvant treatment of ER-positive early breast cancer in postmenopausal women who have received 2 to 3 years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy
- Advanced breast cancer after tamoxifen failure in postmenopausal women

FDA-Approved Dosage

- 25 mg orally, daily after a meal

Dose Modification Criteria

- Renal: no
- Hepatic: no (note: drug exposure is increased with hepatic and/or renal insufficiency. The safety of chronic dosing in these settings has not been studied. Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non–life-threatening adverse effects, dosage adjustment does not appear to be necessary.)

Adverse Reactions

- CV: hot flashes and edema
- GI: nausea and increased appetite
- HEMAT: lymphocytopenia
- NEURO: headache, depression, insomnia, and anxiety
- OTHER: tumor site pain, asthenia, fatigue, increased sweating, and fever

Comments

- Reductions in BMD over time are seen with exemestane use. Women with osteoporosis or at risk for osteoporosis should have BMD assessed and monitored. Assessment of vitamin D levels should be performed prior to start of therapy and

replacement of vitamin D should be provided if deficiency is identified.
- Concomitant use of strong CYP3A4 inducers (eg, rifampin, phenytoin) with exemestane decreases exemestane exposure and require dose modification to 50 mg once daily.

FAM-TRASTUZUMAB DERUXTECAN (ENHERTU)

Mechanism of Action

- As a HER2-directed ADC, fam-trastuzumab deruxtecan binds to HER2 on tumor cells, undergoes internalization, then releases the cytotoxic payload DXd (a topoisomerase I inhibitor) resulting in DNA damage and apoptotic cell death.

FDA-Approved Indications

- Breast cancer: unresectable or metastatic HER2-positive breast cancer after two or more prior anti–HER2-based regimens in the metastatic setting
- Gastric cancer: locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma after a prior trastuzumab-based regimen

FDA-Approved Dosage

- Breast cancer: 5.4 mg/kg as an IV infusion once every 3 weeks until disease progression or unacceptable toxicity
- Gastric cancer: 6.4 mg/kg as an IV infusion once every 3 weeks until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild or moderate): no
- Hepatic (severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: left ventricular dysfunction
- DERM: alopecia
- ELECTRO: hypokalemia
- GI: N/V (moderate), constipation, diarrhea, and decreased appetite
- HEMAT: leukopenia, anemia, neutropenia, thrombocytopenia, and lymphopenia
- HEPAT: increased bilirubin, increased AST, increased ALT, and increased alkaline phosphatase
- PULM: cough and interstitial lung disease/pneumonitis
- OTHER: fatigue and pyrexia

Comments

- Fam-trastuzumab deruxtecan prescribing information contains a boxed warning for interstitial lung disease and pneumonitis. Fatal cases have been reported and patients should be monitored for new or worsening respiratory symptoms.
- Fam-trastuzumab deruxtecan prescribing information contains a boxed warning for embryo-fetal toxicity. Advise patients of the need for effective contraception and verify pregnancy status of females prior to treatment initiation.
- Assess LVEF prior to the start of fam-trastuzumab deruxtecan and at regular intervals. Discontinue in patients with symptomatic CHF.

FEDRATINIB (INREBIC)

Mechanism of Action

- Kinase inhibitor with activity against Janus kinase (JAK2) and FLT3. Fedratinib inhibits the abnormal activation of JAK2 that is associated with myeloproliferative neoplasms.

FDA-Approved Indications

- Myelofibrosis: intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis

FDA-Approved Dosage

- 400 mg orally once daily for patients with a baseline platelet count of ≥50,000/μL. May be taken with or without food but administration with a high-fat meal may reduce the incidence of N/V.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl 15-29 mL/min): yes
- Hepatic (mild to moderate): no significant effect on PK
- Hepatic (severe): avoid use
- CYP3A4 inhibitors (strong): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (moderate-high), diarrhea, amylase elevation, and lipase elevation
- HEMAT: anemia and thrombocytopenia

- HEPAT: hepatotoxicity
- NEURO: encephalopathy

Comments

- Fedratinib is associated with a boxed warning for serious and fatal encephalopathy including Wernicke. Assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. Do not start fedratinib in patients with thiamine deficiency and replete thiamine as indicated.
- Avoid concomitant use of the following medications: strong and moderate CYP3A4 inducers and dual CYP3A4 and CYP2C19 inhibitors. If use of strong CYP3A4 inhibitors cannot be avoided, reduce the fedratinib dose.

FLOXURIDINE

Mechanism of Action

- Antimetabolite (catabolized to FU)

FDA-Approved Indications

- Palliative management of GI adenocarcinoma metastatic to the liver when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means

FDA-Approved Dosage

- 0.1 to 0.6 mg/kg/d by continuous arterial infusion. The higher dose ranges (0.4-0.6 mg/kg/d) are usually employed for hepatic artery infusion because the liver metabolizes the drug, thus reducing the potential for systemic toxicity. Therapy may be

given until adverse reactions appear; when toxicities have subsided, therapy may be resumed. Patients may be maintained on therapy as long as response to floxuridine continues.

Dose Modification Criteria

- Renal: no
- Hepatic: no, use with caution
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: myocardial ischemia
- DERM: alopecia, dermatitis, and rash
- GI: N/V, stomatitis, diarrhea, enteritis, GI ulceration, and bleeding
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- INFUS: procedural complications of regional arterial infusion—arterial aneurysm, arterial ischemia, arterial thrombosis, embolism, fibromyositis, thrombophlebitis, hepatic necrosis, abscesses, infection at catheter site, bleeding at catheter site, catheter blocked, displaced, or leaking
- OTHER: fever, lethargy, malaise, and weakness

FLUDARABINE (FLUDARA)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- B-cell chronic lymphocytic leukemia (CLL): second-line after alkylating agent therapy

FDA-Approved Dosage

- CLL: 25 mg/m^2 IV over 30 minutes daily × 5 days, repeated every 28 days

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- CV: edema
- DERM: rash
- GI: N/V (minimal), diarrhea, and anorexia
- HEMAT: myelosuppression, autoimmune hemolytic anemia, and lymphopenia
- NEURO: weakness, agitation, confusion, visual disturbances, coma (severe neurotoxicity generally seen with high-dose regimens but have been reported rarely at recommended doses), and peripheral neuropathy
- PULM: pneumonitis and cases of severe pulmonary toxicity have been reported
- OTHER: myalgia, tumor lysis syndrome, and fatigue

Comments

- Monitor for hemolytic anemia.
- A high incidence of fatal pulmonary toxicity was seen in a trial investigating the combination of fludarabine with pentostatin. The combined use of fludarabine and pentostatin is not recommended.
- Transfusion-associated graft-versus-host disease (GVHD) has been observed rarely after transfusion of nonirradiated blood in

fludarabine-treated patients. Consideration should be given to using only irradiated blood products if transfusions are necessary in patients undergoing treatment with fludarabine.
- Monitor for tumor lysis syndrome and consider prophylaxis in CLL patients with a large tumor burden initiated on fludarabine.
- Embryo-fetal toxicity: fludarabine may cause fetal toxicity when given to a pregnant woman.

FLUOROURACIL (ADRUCIL AND OTHERS)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Palliative management of colon, rectal, breast, stomach, and pancreatic cancer

FDA-Approved Dosage

- Consult current literature

Adverse Reactions

- CV: angina, ischemia
- DERM: dry skin, photosensitivity, hand-foot syndrome (palmar-plantar erythrodysesthesia), alopecia, dermatitis, and thrombophlebitis
- GI: N/V (low), mucositis, diarrhea, anorexia, GI ulceration, and bleeding
- HEMAT: myelosuppression
- NEURO: acute cerebellar syndrome, nystagmus, headache, visual changes, and photophobia

- OTHER: anaphylaxis and generalized allergic reactions

Comments

- FU may be given as continuous IV infusion or by rapid IV administration (IV bolus or push). The method of administration will change the toxicity profile of FU (eg, greater potential for GI toxicities such as mucositis and diarrhea with continuous IV infusions and more hematologic toxicity with bolus administration).

FLUTAMIDE (EULEXIN)

Mechanism of Action

- Antiandrogen

FDA-Approved Indications

- Prostate cancer: stage D2 metastatic prostate carcinoma (in combination with LHRH agonists) or locally confined stage B2-C prostate carcinoma (in combination with LHRH agonists and radiation therapy)

FDA-Approved Dosage

- Stage D2 metastatic prostate carcinoma: 250 mg orally three times daily (every 8 hours)
- Stage B2-C prostate cancer: 250 mg orally three times daily (every 8 hours) beginning 8 weeks before and continuing through radiation

Adverse Reactions

- DERM: rash

- GI: N/V (not classified), diarrhea, and constipation
- GU: impotence
- ENDO: loss of libido, hot flashes, and gynecomastia
- HEPAT: increased LFTs (monitor LFTs periodically because of rare associations with cholestatic jaundice, hepatic necrosis, and encephalopathy)

Comments

- Interacts with warfarin; monitor INR closely.

FULVESTRANT (FASLODEX)

Mechanism of Action

- ER antagonist

FDA-Approved Indications

- Breast cancer:
  - Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy
  - Treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
  - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine-based therapy or following disease progression on endocrine therapy
  - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy

FDA-Approved Dosage

- 500 mg IM injection (two 5 mL injections, one in each buttock) on days 1, 15, and 29 and once monthly thereafter

Dose Modification Criteria

- Renal: no
- Hepatic (mild impairment): no
- Hepatic (moderate impairment): yes
- Hepatic (severe impairment): not tested

Adverse Reactions

- CV: peripheral edema
- ENDO: hot flashes
- GI: N/V (not classified), constipation, diarrhea, abdominal pain, and anorexia
- HEPAT: increased LFTs
- NEURO: headache
- PULM: cough, dyspnea
- OTHER: pain, fatigue, pharyngitis, injection site reactions, and asthenia

Comments

- Use with caution in patients with bleeding diathesis, thrombocytopenia, or anticoagulant use.
- Embryo-fetal toxicity: fulvestrant may cause fetal harm when used in pregnant women.

GEFITINIB (IRESSA)

Mechanism of Actions

- TKI (primarily EGFR)

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon

19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test

FDA-Approved Dosage

- 250 mg orally once daily

Dose Modification Criteria

- Renal: not evaluated in severe impairment; use with caution
- Hepatic: no; monitor for adverse effects in moderate or severe impairment

Adverse Reactions

- DERM: rash, acne, dry skin, and pruritus
- GI: N/V (minimal-low), diarrhea, anorexia
- HEPAT: elevated LFTs
- Ocular system: conjunctivitis, blepharitis, keratitis, dry eye, eye pain, and corneal erosion/ulcer (sometimes in association with aberrant eyelash growth)
- PULM: interstitial lung disease (interstitial pneumonia, pneumonitis, and alveolitis)
- OTHER: asthenia and weight loss

Comments

- In a patient who presents with acute onset or worsening of pulmonary symptoms (dyspnea, cough, and fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. Fatalities related to interstitial lung disease have been reported.
- Diarrhea can be severe; withhold gefitinib for severe or persistent diarrhea.
- Bullous or exfoliative skin disorders have been reported. Interrupt or discontinue gefitinib for severe bullous, blistering,

or exfoliative skin disorders.
- Embryo-fetal toxicity: gefitinib may cause fetal toxicity when given to a pregnant woman.
- Gefitinib is extensively hepatically metabolized, predominantly by CYP3A4. Be aware of potential drug interactions with either potent inhibitors or inducers of CYP3A4. A dose increase of gefitinib to 500 mg/d may be considered when given concomitantly with a potent CYP3A4 enzyme inducer such as phenytoin or rifampin.
- Gefitinib may potentially interact with warfarin leading to an elevated PT and INR and bleeding events; monitor PT/INR regularly with concomitant use.

GEMCITABINE (GEMZAR)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Pancreatic cancer: first-line treatment for patients with locally advanced (nonresectable stage II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas and in pancreatic cancer patients previously treated with FU.
- Non–small cell lung cancer (NSCLC): first-line treatment (in combination with cisplatin) for patients with inoperable, locally advanced (stage IIIa or IIIb) or metastatic (stage IV) NSCLC.
- Metastatic breast cancer: first-line treatment (in combination with paclitaxel) for patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.
- Ovarian cancer: in combination with carboplatin for advanced ovarian cancer that has relapsed at least 6 months after

completion of platinum-based therapy.

FDA-Approved Dosage

- Pancreatic cancer (single-agent use): 1000 mg/m^2 IV over 30 minutes once weekly for up to 7 weeks, followed by 1 week of rest from treatment. Subsequent cycles should consist of 1000 mg/m^2 IV over 30 minutes once weekly for three consecutive weeks out of every 4 weeks.
- NSCLC (combination therapy with cisplatin):
  - Four-week schedule: 1000 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of each 28-day cycle. Cisplatin (100 mg/m^2 IV × one dose) should be administered after gemcitabine only on day 1, *OR*
  - Three-week schedule: 1250 mg/m^2 IV over 30 minutes on days 1 and 8 of each 21-day cycle. Cisplatin (100 mg/m^2 IV × one dose) should be administered after gemcitabine only on day 1.
- Metastatic breast cancer (combination therapy with paclitaxel): 1250 mg/m^2 IV over 30 minutes on days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 IV over 3 hours × one dose (day 1 only) before gemcitabine administration.
- Ovarian cancer: 1000 mg/m^2 IV over 30 minutes on days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 IV should be administered on day 1 after gemcitabine administration.

Dose Modification Criteria

- Renal: use with caution
- Hepatic: use with caution
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash and alopecia
- GI: N/V (low), constipation, diarrhea, and mucositis
- GU: proteinuria, hematuria, and hemolytic uremic syndrome

- HEMAT: myelosuppression
- HEPAT: increased LFTs and bilirubin and rare reports of severe hepatotoxicity
- PULM: dyspnea and rare reports of severe pulmonary toxicity (pneumonitis, pulmonary fibrosis, pulmonary edema, and acute respiratory distress syndrome)
- OTHER: fever, pain, and rare reports of vascular toxicity (vasculitis)

Comments

- IV administration rate has been shown to influence both efficacy and toxicity. Refer to the published literature for the appropriate rate of administration for a specific regimen.
- Pulmonary toxicity: discontinue gemcitabine for unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity.
- Hemolytic uremic syndrome (HUS) has been reported in patients treated with gemcitabine. Assess renal function prior to initiating therapy and periodically during treatment. Discontinue gemcitabine in patients with HUS or severe renal impairment.
- Exacerbation of radiation therapy toxicity: may cause severe or life-threatening toxicity when administered during or within 7 days of radiation therapy.
- Capillary leak syndrome has been reported in patients treated with gemcitabine.
- Posterior reversible encephalopathy syndrome (PRES) has been reported in patients treated with gemcitabine. Discontinue gemcitabine if PRES develops during therapy.
- Embryo-fetal toxicity: gemcitabine may cause fetal toxicity when given to a pregnant woman.

GEMTUZUMAB OZOGAMICIN (MYLOTARG)

Mechanism of Action

- As a CD33-directed ADC, gemtuzumab ozogamicin binds to CD33-expressing tumor cells, undergoes internalization, and then the payload calicheamicin (a cytotoxic agent that induces double-stranded DNA breaks) is released resulting in apoptotic cell death.

FDA-Approved Indications

- Acute myeloid leukemia (AML):
  - Treatment of newly diagnosed CD33-positive AML in adults and pediatric patients aged 1 month and older
  - Treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years of age and older

FDA-Approved Dosage

- Premedicate with a corticosteroid, antihistamine, and acetaminophen. Monitor patients during infusion and for at least 1 hour after the end of the infusion.
- Newly diagnosed AML (combination regimen):
  - Adults:
    - Induction: 3 mg/m^2 (up to 4.5 mg) on days 1, 4, and 7 in combination with daunorubicin and cytarabine
    - Consolidation: 3 mg/m^2 (up to 4.5 mg) on day 1 in combination with daunorubicin and cytarabine
  - Pediatric patients 1 month and older:
    - 3 mg/m^2 if BSA $\geq$ 0.6 m^2
    - 0.1 mg/kg if BSA < 0.6 m^2
- Newly diagnosed AML (monotherapy):
  - Induction: 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8
  - Consolidation: 2 mg/m^2 on day 1 every 4 weeks for up to 8 continuation courses
  - Not limited to 4.5 mg dose
- Relapsed or refractory AML (monotherapy):
  - Adults and pediatric patients 2 years and older:
    - 3 mg/m^2 (up to 4.5 mg) on days 1, 4, and 7

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Hepatotoxicity during treatment: yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash
- GI: N/V (low), constipation, mucositis, and decreased appetite
- HEMAT: hemorrhage and febrile neutropenia
- HEPAT: hepatotoxicity, veno-occlusive disease, increased AST, and increased ALT
- INFUS: infusion-related reactions (including anaphylaxis)
- NEURO: headache
- OTHER: infection and fever

Comments

- Gemtuzumab ozogamicin is associated with a boxed warning for hepatotoxicity including severe or fatal hepatic veno-occlusive disease.
- Embryo-fetal toxicity: gemtuzumab ozogamicin may cause fetal harm when administered to a pregnant woman.

GILTERITINIB (XOSPATA)

Mechanism of Action

- Small molecule that inhibits tyrosine kinases including FLT3 in cells expressing FLT3-ITD, TKD-FLT3-D835Y, and FLT3-ITD-

D835Y. Gilteritinib therefore inhibits receptor signaling of leukemic cells expressing FLT3-ITD resulting in apoptosis.

FDA-Approved Indications

- Acute myeloid leukemia (AML): relapsed or refractory AML harboring a FLT3 mutation, as detected by an FDA-approved test

FDA-Approved Dosage

- 120 mg orally once daily with or without food. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-80 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild or moderate, Child-Pugh class A or B): no significant effect on PK
- Hepatic (severe, Child-Pugh class C): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: renal impairment
- CV: hypotension and QT prolongation
- DERM: rash
- GI: N/V (minimal-low), mucositis, noninfectious diarrhea, constipation, and pancreatitis
- HEPAT: increased transaminases
- NEURO: headache, dizziness, and posterior reversible encephalopathy syndrome (PRES)

- Ocular system: eye disorders
- PULM: dyspnea and cough
- OTHER: myalgias/arthralgias, fatigue/malaise, fever, edema, and differentiation syndrome

Comments

- Gilteritinib is associated with a boxed warning for differentiation syndrome that can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
- Avoid concomitant administration of combined P-gp and strong CYP3A inducers.
- Consider alternative therapies in place of strong CYP3A inhibitors. If coadministration cannot be avoided, monitor more frequently for gilteritinib adverse reactions.
- Embryo-fetal toxicity: gilteritinib may cause fetal harm when administered to a pregnant woman.

GLASDEGIB (DAURISMO)

Mechanism of Action

- Hedgehog pathway inhibitor that binds to and inhibits smoothened, a transmembrane protein involved in Hedgehog signal transduction

FDA-Approved Indications

- Acute myeloid leukemia (AML): in combination with low-dose cytarabine, for the treatment of newly diagnosed AML in adult patients who are aged 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy

FDA-Approved Dosage

- 100 mg orally once daily in the absence of unacceptable toxicity or loss of disease control. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild to severe, eGFR 15-89 mL/min): no
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): not established
- CYP3A inducers (moderate): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: rash
- GI: N/V (minimal-low), decreased appetite, dysgeusia, mucositis, and constipation
- HEMAT: anemia, hemorrhage, febrile neutropenia, and thrombocytopenia
- PULM: dyspnea
- OTHER: fatigue, musculoskeletal pain, and edema

Comments

- Avoid concomitant use of strong CYP3A4 inhibitors or inducers.
- Avoid concomitant use of moderate CYP3A inducers. If coadministration is required, increase the glasdegib dose.
- Glasdegib may cause QT prolongation; monitor ECGs and electrolytes. Avoid concomitant use of QT-prolonging drugs. If coadministration is required, closely monitor for increased risk of QT prolongation.
- Advise patients not to donate blood or blood products during treatment and for at least 30 days after the last dose.

- Glasdegib prescribing information includes a boxed warning for embryo-fetal toxicity including embryo-fetal death or severe birth defects when administered to a pregnant woman. Conduct pregnancy testing prior to initiation of treatment and advise females of reproductive potential to use effective contraception during treatment and for at least 30 days after the last dose. Advise males of the potential risk of exposure though semen and to use condoms with a pregnant partner or female partner of reproductive potential during treatment and for at least 30 days after the last dose.

GOSERELIN ACETATE IMPLANT (ZOLADEX)

Mechanism of Action

- LHRH agonist; chronic administration leads to sustained suppression of pituitary gonadotropins and subsequent suppression of serum testosterone in men and serum estradiol in women.

FDA-Approved Indications

- Prostate cancer:
  - Palliative treatment of advanced carcinoma of the prostate.
  - Stage T2b-T4 (stage B2-C) prostatic carcinoma: in combination with flutamide and radiation therapy. Goserelin acetate and flutamide treatment should start 8 weeks prior to initiating radiation therapy.
- Breast cancer: palliative treatment of advanced breast cancer in pre- and perimenopausal women.
- Other indications: endometriosis and endometrial thinning.

FDA-Approved Dosage

- Advanced carcinoma of the prostate: 3.6 mg subcutaneous depot monthly, *OR* 10.8 mg subcutaneous depot every 12 weeks.

- Stage B2-C prostatic carcinoma: start 8 weeks prior to initiating RT and continue through radiation. A treatment regimen of 3.6 mg subcutaneous depot, followed in 28 days by 10.8 mg subcutaneous depot. Alternatively, four injections of 3.6 mg subcutaneous depot can be administered at 28-day intervals, two depots preceding and two during RT.
- Breast cancer: 3.6 mg subcutaneous depot every 4 weeks.

Dose Modification Criteria

- Renal: no
- Hepatic: no

Adverse Reactions

- CV: transient changes in BP (hypo- or hypertension)
- ENDO: men—hot flashes, gynecomastia, sexual dysfunction, and decreased erections; women—hot flashes, headache, vaginal dryness, vaginitis, emotional lability, change in libido, depression, increased sweating, and change in breast size
- GU: erectile dysfunction and lower urinary tract symptoms
- NEURO: pain
- OTHER: tumor flare in the first few weeks of therapy, loss of BMD, osteoporosis, bone fracture, and asthenia

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.

HISTRELIN ACETATE IMPLANT (VANTAS)

Mechanism of Action

- LHRH agonist; chronic administration leads to sustained suppression of pituitary gonadotropins and subsequent suppression of serum testosterone in men and serum estradiol in women.

FDA-Approved Indications

- Prostate cancer: palliative treatment of advanced carcinoma of the prostate
- Other indications: central precocious puberty (alternative product: Supprelin LA)

FDA-Approved Dosage

- Advanced carcinoma of the prostate: 50 mg subcutaneous depot every 12 months. The once yearly implant is inserted subcutaneously in the inner aspect of the upper arm. The implant must be removed after 12 months of therapy prior to a new implant insertion for continuation of therapy. Implant insertion is a surgical procedure.

Dose Modification Criteria

- Renal: no
- Hepatic: not studied

Adverse Reactions

- ENDO: men—hot flashes, gynecomastia, sexual dysfunction, decreased erections
- DERM: implant site reactions (pain, soreness, tenderness, erythema)
- GU: erectile dysfunction and renal impairment
- OTHER: tumor flare in the first few weeks of therapy, loss of BMD, osteoporosis, bone fracture, and fatigue

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.

HYDROXYUREA (HYDREA, DROXIA)

Mechanism of Action

- Antimetabolite; inhibits DNA synthesis; radiation sensitizer

FDA-Approved Indications

- Chronic myeloid leukemia (CML): resistant CML
- Locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemoradiation therapy
- Sickle cell anemia with recurrent moderate to severe painful crises

FDA-Approved Dosage

- Dose based on actual or IBW, whichever is less
- Individualize treatment based on tumor type, disease state, and response to treatment, patient risk factors, and current clinical practice standards. Sickle cell anemia: initial starting dose of 15 mg/kg orally daily

Dose Modification Criteria

- Renal: yes
- Hepatic: use with caution
- Myelosuppression: yes

Adverse Reactions

- DERM: rash, peripheral and facial erythema, skin ulceration, dermatomyositis-like skin changes, hyperpigmentation, and cutaneous vasculitic toxicities
- GI: N/V (minimal-low), diarrhea, anorexia, mucositis, and constipation
- HEMAT: myelosuppression (leukopenia, anemia > thrombocytopenia)
- NEURO: drowsiness (large doses)

Comments

- Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders receiving hydroxyurea. If cutaneous vasculitic ulcers occur, discontinue hydroxyurea.
- Radiation recall may occur. Monitor for skin erythema in patients who have previously received radiation therapy.
- Embryo-fetal toxicity: hydroxyurea may cause fetal toxicity when given to a pregnant woman.
- Avoid live vaccines and concomitant antiretroviral agents with hydroxyurea.
- Hydroxyurea may cause a self-limiting macrocytosis early in the course of therapy; prophylactic administration of folic acid is recommended.

IBRUTINIB (IMBRUVICA)

Mechanism of Action

- Small-molecule inhibitor of BTK

FDA-Approved Indications

- Mantle cell lymphoma (MCL): adult patients who have received at least one prior therapy

- Marginal zone lymphoma (MZL): adult patients who require systemic therapy and have received at least one prior anti–CD20-based therapy
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- CLL/SLL with 17p deletion
- Waldenstrom macroglobulinemia (WM)
- Chronic graft-versus-host disease (cGVHD): adult patients with cGVHD after failure of one or more lines of systemic therapy

FDA-Approved Dosage

- MCL and MZL: 560 mg orally once daily until disease progression or unacceptable toxicity.
- CLL/SLL and WM: 420 mg orally once daily until disease progression or unacceptable toxicity.
    - For CLL/SLL, ibrutinib can be administered as a single agent, in combination with rituximab or obinutuzumab or in combination with bendamustine and rituximab. For WM, ibrutinib can be administered as a single agent or in combination with rituximab.
- cGVHD: 420 mg orally once daily until disease progression, recurrence of an underlying malignancy, or unacceptable toxicity.

Dose Modification Criteria

- Renal (CrCl ≥ 25 mL/min): no dose adjustment necessary
- Renal (CrCl < 25 mL/min): no data available
- Hepatic (mild to moderate, Child-Pugh class A and B): yes
- Hepatic (severe, Child-Pugh class C): use not recommended
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: atrial fibrillation, ventricular tachyarrhythmias, hypertension, and cardiac failure

- DERM: rash
- GI: diarrhea, N/V (minimal-low), constipation, abdominal pain, and decreased appetite
- HEMAT: hemorrhage, neutropenia, thrombocytopenia, and anemia
- PULM: upper respiratory tract infection
- OTHER: fatigue, peripheral edema, musculoskeletal pain, pyrexia, and tumor lysis syndrome

Comments

- Ibrutinib is a substrate of CYP3A4. Avoid concomitant use of moderate or strong 3A4 inhibitors and strong inducers of CYP3A4. If a moderate CYP3A4 must be used concomitantly with ibrutinib, a dose reduction of ibrutinib is recommended. See product labeling for dose modification recommendations.
- Bleeding: fatal bleeding events have occurred in patients treated with ibrutinib. Use of either anticoagulant or antiplatelet agents concomitantly increases risk. Monitor for signs and symptoms of bleeding. Consider holding therapy for 3 to 7 days pre- and postsurgery depending on the type of surgery and the risk of bleeding.
- Second primary malignancies have been observed in patients treated with ibrutinib including skin cancer and other carcinomas.
- Embryo-fetal toxicity: ibrutinib may cause fetal harm if administered to a pregnant woman.

IDARUBICIN (IDAMYCIN)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Acute myeloid leukemia (AML) in combination with other agents for adult AML (FAB M1 to M7)

FDA-Approved Dosage

- AML induction in combination with cytarabine: 12 mg/m^2 slow IV injection (over 10-15 minutes) daily for 3 days

Dose Modification Criteria

- Renal: use with caution
- Hepatic: yes
- Nonhematologic toxicity (mucositis): yes

Adverse Reactions

- CV: CHF and arrhythmia
- DERM: alopecia, radiation recall, and rash
- GI: N/V (moderate), mucositis, abdominal cramps, and diarrhea
- HEMAT: myelosuppression

Comments

- Vesicant.
- Myocardial toxicity is increased in patients with prior anthracycline therapy or heart disease. Cumulative dose limit not established within package literature.
- Consider appropriate prophylaxis for tumor lysis syndrome when treating acute leukemias.
- Embryo-fetal toxicity: idarubicin may cause fetal toxicity when given to a pregnant woman.

IDECABTAGENE VICLEUCEL (ABECMA)

Mechanism of Action

- An autologous CAR-positive T-cell therapy targeting BCMA that is expressed on normal and malignant plasma cells. Antigen-specific activation of idecabtagene vicleucel results in CAR-positive T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

FDA-Approved Indications

- Multiple myeloma (MM): relapsed or refractory MM after four or more prior lines of therapy, including an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody

FDA-Approved Dosage

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion.
- Premedicate with acetaminophen and an H_1 antagonist; avoid prophylactic corticosteroids.
- The recommended dosage range is 300 to 460 × 10^6 CAR-positive viable T cells administered as an IV infusion.

Dose Modification Criteria

- No dose modifications of idecabtagene vicleucel are recommended.
- Hepatic and renal impairment studies were not conducted.

Adverse Reactions

- GI: N/V (not classified), diarrhea, and decreased appetite
- HEMAT: prolonged cytopenias and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- INFUS: hypersensitivity reactions
- NEURO: severe or life-threatening neurologic toxicities, encephalopathy, and headache

- PULM: cough
- OTHER: infections, hypogammaglobulinemia, secondary malignancies, CRS, fatigue, musculoskeletal pain, edema, and pyrexia

Comments

- Idecabtagene vicleucel is only available through a REMS program and should only be administered at a certified healthcare facility.
- Idecabtagene vicleucel is associated with boxed warnings for the following:
  - CRS, including fatal and life-threatening reactions. Confirm availability of tocilizumab prior to infusion and treat severe or life-threatening CRS with tocilizumab +/− corticosteroids.
  - Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.
  - HLH/MAS which is associated with a high mortality rate if not recognized early and treated per institutional standards.
  - Prolonged cytopenias with bleeding and infection, including fatal outcomes.
- Idecabtagene vicleucel may have effects on the ability to drive and use machines. Advise patients to refrain from operating heavy or dangerous machinery for at least 8 weeks after administration.

IDELALISIB (ZYDELIG)

Mechanism of Action

- Inhibitor of PI3Kδ kinase, which is expressed in normal and malignant B cells.

FDA-Approved Indications

- Relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab in patients for whom rituximab alone would be

considered appropriate therapy due to other comorbidities
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) patients who have received at least two prior systemic therapies
- Relapsed small lymphocytic lymphoma (SLL) patients who have received at least two prior systemic therapies

FDA-Approved Dosage

- 150 mg orally twice daily until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (≥15 mL/min): no
- Hepatic: no; limited data available for ALT/AST >2.5 × ULN or bilirubin >1.5 × ULN
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, severe cutaneous reactions
- GI: diarrhea or colitis, intestinal perforation, N/V (minimal-low), abdominal pain
- HEMAT: neutropenia
- HEPAT: ALT/AST elevations
- PULM: cough, pneumonia, and pneumonitis
- OTHER: severe allergic reactions, including anaphylaxis, pyrexia, chills, and fatigue

Comments

- Idelalisib is a substrate of CYP3A4. Avoid concomitant administration with strong CYP3A inducers. Monitor for signs of toxicity if used concurrently with a strong CYP3A inhibitor. Idelalisib is also a strong CYP3A inhibitor and increase drug

exposure of other CYP3A substrates. Screen for potential drug interactions.

- Hepatotoxicity: fatal or serious hepatotoxicity has been reported. Monitor hepatic function prior to and during treatment. Interruption of discontinuation of idelalisib may be necessary.
- Severe diarrhea or colitis may occur and require interruption of discontinuation of therapy.
- Pneumonitis may occur. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interruption of discontinuation of therapy may be necessary.
- Severe cutaneous reactions have been reported, which may require interruption of discontinuation of therapy.
- Monitor for signs or symptoms of infection, which can be serious and/or fatal.
- Embryo-fetal toxicity: idelalisib may cause fetal harm if administered to a pregnant woman.

IFOSFAMIDE (IFEX)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Germ cell testicular cancer (third-line therapy in combination with other agents)

FDA-Approved Dosage

- 1.2 g/m^2 IV daily for 5 days, repeated every 3 weeks. Extensive hydration and mesna should be used to reduce the incidence of hemorrhagic cystitis. Mesna is given either as three IV bolus doses or as an IV dose followed by two oral doses. When

administered as three IV bolus injections, give mesna 20% (wt/wt; 240 mg/m^2/dose for a 1.2 g/m^2 ifosfamide dose) at the time of ifosfamide, and then 4 and 8 hours after ifosfamide. Alternatively, give 20% of the ifosfamide dose as an IV bolus injection at the time of ifosfamide, and then 40% of the ifosfamide dose orally at 2 and 6 hours after ifosfamide.

Dose Modification Criteria

- Renal: unknown
- Hepatic: unknown
- Myelosuppression: yes
- Nonhematologic toxicity (neurotoxicity): yes

Adverse Reactions

- DERM: alopecia
- GI: N/V (moderate)
- GU: hemorrhagic cystitis, Fanconi syndrome (proximal tubular impairment), and glomerular or tubular toxicity
- HEMAT: myelosuppression
- HEPAT: increased LFTs
- NEURO: encephalopathy, somnolence, confusion, depressive psychosis, hallucinations, and dizziness

Comments

- Ensure adequate hydration (at least 2 L or oral or IV hydration per day); administer mesna concurrently; monitor for microscopic hematuria.
- Nephrotoxicity can be severe and result in renal failure.
- Discontinue therapy with the occurrence of neurologic toxicity. The incidence of CNS toxicity may be higher in patients with impaired renal function and/or low serum albumin.
- Cardiotoxicity including arrhythmias and cardiomyopathy has been associated with ifosfamide. Use with caution in patients

with cardiac risk factors or preexisting cardiac disease.
- Interstitial pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity with fatal outcomes can occur. Monitor for signs and symptoms of pulmonary toxicity.
- Ifosfamide is a substrate of CYP3A4 and CYP2B6. Inhibitors or inducers of CYP3A4 will alter the metabolism of ifosfamide and impact efficacy or increase risk of toxicity.
- Embryo-fetal toxicity: ifosfamide may cause fetal toxicity when given to a pregnant woman.

IMATINIB MESYLATE (GLEEVEC)

Mechanism of Action

- Inhibitor of multiple tyrosine kinases including the Bcr-Abl tyrosine kinase, which is created by the Philadelphia chromosome abnormality in CML. Imatinib is also an inhibitor of the RTKs for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events.

FDA-Approved Indications

- Chronic myeloid leukemia (CML):
  - First-line therapy for newly diagnosed adult and pediatric patients with Philadelphia chromosome positive (Ph+) CML in chronic phase
  - Second-line therapy for patients in blast crisis, accelerated phase, or in chronic phase after failure of interferon-α therapy
- Acute lymphoblastic leukemia (ALL):
  - Adult patients with relapsed or refractory Ph+ ALL
  - Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy
- Myelodysplastic/myeloproliferative disease (MDS/MPD): adult patients with MDS/MPD associated with PDGFR gene rearrangement

- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown
- Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL): adult patients who have FIP1L1-PDGFRα fusion kinase and patients who are FIP1L1-PDGFRα infusion kinase negative or unknown
- Dermatofibrosarcoma protuberans (DFSP): adult patients with unresectable, recurrent, and/or metastatic DFSP
- Gastrointestinal stromal tumors (GISTs):
  - Treatment of patients with KIT (CD117)-positive unresectable and/or metastatic malignant GIST
  - Adjuvant treatment of adult patients following resection of KIT (CD17)-positive GIST

FDA-Approved Dosage

- CML:
  - Adult patients, chronic phase: 400 mg orally daily. Doses may be escalated to 600 mg/d as clinically indicated (see package insert for criteria).
  - Adult patients, accelerated phase: 600 mg orally daily. Doses may be escalated to 800 mg/d (400 mg orally twice daily) as clinically indicated (see package insert for criteria).
  - Pediatric patients: 340 mg/m^2 orally daily (NTE 600 mg/d).
- ALL:
  - Adult patients: 600 mg orally daily.
  - Pediatric patients: 340 mg/m^2 orally daily (NTE 600 mg/d).
- MDS/MDP: 400 mg orally daily for adult patients.
- ASM—adult patients with
  - ASM without the D816V c-Kit mutation: 400 mg orally daily.
  - Unknown c-Kit mutation status: 400 mg orally daily may be considered for patients not responding to satisfactorily to other therapies.
  - ASM associated with eosinophilia: starting dose of 100 mg/d is recommended, consider increasing dose from 100 to 400 mg/d in the absence of adverse drug reactions and insufficient response to therapy.
- HES and/or CEL: 400 mg orally daily (adults). For HES/CEL with demonstrated FIP1L1-PDGFRα fusion kinase start with 100 mg/d, may consider increasing dose from 100 to 400 mg/d in the absence of adverse drug reactions and insufficient response to therapy.

- DFSP: 800 mg/d (400 mg orally twice daily).
- GIST—metastatic or unresectable disease: 400 mg orally daily; adjuvant therapy: 400 mg orally daily.
- The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. In children, imatinib can be given as a once-daily dose or divided into two doses (bid).

Dose Modification Criteria

- Renal: yes
- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: superficial edema (periorbital, lower limb), severe fluid retention (pleural effusion, ascites, pulmonary edema, and rapid weight gain), CHF, and left ventricular dysfunction
- DERM: rash and bullous exfoliative dermatologic reactions
- GI: N/V (≤400 mg/d: minimal-low; > 400 mg/d: moderate-high), diarrhea, GI irritation, and dyspepsia
- HEMAT: myelosuppression and hemorrhage
- HEPAT: elevated LFTs and severe hepatotoxicity
- NEURO: headache and dizziness
- PULM: cough
- OTHER: muscle cramps, pain (musculoskeletal, joint, abdominal), myalgia, arthralgia, nasopharyngitis, fatigue, and fever

Comments

- The CYP3A4 enzyme is the major enzyme responsible for the metabolism of imatinib. Be aware of potential drug interactions

with either potent inhibitors or inducers of CYP3A4. Dosage of imatinib should be increased at least 50% and clinical response carefully monitored, in patients receiving imatinib with a potent CYP3A4 inducer such as rifampin or phenytoin.

- Monitor regularly for weight gain and signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema is increased with higher doses of imatinib and older than 65 years.
- Monitor LFTs prior to initiation of imatinib therapy and monthly thereafter or as clinically indicated.
- Monitor CBCs prior to initiation of imatinib therapy, weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (eg, every 2-3 months).
- Embryo-fetal toxicity: imatinib may cause fetal harm when administered to a pregnant woman.

INFIGRATINIB (TRUSELTIQ)

Mechanism of Action

- Small molecular inhibitor of FGFR, primarily FGFR1, FGFR2, and FGFR3. As a result, infigratinib inhibits signaling and decreases cell proliferation in cancer cells with activating FGFR amplifications, mutations, or fusions.

FDA-Approved Indications

- Cholangiocarcinoma: previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, as detected by an FDA-approved test

FDA-Approved Dosage

- 125 mg orally once daily for 21 consecutive days followed by 7 days off (28-day cycle) until disease progression or unacceptable toxicity. Take on an empty stomach at least 1 hour before or 2 hours after food.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-89 mL/min): yes
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild or moderate): yes
- Hepatic (severe): not established
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine
- CV: hypertriglyceridemia
- DERM: nail toxicity, alopecia, PPE, eyelash changes, and dry skin
- ELECTRO: hyperphosphatemia, hypophosphatemia, hypercalcemia, hyponatremia, and hypokalemia
- GI: N/V (not classified), stomatitis, dysgeusia, constipation, diarrhea, abdominal pain, dry mouth, decreased appetite, and increased lipase
- HEMAT: anemia, lymphopenia, thrombocytopenia, and leukopenia
- HEPAT: increased alkaline phosphatase, increased ALT, increased AST, and increased bilirubin
- Ocular system: dry eye, vision blurred, and retinal pigment epithelial detachment
- OTHER: fatigue, arthralgia, hypoalbuminemia, and increased urate

Comments

- Retinal pigment epithelial detachment has been reported. Perform ophthalmic examinations, including optical coherence tomography, prior to starting infigratinib, at 1 month, at 3 months, and then every 3 months thereafter during treatment.
- Hyperphosphatemia may lead to soft-tissue mineralization, cutaneous calcinosis, nonuremic calciphylaxis, vascular calcification, and myocardial calcification. Withhold, dose reduce, or permanently discontinue based on severity.
- Avoid concomitant administration with strong or moderate CYP3A inhibitors and with strong or moderate CYP3A inducers.
- Avoid concomitant administration with gastric acid reducing agents, including PPIs. If coadministration cannot be avoided:
  - Separate administration of infigratinib by 2 hours before or 10 hours after an H_2 antagonist.
  - Separate administration of infigratinib by 2 hours before or after a locally acting antacid.
- Embryo-fetal toxicity: infigratinib may cause fetal harm when administered to a pregnant woman.

INGENOL MEBUTATE (PICATO)

Mechanism of Action

- The mechanism by which ingenol mebutate induces cell death in actinic keratosis lesions is unknown.

FDA-Approved Indications

- Topical treatment of actinic keratosis

FDA-Approved Dosage

- Actinic keratosis on the face and scalp: apply 0.015% gel to the affected area once daily for three consecutive days

- Actinic keratosis on the trunk and extremities: apply 0.05% gel to the affected area once daily for 2 consecutive days
- Not for oral, ophthalmic, or intravaginal use

Dose Modification Criteria

- None

Adverse Reactions

- DERM: application site infection, irritation, pruritus, crusting, erosion/ulceration, erythema, flaking/scaling, swelling, and vesiculation/postulation
- NEURO: headache
- Ocular system: periorbital edema
- OTHER: nasopharyngitis

Comments

- Ingenol mebutate may be applied to the affected area, up to one contiguous skin area of approximately 25 cm^2 using one unit dose tube. After spreading evenly over the treatment area, the gel should be allowed to dry for 15 minutes, and patients should avoid washing and touching the treated area for a period of 6 hours. Following this time, patients may wash the area with a mild soap.
- Administration of ingenol mebutate is not recommended until skin is healed from any previous drug or surgical treatment.
- Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema, can occur after exposure. Patients should wash their hands well after applying ingenol mebutate gel, and avoid transfer of the drug to the periocular area during and after application. If accidental exposure occurs, the area should be flushed with water and the patient should seek medical care as soon as possible.

- Local skin reactions typically occurred within 1 day of treatment initiation, peaked in intensity up to 1 week following completion of treatment, and resolved within 2 weeks for areas treated on the face and scalp, and within 4 weeks for areas treated on the trunk and extremities.

INOTUZUMAB OZOGAMICIN (BESPONSA)

Mechanism of Action

- As a CD22-directed ADC, inotuzumab ozogamicin binds to CD22-expressing tumor cells and undergoes internalization, and then the payload calicheamicin (a cytotoxic agent that induces double-stranded DNA breaks) is released resulting in apoptotic cell death.

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): relapsed or refractory B-cell precursor ALL

FDA-Approved Dosage

- Premedicate with a corticosteroid, antipyretic, and antihistamine before all infusions. Monitor for infusion-related reactions during infusion and for at least 1 hour after infusion ends.
- Dosing regimens for cycle 1 and subsequent cycles depend on response to treatment:

	Day 1	Day 8	Day 15
Dosing regimen for cycle 1			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	21 d (may extend to 28 d if needed)		
Subsequent cycles: patients who achieved a CR or CRi			
Dose	0.5 mg/m^2	0.5 mg/m^2	0.5 mg/m^2

	Day 1	Day 8	Day 15
Cycle length	28 d		
Subsequent cycles: patients who have not achieved a CR or CRi			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 d		

Dose Modification Criteria

- Renal (mild to severe, CrCl 15-89 mL/min): no significant effects on PK
- Hepatic (mild): no significant effects on PK
- Hepatic (moderate or severe, total bilirubin >1.5 × ULN): not established
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- GI: N/V (low) and abdominal pain
- HEMAT: thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, and hemorrhage
- HEPAT: increased transaminases, increased GGT, and increased bilirubin
- INFUS: infusion-related reactions
- NEURO: headache
- OTHER: infection, fatigue, and pyrexia

Comments

- Embryo-fetal toxicity: inotuzumab ozogamicin may cause fetal harm when administered to a pregnant woman.

IPILIMUMAB (YERVOY)

Mechanism of Action

- Human cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation.

FDA-Approved Indications

- Malignant melanoma:
  - Treatment of unresectable or metastatic melanoma in adults and pediatric patients aged 12 years and older.
  - Adjuvant treatment of cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
  - Treatment of unresectable or metastatic melanoma in adults in combination with nivolumab.
- Renal cell cancer (RCC): first-line treatment of patients with intermediate or poor-risk advanced RCC, in combination with nivolumab.
- Metastatic colorectal cancer (mCRC): treatment of adult and pediatric patients aged 12 years and older, in combination with nivolumab, with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Hepatocellular carcinoma (HCC): treatment of patients with HCC, in combination with nivolumab, who have been previously treated with sorafenib.
- Non–small cell lung cancer (NSCLC):
  - First-line treatment of adult patients with metastatic NSCLC, in combination with nivolumab, whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test with no EGFR or ALK genomic tumor aberrations.
  - First-line treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations, in combination with nivolumab and two cycles of platinum-doublet chemotherapy.
- Malignant pleural mesothelioma: first-line treatment of adult patients with unresectable malignant pleural mesothelioma, in combination with nivolumab.

FDA-Approved Dosage

- Malignant melanoma: single-agent therapy
  - Unresectable or metastatic melanoma: 3 mg/kg IV over 90 minutes every 3 weeks for a total of four doses.
  - Adjuvant melanoma: 10 mg/kg IV over 90 minutes every 3 weeks for four doses, followed by 10 mg/kg IV every 12 weeks for up to 3 years or until documented recurrence or unacceptable toxicity.
- Malignant melanoma: 3 mg/kg IV over 90 minutes (in combination with nivolumab 1 mg/kg IV over 30 minutes) every 3 weeks × four doses or until unacceptable toxicity, whichever comes first. After four doses of combined therapy, nivolumab is continued as a single agent until disease progression or unacceptable toxicity.
- RCC: 1 mg/kg IV over 30 minutes (in combination with nivolumab 3 mg/kg IV over 30 minutes) every 3 weeks × four doses. After four doses of combined therapy, nivolumab is continued as a single agent until disease progression or unacceptable toxicity.
- MSI-H or dMMR mCRC: 1 mg/kg IV over 30 minutes (in combination with nivolumab 3 mg/kg IV over 30 minutes) every 3 weeks × four doses. After four doses of combined therapy, nivolumab is continued as a single agent until disease progression or unacceptable toxicity.
- HCC: 3 mg/kg IV over 30 minutes (in combination with nivolumab 1 mg/kg IV over 30 minutes) every 3 weeks × four doses. After four doses of combined therapy, nivolumab is continued as a single agent until disease progression or unacceptable toxicity.
- NSCLC (metastatic disease expressing PD-L1): 1 mg/kg IV over 30 minutes every 6 weeks (in combination with nivolumab 3 mg/kg IV over 30 minutes every 2 weeks) until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
- NSCLC (metastatic or recurrent disease): 1 mg/kg IV over 30 minutes every 6 weeks (in combination with nivolumab 360 mg IV over 30 minutes every 3 weeks) until disease progression, unacceptable toxicity, or up to 2 years in patients with disease

progression. Histology-based platinum-doublet chemotherapy every 3 weeks is administered for two cycles.
- Malignant pleural mesothelioma: 1 mg/kg IV over 30 minutes every 6 weeks (in combination with nivolumab 360 mg IV over 30 minutes every 3 weeks) until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.

Dose Modification Criteria

- Renal: no
- Hepatic (mild): none
- Hepatic (moderate, severe): not studied
- Immune-mediated toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: dermatitis, rash, and pruritus
- ENDO: adrenal insufficiency, hypogonadism, hypophysitis, hypopituitarism, hyperthyroidism, hypothyroidism, thyroiditis, and type 1 diabetes mellitus
- GI: N/V (minimal), enterocolitis, and diarrhea
- HEPAT: elevated LFTs, hyperbilirubinemia, and immune-mediated hepatitis
- NEURO: motor or sensory neuropathy and headache
- PULM: pneumonitis
- OTHER: infusion-related reactions, fatigue, weight loss, and pyrexia

Comments

- Ipilimumab can cause severe and fatal immune-mediated adverse reactions (IMAR) due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system or tissue, including the following immune-

mediated toxicities: colitis, hepatitis, dermatitis (and other dermatologic adverse reactions), endocrinopathies, pneumonitis, and nephritis with renal dysfunction. The majority of these reactions manifest during treatment; however, a minority can occur weeks to months after discontinuation of therapy.

- Monitor patients for signs and symptoms that may be clinical manifestations of IMAR and evaluate clinical chemistries including LFTs, creatinine, adrenocorticotropic hormone level, and thyroid function tests at baseline and before each dose.
- In general, withhold ipilimumab for severe (grade 3) and permanently discontinue ipilimumab for life-threatening (grade 4) IMAR and administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions.
- Severe infusion-related reactions may occur. Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions.
- Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive ipilimumab either before or after allogeneic hematopoietic stem cell transplantation (HSCT).
- Do not shake ipilimumab. Administer the diluted solution through a nonpyrogenic, low protein binding in-line filter.
- Embryo-fetal toxicity: use during pregnancy only if potential benefit justifies risk to fetus. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

IRINOTECAN (CAMPTOSAR)

Mechanism of Action

- Topoisomerase I inhibitor

FDA-Approved Indications

- Metastatic colon or rectal cancer:
  - First-line therapy in combination with FU and leucovorin
  - Second-line therapy (single agent) after FU-based therapy

FDA-Approved Dosage

- First-line combination agent dosing: see product labeling for FU/leucovorin dosing.
  - Regimen 1: 125 mg/m^2 IV over 90 minutes weekly × four doses (days 1, 8, 15, 22) followed by 2 weeks of rest. Repeat every 6 weeks.
  - Regimen 2: 180 mg/m^2 IV over 90 minutes every 2 weeks (days 1, 15, 29) for each cycle. Each cycle is 6 weeks in duration.
- Second-line single-agent dosing:
  - Weekly regimen: 125 mg/m^2 IV over 90 minutes weekly for four doses (days 1, 8, 15, 22) followed by 2 weeks rest. Repeat every 6 weeks, *OR*
  - Once-every-3-weeks regimen: 350 mg/m^2 IV over 90 minutes every 3 weeks.

Dose Modification Criteria

- Renal: no data, use with caution
- Hepatic: yes
- Pelvic/abdominal irradiation: yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes (see package labeling for dose modifications)

Adverse Reactions

- CV: vasodilation
- DERM: alopecia, sweating, and rash
- GI: N/V (moderate), diarrhea (early and late), abdominal pain, mucositis, anorexia, and flatulence
- HEMAT: myelosuppression
- HEPAT: increased bilirubin and LFTs
- NEURO: insomnia and dizziness
- PULM: dyspnea, coughing, and rhinitis

- OTHER: asthenia, fever, and hypersensitivity reactions

Comments

- Can induce both early (within 24 hours of administration) and late forms of diarrhea. The early-onset diarrhea is cholinergic in nature and may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. These early cholinergic symptoms can be treated by administration of atropine. Late-onset diarrhea (generally after 24 hours) should be treated aggressively with high-dose loperamide. Each patient should be instructed to have loperamide readily available so that treatment can be initiated at the earliest onset of diarrhea. See package labeling for dosage recommendations for atropine and loperamide.
- Patients with reduced UGT1A1 activity (homozygous for the UGT1A1*28 allele) are at increased risk of neutropenia with irinotecan.
- Interstitial pulmonary disease–like events, including fatalities, have occurred with irinotecan. Interrupt therapy for new or progressive dyspnea, cough, and fever pending evaluation.
- Embryo-fetal toxicity: irinotecan may cause fetal toxicity when given to a pregnant woman.
- Irinotecan and the active metabolite SN-38 are metabolized through CYP3A4 and UGT1A1. Screen for drug interactions with inhibitors or inducers of CYP3A4 and inhibitors of UGT1A1.

IRINOTECAN LIPOSOME INJECTION (ONIVYDE)

Mechanism of Action

- Topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome.

FDA-Approved Indications

- Metastatic adenocarcinoma of the pancreas in combination with FU and leucovorin after progression following gemcitabine-based therapy

FDA-Approved Dosage

- Administer a corticosteroid and an antiemetic 30 minutes prior to infusion
- 70 mg/m^2 infused over 90 minutes every 2 weeks

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic: limited data, use with caution
- Hematologic or nonhematologic toxicity: yes

Adverse Reactions

- ENDO: hypomagnesemia and hypokalemia
- GI: diarrhea, N/V (moderate), stomatitis, and decreased appetite
- HEMAT: neutropenia, anemia, lymphopenia, and thrombocytopenia
- HEPAT: elevated ALT
- INFUS: hypersensitivity reaction
- PULM: interstitial lung disease
- OTHER: fatigue/asthenia, pyrexia, cholinergic reactions, and hypersensitivity reactions

Comments

- Do not substitute for other drugs containing irinotecan.
- Protect diluted solution from light.
- Patients with reduced UGT1A1 activity (homozygous for the UGT1A1*28 allele) are at increased risk of neutropenia with irinotecan liposome and require dose reduction.
- Avoid the use of strong CYP3A4 inducers and strong CYP3A4 or UGT1A1 inhibitors if possible.
- Severe or life-threatening neutropenia and neutropenic sepsis can occur. Monitor blood cell counts during treatment.
- Severe diarrhea (early and late) may occur as with nonliposomal irinotecan. See comments above with nonliposomal irinotecan regarding diarrhea management.
- Embryo-fetal toxicity: irinotecan liposome may cause fetal harm when administered to a pregnant woman.

ISATUXIMAB (SARCLISA)

Mechanism of Action

- An IgG1 monoclonal antibody that binds CD38 expressed on the surface of hematopoietic and tumor cells, including MM cells. Isatuximab induces apoptosis through ADCC, ADCP, and complement-dependent cytotoxicity (CDC).

FDA-Approved Indications

- Multiple myeloma (MM):
  - In combination with pomalidomide and dexamethasone for the treatment of MM after at least two prior therapies including lenalidomide and a proteosome inhibitor
  - In combination with carfilzomib and dexamethasone for the treatment of relapsed or refractory MM after one to three prior lines of therapy

FDA-Approved Dosage

- Premedicate with dexamethasone, acetaminophen, an H_2 antagonist, and diphenhydramine
- 10 mg/kg as an IV infusion every week for 4 weeks followed by every 2 weeks thereafter until disease progression or unacceptable toxicity

Dose Modification Criteria

- No dose reduction of isatuximab is recommended. Consider dose delays for toxicity.
- Renal (eGFR < 90 mL/min/1.73 m^2): no significant effect on PK
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available

Adverse Reactions

- CV: hypertension
- GI: N/V (low) and diarrhea
- HEMAT: anemia, neutropenia, lymphopenia, and thrombocytopenia
- INFUS: infusion-related reactions
- PULM: pneumonia, dyspnea, bronchitis, and cough
- OTHER: upper respiratory tract infection, fatigue, insomnia, back pain, and second primary malignancies

Comments

- Isatuximab binds to CD38 on red blood cells, resulting in a positive indirect antiglobulin test (Coombs test).
- Isatuximab may be detected on SPEP and immunofixation assays and interfere with clinical monitoring of endogenous M protein.
- Embryo-fetal toxicity: isatuximab may cause fetal harm when administered to a pregnant woman.

IVOSIDENIB (TIBSOVO)

Mechanism of Action

- Small molecule inhibitor of mutant IDH1 variants that results in decreased 2HG levels, reduced blast counts, and increased percentages of mature myeloid cells

FDA-Approved Indications

- Acute myeloid leukemia (AML): treatment of AML with a susceptible IDH1 mutation as detected by an FDA-approved test in
  - Patients with newly diagnosed AML who are aged 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy
  - Adult patients with relapsed or refractory AML

FDA-Approved Dosage

- 500 mg orally once daily with or without food until disease progression or unacceptable toxicity. Avoid a high-fat meal.

Dose Modification Criteria

- Renal (mild or moderate, eGFR ≥ 30 mL/min/1.73 m^2 by MDRD): no
- Renal (severe, eGFR < 30 mL/min/1.73 m^2 by MDRD): no data available
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): no data available
- CYP3A4 inhibitor (strong): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: creatinine increased
- CV: QT prolongation
- DERM: rash
- ELECTRO: hypocalcemia, hyponatremia, hypomagnesemia, hypokalemia, and hypophosphatemia
- GI: N/V (minimal-low), diarrhea, constipation, mucositis, and decreased appetite
- HEMAT: leukocytosis and anemia
- HEPAT: increased AST and increased alkaline phosphatase
- NEURO: Guillain-Barré syndrome
- PULM: dyspnea and cough
- OTHER: fatigue, arthralgia, myalgia, edema, pyrexia, and hyperuricemia

Comments

- Ivosidenib is associated with a boxed warning for differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
- Guillain-Barré syndrome has been reported. Monitor patients for signs and symptoms of new motor and/or sensory findings.
- Avoid concomitant use of QT prolonging medications. If coadministration is necessary, closely monitor patients for increased risk.
- Avoid concomitant administration of strong CYP3A4 inhibitors. If coadministration cannot be avoided, reduce the ivosidenib dose and monitor patients for increased toxicities (eg, QT prolongation).
- Avoid concomitant use of strong CYP3A4 inducers. Sensitive CYP3A4 substrates, including hormonal contraceptives, should also be avoided.

IXABEPILONE (IXEMPRA)

Mechanism of Action

- Microtubule inhibitor

FDA-Approved Indications

- Breast cancer:
  - In combination with capecitabine in patients with metastatic or locally advanced breast cancer after failure of an anthracycline and a taxane.
  - Monotherapy in patients with metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, and a capecitabine.

FDA-Approved Dosage

- 40 mg/m^2 IV over 3 hours every 3 weeks

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia
- GI: N/V (low), stomatitis/mucositis, and diarrhea
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- INFUS: hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- NEURO: peripheral neuropathy
- OTHER: fatigue, asthenia, myalgia/arthralgia, and alopecia

Comments

- Patients should be premedicated approximately 1 hour before the infusion of ixabepilone with an H_1 antagonist (eg, diphenhydramine) and an H_2 antagonist (eg, ranitidine).
- Monitor for peripheral neuropathy. Neuropathy is cumulative, generally reversible, and should be managed by dose adjustment and delays.
- Ixabepilone is metabolized through CYP3A4 isoenzyme. Screen for drug interactions with CYP3A4 inhibitors or inducers. A dose modification is suggested if concomitantly used with a potent CYP3A4 inhibitor.
- Embryo-fetal toxicity: ixabepilone may cause fetal harm when administered to a pregnant woman.

IXAZOMIB (NINLARO)

Mechanism of Action

- Reversible PI

FDA-Approved Indications

- Multiple myeloma in combination with lenalidomide and dexamethasone for patients who have received at least 1 prior therapy

FDA-Approved Dosage

- 4 mg orally once a week on days 1, 8, and 15 of a 28-day cycle in combination with lenalidomide and dexamethasone

Dose Modification Criteria

- Renal (severe, CrCl < 30 mL/min or dialysis): yes
- Hepatic (moderate to severe, total bilirubin >1.5 × ULN): yes
- Hematologic toxicity: yes

- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash
- GI: diarrhea, constipation, and N/V (minimal-low)
- HEMAT: thrombocytopenia and neutropenia
- HEPAT: increased LFTs and hepatotoxicity
- NEURO: peripheral neuropathy
- OTHER: peripheral edema and back pain

Comments

- Avoid concomitant administration with strong CYP3A inducers.
- Embryo-fetal toxicity: ixazomib may cause fetal harm when administered to a pregnant woman.

LAPATINIB (TYKERB)

Mechanism of Action

- TKI of EGFR type I (EGFR/HER1) and HER2/ErbB2

FDA-Approved Indications

- Breast cancer:
  - In combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer who overexpress HER2 and who have received prior therapy, including an anthracycline, a taxane, and a trastuzumab.
  - In combination with letrozole for the treatment of postmenopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

FDA-Approved Dosage

- Breast cancer:

- HER2-positive metastatic breast cancer: 1250 mg orally once daily on days 1 to 21 continuously in combination with capecitabine (dosed on days 1-14) in a repeating 21-day cycle.
- HR-positive, HER2-positive metastatic breast cancer: 1500 mg orally once daily continuously in combination with letrozole.
- Lapatinib should be administered once daily (not in divided doses) at least 1 hour before or 1 hour after the ingestion of food.

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: reduced LVEF and QT prolongation
- DERM: palmar-plantar erythrodysesthesia and rash
- GI: N/V (minimal-low), diarrhea, and stomatitis
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- PULM: interstitial lung disease and pneumonitis
- OTHER: fatigue

Comments

- Product labeling suggests monitoring LVEF at baseline and during therapy. Interrupt therapy for grade 2 or greater reductions in LVEF. Upon recovery, restart at lower dose.
- Monitor patients for interstitial lung disease or pneumonitis. Lapatinib should be discontinued in patients who experience pulmonary symptoms indicative of ≥grade 3 toxicity.
- Severe cutaneous reactions have been reported. Discontinue lapatinib if life-threatening reactions are suspected.
- Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.

- Diarrhea generally occurs early during treatment and can be severe. Early intervention and intervention is critical for the optimal management of diarrhea.
- Lapatinib is metabolized through CYP3A4 isoenzyme. Screen for drug interactions with CYP3A4 inhibitors or inducers. Dose modifications may be necessary if concomitant use is unavoidable with potent inhibitors or inducers.
- Embryo-fetal toxicity: lapatinib may cause fetal harm when administered to a pregnant woman.

LAROTRECTINIB (VITRAKVI)

Mechanism of Action

- Inhibitor of TRKA, TRKB, and TRKC (encoded by the *NTRK* genes). Larotrectinib halts the hyperactivation of downstream signaling pathways that are driven by TRK fusion proteins.

FDA-Approved Indications

- Adult and pediatric patients with solid tumors that:
  - have an NTRK gene fusion without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have progressed following treatment or have no satisfactory alternate therapy.

FDA-Approved Dosage

- Adult and pediatric patients with BSA ≥ 1 m^2: 100 mg orally twice daily
- Pediatric patients with BSA < 1 m^2: 100 mg/m^2 orally twice daily
- All patients: may be taken without regarding to food and treatment should continue until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate or severe, Child-Pugh class B or C): yes
- CYP3A4 inhibitors (strong): yes
- CYP3A4 inducers (strong): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- ELECTRO: hypocalcemia
- GI: N/V (minimal-low), constipation, diarrhea, and abdominal pain
- HEMAT: anemia, neutropenia, leukopenia, and lymphopenia
- HEPAT: hepatotoxicity, increased ALT, increased AST, and increased alkaline phosphatase
- NEURO: dizziness, cognitive impairment, mood disorders, and sleep disturbances
- PULM: cough
- OTHER: musculoskeletal pain, fatigue, hypoalbuminemia, pyrexia, and skeletal fractures

Comments

- Avoid concomitant administration of strong CYP3A4 inhibitors. If coadministration is unavoidable, reduce the larotrectinib dose.
- Avoid concomitant administration of strong CYP3A4 inducers. If coadministration is unavoidable, increase the larotrectinib dose.
- Embryo-fetal toxicity: larotrectinib may cause fetal harm when administered to a pregnant woman.

LENALIDOMIDE (REVLIMID)

Mechanism of Action

- Immunomodulatory agent with antineoplastic and antiangiogenic properties

FDA-Approved Indications

- Myelodysplastic syndrome (MDS): treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
- Multiple myeloma (MM):
  - In combination with dexamethasone in the treatment of adult patients with MM
  - Maintenance therapy in adult patients with MM following auto-HSCT
- Mantle cell lymphoma (MCL): treatment of relapsed or progressive disease after two prior therapies, one of which included bortezomib
- Follicular lymphoma (FL): in combination with a rituximab product in the treatment of adult patients with previously treated FL
- Marginal zone lymphoma (MZL): in combination with a rituximab product in the treatment of adult patients with previously treated MZL

FDA-Approved Dosage

- MDS: 10 mg orally daily
- Multiple myeloma:
  - Combination therapy: 25 mg orally daily on days 1 to 21 of a 28-day treatment cycle in combination with dexamethasone.
  - Maintenance therapy post auto-HSCT: 10 mg orally once daily continuously (days 1 to 28 of repeated 28-day cycles). After three cycles of maintenance therapy, the dose can be increased to 15 mg orally once daily if tolerated.
- MCL: 25 mg orally once daily on days 1 to 21 of a 28-day treatment cycle
- FL or MZL: 20 mg orally once daily on days 1 to 21 of a 28-day treatment cycle for up to 12 cycles of treatment in combination with a rituximab product

Dose Modification Criteria

- Renal: yes
- Hepatic: no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: edema
- DERM: rash, pruritus, and dry skin
- ELECTRO: hypokalemia
- GI: diarrhea, constipation, N/V (minimal-low), abdominal pain, and anorexia
- HEMAT: myelosuppression
- HEPAT: hepatotoxicity
- NEURO: dizziness, headache, insomnia, and tremor
- PULM: dyspnea, cough, and nasopharyngitis
- OTHER: thromboembolic events, fatigue, fever, arthralgia, back or limb pain, muscle cramps, asthenia, hypersensitivity reactions, and tumor lysis syndrome

Comments

- Lenalidomide is only available through a restricted distribution program (Revlimed REMS program). Only prescribers and pharmacists registered with the program are allowed to prescribe and dispense lenalidomide.
- Embryo-fetal toxicity: lenalidomide is an analog of thalidomide, which is a known teratogen. Lenalidomide may cause severe birth defects or death to an unborn baby. Refer to the product labeling for information regarding requirements for pregnancy testing, and patient consent as part of the Revlimid REMS program.
- Myelosuppression (particularly neutropenia and thrombocytopenia) is a common and dose-limiting toxicity.

Monitor blood counts closely as indicated in the product labeling.

- Lenalidomide may cause venous thromboembolic events. There is an increased risk of thrombotic events when lenalidomide is combined with standard chemotherapeutic agents, including dexamethasone. Consider concurrent prophylactic anticoagulation or aspirin treatment.
- Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms have been reported with lenalidomide. Consider interruption of therapy or discontinuation for grade 2 to 3 skin rash and permanently discontinue for grade 4 rash.
- Lenalidomide is not indicated or recommended for the treatment of chronic lymphocytic leukemia (CLL) per product labeling. Serious and fatal cardiac adverse events occurred in CLL patients treated with lenalidomide.
- A higher incidence of second primary malignancies have been observed in multiple myeloma patients treated with lenalidomide.
- Tumor flare reactions have been observed in clinical trials of lenalidomide in CLL and lymphoma.
- Impaired stem cell mobilization: a decrease in the number of $CD34^+$ cells collected after treatment (>4 cycles) with lenalidomide has been reported.

LENVATINIB (LENVIMA)

Mechanism of Action

- RTK inhibitor that inhibits the kinase activity of VEGFR-1, VEGFR-2, and VEGFR-3; FGFR1, FGFR2, FGFR3, and FGFR4; PDGFRα; KIT; and RET.

FDA-Approved Indications

- Differentiated thyroid cancer (DTC): single agent for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC
- Renal cell cancer (RCC): in combination with everolimus, for patients with advanced RCC following one prior antiangiogenic therapy
- Hepatocellular carcinoma (HCC): first-line treatment with unresectable HCC
- Endometrial carcinoma: in combination with pembrolizumab, for patients with advanced disease that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation

FDA-Approved Dosage

- DTC: 24 mg orally once daily
- RCC: 18 mg orally once daily in combination with everolimus 5 mg once daily
- HCC: 12 mg orally once daily for patients with a body weight ≥ 60 kg or 8 mg orally once daily for patients with a body weight < 60 kg
- Endometrial carcinoma: 20 mg orally once daily in combination with pembrolizumab 200 mg IV infusion over 30 minutes every 3 weeks

For all indications, lenvatinib may be continued until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (severe, CrCl <30 mL/min): yes; ESRD not studied
- Hepatic (severe, Child-Pugh class C): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, cardiac dysfunction, arterial thromboembolic events, and QT interval prolongation
- DERM: palmar-plantar erythrodysesthesia and rash
- ELECTRO: hypocalcemia
- ENDO: hypothyroidism
- GI: diarrhea, GI perforation, fistula formation, N/V (moderate-high), stomatitis, constipation, abdominal pain, oral pain, decreased appetite, and dysgeusia
- GU: proteinuria and renal failure/impairment
- HEMAT: hemorrhagic events
- HEPAT: increased LFTs and hepatotoxicity
- NEURO: headache and dizziness
- PULM: dysphonia and cough
- OTHER: fatigue, peripheral edema, arthralgia/myalgia, and pyrexia

Comments

- Hypertension: control BP before starting lenvatinib. Monitor BP after 1 week, then every 2 weeks for the first 2 months, then at least monthly thereafter. Hypertension may require withholding therapy or discontinuation.
- Hepatotoxicity: monitor LFTs before starting lenvatinib. Monitor LFTs every 2 weeks for the first 2 months, then at least monthly thereafter.
- Proteinuria: monitor for proteinuria before starting lenvatinib and periodically throughout therapy.
- Diarrhea may be severe and recurrent. Promptly initiate standard antidiarrheal therapy if needed. Monitor for dehydration and withhold therapy for grade 3 or 4 diarrhea.
- Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported with lenvatinib.
- Lenvatinib may impair wound healing. Withhold therapy for at least 1 week before elective surgery and do not administer for at

least 2 weeks following major surgery and until adequate wound healing.
- Osteonecrosis of the jaw has been reported in patients treated with lenvatinib. Avoid invasive dental procedures, if possible, while taking lenvatinib, particularly in patients at higher risk.
- Patients who cannot swallow capsules whole may dissolve capsules in 1 tablespoon of water or apple juice.
- Embryo-fetal toxicity: lenvatinib may cause fetal harm when administered to a pregnant woman.

LETROZOLE (FEMARA)

Mechanism of Action

- Selective, nonsteroidal aromatase inhibitor

FDA-Approved Indications

- Breast cancer:
  - For adjuvant treatment of postmenopausal women with HR-positive early breast cancer
  - For the extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy
  - First-line and second-line treatment of postmenopausal women with HR-positive or HR-unknown locally advanced or metastatic breast cancer

FDA-Approved Dosage

- 2.5 mg orally daily

Dose Modification Criteria

- Renal (CrCl ≥ 10 mL/min): no
- Hepatic (mild to moderate impairment): no
- Hepatic (severe impairment): yes

Adverse Reactions

- GI: nausea (not classified), constipation, and diarrhea
- NEURO: headache and dizziness
- OTHER: hot flashes, fatigue, somnolence, musculoskeletal pain, arthralgia, increased sweating, hypercholesterolemia, and peripheral edema

Comments

- Letrozole may cause a decrease in BMD and an increase in total cholesterol. Consider monitoring for both parameters.

LEUPROLIDE ACETATE (LUPRON, ELIGARD)

Mechanism of Action

- GnRH or LHRH agonist; chronic administration leads to sustained suppression of pituitary gonadotropins and subsequent suppression of serum testosterone in men and serum estradiol in women.

FDA-Approved Indications

- Palliative treatment of advanced prostate cancer
- Other indications: endometriosis, uterine leiomyomata (fibroids), and central precocious puberty

FDA-Approved Dosage

- Prostate cancer: Lupron—1 mg SC daily; Lupron depot injections: 7.5 mg IM monthly; 22.5 mg IM every 3 months; 30 mg IM every 4 months; 45 mg IM every 6 months; Eligard depot injections: 7.5 mg SC monthly; 22.5 mg SC every 3 months; 30 mg SC every 4 months; 45 mg SC every 6 months

Adverse Reactions

- CV: transient changes in BP (hypo- or hypertension) and QT interval prolongation
- ENDO: hot flashes, gynecomastia, sexual dysfunction, and decreased erections
- GU: erectile dysfunction, lower urinary tract symptoms, and testicular atrophy
- OTHER: tumor flare in the first few weeks of therapy, bone pain, injection site reactions, loss of BMD, osteoporosis, bone fracture, convulsions, and asthenia

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.
- Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs such as leuprolide. Monitor blood glucose.
- An increased risk of cardiovascular disease (myocardial infarction, sudden cardiac death, stroke) has been associated in men receiving GnRH analogs such as leuprolide.
- Because of different release characteristics, a fractional dose of the 3- or 4-month Lupron depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

LISOCABTAGENE MARALEUCEL (BREYANZI)

Mechanism of Action

- An autologous CAR-positive T-cell therapy targeting CD19-expressing cancer cells and normal B cells. Antigen-specific

activation of lisocabtagene maraleucel results in T-cell activation, cytokine secretion, and subsequent cytolytic killing of CD19-expressing cells.

FDA-Approved Indications

- Non-Hodgkin lymphoma (NHL): relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and follicular lymphoma (FL)

FDA-Approved Dosage

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion.
- Premedicate with acetaminophen and an H_1 antagonist; avoid prophylactic corticosteroids.
- The dose is 50 to 110 × 10^6 CAR-positive viable T cells administered as an IV infusion.

Dose Modification Criteria

- No dose modifications of lisocabtagene maraleucel are recommended.
- Hepatic and renal impairment studies were not conducted.

Adverse Reactions

- CV: hypotension and tachycardia
- GI: N/V (not classified), decreased appetite, diarrhea, constipation, and abdominal pain
- HEMAT: prolonged cytopenias
- INFUS: hypersensitivity reactions
- NEURO: severe or life-threatening neurologic toxicities, encephalopathy, and dizziness

- PULM: cough
- OTHER: infections, fatigue, CRS, musculoskeletal pain, edema, hypogammaglobulinemia, and secondary malignancies

Comments

- Lisocabtagene maraleucel is only available through a REMS program and should only be administered at a certified healthcare facility.
- Lisocabtagene maraleucel is associated with boxed warnings for the following:
  - CRS, including fatal and life-threatening reactions. Confirm availability of tocilizumab prior to infusion and treat severe or life-threatening CRS with tocilizumab +/− corticosteroids.
  - Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.
- Lisocabtagene maraleucel may have effects on the ability to drive and use machines. Advise patients to refrain from operating heavy or dangerous machinery for at least 8 weeks after administration.

LOMUSTINE, CCNU (CEENU)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Primary and metastatic brain tumors; Hodgkin disease (second-line therapy in combination with other agents)

FDA-Approved Dosage

- Single-agent therapy: 100 to 130 mg/m^2 as a single oral dose every 6 weeks

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- GI: N/V (moderate-high) and mucositis
- GU: increased BUN and Cr
- HEMAT: severe delayed myelosuppression and cumulative myelosuppression
- HEPAT: increased LFTs
- PULM: pulmonary infiltrates and/or fibrosis (cumulative and usually occurs after 6 months of therapy or a cumulative lifetime dose of 1100 mg/m^2, although it has been reported with total lifetime doses as low as 600 mg)
- OTHER: secondary malignancies

Comments

- A single dose is given every 6 weeks.
- Monitor blood counts at least weekly for 6 weeks after a dose.
- Embryo-fetal toxicity: lomustine may cause fetal harm when administered to a pregnant woman.

LONCASTUXIMAB TESIRINE (ZYNLONTA)

Mechanism of Action

- As a CD19-directed ADC, loncastuximab tesirine binds to CD19 on cells of B-lineage origin, undergoes internalization, and then releases the cytotoxic payload SG3199 (an alkylating agent)

resulting in DNA interstrand cross-links and subsequent cell death.

FDA-Approved Indications

- Non-Hodgkin lymphoma (NHL): relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma

FDA-Approved Dosage

- Premedicate with dexamethasone twice daily for 3 days beginning the day before loncastuximab tesirine.
- 0.15 mg/kg every 3 weeks for two cycles then 0.075 mg/kg every 3 weeks for subsequent cycles.
- Administered as an IV infusion over 30 minutes.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no
- Hepatic (moderate or severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: pericardial effusion
- DERM: rash, cutaneous reactions, and photosensitivity reactions
- ENDO: hyperglycemia
- GI: N/V (not classified)
- HEMAT: thrombocytopenia, neutropenia, and anemia

- HEPAT: increased GGT and transaminase elevation
- PULM: pleural effusion
- OTHER: fatigue, hypoalbuminemia, edema, ascites, musculoskeletal pain, and infections

Comments

- Monitor for the development of pleural effusions, pericardial effusions, ascites, peripheral edema, and general edema. Consider diagnostic imaging when symptoms develop or worsen.
- Embryo-fetal toxicity: loncastuximab tesirine may cause fetal harm when administered to a pregnant woman.

LORLATINIB (LORBRENA)

Mechanism of Action

- Kinase inhibitor targeting ALK and ROS1. Lorlatinib has demonstrated activity against mutant forms of the ALK enzyme.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): ALK-positive metastatic NSCLC, as detected by an FDA-approved test

FDA-Approved Dosage

- 100 mg orally once daily until disease progression or unacceptable toxicity. May take without regard to food.

Dose Modification Criteria

- Renal (mild or moderate): no

- Renal (severe, CrCl 15 to < 30 mL/min): yes
- Hepatic (mild): no
- Hepatic (moderate or severe): not established
- CYP3A inducers (moderate): yes
- CYP3A inducers (strong): contraindicated
- CYP3A inhibitors (strong): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypercholesterolemia, hypertriglyceridemia, atrioventricular block, and hypertension
- ENDO: hyperglycemia
- GI: N/V (minimal-low) and diarrhea
- NEURO: CNS effects (seizures, psychotic effects, changes in cognitive function, mood, speech, metal status, and sleep) and peripheral neuropathy
- PULM: dyspnea, cough, and interstitial lung disease/pneumonitis
- OTHER: edema, weight gain, fatigue, and arthralgias

Comments

- Concomitant use of strong CYP3A inducers with lorlatinib is contraindicated due to risk of serious hepatotoxicity with concurrent use.
- Avoid concomitant use of moderate CYP3A inducers. If coadministration cannot be avoided, increase the lorlatinib dose.
- Avoid concomitant use of strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the lorlatinib dose.
- Concomitant use with fluconazole should be avoided. If coadministration cannot be avoided, reduce the lorlatinib dose.
- Avoid concomitant use with CYP3A or P-gp substrates for which minimal concentration changes may lead to serious therapeutic failures.

- Embryo-fetal toxicity: lorlatinib may cause fetal harm when administered to a pregnant woman.

LURBINECTEDIN (ZEPZELCA)

Mechanism of Action

- An alkylating agent that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix toward the major groove

FDA-Approved Indications

- Small cell lung cancer (SCLC): metastatic SCLC following progression on or after platinum-based chemotherapy

FDA-Approved Dosage

- 3.2 mg/m^2 as an IV infusion over 60 minutes every 21 days

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate to severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine
- ELECTRO: hyponatremia and hypomagnesemia
- ENDO: hyperglycemia

- GI: N/V (moderate), decreased appetite, constipation, and diarrhea
- HEMAT: leukopenia, lymphopenia, anemia, neutropenia, and thrombocytopenia
- HEPAT: hepatotoxicity, increased ALT, and increased AST
- PULM: dyspnea and cough
- OTHER: fatigue, musculoskeletal pain, and hypoalbuminemia

Comments

- Avoid concomitant administration of strong or moderate CYP3A inhibitors or inducers.
- Embryo-fetal toxicity: lurbinectedin may cause fetal harm when administered to a pregnant woman.

MARGETUXIMAB (MARGENZA)

Mechanism of Action

- A chimeric IgG1 monoclonal antibody that binds to the extracellular domain of HER2 resulting in ADCC and NK cell activation

FDA-Approved Indications

- Breast cancer: in combination with chemotherapy for the treatment of HER2-positive breast cancer after two or more prior anti-HER2 regimens, including at least one for metastatic disease

FDA-Approved Dosage

- 15 mg/kg IV infusion every 3 weeks. Administer over 120 minutes for the initial dose then over 30 minutes for subsequent doses.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: left ventricular dysfunction
- DERM: alopecia and PPE
- GI: N/V (not classified), diarrhea, constipation, abdominal pain, and decreased appetite
- INFUS: infusion-related reactions
- NEURO: headache and peripheral neuropathy
- PULM: cough and dyspnea
- OTHER: fatigue/asthenia, pyrexia, arthralgia/myalgia, and extremity pain

Comments

- Margetuximab prescribing information contains a boxed warning for left ventricular dysfunction. Evaluate cardiac function prior to and during treatment and discontinue for a confirmed clinically significant decrease in left ventricular function.
- Margetuximab prescribing information contains a boxed warning for embryo-fetal toxicity. Exposure can result in fetal harm. Advise patients regarding the need for effective contraception and verify the pregnancy status of females prior to treatment initiation.

MECHLORETHAMINE (MUSTARGEN)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Systemic (IV) palliative treatment of bronchogenic carcinoma, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), Hodgkin disease (stages III and IV), lymphosarcoma, malignant effusions, mycosis fungoides, and polycythemia vera
- Palliative treatment of malignant effusions from metastatic carcinoma administered intrapleurally, intraperitoneally, or intrapericardially

FDA-Approved Dosage

- IV administration: consult current literature for dose recommendations. A total dose of 0.4 mg/kg IV × one dose per course *OR* in divided doses of 0.1 to 0.2 mg/kg/d. Dosage should be based on ideal dry body weight.
- MOPP regimen (Hodgkin disease): mechlorethamine 6 mg/m^2 IV × one dose administered on days 1 and 8 of a 28-day cycle (combined with vincristine, prednisone, and procarbazine).
- Intracavitary administration: 0.2 to 0.4 mg/kg for intracavitary injection. Consult current literature for dose and administration technique. The technique and the dose used for the various intracavitary routes (intrapleural, intraperitoneal, and intrapericardial) vary.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: alopecia, phlebitis, tissue damage/necrosis with extravasation, and rash
- GI: N/V (high), metallic taste in mouth, and diarrhea
- HEMAT: myelosuppression
- NEURO: vertigo, tinnitus, and diminished hearing
- OTHER: hyperuricemia, secondary malignancies, infertility, and azoospermia

Comments

- Vesicant
- Embryo-fetal toxicity: mechlorethamine may cause fetal harm when administered to a pregnant woman

MEDROXYPROGESTERONE ACETATE (DEPO-PROVERA)

Mechanism of Action

- Derivative of progesterone

FDA-Approved Indications

- Adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal cancer

FDA-Approved Dosage

- 400 to 1000 mg IM injection × one dose. Doses may be repeated weekly initially; if improvement is noted, the dose may be reduced to maintenance doses as low as 400 mg IM monthly.

Adverse Reactions

- CV: edema, weight gain, and thromboembolic events

- DERM: urticaria, pruritus, rash, acne, alopecia, and hirsutism
- ENDO: breast tenderness and galactorrhea
- GI: nausea (not classified) and cholestatic jaundice
- GU: breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, changes in cervical erosion, and secretions
- NEURO: headache, nervousness, dizziness, and depression
- Ocular system: neuro-ocular lesions (retinal thrombosis, optic neuritis)
- OTHER: hypersensitivity reactions, fever, fatigue, insomnia, somnolence, and injection site reactions

Comments

- The oncology indications only apply to the 400 mg/mL formulation for IM administration.

MEGESTROL (MEGACE AND OTHERS)

Mechanism of Action

- Progestational agent

FDA-Approved Indications

- Palliative therapy of advanced breast cancer and endometrial cancer

FDA-Approved Dosage

- Breast cancer: 40 mg PO QID (four times daily; total daily dose: 160 mg/d)
- Endometrial cancer: 10 mg PO QID to 80 mg PO QID (four times daily; total daily dose: 40 to 320 mg/d)

Adverse Reactions

- CV: deep vein thrombosis
- DERM: alopecia
- ENDO: Cushing-like syndrome, hyperglycemia, glucose intolerance, weight gain, and hot flashes
- GU: vaginal bleeding
- NEURO: mood changes
- OTHER: carpal tunnel syndrome and tumor flare

Comments

- Other indications include cancer and AIDS-related anorexia and cachexia as an appetite stimulant and to promote weight gain. Usual dose range is 160 to 800 mg/d (consult current literature).

MELPHALAN (ALKERAN, EVOMELA)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Multiple myeloma:
  - Palliative treatment of multiple myeloma (oral tablets and injection)
  - For use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma
- Ovarian cancer: palliative treatment of nonresectable epithelial carcinoma of the ovary (oral tablets)

FDA-Approved Dosage

- Multiple myeloma:
  - Oral administration: 6 mg orally daily × 2 to 3 weeks. Wait up to 4 weeks for count recovery, and then a maintenance dose of 2 mg orally daily may be initiated to achieve mild myelosuppression. Refer to package insert and current literature for other dosing regimens.

    - IV administration (if oral therapy not appropriate): 16 mg/m^2 IV over 15 to 20 minutes every 2 weeks × four doses, and then after adequate recovery from toxicity, repeat administration at 4-week intervals. Refer to current literature for other dosing regimens.
    - For conditioning treatment, the recommended dose of melphalan is 100 mg/m^2/d IV over 30 minutes once daily for two consecutive days (days -3 and -2) prior to ASCT (day 0).
- Ovarian cancer: 0.2 mg/kg orally daily × 5 days, repeated every 4 to 5 weeks depending on hematologic tolerance. Refer to current literature for other dosing regimens.

Dose Modification Criteria

- Renal: yes
- Myelosuppression: yes

Adverse Reactions

- DERM: vasculitis, alopecia, and skin ulceration/necrosis at injection site (rare)
- HEMAT: myelosuppression and hemolytic anemia
- GI: N/V (oral: minimal-low; IV < 140 mg/m^2: moderate; IV ≥ 140 mg/m^2: high), diarrhea, mucositis, and anorexia
- HEPAT: increased LFTs
- PULM: pulmonary toxicity (pulmonary fibrosis and interstitial pneumonitis)
- OTHER: hypersensitivity reactions, secondary malignancies, and infertility

Comments

- Oral absorption is highly variable with considerable patient-to-patient variability in systemic availability. Oral dosages may be adjusted based on the basis of blood counts to achieve some level of myelosuppression to assure that potentially therapeutic levels of the drug have been reached.
- High-dose IV regimens of melphalan are utilized in preparative regimens prior to autologous and allogeneic blood and marrow

stem cell transplants. Consult current literature for dosing regimens.
- Embryo-fetal toxicity: melphalan may cause fetal harm when administered to a pregnant woman.

MERCAPTOPURINE (PURINETHOL)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): indicated in the maintenance therapy of ALL as part of a combination regimen

FDA-Approved Dosage

- ALL maintenance therapy: 1.5 to 2.5 mg/kg orally once daily

Dose Modification Criteria

- Renal: yes (consider dose reduction)
- Hepatic: yes (consider dose reduction)
- Myelosuppression: yes

Adverse Reactions

- DERM: rash and alopecia
- GI: anorexia, N/V (minimal-low), and mucositis
- HEMAT: myelosuppression
- HEPAT: hepatotoxicity
- OTHER: TLS

Comments

- Monitor LFTs and bilirubin at weekly intervals initially and then at monthly intervals.
- Usually there is complete cross-resistance with thioguanine.
- Oral mercaptopurine dose should be reduced to 25% to 33% of usual daily dose in patients receiving allopurinol concomitantly.
- Variability in mercaptopurine metabolism may occur in patients due to genetic polymorphisms in the gene for the enzyme thiopurine *S*-methyltransferase (TPMT). TPMT genotyping or phenotyping can identify patients who are homozygous deficient or who have low or intermediate TPMT activity and who would need dose reduction to avoid mercaptopurine toxicity.
- Embryo-fetal toxicity: mercaptopurine may cause fetal harm when administered to a pregnant woman.

METHOTREXATE

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Neoplastic disease indications: gestational tumors (choriocarcinoma, chorioadenoma destruens, hydatidiform mole), acute lymphoblastic leukemia (ALL)-maintenance therapy in combination with other agents and in the prophylaxis of meningeal leukemia, treatment of meningeal leukemia, breast cancer, epidermoid cancers of the head or neck, advanced mycosis fungoides, lung cancers (particularly squamous cell and small cell types), advanced-stage non-Hodgkin lymphoma (NHL), and nonmetastatic osteosarcoma (high-dose therapy followed by leucovorin rescue)
- Other indications: psoriasis (severe, recalcitrant, disabling), rheumatoid arthritis, and polyarticular juvenile idiopathic

arthritis

FDA-Approved Dosage

- Choriocarcinoma and similar trophoblastic diseases: 15 to 30 mg orally or intramuscularly daily × 5 days. Treatment courses are repeated three to five times with rest periods of 1 or more weeks between courses to allow for toxic symptoms to subside. Refer to current literature.
- ALL maintenance therapy (following induction): 15 mg/m^2 orally or intramuscularly twice weekly (total weekly dose of 30 mg/m^2) *OR* 2.5 mg/kg IV every 14 days (in combination with other agents). Refer to current literature for combination regimens for both induction and maintenance regimens in ALL.
- Meningeal leukemia (intrathecal administration): younger than 1 year: 6 mg intrathecally; 1 to younger than 2 years: 8 mg intrathecally; 2 to younger than 3 years: 10 mg intrathecally; older than 3 years: 12 mg intrathecally. Refer to current literature.
- Nonmetastatic osteosarcoma: 12 g/m^2 IV over 4 hours × one dose (with leucovorin rescue, vigorous hydration, and urinary alkalinization) given weekly (weeks 4, 5, 6, and 7 after surgery), and then weeks 11, 12, 15, 16, 29, 30, 44, and 45. Leucovorin doses should be adjusted based on methotrexate concentrations. Methotrexate is generally given with other agents. Refer to current literature.
- Other indications: refer to current literature.

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: alopecia, rash, urticaria, telangiectasia, acne, photosensitivity, and severe dermatologic reactions

- GI: N/V (≤50 mg/m^2: minimal, >50 to <250 mg/m^2: low, ≥250 mg/m^2: moderate), mucositis/stomatitis, and diarrhea
- GU: renal failure (high-dose therapy) and cystitis
- HEMAT: myelosuppression
- HEPAT: increased LFTs and acute and chronic hepatotoxicity
- NEURO: acute chemical arachnoiditis (intrathecal), subacute myelopathy (intrathecal), chronic leukoencephalopathy (intrathecal), acute neurotoxicity, or encephalopathy (high-dose IV therapy)
- PULM: interstitial pneumonitis
- OTHER: fever, malaise, chills, fatigue, teratogenic, and tumor lysis syndrome

Comments

- Clearance reduced in patients with impaired renal function or third space fluid accumulations (eg, ascites and pleural effusions). Methotrexate distributes to third space fluid accumulations with subsequent slow and delayed clearance leading to prolonged terminal plasma half-life and toxicity.
- NSAIDs and acidic drugs inhibit methotrexate clearance. Multiple potential drug interactions; review current literature.
- Use vigorous hydration, urinary alkalinization, and leucovorin rescue with high-dose therapy.
- Use preservative-free product and diluents when administering intrathecally or with high-dose IV regimens.
- Embryo-fetal toxicity: methotrexate is teratogenic and may cause fetal harm when administered to a pregnant woman.

MIDOSTAURIN (RYDAPT)

Mechanism of Action

- Small molecule that inhibits the activity of wild-type FLT3, FLT3 mutant kinases (internal tandem duplications [ITDs] and TKD),

KIT (wild type and D816V), PDGFRA/B, and several members of the protein kinase C family. Midostaurin induces apoptosis in leukemic cells expressing ITD and TKD mutant FLT3 or overexpressing wild-type FLT3 and PDGFR receptors.

FDA-Approved Indications

- Acute myeloid leukemia (AML): newly diagnosed AML that is FLT3 mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
- Aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia

FDA-Approved Dosage

- AML: 50 mg orally twice daily with food on days 8 to 21 of each cycle of induction with cytarabine and daunorubicin or consolidation with high-dose cytarabine
- Other indications: 100 mg orally twice daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild or moderate): no significant effect on PK
- Hepatic (severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: petechiae

- ENDO: hyperglycemia
- GI: N/V (moderate-high), mucositis, diarrhea, constipation, and abdominal pain
- HEMAT: febrile neutropenia
- NEURO: headache
- PULM: interstitial lung disease/pneumonitis and dyspnea
- OTHER: musculoskeletal pain, epistaxis, upper respiratory tract infection, device-related infection, edema, fatigue, and pyrexia

Comments

- Strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites. Consider alternative therapies or monitor for increased risk of adverse reactions.
- Avoid concomitant administration of strong CYP3A4 inducers.
- Embryo-fetal toxicity: midostaurin may cause fetal harm when administered to a pregnant woman.

MITOMYCIN (MUTAMYCIN, JELMYTO)

Mechanism of Action

- Induces DNA cross-links through alkylation; inhibits DNA and RNA synthesis.

FDA-Approved Indications

- Disseminated gastric cancer or pancreatic cancer (in combination with other agents and as palliative treatment when other modalities have failed) (Mutamycin and generics only)
- Urothelial cancer: treatment of adult patients with low-grade upper tract urothelial cancer (Jelmyto only)

FDA-Approved Dosage

- Gastric cancer and pancreatic cancer:
  - Single-agent therapy: 20 mg/m^2 IV × one dose repeated every 6 to 8 weeks.
  - Refer to current literature for alternative dosing regimens and combination regimens.
- Upper tract urothelial cancer (Jelmyto): pyelocalyceal instillation with 4 mg/mL via ureteral catheter or a nephrostomy tube, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). Pyelocalyceal installation doses of mitomycin (Jelmyto) are repeated once weekly for 6 weeks. For patients with a complete response at 3 months, doses may be administered once monthly for a maximum of 11 additional installations.

Dose Modification Criteria

- Renal: yes
- Myelosuppression: yes

Adverse Reactions

- CV: congestive heart failure (patients with prior doxorubicin exposure)
- DERM: alopecia, pruritus, and tissue damage/necrosis with extravasation
- GI: anorexia, N/V (low), mucositis, and diarrhea
- GU: hemolytic uremic syndrome and increased Cr
- HEMAT: myelosuppression (may be cumulative)
- PULM: nonproductive cough, dyspnea, and interstitial pneumonia
- OTHER: fever, malaise, and weakness

Comments

- Vesicant.
- Alternative routes of administration for mitomycin injection include intravesical instillation (bladder cancer), intracavitary

administration for malignant pleural or pericardial administration, and topical application (adjunct for glaucoma filtration surgery). See primary literature for more information.

- The Jelmyto brand of mitomycin is for pyelocalyceal use only. It is not for IV use, topical use, or oral administration. The dose formulation is prepared under chilled conditions with a gel diluent that results in a viscous liquid for installation (pyelocalyceal solution). Prior to every installation, patients should take 1.3 g of sodium bicarbonate orally, the evening prior to, the morning of, and 30 minutes prior to the installation procedure (total of 3.9 g).

MITOTANE (LYSODREN)

Mechanism of Action

- Adrenal cytotoxic agent

FDA-Approved Indications

- Inoperable, functional, and nonfunctional adrenal cortical carcinoma

FDA-Approved Dosage

- Initial dose: 2 to 6 g orally per day in three to four divided doses. Increase dose incrementally to achieve a blood concentration of 14 to 20 mg/L, or as tolerated.

Adverse Reactions

- DERM: transient skin rashes
- GI: anorexia, N/V (moderate-high), and diarrhea
- NEURO: vertigo, depression, lethargy, somnolence, and dizziness

- OTHER: adrenal insufficiency

Comments

- Institute adrenal insufficiency precautions. In patients taking mitotane, adrenal crisis occurs in the setting of shock or severe trauma and response to shock is impaired.
- Patients should be counseled regarding the common CNS side effects and ambulatory patients should be cautioned about driving, operating machinery, and other hazardous pursuits requiring mental and physical alertness. Plasma concentrations greater than 20 mg/L (µg/mL) are associated with a greater incidence of CNS toxicity.
- Mitotane is a strong inducer of CYP3A4. Screen patients for potential drug interactions with medications that are substrates of CYP3A4.
- Embryo-fetal toxicity: mitotane may cause fetal harm when administered to a pregnant woman.

MITOXANTRONE (NOVANTRONE)

Mechanism of Action

- Interacts with DNA; intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Acute nonlymphocytic leukemia (ANLL) (including myelogenous, promyelocytic, monocytic, and erythroid leukemias): initial therapy in combination with other agents
- Advanced hormone-refractory prostate cancer (in combination with corticosteroids)
- Other indications: multiple sclerosis

FDA-Approved Dosage

- ANLL: induction, 12 mg/m^2 IV daily × 3 days (days 1, 2, and 3) in combination with cytarabine; consolidation, 12 mg/m^2 IV daily × 2 days (days 1 and 2) in combination with cytarabine
- Prostate cancer: 12 to 14 mg/m^2 IV × one dose every 21 days with prednisone or hydrocortisone

Dose Modification Criteria

- Renal: no data, unknown
- Hepatic: yes (use with caution; consider dose adjustment)

Adverse Reactions

- CV: CHF (clinical risk increases after a lifetime cumulative dose of 140 mg/m^2), tachycardia, ECG changes, and chest pain
- DERM: rash, alopecia, urticaria, and nail bed changes
- GI: N/V (low), mucositis, constipation, and anorexia
- HEMAT: myelosuppression
- HEPAT: increased LFTs
- PULM: dyspnea
- OTHER: bluish-green urine, sclera may turn bluish, phlebitis (irritant), fatigue, secondary leukemias, and tumor lysis syndrome

Comments

- Consider appropriate prophylaxis for tumor lysis syndrome when treating acute leukemias.
- Mitoxantrone may increase the risk of secondary malignancies such as leukemias.
- Embryo-fetal toxicity: mitoxantrone may cause fetal harm when administered to a pregnant woman.

MOGAMULIZUMAB (POTELIGEO)

Mechanism of Action

- Recombinant humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4)–expressing cells resulting in antibody-dependent cellular cytotoxicity. CCR4 is expressed on the surface of some T-cell malignancies.

FDA-Approved Indications

- Mycosis fungoides (MF) or Sézary syndrome (SS): treatment of adult patients with relapsed or refractory MF or SS after at least one prior therapy.

FDA-Approved Dosage

- 1 mg/kg IV infusion over at least 60 minutes on days 1, 8, 15, and 22 of a 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate): no
- Hepatic (severe): no data
- Non-hematologic toxicity: yes (holding parameters)

Adverse Reactions

- CV: hypertension
- DERM: rash, dermatitis, and severe dermatologic toxicities
- GI: N/V (low), diarrhea, constipation, and mucositis
- HEMAT: anemia and thrombocytopenia
- NEURO: headache

- PULM: cough
- OTHER: infusion reactions, infection, fatigue, pyrexia, musculoskeletal pain, and edema

Comments

- Dermatologic toxicity: fatal and life-threatening skin adverse reactions, including Stevens-Johnson syndrome (SJS and toxic epidermal necrolysis (TEN), have occurred in patients treated with mogamulizumab. Rash (drug eruption) is a common toxicity. Monitor for rash and consider topical corticosteroids for grade 1 rash and interrupt therapy for grade 2 or 3 rash and administer corticosteroids for at least 2 weeks. Permanently discontinue therapy for grade 4 rash.
- Infusion reactions: fatal and life-threatening infusion reactions have been reported. Consider premedication (eg, acetaminophen and diphenhydramine) for the first infusion in all patients. Monitor patients closely for signs and symptoms of infusion reactions and interrupt infusion for any grade reaction and treat promptly.
- Autoimmune complications have been reported and may require interruption or discontinuation of therapy.
- Increased risk of transplant complications including severe graft-versus-host disease and transplant-related death have been reported in patients who receive allogeneic HSCT after mogamulizumab.
- Embryo-fetal toxicity: mogamulizumab may cause fetal harm when administered to a pregnant woman.

MOXETUMOMAB PASUDOTOX (LUMOXITI)

Mechanism of Action

- Binds CD22 on the cell surface of B cells then is internalized resulting in ADP-ribosylation of elongation factor 2, inhibition

of protein synthesis, and apoptotic cell death. Moxetumomab pasudotox is a murine immunoglobulin fused to *Pseudomonas* exotoxin.

FDA-Approved Indications

- Hairy cell leukemia (HCL): relapsed or refractory HCL following at least two prior systemic therapies, including treatment with a purine nucleoside analog

FDA-Approved Dosage

- Supportive care:
  - Premedicate with acetaminophen, antihistamine, and H_2 antagonist prior to all infusions.
  - Maintain adequate hydration throughout treatment.
  - Consider low-dose aspirin on days 1 to 8 of each 28-day cycle.
- 0.04 mg/kg as an IV infusion over 30 minutes on days 1, 3, and 5 of each 28-day cycle

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): avoid use
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): not established

Adverse Reactions

- Cr: creatinine increased
- ELECTRO: hypocalcemia and hypophosphatemia
- GI: N/V (low), constipation, and diarrhea
- HEMAT: anemia
- HEPAT: increased ALT and increased AST
- INFUS: infusion-related reactions
- NEURO: headache

- OTHER: edema, fatigue, pyrexia, and hypoalbuminemia

Comments

- Embryo-fetal risk: moxetumomab pasudotox may cause fetal harm when administered to a pregnant woman.

NAXITAMAB (DANYELZA)

Mechanism of Action

- Binds to the glycolipid GD2, which is expressed on neuroblastoma cells and normal cells of neuroectodermal origin. The binding of the naxitamab monoclonal antibody to cell surface GD2 induces cell lysis through ADCC and CDC.

FDA-Approved Indications

- Neuroblastoma: in combination with GM-CSF for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy

FDA-Approved Dosage

- Supportive care:
  - Five days prior to the first naxitamab infusion in each cycle, initiate a 12-day course (days -4 through day 7) of prophylactic medication for neuropathic pain (eg, gabapentin).
  - Administer oral opioids 45 to 60 minutes prior to each infusion and additional opioids as needed for breakthrough pain.
- Additional premedications:
  - Corticosteroids (eg, methylprednisolone 2 mg/kg, maximum 80 mg) 30 minutes to 2 hours prior to the first infusion and then prior to subsequent infusions if a severe infusion reaction occurred.

    - Administer an antihistamine, an H_2 antagonist, acetaminophen, and an antiemetic 30 minutes prior to each infusion.
- 3 mg/kg/d (up to 150 mg/d) as an IV infusion on days 1, 3, and 5 of each treatment cycle.
- Administer the first infusion over 60 minutes and subsequent infusions over 30 to 60 minutes, as tolerated. Observe patients for a minimum of 2 hours following each infusion.
- Treatment cycles are repeated every 4 weeks until complete or partial response, followed by five additional cycles every 4 weeks. Subsequent cycles are repeated every 8 weeks.

Dose Modification Criteria

- Renal: no data available
- Hepatic: no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: tachycardia and hypertension
- DERM: erythema multiforme, urticaria, and injection site reaction
- ELECTRO: hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia
- ENDO: hypoglycemia
- GI: N/V (not classified), diarrhea, and decreased appetite
- HEMAT: lymphocytopenia, neutropenia, anemia, and thrombocytopenia
- HEPAT: increased ALT
- INFUS: serious infusion-related reactions
- NEURO: pain, headache, and other neurotoxicities (peripheral neuropathy, neurological disorders of the eye, prolonged urinary retention)
- PULM: cough
- OTHER: fatigue, pyrexia, edema, anxiety, irritability, and hypoalbuminemia

Comments

- Naxitamab includes a boxed warning for severe infusion-related reactions including cardiac arrest, anaphylaxis, hypotension, bronchospasm, and stridor. Premedicate and reduce rate, interrupt infusion, or discontinue naxitamab based on severity.
- Naxitamab includes a boxed warning for severe neurotoxicity including severe neuropathic pain, transverse myelitis, and

RPLS. Premedicate and treat neuropathic pain as outlined above.
- Monitor for hypertension during and after the infusion and withhold, reduce infusion rate, or discontinue based on severity.
- Embryo-fetal toxicity: naxitamab may cause fetal harm when administered to a pregnant woman.

NECITUMUMAB (PORTRAZZA)

Mechanism of Action

- Recombinant human IgG1 monoclonal antibody that binds to human EGFR and blocks the binding of EGFR to its ligand

FDA-Approved Indications

- Squamous non–small cell lung cancer (NSCLC): first-line treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin

FDA-Approved Dosage

- 800 mg by IV infusion over 60 minutes on days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate): no
- Hepatic (severe): no data available
- Nonhematologic toxicity (dermatologic): yes

Adverse Reactions

- DERM: rash, dermatitis acneiform, acne, dry skin, and pruritus

- ELECTRO: hypomagnesemia, hypokalemia, hypocalcemia, and hypophosphatemia
- INFUS: infusion-related reactions (usually occurs during first or second infusion)

Comments

- Necitumumab is not indicated for the treatment of nonsquamous NSCLC.
- Infusion-related reactions may require rate reductions or interruptions in infusion. Patients who experience a grade 1 or 2 infusion-related reaction should receive diphenhydramine prior to subsequent infusions. Patients who experience a second infusion reaction should receive diphenhydramine, acetaminophen, and dexamethasone prior to future infusions.
- Cardiopulmonary arrest and/or sudden death has been reported in patients treated with necitumumab in combination with gemcitabine and cisplatin. Closely monitor serum electrolytes including serum magnesium, potassium, and calcium with aggressive replacement when warranted.
- Venous and arterial thromboembolic events may occur while on therapy.
- Embryo-fetal toxicity: necitumumab may cause fetal harm when administered to a pregnant woman.

NELARABINE (ARRANON)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- T-cell acute lymphoblastic leukemia (ALL) and T-cell lymphoblastic lymphoma: in adult and pediatric patients (age

1 year and older) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens

FDA-Approved Dosage

- Adult: 1500 mg/m^2 IV infusion over 2 hours on days 1, 3, and 5 repeated every 21 days
- Pediatric: 650 mg/m^2 IV infusion over 1 hour daily for 5 consecutive days repeated every 21 days

Dose Modification Criteria

- Renal: unknown, use with caution in patients with moderate or severe renal impairment
- Hepatic: unknown, use with caution in patients with severe hepatic impairment
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (low), diarrhea, and constipation
- HEMAT: myelosuppression
- HEPAT: increased LFTs
- NEURO: neurotoxicity (see comments), somnolence, dizziness, headache, and peripheral neuropathy
- PULM: cough, dyspnea, and pleural effusion
- OTHER: tumor lysis syndrome, fever, asthenia, fatigue, edema, and myalgia/arthralgia

Comments

- Neurotoxicity is the dose-limiting toxicity of nelarabine. Common signs of nelarabine-induced neurotoxicity include somnolence, confusion, convulsions, ataxia, paresthesias, and

hypoesthesia. Severe neurologic toxicity can manifest as coma, status epilepticus, craniospinal demyelination, or ascending neuropathy similar in presentation to Guillain-Barré syndrome. Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation may be at increased risk for neurologic adverse events.

- Appropriate prevention measures for tumor lysis syndrome (eg, IV hydration, urinary alkalization, and allopurinol) should be initiated prior to nelarabine therapy for patients considered to be at risk.
- Embryo-fetal toxicity: nelarabine may cause fetal harm when administered to a pregnant woman.

NERATINIB (NERLYNX)

Mechanism of Action

- Kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4, resulting in the inhibition of downstream MAPK and AKT signaling and cell proliferation

FDA-Approved Indications

- Breast cancer:
  - Monotherapy for the extended adjuvant treatment of early-stage HER2-positive breast cancer following adjuvant trastuzumab-based therapy
  - In combination with capecitabine for the treatment of advanced or metastatic HER2-positive breast cancer after two or more prior anti–HER2-based regimens in the metastatic setting

FDA-Approved Dosage

- Extended adjuvant treatment: 240 mg orally once daily with food continuously until disease recurrence for up to 1 year
- Advanced or metastatic treatment: 240 mg orally once daily with food on days 1 to 21 of a 21-day cycle (in combination with

capecitabine) until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: not established
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: renal impairment
- DERM: rash, nail disorder, and dry skin
- GI: N/V (minimal-low), diarrhea, constipation, abdominal pain, stomatitis, decreased appetite, and dyspepsia
- GU: urinary tract infection
- HEPAT: hepatotoxicity, increased ALT, and increased AST
- NEURO: dizziness
- OTHER: upper respiratory tract infection, fatigue/asthenia, muscle spasms, abdominal distension, epistaxis, weight decreased, back pain, and arthralgias

Comments

- Diarrhea should be managed through either neratinib dose escalation or loperamide prophylaxis. If diarrhea occurs, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold or discontinue with severe or persistent diarrhea.
- Avoid concomitant use of the following medications: strong CYP3A4 inhibitors; dual P-gp and moderate CYP3A4 inhibitors; and strong or moderate CYP3A4 inducers.
- Monitor for adverse reactions of P-gp substrates for which a minimal concentration change may lead to serious adverse reactions when given concurrently with neratinib.

- Avoid concomitant administration of PPIs. Alternately, administer neratinib 3 hours after locally acting antacids or at least 2 hours before or 10 hours after an H_2 antagonist.
- Embryo-fetal toxicity: neratinib may cause fetal harm when administered to a pregnant woman.

NILOTINIB (TASIGNA)

Mechanism of Action

- TKI (Bcr-Abl, PDGFR, and c-KIT)

FDA-Approved Indications

- Chronic myeloid leukemia (CML):
  - Initial therapy in newly diagnosed adult and pediatric patients (age 1 year and older) with Philadelphia chromosome positive (Ph+) CML in chronic phase (CML-CP)
  - Treatment of chronic-phase and accelerated-phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib
  - Treatment of pediatric patients (age 1 year and older) with Ph+ CML-CP with resistance or intolerance to prior TKI therapy

FDA-Approved Dosage

- CML, adult patients: newly diagnosed Ph+ CML-CP: 300 mg orally twice daily; resistant or intolerant Ph+ CML-CP or AP: 400 mg orally twice daily
- CML, pediatric patients: newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP: 230 mg/m^2 orally twice daily rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg)

Nilotinib should be taken approximately 12 hours apart on an empty stomach (no food 2 hours before and 1 hour after taking dose).

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: rash and pruritus
- ELECTRO: hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia
- GI: N/V (minimal-low), constipation, and diarrhea
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- NEURO: headache
- PULM: cough and dyspnea
- OTHER: fatigue, pancreatitis and elevated lipase, fever, asthenia, peripheral edema, fluid retention (eg, pleural or pericardial effusions), arthralgia/myalgia, nasopharyngitis, pyrexia, night sweats, and tumor lysis syndrome

Comments

- Myelosuppression common. Monitor CBC every 2 weeks for the first 2 months of therapy and at least monthly thereafter, or as clinically indicated.
- Correct electrolyte abnormalities (eg, hypokalemia and hypomagnesemia) prior to initiating therapy and monitor periodically during therapy. Obtain an ECG at baseline, 7 days after initiation, and periodically as clinically indicated. Do not use nilotinib concomitantly with other agents that cause QT prolongation. Sudden deaths have been reported in patients treated with nilotinib.

- Cardiac and arterial vascular occlusive events have been associated with patients treated with nilotinib. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during nilotinib therapy.
- Nilotinib is metabolized through the CYP3A4 isoenzyme. Screen for potential drug interactions with CYP3A4 inhibitors or inducers. Dose modification may be necessary if concomitant use with a potent CYP3A4 inducer or inhibitor cannot be avoided. In addition, nilotinib is a competitive inhibitor and inducer of multiple CYP isoenzymes and P-gp, and subsequently may either increase or decrease concentrations of concomitant medications. Refer to product labeling for additional information.
- Embryo-fetal toxicity: nilotinib may cause fetal harm when administered to a pregnant woman.

NILUTAMIDE (NILANDRON)

Mechanism of Action

- Antiandrogen

FDA-Approved Indications

- Metastatic prostate cancer (stage D2; in combination therapy with surgical castration). Dosing should begin on same day or day after surgical castration.

FDA-Approved Dosage

- Give 300 mg orally daily × 30 days, and then 150 mg orally daily (with or without food)

Adverse Reactions

- CV: hypertension and angina
- ENDO: hot flashes, impotence, and decreased libido
- GI: nausea (not classified), anorexia, and constipation
- HEPAT: increased LFTs (monitor LFTs periodically because of rare associations with cholestatic jaundice, hepatic necrosis, and encephalopathy)
- NEURO: dizziness
- Ocular system: visual disturbances and impaired adaptation to dark
- PULM: interstitial pneumonitis and dyspnea

Comments

- Obtain baseline chest x-ray prior to initiating therapy (with consideration of baseline pulmonary function tests). Patients should be instructed to report any new or worsening shortness of breath, and if symptoms occur, nilutamide should be immediately discontinued.
- Monitor LFTs at baseline and at regular intervals × 4 months and then periodically thereafter.

NIRAPARIB (ZEJULA)

Mechanism of Action

- Inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair

FDA-Approved Indications

- Ovarian cancer:
  - Maintenance treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer after achieving a complete or partial response to first-line platinum-based chemotherapy
  - Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after achieving a complete or partial response to

platinum-based chemotherapy
- Advanced ovarian, fallopian tube, or primary peritoneal cancer after treatment with three or more prior chemotherapy regimens and with homologous recombination deficiency (HRD)–positive status defined by either
  - a deleterious or suspected deleterious BRCA mutation OR
  - genomic instability with progression >6 months after response to the last platinum-based chemotherapy

FDA-Approved Dosage

- First-line maintenance of advanced ovarian cancer:
  - For patients weighing <77 kg OR with platelets <150,000/μL, the recommended dosage is 200 mg orally once daily
  - For patients weighing ≥77 kg AND platelets ≥150,000/μL, the recommended dosage is 300 mg orally once daily
- Other indications: 300 mg orally once daily
- All indications: may be taken without regard to food. Continue treatment until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30): no data available
- Hepatic (mild): no
- Hepatic (moderate): yes
- Hepatic (severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: acute kidney injury
- CV: hypertension
- DERM: rash
- ELECTRO: hypomagnesemia
- GI: N/V (moderate-high), constipation, diarrhea, abdominal pain, and decreased appetite
- GU: urinary tract infection

- HEMAT: thrombocytopenia, anemia, neutropenia, leukopenia, and MDS/AML
- NEURO: PRES, headache, and dizziness
- PULM: dyspnea and cough
- OTHER: fatigue, musculoskeletal pain, and insomnia

Comments

- MDS/AML, including cases with fatal outcomes, has been reported in patients receiving niraparib after a duration of therapy ranging from 0.5 months to 4.9 years. Monitor for hematological toxicity.
- Niraparib capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in susceptible persons.
- Embryo-fetal toxicity: niraparib may cause fetal harm when administered to a pregnant woman.

NIVOLUMAB (OPDIVO)

Mechanism of Action

- Human monoclonal antibody that binds to PD-1 receptors, blocking the binding of PD-1 ligands

FDA-Approved Indications

- Melanoma:
  - Unresectable or metastatic melanoma as a single agent or in combination with ipilimumab.
  - Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- Non–small cell lung cancer (NSCLC), metastatic:
  - In combination with ipilimumab for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic aberrations.
  - In combination with ipilimumab and two cycles of platinum-doublet chemotherapy for the first-line treatment of adult patients with metastatic or

recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.
    - Single-agent therapy for metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have progressed on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- Malignant pleural mesothelioma: first-line treatment of adult patients with unresectable malignant pleural mesothelioma in combination with ipilimumab.
- Advanced renal cell carcinoma (RCC):
    - In combination with ipilimumab for the first-line treatment of patients with intermediate or poor-risk advanced RCC.
    - In combination with cabozantinib for the first-line treatment of patients with advanced RCC.
    - Single-agent therapy for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy.
- Classical Hodgkin lymphoma (cHL): treatment of adult patients with cHL that has relapsed or progressed after:
    - auto-HSCT and posttransplant brentuximab vedotin, or
    - three or more lines of systemic therapy that includes auto-HSCT.
- Squamous cell carcinoma of the head and neck (SCCHN): treatment of patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- Urothelial carcinoma: treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC): single agent or in combination with ipilimumab for the treatment of adult and pediatric patients 12 years and older with MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Hepatocellular carcinoma (HCC): single agent or in combination with ipilimumab for the treatment of patients with HCC who have been previously treated with sorafenib.
- Esophageal cancer:
    - Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant CRT.

    - Treatment of patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma: in combination with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

FDA-Approved Dosage

Single-Agent Therapy

- Unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, cHL, SCCHN, urothelial carcinoma, HCC, ESCC: 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity.
- Adjuvant treatment of melanoma: 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year.
- MSI-H or dMMR mCRC:
    - Adult patients and pediatric patients aged 12 years and older and weighing 40 kg or more: 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity.
    - Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg IV infusion over 30 minutes every 2 weeks until disease progression or unacceptable toxicity.
- Adjuvant treatment of resected esophageal or GEJ cancer: 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity for a total treatment duration of 1 year.

Combination Therapy

- Unresectable or metastatic melanoma: 1 mg/kg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 3 mg/kg IV infusion over 90 minutes) for four doses or until unacceptable toxicity whichever occurs earlier, followed by single agent nivolumab 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity.
- Metastatic NSCLC expressing PD-L1: 3 mg/kg IV infusion over 30 minutes every 2 weeks (in combination with ipilimumab 1 mg/kg IV infusion over 30 minutes every 6 weeks) until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
- Metastatic or recurrent NSCLC: 360 mg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 1 mg/kg IV infusion over 30 minutes every 6 weeks and two cycles of histology-based platinum doublet chemotherapy every 3 weeks). Nivolumab and ipilimumab may be continued until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
- Malignant pleural mesothelioma: 360 mg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 1 mg/kg IV infusion over 30 minutes every 6 weeks) until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
- Advanced RCC:
    - 3 mg/kg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 1 mg/kg IV infusion over 30 minutes) for four doses followed by single-agent nivolumab 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity.
    - 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks (in combination with cabozantinib 40 mg orally once daily) until disease progression or unacceptable toxicity or up to 2 years of nivolumab.
- MSI-H or dMMR mCRC: 3 mg/kg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 1 mg/kg IV infusion over 30 minutes) for four doses followed by single-agent nivolumab 240 mg IV infusion over 30 minutes every

2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity. For pediatric patients aged 12 and older and weighing less than 40 kg, single-agent nivolumab is dosed at 3 mg/kg IV infusion over 30 minutes every 2 weeks.

- HCC: 1 mg/kg IV infusion over 30 minutes every 3 weeks (in combination with ipilimumab 3 mg/kg IV infusion over 30 minutes) for four doses followed by single-agent nivolumab 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks until disease progression or unacceptable toxicity.
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma:
  - 240 mg IV infusion over 30 minutes every 2 weeks (in combination with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks) OR
  - 360 mg IV infusion over 30 minutes every 3 weeks (in combination with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks).
  - Continue until disease progression or unacceptable toxicity or up to 2 years.
- When sequencing nivolumab combination therapy administered on the same day: in combination with ipilimumab, administer nivolumab first followed by ipilimumab. In combination with ipilimumab and platinum-doublet chemotherapy, administer nivolumab first followed by ipilimumab followed by chemotherapy. In combination with fluoropyrimidine- and/or platinum-containing chemotherapy, administer nivolumab prior to chemotherapy.

Dose Modification Criteria

- Renal: no.
- Hepatic (mild or moderate): no.
- Hepatic (severe): has not been studied.
- Doses should be held, not reduced due to toxicities. See package insert for specific recommendations regarding holding doses and starting corticosteroids.

Adverse Reactions

- DERM: rash, pruritus, and immune-mediated dermatologic toxicities
- ELECTRO: hyponatremia and hyperkalemia
- ENDO: immune-mediated endocrinopathies (hypophysitis, adrenal insufficiency, hypo/hyperthyroidism, and type 1 diabetes mellitus)
- GI: immune-mediated colitis, N/V (minimal), diarrhea, and constipation
- GU: immune-mediated nephritis and renal dysfunction
- HEPAT: immune-mediated hepatitis and increased LFTs
- INFUS: infusion-related reactions
- NEURO: immune-mediated encephalitis
- PULM: immune-mediated pneumonitis, cough, and dyspnea
- OTHER: arthralgia, musculoskeletal pain, fatigue, asthenia, and pyrexia

Comments

- Nivolumab can cause severe and fatal immune-mediated adverse reactions (IMAR) due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system or tissue, including the following immune-mediated toxicities: colitis, hepatitis, dermatitis (and other dermatologic adverse reactions), endocrinopathies, pneumonitis, and nephritis with renal dysfunction. The majority of these reactions manifest during treatment; however, a minority can occur weeks to months after discontinuation of therapy.
- Monitor patients for signs and symptoms that may be clinical manifestations of IMAR and evaluate clinical chemistries including LFTs, creatinine, and thyroid function tests at baseline and periodically during treatment.
- In general, withhold nivolumab for severe (grade 3) and permanently discontinue nivolumab for life-threatening (grade 4) IMAR, recurrent severe IMAR that require systemic immunosuppressive treatment, or an inability to reduce

corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

- If nivolumab requires interruption or discontinuation for severe IMAR, administer systemic high-dose corticosteroids (1 to 2 mg/kg/d of prednisone or equivalent) until improvement to grade 1 or less and then taper corticosteroids over at least 1 month. Consider administration of other systemic immunosuppressants in patients who develop IMAR that are not controlled with corticosteroid therapy.
- Severe infusion-related reactions may occur. Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions.
- Severe transplant-related complications, including fatal events, have occurred in patients who have received an allogeneic HSCT after having received nivolumab. Follow patients closely for early evidence of transplant-related complications such as graft-versus-host disease (GVHD), febrile syndromes, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.
- Embryo-fetal toxicity: nivolumab may cause fetal harm when administered to a pregnant woman.

OBINUTUZUMAB (GAZYVA)

Mechanism of Action

- Monoclonal antibody that targets the CD20 antigen expressed on the surface of pre–B and mature B lymphocytes

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL): previously untreated CLL in combination with chlorambucil
- Follicular lymphoma (FL):

- Patients with FL with relapsed disease or are refractory to a rituximab containing regimen in combination with bendamustine followed by obinutuzumab monotherapy
- Adult patients with previously untreated stage II bulky, III, or IV FL in combination with chemotherapy followed by obinutuzumab monotherapy in patients who achieve at least a partial remission

FDA-Approved Dosage

- CLL:
  - Cycle 1, day 1: 100 mg IV infusion over 4 hours
  - Cycle 1, day 2: 900 mg IV initiated at a rate of 50 mg/h and increased by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h
  - Cycle 1, days 8 and 15, and cycles 2 to 6, day 1: 1000 mg IV initiated at a rate of 100 mg/h if the previous infusion was well tolerated, and increased by 100 mg/h every 30 minutes to a maximum rate of 400 mg/h. Each cycle is 28 days
- FL:
  - Cycle 1: 1000 mg IV infusion weekly × three doses on days 1, 8, and 15.
  - Cycles 2 to 6: 1000 mg IV infusion on day 1 only.
  - Initiate the first dose at 50 mg/h and increase by 50 mg/h every 30 minutes at maximum of 400 mg/h. If the previous infusion was well tolerated, subsequent infusions may be initiated at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h.
  - Relapsed or refractory FL in combination with bendamustine: continue combination therapy for six 28-day cycles. After cycle 6, in patients with at least a partial response, continue obinutuzumab as monotherapy 1000 mg IV every 2 months for up to 2 years.
- Previously untreated FL in combination with chemotherapy:
  - Bendamustine combination: continue for six 28-day cycles of combination therapy.
  - CHOP combination: continue for six 21-day cycles of combination therapy followed by two additional 21-day cycles of obinutuzumab monotherapy.
  - CVP combination: continue for eight 21-day cycles of combination therapy.
  - In patients who achieve a complete or partial response after the six to eight cycles of combination therapy, follow with obinutuzumab monotherapy 1000 mg IV infusion every 2 months for up to 2 years.

Dose Modification Criteria

- Renal (mild to moderate, CrCl > 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data
- Hepatic: no data

- Hematologic and nonhematologic toxicity: doses should be held, not reduced due to toxicities. See package insert for specific recommendations regarding holding parameters

Adverse Reactions

- ELECTRO: hypocalcemia, hyponatremia, and tumor lysis syndrome
- GI: N/V (minimal), diarrhea, and constipation
- HEMAT: neutropenia, thrombocytopenia, lymphopenia, and anemia
- INFUS: hypotension, tachycardia, dyspnea, respiratory symptoms, nausea, fatigue, dizziness, diarrhea, hypertension, flushing, headache, pyrexia and chills. May occur in 38% to 65% of patients during first infusion
- OTHER: hepatitis B virus (HBV) reactivation, fatigue, asthenia, arthralgia, and tumor lysis syndrome

Comments

- Assess risk for tumor lysis syndrome prior to initiation of treatment.
- Premedicate with an IV glucocorticoid, acetaminophen, and antihistamine prior to first infusion. Subsequent premedication recommendations are based on the patient's disease state and tolerability of previous infusions. Refer to product labeling for premedication recommendations.
- Screen all patients for HBV infection before initiating therapy. For patients who show evidence of HBV infection, consult physicians with expertise in managing HBV regarding monitoring and consideration for HBV antiviral therapy.
- Progressive multifocal leukoencephalopathy (PML) has been observed in patients treated with obinutuzumab.
- Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

- Embryo-fetal toxicity: obinutuzumab may cause fetal harm when administered to a pregnant woman.

OFATUMUMAB (ARZERRA)

Mechanism of Action

- Cytolytic monoclonal antibody that targets CD20, which is expressed on normal B lymphocytes and on B-cell CLL.

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL):
  - Treatment of previously untreated patients with CLL in combination with chlorambucil in patients for whom therapy with fludarabine is considered inappropriate.
  - Treatment of patients with relapsed CLL in combination with fludarabine and cyclophosphamide.
  - Extended treatment of patients with recurrent or progressive CLL who are in complete or partial response after at least two lines of therapy.
  - Treatment of CLL patients refractory to fludarabine and alemtuzumab.

FDA-Approved Dosage

- Previously untreated CLL in combination with chlorambucil:
  - 300 mg IV infusion on day 1 followed by 1000 mg IV infusion on day 8 (cycle 1) followed by:
  - 1000 mg IV infusion on day 1 of 28-day cycle for a minimum of 3 cycles until best response or a maximum of 12 cycles.
- Relapsed CLL in combination with fludarabine and cyclophosphamide:
  - 300 mg IV infusion on day 1 followed by 1000 mg IV infusion on day 8 (cycle 1) followed by:
  - 1000 mg IV infusion on day 1 of 28-day cycle for a maximum of six cycles.
- Extended treatment in CLL:
  - 300 mg IV infusion on day 1 followed by 1000 mg IV infusion on day 8 (cycle 1) followed by:
  - 1000 mg IV infusion 7 weeks later and every 8 weeks thereafter for up to a maximum of 2 years.

- Refractory CLL:
  - 300 mg IV infusion on day 1 followed 1 week later by:
  - 2000 mg IV infusion weekly × seven doses, followed 4 weeks later with:
  - 2000 mg IV infusion every 4 weeks × four doses.
- Do not administer as an IV push or bolus.
- Premedicate with acetaminophen, antihistamine, and corticosteroid.

Dose Modification Criteria

- Infusion reactions: modify rate
- Renal (CrCl >30 mL/min): no
- Hepatic: unknown

Adverse Reactions

- DERM: rash
- GI: diarrhea and N/V (minimal)
- HEMAT: anemia, neutropenia, and thrombocytopenia
- INFUS: abdominal pain, angioedema, back pain, bronchospasm, cardiac ischemia/infarction, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, pyrexia, rash, syncope, and urticaria
- PULM: bronchitis, cough, dyspnea, pneumonia, and upper respiratory tract infections
- OTHER: pyrexia, fatigue, and tumor lysis syndrome

Comments

- Serious infusion reactions can occur. Premedicate prior to each dose with oral acetaminophen, oral or IV antihistamine, and IV corticosteroid. Refer to product labeling for recommendations on premedication agents and doses and corticosteroid dose modifications. Infusion reactions occur more frequently with the first two infusions.
- Anticipate and provide prophylaxis for tumor lysis syndrome in high-risk patients.

- Severe cytopenias may occur. Late onset (>42 days after last treatment) and prolonged neutropenia (not resolved between 24 and 42 days after last treatment) has been reported. Monitor CBCs at regular intervals during and after conclusion of therapy.
- Progressive multifocal leukoencephalopathy (PML) can occur. Monitor for neurologic signs or symptoms.
- Screen patients at high risk of HBV infection before initiation of ofatumumab. Reactivation of HBV can occur following treatment.
- Obstruction of the small intestine can occur.
- Do not administer live viral vaccines to patients who have recently received ofatumumab.
- Embryo-fetal toxicity: there are no adequate or well-controlled studies of ofatumumab in pregnant women.

OLAPARIB (LYNPARZA)

Mechanism of Action

- Inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3, which play a role in DNA repair

FDA-Approved Indications

- Ovarian cancer:
  - First-line maintenance treatment of adult patients with *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
  - First-line maintenance treatment in combination with bevacizumab of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status.
  - Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
  - Treatment of adult patients with *BRCA*-mutated advanced ovarian cancer who have received three or more prior lines of chemotherapy.

- Breast cancer: treatment of adult patients with germline *BRCA*-mutated, HER-2 negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
- Pancreatic adenocarcinoma: maintenance treatment of adult patients with germline *BRCA*-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
- Prostate cancer: treatment of adult patients with germline or somatic homologous recombination repair gene–mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

FDA-Approved Dosage

- 300 mg orally, twice daily, with or without food.
- mCRPC: patients receiving olaparib for mCRPC should also receive a GnRH analog concurrently or should have had bilateral orchiectomy.
- Treatment duration:
    - First-line maintenance treatment of *BRCA*-mutated or HRD-positive advanced ovarian cancer: continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years who in the opinion of the treating healthcare provider can derive further benefit from continuous olaparib treatment can be treated beyond 2 years.
    - All other indications: continue treatment until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild, CrCl 51-80 mL/min): no
- Renal (moderate, CrCl 31-50 mL/min): yes
- Renal (severe, CrCl <30 mL/min): no data

- Hepatic (mild to moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): no data available
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash and dermatitis
- GI: abdominal pain/discomfort, decreased appetite, N/V (moderate-high), diarrhea, and dyspepsia
- HEMAT: anemia, neutropenia, thrombocytopenia, and lymphopenia
- NEURO: headache and dysgeusia
- PULM: cough, upper respiratory infection/nasopharyngitis, and pneumonitis
- OTHER: fatigue/asthenia, arthralgia/musculoskeletal pain, and myalgia

Comments

- Myelodysplastic syndrome/acute myeloid leukemia has been reported in patients who have received olaparib. Monitor patients for hematologic toxicity at baseline and monthly thereafter.
- Pneumonitis, including fatal cases, has been reported in patients receiving olaparib. Interrupt therapy and evaluate if patients present with new or worsening pulmonary symptoms.
- Venous thromboembolic events occurred at a higher incidence in mCRPC patients who received olaparib plus ADT compared to patients treated with enzalutamide or abiraterone plus ADT in a randomized clinical trial. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism (PE) and treat as medically appropriate.
- Olaparib is a substrate of CYP3A4. Avoid concomitant use of CYP3A inducers and strong or moderate CYP3A4 inhibitors.

Dose reduction of olaparib is recommended if a moderate or strong CYP3A4 inhibitor must be used concomitantly.
- Embryo-fetal toxicity: olaparib may cause fetal harm when administered to a pregnant woman.

OMACETAXINE MEPESUCCINATE (SYNRIBO)

Mechanism of Action

- Inhibits protein synthesis and is independent of direct Bcr-Abl binding

FDA-Approved Indications

- Chronic myeloid leukemia (CML): chronic or accelerated-phase CML with resistance and/or intolerance to two or more TKIs

FDA-Approved Dosage

- CML induction dose: 1.25 mg/m^2 administered by SC injection twice daily for 14 consecutive days of a 28-day cycle.
- CML maintenance dose: 1.25 mg/m^2 administered by SC injection twice daily for seven consecutive days of a 28-day cycle.
- Cycles should be repeated every 28 days until patients achieve a hematologic response. Treatment should continue as long as patients are clinically benefiting from therapy.

Dose Modification Criteria

- Renal: no data
- Hepatic: no data
- Myelosuppression: yes

Adverse Reactions

- Cr: increased serum creatinine
- DERM: alopecia and rash
- ELECTRO: increased uric acid
- ENDO: hyperglycemia and hypoglycemia
- GI: abdominal pain, constipation, diarrhea, N/V (low), and upper abdominal pain
- HEMAT: anemia, leukocytopenia, neutropenia, and thrombocytopenia
- INFUS: injection site reaction
- PULM: cough
- OTHER: arthralgia, asthenia, edema, epistaxis, fatigue, hemorrhage, infection, pain in extremity, and pyrexia

Comments

- Monitor CBCs weekly during induction and initial maintenance cycles and every 2 weeks during maintenance cycles, as clinically indicated. A high incidence of grade 3/4 thrombocytopenia, neutropenia, and anemia was seen in trials with omacetaxine mepesuccinate.
- Fatalities from cerebral hemorrhage and severe, nonfatal, GI hemorrhage occurred in 2% of patients treated with omacetaxine mepesuccinate in the clinical trials that evaluated for safety.
- Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes.
- Embryo-fetal toxicity: omacetaxine mepesuccinate may cause fetal harm when administered to a pregnant woman. Omacetaxine mepesuccinate may impair male fertility.

OSIMERTINIB (TAGRISSO)

Mechanism of Action

- Kinase inhibitor of EGFR that binds irreversibly to the T790M, L858R, and exon 19 deletion mutant forms of EGFR at ninefold lower concentrations than wild type

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC):
  - Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations
  - First-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations
  - Treatment of adult patients with metastatic NSCLC with the EGFR T790M mutation that has progressed on or after EGFR TKI therapy

FDA-Approved Dosage

- 80 mg orally, once daily, with or without food
- Treatment duration:
  - Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or for up to 3 years
  - Treat patients with metastatic disease until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (CrCl ≥ 15 mL/min): no
- Renal (ESRD, CrCl < 15 mL/min): no data
- Hepatic (mild to moderate, Child-Pugh class A and B): no
- Hepatic (severe, Child-Pugh class C): no data
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation and cardiomyopathy
- DERM: rash, dry skin, and nail toxicity
- ELECTRO: hyponatremia and hypermagnesemia

- GI: diarrhea and N/V (minimal-low)
- HEMAT: lymphopenia, thrombocytopenia, anemia, and neutropenia
- Ocular system: keratitis
- PULM: pneumonitis

Comments

- Patients who have difficulty swallowing may dissolve the tablet in 2 oz (60 mL) of noncarbonated water.
- Cardiomyopathy: assess LVEF prior to initiation, then every 3 months thereafter.
- Interstitial lung disease/pneumonitis has been reported with osimertinib. Withhold therapy and evaluate for new or worsening pulmonary symptoms.
- Keratitis has been observed in patients treated with osimertinib. Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist for evaluation.
- Postmarketing cases of cutaneous vasculitis have been reported with osimertinib. Withhold therapy if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation.
- Postmarketing cases of severe dermatologic toxicities (Stevens-Johnson syndrome and erythema multiforme major) have been reported with osimertinib. Withhold therapy if these toxicities are suspected and permanently discontinue if confirmed.
- Osimertinib is a substrate of CYP3A4. Avoid concomitant use with strong CYP3A4 inducers or consider dose modification if concomitant administration is necessary. Osimertinib is an inhibitor of BCRP and will impact the drug exposure of BCRP substrates. Screen for drug interactions.
- Embryo-fetal toxicity: osimertinib may cause fetal harm when administered to a pregnant woman.

OXALIPLATIN (ELOXATIN)

Mechanism of Action

- Alkylating-like agent producing interstrand DNA cross-links

FDA-Approved Indications

- Colorectal cancer:
  - Adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor in combination with infusional FU and leucovorin
  - Treatment of advanced colorectal cancer in combination with infusional FU and leucovorin

FDA-Approved Dosage

- Combined therapy with infusional FU and leucovorin (FOLFOX regimen).
- **Day 1**: oxaliplatin 85 mg/m^2 IV infusion over 120 minutes × one dose given concurrently with leucovorin 200 mg/m^2 IV infusion over 120 minutes × one dose *followed by* FU 400 mg/m^2 IV bolus over 2 to 4 minutes × one dose *followed by* FU 600 mg/m^2 IV continuous infusion over 22 hours.
- **Day 2**: leucovorin 200 mg/m^2 IV infusion over 120 minutes × one dose *followed by* FU 400 mg/m^2 IV bolus over 2 to 4 minutes × one dose *followed by* FU 600 mg/m^2 IV continuous infusion over 22 hours.
- Cycles are repeated every 2 weeks. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles). For advanced disease, treatment is recommended until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to moderate, CrCl > 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): yes

- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CNS: peripheral sensory neuropathies (see comments below) and headache
- CV: edema, thromboembolic events, and QT prolongation
- DERM: injection site reactions
- GI: N/V (moderate), diarrhea, mucositis/stomatitis, abdominal pain, anorexia, and taste perversion
- GU: elevated serum creatinine
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- PULM: cough, dyspnea, and interstitial lung disease
- OTHER: fatigue, fever, back pain, pain, hemorrhage, rhabdomyolysis, and hypersensitivity reaction

Comments

- Anaphylactic reactions have been reported and may occur within minutes of oxaliplatin administration. Epinephrine, corticosteroids, and antihistamines have been used to alleviate symptoms of anaphylaxis.
- Embryo-fetal toxicity: oxaliplatin may cause fetal harm when administered to a pregnant woman.
- Oxaliplatin is associated with two types of peripheral neuropathy:
    1. An acute, reversible, primarily peripheral, and sensory neuropathy that is of early onset (within hours to 1-2 days of dosing), that resolves within 14 days, and that frequently recurs with further dosing. The symptoms include transient paresthesia, dysesthesia, and hypoesthesia in the hands, feet, perioral area, or throat. Symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects. Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.
    2. A persistent (>14 days), primarily peripheral, sensory neuropathy usually characterized by paresthesias, dysesthesias, and hypoesthesias, but may also

include deficits in proprioception that can interfere with daily activities. Dose modifications are recommended for persistent grade 2 neurotoxicity, and discontinuation of therapy is recommended for persistent grade 3 neurotoxicity.

PACLITAXEL (TAXOL)

Mechanism of Action

- Microtubule assembly stabilization

FDA-Approved Indications

- Advanced ovarian cancer (first-line and subsequent therapy). As first-line therapy, paclitaxel is indicated in combination with cisplatin.
- Breast cancer:
  - Adjuvant treatment of node-positive breast cancer (administered sequentially to standard doxorubicin-containing combination chemotherapy).
  - Second-line therapy for breast cancer (after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant therapy).
- Non–small cell lung cancer (NSCLC): first-line therapy in combination with cisplatin in patients who are not candidates for potentially curative surgery and/or radiation therapy.
- AIDS-related Kaposi sarcoma (second-line treatment).

FDA-Approved Dosage

- Premedicate patients with dexamethasone, diphenhydramine (or its equivalent), and an H_2 antagonist to prevent severe hypersensitivity reactions. Suggested package literature premedication regimen: dexamethasone 20 mg orally × two doses administered approximately 12 and 6 hours before paclitaxel; diphenhydramine 50 mg IV 30 to 60 minutes before paclitaxel; and cimetidine 300 mg IV *OR* ranitidine 50 mg IV 30

to 60 minutes before paclitaxel. Consult current literature for alternative premedication regimens.

- First-line ovarian cancer: 135 mg/m^2 IV continuous infusion over 24 hours *OR* 175 mg/m^2 IV infusion over 3 hours (followed by cisplatin 75 mg/m^2 IV) every 3 weeks.
- Second-line ovarian cancer: 135 mg/m^2 *OR* 175 mg/m^2 IV infusion over 3 hours every 3 weeks. Consult current literature for alternative regimens.
- Adjuvant therapy of node-positive breast cancer: 175 mg/m^2 IV infusion over 3 hours every 3 weeks × four cycles (administered sequentially with doxorubicin-containing chemotherapy).
- Second-line breast cancer: 175 mg/m^2 IV over 3 hours every 3 weeks.
- NSCLC: 135 mg/m^2 IV continuous infusion over 24 hours (followed by cisplatin 75 mg/m^2 IV) every 3 weeks.
- AIDS-related Kaposi sarcoma: 135 mg/m^2 IV infusion over 3 hours every 3 weeks or 100 mg/m^2 IV infusion over 3 hours every 2 weeks (note: reduce the dose of dexamethasone premedication dose to 10 mg orally) per dose (instead of the suggested 20 mg oral dose).

Dose Modification Criteria

- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity (neuropathy): yes

Adverse Reactions

- CV: hypotension, bradycardia, and ECG changes
- DERM: alopecia, onycholysis (more common with weekly dosing), and injection site reactions
- GI: N/V (low), diarrhea, and mucositis
- HEMAT: myelosuppression
- INFUS: acute hypersensitivity-type reactions

- NEURO: peripheral neurosensory toxicity (paresthesia, dysesthesia, and pain)
- OTHER: arthralgia and myalgia

Comments

- Use non-DEHP plasticized solution containers and administration sets.
- In-line filtration (0.22 μm filter) required during administration.
- Lower dose, weekly dosage regimens are commonly utilized. Consult current literature for dose guidelines.
- Embryo-fetal toxicity: paclitaxel may cause fetal harm when administered to a pregnant woman.

PROTEIN-BOUND PACLITAXEL (ABRAXANE)

Mechanism of Action

- Microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization.

FDA-Approved Indications

- Breast cancer: after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Non–small cell lung cancer (NSCLC): locally advanced or metastatic disease as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Pancreatic cancer: metastatic adenocarcinoma of the pancreas as first-line treatment in combination with gemcitabine.

FDA-Approved Dosage

- Metastatic breast cancer: 260 mg/m^2 IV infusion over 30 minutes every 3 weeks.
- NSCLC: 100 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of each 21-day cycle; carboplatin is given intravenously on day 1 of each 21-day cycle immediately after protein-bound paclitaxel administration.
- Pancreatic cancer: 125 mg/m^2 IV infusion over 30 to 40 minutes on days 1, 8, and 15 of each 28-day cycle; administer gemcitabine immediately after protein-bound paclitaxel on days 1, 8, and 15 of each 28-day cycle.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30 to < 90 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data
- Hepatic (mild): no
- Hepatic (moderate, severe): yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Effects

- Cr: increased serum creatinine
- CV: abnormal ECG
- DERM: alopecia and rash
- GI: diarrhea, N/V (low), and decreased appetite
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: alkaline phosphatase elevation and increased LFTs
- INFECT: infections
- INFUS: anaphylaxis, arrhythmia, chest pain, dyspnea, flushing, and hypotension
- NEURO: sensory neuropathy
- Ocular system: blurred vision, keratitis, and ocular/visual disturbances

- PULM: pneumonitis
- OTHER: arthralgia, asthenia, edema, fatigue, pyrexia, myalgia, and nail changes

Comments

- Contraindicated if neutrophil count is <1500 cells/mm^3.
- Do not substitute for or with other paclitaxel formulations.
- Protein-bound paclitaxel contains albumin (human). Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases.
- No premedication is required prior to administration, but premedication may be needed in patients who have had prior hypersensitivity reactions.
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not rechallenge.
- The use of an in-line filter is not recommended.
- Embryo-fetal toxicity: protein-bound paclitaxel may cause fetal harm when administered to a pregnant woman. Men should be advised not to father a child while receiving protein-bound paclitaxel.

PALBOCICLIB (IBRANCE)

Mechanism of Action

- Inhibitor of CDK4 and CDK6, which is downstream of signaling pathways that lead to cellular proliferation

FDA-Approved Indications

- Breast cancer: HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal

women or in men, or with fulvestrant in patients with disease progression following endocrine therapy

FDA-Approved Dosage

- 125 mg orally once daily on days 1 to 21 of a 28-day cycle in combination with an aromatase inhibitor or fulvestrant.
- Palbociclib is available in capsule and tablet formulations. Palbociclib capsules should be administered with food, and tablets may be taken with or without food.
- Pre/perimenopausal women treated with the combination of palbociclib and fulvestrant should also be treated with LHRH agonists according to current clinical practice standards. Men treated with the combination of palbociclib with an aromatase inhibitor should also be considered for treatment with LHRH agonists according to current clinical practice standards.

Dose Modification Criteria

- Renal (mild to moderate, CrCl > 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data
- Hepatic (mild to moderate, Child-Pugh class A and B): no
- Hepatic (severe, Child-Pugh class C): yes
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia and rash
- GI: decreased appetite, stomatitis, N/V (minimal-low), diarrhea, and constipation
- HEMAT: neutropenia, leukopenia, anemia, and thrombocytopenia
- NEURO: headache
- PULM: upper respiratory tract infection and ILD/pneumonitis
- OTHER: fatigue, asthenia, and pyrexia

Comments

- Severe, life-threatening, and fatal cases of interstitial lung disease (ILD) and/or pneumonitis have been reported in patients treated with palbociclib when taken in combination with endocrine therapy. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (eg, hypoxia, cough, dyspnea) and permanently discontinue therapy in patients with severe ILD or pneumonitis.
- Palbociclib is both a substrate and a time-dependent inhibitor of CYP3A. Avoid concomitant use of strong CYP3A inhibitors or inducers with palbociclib and evaluate for drug interactions with drugs that may have their plasma concentrations altered by palbociclib.
- Embryo-fetal toxicity: palbociclib may cause fetal harm when administered to a pregnant woman.

PANITUMUMAB (VECTIBIX)

Mechanism of Action

- Monoclonal antibody to the human EGFR.

FDA-Approved Indications

- Colorectal cancer: wild-type *RAS* (defined as wild type in both *KRAS* and *NRAS*) metastatic disease determined by an FDA-approved test as follows:
  - First-line treatment in combination with FOLFOX combination chemotherapy.
  - Monotherapy for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA-Approved Dosage

- 6 mg/kg IV infusion over 60 minutes every 14 days. Doses higher than 1000 mg should be administered over 90 minutes.

Dose Modification Criteria

- Renal (mild to moderate): no
- Renal (severe): no data
- Hepatic (mild to moderate): no
- Hepatic (severe): no data
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, skin fissures, and photosensitivity
- ELECTRO: hypomagnesemia and hypocalcemia
- GI: N/V (low), abdominal pain, diarrhea, and stomatitis/mucositis
- INFUS: infusion reactions may include fever, chills, dyspnea, bronchospasm, and hypotension
- Ocular system: conjunctivitis, ocular hyperemia, and increased lacrimation
- PULM: interstitial lung disease and pulmonary fibrosis (rare)
- OTHER: fatigue

Comments

- *RAS* mutation predicts for a lack of response to anti-EGFR agents like panitumumab. Panitumumab is not indicated for the treatment of patients with *RAS* mutation-positive metastatic colorectal cancer or for whom *RAS*-mutation status is unknown.
- Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR

expression; these are the only patients studied and for whom benefit has been shown.
- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion. Immediately and permanently discontinue panitumumab in patients experiencing a severe (grade 3 or 4) infusion reaction. The use of premedication was not standardized in the clinical trials and thus the utility of premedication is not known.
- Withhold panitumumab for dermatologic toxicities that are grade 3 or higher or considered intolerable. Refer to product labeling for dose modifications for dermatologic toxicity.
- Embryo-fetal toxicity: panitumumab may cause fetal harm when administered to a pregnant woman.

PANOBINOSTAT (FARYDAK)

Mechanism of Action

- HDAC inhibitor

FDA-Approved Indications

- Multiple myeloma (MM): treatment of patients with MM in combination with bortezomib and dexamethasone after receiving at least two prior regimens, including bortezomib and an immunomodulatory agent

FDA-Approved Dosage

- 20 mg orally once every other day for three doses per week (on days 1, 3, 5, 8, 10, and 12) during weeks 1 and 2 of a 3-week cycle for eight cycles. Extended therapy may be considered for another eight cycles if there is clinical benefit.

Dose Modification Criteria

- Renal (mild to severe): no (not studied in end stage renal disease)
- Hepatic (mild to moderate): yes
- Hepatic (severe impairment): avoid use
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiac ischemic events, severe arrhythmias, and ECG changes
- ELECTRO: hypokalemia, hypophosphatemia, and hyponatremia
- GI: diarrhea, N/V (minimal-low), and decreased appetite
- HEMAT: thrombocytopenia, neutropenia, anemia, and hemorrhage
- HEPAT: elevated ALT/AST and elevated total bilirubin
- OTHER: fatigue, peripheral edema, and pyrexia

Comments

- Panobinostat is a substrate of CYP3A4 and P-gp. Avoid strong inhibitors or inducers of CYP3A4. Dose reductions of panobinostat may be considered if strong CYP3A4 inhibitors must be used concomitantly. Panobinostat is an inhibitor of CYP2D6. Screen for drug interactions.
- Diarrhea may be severe. Promptly initiate antidiarrheal medication at the onset of diarrhea. Monitor hydration status and electrolytes. Interrupt panobinostat for moderate diarrhea (4-6 stools per day) and evaluate for consideration of dose reduction or discontinuation.
- Severe and fatal ischemic events, severe arrhythmias, and ECG changes have occurred in patients treated with panobinostat. Obtain ECG and electrolytes at baseline and periodically during

treatment as clinically indicated. Concomitant use with antiarrhythmics and medications that prolong the QT interval is not recommended.
- Embryo-fetal toxicity: panobinostat may cause fetal harm when administered to a pregnant woman.

PAZOPANIB (VOTRIENT)

Mechanism of Action

- Multityrosine kinase inhibitor of VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3; PDGFR-α and PDGFR-β; FGFR1 and FGFR3; cytokine receptor (Kit); IL-2 receptor inducible T-cell kinase (Itk); leukocyte-specific protein tyrosine kinase (Lck); and transmembrane glycoprotein RTK (c-Fms).

FDA-Approved Indications

- Advanced renal cell carcinoma (RCC).
- Advanced soft-tissue sarcoma (STS) in patients who have received prior chemotherapy.
- Limitations of use: the efficacy of pazopanib for adipocytic STS or GISTs has not been demonstrated.

FDA-Approved Dosage

- 800 mg orally once daily without food, at least 1 hour before or 2 hours after a meal

Dose Modification Criteria

- Renal (mild to severe): no (not studied in end stage renal disease)
- Hepatic (mild): no
- Hepatic (moderate): yes

- Hepatic (severe): not recommended
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Effects

- CV: cardiac dysfunction, hypertension, and QT prolongation
- DERM: hair color changes, skin hypopigmentation, and wound healing complications
- ELECTRO: hypomagnesemia, hyponatremia, and hypophosphatemia
- ENDO: hyperglycemia and hypothyroidism
- GI: diarrhea, N/V (minimal-low)
- GU: proteinuria
- HEMAT: leukopenia, lymphocytopenia, neutropenia, and thrombocytopenia
- HEPAT: increased bilirubin and increased LFTs
- NEURO: headache and dysgeusia
- PULM: dyspnea and interstitial lung disease
- OTHER: fatigue, decreased appetite, decreased weight, hemorrhage, infection, musculoskeletal pain, thrombosis, tumor pain, and increased lipase

Comments

- Severe and fatal hepatotoxicity has occurred. Measure liver chemistries before the initiation of treatment and regularly during treatment.
- Pazopanib is not indicated for use in combination with other cancer therapy.
- CYP3A4 inhibitors: avoid use of strong inhibitors. If concomitant administration is necessary, reduce the dose of pazopanib. Avoid grapefruit and grapefruit juice.
- CYP3A4 inducers: consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid pazopanib.

- CYP substrates: concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.
- Avoid concomitant use of gastric acid–reducing agents.
- Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring.
- Use with caution in patients at higher risk of developing QT interval prolongation. Monitoring ECGs and electrolytes should be considered.
- CHF and decreased LVEF have occurred. Monitor BP and manage hypertension promptly. Baseline and period evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.
- Pazopanib has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant GI hemorrhage in the past 6 months and should not be used in those patients.
- Use with caution in patients who are at an increased risk for arterial and venous thrombotic events. Monitor for signs and symptoms of venous thromboembolism (VTE) and pulmonary embolism (PE).
- Use with caution in patients at risk for GI perforation or fistula.
- Permanently discontinue pazopanib if signs or symptoms of RPLS occur.
- BP should be well controlled prior to initiating pazopanib. Monitor BP within 1 week after starting pazopanib and frequently thereafter.
- Interruption of therapy with pazopanib is recommended in patients undergoing surgical procedures. Pazopanib should be stopped at least 7 days prior to scheduled surgery.
- Interrupt pazopanib for 24-hour urine protein ≥3 g and discontinue for repeat episodes despite dose reductions.
- Serious infections (with or without neutropenia), some with fatal outcome, have been reported. Monitor for signs and symptoms and treat active infection promptly.

- Embryo-fetal toxicity: pazopanib may cause fetal harm when administered to a pregnant woman.

PEMBROLIZUMAB (KEYTRUDA)

Mechanism of Action

- Humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1, and PD-L2

FDA-Approved Indications

- Melanoma:
  - Treatment of patients with unresectable or metastatic melanoma.
  - Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- Non–small cell lung cancer (NSCLC):
  - First-line treatment of patients with metastatic nonsquamous NSCLC in combination with pemetrexed and platinum chemotherapy, with no EGFR or ALK genomic tumor aberrations.
  - First-line treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or protein-bound paclitaxel.
  - First-line single-agent therapy in patients with NSCLC expressing PD-L1 (Tumor Proportion Score [TPS] ≥ 1%), with no EGFR or ALK genomic tumor aberrations and is either stage III and not a candidate for surgical resection or definitive chemoradiation or metastatic.
  - Single-agent therapy in patients with metastatic NSCLC expressing PD-L1 (TPS ≥1%), with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving pembrolizumab.
- Head and neck squamous cell carcinoma (HNSCC):
  - First-line treatment of patients with metastatic or with unresectable, recurrent HNSCC in combination with platinum and fluorouracil.
  - Single-agent first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1).
- Single-agent treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

- Classical Hodgkin lymphoma (cHL):
  - Treatment of adult patients with relapsed or refractory cHL.
  - Treatment of pediatric patients with refractory cHL, or cHL that has relapsed after two or more lines of therapy.
- Primary mediastinal large B-cell lymphoma (PMBCL):
  - Treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after two or more lines of therapy.
  - Limitations of use: pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- Urothelial carcinoma:
  - Treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
  - Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - Treatment of patients with BCG-unresponsive, high-risk, non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- Microsatellite instability-high (MSI-H) or mismatch repair deficient cancer (dMMR):
  - Treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
  - Limitations of use: the safety and effectiveness of pembrolizumab in pediatric patients with MSI-H CNS cancers have not been established.
- MSI-H or dMMR CRC:
  - Treatment of patients with unresectable or metastatic MSI-H or dMMR CRC.
- Gastric cancer:
  - First-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy.
  - Single-agent treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1) with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.
- Esophageal cancer:
  - Treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 cm above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation therapy either
    - in combination with platinum- and fluoropyrimidine-based chemotherapy or

    - single-agent therapy after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10).
- Cervical cancer:
    - Treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1).
- Hepatocellular carcinoma (HCC):
    - Treatment of patients with HCC who have been previously treated with sorafenib.
- Merkel cell carcinoma:
    - Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.
- Renal cell carcinoma (RCC):
    - First-line treatment of patients with advanced RCC in combination with axitinib.
- Endometrial carcinoma:
    - Treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation in combination with lenvatinib.
- Tumor mutational burden high (TMB-H) cancer:
    - Treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥10 mutations/megabase [mut/mB]) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
    - Limitations of use: the safety and effectiveness of pembrolizumab in pediatric patients with TMB-H CNS cancers have not been established.
- Cutaneous squamous cell carcinoma (cSCC):
    - Treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.
- Triple-negative breast cancer (TNBC):
    - Treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant, and then continued as a single agent as adjuvant treatment after surgery.
    - Treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10).

FDA-Approved Dosage

- Adult patients: 200 mg IV infusion over 30 minutes every 3 weeks or 400 mg IV infusion over 30 minutes every 6 weeks.
- Pediatric patients: 2 mg/kg (up to 200 mg) IV infusion over 30 minutes every 3 weeks.

- When combined with chemotherapy, administer pembrolizumab prior to chemotherapy when given on the same day.

Treatment Duration

- Adult patients with unresectable or metastatic melanoma: continue until disease progression or unacceptable toxicity.
- Adjuvant treatment of adult patients with melanoma: continue until disease progression, unacceptable toxicity, or up to 12 months.
- Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic urothelial carcinoma, MSI-H or dMMR cancer, MSI-H or dMMR CRC, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, TMB-H Cancer, or cSCC: continue until disease progression, unacceptable toxicity, or up to 24 months.
- Adult patients with high-risk BCG-unresponsive NMIBC: continue until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months.
- Adult patients with high-risk, early-stage TNBC: continue neoadjuvant treatment in combination with chemotherapy for 24 weeks or until disease progression or unacceptable toxicity, followed by adjuvant treatment with pembrolizumab as a single agent for up to 27 weeks or until disease progression or unacceptable toxicity.
- Adult patients with locally recurrent unresectable or metastatic TNBC: continue until disease progression, unacceptable toxicity, or up to 24 months.
- Pediatric patients with cHL, PMBCL, MSI-H cancer, MCC, or TMB-H cancer: continue until disease progression, unacceptable toxicity, or up to 24 months.

Dose Modification Criteria

- Renal (CrCl > 15 mL/min): no.

- Hepatic (mild): no.
- Hepatic (moderate to severe): no data.
- Doses should be held, not reduced due to toxicities. See package insert for specific recommendations regarding holding doses and starting corticosteroids.

Adverse Reactions

- DERM: rash and pruritus
- ELECTRO: hyponatremia
- ENDO: immune-mediated endocrinopathies (hypophysitis, hypo/hyperthyroidism, type 1 diabetes mellitus)
- GI: immune-mediated colitis, N/V (minimal), diarrhea, constipation, and decreased appetite
- GU: immune-mediated nephritis and renal dysfunction
- HEMAT: anemia and lymphopenia
- HEPAT: immune-mediated hepatitis
- INFUS: infusion-related reactions
- PULM: immune-mediated pneumonitis and dyspnea
- OTHER: fatigue and arthralgia

Comments

- Pembrolizumab can cause severe and fatal immune-mediated adverse reactions (IMAR) due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system or tissue, including the following immune-mediated toxicities: colitis, hepatitis, dermatitis (and other dermatologic adverse reactions), endocrinopathies, pneumonitis, and nephritis with renal dysfunction. The majority of these reactions manifest during treatment; however, a minority can occur weeks to months after discontinuation of therapy.
- Monitor patients for signs and symptoms that may be clinical manifestations of IMAR and evaluate clinical chemistries

including LFTs, creatinine, and thyroid function tests at baseline and periodically during treatment.

- In general, withhold pembrolizumab for severe (grade 3) and permanently discontinue pembrolizumab for life-threatening (grade 4) IMAR, recurrent severe IMAR that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.
- If pembrolizumab requires interruption or discontinuation for severe IMAR, administer systemic high-dose corticosteroids (1 to 2 mg/kg/d of prednisone or equivalent) until improvement to grade 1 or less and then taper corticosteroids over at least 1 month. Consider administration of other systemic immunosuppressants in patients who develop IMAR that are not controlled with corticosteroid therapy.
- Severe infusion-related reactions may occur. Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions.
- Severe transplant-related complications, including fatal events, have occurred in patients who have received an allogeneic HSCT after having received pembrolizumab. Follow patients closely for early evidence of transplant-related complications such as graft-versus-host disease (GVHD), febrile syndromes, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.
- Embryo-fetal toxicity: pembrolizumab may cause fetal harm when administered to a pregnant woman.

PEGASPARGASE (ONCASPAR)

Mechanism of Action

- A modified (pegylated) version of the enzyme l-asparaginase. l-asparaginase depletes asparagine, an amino acid required by

some leukemic cells.

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL):
  - First-line therapy in adult and pediatric patients with ALL as a component of a multiagent chemotherapeutic regimen
  - Treatment of ALL in adult and pediatric patients with hypersensitivity to native forms of l-asparaginase as a component of a multiagent chemotherapeutic regimen

FDA-Approved Dosage

- ALL:
  - Patients 21 years of age and younger: 2500 IU/m^2 IM or IV infusion over 1 to 2 hours × one dose every 14 days
  - Patients more than 21 years of age: 2000 IU/m^2 IM or IV infusion over 1 to 2 hours × one dose every 14 days

Adverse Reactions

- CV: chest pain, hypertension, and hypotension
- DERM: alopecia, itching, and injection site reactions
- ENDO: hyperglycemia
- GI: anorexia; N/V (minimal), and pancreatitis
- GU: increased BUN and Cr
- HEMAT: hypofibrinogenemia and coagulopathy (thrombosis or hemorrhage)
- HEPAT: hepatotoxicity and increased LFTs
- NEURO: malaise, confusion, lethargy, and depression
- PULM: respiratory distress, cough, and epistaxis
- OTHER: hypersensitivity reaction, fever, arthralgia, musculoskeletal pain, and tumor lysis syndrome

Comments

- Contraindications: history of pancreatitis with prior l-asparaginase therapy, history of serious hemorrhagic event or

thrombosis with prior l-asparaginase therapy, history of serious allergic reactions to pegaspargase, and severe hepatic impairment.

PEGINTERFERON ALFA-2B (SYLATRON)

Mechanism of Action

- Pleiotropic cytokine; the mechanism by which it exerts its effects in patients with melanoma is unknown.

FDA-Approved Indications

- Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy

FDA-Approved Dosage

- 6 μg/kg SC weekly for eight doses followed by,
- 3 μg/kg SC weekly for up to 5 years.

Dose Modification Criteria

- Renal (moderate to severe): yes
- Hepatic: not studied (contraindicated in moderate to severe impairment for viral hepatitis)
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Performance status, tolerability: yes

Adverse Effects

- CV: angina pectoris, arrhythmias, cardiomyopathy, hypotension, and tachycardia

- DERM: alopecia, injection site reactions, and rash
- ENDO: diabetes mellitus, hyperthyroidism, and hypothyroidism
- GI: anorexia, diarrhea, and N/V (minimal)
- HEPAT: hyperbilirubinemia, increased alkaline phosphatase, and increased LFTs
- NEURO: dysgeusia, aggressive behavior, bipolar disorders, depression, encephalopathy, hallucinations, headache, increased risk of relapse in recovering drug addicts, mania, psychoses, and suicidal and homicidal ideation
- Ocular system: retinopathy
- OTHER: chills, decreased weight, dizziness, fatigue, myalgia, olfactory nerve disorder, and pyrexia

Comments

- Peginterferon α-2b is contraindicated if the patient has a known hypersensitivity reaction to interferon α-2b or peginterferon α-2b, autoimmune hepatitis, or hepatic decompensation (Child-Pugh classes B and C).
- Premedicate with acetaminophen 500 to 1000 mg PO 30 minutes prior to the first dose of peginterferon α-2b and as needed for subsequent doses.
- Use caution with concomitant medications that are metabolized by CYP2C9 or CYP2D6.
- Advise patients and their caregivers to immediately report any symptoms of depression or suicidal ideation to their healthcare provider. Monitor patients frequently during treatment and for at least 6 months after the last dose.
- Hepatic function should be monitored at 2 and 8 weeks, and 2 and 3 months following initiation of peginterferon α-2b, then every 6 months while receiving peginterferon α-2b.
- TSH levels should be obtained within 4 weeks prior to initiation of peginterferon α-2b, and at 3 and 6 months following initiation, then every 6 months thereafter while receiving peginterferon α-2b.

- Embryo-fetal toxicity: use peginterferon α-2b only if the potential benefit justifies the potential risk to the fetus.

PEMETREXED (ALIMTA)

Mechanism of Action

- Antimetabolite. An antifolate that disrupts folate-dependent metabolic process essential for cell replication

FDA-Approved Indications

- Malignant pleural mesothelioma: in combination with cisplatin in patients whose disease is unresectable or who are otherwise not candidates for curative surgery
- Nonsquamous non–small cell lung cancer (NSCLC):
  - First-line therapy in patients with metastatic, nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations in combination with pembrolizumab and platinum chemotherapy
  - First-line therapy in patients with locally advanced or metastatic nonsquamous NSCLC in combination with cisplatin
  - Maintenance therapy in patients with locally advanced or metastatic nonsquamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy
  - Second-line therapy as a single agent in patients with recurrent, metastatic nonsquamous NSCLC after prior chemotherapy

FDA-Approved Dosage

- Malignant pleural mesothelioma: 500 mg/m^2 IV infusion over 10 minutes on day 1 of each 21-day cycle in combination with cisplatin until disease progression or unacceptable toxicity.
- NSCLC:
  - First-line therapy of metastatic NSCLC in combination with pembrolizumab and platinum chemotherapy: 500 mg/m^2 IV infusion over 10 minutes on day 1 of each 21-day cycle for four cycles. Administer pemetrexed after pembrolizumab and prior to carboplatin and cisplatin. Following completion of platinum-based therapy, treatment with pemetrexed with or without

pembrolizumab may be continued until disease progression or unacceptable toxicity.
  - First-line therapy of locally advanced or metastatic NSCLC: 500 mg/m^2 IV infusion over 10 minutes administered prior to cisplatin on day 1 of each 21-day cycle for up to six cycles in the absence of disease progression or unacceptable toxicity.
  - Maintenance treatment of NSCLC: 500 mg/m^2 IV infusion over 10 minutes on day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy.
  - Treatment of recurrent NSCLC: 500 mg/m^2 IV infusion over 10 minutes on day 1 of each 21-day cycle until disease progression or unacceptable toxicity.
- See comments below regarding premedication regimen for pemetrexed.

Dose Modification Criteria

- Renal (CrCl > 45 mL/min): no
- Renal (CrCl < 45 mL/min): yes—administration is not recommended
- Hepatic: no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash and desquamation
- GI: N/V (low), mucositis, pharyngitis, diarrhea, and anorexia
- HEMAT: neutropenia, thrombocytopenia, and anemia
- HEPAT: increased LFTs
- OTHER: fatigue and fever

Comments

- Vitamin supplementation: patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related hematologic and GI toxicity. Patients should receive at least five daily doses of folic acid (400 μg to 1000 μg orally once daily) during the 7-

day period prior to the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose. Patients must also receive one IM dose of vitamin B_{12} (1000 μg) during the week prior to the first dose of pemetrexed and every three cycles (9 weeks) thereafter.

- Corticosteroid premedication: pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reactions. Recommended regimen (product labeling): dexamethasone 4 mg orally twice daily × 3 days (six doses) beginning the day prior to each dose of pemetrexed (the day before, the day of, and the day after pemetrexed).
- Embryo-fetal toxicity: pemetrexed may cause fetal harm when administered to a pregnant woman. pemetrexed is fetotoxic and teratogenic in mice; there are no studies of pemetrexed in pregnant women.

PEMIGATINIB (PEMAZYRE)

Mechanism of Action

- Kinase inhibitor that targets FGFR1, 2, and 3, thereby inhibiting FGFR signaling that leads to the proliferation and survival of malignant cells

FDA-Approved Indications

- Cholangiocarcinoma: previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, as detected by an FDA-approved test

FDA-Approved Dosage

- 13.5 mg orally once daily for 14 consecutive days followed by 7 days off (21-day cycles). May be taken without regard to food and treatment should continue until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, eGFR 30-89 mL/min/1.73 m^2 by MDRD): no
- Renal (severe, eGFR 15-29 mL/min/1.73 m^2 by MDRD): yes
- Hepatic (mild or moderate): no
- Hepatic (severe): yes
- CYP3A inhibitors (strong or moderate): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia, nail toxicity, and dry skin
- ELECTRO: hyperphosphatemia and hypophosphatemia
- GI: N/V (minimal-low), diarrhea, dysgeusia, constipation, stomatitis, dry mouth, decreased appetite, and abdominal pain
- Ocular system: dry eye and retinal pigment detachment
- OTHER: fatigue, arthralgia, and back pain

Comments

- Hyperphosphatemia is a pharmacodynamic effect and a result of the inhibition of the FGFR pathway involved in a sodium-dependent phosphate cotransporter in the proximal tubule.
- Perform ophthalmological examinations prior to initiation, every 2 months for the first 6 months of treatment, then every 3 months thereafter.
- Avoid concomitant use of strong and moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the pemigatinib dose.

- Avoid concomitant use of strong and moderate CYP3A inducers.
- Embryo-fetal toxicity: pemigatinib may cause fetal harm when administered to a pregnant woman.

PENTOSTATIN (NIPENT)

Mechanism of Action

- Antimetabolite (adenosine deaminase inhibitor)

FDA-Approved Indications

- Hairy cell leukemia (first-line and in α-interferon refractory disease)

FDA-Approved Dosage

- 4 mg/m^2 IV every other week. Pentostatin may be given as a bolus injection or diluted in a larger volume and infused over 20 to 30 minutes. The optimal treatment duration has not been determined. The package insert suggests continued treatment until a complete response has been achieved followed by two additional doses.

Dose Modification Criteria

- Renal: yes
- Hepatic: no
- Myelosuppression: yes

Adverse Reactions

- DERM: rash
- GI: N/V (low)

- GU: elevated serum creatinine (generally mild and reversible but mild-to-moderate renal toxicity may occur)
- HEMAT: leukopenia, anemia, and thrombocytopenia
- HEPAT: elevated LFTs
- OTHER: fever, infection, and fatigue

Comments

- A high incidence of fatal pulmonary toxicity was seen in a trial investigating the combination of fludarabine with pentostatin. The combined use of fludarabine and pentostatin is not recommended.
- Patients should receive IV hydration (500-1000 mL) before and after each pentostatin dose to reduce the risk of nephrotoxicity.
- Embryo-fetal toxicity: pentostatin may cause fetal harm when administered to a pregnant woman.

PERTUZUMAB (PERJETA)

Mechanism of Action

- Recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of the HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4.

FDA-Approved Indications

- Breast cancer:
  - HER2-positive metastatic breast cancer (MBC) in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
  - Neoadjuvant treatment in combination with trastuzumab and chemotherapy for patients with HER2-positive, locally advanced, inflammatory, or early-stage

breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
- Adjuvant treatment in combination with trastuzumab and chemotherapy for patients with HER2-positive early breast cancer at high risk of recurrence.

FDA-Approved Dosage

- Initial dose is 840 mg administered as a 60-minute IV infusion.
- Followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute IV infusion.
- MBC: administer pertuzumab, trastuzumab or trastuzumab and hyaluronidase-oysk, and docetaxel every 3 weeks.
- Neoadjuvant: administer pertuzumab, trastuzumab or trastuzumab and hyaluronidase-oysk, and chemotherapy preoperatively every 3 weeks for three to six cycles.
- Adjuvant: administer pertuzumab, trastuzumab or trastuzumab and hyaluronidase-oysk, and chemotherapy postoperatively every 3 weeks for a total of 1 year (up to 18 cycles).

Dose Modification Criteria

- Renal (mild to moderate): no
- Renal (severe CrCl <30 mL/min): unknown
- Hepatic: no data
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: left ventricular dysfunction
- DERM: alopecia, mucosal inflammation, paronychia, and rash
- GI: diarrhea and N/V (low)
- HEMAT: anemia, leukopenia, and neutropenia
- INFUS: chills, dysgeusia, fatigue, headache, hypersensitivity, myalgia, pyrexia, and vomiting
- NEURO: headache and peripheral neuropathy
- PULM: upper respiratory tract infection
- OTHER: asthenia and fatigue

Comments

- Detection of HER2 protein overexpression is necessary for appropriate patient selection.
- If a significant infusion reaction occurs, slow or interrupt the infusion.
- For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks, administer 420 mg IV. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg should be readministered as a 60-minute infusion followed by the normal dosing schedule.
- Left ventricular dysfunction, which includes symptomatic left ventricular systolic dysfunction and decreases in LVEF, may occur. Assess LVEF prior to initiation and at regular intervals during treatment. Withhold pertuzumab and trastuzumab and repeat LVEF assessment within 3 weeks in patients with significant decrease in LVEF (ie, a drop in LVEF to <45% or LVEF of 45% to 49% with a 10% or greater absolute decrease below pretreatment values); discontinue if the LVEF has not improved or has declined further after 3 weeks unless the benefits for the patient outweigh the risks.
- Pertuzumab should be withheld or discontinued if trastuzumab is withheld or discontinued. If docetaxel is discontinued, treatment with pertuzumab and trastuzumab may continue.
- Dose reductions are not recommended for pertuzumab.
- Embryo-fetal toxicity: pertuzumab may cause fetal harm when administered to a pregnant woman. Studies in animals have resulted in oligohydramnios, delayed renal development, and death.

PERTUZUMAB, TRASTUZUMAB, AND HYALURONIDASE (PHESGO)

Mechanism of Action

- See pertuzumab and trastuzumab
- Hyaluronidase degrades hyaluronan, an essential component of the extracellular matrix, resulting in a more permeable subcutaneous tissue thereby providing greater diffusion capacity and bioavailability

FDA-Approved Indications

- Breast cancer:
  - In combination with chemotherapy as neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either > than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer
  - In combination with chemotherapy as adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence
  - In combination with docetaxel for HER2-positive metastatic breast cancer after prior anti-HER2 therapy or chemotherapy for metastatic disease

FDA-Approved Dosage

- Initial dose: 1200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase SC in the thigh over approximately 8 minutes
- Subsequent doses: 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase SC in the thigh over approximately 5 minutes
- Neoadjuvant: every 3 weeks preoperatively for three to six cycles
- Adjuvant: every 3 weeks postoperatively for a total of 1 year (up to 18 cycles)
- Metastatic: every 3 weeks

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic: no data available

Adverse Reactions

- CV: cardiomyopathy
- DERM: alopecia and rash
- GI: N/V (minimal) and diarrhea
- HEMAT: anemia and neutropenia
- INFUS: anaphylaxis and severe hypersensitivity reactions
- NEURO: peripheral neuropathy
- PULM: interstitial pneumonitis and acute respiratory distress syndrome
- OTHER: asthenia and fatigue

Comments

- Phesgo prescribing information contains boxed warnings for cardiomyopathy, embryo-fetal toxicity, and pulmonary toxicity.
- Subclinical and clinical cardiac failure has been reported manifesting as CHF and decreased LVEF. Evaluate cardiac function prior to and during treatment and discontinue for cardiomyopathy.
- Exposure can result in embryo-fetal death and birth defects. Advise patients of the need for effective contraception and verify pregnancy status of females prior to treatment initiation.
- Discontinue Phesgo for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

PEXIDARTINIB (TURALIO)

Mechanism of Action

- TKI that targets CSF1R, KIT, and FLT3 harboring an internal tandem duplication mutation. Pexidartinib inhibits proliferation of CSF1R cell lines.

FDA-Approved Indications

- Symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery

FDA-Approved Dosage

- 400 mg orally twice daily until disease progression or unacceptable toxicity. Take on an empty stomach, at least 1 hour before or 2 hours after food.

Dose Modification Criteria

- Renal (mild to severe, CrCl 15-89 mL/min): yes
- Hepatic (mild): no
- Hepatic (moderate or severe): not established
- CYP3A inhibitors (strong or moderate): yes
- UGT inhibitors (strong or moderate): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypercholesterolemia
- DERM: hair color changes and rash
- ELECTRO: hypophosphatemia
- GI: dysgeusia
- HEMAT: neutropenia, lymphopenia, and anemia
- HEPAT: increased LDH, increased ALT, increased AST, and increased alkaline phosphate
- OTHER: fatigue and eye edema

Comments

- Pexidartinib is associated with a boxed warning for hepatotoxicity and is only available through a REMS program. Pexidartinib can cause serious and potentially fatal liver injury, and liver tests must be monitored prior to treatment initiation

and at prespecified intervals. Concurrent use of other products known to cause hepatotoxicity should be avoided.
- Avoid concomitant use with moderate or strong CYP3A inhibitors or UGT inhibitors. If coadministration cannot be avoided, reduce the pexidartinib dose.
- Avoid coadministration with CYP3A inducers.
- Avoid concomitant use of PPIs. Alternately, administer pexidartinib 2 hours before or 2 hours after a locally acting antacid or 2 hours before or 10 hours after an H_2 antagonist.
- Embryo-fetal toxicity: pexidartinib may cause fetal harm when administered to a pregnant woman.

POLATUZUMAB VEDOTIN (POLIVY)

Mechanism of Action

- As an ADC, polatuzumab vedotin binds to CD79b (a B cell–specific surface protein), undergoes internalization, then releases the cytotoxic payload MMAE (a microtubule-disrupting agent) resulting in DNA damage and apoptotic cell death

FDA-Approved Indications

- Diffuse large B-cell lymphoma (DLBCL): in combination with bendamustine and a rituximab product for relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies

FDA-Approved Dosage

- Supportive care:
  - Administer prophylaxis for *P. jirovecii* pneumonia and herpesvirus throughout treatment with polatuzumab vedotin.
  - Consider prophylactic G-CSF for neutropenia.
  - Administer tumor lysis syndrome prophylaxis for patients at increased risk of tumor lysis syndrome.

    - Premedicate with an antihistamine and antipyretic.
- 1.8 mg/kg as an IV infusion over 90 minutes every 21 days for six cycles in combination with bendamustine and a rituximab product. Subsequent infusions may be administered over 30 minutes if well tolerated.

Dose Modification Criteria

- Renal (mild to moderate, CrCl 30-89 mL/min by MDRD): no significant effects on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effects on PK
- Hepatic (moderate to severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (no classification consensus), diarrhea, and decreased appetite
- HEMAT: neutropenia, thrombocytopenia, and anemia
- HEPAT: hepatotoxicity
- INFUS: infusion-related reactions
- NEURO: peripheral neuropathy and progressive multifocal leukoencephalopathy (PML)
- PULM: pneumonia
- OTHER: fatigue, pyrexia, serious and opportunistic infections (bacterial, fungal, or viral), and tumor lysis syndrome

Comments

- Embryo-fetal toxicity: polatuzumab vedotin may cause fetal harm when administered to a pregnant woman.

POLIFEPROSAN 20 WITH CARMUSTINE IMPLANT (GLIADEL WAFER)

Mechanism of Action

- The polifeprosan 20 with carmustine implant is designed to deliver carmustine directly into the surgical cavity created when a brain tumor is resected. On exposure to the aqueous environment of the resection cavity, carmustine is released from the copolymer and diffuses into the surrounding brain tissue. Carmustine is an alkylating agent.

FDA-Approved Indications

- High-grade malignant glioma: first-line treatment in newly diagnosed patients as an adjunct to surgery and radiation
- Recurrent glioblastoma multiforme as an adjunct to surgery

FDA-Approved Dosage

- Each wafer contains 7.7 mg of carmustine. Up to eight wafers should be implanted at time of surgery (eight wafers result in a dose of 61.6 mg).

Adverse Reactions

- GI: N/V (low)
- NEURO: meningitis, abscess, and brain edema
- OTHER: abnormal wound healing, pain, asthenia, and fever

Comments

- Wafers can be broken in half. Proper handling and disposal precautions should be observed.

POMALIDOMIDE (POMALYST)

Mechanism of Action

- Immunomodulatory agent with antineoplastic activity

FDA-Approved Indications

- Multiple myeloma in combination with dexamethasone after at least two prior therapies including lenalidomide and a PI and have demonstrated disease progression on or within 60 days of completion of last therapy
- Kaposi Sarcoma (KS):
  - Treatment of adult patients with AIDS-related KS after failure of highly active antiretroviral therapy (HAART)
  - Treatment of KS in adult patients who are HIV negative

FDA-Approved Dosage

- Multiple myeloma: 4 mg orally, once daily on days 1 to 21 of a 28-day cycle in combination with dexamethasone until disease progression.
- KS: 5 mg orally, once daily on days 1 to 21 of a 28-day cycle until disease progression or unacceptable toxicity. Continue HAART as HIV treatment in patients with AIDS-related KS.

Dose Modification Criteria

- Renal (mild to severe, not requiring dialysis): no
- Renal (severe impairment requiring dialysis): yes
- Hepatic (mild to severe, Child-Pugh classes A, B, and C): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: venous and arterial thromboembolism
- DERM: rash
- GI: N/V (minimal-low), constipation, diarrhea, and decreased appetite
- HEMAT: neutropenia, anemia, and thrombocytopenia
- HEPAT: elevated ALT and bilirubin and hepatic failure
- NEURO: neuropathy, fatigue, and dizziness
- PULM: upper respiratory tract infection and dyspnea
- OTHER: hypersensitivity reactions (angioedema, severe dermatologic reactions), peripheral edema, pyrexia, back pain, muscle spasms, arthralgia, fatigue, asthenia, and tumor lysis syndrome

Comments

- Pomalidomide is only available through a restricted distribution program (Pomalyst REMS program). Only prescribers and pharmacists registered with the program are allowed to prescribe and dispense pomalidomide.
- Embryo-fetal toxicity: pomalidomide is an analog of thalidomide, which is a known teratogen. Pomalidomide may cause severe birth defects or death to an unborn baby. Refer to the product labeling for information regarding requirements for pregnancy testing, and patient consent as part of the Pomalyst REMS program.
- Myelosuppression (particularly neutropenia and thrombocytopenia) is a common and dose-limiting toxicity. Monitor blood counts closely as indicated in the product labeling.
- Pomalidomide may cause venous and arterial thromboembolic event. Prophylactic anticoagulation treatment is recommended.
- Pomalidomide is a substrate of CYP1A2. Avoid concomitant use with strong CYP1A2 inhibitors. If concomitant use with a CYP1A2 inhibitor is unavoidable, a dose reduction of pomalidomide is recommended.

- Smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction. Advise patients that smoking may reduce efficacy.

PONATINIB (ICLUSIG)

Mechanism of Action

- TKI of BCR-ABL and T315I mutant ABL, and additional kinases including members of the VEGFR, PDGFR, FGFR, and EPH receptors and SRC families of kinase, and KIT, RET, TIE2, and FLT-3

FDA-Approved Indications

- Chronic myeloid leukemia (CML):
  - Treatment of adults with chronic-phase (CP) CML with resistance or intolerance to at least two prior kinase inhibitors
  - Treatment of accelerated-phase, or blast-phase CML in patients for whom no other TKI is indicated
  - Treatment of T315I-positive CML (CP, accelerated phase, or blast-phase)
- Acute lymphoblastic leukemia (Ph+ ALL) : treatment of adults for whom no other TKI is indicated or with T315I-positive disease

FDA-Approved Dosage

- 45 mg orally once daily with or without food. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal: not studied
- Hepatic (mild to severe): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Effects

- CV: cardiac arrhythmias, CHF, hypertension, left ventricular dysfunction, myocardial infarction, and worsening coronary artery disease
- DERM: dry skin and rash
- ELECTRO: decreased bicarbonate, hyperglycemia, hyperkalemia, hypernatremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, and hyponatremia
- GI: abdominal pain, constipation, mucositis, N/V (minimal-low), and pancreatitis
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- NEURO: headache, peripheral neuropathy, and stroke
- Ocular system: retinal and other ocular toxicities
- PULM: cough, dyspnea, nasopharyngitis, pneumonia, and upper respiratory tract infection
- OTHER: arterial thrombosis, arthralgia, asthenia, back pain, fatigue, fluid retention, hemorrhage, impaired wound healing, infections, muscle spasms, myalgia, pain in extremity, pyrexia, tumor lysis syndrome, venous thromboembolism, and increased lipase

Comments

- Patients with CV risk factors are at increased risk for arterial thrombosis with ponatinib.
- Monitor LFTs as baseline, at least monthly, or as clinically indicated.
- Monitor patients for signs or symptoms consistent with CHF.
- Monitor and manage BP elevations.
- Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse.

- Interrupt ponatinib for at least 1 week prior to major surgery. The decision when to resume ponatinib after surgery should be based on clinical judgment of adequate wound healing.
- Conduct a comprehensive eye examination at baseline and periodically during treatment to monitor for ocular toxicity.
- Patients taking strong inhibitors of CYP3A require a dose reduction of ponatinib. Concomitant strong inhibitors may increase risk for adverse reactions.
- Coadministration of strong CYP3A inducers should be avoided.
- Elevated gastric pH may reduce bioavailability and exposure of ponatinib. Coadministration of ponatinib with PPIs, H_2 blockers, or antacids should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure.
- Patients aged 65 years and older may be more likely to experience adverse reactions including decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. Dose selection for an elderly patient should be cautious.
- Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in ponatinib-treated patients. Interrupt therapy for signs and symptoms consistent with RPLS.
- Embryo-fetal toxicity: ponatinib can cause fetal harm when administered to a pregnant woman.

PORFIMER (PHOTOFRIN)

Mechanism of Action

- Photosensitizing agent

FDA-Approved Indications

- Esophageal cancer: palliation of complete or partial obstruction
- Endobronchial non–small cell lung cancer (NSCLC):

    - For reduction of obstruction and palliation of symptoms in patients with completely or partially obstructed endobronchial NSCLC.
    - For treatment of microinvasive endobronchial NSCLC in patients for whom surgery and RT are not indicated.
- High-grade dysplasia in Barrett esophagus: ablation of high-grade dysplasia in patients who do not undergo esophagectomy.

FDA-Approved Dosage

- 2 mg/kg IV injection over 3 to 5 minutes × one dose followed by photodynamic therapy. For the treatment of esophageal and endobronchial cancer, patients may receive up to three additional courses; each course should be administered no sooner than 30 days after the prior course. For the ablation of high-grade dysplasia in Barrett esophagus, patients may receive up to three additional courses; each course should be administered no sooner than 90 days after the prior course.

Adverse Reactions

- CV: hypertension, hypotension, heart failure, chest pain, atrial fibrillation, and tachycardia
- DERM: photosensitivity
- HEMAT: anemia
- GI: N/V (not classified), abdominal pain, anorexia, constipation, dysphagia, esophageal edema, and esophageal stricture
- NEURO: anxiety, confusion, and insomnia
- PULM: pleural effusion, dyspnea, pneumonia, pharyngitis, cough, respiratory insufficiency, and tracheoesophageal fistula
- OTHER: fever

Comments

- Patients are photosensitive (including eyes) for at least 30 days after administration.

PRALATREXATE (FOLOTYN)

Mechanism of Action

- Folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. It is also a competitive inhibitor for polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biologic molecules, the synthesis of which depends on single carbon transfer.

FDA-Approved Indications

- Treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL)

FDA-Approved Dosage

- 30 mg/m^2 administered as an IV push over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles

Dose Modification Criteria

- Renal (mild to moderate): no; monitor for toxicity
- Renal (severe eGFR 15-30 mL/min/1.73 m^2): yes and monitor for toxicity
- Renal (end stage renal disease and/or dialysis): avoid use
- Hepatic: not evaluated
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Effects

- Cr: increased serum creatinine
- CV: tachycardia

- DERM: bullous exfoliative skin reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, pruritus, and rash
- ELECTRO: hypokalemia
- GI: abdominal pain, constipation, diarrhea, mucositis, and N/V (low)
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- PULM: cough, dyspnea, and upper respiratory tract infection
- OTHER: asthenia, back pain, dehydration, edema, epistaxis, fatigue, night sweats, pain in extremity, pharyngolaryngeal pain, pyrexia, sepsis, and tumor lysis syndrome

Comments

- Prior to initiating pralatrexate, patients should be supplemented with vitamin B_{12} 1 mg IM every 8 to 10 weeks and folic acid 1 to 1.25 mg orally on a daily basis.
- Monitor for mucositis weekly, and if ≥grade 2 mucositis is observed, omit or reduce dose as recommended in product labeling.
- Pralatrexate should not be diluted. It is a clear, yellow solution.
- Coadministration with probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs) require close monitoring for signs of systemic toxicity.
- Embryo-fetal toxicity: pralatrexate can cause fetal harm when administered to a pregnant woman. Women should be advised against breastfeeding while being treated with pralatrexate.

PRALSETINIB (GAVRETO)

Mechanism of Action

- Kinase inhibitor of wild-type *RET*, oncogenic *RET* fusions, and select mutations. Pralsetinib may also inhibit other pathways including those through FLT3, JAK1-2, PDGFRB, VEGFR-2, and FGFR1. *RET* fusion proteins and activating point mutations can act as oncogenic drivers by promoting cell proliferation of tumor cell lines and pralsetinib inhibits this process.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): treatment of adult patients with metastatic *RET* fusion–positive NSCLC as detected by an FDA-approved test
- Medullary thyroid cancer:
  - Treatment of adult and pediatric patients 12 years and older with advanced or metastatic *RET*-mutant medullary thyroid cancer who require systemic therapy
  - Treatment of adult and pediatric patients 12 years and older with advanced or metastatic *RET* fusion–positive thyroid cancer who require systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate)

FDA-Approved Dosage

- 400 mg orally once daily until disease progression or unacceptable toxicity. Take on an empty stomach, no food intake for at least 2 hours before and 1 hour after taking pralsetinib.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 15 mL/min): no data available
- Hepatic (mild): no significant effect on exposure
- Hepatic (moderate or severe): no data available
- Dual P-gp and CYP3A inhibitor (strong): yes
- CYP3 inducer (strong): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension
- ELECTRO: hypophosphatemia, hypocalcemia, and hyponatremia
- GI: N/V (minimal-low), constipation, and diarrhea
- HEMAT: lymphopenia, neutropenia, anemia, thrombocytopenia, and hemorrhage
- HEPAT: hepatotoxicity, increased AST, increased ALT, and increased alkaline phosphatase
- PULM: interstitial lung disease/pneumonitis
- OTHER: fatigue, musculoskeletal pain, tumor lysis syndrome, and impaired wound healing

Comments

- In adolescent patients with open growth plates, monitor for growth plate abnormalities.
- Withhold pralsetinib for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.
- Avoid concomitant administration with strong CYP3A inhibitors.
- Avoid concomitant administration with dual P-gp and strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the pralsetinib dose.
- Avoid concomitant administration with strong CYP3A inducers. If coadministration cannot be avoided, increase the pralsetinib dose.
- Embryo-fetal toxicity: pralsetinib may cause fetal harm when administered to a pregnant woman.

PROCARBAZINE (MATULANE)

Mechanism of Action

- The mechanism is unknown. There is evidence that the drug may act by inhibition of protein, and RNA and DNA synthesis.

FDA-Approved Indications

- Stage III and IV Hodgkin lymphoma: first-line treatment in combination with other anticancer drugs. (Procarbazine is used as part of the MOPP [mechlorethamine, vincristine, procarbazine, and prednisone] chemotherapy regimen.)

FDA-Approved Dosage

- All doses based on actual body weight unless the patient is obese or there has been a spurious weight increase, in which case lean body weight (dry weight) should be used.
- Doses may be given as a single daily dose or divided throughout the day.
- MOPP regimen for Hodgkin lymphoma: 100 mg/m^2 orally daily × 14 days (in combination with mechlorethamine, vincristine, and prednisone).
- Adult single-agent therapy: 2 to 4 mg/kg orally daily × 7 days, and then 4 to 6 mg/kg orally daily until maximal response is obtained. Maintenance dose: 1 to 2 mg/kg orally daily.
- Pediatric single-agent therapy: 50 mg/m^2 orally daily × 7 days, and then 100 mg/m^2 orally daily until maximum response is obtained. Maintenance dose: 50 mg/m^2 orally daily.

Adverse Reactions

- DERM: pruritus, hyperpigmentation, and alopecia
- GI: anorexia, N/V (moderate-high), stomatitis, xerostomia, diarrhea, and constipation
- HEMAT: myelosuppression

- NEURO: paresthesias, confusion, lethargy, and mental depression
- OTHER: fever and myalgia

Comments

- Disulfiram-like (Antabuse) reaction can occur; avoid alcoholic beverages while taking procarbazine.
- Procarbazine is a weak monoamine oxidase inhibitor; avoid tyramine-rich foods, sympathomimetic drugs, and antidepressant agents (eg, tricyclic or selective serotonin reuptake inhibitors). Screen for other potential drug-drug interactions.

RALOXIFENE (EVISTA)

Mechanism of Action

- Estrogen agonist/antagonist (selective ER modulator)

FDA-Approved Indications

- Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis
- Reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer
- Treatment and prevention of osteoporosis in postmenopausal women

FDA-Approved Dosage

- 60 mg orally once daily

Dose Modification Criteria

- Renal: no (use with caution in patients with moderate or severe impairment)
- Hepatic: no (use with caution in patients with impairment)
- Myelosuppression: no
- Nonhematologic toxicity: no

Adverse Reactions

- CV: peripheral edema
- GI: N/V (not classified)
- OTHER: hot flashes, leg cramps, flu syndrome, arthralgia, sweating, and venous thromboembolic events (deep venous thrombosis, PE, retinal vein thrombosis, and superficial thrombophlebitis)

Comments

- Women with active or past history of VTE should not take raloxifene. Raloxifene should be discontinued at least 72 hours prior to and during prolonged immobilization (eg, postsurgical recovery and prolonged bed rest), and raloxifene should be resumed only after the patient is fully ambulatory. Women should be advised to move about periodically during prolonged travel.
- In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk of coronary events, an increased risk of death due to stroke was observed after treatment with raloxifene. However, there was no statistically significant difference between treatment groups in the incidence of stroke.
- Cholestyramine (and other anion exchange resins) should not be used concurrently with raloxifene.
- If used concomitantly with warfarin, monitor PT when starting or stopping raloxifene.
- Raloxifene is highly protein bound (95%); use with caution with other highly protein-bound drugs.

- Embryo-fetal toxicity: raloxifene may cause fetal harm when administered to a pregnant woman.

RAMUCIRUMAB (CYRAMZA)

Mechanism of Action

- Recombinant human IgG1 monoclonal antibody that binds to VEGFR-2.

FDA-Approved Indications

- Gastric cancer: treatment of advanced or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma that has progressed on or after prior fluoropyrimidine or platinum-containing chemotherapy. May be used as a single agent or in combination with paclitaxel.
- Non–small cell lung cancer (NSCLC):
  - First-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in combination with erlotinib.
  - Treatment of metastatic NSCLC with disease progression on or after platinum-based therapy in combination with docetaxel. Patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy specific for these mutations.
- Colorectal cancer (CRC): treatment of metastatic CRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine in combination with FOLFIRI.
- Hepatocellular carcinoma (HCC): single-agent treatment of patients with HCC who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

FDA-Approved Dosage

- Gastric cancer: 8 mg/kg IV infusion over 60 minutes every 2 weeks as either a single agent or in combination with weekly paclitaxel
- NSCLC:
  - First-line treatment in combination with erlotinib: 10 mg/kg IV infusion over 60 minutes every 2 weeks
  - Disease progression on or after platinum-based chemotherapy with docetaxel: 10 mg/kg IV infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion
- Metastatic CRC: 8 mg/kg IV infusion over 60 minutes every 2 weeks prior to FOLFIRI administration
- HCC: 8 mg/kg IV infusion over 60 minutes every 2 weeks
- If initial 60-minute IV infusion of ramucirumab is tolerated, subsequent infusions may be administered over 30 minutes
- All indications: continue until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate, total bilirubin <3 × ULN): no; clinical deterioration was reported in patients with Child-Pugh class B or C cirrhosis who received single-agent ramucirumab
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension and arterial thromboembolic events
- ENDO: hypothyroidism
- GI: GI perforations, N/V (minimal) diarrhea, and stomatitis
- GU: proteinuria
- HEMAT: hemorrhage, neutropenia, and thrombocytopenia
- INFUS: rigors/tremors, back pain/spasms, chest pain, chills, flushing, dyspnea, wheezing, and hypoxia
- OTHER: impaired wound healing, fatigue, asthenia, and infusion reactions

Comments

- Premedicate with an IV histamine H_1 antagonist prior to each infusion. Patients who have experienced a grade 1 or 2 infusion-related reaction should also receive dexamethasone and acetaminophen as premedication.
- Hemorrhage: ramucirumab increased the risk of hemorrhage and GI hemorrhage, including severe and sometimes fatal hemorrhagic events. Discontinue therapy in patients who experience severe bleeding.
- Ramucirumab is an antiangiogenic therapy, which can lead to complications such as GI perforation and impaired wound healing. Discontinue ramucirumab prior to surgery and in patients who develop GI perforation or develop wound healing complications.
- Hypertension: control hypertension prior to initiating therapy and monitor BP every 2 weeks or more frequently as indicated during therapy.
- Proteinuria: monitor for proteinuria. Withhold for urine protein levels ≥2 g/24 h and permanently discontinue for urine protein levels ≥3 g/24 h or nephrotic syndrome.
- Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported rarely with ramucirumab.
- Embryo-fetal toxicity: ramucirumab may cause fetal harm when administered to a pregnant woman.

REGORAFENIB (STIVARGA)

Mechanism of Action

- Kinase inhibitor of multiple membrane-bound and intracellular kinases

FDA-Approved Indications

- Colorectal cancer (CRC): treatment of metastatic CRC in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild type, an anti-EGFR therapy.
- Gastrointestinal stromal tumor (GIST): treatment of locally advanced, unresectable, or metastatic GIST in patients who have been previously treated with imatinib mesylate and sunitinib malate.
- Hepatocellular carcinoma (HCC): treatment of patients with HCC who have been previously treated with sorafenib.

FDA-Approved Dosage

- 160 mg orally once daily with a low-fat meal for the first 21 days of each 28-day cycle

Dose Modification Criteria

- Renal (mild to severe): no
- Renal (end stage renal disease or dialysis): no data
- Hepatic (mild to moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): not studied
- Nonhematologic toxicity: yes

Adverse Effects

- CV: cardiac ischemia, cardiac infarction, and hypertension
- DERM: hand-foot skin reaction and rash
- ELECTRO: hypocalcemia, hypokalemia, hyponatremia, and hypophosphatemia
- GI: decreased appetite, diarrhea, mucositis, abdominal pain, and N/V (minimal-low)
- GU: proteinuria
- HEMAT: anemia, lymphopenia, and thrombocytopenia
- HEPAT: increased bilirubin and increased LFTs

- OTHER: asthenia, dysphonia, fatigue, hemorrhage, infection, weight loss, wound healing complications, fever, and increased amylase and/or lipase

Comments

- Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Obtain LFTs before initiation of regorafenib and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor LFTs weekly in patients experiencing elevated LFTs until improvement to <3 times the ULN or baseline. Temporarily hold and then reduce or permanently discontinue regorafenib depending on the severity and persistence of hepatotoxicity as manifested by elevated LFTs or hepatocellular necrosis.
- For dermatologic toxicity, withhold regorafenib, reduce dose, or permanently discontinue therapy depending on the severity and persistence of toxicity.
- Regorafenib caused an increased incidence of hemorrhage. Permanently discontinue regorafenib in patients with severe or life-threatening hemorrhage. Monitor INR levels more frequently in patients receiving warfarin.
- Regorafenib increased the incidence of myocardial ischemia and infarction. Withhold regorafenib in patients who develop new or acute-onset cardiac ischemia or infarction.
- Monitor BP weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold regorafenib for severe or uncontrolled hypertension.
- GI perforation or fistula can occur. Permanently discontinue regorafenib in these patients.
- Treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery.
- Regorafenib should be discontinued in patients with wound dehiscence.

- Monitor for RPLS. Confirm the diagnosis of RPLS with MRI and discontinue regorafenib in patients who develop RPLS.
- Strong CYP3A4 inhibitors and inducers should be avoided with regorafenib. Regorafenib and its metabolites competitively inhibit UGT1A9 and UGT1A1, which may increase the exposure of UGT1A1 substrates (eg, irinotecan). Regorafenib may also increase the exposure to BCRP substrates (eg, methotrexate, rosuvastatin).
- Embryo-fetal toxicity: regorafenib may cause fetal harm when administered to a pregnant woman. Results from animal studies indicate that regorafenib can impair male and female infertility.

RELUGOLIX (ORGOVYX)

Mechanism of Action

- GnRH antagonist that competitively binds to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone

FDA-Approved Indications

- Treatment of patients with advanced prostate cancer

FDA-Approved Dosage

- 360 mg orally on the first day followed by 120 mg once daily thereafter. May be taken with or without food.

Dose Modification Criteria

- Renal (mild to severe, CrCl 15-89 mL/min): no significant effect on PK
- Hepatic (mild or moderate, Child-Pugh class A or B): no significant effect on PK

- Hepatic (severe, Child-Pugh class C): no data available
- Dual P-gp and CYP3A inhibitors (strong): yes

Adverse Reactions

- CV: hypertriglyceridemia and QT prolongation
- ENDO: hot flush and hyperglycemia
- GI: constipation and diarrhea
- HEMAT: anemia
- HEPAT: increased ALT and increased AST
- OTHER: musculoskeletal pain and fatigue

Comments

- Avoid concurrent administration with oral P-gp inhibitors. If coadministration is unavoidable, take relugolix first and separate dosing by at least 6 hours.
- Avoid concurrent administration with dual P-gp and strong CYP3A inducers. If coadministration is unavoidable, increase the relugolix dose.
- Embryo-fetal toxicity: relugolix can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception.

RIBOCICLIB (KISQALI)

Mechanism of Action

- Inhibitor of CDK4 and CDK6 that results in the blockade of retinoblastoma protein phosphorylation leading to arrest in the G1 phase of the cell cycle

FDA-Approved Indications

- Breast cancer:

- In combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer, as initial endocrine-based therapy
- In combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy

FDA-Approved Dosage

- 600 mg orally once daily with or without food for 21 consecutive days followed by 7 days off treatment (28-day cycle). Continue therapy until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no
- Renal (severe, CrCl 15 to < 30 mL/min): yes
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate or severe, Child-Pugh class B or C): yes
- CYP3A inhibitors (strong): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: alopecia, rash, and severe cutaneous adverse reactions
- GI: N/V (no classification consensus), diarrhea, and constipation
- HEMAT: neutropenia and leukopenia
- HEPAT: increased serum transaminases
- NEURO: headache
- PULM: cough and interstitial lung disease/pneumonitis
- OTHER: infections and fatigue

Comments

- Avoid concomitant use of CYP3A inhibitors. If coadministration cannot be avoided, reduce the ribociclib dose.
- The dose of sensitive CYP3A substrates with narrow therapeutic indices may need to be reduced if administered concurrently with ribociclib.
- Avoid concomitant use of drugs known to prolong the QT interval. Monitor ECGs and electrolytes.
- Embryo-fetal toxicity: ribociclib may cause fetal harm when administered to a pregnant woman.

RIPRETINIB (QINLOCK)

Mechanism of Action

- Kinase inhibitor that targets KIT and PDGFRA. Ripretinib also inhibits PDGFRB, TIE2, VEGFR-2, and BRAF.

FDA-Approved Indications

- Gastrointestinal stromal tumor (GIST): advanced GIST after prior treatment with three or more kinase inhibitors, including imatinib

FDA-Approved Dosage

- 150 mg orally once daily with or without food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30 to < 90 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available

- CYP3A inducers (moderate): yes
- Nonhematologic toxicities: yes

Adverse Reactions

- CV: hypertension and cardiac dysfunction
- DERM: alopecia, PPE, and new primary cutaneous malignancies
- ELECTRO: hypophosphatemia
- GI: N/V (minimal-low), abdominal pain, constipation, diarrhea, decreased appetite, and increased lipase
- OTHER: fatigue, myalgia, and compromised wound healing

Comments

- Assess LVEF prior to initiating treatment with ripretinib and monitor throughout treatment.
- Withhold ripretinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing.
- Avoid concomitant administration of strong CYP3A inducers.
- If concomitant administration of a CYP3A inhibitor is necessary, monitor more frequently for ripretinib adverse reactions.
- Avoid concomitant administration of moderate CYP3A4 inducers. If coadministration cannot be avoided, increase the ripretinib dose frequency.
- Embryo-fetal toxicity: ripretinib may cause fetal harm when administered to a pregnant woman.

RITUXIMAB (RITUXAN)

Mechanism of Action

- Chimeric (murine, human) monoclonal antibody directed at the CD20 antigen found on the surface of normal and malignant B lymphocytes.

FDA-Approved Indications

- Non-Hodgkin's lymphoma (NHL):
  - Relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL as a single agent
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Nonprogressive (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic lymphocytic leukemia (CLL): in combination with fludarabine and cyclophosphamide in previously untreated and previously treated CD20-positive CLL
- Other: rheumatoid arthritis, granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, and pemphigus vulgaris (PV)

FDA-Approved Dosage

- Premedication with acetaminophen and an antihistamine (eg, diphenhydramine) should be considered before each infusion.
- If a patient experiences an infusion-related reaction, the infusion should be stopped, the patient managed symptomatically, and then the infusion should be restarted at half the rate once the symptoms have resolved.
- NHL—375 mg/m^2/dose IV infusion according to the following schedules:
  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL: administer once weekly for four or eight doses.
  - Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL: administer once weekly for four doses.
  - Previously untreated, follicular, CD20-positive, B-cell NHL: administer on day 1 of each cycle of chemotherapy, for up to eight doses. For maintenance therapy in patients who obtain a complete or partial response, administer as a single-agent every 8 weeks for 12 doses.
  - Nonprogressing, low-grade, CD20-positive, B-cell NHL, after first-line CVP chemotherapy: administer once weekly for four doses at 6-month intervals to a

maximum of 16 doses.
    - Diffuse large B-cell NHL: administer on day 1 of each cycle of chemotherapy for up to eight infusions.
- CLL: 375 mg/m^2 IV infusion × one dose the day prior to initiation of fludarabine and cyclophosphamide chemotherapy, followed by 500 mg/m^2 IV infusion on day 1 of cycles 2 to 6 (every 28 days).
- Rate titration: for the first infusion start at 50 mg/h, and then may increase by 50 mg/h every 30 minutes up to a maximum of 400 mg/h. If the initial infusion is tolerated, subsequent infusions can be administered at an advanced rate either in a standard infusion rate titration or a more rapid 90 minute titration format for certain patient populations.
    - Standard infusion titration: start at 100 mg/h, and then may increase by 100 mg/h every 30 minutes up to a maximum of 400 mg/h.
    - Advanced rate 90-minute infusion (evaluated in previously untreated follicular NHL and DLBCL patients with a glucocorticoid-containing chemotherapy regimen): start at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes.

Adverse Reactions

- CV: hypotension, arrhythmias, and peripheral edema
- DERM: rash, pruritus, urticaria, and severe mucocutaneous reactions
- GI: N/V (minimal) and abdominal pain
- HEMAT: leukopenia, thrombocytopenia, and neutropenia
- INFUS: fever, chills, rigors, hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, angioedema, myocardial infarction, ventricular fibrillation, or cardiogenic shock
- NEURO: headache and dizziness
- OTHER: throat irritation, rhinitis, bronchospasm, hypersensitivity reaction, myalgia, back pain, tumor lysis syndrome, asthenia, and infections

Comments

- Tumor lysis syndrome has been reported within 12 to 24 hours after the infusion (high-risk: high numbers of circulating malignant cells).
- Mild to moderate infusion reactions consisting of fever, chills, and rigors occur in the majority of patients during the first infusion. The reactions resolve with slowing or interruption of the infusion and with supportive care measures. The incidence of infusion reactions declines with subsequent infusions.
- A more severe infusion-related complex, usually reported with the first infusion (hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock) has resulted in fatalities.
- Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with rituximab treatment.
- Serious infections including bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab-based therapy. Reported infectious complications include PML secondary to the JC virus, and HBV reactivation resulting in fulminant hepatitis, hepatic failure, and death.
- HBV reactivation: screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating rituximab therapy. For patients who show evidence of prior HBV (HBsAg positive or HBsAg negative but anti-HBc positive), monitor for reactivation during and for several months after rituximab therapy. Consult with physicians with expertise in managing hepatitis B in regards to monitoring and consideration of antiviral prophylaxis.
- Rituximab is commonly combined with cytotoxic chemotherapy agents in various subtypes of B-cell NHL. Consult current literature for dosing regimens.

RITUXIMAB AND HYALURONIDASE (RITUXAN HYCELA)

Mechanism of Action

- Rituximab: chimeric (murine, human) monoclonal antibody directed at the CD20 antigen found on the surface of normal and malignant B lymphocytes
- Hyaluronidase: degrades hyaluronan, an essential component of the extracellular matrix, resulting in a more permeable subcutaneous tissue thereby providing greater diffusion capacity and bioavailability

FDA-Approved Indications

- Follicular lymphoma (FL):
  - Relapsed or refractory FL as a single agent
  - Previously untreated FL in combination with first-line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
- Diffuse large B-cell lymphoma (DLBCL): previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone, or other anthracycline-based chemotherapy regimens
- Chronic lymphocytic leukemia (CLL): previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide

FDA-Approved Dosage

- Premedicate with acetaminophen and antihistamine before each dose; also consider premedication with glucocorticoids
- FL/DLBCL: 1400 mg rituximab and 23,400 units hyaluronidase SC over approximately 5 minutes according the schedule outlined in the prescribing information

- CLL: 1600 mg rituximab and 26,800 units hyaluronidase SC over approximately 7 minutes according to the schedule outlined in the prescribing information

Dose Modification Criteria

- No dose reduction of rituximab/hyaluronidase is recommended
- Renal: no data available
- Hepatic: no data available

Adverse Reactions

- Cr: renal toxicity
- CV: cardiac events (ventricular fibrillation, myocardial infarction, and cardiogenic shock)
- DERM: alopecia and severe mucocutaneous reactions
- GI: N/V (minimal), bowel obstruction, perforation, and constipation
- HEMAT: neutropenia, anemia, and thrombocytopenia
- HEPAT: hepatitis B reactivation
- INFUS: hypersensitivity reaction and local cutaneous reactions
- NEURO: PML
- PULM: cough
- OTHER: tumor lysis syndrome, infections, fatigue, and pyrexia

Comments

- Initiate treatment with rituximab/hyaluronidase only after patients have received at least one full dose of a rituximab product by IV infusion.
- Rituximab/hyaluronidase is associated with the following boxed warnings:
  - Severe mucocutaneous reactions, some with fatal outcomes.
  - HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death.
  - PML resulting in death.

- Vaccination with a live virus prior to and during treatment is not recommended.
- Embryo-fetal toxicity: rituximab/hyaluronidase may cause fetal harm when administered to a pregnant woman.

ROMIDEPSIN (ISTODAX)

Mechanism of Action

- HDAC inhibitor

FDA-Approved Indications

- Cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy

FDA-Approved Dosage

- 14 mg/m^2 administered IV over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Repeat cycles every 28 days provided that the patient continues to benefit from and tolerates the drug.

Dose Modification Criteria

- Renal (mild to severe): no
- Renal (end-stage renal disease): no data, use with caution
- Hepatic (mild): no
- Hepatic (moderate to severe): no data, use with caution
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: ECG T wave and ST segment changes, hypotension, and tachycardia

- DERM: dermatitis, exfoliative dermatitis, and pruritus
- ELECTRO: hypermagnesemia, hyperuricemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, and hypophosphatemia
- ENDO: hyperglycemia
- GI: abdominal pain, anorexia, constipation, diarrhea, N/V (moderate), and stomatitis
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs and hypoalbuminemia
- NEURO: dysgeusia
- PULM: cough and dyspnea
- OTHER: asthenia, chills, decreased weight, fatigue, infections, peripheral edema, pyrexia, and tumor lysis syndrome

Comments

- Serious and sometimes fatal infections have been reported during treatment and within 30 days after treatment with romidepsin. Viral reactivation, including Epstein-Barr and hepatitis B, has been reported in clinical trials. In patients with evidence of prior hepatitis B infection, consider monitoring for reactivation and antiviral prophylaxis.
- Carefully monitor PT and INR in patients concurrently administered romidepsin and warfarin derivatives.
- Strong CYP3A4 inhibitors and inducers should be avoided with romidepsin.
- In patients with congenital long QT syndrome, those with a history of significant CV disease, and in those taking antiarrhythmic medicines that lead to significant QT prolongation, appropriate CV monitoring precautions should be considered, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment. Potassium and magnesium should be within the normal range before administration of romidepsin.

- Embryo-fetal toxicity: based on its mechanism of action and findings in animals, romidepsin may cause fetal harm when administered to a pregnant woman.

RUCAPARIB (RUBRACA)

Mechanism of Action

- Inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3, which play a role in DNA repair

FDA-Approved Indications

- Ovarian cancer:
  - Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.
  - Treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.
- Prostate cancer:
  - Treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)–associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen-directed therapy and a taxane-based chemotherapy.

FDA-Approved Dosage

- 600 mg orally, twice daily with or without food until disease progression or unacceptable toxicity.
- Patients receiving rucaparib for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dose Modification Criteria

- Renal (mild to moderate, CrCl > 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data
- Hepatic (mild): no
- Hepatic (moderate to severe): no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reaction

- GI: abdominal pain, decreased appetite, N/V (moderate-high), diarrhea, and constipation
- GU: increased serum creatinine
- HEMAT: anemia, neutropenia, thrombocytopenia, and lymphopenia
- HEPAT: increased AST/ALT
- NEURO: dysgeusia
- PULM: dyspnea
- OTHER: fatigue/asthenia and hypercholesterolemia

Comments

- Myelodysplastic syndrome/acute myeloid leukemia has been reported in patients who have received rucaparib. Monitor patients for hematologic toxicity at baseline and monthly thereafter.
- Embryo-fetal toxicity: rucaparib may cause fetal harm when administered to a pregnant woman.

RUXOLITINIB (JAKAFI)

Mechanism of Action

- Inhibits Janus-associated kinases (JAKs), JAK1 and JAK2, which mediate the signaling of cytokines and growth factors that are important for hematopoiesis and immune function. JAK

signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

FDA-Approved Indications

- Myelofibrosis: treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis.
- Polycythemia vera: treatment of adult patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.
- Acute graft-versus host disease (GVHD): treatment of steroid-refractory acute GVHD in adult and pediatric patients 12 years and older.

FDA-Approved Dosage

- Myelofibrosis:
  - Starting dose is based on patient's baseline platelet count:
    - 20 mg orally twice daily for patients with a platelet count greater than 200×10^9/L.
    - 15 mg orally twice daily for patients with a platelet count between 100×10^9/L and 200×10^9/L.
    - 5 mg orally twice daily for patients with a platelet count between 50×10^9/L and less than 100×10^9/L.
  - Increase dose based on response to a maximum of 25 mg orally twice daily.
  - Discontinue after 6 months if no spleen reduction or symptom improvement.
- Polycythemia vera:
  - Starting dose is 10 mg orally twice daily. Doses may be titrated based on safety and efficacy.
- Acute GVHD:
  - Recommended starting dose is 5 mg orally twice daily. Consider increasing the dose to 10 mg orally twice daily after 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with ruxolitinib. Tapering may be considered after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids.

Dose Modification Criteria

- Renal (mild): no
- Renal (moderate, severe, end-stage renal disease): use and dose modification depend on platelet count
- Hepatic impairment: use and dose modification depend on platelet count
- Hematologic toxicity: yes

Adverse Reactions

- DERM: bruising
- GI: flatulence
- GU: urinary tract infection
- HEME: anemia, neutropenia, and thrombocytopenia
- NEURO: dizziness and headache
- OTHER: infection and weight gain

Comments

- Can be administered through a nasogastric (NG) tube (≥8 Fr). Suspend one tablet in 40 mL of water with stirring for approximately 10 minutes. Within 6 hours after the tablet hast dispersed, the suspension can be administered through a NG tube using an appropriate syringe. Flush NG tube with 75 mL of water.
- Active serious infections should have resolved before starting therapy.
- May cause lipid elevations. Monitor lipid levels 8 to 12 weeks after starting therapy.
- Screen for drug interactions. Concomitant use with strong CYP3A4 inhibitors or fluconazole may require dose interruption, reduction, or discontinuation.
- Ruxolitinib may increase the risk of nonmelanoma skin cancer; perform periodic skin examinations.
- Embryo-fetal toxicity: there are no adequate and well-controlled studies of ruxolitinib in pregnant women.

SACITUZUMAB GOVITECAN (TRODELVY)

Mechanism of Action

- As a Trop2-directed ADC, sacituzumab govitecan binds to Trop2 expressing cancer cells, undergoes internalization, then releases the cytotoxic payload SN-38 (a topoisomerase I inhibitor) resulting in DNA damage and apoptotic cell death.

FDA-Approved Indications

- Breast cancer: unresectable locally advanced or metastatic triple-negative breast cancer following two or more prior systemic therapies, including at least one for metastatic disease
- Urothelial cancer: locally advanced or metastatic urothelial cancer following previous treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor

FDA-Approved Dosage

- Premedications:
  - For prevention of infusion-related reactions: antipyretics, H_1 antagonist, and H_2 antagonist. Consider corticosteroids for patients with prior reactions.
  - Antiemetics per established guidelines.
- 10 mg/kg as an IV infusion on days 1 and 8 of a 21-day treatment cycle. Continue treatment until disease progression or unacceptable toxicity.
- Administer the first infusion over 3 hours and subsequent infusions over 1 to 2 hours if prior infusions were tolerated. Observe for at least 30 minutes after the end of the infusion.

Dose Modification Criteria

- Renal (mild): no significant effect on PK
- Renal (moderate or severe): no data available
- Hepatic (mild): no significant effect on PK

- Hepatic (moderate or severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia and rash
- GI: N/V (high), diarrhea, constipation, decreased appetite, and abdominal pain
- HEMAT: neutropenia and anemia
- INFUS: hypersensitivity and infusion-related reactions (including anaphylaxis)
- OTHER: fatigue

Comments

- SN-38 is metabolized via UGT1A1. Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia.
- Avoid concomitant UGT1A1 inhibitors or inducers.
- Embryo-fetal toxicity: sacituzumab govitecan may cause fetal harm when administered to a pregnant woman.

SELINEXOR (XPOVIO)

Mechanism of Action

- Reversible inhibitor of the nuclear export of tumor suppressor proteins, growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition leads to accumulation of tumor suppressor proteins in the nucleus, thus resulting in cell cycle arrest and apoptosis of cancer cells.

FDA-Approved Indications

- Multiple myeloma (MM):
  - In combination with bortezomib and dexamethasone for the treatment of MM following at least one prior therapy.
  - In combination with dexamethasone for the treatment of relapsed or refractory MM following at least four prior therapies and refractory to at least two proteosome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
- Diffuse large B-cell lymphoma (DLBCL): for the treatment of relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from FL, after at least two lines of therapy.

FDA-Approved Dosage

- MM in combination with bortezomib and dexamethasone: 100 mg orally once weekly
- MM in combination with dexamethasone: 80 mg orally on days 1 and 3 of each week
- DLBCL: 60 mg orally on days 1 and 3 of each week

Dose Modification Criteria

- Renal (mild to severe, CrCl 15-89 mL/min): no significant effect on PK
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate to severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- ELECTRO: hyponatremia
- GI: N/V (moderate-high), decreased appetite, diarrhea, and constipation
- HEMAT: anemia, neutropenia, leukopenia, thrombocytopenia, and lymphopenia

- NEURO: peripheral neuropathy, dizziness, and metal status changes
- Ocular system: cataract
- PULM: dyspnea
- OTHER: fatigue, upper respiratory tract infection, severe infection, decreased weight, and pyrexia

Comments

- Neurologic toxicity can occur including dizziness and metal status changes. Advise patients to refrain from driving and engaging in hazardous occupations or activities until neurologic toxicity resolves.
- Embryo-fetal toxicity: selinexor may cause fetal harm when administered to a pregnant woman.

SELPERCATINIB (RETEVMO)

Mechanism of Action

- Kinase inhibitor of wild-type RET and multiple-mutated RET isoforms as well as VEGFR-1, VEGFR-3, and FGFR1, 2, and 3. Point mutations in *RET* or chromosomal rearrangements involving in-frame fusions of *RET* can act as oncogenic drivers by promoting cell proliferation of tumor cell lines, and selpercatinib inhibits this process.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): treatment of adult patients with metastatic *RET* fusion–positive NSCLC
- Medullary thyroid cancer:
  - Treatment of adult and pediatric patients 12 years and older with advanced or metastatic *RET*-mutant medullary thyroid cancer who require systemic therapy
  - Treatment of adult and pediatric patients 12 years and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy

and who are radioactive iodine refractory (if radioactive iodine is appropriate)

FDA-Approved Dosage

- Weight <50 kg: 120 mg orally twice daily
- Weight ≥50 kg: 160 mg orally twice daily

Dose Modification Criteria

- Renal (mild to severe, eGFR ≥ 15-89 mL/min by MDRD): no
- Hepatic (mild or moderate): no
- Hepatic (severe): yes
- CYP3A inhibitors (strong or moderate): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine
- CV: hypertension, hypercholesterolemia, and QT prolongation
- DERM: rash
- ELECTRO: hypocalcemia and hyponatremia
- ENDO: hyperglycemia
- GI: N/V (minimal-low), dry mouth, diarrhea, and constipation
- HEMAT: leukocytosis, thrombocytopenia, and hemorrhage
- HEPAT: hepatotoxicity, increased AST, increased ALT, and increased alkaline phosphatase
- OTHER: hypoalbuminemia, fatigue, edema, hypersensitivity, tumor lysis syndrome, and impaired wound healing

Comments

- In adolescent patients with open growth plates, monitor for growth plate abnormalities.
- Withhold selpercatinib for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.

- Avoid concomitant use of gastric acid-reducing agents. If concomitant use cannot be avoided:
  - Take selpercatinib with food when coadministered with a PPI.
  - Take selpercatinib 2 hours before or 10 hours after administration of an H_2 antagonist.
  - Take selpercatinib 2 hours before or 2 hours after administration of a locally acting antacid.
- Avoid concomitant administration of strong and moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the selpercatinib dose.
- Avoid concomitant administration with strong and moderate CYP3A inducers.
- Avoid concomitant administration with CYP2C8 and CYP3A substrates. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling.
- Embryo-fetal toxicity: selpercatinib may cause fetal harm when administered to a pregnant woman.

SELUMETINIB (KOSELUGO)

Mechanism of Action

- Kinase inhibitor of MEK1 and MEK2 activity that results in the inhibition of downstream signaling of the ERK pathway

FDA-Approved Indications

- Neurofibromatosis type 1 (NF1): pediatric patients 2 years and older with NF1 who have symptomatic, inoperable plexiform neurofibromas

FDA-Approved Dosage

- 25 mg/m^2 orally twice daily until disease progression or unacceptable toxicity. Take on an empty stomach (no food 2 hours before or 1 hour after each dose).

Dose Modification Criteria

- Renal: no
- Hepatic (mild, Child-Pugh class A): no
- Hepatic (moderate, Child-Pugh class B): yes
- Hepatic (severe, Child-Pugh class C): not established
- CYP3A4 inhibitors (strong or moderate, fluconazole): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy
- DERM: rash, dry skin, paronychia, and pruritus
- GI: N/V (moderate-high), abdominal pain, diarrhea, and stomatitis
- HEMAT: increased risk of bleeding
- NEURO: headache
- Ocular system: visual changes, retinal vein occlusion, and retinal pigment epithelial detachment
- OTHER: fatigue, musculoskeletal pain, CPK elevation, and pyrexia

Comments

- Avoid concomitant administration of strong or moderate CYP3A4 inhibitors or fluconazole. If coadministration cannot be avoided, reduce the selumetinib dose.
- Avoid concomitant use of strong and moderate CYP3A4 inducers.
- Assess LVEF prior to treatment, every 3 months during the first year, then every 6 months thereafter.
- Conduct ophthalmic assessment prior to treatment and at regular intervals.
- Selumetinib capsules contain vitamin E and daily intake of vitamin E may exceed the recommended limits and may increase the risk of bleeding.

- Embryo-fetal toxicity: selumetinib may cause fetal harm when administered to a pregnant woman.

SIPULEUCEL-T (PROVENGE)

Mechanism of Action

- Autologous cellular immunotherapy designed to induce an immune response targeted against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers. Sipuleucel-T consists of autologous peripheral blood mononuclear cells that have been activated with a recombinant human protein consisting of PAP linked to granulocyte macrophage colony-stimulating factor.

FDA-Approved Indications

- Asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer

FDA-Approved Dosage

- Administer three doses at approximately 2-week intervals.
- Each dose of sipuleucel-T contains a minimum of 50 million autologous $CD54^{+}$ cells activated with PAP-GM-CSF.

Dose Modification Criteria

- Infusion reactions: slow rate

ADVERSE REACTIONS

- INFUS: fever, chills, fatigue, syncope, hypotension, hypertension, nausea, joint ache, back pain, respiratory events

(dyspnea, hypoxia, bronchospasm), and tachycardia

Comments

- Thromboembolic events, including deep venous thrombosis and pulmonary embolism, can occur following infusion of sipuleucel-T. Use with caution in patients with risk factors for thromboembolic events.
- The patient's peripheral blood mononuclear cells are obtained via a standard leukapheresis procedure 3 days prior to the infusion date. The cellular composition of sipuleucel-T depends on the composition of cells obtained from the patient's leukapheresis. In addition to antigen-presenting cells, the final product contains T cells, B cells, NK cells, and other cells.
- Sipuleucel-T is not routinely tested for transmissible infectious diseases; thus universal precautions should be employed when handling sipuleucel-T or leukapheresis material.
- For autologous use only. For IV use only. Do not use a cell filter. Do not infuse expired product. The sipuleucel-T infusion bag must remain within the insulated polyurethane container until the time of administration.
- If the infusion must be interrupted, it should not be resumed if the sipuleucel-T infusion bag will be held at room temperature for more than 3 hours.
- Premedicate with acetaminophen and an oral antihistamine 30 minutes prior to infusion of sipuleucel-T.
- If the patient is unable to receive a scheduled infusion of sipuleucel-T, the patient will need to undergo an additional leukapheresis procedure.
- Concomitant use of chemotherapy and immunosuppressive medications with sipuleucel-T has not been studied.

SONIDEGIB (ODOMZO)

Mechanism of Action

- Inhibits the Hedgehog pathway

FDA-Approved Indications

- Locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy or BCC patients who are not candidates for surgery or radiation therapy

FDA-Approved Dosage

- 200 mg orally once daily until disease progression or unacceptable toxicity. Take on an empty stomach, at least 1 hour before or 2 hours after a meal.

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Hepatic (mild to severe, Child-Pugh class A, B, or C): no
- Nonhematologic toxicity (musculoskeletal and elevated CK): yes

Adverse Reactions

- DERM: alopecia and pruritus
- GI: N/V (minimal-low), diarrhea, decreased appetite, and abdominal pain
- NEURO: headache and dysgeusia
- OTHER: serum CPK elevations, muscle spasms, musculoskeletal pain, myalgia, and fatigue

Comments

- Embryo-fetal toxicity: verify pregnancy status of females of reproductive potential prior to initiating sonidegib. Sonidegib

can cause embryo-fetal death or severe birth defects when administered to a pregnant woman.
- Musculoskeletal toxicity: obtain serum CPK levels prior to initiating sonidegib and periodically during treatment and as clinically indicated.
- Blood donation: advise patients not to donate blood or blood products during therapy with sonidegib and for at least 20 months after the last dose.
- Sonidegib is a substrate of CYP3A4. Avoid concomitant administration with strong or moderate CYP3A4 inhibitors or inducers.

SORAFENIB (NEXAVAR)

Mechanism of Action

- TKI (Raf kinases, VEGFR-2, VEGFR-3, FLT-3, KIT, PDGFR-β)

FDA-Approved Indications

- Advanced renal cell carcinoma (RCC)
- Unresectable hepatocellular carcinoma (HCC)
- Differentiated thyroid carcinoma (DTC): locally recurrent or metastatic, progressive, DTC refractory to radioactive iodine treatment

FDA-Approved Dosage

- 400 mg orally twice daily without food (1 hour before or 2 hours after eating). Continue until patient is no longer clinically benefiting from therapy or until unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to severe): no (not studied in patients who are on dialysis)
- Hepatic (mild to moderate): no
- Hepatic (severe, Child-Pugh class C): no data
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, cardiac ischemia/infarction (see comments), and QT prolongation
- DERM: palmar-plantar erythrodysesthesia, rash, alopecia, pruritus, dry skin, erythema, severe bullous, and exfoliative skin reactions
- ELECTRO: hypophosphatemia
- GI: N/V (minimal-low), diarrhea, anorexia, abdominal pain, and GI perforation (rare)
- HEMAT: myelosuppression
- HEPAT: elevated LFTs and drug-induced hepatitis
- NEURO: peripheral neuropathy (sensory)
- OTHER: bleeding/hemorrhage, fatigue, asthenia, weight loss, and increased lipase/amylase

Comments

- Hand-foot skin reaction (palmar-plantar erythrodysesthesia) and rash are the most common adverse events with sorafenib. Monitor closely, provide supportive care, and evaluate for dose interruption or modification for severe toxicity (see product labeling).
- Monitor BP weekly during the first 6 weeks of therapy and thereafter monitor and treat according to standard medical practice.
- Sorafenib may impair wound healing. Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures.

- In placebo-controlled trials for the FDA-approved indications, the incidence of cardiac ischemia/infarction was higher in the sorafenib-treated patients compared to the placebo group. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.
- Sorafenib impairs exogenous thyroid suppression. In patients with differentiated thyroid carcinoma, monitor TSH levels monthly and adjust thyroid replacement medication as needed.
- Sorafenib is hepatically metabolized undergoing oxidative metabolism through CYP isoenzyme 3A4 as well as glucuronidation mediated by UGT1A9 and thus drug exposure may be influenced by inhibitors or inducers of CYP3A4 or UGT1A9. Sorafenib is also a competitive inhibitor of multiple cytochrome enzymes (eg, CYP2B6, CYP2C8) and of glucuronidation by the UGT1A1 and UGT1A9 pathways. Refer to product labeling and other appropriate references to screen for potential drug interactions.
- Embryo-fetal toxicity: sorafenib may cause fetal harm when administered to a pregnant woman.

SOTORASIB (LUMAKRAS)

Mechanism of Action

- Inhibitor of $KRAS^{G12C}$, a tumor-restricted, mutant-oncogenic form of KRAS. Through forming an irreversible, covalent bond, sotorasib locks the protein in an inactive state preventing downstream signaling.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): *KRAS* ^{G12C}-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, following at least 1 prior systemic chemotherapy

FDA-Approved Dosage

- 960 mg orally once daily with or without food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, eGFR ≥ 30 mL/min/1.73 m^2): no significant effect on PK
- Renal (severe, eGFR < 30 mL/min/1.73 m^2): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased urine protein
- ELECTRO: hypocalcemia and hyponatremia
- GI: N/V (not classified) and diarrhea
- HEMAT: lymphopenia and anemia
- HEPAT: hepatotoxicity, increased AST, increased ALT, and increased alkaline phosphatase
- PULM: cough and interstitial lung disease/pneumonitis
- OTHER: musculoskeletal pain and fatigue

Comments

- Avoid coadministration with PPIs and H_2 antagonists. If an acid-reducing agent cannot be avoided, administer sotorasib 4 hours before or 10 hours after a locally acting antacid.
- Avoid concomitant administration with strong CYP3A4 inducers.
- Avoid concomitant administration with CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrates. If coadministration cannot be avoided,

adjust the substrate dosage according to its prescribing information.
- Avoid concomitant administration with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage according to its prescribing information.

STREPTOZOTOCIN (ZANOSAR)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Metastatic islet cell carcinoma of the pancreas (functional and nonfunctional carcinomas)

FDA-Approved Dosage

- Daily schedule:
  - 500 mg/m^2 IV daily × 5 days every 6 weeks until maximum benefit or treatment limiting toxicity is observed, *OR*
- Weekly schedule:
  - Initial dose: 1 g/m^2 IV weekly for the first two courses (weeks). In subsequent courses, drug doses may be escalated in patients who have not achieved a therapeutic response and who have not experienced significant toxicity with the previous course of treatment. However, a single dose should not exceed 1500 mg/m^2.

Dose Modification Criteria

- Renal: use with caution, consider dose reduction

Adverse Reactions

- DERM: injection site reactions (irritant)

- ELECTRO: hypophosphatemia
- ENDO: dysglycemia, may lead to insulin-dependent diabetes
- GI: N/V (high) and diarrhea
- GU: azotemia, anuria, renal tubular acidosis, increased BUN and serum creatinine, and glycosuria
- HEMAT: myelosuppression
- HEPAT: increased LFTs

Comments

- Renal complications are dose-related and cumulative. Mild proteinuria is usually an early sign of impending renal dysfunction. Serial urinalysis is important for the early detection of proteinuria and should be quantified with a 24-hour collection when proteinuria is detected. Adequate hydration may help reduce the risk of nephrotoxicity. Avoid other nephrotoxic agents.

SUNITINIB MALATE (SUTENT)

Mechanism of Action

- TKI (VEGFR-1, VEGFR-2, VEGFR-3, FLT-3, KIT, PDGFR-α, β, CSF-1R, RET)

FDA-Approved Indications

- Gastrointestinal stromal tumor (GIST): treatment of adult patients with GIST after disease progression on or intolerance to imatinib mesylate
- Renal cell carcinoma (RCC):
  - Treatment of adult patients with advanced RCC
  - Adjuvant treatment of adult patients at high risk of recurrent RCC after nephrectomy

- Advanced pancreatic neuroendocrine tumors (pNET): treatment of progressive, well-differentiated pNET in adult patients with unresectable locally advanced or metastatic disease

FDA-Approved Dosage

- GIST and advanced RCC: 50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off until disease progression or unacceptable toxicity.
- Adjuvant treatment of RCC: 50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off for nine 6-week cycles.
- pNET: 37.5 mg orally once daily continuously without a scheduled off-treatment period. Continue until disease progression or unacceptable toxicity.
- Sunitinib may be taken with or without food.

Dose Modification Criteria

- Renal (mild to severe): no
- Hepatic (mild to moderate; Child-Pugh classes A and B): no
- Hepatic (severe; Child-Pugh class C): no data
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, left ventricular dysfunction, and QT interval prolongation
- DERM: palmar-plantar erythrodysesthesia, rash, skin discoloration (yellow), and dry skin
- ENDO: hypothyroidism and hypoglycemia
- GI: N/V (minimal-low), diarrhea, mucositis/stomatitis, dyspepsia, abdominal pain, constipation, altered taste, and anorexia
- GU: proteinuria and nephrotic syndrome

- HEMAT: myelosuppression
- HEPAT: increased LFTs and hepatotoxicity
- NEURO: peripheral neuropathy (sensory)
- OTHER: bleeding/hemorrhage, fatigue, asthenia, myalgia/limb pain, increased amylase/lipase, osteonecrosis of the jaw, and tumor lysis syndrome

Comments

- Hepatotoxicity, including liver failure, has been observed. Monitor LFTs before initiation of sunitinib, during each cycle, and as clinically indicated. Interrupt therapy for grade 3 or 4 drug-related hepatic adverse events and discontinue therapy if there is no resolution.
- Hypertension may occur. Monitor BP and treat as needed.
- Proteinuria and nephrotic syndrome have been reported with sunitinib. Monitor for the development or worsening of proteinuria.
- Severe cutaneous reactions have been reported such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and necrotizing fasciitis. Discontinue sunitinib if severe cutaneous reactions are observed or suspected.
- Thrombotic microangiopathy (TMA) has been associated with sunitinib therapy. Discontinue sunitinib if TMA occurs during therapy.
- Left ventricular ejection declines have occurred. Monitor patients for signs or symptoms of CHF.
- Prolonged QT intervals and torsades de pointes have been observed. Use with cation in patients at higher risk. Consider baseline and on treatment ECGs and monitor electrolytes.
- Hemorrhagic events including tumor-related hemorrhage have occurred. Perform serial CBCs and physical examination.
- Hypothyroidism may occur. Patients with signs or symptoms suggestive of hypothyroidism should have laboratory

monitoring of thyroid function and be treated as per standard medical practice.
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.
- Temporary interruption of sunitinib is recommended in patients undergoing major surgical procedures.
- Sunitinib is hepatically metabolized undergoing oxidative metabolism through CYP isoenzyme 3A4 and thus drug exposure may be influenced by potent inhibitors or inducers of CYP3A4. Refer to product labeling and other appropriate references to screen for potential drug interactions.
- Embryo-fetal toxicity: sunitinib may cause fetal harm when administered to a pregnant woman.

TAGRAXOFUSP (ELZONRIS)

Mechanism of Action

- CD123-directed cytotoxin composed of recombinant human IL-3 and truncated diphtheria toxin fusion protein

FDA-Approved Indications

- Blastic plasmacytoid dendritic cell neoplasm in adults and pediatric patients 2 years and older

FDA-Approved Dosage

- Premedication: an H_1 antagonist, acetaminophen, corticosteroid, and H_2 antagonist
- 12 μg/kg IV over 15 minutes once daily on days 1 through 5 of each 21-day cycle

Dose Modification Criteria

- Renal (mild or moderate, eGFR 30-89 mL/min/1.73 m^2 by MDRD): no significant effect on PK
- Renal (severe, eGFR < 30 by MDRD): no data available
- Hepatic (mild or moderate): no significant effect on PK
- Hepatic (severe): no data available
- Nonhematologic toxicity: yes

Adverse Reactions

- ELECTRO: hypocalcemia and hyponatremia
- ENDO: hyperglycemia
- GI: N/V (low)
- HEMAT: thrombocytopenia and anemia
- HEPAT: hepatotoxicity, increased ALT, and increased AST
- INFUS: hypersensitivity reaction
- OTHER: capillary leak syndrome, fatigue, peripheral edema, pyrexia, weight increase, and hypoalbuminemia

Comments

- Tagraxofusp is associated with a boxed warning for capillary leak syndrome.
- The first cycle of tagraxofusp must be administered in the inpatient setting. Subsequent cycles may be administered either in the inpatient or outpatient setting, as appropriate.

TAFASITAMAB (MONJUVI)

Mechanism of Action

- An Fc-modified monoclonal antibody that binds to the CD19 antigen expressed on several B-cell malignancies, which results in B-cell lysis through ADCC and ADCP

FDA-Approved Indications

- Diffuse large B-cell lymphoma (DLBCL): in combination with lenalidomide for the treatment of relapsed or refractory DLBCL, not otherwise specified, in patients who are not eligible for ASCT

FDA-Approved Dosage

- Premedication prior to the first three infusions is required to minimize the risk of infusion-related reactions. Patients who experience a reaction should continue premedications before each subsequent infusion. Examples of premedications include: acetaminophen, H_1 antagonist, H_2 antagonist, and/or glucocorticosteroids.
- 12 mg/kg as an IV infusion according to the following schedule (each cycle is 28-days):
  - Cycle 1: days 1, 4, 8, 15, and 22
  - Cycle 2 and 3: days 1, 8, 15, and 22
  - Cycle 4 and beyond: days 1 and 15
- For the first infusion, use an infusion rate of 70 mL/h for the first 30 minutes then increase the rate so the infusion is completed within 1.5 to 2.5 hours. Administer all subsequent infusions within 1.5 to 2 hours.
- Administer in combination with lenalidomide for a maximum of 12 cycles then continue tafasitamab as monotherapy until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no significant effect on PK
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no significant effect on PK
- Hepatic (moderate or severe): no data available
- Hematologic toxicity: yes

- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (low), diarrhea, and decreased appetite
- HEMAT: neutropenia, anemia, and thrombocytopenia
- INFUS: infusion-related reactions
- PULM: cough and respiratory tract infection
- OTHER: infections (bacterial, fungal, and viral), fatigue, pyrexia, and peripheral edema

Comments

- Embryo-fetal toxicity: tafasitamab may cause fetal harm when administered to a pregnant woman.

TALAZOPARIB (TALZENNA)

Mechanism of Action

- Inhibitor of PARP enzymes, including PARP1 and PARP2, which play a role in DNA repair

FDA-Approved Indications

- Breast cancer: deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer

FDA-Approved Dosage

- 1 mg orally once daily with or without food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild, CrCl ≥ 60-89 mL/min): no
- Renal (moderate or severe, CrCl 15-59 mL/min): yes
- Hepatic (mild): no
- Hepatic (moderate or severe): no data available
- P-gp inhibitors (select agents): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia
- ELECTRO: hypocalcemia
- ENDO: hyperglycemia
- GI: N/V (minimal-low), diarrhea, and decreased appetite
- HEMAT: anemia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, and MDS/AML
- HEPAT: increased ALT, increased AST, and increased alkaline phosphatase
- NEURO: headache
- OTHER: fatigue

Comments

- MDS/AML, including cases with fatal outcomes, has been reported in patients receiving talazoparib after a duration of therapy ranging from 4 to 24 months. Monitor for hematological toxicity.
- Concomitant administration with the following P-gp inhibitors should be avoided: itraconazole, amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. When administering talazoparib concurrently with other P-gp inhibitors, monitor for potential increased adverse reactions.
- Concomitant administration with BCRP inhibitors may increase talazoparib exposure. If coadministration cannot be avoided, monitor for potential increased adverse reactions.

- Embryo-fetal toxicity: talazoparib may cause fetal harm when administered to a pregnant woman.

TALIMOGENE LAHERPAREPVEC (IMLYGIC)

Mechanism of Action

- Talimogene laherparepvec is a live, attenuated HSV-1 genetically modified to replicate within tumors and produce the immune stimulatory protein GM-CSF, which leads to lysis of tumors and is followed by release of tumor-derived antigens, promoting an antitumor immune response.

FDA-Approved Indications

- Melanoma: local treatment of unresectable cutaneous, subcutaneous, and nodal lesions of melanoma that is recurrent after initial surgery

FDA-Approved Dosage

- 10^6 plaque-forming units (PFU) per mL—for initial dose only.
- 10^8 PFU per mL—for all subsequent doses.
  - Second treatment should be 3 weeks after initial injection. All subsequent injections should be every 2 weeks.
- Maximum injection volume per visit is 4 mL. See product labeling for injection volume based on lesion size. Continue for at least 6 months or until there are no injectable lesions to treat.

Dose Modification Criteria

- Renal: not studied
- Hepatic: not studied

Adverse Reactions

- DERM: injection site pain and complications (eg, necrosis or ulceration of tumor tissue)
- GI: N/V (low) and diarrhea
- NEURO: headache
- OTHER: herpetic infection (including cold sores and herpetic keratitis), fatigue, chills, pyrexia, and influenza-like illness

Comments

- Immune-mediated events: in clinical studies, immune-mediated events including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with talimogene laherparepvec. Consider the risks and benefits before initiating therapy in patients who have underlying autoimmune disease or before continuing therapy in patients who have developed immune-mediated events.
- For intralesional injection only. Do not administer intravenously.
- Do not administer to immunocompromised patients.
- Healthcare providers who are immunocompromised or pregnant should not prepare or administer talimogene laherparepvec or come into contact with injection sites, dressings, or body fluids of treated patients.
- Do not administer to pregnant patients.
- Talimogene laherparepvec is sensitive to acyclovir and other antiviral agents and thus concurrent use of antiviral agents may compromise efficacy of therapy.
- Follow universal biohazard precautions for preparation, administration, and handling.

TAMOXIFEN (NOLVADEX)

Mechanism of Action

- Nonsteroidal antiestrogen

FDA-Approved Indications

- Breast cancer:
  - Treatment of adult patients with ER-positive (ER+) metastatic breast cancer
  - Adjuvant treatment of adult patients with early stage ER+ breast cancer; to reduce the incidence of contralateral breast cancer when used as adjuvant therapy for the treatment of breast cancer
  - Ductal carcinoma in situ (DCIS): to reduce the risk of invasive breast cancer following breast surgery and radiation
  - Reduction in breast cancer incidence in women at high-risk for breast cancer

FDA-Approved Dosage

- Metastatic breast cancer treatment: 20 mg orally daily or 10 to 20 mg PO twice daily (20-40 mg/d). Doses >20 mg/d should be given in divided doses (morning and evening).
- Adjuvant therapy: 20 mg orally daily for 5 to 10 years.
- DCIS and breast cancer incidence reduction in high-risk women: 20 mg orally daily for 5 years.

Adverse Reactions

- CV: thromboembolism, stroke, and pulmonary embolism
- DERM: skin rash
- ENDO: hot flashes
- GI: N/V (not classified) and anorexia
- GU: menstrual irregularities, pruritus vulvae, vaginal discharge, or bleeding
- HEMAT: bone marrow depression
- Ocular system: vision disturbances and cataracts
- PULM: dyspnea, chest pain, and hemoptysis
- OTHER: dizziness, headaches, tumor or bone pain, pelvic pain, and uterine malignancies

Comments

- For the indication of breast cancer risk reduction, high risk is defined as women at least 35 years old with a 5-year predicted

risk of breast cancer of 1.67%, as predicted by the Gail model based on the Breast Cancer Prevention Trial (NSABP P-1). Healthcare professionals can access a breast cancer risk assessment tool on the National Cancer Institute website www.cancer.gov/bcrisktool.

- Serious and life-threatening events associated with tamoxifen in the risk reduction setting include uterine malignancies, stroke, and PE. Consult package insert for additional information.

TAZEMETOSTAT (TAZVERIK)

Mechanism of Action

- Inhibitor of the methyltransferase, EZH2 (enhancer of zeste homolog 2), and some EZH2 gain-of-function mutations including Y646X, A682G, and A692V. EZH2 is overexpressed or mutated in many cancers.

FDA-Approved Indications

- Epithelioid sarcoma: adults and pediatric patients aged 16 and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
- Follicular lymphoma (FL):
  - Adult patients with relapsed or refractory FL in whom tumors harbor an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies.
  - Adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options.

FDA-Approved Dosage

- 800 mg orally twice daily until disease progression or unacceptable toxicity. May be taken without regard to food.

Dose Modification Criteria

- Renal (mild to severe): no
- Hepatic (mild): no
- Hepatic (moderate or severe): no data available
- CYP3A inhibitors (strong or moderate): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (minimal-low), decreased appetite, and constipation
- NEURO: pain
- OTHER: upper respiratory tract infection, fatigue, musculoskeletal pain, and secondary malignancies

Comments

- Avoid concomitant administration with strong or moderate CYP3A inhibitors. If coadministration cannot be avoided, reduce the tazemetostat dose.
- Avoid concomitant administration with strong or moderate CYP3A inducers.
- Embryo-fetal toxicity: tazemetostat may cause fetal harm when administered to a pregnant woman.

TEMOZOLOMIDE (TEMODAR)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Glioblastoma: newly diagnosed patients used concomitantly with RT and then as maintenance treatment in adults.

- Anaplastic astrocytoma: second-line treatment in adults with progressive disease after a regimen-containing nitrosourea and procarbazine.

FDA-Approved Dosage

- Newly diagnosed glioblastoma: 75 mg/m^2 orally or IV daily for 42 days concomitant with focal RT followed by maintenance temozolomide for six cycles. The temozolomide dose should be continued throughout the 42-day concomitant period up to 49 days to achieve acceptable hematologic and nonhematologic parameters (see package insert). *P. jirovecii* prophylaxis is required during the concomitant administration of temozolomide and RT and should be continued in patients who develop lymphocytopenia.
- Maintenance phase:
  - Cycle 1: 150 mg/m^2 orally or IV daily for 5 days followed by 23 days without treatment starting 4 weeks after the temozolomide + RT phase.
  - Cycles 2 to 6: dose may be escalated to 200 mg/m^2 if the nonhematologic and hematologic parameters are met (see package insert). The dose remains at 200 mg/m^2/d for the first 5 days of each subsequent cycle except if toxicity occurs.
- Refractory anaplastic astrocytoma—initial dose: 150 mg/m^2 orally or IV daily for 5 consecutive days every 28 days. If the initial dose leads to acceptable hematologic parameters at the nadir and on day of dosing (see criteria in package insert), the temozolomide dose may be increased to 200 mg/m^2 orally or IV daily × 5 consecutive days per 28-day treatment cycle.
- Bioequivalence between the oral and IV formulations has only been established when the IV infusion is administered over 90 minutes. Infusion over a shorter or longer period may lead to suboptimal dosing.

Dose Modification Criteria

- Renal (severe impairment): use with caution
- Hepatic (severe impairment): use with caution

- Myelosuppression: yes

Adverse Reactions

- HEMAT: myelosuppression
- GI: N/V (oral: moderate-high; IV: moderate), constipation, and anorexia
- HEPAT: increased LFTs and hepatotoxicity
- NEURO: headache
- OTHER: asthenia, fatigue, and alopecia. Myelodysplastic syndrome (MDS) and secondary malignancies have been reported

Comments

- Capsules should be taken with water. Administer consistently with respect to food, and to reduce the risk of N/V, it is recommended that temozolomide be taken on an empty stomach. Bedtime administration may be advised.
- Myelosuppression occurs late in the treatment cycle. The median nadirs in a study of 158 patients with anaplastic astrocytoma occurred at 26 days for platelets (range 21-40 days) and 28 days for neutrophils (range 1-44 days). The package insert recommends obtaining a CBC on day 22 (21 days after the first dose) and then weekly until the ANC is above 1.5×10^9/L and the platelet count exceeds 100×10^9/L. The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels. See the package insert for dose modification guidelines.
- Fatal and severe hepatotoxicity has been reported with temozolomide. Monitor LFT's at baseline, midway through the first cycle, prior to each subsequent cycle, and 2 to 4 weeks after the last dose.
- Embryo-fetal toxicity: temozolomide can cause fetal harm when administered to a pregnant woman.

TEMSIROLIMUS (TORISEL)

Mechanism of Action

- Inhibitor of mTOR

FDA-Approved Indications

- Advanced renal cell carcinoma (RCC)

FDA-Approved Dosage

- 25 mg infused IV over 30 to 60 minutes once a week. Treat until disease progression or unacceptable toxicity. Antihistamine pretreatment is recommended.

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity: no

Adverse Reactions

- DERM: rash, pruritus, nail disorder, and dry skin
- ENDO: hyperglycemia/glucose intolerance
- ELECTRO: hypophosphatemia and hypokalemia
- GI: N/V (not classified); mucositis, anorexia, weight loss, diarrhea, constipation, taste loss/perversion, and bowel perforation (rare)
- GU: elevated serum creatinine and renal failure
- HEMAT: myelosuppression
- HEPAT: elevated LFTs (AST, alkaline phosphatase)
- INFUS: hypersensitivity reactions (anaphylaxis, dyspnea, flushing, and chest pain)

- NEURO: headache and insomnia
- PULM: interstitial lung disease
- OTHER: asthenia, fever, immunosuppression, hyperlipidemia, hypertriglyceridemia, impaired wound healing, bleeding/hemorrhage, edema, and back pain/arthralgias

Comments

- To reduce the risk of hypersensitivity reactions, premedicate patients with an H_1 antihistamine prior to the administration of temsirolimus. Interrupt the infusion if a patient develops an infusion reaction for patient observation. At the discretion of the physician, the infusion may be resumed after administration of additional antihistamine therapy (H_1 and/or H_2 receptor antagonists) and with a slower rate of infusion for the temsirolimus.
- Serum glucose should be tested before and during treatment with temsirolimus. Patients may require an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.
- Elevations in triglycerides and/or lipids are common side effects and may require treatment. Monitor lipid profiles.
- Monitor for symptoms or radiographic changes of interstitial lung disease. Therapy with temsirolimus should be discontinued if toxicity occurs and corticosteroid therapy should be considered.
- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly.
- Renal failure has occurred; monitor renal function at baseline and while on therapy.
- Due to abnormal wound healing, use temsirolimus with caution in the perioperative period.
- Live vaccinations and close contact with those who received live vaccines should be avoided.

- Temsirolimus is hepatically metabolized undergoing oxidative metabolism through CYP isoenzyme 3A4 and thus drug exposure may be influenced by potent inhibitors or inducers of CYP3A4. Refer to product labeling and other appropriate references to screen for potential drug interactions.
- Embryo-fetal toxicity: temsirolimus may cause fetal harm when administered to a pregnant woman.

TENIPOSIDE (VUMON)

Mechanism of Action

- Topoisomerase II inhibitor

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): treatment of refractory childhood ALL as a second-line treatment in combination with other chemotherapy

FDA-Approved Dosage

- Refer to current literature for dosing regimens. The package insert cites two dosage regimens based on two different studies:
  - In combination with cytarabine: 165 mg/m^2 IV over 30 to 60 minutes twice weekly × eight to nine doses
  - In combination with vincristine and prednisone: 250 mg/m^2 IV over 30 to 60 minutes weekly × four to eight doses

Dose Modification Criteria

- Renal: use with caution, no guidelines available
- Hepatic: use with caution, no guidelines available

Adverse Reactions

- CV: hypotension with rapid infusion
- DERM: alopecia, thrombophlebitis, and tissue damage secondary to drug extravasation
- GI: diarrhea, N/V (not classified), and mucositis
- HEMAT: myelosuppression
- INFUS: anaphylaxis and hypersensitivity reactions (fever, chills, urticarial, tachycardia, bronchospasm, dyspnea, hypertension, hypotension, rash, and facial flushing)

Comments

- Hypersensitivity reactions may occur with the first dose of teniposide. The reactions may be due to the presence of cremophor EL (polyoxyethylated castor oil) in the vehicle or to teniposide itself. Observe the patient for at least 60 minutes after dose.
- Consider premedication with antihistamines and/or corticosteroids for retreatment (if indicated) after a hypersensitivity reaction.
- Use non-DEHP plasticized solution containers and administration sets.
- Embryo-fetal toxicity: teniposide may cause fetal harm when administered to a pregnant woman.

TEPOTINIB (TEPMETKO)

Mechanism of Action

- Kinase inhibitor that targets MET including the mutant variant produced by exon 14 skipping. As a result, tepotinib inhibits downstream signaling and ultimately the survival of MET-dependent cancer cells.

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): metastatic NSCLC harboring MET exon 14 skipping alterations

FDA-Approved Dosage

- 450 mg orally once daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): not established
- Nonhematologic toxicity: yes

Adverse Reactions

- ELECTRO: hyponatremia
- GI: N/V (not classified), diarrhea, and increased amylase
- HEMAT: lymphopenia and anemia
- HEPAT: hepatotoxicity, increased GGT, increased ALT, and increased AST
- PULM: interstitial lung disease/pneumonitis and dyspnea
- OTHER: edema, fatigue, musculoskeletal pain, and hypoalbuminemia

Comments

- Avoid concomitant use of the following medications: dual strong CYP3A and P-gp inhibitors; strong CYP3A inducers; and P-gp substrates where minimal concentration changes may lead to significant toxicities.
- Embryo-fetal toxicity: tepotinib may cause fetal harm when administered to a pregnant woman.

THALIDOMIDE (THALOMID)

Mechanism of Action

- Immunomodulatory agent with antineoplastic and antiangiogenic properties

FDA-Approved Indications

- Multiple myeloma: first-line therapy of newly diagnosed multiple myeloma in combination with dexamethasone
- Other indications: erythema nodosum leprosum

FDA-Approved Dosage

- Multiple myeloma: 200 mg orally once daily, preferably at bedtime and at least 1 hour after the evening meal. Thalidomide is administered in combination with dexamethasone in 28-day treatment cycles. Dexamethasone is dosed at 40 mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 every 28 days. Refer to current literature for alternative dosing recommendations.

Dose Modification Criteria

- Renal: no (not studied except in patients on dialysis)
- Hepatic: no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: edema, orthostatic hypotension, and bradycardia
- DERM: rash, desquamation, dry skin, and bullous exfoliative skin reactions
- ELECTRO: hypocalcemia
- GI: constipation and N/V (minimal-low)

- HEMAT: myelosuppression
- NEURO: peripheral neuropathy (sensory and motor), drowsiness, somnolence, dizziness, confusion, tremor, and seizures
- PULM: dyspnea
- OTHER: thromboembolic events, hypersensitivity reactions, fatigue, and tumor lysis syndrome

Comments

- Thalidomide is only available through a restricted distribution program (Thalomid REMS). Only prescribers and pharmacists registered with the program are allowed to prescribe and dispense thalidomide.
- Embryo-fetal toxicity: thalidomide is a known teratogen and can cause severe birth defects or death to an unborn baby. Refer to the product labeling for information regarding requirements for pregnancy testing, and patient consent as part of the Thalomid REMS program.
- Thalidomide may cause venous thromboembolic events. There is an increased risk of thrombotic events when thalidomide is combined with standard chemotherapeutic agents, including dexamethasone. Ischemic heart disease and stroke have also occurred in patients treated with thalidomide and dexamethasone. Consider concurrent prophylactic anticoagulation or aspirin treatment.
- Peripheral neuropathy is a common, potentially severe toxicity that may be irreversible. Consideration should be given to electrophysiologic testing at baseline and periodically thereafter.
- Serious dermatologic reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with thalidomide. Discontinue if a dermatological reaction is suspected.

THIOGUANINE (TABLOID)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Acute nonlymphocytic leukemias (ANLL): remission induction and remission consolidation. Thioguanine is not recommended for use during maintenance therapy or similar long-term continuous treatments due to high risk of liver toxicity.

FDA-Approved Dosage

- Combination therapy: refer to current literature.
- Single-agent therapy: 2 mg/kg orally daily as a single daily dose. May increase to 3 mg/kg orally daily as a single daily dose after 4 weeks if no clinical improvement.

Adverse Reactions

- GI: anorexia, stomatitis, and N/V (minimal-low)
- HEMAT: myelosuppression
- HEPAT: increased LFTs and increased bilirubin (cases of veno-occlusive hepatic disease have been reported in patients receiving combination chemotherapy for leukemia)
- OTHER: hyperuricemia and tumor lysis syndrome

Comments

- Variability in thioguanine metabolism may occur in patients due to genetic polymorphisms in the gene for the enzyme TPMT. TPMT genotyping or phenotyping can identify patients who are homozygous deficient or who have low or intermediate TPMT

activity and who would need dose reduction to avoid thioguanine toxicity.
- Cross-resistance with mercaptopurine.
- Consider appropriate prophylaxis for tumor lysis syndrome when treating acute leukemias.
- Embryo-fetal toxicity: thioguanine may cause fetal harm when administered to a pregnant woman.

THIOTEPA (THIOPLEX, TEPADINA)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Superficial papillary carcinoma of the bladder
- Controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities
- Adenocarcinoma of the breast
- Adenocarcinoma of the ovary
- To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation for pediatric patients with class 3 beta-thalassemia (Tepadina)

Dose Modification Criteria

- Renal (moderate to severe): use caution and monitor for toxicity
- Hepatic (moderate to severe): use caution and monitor for toxicity

FDA-Approved Dosage

- Adenocarcinoma of the breast or ovary: 0.3 to 0.4 mg/kg IV × one dose repeated at 1- to 4-week intervals. Consult current literature for alternative dosing regimens.
- Superficial papillary carcinoma of the bladder: intravesical administration: patients are dehydrated for 8 to 12 hours before procedure. Then 60 mg of thiotepa in 30 to 60 mL of sodium chloride injection is instilled into the bladder. For maximum effect, the solution should be retained in the bladder for 2 hours. If desired, reposition the patient every 15 minutes to maximize contact. Repeat administration weekly × 4 weeks. A course of treatment (four doses) may be repeated for up to two more courses if necessary, but with caution secondary to bone marrow depression.
- Intracavitary administration: 0.6 to 0.8 mg/kg × one dose through tubing used to remove fluid from cavity.
- Preparative regimen for class 3 beta-thalassemia: 5 mg/kg IV infusion over 3 hours administered every 12 hours for two doses on day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide.

Adverse Reactions

- CNS: dizziness, headache, blurred vision, conjunctivitis, and encephalopathy (high dose)
- DERM: alopecia and pain at the injection site, rash, and cutaneous toxicity (high dose)
- GI: anorexia, N/V (moderate), diarrhea, and mucositis at high doses
- GU: amenorrhea, reduced spermatogenesis, dysuria, and chemical or hemorrhagic cystitis (intravesical)
- HEMAT: myelosuppression and hemorrhage
- HEPAT: increased LFTs (AST, ALT, bilirubin) and hepatic veno-occlusive disease (high dose)
- OTHER: fever, hypersensitivity reactions, fatigue, weakness, and anaphylaxis

Comments

- Cutaneous toxicity: in high doses, thiotepa and/or its active metabolites may be excreted in part via skin, which may cause skin discoloration, pruritus, blistering, desquamation, and peeling. Patients should be instructed to shower or bathe with water at least twice daily through 48 hours postadministration and bed sheets should be changed daily.
- Embryo-fetal toxicity: thiotepa may cause fetal harm when administered to a pregnant woman.

TISAGENLECLEUCEL (KYMRIAH)

Mechanism of Action

- An autologous CAR-positive T-cell therapy targeting CD19-expressing cancer cells and normal B cells. Upon binding to the CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, and target cell elimination.

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): B-cell precursor ALL that is refractory or in secondary or later relapse in patients up to 25 years of age
- Non-Hodgkin lymphoma (NHL): adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)

FDA-Approved Dosage

- Administer a lymphodepleting chemotherapy regimen if needed before infusion.

- Premedicate with acetaminophen and an H_1 antagonist; avoid prophylactic corticosteroids.
- ALL:
  - Patients ≤ 50 kg, administer 0.2 to 5 × 10^6 CAR-positive viable T cells per kg body weight intravenously.
  - Patients > 50 kg, administer 0.1 to 2.5 × 10^8 CAR-positive viable T cells (non–weight-based) intravenously.
- DLBCL:
  - 0.6 to 6 × 10^8 CAR-positive viable T cells intravenously.

Dose Modification Criteria

- No dose modifications of tisagenlecleucel are recommended.
- Hepatic and renal impairment studies were not conducted.

Adverse Reactions

- Cr: acute kidney injury
- CV: hypotension and arrhythmias
- GI: N/V (low), diarrhea, and decreased appetite
- HEMAT: prolonged cytopenias, febrile neutropenia, and bleeding episodes
- INFUS: hypersensitivity reactions
- NEURO: severe or life-threatening neurological toxicities, headache, and encephalopathy
- PULM: cough, hypoxia, and dyspnea
- OTHER: serious infections, hypogammaglobulinemia, secondary malignancies, CRS, fever, fatigue, pain, and edema

Comments

- Tisagenlecleucel is only available through a REMS program and should only be administered at a certified healthcare facility.
- Tisagenlecleucel is associated with boxed warnings for the following:
  - CRS, including fatal and life-threatening reactions. Confirm availability of tocilizumab prior to infusion and treat severe or life-threatening CRS with tocilizumab +/− corticosteroids.

    - Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.
- Tisagenlecleucel may have effects on the ability to drive and use machines. Advise patients to refrain from operating heavy or dangerous machinery for at least 8 weeks after administration.

TIVOZANIB (FOTIVDA)

Mechanism of Action

- Kinase inhibitor that targets VEGFR-1, VEGFR-2, and VEGFR-3 resulting in the inhibition of angiogenesis, vascular permeability, and tumor growth. Tivozanib also targets c-kit and PDGFRB.

FDA-Approved Indications

- Renal cell cancer (RCC): relapsed or refractory advanced RCC following two or more prior systemic therapies

FDA-Approved Dosage

- 1.34 mg orally once daily with or without food for 21 consecutive days followed by 7 days off (28-day cycle) until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild to severe, CrCl 15-89 mL/min): no
- Hepatic (mild): no
- Hepatic (moderate): yes
- Hepatic (severe): not established
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, hypertensive crisis, cardiac failure, cardiac ischemia, arterial thromboembolic events, and venous thromboembolic events
- ELECTRO: hyponatremia and hypophosphatemia
- ENDO: thyroid dysfunction
- GI: N/V (not classified), diarrhea, decreased appetite, stomatitis, and lipase increased
- GU: proteinuria
- HEMAT: hemorrhage
- NEURO: RPLS
- PULM: cough
- OTHER: fatigue, dysphonia, and impaired wound healing

Comments

- Withhold tivozanib for at least 24 days before elective surgery. Do not administer for at least 2 weeks following major surgery and adequate wound healing.
- Tivozanib capsules contain FD&C Yellow No. 5 (tartrazine) that may cause allergic-type reactions in susceptible persons.
- Embryo-fetal toxicity: tivozanib may cause fetal harm when administered to a pregnant woman. Based on findings in animal studies, tivozanib can impair fertility in females and males of reproductive potential.

TOPOTECAN (HYCAMTIN)

Mechanism of Action

- Topoisomerase I inhibitor

FDA-Approved Indications

- Metastatic ovarian cancer: second-line therapy after failure of initial or subsequent chemotherapy (topotecan injection)
- Small cell lung cancer (SCLC): second-line therapy in sensitive disease after failure of first-line chemotherapy (topotecan injection and oral capsules)
- Cervical cancer: combination therapy with cisplatin for stage IV-B, recurrent, or persistent carcinoma of the cervix, which is not amenable to curative treatment with surgery and/or radiation therapy

FDA-Approved Dosage

- Ovarian cancer: 1.5 mg/m^2 IV over 30 minutes daily × 5 days, starting on day 1 of a 21-day course
- SCLC:
  - Injection: 1.5 mg/m^2 IV over 30 minutes daily × 5 days, repeated every 21 days
  - Oral capsules: 2.3 mg/m^2 orally once daily × 5 days, repeated every 21 days
- Cervical cancer: 0.75 mg/m^2 IV over 30 minutes daily × 3 days (days 1, 2, and 3), followed by cisplatin 50 mg/m^2 by IV infusion on day 1 only; repeated every 21 days (21-day cycle)

Dose Modification Criteria

- Renal (mild impairment, CrCl 40-60 mL/min): no
- Renal (moderate impairment, CrCl 20-39 mL/min): yes
- Renal (severe impairment, <20 mL/min): unknown
- Hepatic (bilirubin, mild to moderate elevation): no
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: alopecia, rash, and injection site reactions
- HEMAT: myelosuppression
- GI: N/V (low), diarrhea, constipation, abdominal pain, stomatitis, and anorexia

- NEURO: headache and pain
- PULM: dyspnea, coughing, and interstitial lung disease
- OTHER: fatigue, asthenia, and fever

Comments

- Bone marrow suppression (primarily neutropenia) is a dose-limiting toxicity of topotecan. Topotecan should be administered only to patients with baseline neutrophil counts of ≥1500 cells/mm^3 and a platelet count ≥100,000 cells/mm^3.
- Topotecan-induced neutropenia can lead to neutropenic colitis.
- Severe diarrhea requiring hospitalization has been reported with oral topotecan capsules. Dose may need to be adjusted.
- Concomitant filgrastim may worsen neutropenia. If used, start filgrastim at least 24 hours after last topotecan dose.
- P-gp inhibitors (eg, cyclosporine, elacridar, ketoconazole, ritonavir, saquinavir) can cause significant increases in topotecan exposure.
- Embryo-fetal toxicity: topotecan may cause fetal harm if administered to a pregnant woman.

TOREMIFENE (FARESTON)

Mechanism of Action

- Nonsteroidal antiestrogen

FDA-Approved Indications

- Metastatic breast cancer in postmenopausal women with ER-positive or unknown tumors

FDA-Approved Dosage

- 60 mg orally once daily until disease progression

Adverse Reactions

- CV: thromboembolism, stroke, PE, and QT prolongation
- DERM: skin discoloration and dermatitis
- ELECTRO: hypercalcemia
- ENDO: hot flashes
- GI: N/V (not classified), constipation, and elevated LFTs
- GU: vaginal discharge and vaginal bleeding
- NEURO: dizziness and depression
- Ocular system: dry eyes, ocular changes, and cataracts
- OTHER: sweating and tumor flare

Comments

- Do not use in patients with a history of thromboembolic disease or endometrial hyperplasia.
- Toremifene has been shown to prolong the QT interval in a dose- and concentration-related manner. Avoid in patients with long QT syndrome. Use with caution in patients with CHF, hepatic impairment, and electrolyte abnormalities. Concomitant use with other drugs that may prolong the QT interval should be avoided. Monitor ECG in patients at increased risk.
- Toremifene is extensively metabolized principally by CYP3A4. Coadministration with strong inhibitors or inducers of CYP3A4 will significantly impact serum concentrations of toremifene and should be avoided or used with caution. Toremifene is a weak inhibitor of CYP2C9 and may interact with CYP2C9 substrates (eg, warfarin and phenytoin).
- Embryo-fetal toxicity: toremifene may cause fetal harm when administered to a pregnant woman.

TRABECTEDIN (YONDELIS)

Mechanism of Action

- An alkylating agent that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix toward the major groove

FDA-Approved Indications

- Unresectable or metastatic liposarcoma or leiomyosarcoma after prior anthracycline-containing regimen

FDA-Approved Dosage

- 1.5 mg/m^2 as an IV infusion over 24 hours through a central venous line every 21 days until disease progression or unacceptable toxicity
- Administer dexamethasone 20 mg IV 30 minutes prior to each dose

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data
- Hepatic (moderate): yes
- Hepatic (severe): avoid use
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy
- DERM: tissue damage/necrosis with extravasation
- GI: N/V (moderate), constipation, diarrhea, and decreased appetite
- GU: increased creatinine
- HEMAT: neutropenia, anemia, and thrombocytopenia
- HEPAT: elevated AST/ALT and increased alkaline phosphatase
- NEURO: headache and insomnia

- PULM: dyspnea
- OTHER: rhabdomyolysis/musculoskeletal toxicity, arthralgia, myalgia, elevated CPK, fatigue, and peripheral edema

Comments

- Vesicant.
- Rhabdomyolysis: trabectedin has been associated with rhabdomyolysis and musculoskeletal toxicity. Assess CPK levels prior to each dose of trabectedin and withhold therapy if serum CPK levels exceed 2.5 × the upper level of normal.
- Cardiomyopathy: assess LVEF prior to starting therapy and at 2 to 3 month intervals during therapy.
- Capillary leak syndrome (CLS) characterized by hypotension, edema, and hypoalbuminemia has been reported with trabectedin. Monitor for signs and symptoms and discontinue if CLS develops and initiate prompt standard management for CLS.
- Trabectedin is a substrate of CYP3A4. Avoid coadministration with strong CYP3A inhibitors or inducers.
- Embryo-fetal toxicity: trabectedin may cause fetal harm when administered to a pregnant woman.

TRAMETINIB (MEKINIST)

Mechanism of Action

- A reversible inhibitor of MEK1 and MEK2 activation and MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the ERK pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2.

FDA-Approved Indications

- Melanoma:
  - Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, given as a single agent or in combination with dabrafenib.
  - Adjuvant treatment of patients with melanoma with BFAF V600E or V600K mutations and involvement of lymph node(s) after complete resection.
- Non–small cell lung cancer (NSCLC): treatment of patients with metastatic NSCLC with BRAF V600E mutation in combination with dabrafenib.
- Anaplastic thyroid cancer (ATC): treatment of patients with locally advanced or metastatic ATC with BRAF V600E mutation and with no satisfactory locoregional treatment options in combination with dabrafenib.

FDA-Approved Dosage

- 2 mg orally once daily. Take at least 1 hour before or 2 hours after a meal.
- Treatment duration:
  - Unresectable or metastatic melanoma, NSCLC, ATC: continue until disease progression or unacceptable toxicity.
  - Adjuvant treatment of melanoma: continue trametinib and dabrafenib adjuvant treatment until disease recurrence or unacceptable toxicity for up to 1 year.

Dose Modification Criteria

- Renal (mild to moderate): no
- Renal (severe): no data
- Hepatic (mild): no
- Hepatic (moderate or severe): no data
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiomyopathy and hypertension
- DERM: new primary malignancies (cutaneous squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, and second

primary melanoma), rash, acneiform dermatitis, palmar-plantar erythrodysesthesia, erythema, and pruritus
- ELECTRO: hyponatremia
- ENDO: hyperglycemia
- GI: diarrhea, stomatitis, and N/V (minimal-low)
- HEMAT: hemorrhage, venous thromboembolism, anemia, neutropenia, lymphopenia, and thrombocytopenia
- HEPAT: increased AST/ALT and increased alkaline phosphatase
- Ocular system: retinal vein occlusion and retinal pigment epithelial detachment
- PULM: interstitial lung disease
- OTHER: serious febrile reactions (when administered with dabrafenib), chills, lymphedema, and hypoalbuminemia

Comments

- New primary malignancies (cutaneous and noncutaneous) may occur following trametinib. Monitor prior to initiation of therapy, while on therapy, and for 6 months following the last dose of trametinib.
- Cardiomyopathy: evaluate LVEF prior to initiation of therapy, 1 month after initiation, and then every 2 to 3 months during therapy with trametinib.
- Monitor for severe skin rashes and interrupt, reduce, or discontinue trametinib if necessary.
- Ocular toxicity: perform an ophthalmological examination at regular intervals and for any visual disturbances.
- Embryo-fetal toxicity: trametinib may cause fetal harm when administered to a pregnant woman.

TRASTUZUMAB (HERCEPTIN)

Mechanism of Action

- Humanized monoclonal antibody directed at HER2

FDA-Approved Indications

- Adjuvant breast cancer:
  - For the adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer as part of a regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel OR with docetaxel and carboplatin OR as a single agent following multimodality anthracycline-based therapy
- Metastatic breast cancer in patients in which tumor overexpresses the HER2 protein including:
  - First-line treatment in combination with paclitaxel
  - Single-agent therapy in patients who have received one or more chemotherapy regimens for metastatic disease
- Metastatic gastric cancer: first-line therapy in patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and capecitabine or fluorouracil

FDA-Approved Dosage

- Adjuvant breast cancer—administer according to one of the following doses and schedules for a total of 52 weeks of therapy.
  - During and following paclitaxel, docetaxel, or docetaxel/carboplatin.
    - Initial dose of 4 mg/kg by IV infusion over 90 minutes followed by subsequent once-weekly doses of 2 mg/kg by IV infusion over 30 minutes for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin). One week following the last weekly dose, administer trastuzumab at 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks.
  - As a single agent within 3 weeks following completion of multimodality, anthracycline-based chemotherapy regimens.
    - Initial dose of 8 mg/kg as an IV infusion over 90 minutes followed by subsequent doses of 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks.
- Metastatic breast cancer—administered alone or in combination with paclitaxel: initial dose of 4 mg/kg by IV infusion over 90 minutes followed by subsequent once weekly doses of 2 mg/kg by IV infusion over 30 minutes until disease progression.
- Metastatic gastric cancer: initial dose of 8 mg/kg as an IV infusion over 90 minutes followed by subsequent doses of 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks until disease progression.

Adverse Reactions

- CV: cardiomyopathy, ventricular dysfunction, CHF (incidence higher in patients receiving concurrent chemotherapy), and hypotension (infusion reactions)
- DERM: rash
- HEMAT: myelosuppression (anemia and leukopenia with concurrent chemotherapy)
- GI: diarrhea, N/V (minimal), and anorexia
- INFUS: (first infusion) chills, fever, nausea, vomiting, pain (at tumor sites), rigors, headache, dizziness, dyspnea, rash, hypotension, and asthenia
- NEURO: headache, dizziness (see infusion reactions)
- PULM: cough, dyspnea, rhinitis, adult respiratory distress syndrome, bronchospasm, angioedema, wheezing, pleural effusions, pulmonary infiltrates, noncardiogenic pulmonary edema, pulmonary insufficiency, and hypoxia (some severe pulmonary reactions required supplemental oxygen or ventilatory support)
- OTHER: infection (higher incidence of mild upper respiratory infections and catheter infections observed in one randomized trial), asthenia, allergic reactions, and anaphylaxis

Comments

- Cardiomyopathy: evaluate left ventricular function in all patients prior to and during treatment with trastuzumab. Discontinue trastuzumab in patients receiving adjuvant therapy and withhold trastuzumab in patients with metastatic disease for clinically significant decrease in left ventricular function.
- Serious and fatal infusion reactions and pulmonary toxicity can occur with trastuzumab. Death within 24 hours of a trastuzumab infusion has been reported. The most severe reactions seem to occur in patients with significant preexisting pulmonary compromise secondary to intrinsic lung disease and/or malignant pulmonary involvement.
- Do not administer by IV push or bolus.

- May use sterile water for injection for reconstitution if patient is allergic to benzyl alcohol (supplied diluent is bacteriostatic water for injection); product should be used immediately and unused portion discarded.
- Alternative dosing regimens have been studied including dosing at longer dosing intervals; consult current literature.
- Embryo-fetal toxicity: trastuzumab can cause fetal harm when administered to a pregnant woman.

TRASTUZUMAB AND HYALURONIDASE (HERCEPTIN HYLECTA)

Mechanism of Action

- Trastuzumab: humanized monoclonal antibody directed at HER2
- Hyaluronidase: degrades hyaluronan, an essential component of the extracellular matrix, resulting in a more permeable subcutaneous tissue thereby providing greater diffusion capacity and bioavailability

FDA-Approved Indications

- HER2-overexpressing breast cancer

FDA-Approved Dosage

- 600 mg trastuzumab and 10,000 units hyaluronidase administered subcutaneously over approximately 2 to 5 minutes once every 3 weeks

Dose Modification Criteria

- No dose reduction of trastuzumab/hyaluronidase is recommended
- Renal: no data available
- Hepatic: no data available

Adverse Reactions

- CV: CHF
- DERM: rash
- GI: N/V (minimal) and diarrhea
- HEMAT: exacerbation of chemotherapy-induced neutropenia
- INFUS: injection site reaction and hypersensitivity (including anaphylaxis)
- NEURO: headache
- PULM: cough, interstitial pneumonitis, and acute respiratory distress syndrome
- OTHER: fatigue, arthralgia, infection, myalgia, edema, flushing, pyrexia, chills, pain in extremity, and insomnia

Comments

- Trastuzumab/hyaluronidase is associated with the following boxed warnings:
  - Cardiomyopathy: subclinical and clinical cardiac failure manifesting as CHF and decreased LVEF has been reported. Evaluate cardiac function prior to and during treatment.
  - Pulmonary toxicity: trastuzumab/hyaluronidase should be discontinued in patients who develop anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
  - Embryo-fetal toxicity: exposure to trastuzumab/hyaluronidase during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception.

TUCATINIB (TUKYSA)

Mechanism of Action

- Kinase inhibitor of HER2 and HER3, resulting in the inhibition of downstream MAPK and AKT signaling and cell proliferation

FDA-Approved Indications

- Breast cancer: in combination with trastuzumab and capecitabine for advanced unresectable or metastatic HER2-positive breast cancer, including brain metastases, after one or more prior anti–HER2-based regimens in the metastatic setting

FDA-Approved Dosage

- 300 mg orally twice daily until disease progression or unacceptable toxicity. May take without regard to food.

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): not established
- Hepatic (mild or moderate, Child-Pugh class A or B): no
- Hepatic (severe, Child-Pugh class C): yes
- CYP2C8 inhibitors (strong): yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: PPE and rash
- GI: N/V (minimal-low), diarrhea, stomatitis, decreased appetite, and abdominal pain
- HEMAT: anemia
- HEPAT: hepatotoxicity
- NEURO: headache
- OTHER: fatigue

Comments

- Severe diarrhea including dehydration, acute kidney injury, and death has been reported. Administer antidiarrheal treatment as clinically indicated and interrupt, reduce dose, or discontinue based on severity.
- Avoid concomitant administration of strong CYP3A or moderate CYP2C8 inducers.
- Avoid concomitant administration of strong CYP2C8 inhibitors. If coadministration is required, reduce the tucatinib dose.
- Avoid concomitant administration of CYP3A substrates where minimal concentration changes may lead to significant toxicities.
- Consider reducing the dose of P-gp substrates where minimal concentration changes may lead to significant toxicities.
- Embryo-fetal toxicity: tucatinib may cause fetal harm when administered to a pregnant woman.

TRETINOIN (VESANOID)

Mechanism of Action

- Induces maturation, cytodifferentiation, and decreased proliferation of acute promyelocytic leukemia (APL) cells.

FDA-Approved Indications

- APL: induction of remission in patients with APL FAB M3 (including the M3 variant), characterized by the t(15;17) translocation and/or the presence of the PML/RAR α gene, who are refractory to or relapsed after anthracycline chemotherapy or for whom anthracycline therapy is contraindicated

FDA-Approved Dosage

- 22.5 mg/m^2 orally twice daily (total daily dose: 45 mg/m^2) until CR is documented. Therapy should be discontinued 30 days

after CR is obtained or after 90 days of treatment, whichever comes first.

Adverse Reactions

- CV: hypertension, arrhythmias, and flushing
- DERM: dry skin/mucous membranes, rash, pruritus, alopecia, and mucositis
- GI: N/V (minimal-low), diarrhea, constipation, and dyspepsia
- HEMAT: leukocytosis
- HEPAT: elevated LFTs
- NEURO: dizziness, anxiety, insomnia, headache, depression, confusion, intracranial hypertension, agitation, earaches, hearing loss, and pseudotumor cerebri
- Ocular system: visual changes
- OTHER: dyspnea, fever, shivering, retinoic acid-APL (RA-APL) syndrome (fever, dyspnea, weight gain, radiographic pulmonary infiltrates, and pleural or pericardial effusion), and hyperlipidemia

Comments

- Teratogenic; women must use effective contraception during and for 1 month after therapy.
- RA-APL syndrome occurs in up to 25% of patients usually within the first month. Early recognition and high-dose corticosteroids (dexamethasone 10 mg IV every 12 hours × 3 days or until the resolution of symptoms) have been used for management.
- During tretinoin treatment about 40% of patients will develop rapidly evolving leukocytosis, which is associated with a higher risk of life-threatening complications. If signs and symptoms of the RA-APL syndrome are present together with leukocytosis, high-dose corticosteroids should be initiated immediately. Chemotherapy is often combined with tretinoin in patients who

present with leukocytosis (WBC count of >5 × 10^9/L) or with rapidly evolving leukocytosis.
- Consult current literature for APL treatment regimens.

TRIFLURIDINE/TIPIRACIL (LONSURF)

Mechanism of Action

- Trifluridine is a thymidine-based nucleoside analog and tipiracil is a thymidine phosphorylase inhibitor. Tipiracil increases exposure to trifluridine by inhibiting its metabolism by thymidine phosphorylase.

FDA-Approved Indications

- Metastatic colorectal cancer (mCRC): treatment of adult patients with mCRC that has previously been treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.
- Metastatic gastric cancer: treatment of adult patients with metastatic gastric cancer or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

FDA-Approved Dosage

- 35 mg/m^2 up to a maximum of 80 mg/dose (based on the trifluridine component) orally twice daily with food on days 1 to 5 and 8 to 12 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no (monitor for toxicity)
- Renal (severe, CrCl 15-29 mL/min): yes
- Hepatic (mild): no
- Hepatic (moderate to severe): avoid use
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: N/V (minimal-low), diarrhea, abdominal pain, decreased appetite
- HEMAT: anemia, neutropenia, thrombocytopenia (myelosuppression may be severe)
- OTHER: asthenia/fatigue, pyrexia

Comments

- Embryo-fetal toxicity: trifluridine/tipiracil may cause fetal harm when administered to a pregnant woman.

TRIPTORELIN (TRELSTAR)

Mechanism of Action

- GnRH or LHRH agonist; chronic administration leads to sustained suppression of pituitary gonadotropins and subsequent suppression of serum testosterone in men and serum estradiol in women.

FDA-Approved Indications

- Palliative treatment of advanced prostate cancer

FDA-Approved Dosage

- Trelstar 3.75 mg IM injection every 4 weeks
- Trelstar 11.25 mg IM injection every 12 weeks
- Trelstar 22.5 mg IM injection every 24 weeks

Adverse Reactions

- CV: hypertension, peripheral edema, QT interval prolongation
- ENDO: hot flashes, gynecomastia, breast pain, sexual dysfunction, decreased erections, and hyperglycemia
- GU: erectile dysfunction, lower urinary tract symptoms, and testicular atrophy
- OTHER: tumor flare in the first few weeks of therapy, bone pain, injection site reactions, loss of BMD, osteoporosis, bone fracture, and asthenia

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.

UMBRALISIB (UKONIQ)

Mechanism of Action

- Inhibitor of PI3Kδ (expression on malignant B-cells) and casein kinase CK1ε (implicated in the pathogenesis of lymphoid malignancies)

FDA-Approved Indications

- Marginal zone lymphoma (MZL): relapsed or refractory MZL after at least one prior anti–CD20-based regimen
- Follicular lymphoma (FL): relapsed or refractory FL after at least three prior lines of systemic therapy

FDA-Approved Dosage

- 800 mg orally once daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild or moderate, CrCl 30-89 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild): no
- Hepatic (moderate or severe): no data available
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: increased creatinine
- DERM: rash and severe cutaneous reactions
- GI: N/V (not classified), diarrhea/colitis, abdominal pain, and decreased appetite
- HEMAT: neutropenia, anemia, and thrombocytopenia
- HEPAT: hepatotoxicity and increased transaminases
- OTHER: fatigue, musculoskeletal pain, infections, and upper respiratory tract infection

Comments

- Umbralisib tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in susceptible persons.
- Embryo-fetal toxicity: umbralisib may cause fetal harm when administered to a pregnant woman.

VALRUBICIN (VALSTAR)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Carcinoma in situ of the urinary bladder: second-line intravesical treatment after BCG therapy in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.

FDA-Approved Dosage

- 800 mg intravesically weekly × 6 weeks. For each instillation, 800 mg of valrubicin is diluted with 0.9% sodium chloride to a total volume of 75 mL. Once instilled into the bladder, the patient should retain drug in bladder for 2 hours before voiding.

Adverse Reactions

- GU: irritable bladder symptoms, urinary frequency, dysuria, urinary urgency, hematuria, bladder spasm, bladder pain, urinary incontinence, cystitis, local burning symptoms related to the procedure, and red-tinged urine

Comments

- Patients should maintain adequate hydration after treatment.
- Irritable bladder symptoms may occur during instillation and retention of valrubicin and for a limited period following voiding. For the first 24 hours following administration, red-tinged urine is typical. Patients should report prolonged irritable bladder symptoms or prolonged passage of red-colored urine immediately to their physician.
- Use non-DEHP plasticized solution containers and administration sets.

VANDETANIB (CAPRELSA)

Mechanism of Action

- Kinase inhibitor. In vitro studies have shown that vandetanib inhibits the activity of EGFR, VEGF, RET, protein tyrosine kinase 6 (BRK), TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases.

FDA-Approved Indications

- Medullary thyroid cancer: treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease

FDA-Approved Dosage

- 300 mg orally once daily with or without food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal (mild): no
- Renal (CrCl < 30-49 mL/min): yes
- Hepatic (mild): no
- Hepatic (moderate, severe): use is not recommended
- Nonhematologic toxicities: yes

Adverse Reactions

- CV: heart failure, hypertension, and QT prolongation
- DERM: acne, dermatitis acneiform, dry skin, pruritus, rash, photosensitivity, palmar-plantar erythrodysesthesia, and severe bullous/exfoliative skin reactions (including Stevens -Johnson syndrome)

- ELECTRO: hypocalcemia, hypoglycemia, hypokalemia, and hyperkalemia
- ENDO: hypothyroidism
- GI: abdominal pain, anorexia, diarrhea, dyspepsia, and nausea (minimal-low)
- GU: proteinuria
- HEPAT: increased ALT
- NEURO: headache and ischemic cerebrovascular events
- PULM: interstitial lung disease and upper respiratory tract infection
- OTHER: asthenia, fatigue, and hemorrhage

Comments

- Only prescribers and pharmacies certified with the restricted distribution program (Caprelsa REMS Program) are able to prescribe and dispense vandetanib.
- Vandetanib should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Electrolyte abnormalities should be corrected before drug administration. Drugs known to prolong the QT interval should be avoided. Given the half-life of 19 days, ECGs should be obtained to monitor the QT at baseline, at 2 to 4 weeks and 8 to 12 weeks after starting treatment with vandetanib, and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than weeks, QT assessment should be conducted.
- Use of vandetanib in patients with indolent, asymptomatic, or slowly progressing disease should be carefully considered because of the treatment-related risks of vandetanib.
- Interrupt vandetanib and investigate unexplained dyspnea, cough, and fever. Advise patients to report promptly any new or worsening respiratory symptoms.
- Do not administer vandetanib to patients with recent history of hemoptysis of ≥1/2 teaspoon of red blood.

- Consider RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function.
- Routine antidiarrheal agents are recommended. If severe diarrhea develops, vandetanib treatment should be stopped until diarrhea improves, and upon improvement, treatment should be resumed at a reduced dose.
- Avoid the concomitant use of strong CYP3A4 inducers and with agents that may prolong the QT interval.
- Mild to moderate skin reactions have been treated with topical and systemic corticosteroids, oral antihistamines, and topical and systemic antibiotics. If CTCAE grade 3 or greater skin reactions occur, vandetanib should be stopped until improved, and upon improvement, consideration should be given to continuing treatment at a reduced dose or permanent discontinuation of vandetanib.
- Vandetanib may impair wound healing. Withhold for 1 month prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing.
- Patients should be advised to wear sunscreen and protective clothing when exposed to the sun. Due to the long half-life of vandetanib, protective clothing and sunscreen should continue for 4 months after discontinuation of treatment.
- Vandetanib tablets should not be crushed. If patients have difficulty swallowing tablets, the tablets can be dispersed in a glass containing two ounces of noncarbonated water and stirred for approximately 10 minutes until the tablet is dispersed (it will not completely dissolve). See product labeling for additional information.
- Embryo-fetal toxicity: vandetanib may cause fetal harm when administered to a pregnant woman.

VEMURAFENIB (ZELBORAF)

Mechanism of Action

- Inhibits some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Some mutations in the *BRAF* gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

FDA-Approved Indications

- Melanoma: treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation
- Erdheim-chester disease (ECD): treatment of patients with ECD with BRAF V600 mutation

FDA-Approved Dosage

- 960 mg orally every 12 hours, until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to moderate): no
- Renal (severe): no data, exercise caution
- Hepatic (mild to moderate): no
- Hepatic (severe): no data, exercise caution
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: alopecia, cutaneous squamous cell carcinoma, dry skin, erythema, hyperkeratosis, hypersensitivity reaction (generalized rash, erythema, bullous exfoliative skin reactions [eg, Stevens-Johnson syndrome, toxic epidermal necrolysis), new primary

malignant melanoma, photosensitivity, pruritus, rash, and skin papilloma
- GI: decreased appetite, constipation, diarrhea, and N/V (minimal-low)
- GU: increased serum creatinine, interstitial nephritis, acute tubular necrosis
- HEPAT: increased alkaline phosphatase, increased bilirubin, and increased LFTs
- NEURO: headache
- Ocular system: blurry vision, iritis, photophobia, retinal vein occlusion, and uveitis
- OTHER: arthralgia, edema, fatigue, myalgia, and pain in extremity

Comments

- Vemurafenib is not recommended for use in patients with wild-type BRAF melanoma. An FDA-approved test must be used to detect the BRAF V600E mutation.
- Vemurafenib increases photosensitivity to UVA light, which can penetrate glass. Patients should be advised to apply broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥30) when outdoors and when driving.
- Cutaneous squamous cell carcinomas occurred in 24% of patients. Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage with excision and continue treatment without dose adjustment. Dose modifications or interruptions are not recommended. Vemurafenib may also promote new noncutaneous squamous cell carcinoma and other malignancies.
- Radiation sensitization and recall involving cutaneous and visceral organs have been reported in patients treated with radiation therapy prior to, during, or subsequent to vemurafenib treatment.
- Concomitant use of vemurafenib with drugs with narrow therapeutic windows that are metabolized by CYP3A4,

CYP1A2, or CYP2D6 is not recommended.
- Vemurafenib may increase exposure to concomitantly administered warfarin. Exercise caution and consider additional INR monitoring.
- Vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities, with long QT syndrome, or who are taking QT prolonging drugs.
- Embryo-fetal toxicity: vemurafenib may cause fetal harm when administered to a pregnant woman.

VENETOCLAX (VENCLEXTA)

Mechanism of Action

- Selective inhibitor of the antiapoptotic protein BCL-2.

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
- Acute myeloid leukemia (AML): treatment of newly diagnosed AML in adults 75 years or older or who have comorbidities that preclude use of intensive induction therapy in combination with azacitidine, or decitabine, or low-dose cytarabine.

FDA-Approved Dosage

- CLL/SLL: dose is increased from 20 to 400 mg using the following 5 week ramp-up schedule: 20 mg daily × 1 week, 50 mg daily × 1 week, 100 mg daily × 1 week, 200 mg daily × 1 week, 400 mg daily during week 5, and beyond. Venetoclax may be used as monotherapy or in combination with obinutuzumab or rituximab. Refer to product labeling for details of combination therapy.

- AML: dose is increased from 100 mg to either 400 mg or 600 mg, depending on the combination agent utilized, using a 3 or 4 day ramp-up schedule: 100 mg orally on day 1, 200 mg orally on day 2, 400 mg orally on day 3, followed by either 400 mg orally daily of each 28-day cycle with azacitidine or decitabine or 600 mg orally daily of each 28-day cycle in combination with low-dose cytarabine.
- Venetoclax tablets should be taken orally once daily with a meal and water.

Dose Modification Criteria

- Renal (mild to severe, CrCl ≥ 15 mL/min): no
- Renal (ESRD, CrCl < 15 mL/min): no data
- Hepatic (mild to moderate): no (monitor for toxicity)
- Hepatic (severe, total bilirubin >3 × ULN): no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- GI: diarrhea, N/V (minimal-low)
- HEMAT: neutropenia, anemia, and thrombocytopenia
- NEURO: headache
- PULM: upper respiratory tract infection
- OTHER: fatigue, pyrexia, and tumor lysis syndrome

Comments

- Anticipate and assess risk for tumor lysis syndrome and provide prophylaxis as appropriate. Laboratories may suggest tumor lysis syndrome as early as 6 to 8 hours following the first dose. The slow ramp up of dosing is to reduce the potential for tumor lysis syndrome.
- Venetoclax is a substrate of CYP3A4/5, P-gp, and BCRP. Concomitant use of strong CYP3A inhibitors during the ramp-

up phase is contraindicated. When possible, avoid moderate or strong CYP3A4 inhibitors, strong CYP3A4 inducers, and P-gp inhibitors. Venetoclax dose reductions may be employed when moderate or strong inhibitors must be used concurrently. Screen for drug interactions.
- Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery.
- Embryo-fetal toxicity: venetoclax may cause fetal harm when administered to a pregnant woman.

VINBLASTINE (VELBAN)

Mechanism of Action

- Inhibits microtubule formation

FDA-Approved Indications

- Palliative treatment of the following malignancies:
  - Frequently responsive malignancies: testicular cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, mycosis fungoides, Kaposi sarcoma, histiocytic lymphoma, and Letterer-Siwe disease (histiocytosis X)
  - Less frequently responsive malignancies: breast cancer and resistant choriocarcinoma

FDA-Approved Dosage

- Initial (adults): 3.7 mg/m^2 IV weekly. May increase weekly dose in a stepwise format up to a maximum dose of 18.5 mg/m^2 to maintain WBC >3000 cells/mm^3 (see package insert for schema).
- Pediatric: consult current literature for dose regimens.
- Consult current literature for alternative dosing regimens.

Dose Modification Criteria

- Renal: no

- Hepatic: yes
- Myelosuppression: yes

Adverse Reactions

- CV: hypertension
- DERM: alopecia and tissue damage/necrosis with extravasation
- GI: N/V (minimal), stomatitis, constipation, and ileus
- GU: urinary retention and polyuria
- HEMAT: myelosuppression
- NEURO: peripheral neuropathy, paresthesias, loss of deep tendon reflexes, and SIADH
- OTHER: bone pain, jaw pain, tumor pain, weakness, malaise, and Raynaud phenomenon

Comments

- Vesicant.
- Administer only by the IV route. Fatalities have been reported when vinca alkaloids have been given intrathecally.
- To reduce the potential for fatal medication errors due to incorrect route of administration, vinblastine should be diluted in a flexible plastic container (minibag) and prominently labeled as indicated "FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES." The Institute for Safe Medication Practices (www.ismp.org) strongly recommends dispensing vinblastine in a minibag (NOT a syringe). If prepared in a syringe, it must be packaged in an overwrap, which is labeled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES."
- Embryo-fetal toxicity: vinblastine may cause fetal harm when administered to a pregnant woman.

VINCRISTINE (ONCOVIN AND OTHERS)

Mechanism of Action

- Inhibits microtubule formation

FDA-Approved Indications

- Acute lymphocytic leukemia (ALL)
- Vincristine has shown to be useful in combination with other agents for Hodgkin lymphoma, non-Hodgkin lymphomas, neuroblastoma, Wilms tumor, and rhabdomyosarcoma.

FDA-Approved Dosage

- Adults: 1.4 mg/m^2 IV × one dose. Doses may be repeated at weekly intervals. Some clinicians will limit ("cap") individual doses to a maximum of 2 mg.
- Pediatrics: 1.5 to 2 mg/m^2 IV × one dose. For pediatric patients weighing 10 kg or less: 0.05 mg/kg IV × one dose. Doses may be repeated at weekly intervals. Some clinicians will limit ("cap") individual doses to a maximum of 2 mg.

Dose Modification Criteria

- Renal: no
- Hepatic: yes

Adverse Reactions

- DERM: alopecia and tissue damage/necrosis with extravasation
- GI: N/V (minimal), stomatitis, anorexia, diarrhea, constipation, and ileus
- GU: urinary retention
- NEURO: peripheral neuropathy, paresthesias, numbness, loss of deep tendon reflexes, and SIADH
- Ocular system: ophthalmoplegia and extraocular muscle paresis
- PULM: pharyngitis

- OTHER: jaw pain

Comments

- Vesicant.
- Administer only by the IV route. Fatalities have been reported when vinca alkaloids have been given intrathecally.
- To reduce the potential for fatal medication errors due to incorrect route of administration, vincristine should be diluted in a flexible plastic container (minibag) and prominently labeled as indicated "FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES." The Institute for Safe Medication Practices (www.ismp.org) strongly recommends dispensing vinblastine in a minibag (NOT a syringe).
- Medications that are inhibitors of cytochrome 3A4 will increase vincristine drug exposure and increase the risk of neurotoxicity.
- A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine.
- Embryo-fetal toxicity: vincristine may cause fetal harm when administered to a pregnant woman.

VINCRISTINE SULFATE LIPOSOME (MARQIBO)

Mechanism of Action

- Binds to tubulin, altering the tubulin polymerization equilibrium, resulting in altered microtubule structure and function, and stabilizes the spindle apparatus, preventing chromosome segregation, triggering metaphase arrest, and inhibition of mitosis.

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): treatment of adult patients with Philadelphia chromosome-negative ALL in second or greater relapse or whose disease has progressed following two or more antileukemia therapies.

FDA-Approved Dosages

- 2.25 mg/m^2 IV over 1 hour once every 7 days
- For IV use only; fatal if given by other routes

Dose Modification Criteria

- Renal: no data
- Hepatic (mild, moderate): no
- Hepatic (severe): no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Effects

- CV: hypotension
- GI: bowel obstruction, constipation, diarrhea, ileus, and N/V (minimal)
- HEMAT: anemia, febrile neutropenia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- NEURO: motor and sensory peripheral neuropathy
- OTHER: fatigue, insomnia, pain, pyrexia, and tumor lysis syndrome

Comments

- Fatal if given intrathecally.
- Vincristine sulfate liposome has different dosage recommendations than vincristine sulfate injection.

- Vincristine sulfate liposome requires extensive preparation time (60-90 minutes to prepare).
- Vincristine sulfate liposome is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome.
- Vincristine sulfate liposome is a vesicant. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures.
- Monitor patients for peripheral motor and sensory, central, and autonomic neuropathy and reduce, interrupt, or discontinue dosing. Sensory and motor neuropathies are cumulative.
- Institute a prophylactic bowel regimen to prevent potential constipation, bowel obstruction, and/or paralytic ileus.
- Vincristine sulfate liposome is expected to interact with drugs known to interact with nonliposomal vincristine sulfate. The concomitant use of strong CYP3A inhibitors and inducers should be avoided, as well as P-gp inhibitors or inducers.
- Embryo-fetal toxicity: vincristine sulfate liposome may cause fetal harm when administered to a pregnant woman.

VINORELBINE (NAVELBINE)

Mechanism of Action

- Inhibits microtubule formation

FDA-Approved Indications

- Non–small cell lung cancer (NSCLC): first-line treatment as a single agent for metastatic NSCLC or in combination with cisplatin for patients with locally advanced or metastatic NSCLC.

FDA-Approved Dosage

- Single agent: 30 mg/m^2 IV over 6 to 10 minutes weekly.
- Vinorelbine in combination with cisplatin:
  - Vinorelbine 25 mg/m^2 IV over 6 to 10 minutes weekly on days 1, 8, 15, and 22 of a 28-day cycle, *plus* cisplatin 100 mg/m^2 IV every 4 weeks *OR*
  - Vinorelbine 30 mg/m^2 IV over 6 to 10 minutes weekly, *plus* cisplatin 120 mg/m^2 IV × one dose on days 1 and 29, then every 6 weeks.
- Flush line with 75 to 125 mL of fluid (eg, 0.9% sodium chloride) after administration of vinorelbine.

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Myelosuppression: yes
- Nonhematologic toxicity (neurotoxicity): yes

Adverse Reactions

- CV: thromboembolic events and chest pain
- DERM: alopecia, vein discoloration, venous pain, chemical phlebitis, and tissue damage/necrosis with extravasation
- GI: N/V (minimal), stomatitis, anorexia, constipation, and ileus
- HEMAT: myelosuppression (granulocytopenia > thrombocytopenia or anemia)
- HEPAT: elevated LFTs
- NEURO: peripheral neuropathy and loss of deep tendon reflexes
- PULM: interstitial pulmonary changes and shortness of breath
- OTHER: jaw pain, tumor pain, fatigue, and anaphylaxis

Comments

- Vesicant.
- Administer only by the IV route. Fatalities have been reported when vinca alkaloids have been given intrathecally.
- Embryo-fetal toxicity: vinorelbine may cause fetal harm when administered to a pregnant woman.

VISMODEGIB (ERIVEDGE)

Mechanism of Action

- Hedgehog pathway inhibitor that binds to and inhibits smoothened, a transmembrane protein involved in Hedgehog signal transduction

FDA-Approved Indications

- Metastatic basal cell carcinoma
- Locally advanced basal cell carcinoma that has recurred following surgery or in patients who are not candidates for surgery, and who are not candidates for radiation

FDA-Approved Dosage

- 150 mg orally once daily until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic: no

Adverse Reactions

- DERM: alopecia
- ELECTRO: azotemia, hypokalemia, and hyponatremia
- GI: anorexia, constipation, diarrhea, and N/V (minimal-low)
- NEURO: taste disorders (ageusia and dysgeusia)
- OTHER: amenorrhea, decreased appetite, fatigue, muscle spasms, and arthralgias

Comments

- Embryo-fetal toxicity: vismodegib can result in embryo-fetal death or severe birth defects. Verify pregnancy status prior to initiation. Advise females of the need for contraception during and for 7 months after treatment, and advise males of the potential risk of vismodegib exposure through semen. Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners during treatment and for 2 months after the last dose. Report immediate exposure during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage patient participation in the vismodegib pregnancy pharmacovigilance program.
- Advise patients not to donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose.

VORINOSTAT (ZOLINZA)

Mechanism of Action

- HDAC inhibitor

FDA-Approved Indications

- Cutaneous T-cell lymphoma (CTCL): treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies.

FDA-Approved Dosage

- 400 mg orally once daily with food until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no (use with caution)
- Hepatic: yes (mild to moderate impairment, limited data with severe impairment)
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QT prolongation
- DERM: alopecia
- ENDO: hyperglycemia
- GI: N/V (minimal-low), diarrhea, anorexia, weight loss, constipation, and dry mouth
- GU: increased Cr and proteinuria
- HEMAT: myelosuppression (thrombocytopenia and anemia)
- NEURO: taste disorders (dysgeusia)
- OTHER: constitutional symptoms (fatigue and chills), thromboembolic events (including PE), dehydration, and muscle spasms

Comments

- Deep venous thrombosis and PE have been reported. Monitor for pertinent signs and symptoms.
- Patients may require antiemetics, antidiarrheals, and fluid and electrolyte replacement to prevent dehydration.
- Hyperglycemia has been commonly reported. Adjustment of diet and/or therapy for increased glucose may be necessary.
- QT prolongation has been observed. Monitor electrolytes and ECGs at baseline and periodically during treatment.
- Monitor blood counts and chemistry tests every 2 weeks during the first 2 months of therapy and monthly thereafter.
- Severe thrombocytopenia and GI bleeding have been reported with concomitant use of vorinostat and other HDAC inhibitors (eg, valproic acid).

- Embryo-fetal toxicity: vorinostat may cause fetal harm when administered to a pregnant woman.

ZANUBRUTINIB (BRUKINSA)

Mechanism of Action

- Small molecule inhibitor of BTK leading to the inhibition of BTK enzymatic activity

FDA-Approved Indications

- Mantle cell lymphoma following at least one prior therapy

FDA-Approved Dosage

- 160 mg orally twice daily or 320 mg orally once daily with or without food. Continue treatment until disease progression or unacceptable toxicity.

Dose Modification Criteria

- Renal (mild to moderate, CrCl ≥ 30 mL/min): no
- Renal (severe, CrCl < 30 mL/min): no data available
- Hepatic (mild or moderate): no
- Hepatic (severe): yes
- CYP3A inhibitor (strong or moderate): yes
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: cardiac arrhythmias
- DERM: rash
- GI: N/V (minimal-low) and diarrhea

- HEMAT: neutropenia, thrombocytopenia, leukopenia, anemia, and hemorrhage
- PULM: cough
- OTHER: bruising, infections, and second primary malignancies

Comments

- Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with zanubrutinib. Skin cancer was reported in 6% of patients; monitor and advise protection from sun exposure.
- Avoid concomitant administration of moderate or strong CYP3A inducers.
- If concomitant administration of moderate or strong CYP3A inhibitors is necessary, modify the zanubrutinib dose.
- Embryo-fetal toxicity: zanubrutinib may cause fetal harm when administered to a pregnant woman.

ZIV-AFLIBERCEPT (ZALTRAP)

Mechanism of Action

- Ziv-aflibercept acts as a soluble receptor that binds to VEGF-A, VEGF-B, and PIGF. By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability.

FDA-Approved Indications

- Metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen: ziv-aflibercept is used in combination with FOLFIRI.

FDA-Approved Dosage

- 4 mg/kg IV over 1 hour every 2 weeks in combination with FOLFIRI chemotherapy until disease progression or unacceptable toxicity

Dose Modification Criteria

- Renal: no
- Hepatic (mild to moderate): no
- Hepatic (severe): no data
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension and arterial thromboembolic events
- GI: diarrhea, stomatitis, weight loss, decreased appetite, abdominal pain, GI fistula, perforation, or hemorrhage
- GU: increased serum creatinine and proteinuria
- HEMAT: myelosuppression (leukopenia, neutropenia, and thrombocytopenia)
- HEPAT: increased LFTs
- NEURO: headache and RPLS
- OTHER: fatigue, epistaxis, dysphonia, and compromised wound healing

Comments

- Ziv-aflibercept/FOLFIRI should not be administered until the neutrophil count is $\geq 1.5 \times 10^9$/L.
- Ziv-aflibercept should be held for at least 4 weeks prior to elective surgery, and for at least 4 weeks following major surgery. Do not resume ziv-aflibercept until the surgical wound has fully healed.
- Monitor BP at least every 2 weeks. Suspend ziv-aflibercept for recurrent or severe hypertension. Once hypertension is controlled, reduce the dose of ziv-aflibercept upon restarting treatment.

- Ziv-aflibercept should be suspended for proteinuria of 2 g/24 h. Reduce the dose of ziv-aflibercept for recurrent proteinuria.
- Elderly patients may be at a higher risk for diarrhea and dehydration with ziv-aflibercept/FOLFIRI and should be monitored closely.
- Ziv-aflibercept should be administered through a 0.2 μm polyethersulfone filter. Polyvinylidene fluoride or nylon filters should not be used.
- Embryo-fetal toxicity: there are no adequate and well-controlled studies with ziv-aflibercept in pregnant women. Male and female contraception should be used during treatment and for at least 3 months following the last dose of ziv-aflibercept.

Suggested Reading

1. Kohler DR, Montello MJ, Green L, et al. Standardizing the expression and nomenclature of cancer treatment regimens. *Am J Health Syst Pharm*. 1998;55:137-144.

Appendix 1

PERFORMANCE STATUS SCALES/SCORES: PERFORMANCE STATUS CRITERIA

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalisation indicated through death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20		

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Moribund	10		
Dead	0	5	Dead

Information from OncologyPro (http://oncologypro.esmo.org/Oncology-in-Practice/Practice-Tools/Performance-Scales)

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