The Bethesda Handbook of Clinical Oncology

Fourth Edition

Jame Abraham
James L. Gulley
Carmen J. Allegra

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THE BETHESDA HANDBOOK OF CLINICAL ONCOLOGY

FOURTH EDITION

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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 his or her daily patient encounters. The book has been compiled by clinicians who are working at the National Cancer Institute and National Institutes of Health, Johns Hopkins, Mayo Clinic, and Cleveland Clinic, as well as scholars 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 oncologists, oncology fellows, residents, students, oncology nurses, and allied health professionals.

The landscape of oncology has changed substantially since we published the first edition of the book more than 13 years ago. For the fourth edition, we have updated all chapters and added two new chapters, "Clinical Genetics" and "Diagnosis-Driven Individualization of Cancer Care." In addition, we have included multiple-choice questions for most chapters to enhance the learning experience and help clinicians prepare for their board examinations.

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
James L. Gulley
Carmen J. Allegra

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We express our deep gratitude to Jonathan W. Pine, Jr., Executive Editor at LWW, our friend and colleague, whose vision, determination and professionalism made this handbook possible and whose life was tragically cut short by cancer.

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SECTION One

Head and Neck

1

Head and Neck Cancer

Carter Van Waes, Karl E. Haglund, and Barbara A. Conley

EPIDEMIOLOGY

The incidence of head and neck squamous cancer is more than 500,000 cases per year worldwide, and 40,000 to 60,000 cases per year in the United States, where it comprises approximately 3% to 5% of all new cancers and 2% of all cancer deaths. Most patients are older than 50 years, and incidence increases with age; 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 last decade. Ninety percent of these cancers are squamous cell histology. The most common sites 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.

RISK FACTORS

Heavy alcohol consumption increases the risk of developing squamous head and neck cancer twofold to sixfold, 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 tobacco and snuff are associated with oral cavity cancers. Use of smokeless tobacco, or chewing betel 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.

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 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 virtually all nonkeratinizing and undifferentiated nasopharyngeal cancers but less consistently in squamous nasopharyngeal cancers. Human papillomavirus (HPV) infection is associated with up to 70% of cancers of the oropharynx and tonsil, and some larynx and squamous nasopharyngeal cancers. The incidence of HPV+ cancers seems to be increasing in several countries, and HPV positivity is more common in cancers in nonsmokers. Disorders of DNA repair (e.g., Fanconi anemia, dyskeratosis congenita) as well as organ transplantation with immunosuppression are also associated with increased risk of squamous head and neck cancer.

SCREENING

The U.S. Preventive Task Force makes no recommendations regarding regular screening for oral cancer in the general population, due to the low incidence and lack of sensitivity studies. They do recommend counseling for cessation of tobacco use and limitation of alcohol intake.

The American Cancer Society recommends oral examination during physician or dental appointments. The oral examination should include inspection of all mucosal areas, assessment of range of motion of tongue, bimanual palpation of floor of mouth, palpation of the tongue, and assessment of dental health.

Careful examination of the head and neck is warranted in individuals with risk factors (e.g., tobacco and/or alcohol use) and suggestive symptoms. Any local/regional complaints require evaluation, especially if symptoms persist for more than 4 weeks or after treatment for presumed infection.

PREVENTION AND CHEMOPREVENTION

The most important recommendation for prevention of head and neck cancer is to encourage smoking cessation and to limit alcohol intake. As risk for HPV-associated head and neck cancer is associated with multiple sexual partners, education on safer sexual practices may also be helpful. Consideration should be given to prophylactic administration of HPV vaccines to adolescents, a treatment currently approved by the U.S. Food and Drug administration for prevention of cervical cancer (bivalent or quadrivalent vaccines) in females and genital warts in males (quadrivalent vaccine), as well as for prevention of anal precancers (quadrivalent vaccine). Data are currently being gathered on the effect of vaccination on incidence of HPV-related head and neck 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. A recent trial with PPAR agonist pioglitazone showed regression or reduction in size of leukoplakia in ~80% of subjects. A multicenter phase II study is underway. Chemoprevention outside a clinical trial is not recommended.

ANATOMY

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 (NP); oral cavity (OC; lips, gingiva, buccal areas, floor of mouth, hard palate, and tongue anterior to the circumvallate papillae); oropharynx (OP; soft palate, tonsils, base of tongue and lingual tonsils, and pharyngeal wall between palate and vallecula); hypopharynx (HP; pharyngeal wall and piriform sinuses, between vallecula and esophageal inlet); and larynx (epiglottis, glottis, and subglottic trachea).

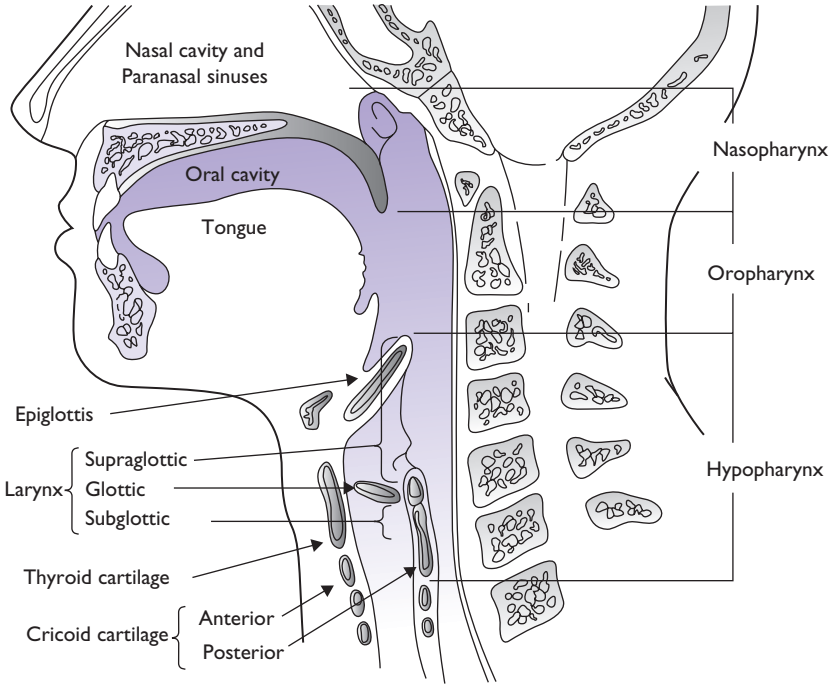

FIGURE 1.1 Sagittal section of the upper aerodigestive tract. (Adapted from Oatis CA. *Kinesiology: The Mechanics and Pathomechanics of Human Movement*. Baltimore, MD: Lippincott Williams & Wilkins; 2004.)

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 (Fig. 1.2). Level I comprises the submental or submandibular nodes, which are most often involved with lesions of the oral 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. Level VII is the area of the superior mediastinum, and portends distant metastasis.

PRESENTATION

Symptoms and signs most often include pain and/or mass effects of tumor, involving adjacent structures, nerves, or regional lymph nodes (Table 1.1). Adult patients with any of these symptoms for more than 4 weeks should be referred to an otolaryngologist. Delay in diagnosis is common due to patient

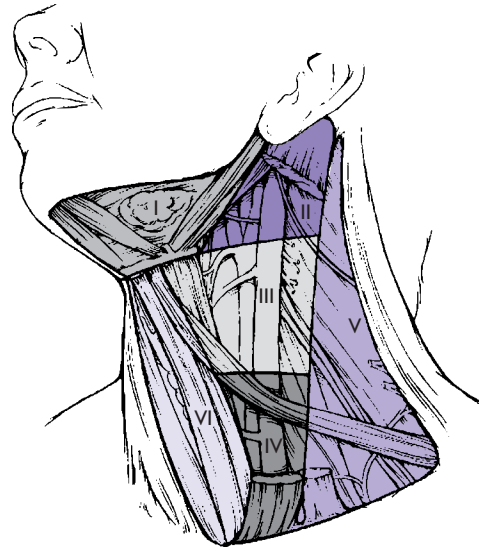

FIGURE 1.2 Diagram of the neck showing levels of lymph nodes. Level I, submandibular; level II, high jugular; level III, midjugular; level IV, low jugular; level V, posterior triangle; level VI, tracheoesophageal; level VII, superior mediastinal, is not shown. (From Robbins KT, Samant S, Ronen O. Neck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

delay, repeated courses of antibiotics for otitis media or sore throat, or lack of follow-up. A persistent lateralized symptom or firm cervical mass in an elderly smoker or sexually active middle-aged adult at risk for HPV is highly suggestive of squamous cell carcinoma (Fig. 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. 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 CNS involvement is less common.

DIAGNOSIS, WORKUP, AND STAGING EVALUATIONS

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)

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

3. Alcohol exposure (number of drinks per day and duration of habit)
4. Other risk factors (chewing betel nut)
5. In nonsmokers with oropharyngeal symptoms or cervical nodes, history of HPV or oral sexual practice, particularly with multiple partners
6. In nonsmokers aged 18 to 50, history or family history of anemia, Fanconi anemia, or dyskeratosis congenita
7. Cancer history of patient and family
8. Thorough review of systems

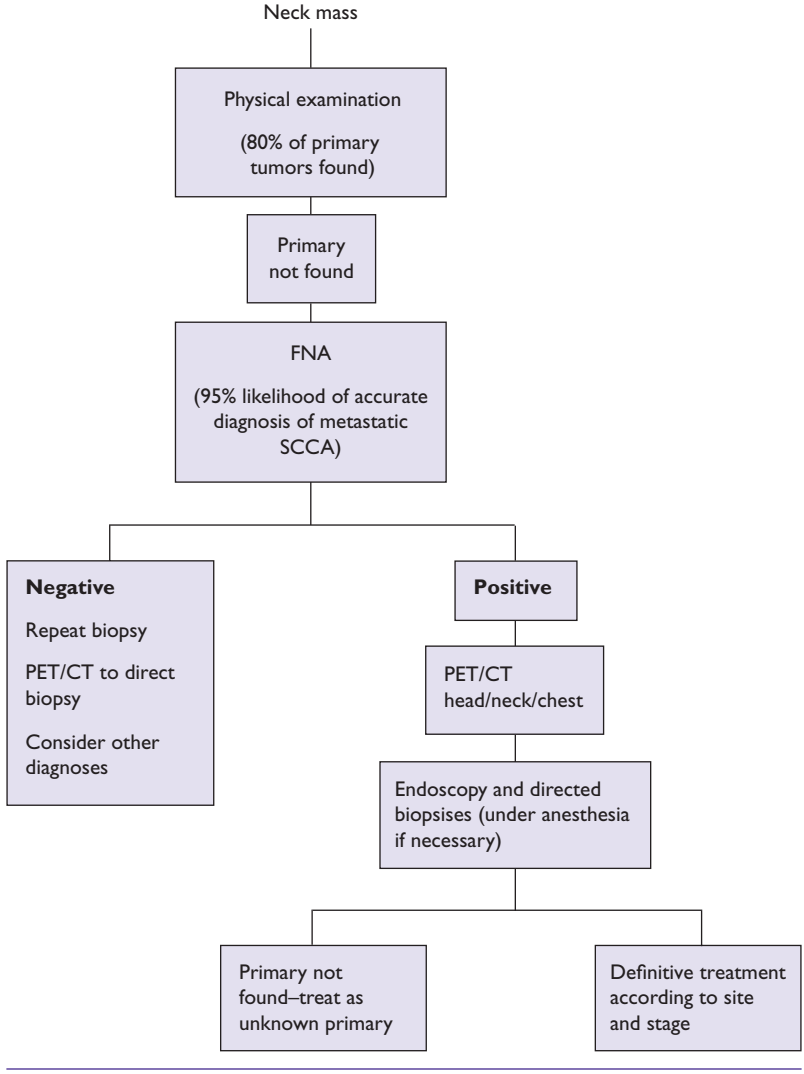

FIGURE 1.3 Evaluation of cervical adenopathy when a primary cancer of the head and neck is suspected.

The head and neck physical examination should include the following:

1. Careful inspection of the scalp, ears, nose, and mouth
2. Palpation of the neck and mouth, 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, NP, 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 to the examination of cranial nerves

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, NP, 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 contraindicated if a squamous cell carcinoma is suspected. Open biopsy may worsen local control, increase the rate of distant metastases, and decrease overall survival rate, possibly by spreading the disease at the time of the biopsy. An open biopsy does not provide any information additional to that obtained from fine needle aspiration (FNA), and 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.

After the 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 for disease recurrence in patients with advanced locoregional disease treated with concurrent chemotherapy and radiotherapy. PET/CT scanning is indicated for staging patients with unknown primaries and for advanced head and neck cancers. A chest CT or PET/CT is indicated for all patients because of the risk of metastasis or a second lung malignancy. Body CT is not usually necessary.

Additional studies vary according to the clinical stage, symptoms, and primary site.

Specialized tests include tissue p16 immunostaining and in situ hybridization for HPV for oropharyngeal carcinoma, and tissue EBV IgA and DNA tests 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 is to be given), baseline thyroid function tests, and pregnancy testing in females of child-bearing age. In patients with unexplained anemia, short stature, and/or micro-ophthalmia, consideration should be given to mitomycin C testing for chromosomal fragility for Fanconi anemia, as chemo- or radiotherapy is contraindicated.

Dental evaluation should be performed and any necessary extractions should be carried out 10 to 14 days prior to any planned radiation. Baseline speech, swallow, and audiometry evaluation should be performed.

STAGING CLASSIFICATION

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 seventh edition in 2009, should be consulted for details for each site and subsite. The T classification indicates the extent of the primary tumor. For primary tumors of the oral cavity, hypopharynx, and oropharynx, lesions up to 2 cm in diameter are T1, 2 to 4 cm are T2, and greater than 4 cm are classified as T3. For laryngeal carcinomas, limited involvement of one or more subsites are staged T1 and T2, respectively, while vocal cord immobility or pre-epiglottic space involvement with a larynx or hypopharynx primary indicates at least stage T3. Lesions with local invasion of adjacent cartilage, bone, or soft tissues indicate stage T4.

The N classification is uniform for all primary sites, except NP. Any clinical lymph node involvement indicates at least stage III. The presence of a single ipsilateral lymph node 3 cm or larger, multiple ipsilateral lymph nodes of any size, or contralateral lymph nodes of any size is classified as stage IV regardless of T stage.

The presence of distant metastasis (M1) indicates stage IVC disease. Mediastinal lymph node involvement is considered distant metastasis.

Tumor differentiation grade has not shown clear association with outcome and is not considered when staging head and neck cancers.

PROGNOSIS

The most important determinant of prognosis is stage at diagnosis. The 5-year survival for stage I patients exceeds 80% but is less than 40% in stage III and IV disease. Most patients have locally advanced disease involving one or several lymph nodes on one or both sides of the neck. The presence of a palpable lymph node in the neck generally decreases the survival rate by 50% compared to the same T stage without node involvement.

Prognoses for oropharynx cancers associated with HPV, even when locally advanced, are about 30% to 50% better than similar cancers that are not associated with HPV, but this improved outlook is reduced in smokers. A subset of patients with matted lymph nodes has been reported to have poorer prognosis.

Most relapses occur locoregionally. Distant metastases are more commonly seen later in the course of the disease or as part of relapse after successful initial treatment, and predominantly involve lung, bone, and less commonly liver. Second primary cancers after an index head and neck cancer in smokers commonly occur in the head and neck region, the lung, or the esophagus, and may represent a significant mortality risk after curative treatment of the initial head and neck cancer. Recently, there seems to have been a decline in second primary cancer incidence in patients with an index oropharyngeal cancer. This may be due to the higher incidence of HPV-related oropharyngeal cancers, as well as the likelihood that such patients are less likely to be heavy smokers.

TREATMENT

The management of patients with squamous head and neck cancer is complex (Fig. 1.4). The choice of treatment modality depends on the stage and site of disease as well as the condition of the patient. In general, either surgery or radiation is effective as single-modality therapy for patients with early-stage disease (stage I or II) for most sites. The choice of modality depends on local expertise, patient

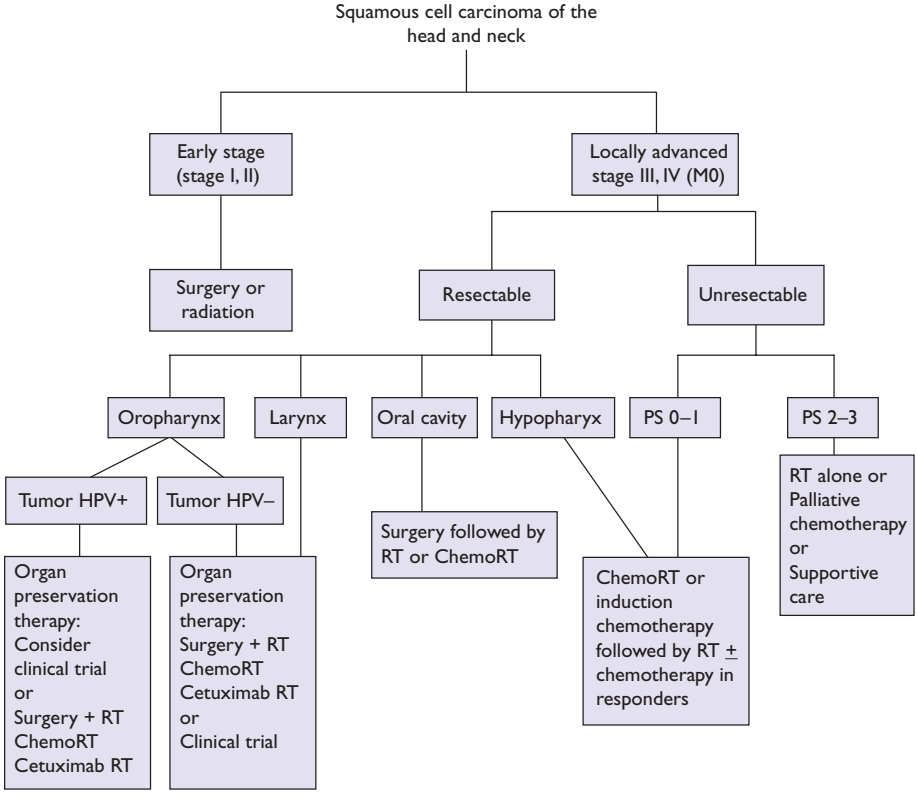

FIGURE 1.4 Treatment for head and neck squamous cell carcinomas (M0).

preference, and functional result. For the 60% of patients with locally advanced disease (stages III, IV, and M0), curative combined-modality therapy is indicated. These therapies could include primary surgery with adjuvant radiation (with or without concomitant chemotherapy), radiation with or without concomitant systemic therapy, and neoadjuvant chemotherapy followed by radiation with or without concomitant systemic therapy. Investigational paradigms using response to one cycle of neoadjuvant chemotherapy and biomarkers in selection of patients for chemoradiation or surgery and radiation have been reported for oropharyngeal and laryngeal cancers.

Patients with recurrent locoregional disease or solitary lung metastasis have benefited from surgical salvage. Some patients may be best treated with radiation, or with reirradiation to a limited field. Unresectable recurrent or distant metastatic disease is usually treated with systemic therapy with palliative intent.

Patients with squamous head and neck cancer should be evaluated before treatment is initiated by a multidisciplinary team including an otolaryngologist or head and neck surgical oncologist, radiation oncologist, medical oncologist, dentist, nutritionist, speech and swallowing pathologist, and personnel involved in rehabilitation.

Surgery

The nature of the surgical procedure is determined primarily by the size of the tumor and the structures involved. Resectability depends on the experience of the surgeon and the rehabilitation team. In general, a tumor is unresectable if the surgeon anticipates that all gross tumor cannot be removed or that local

and distant control will not be achieved after surgery even with adjuvant radiation therapy. Generally, involvement of the skull base, pterygoid, prevertebral fascia and deep neck musculature, and/or the carotid artery, portends a poor outcome with surgery or other modalities. Involvement of these structures may be indicated by clinical findings such as limitation of ocular movements, tumor involving the pterygoid fossa, severe trismus, laryngeal fixation to the prevertebra, neuropathies of cranial nerves, or nodal fixation in the neck, or by CT, MRI, and PET scans.

T1 and T2 lesions of the oral cavity, oropharynx, and hypopharynx may be amenable to wide local excision with a 2-cm margin, and closed by primary or secondary intention, skin graft, or local tissue flap reconstruction. Limited carcinoma in situ and T1 and T2 lesions of the larynx may be treated by microlaryngoscopic mucosal excision or cordectomy. T2 and selected T3 cancers may be approached using one of the various external supraglottic, hemilaryngectomy or extended partial laryngectomy procedures that have been developed. Newer technologies for transoral and transnasal endoscopic surgical approaches have been recently investigated for resection of T1, T2, and selected T3 carcinomas involving the oropharynx, larynx, paranasal, and skull base region. The feasibility and outcomes for transoral laser and transoral robotic surgery (TORS) coupled with neck dissection or radiation have provided an alternative approach to chemoradiation for function sparing treatment of selected T1/T2 oropharyngeal and supraglottic primaries, and multicenter trials for comparison of these treatments have been proposed. More extensive surgeries, especially those involving the function of the tongue, oral cavity, or oropharynx, may require myocutaneous or microvascular free flaps to achieve functional reconstruction of deficits affecting mucosa, innervated muscle, and/or bone. However, as will be discussed below, with the advent of primary therapy with concurrent chemoradiotherapy for advanced T3/4 cancers of the larynx, NP, oropharynx, and hypopharynx, surgery is also being used for treatment of advanced neck disease (N2, N3) and for salvage of nonresponding or recurrent tumors of the primary site.

Cervical lymph node dissections may be elective or therapeutic. Elective neck dissections are done at the time of initial surgery in patients with necks that are clinically negative when the risk of a microscopically positive lymph node is at least 30%. Therapeutic neck dissections are done for clinically obvious masses at the time of primary surgical treatment, or persistent clinical mass, radiographic, or PET abnormalities after neoadjuvant or concurrent chemoradiotherapy. Cervical lymph node dissections are classified as radical, modified radical, or selective. The radical dissection includes removal of all lymph nodes in the neck from levels I to V (see Fig. 1.2), including removal of the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle. Due to excessive morbidity of loss of shoulder function, this surgery is now reserved primarily for very extensive disease such as N2- or N3-stage disease with extracapsular spread involving CNXI and the sternocleidomastoid muscle. The modified radical dissection preserves one or more of the nonlymphatic structures, usually CNXI without or with the sternocleidomastoid muscle. In selective neck dissections, only certain levels of lymph nodes are removed, based on the specific lymphatic drainage from the primary site, and lack of extracapsular spread. With no palpable adenopathy, and no CT or PET scan evidence of clinical nodal involvement, nodal metastases will be present beyond the confines of an appropriate selective neck dissection less than 10% of the time. Sentinel lymph node dissection and PET scanning are currently being evaluated for use in diagnosing positive lymph nodes in patients with neck examinations that are clinically negative.

Radiation Therapy

Over the past two decades, radiation therapy has evolved to a fine art that demands a keen appreciation of both tumor biology and radiation physics. The use of CT for simulation and three-dimensional techniques for treatment planning has improved accuracy in portal design based on an improved understanding of the radiographic extent of the tumor. IMRT techniques have helped to reduce normal tissue toxicity while maintaining high doses to the target volume. The advantages of these advances have been demonstrated by an improvement in locoregional control and a decrease in normal tissue toxicity. Brachytherapy offers similar advantages when performed by experienced physicians. In addition, radiation using charged particles, such as protons or carbon ions, rather than conventional photons, has theoretical advantages for sparing of sensitive normal tissues. With the number of facilities offering charged particle radiation on the rise, direct evidence supporting the theoretical advantages is now being amassed.

Advances in diagnostic imaging have contributed to improvements in radiation therapy planning. Both PET and MRI allow better tumor delineation. Current technology allows fusion of the images from various imaging techniques on each patient so that the radiation oncologist may define the tumor and critical normal structures more accurately. While the goal of IMRT is to improve treatment planning, the goal of image-guided radiation therapy (IGRT) is to improve the accuracy of treatment delivery. IGRT involves imaging patient anatomy and adapting to patient position while the patient is positioned on the treatment machine, with the goal of targeting disease more accurately, minimizing treatment delivery variation, and more effectively sparing normal tissues. Traditionally, radiation therapy has been delivered at 1.8 to 2 Gy once daily for a total of 50 to 70 Gy with successive field reductions based on risk assessment. IMRT allows the integration of all sites into a single plan with lower-risk areas receiving lower doses per fraction while higher-risk areas receive higher doses per fraction. With this technique, gross tumor is typically administered daily doses higher than 2.1 Gy.

Altered fractionation schemes have had mixed success. These include hyperfractionation (1.2 to 1.5 Gy twice or thrice daily) and the concomitant boost technique (1.8 Gy in the morning to the entire field followed by 1.5 Gy in the evening to a smaller field encompassing high-risk disease). With either schedule, it is essential to maintain 4 to 6 hours between fractions to allow normal tissue repair. Although altered fractionation improves outcome, this is offset by an increase in acute toxicity without increase in long-term complications. The integration of chemotherapy with altered fraction schedules is under investigation. However, preliminary results of a phase III trial (RTOG 0129) comparing standard fractionated to accelerated fractionated chemoradiation showed no difference in outcome or late toxicity between the groups. Early-stage (T1, T2, N0) disease responds well to single-modality treatment with either surgery or radiation therapy. Radiation therapy allows organ preservation—as evidenced by its role in the management of early-stage cancers of the glottic larynx and pharynx. However, more advanced disease (generally, stage III and IV) requires the integration of radiation therapy with other modalities.

Toxicity of Radiation

With the advances in radiation treatment planning and delivery, toxicities associated with radiation are less than they were two decades ago. Common severe acute radiation toxicity includes dermatitis, mucositis, loss of taste, xerostomia, dysphagia, and hair loss. Decreased hearing is uncommon. Dental evaluation and necessary extractions should be performed before radiation because dental extractions in a radiated mandible can lead to osteonecrosis. Dentulous patients should be given prophylactic fluoride. Patients receiving radiation are at high risk for tooth decay due to the xerostomia caused by injury to the salivary glands as well as mucosal damage. Radioprotectors such as amifostine and pilocarpine have not demonstrated a consistent ability to decrease xerostomia. IMRT techniques enabling the reduction of dose to the parotid glands have had more success. Similarly, permanent swallowing dysfunction can be avoided by decreasing the dose to the pharyngeal musculature. Prophylactic, pretreatment, and posttreatment evaluations by a speech therapist also help in preventing and alleviating dysphagia in these patients.

Concomitant Chemoradiation

Radiation with concomitant chemotherapy is used with the intent of organ preservation when surgery would result in the compromise of voice and swallowing functions. It is also used in patients who have stage IVB disease in attempt to cure a patient for whom surgery is not considered a good option (patient not medically fit for surgery or is disease is considered "unresectable") or IVC disease when, although palliative, local control is desired. Studies have evaluated the use of chemotherapy administered before radiation or surgery (i.e., neoadjuvant or induction chemotherapy), instead of surgery (i.e., concomitant chemotherapy and radiation) or after surgery (i.e., adjuvant chemotherapy and radiation). The rationale for concomitant chemoradiation is based on experimental evidence of synergism between chemotherapy and radiation that is theoretically mediated by interference by chemotherapy with multiple intracellular radiation-induced stress-response pathways involved in apoptosis, proliferation, and DNA repair. The finding that certain chemotherapeutic agents (e.g., cisplatin, 5-fluorouracil [5-FU], taxanes, and hydroxyurea) can induce radiosensitivity and increase log cell kill from radiation supports

this treatment strategy. Cisplatin, the most extensively evaluated drug in large randomized trials, has the advantage of not having mucositis as toxicity; although as a radiation enhancer, it does increase radiation-induced mucositis.

Radiation administered concurrently with chemotherapy or the anti-EGFR antibody cetuximab has been shown to improve survival in patients with advanced head and neck cancers (Table 1.2). Randomized clinical trials and meta-analyses show that for locally advanced head and neck squamous cell carcinoma, concomitant chemoradiation (with cisplatin) produces a small but significant survival advantage of about 8% at 5 years compared to radiation therapy alone. The U.S. Intergroup compared concomitant cisplatin and radiation to split-course radiation with cisplatin and 5-FU to standard radiation alone in patients with *unresectable* head and neck squamous cancer and showed that concurrent cisplatin at 100 mg/m^2 every 21 days with daily radiation (5 days per week) significantly improved survival rates. Administration of concurrent cisplatin with radiation is also associated with higher rates of larynx preservation in locally advanced larynx cancer, compared to radiation alone. More frequent dosing of cisplatin (e.g., weekly or daily) is postulated to increase sensitization, and is an area of active investigation. A randomized trial of neoadjuvant cisplatin and 5-FU followed by radiation versus concurrent cisplatin and 5-FU with radiation in patients with *unresectable* head and neck cancer showed similar survival rates but improved locoregional control for the concomitant arm. Results have been presented in abstract form for patients with stage II to IV resectable cancers, comparing a taxane-based triplet neoadjuvant regimen followed by radiation and concomitant weekly carboplatin (or accelerated boost radiation with weekly Docetaxel) to concomitant accelerated boost radiation with cisplatin given every 21 days. This phase III trial showed no difference in 3-year survival, though poor accrual caused early stopping. A second phase II trial, comparing radiation given concurrent with docetaxel, 5FU and hydroxyurea, both given every other week with or without neoadjuvant taxane-based triplet chemotherapy showed better disease-free survival but similar overall survival for the neoadjuvant arm. Consequently, concomitant platinum-based chemoradiation may be considered for patients with unresectable advanced head and neck cancer with good performance status.

Concomitant chemoradiation regimens using taxanes with either 5-FU or cisplatin show promising results as do regimens containing 5-FU and hydroxyurea with concomitant twice-daily radiation, with both chemotherapy and radiation administered together every other week. Agents that inhibit EGFR signaling have been evaluated as radiation enhancers in head and neck squamous cancer. More than 90% of head and neck squamous cancers express EGFR, and increased expression has been correlated with poorer survival rates after radiation therapy. The EGFR inhibitory monoclonal antibody cetuximab has been shown to result in an enhancement of response and survival over radiation alone, although more than 50% of the trial participants had oropharyngeal primary tumors, a type previously associated with greater responsiveness to radiation. In contrast to trials comparing radiotherapy with or without chemotherapy, there was no reduction in distant metastases in the cetuximab arm. Clinical studies are ongoing with combinations of EGFR inhibitors, with radiation and with standard chemotherapy agents. Preliminary reports of RTOG 0522 showed no progression-free or overall survival benefit with the addition of cetuximab to standard cisplatin-based chemoradiation, although mature results

Table 1.2 Common Chemoradiation Regimens

Regimens	Common toxicities
Cisplatin 100 mg/m^2 IV every 21 days during radiation	Renal dysfunction, severe nausea/delayed vomiting, dehydration, increased mucositis, hearing toxicity,
Carboplatin AUC 1–2 IV with paclitaxel 35–50 mg/m^2 IV weekly during radiation	Myelotoxicity, increased mucositis
Cetuximab loading dose 400 mg/m^2 IV followed by 250 mg/m^2/week IV (can be given as single agent or with cisplatin and 5-FU regimen as neoadjuvant therapy prior to RT, or concomitantly with RT)	acneiform rash, mucositis, allergic reaction

are awaited. Recent studies suggest that additional molecular alterations, in addition to EGFR, are likely to be important for response, such as nuclear factor-kappaB (NFκB), signal transduction and transcription-3 (STAT-3), and inactivation or mutation of tumor suppressor p53, mutation or overexpression of MET, as well as epithelial-to-mesenchymal transition. Agents targeting these pathways individually, such as bortezomib, quinacrine (NF-κB, p53), and STAT decoy, have shown limited activity.

After chemoradiation in patients with N2, N3, or multiple nodes at diagnosis, elective lymph node dissection may be carried out when complete response is obtained at the primary site, especially when there is less than complete nodal response to chemoradiation. N2 or greater nodes often (about 20%) harbor tumor even if a clinically complete response is obtained in the neck with chemoradiation. Surgical salvage may be attempted if complete control is not achieved at the primary or locoregional site. Major complications with surgical salvage are found in about 52% of patients previously treated with organ-preserving regimens.

Postoperative/Adjuvant Therapy

The decision to administer adjuvant radiation or chemoradiation is typically guided by pathologic findings. When surgery is the primary modality, postoperative radiation therapy or chemoradiation is generally preferred to the preoperative setting.

Adjuvant concomitant cisplatin and radiation in patients at high risk for recurrence after surgery has been studied both in Europe and in the United States. Both studies found a benefit in locoregional control and disease-free survival for patients receiving adjuvant concomitant cisplatin and radiation over radiation alone. The European study also identified an overall survival benefit, which the American study did not. Both the initial analysis and subsequent reanalysis of pooled data from both trials suggested that the benefits were particularly prominent and enduring in patients with positive margins or extracapsular extension of tumor. Therefore, this population is considered to be at high risk of recurrence and is typically recommended to receive postoperative concurrent cisplatin-based chemoradiation. On the other hand, radiation alone is typically recommended for patients considered to be at intermediate risk of recurrence, with risk factors such as pathologic T3–4/N0 disease, multiple positive nodes (without extracapsular extension), perineural or lymphovascular invasion, or oropharyngeal cancers with cervical nodal level IV or V involvement. Studies are ongoing to evaluate the addition of cetuximab to postoperative radiation in patients with intermediate risk factors.

Induction/Neoadjuvant Chemotherapy Followed by Radiation

The advantages of induction (neoadjuvant) chemotherapy include reduction of tumor burden potentially allowing more effective local control with surgery or radiation, as well as organ preservation, though at the price of increased toxicity, cost, and length of treatment. Induction chemotherapy has also been used experimentally as a predictive indicator of benefit for chemoradiation—responders are given definitive chemoradiation and nonresponders are treated with definitive surgery followed by radiation. In stage III and IV larynx and hypopharynx cancer, chemotherapy followed by radiotherapy compared to laryngectomy followed by radiotherapy showed no decrement in overall survival, and larynx preservation was achieved in two-thirds of surviving patients who received chemoradiation. Surgical salvage was eventually necessary for about one-third of the patients with larynx cancer treated with chemoradiation, and therefore close follow-up is required in the event that salvage surgery is needed. For laryngeal cancer, concomitant cisplatin and radiation therapy has since been shown to result in better local control and organ preservation, but not survival, compared to neoadjuvant chemotherapy followed by radiation or radiation alone.

Recently, several investigators have studied combinations of a taxane, a platinum, and 5-FU as induction chemotherapy prior to radiation or to concomitant chemoradiation. A phase III study in stage III and IV cancers of the oral cavity, oropharynx, hypopharynx, and larynx demonstrated improved disease-free and overall survival after follow-up of 32.5 months, for patients receiving cisplatin, 5-FU, and taxane chemotherapy compared to cisplatin and 5-FU for up to four courses prior to radiation alone. A second study used cisplatin and 5-FU with or without paclitaxel for three courses, followed by chemoradiation with high-dose cisplatin on days 1, 22, and 43 if response was at least 80%. This trial also showed that complete response rate (the primary end point of the trial) was improved (33% vs. 14%) in the triplet arm. With a median follow-up of 23 months, survival data had not yet matured. A third phase

III trial randomized unresectable or organ preservation patients to induction therapy with cisplatin and 5-FU with or without docetaxel, followed by radiation with weekly carboplatin at AUC 1.5. With a median follow-up time of 42 months, treatment with the triple drug neoadjuvant therapy showed a 30% improvement in survival.

Induction therapy with a taxane, platinum agent, and 5-FU combination has shown response rates up to 70% in chemotherapy naïve patients with unresectable head and neck squamous cancers. Presently, induction chemotherapy with a taxane, cisplatin, and 5-FU combination, with adequate supportive care for hematologic toxicity, followed by radiation therapy can be considered as a reasonable treatment strategy, particularly in patients with unresectable cancers, advanced nodal disease (N2c/N3), and good performance status. Preliminary (abstract) reports (noted above) on trials that randomized advanced-stage resectable patients to concomitant chemoradiation treatment with or without induction chemotherapy have not yet shown a survival advantage, though seem to show a disease-free survival advantage to the neoadjuvant arm.

Reirradiation

Reirradiation without and with chemotherapy has been studied in patients with recurrent local and regional disease. Reirradiation has usually been studied in selected patients with relatively limited recurrent disease, so that the volume of reirradiated tissue can be minimized. Highly conformal radiation methods such as IMRT are employed to minimize dose to surrounding tissues. The total spinal cord and brain stem doses are typically of primary concern. The interval between the courses of radiation is also important for minimizing toxicities, and most trials have used 6 months as the minimum interval. In the setting of recurrence, multidisciplinary management remains important, since reirradiation has been evaluated with favorable results when delivered as a solitary modality or when delivered postoperatively or with concurrent chemotherapy. Radiation doses in the range of 60 Gy are typically delivered. Short-term local control rates of 15% to 65% are observed, and median survival times of 8 to 28 months are reported.

Supportive Care

Acute Toxicities of Treatment

Patients treated with concomitant chemoradiation therapy require frequent clinical assessment and prompt institution of supportive care to avoid severe or fatal consequences during the acute phase of treatment (during chemoradiation and 1 to 2 months following chemoradiation).

Nutrition Careful assessment of the need for a percutaneous enteral feeding device should be done. 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. A good rule of thumb is to place these devices if the patient loses 10% of their normal weight prior to treatment or in the initial 4 weeks of concomitant chemoradiation.

Hydration Combined chemoradiation leads to increased fluid loss, especially with severe mucositis, and/or with loss of normal taste or appetite secondary to chemoradiation. Patients should be assessed every 1 to 2 weeks for skin turgor, orthostatic blood pressure changes, lightheadedness on standing, or increased creatinine (especially with platinum combinations). If any of these symptoms or signs is present, saline hydration should be given intravenously.

Mucositis A significant number of patients receiving chemoradiation therapy will develop severe mucositis that impairs nutrition and causes severe pain. If a patient cannot swallow, or loses 10% of body weight, then assistance to nutrition, such as percutaneous enteral feeding, is indicated. 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.

Hypomagnesemia This is common with high-dose platinum agents and is managed with oral or intravenous replacement.

Hypothyroidism Up to 50% of patients may have increased thyroid stimulating hormone levels (TSH) after radiation therapy. Prior to and following acute treatment and every 3 months during follow-up, TSH should be monitored and appropriate replacement therapy instituted.

Rash 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 not be present in the radiation fields.

Allergic Reactions Severe and life-threatening allergic reactions have occurred with cisplatin, carboplatin, and antiepidermal growth factor receptor (EGFR) antibodies. Infusion of these agents should only be done when appropriate emergency equipment and trained personnel are available.

Late Toxicities of Treatment

A significant 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.

Xerostomia Risk of dry mouth due to incidental radiation to the salivary glands is present but has been lessened by more accurate treatment planning and delivery with intensity-modulated radiation therapy (IMRT) methods. 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 (ALTENS) in palliation of xerostomia as well.

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.

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. The combination of tocopherol (1,000 International Units per day) and pentoxifylline (400 mg BID) improves symptoms of fibrosis, can result in some degree of regression of fibrosis, and is well tolerated. Greater regression is generally achieved with earlier initiation of therapy.

Palliative Chemotherapy

Chemotherapy is effective as palliative treatment for recurrent or metastatic squamous head and neck cancer, or in unresectable cancers in patients who cannot undergo combined modality treatment. The median survival for patients with locally recurrent or disseminated disease is 6 to 9 months, and only 20% to 30% are alive at 1 year. Whenever possible, patients should be encouraged to enroll in clinical trials that evaluate new agents or new combination regimens.

The choice of single-agent or combination chemotherapy depends largely on whether chemotherapy is used as part of a curative regimen, or for palliation, as well as the patient's overall health and performance status. Combination chemotherapy yields higher response rates but has increased toxicity when compared with single agents. Common chemotherapy agents used for head and neck cancer include cisplatin, carboplatin, docetaxel, paclitaxel, 5-FU, methotrexate, and the anti-EGFR antibody cetuximab (Table 1.3). Cisplatin is considered to be standard chemotherapy for head and neck cancer either alone or in combination with 5-FU or a taxane and/or cetuximab. Carboplatin (AUC 5) may be slightly less active than cisplatin for head and neck squamous cancer, but is preferred in patients at high risk for cisplatin toxicity, e.g., patients with renal dysfunction, neuropathy, or hearing loss. Small studies have also evaluated pemetrexed, gemcitabine, ifosfamide, irinotecan, vinorelbine, and others, showing response rates of 10 to 25% and median survival of 4 to 7 months in nonrandomized clinical trials. Prior to the use of taxane combinations, meta-analyses and randomized trials demonstrated improved response for cisplatin compared with methotrexate, and improved response for cisplatin and 5-FU combination compared with single drugs, although improvement in survival with combinations versus single agents is less clear. In the metastatic setting, the combination of cisplatin and infusional 5-FU produces a 70% response rate and a 27% complete remission rate in chemotherapy-naive patients, but the response rate is 30% to 35% with less than 10% complete responses in patients who have relapsed after radiation therapy. An older randomized trial of cisplatin and 5-FU versus carboplatin (fixed dose of 300 mg/m^2) and 5-FU versus weekly methotrexate in patients with recurrent or metastatic head and neck squamous cancer demonstrated response rates of 32%, 21%, and 10%, respectively. Median survival was not improved by combination chemotherapy (6.6, 5.0, and 5.6 months, respectively).

Both docetaxel and paclitaxel have shown antitumor activity. Paclitaxel doses of 75 mg/m^2 every 3 to 4 weeks are usually tolerable in combination with a platin and/or 5-FU. Docetaxel is usually administered at doses of 60 to 100 mg/m^2 every 3 to 4 weeks. Weekly schedules are being evaluated. Taxane combinations, including paclitaxel or docetaxel, cisplatin or carboplatin, with 5-FU, show promising response rates and can be given with modest toxicity if growth factors are used.

The EGFR inhibitor cetuximab is approved by the FDA for use combined with platinum-containing chemotherapy or as a single agent after progression on a platinum regimen for recurrent or metastatic disease. Cetuximab is also approved for use with radiation therapy for treatment of locally advanced squamous head and neck cancer, where there is a survival advantage compared to radiation alone (see above).

Table 1.3 Common Chemotherapy Regimens for Head and Neck Squamous Cancer

Regimens	Common Toxicities
Methotrexate 40–60 mg/m^2/week IV, depending on patient tolerance	Mucositis, myelosuppression
Cisplatin 70–100 mg/m^2 IV every 21–28 days (can be used concomitantly with radiation)	Renal dysfunction, hearing loss, dehydration, severe nausea/vomiting (highly emetogenic)
Paclitaxel 75 mg/m^2 IV over 1–3 h every 21–28 days	neurotoxicity, myelosuppression, allergic reactions
Cetuximab loading dose 400 mg/m^2 IV followed by 250 mg/m^2/week IV (can be given as single agent or with cisplatin and 5-FU regimen, or concomitantly with radiation)	Acneiform rash, diarrhea, myelosuppression Allergic reactions
Cisplatin 100 mg/m^2 IV day 1 and 5 FU 800–1000 mg/m^2/day IV by continuous infusion × 4–5 days, every 21–28 days	Highly emetogenic; renal dysfunction, hearing loss, dehydration, diarrhea, hand-foot syndrome, myelosuppression
Docetaxel 75 mg/m^2 IV day 1, cisplatin 75 mg/m^2 IV day 1 and 5 FU 750 mg/m^2 iv over 24 h by continuous infusion × 5 days, every 21–28 days	Severe myelosuppression (supportive filgrastim needed); renal dysfunction, dehydration, hearing loss, neurotoxicity, edema, hand-foot syndrome, diarrhea

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. Imaging studies should be done approximately 10 to 12 weeks after completion of radiation therapy (if given) and then every 3 to 6 months for the first 3 years, or for any symptoms or signs suggesting recurrence or second primary cancer. The TSH level should be obtained every 3 to 6 months if the thyroid is irradiated. Generally, thyroid hormone replacement therapy should begin when, and if, TSH remains stably elevated, before symptoms of hypothyroidism appear. Up to 50% of patients will develop hypothyroidism by 5 years after radiation therapy to the head and neck. Patients with nasopharyngeal tumors who were treated with radiation are at risk for pituitary failure (121,122).

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, a semiannual chest radiograph or CT is recommended. Some recurrences, as well as second primaries, can be treated with curative intent.

SITE-SPECIFIC TREATMENT OF HEAD AND NECK TUMORS

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. Approximately 20,000 new cases are diagnosed annually in the United States. Squamous cell carcinoma is the histologic type observed in most cases. The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites are shown in Table 1.4.

Early lesions (stages I and II) are treated with either surgery or radiation therapy as single-modality therapy. Treatment of the neck by sentinel node or supraomohyoid selective neck dissection or radiation is indicated for invasive cancers due to the significant risk of nodal metastasis. For resectable locally advanced disease (stages III and IV, and M0), surgery for the primary tumor and appropriate neck dissection is indicated (see Fig. 1.4). Postoperative radiotherapy or chemoradiotherapy is indicated for close margins, perineural or lymphatic invasion, nodal disease stage N2 or greater, or with extracapsular spread. Definitive radiation therapy with or without chemotherapy is an option for patients with resectable disease at any stage who have high medical or surgical risk, or according to patients' preference (based on discussions about quality of life, functional outcome, and toxicity profile of each treatment). Treatment for unresectable locally advanced and metastatic disease is included in sections on chemo- and radiotherapy.

Oropharynx

The oropharynx includes the base of the tongue, tonsils, posterior pharyngeal wall, and the soft palate. The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites of the oropharynx are shown in Table 1.5. In the last 10 years, it has become apparent that there are at least two different subtypes of oropharynx cancer. Oropharynx cancer associated with HPV infection has increased in incidence by over 200%, while the incidence non-HPV-related oropharynx cancer has decreased. Currently half or more oropharynx cancers are HPV+. Patients tend to be slightly younger than those with HPV− oropharynx cancer, and tend to have less tobacco exposure. Most of these tumors are due to high risk HPV, particularly types 16 and 18. Patients with oropharynx cancer should have their tumors assessed for HPV subtypes, and for the presence of p16 immunostaining. Oncogenes expressed by the virus (E6 and E7) interfere with the function of p53 and Rb, and drive proliferation. The absence of a functional Rb leads to p16 overexpression. The prognosis for HPV+ oropharynx cancer is 30% to 50% better compared with HPV− oropharynx cancer. Currently, treatment of both HPV+ and HPV− oropharynx cancers are similar. Treatment may include primary surgery with postoperative radiation or chemoradiation as necessary (multiple positive lymph nodes, extracapsular spread). TORS may be an option for some tumors, and may provide a functional surgical result. Primary

Table 1.4 Head and Neck Cancer: Oral Cavity

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement	Prognosis (5-y Survival)
Lip	Risk factors are sun exposure and tobacco; 3,600 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	T1, 90% T2, 84% With lymph node involvement, 50%
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	T1, 85% T2, 80% T3, 60% T4, 20%
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	By stage: I, 85–90% II, 80% III, 66% IV, 32% Advanced stage, 30%
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%	By stage: I, 75% II, 46% III, 36% IV, 11%
Buccal mucosa	8% of oral cavity cancers in United States; women > men	Exophytic more often, silent presentation; pain, bleeding, difficulty in chewing	10% at diagnosis	18–77% all stages

M:F, male-to-female ratio.

chemoradiation therapy is frequently used for stage III or IV disease as a result of superior organ preservation and swallowing when compared to nonfunction sparing surgical resection and reconstruction of the tongue base, reserving surgery for management of regional node metastases or for salvage of persistent disease. The adoption of IMRT has resulted in improved functional outcomes as well. Older randomized trials, which did not assess for HPV status, show that concurrent chemoradiation significantly

Table 1.5 Head and Neck Cancer: Oropharynx and Larynx

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement	Prognosis (5-y Survival)
Base of tongue	4,000 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 common, also IV, V, and VI	By stage: I, 60% II, 40% III, 30–90% IV, 15–70%
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)	Tonsillar fossa, 93% (stage I) to 17–65% (stage IV) Soft palate, 85% (stage I) to 21% (stage IV)
Posterior Pharyn geal 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	By stage: I, 75% II, 70% III, 42% IV, 27%
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	By stage: I, 70–100% II, 50–90% III, 45–70% IV, 20–60%
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% 2%	T1, 74–86% T2, 67–75% T3, 55 T4, 50
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	26% overall

M:F, male-to-female ratio.

improves locoregional control and survival compared with radiotherapy alone. Increased complexity, toxicity, and need for close follow-up of this combined-modality approach mandates that the patient has adequate performance status and psychosocial resources.

Because of the much improved prognosis of HPV+ oropharynx cancers, clinical trials are assessing the efficacy of less intense treatments. RTOG 1016 (NCT01302834) compares IMRT with cisplatin versus IMRT with cetuximab in locally advanced stage III/IV oropharynx cancer that is positive for p16 expression. Several phase II trials are also evaluating TORS and reduced radiation dose for HPV+ oropharynx cancers. The Eastern Cooperative Oncology Group has completed accrual to a phase II trial of paclitaxel, cisplatin, and cetuximab followed by cetuximab in combination with low-dose or standard-dose intensity-modulated radiotherapy in HPV+ stage III or IV resectable oropharynx cancer (NCT01084083) and 2-year progression-free survival (PFS) results are awaited.

Non-HPV-associated cancers usually present at a locally advanced stage, and are treated with chemoradiation or induction chemotherapy followed by chemoradiation, with surgery reserved for residual disease or recurrence. In selected advanced patients, surgery could also be used as the primary modality, followed by radiation or chemoradiation as indicated. If available, clinical trials are recommended for this group, as well.

Nasopharynx

The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for nasopharyngeal cancer are shown in Table 1.6. It is rare in most parts of the world, with an incidence of less than 1 case per 100,000 population. However, it is endemic in certain areas, including North Africa, Southeast Asia, China, and the far northern hemisphere. EBV is strongly associated with nasopharyngeal carcinoma. This association has been demonstrated by serologic studies and by the detection of the viral genome in tumor samples. Diet (salt-cured fish and meat) and genetic susceptibility are other probable risk factors; tobacco and alcohol are not risk factors, except in a minority of cases.

The World Health Organization (WHO) classification divides nasopharyngeal carcinoma into three types: type I, keratinizing squamous cell carcinoma; type II, differentiated nonkeratinizing squamous cell carcinoma; and type III, undifferentiated nonkeratinizing carcinoma. Type II, the most common, is also sometimes referred to as lymphoepithelioma because of the characteristic exuberant lymphoid infiltrate accompanying malignant epithelial cells.

The most common initial presentation is a neck mass. Other presenting signs and symptoms are related to tumor growth, with resulting compression or infiltration of neighboring organs. These include serous otitis media, nasal obstruction, tinnitus, pain, and involvement of one or multiple cranial nerves.

Nasopharyngeal carcinoma has a high metastatic potential to regional nodes and distant sites. WHO type I has the greatest propensity for uncontrolled local tumor growth and the lowest propensity for metastatic spread (60% clinically positive nodes) compared with WHO type II and type III cancers (80% to 90% clinically positive nodes). Even though WHO type I cancer is associated with a lower incidence of lymphatic and distant metastases than are types II and III, its prognosis is worse because of a higher incidence of deaths from uncontrolled primary tumors and nodal metastases.

Staging for nasopharyngeal carcinoma differs from that of other head and neck sites, particularly with regard to nodal staging. For full details, see the *AJCC Cancer Staging Manual*. Stage I is node-negative disease confined to the NP. In stage II disease, the tumor extends to the parapharyngeal region with or without unilateral lymph node(s) measuring 6 cm or less. The disease is considered locally advanced disease (stages III and IV) when the tumor extends beyond the parapharyngeal region to involve other structures (bone, orbit, cranial nerves, intracranial extension) or when bilateral or any supraclavicular lymph nodes are involved.

The prognoses for different stages of nasopharyngeal carcinoma are shown in Table 1.6.

General treatment guidelines are shown in Figure 1.5. Surgery is usually not recommended because of anatomic considerations and the pattern of spread of the cancer via the retropharyngeal lymphatics. Radiation has been the standard treatment, with good results (local control rates: T1–T2, 80% to 90%; T3–T4, 70% to 80%), and remains the standard of care for stage I cancer. However, for stage II disease, a recent randomized trial showed that concurrent weekly cisplatin (30 to 40 mg/m^2) added to radiation confers an overall survival benefit over radiation alone. Thus, consideration of chemoradiation is advisable in stage II disease.

Table 1.6 Head and Neck Cancer: Hypopharynx, Nasal Cavity, Paranasal Sinuses, and NP

Site	Epidemiology	Natural History and Common Presenting Symptoms	Nodal Involvement	Prognosis (5-y Survival)
Hypopharynx	2,500 new cases yearly in 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	Survival varies between sites within hypopharynx T1, T2, 40% T3–T4, 16–37%
Nasal cavity and paranasal sinuses	Rare, 0.75/100,000 occurrence in 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	60% for all sites all stages, 30% for T4
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%	By stage: I, 90% II, 85% III, 75% IV, 58%

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

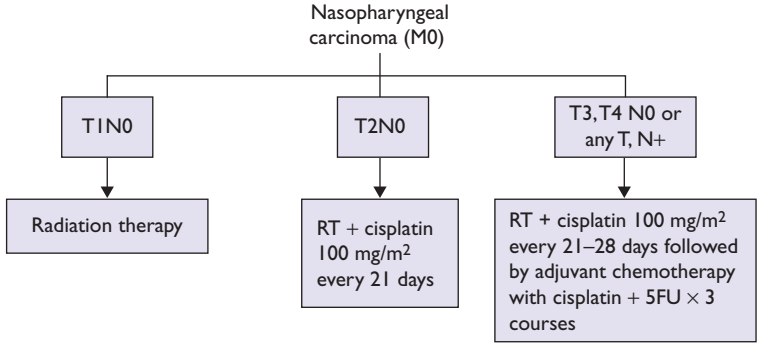

FIGURE 1.5 Treatment of nasopharyngeal carcinoma (M0).

In a randomized trial in the United States in the 1990s, concurrent cisplatin (cisplatin 100 mg/m^2 every 21 to 28 days) and daily radiation followed by three courses of adjuvant cisplatin and 5-FU was shown to improve overall survival (76% for concurrent chemoradiation vs. 46% for radiation therapy alone). On the basis of this study, concurrent chemoradiation followed by adjuvant chemotherapy is still considered standard treatment for locally advanced nonmetastatic (stage III and IV) nasopharyngeal cancer in the United States. Other drugs, such as taxanes, appear to have activity but have not been evaluated extensively.

Larynx

Risk factors include a history of tobacco and/or alcohol intake. HPV is detected in subset of laryngeal cancers. In addition, certain dietary factors and exposure to wood dust, nitrogen mustard, asbestos, and nickel have been implicated as etiologic factors. The male-to-female ratio for laryngeal cancer is 4.5:1, with a peak incidence in the sixth decade of life. This disease is 50% more common in African Americans than in whites and 100% more common in whites than in Hispanics and Asians. More than 95% of laryngeal cancers are squamous cell carcinomas.

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 1.5.

Early glottic cancers not requiring laryngectomy (T1–T2 N0) are usually treated with microendoscopic surgery or radiation. Transoral robotic or laser surgery has been used for T1–2 and selected T3 supraglottic cancers. Locally advanced resectable tumors (T3–T4 or T2 N+) may be treated with surgery, with addition of adjuvant radiation if locoregional risk factors are present (i.e., close or positive margins, T3/4 tumor involving pre-epiglottic space, laryngeal-cricoid cartilage or hyoid bone, lymphatic or vascular or perineural involvement, multiple positive nodes, extracapsular invasion, subglottic extension, or prior tracheostomy). For supraglottic cancers with high risk of neck metastasis or other sites with lymph node involvement, neck dissection, and/or neck radiation is indicated. An alternative is the use of combined radiation and chemotherapy. In 1991, the Veterans Administration Laryngeal Study Group trial established that sequential chemotherapy with cisplatin and infusional 5-FU followed by radiation therapy in highly responsive patients resulted in equivalent survival and a larynx preservation rate of about 66% compared to treatment with surgery followed by radiation. A subsequent randomized phase III trial conducted in the United States demonstrated that concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43) and radiation therapy resulted in better laryngectomy-free survival, larynx preservation rate, and local–regional control rate than either sequential (induction) cisplatin and 5-FU followed by radiation therapy or radiation therapy alone. Survival rate was not significantly different for the three treatments, in part reflecting the ability to surgically salvage laryngeal cancer patients treated for organ preservation. Patients who received any chemotherapy had a lower metastatic rate at 2 years than did patients who received radiation alone. Patients with high-volume T4 disease (with destruction of larynx or massive extension of supraglottic laryngeal cancer to the base of tongue), who were not likely to

obtain functional laryngeal and swallowing preservation without aspiration with chemoradiation, have traditionally been treated with surgery followed by radiation therapy rather than by organ preservation therapy. Recently, however, an investigational hybrid paradigm using one cycle of neoadjuvant cisplatin has been used to "chemoselect" patients with >50% tumor reduction for concurrent chemoradiation with significant organ preservation rates, even in patients with T4 disease. Those patients with <50% tumor reduction after cisplatin or incomplete response after chemoradiation undergo total laryngectomy.

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.

Patients whose lesions are unresectable or patients who are considered to have high surgical risks are candidates for definitive radiation therapy with chemotherapy if performance status is good. The treatment for a patient with metastatic disease is discussed under Palliative Chemotherapy in this chapter.

Hypopharynx

The epidemiology, natural history, common presenting symptoms, risk of nodal involvement, and prognosis for specific subsites of the hypopharynx are shown in Table 1.6.

Early cancers not requiring laryngectomy (most T1 N0–N1; small T2 N0) can be treated with surgery or radiation. Transoral robotic and laser surgery has been shown to be feasible in selected cases. Locally advanced resectable tumors (T3–T4 any N) may be treated with surgery followed by radiation or sequential or concomitant chemoradiation. In these cases, surgery usually involves total laryngectomy and/or partial or total pharyngectomy and neck dissection. Even with this radical surgery and the consequent functional impairment, the survival prognosis is poor.

Combined-modality treatment with chemoradiation allows organ function preservation with chances of survival being equivalent to that after surgery (Table 1.6). Recently, the European Organisation for the Research and Treatment of Cancer (EORTC) reported on a larynx/hypopharynx preservation study. Two hundred and two patients were randomized to either total laryngectomy with partial pharyngectomy and neck dissection, followed by irradiation, or to chemotherapy with up to three cycles of induction chemotherapy (cisplatin 100 mg/m^2 on day 1 + 5-FU 1,000 mg/m^2 on days 1 to 5) followed by irradiation for complete responders or conventional treatment for incomplete responders. At a median follow-up of 10.5 years on 194 eligible patients, the 10-year OS rate was 13.8% in the surgery arm and 13.1% in the chemotherapy arm. The 10-year PFS rates were 8.5% and 10.8%, respectively. In the chemotherapy arm, the 10-year survival with a functional larynx (SFL) rate was 8.7%. This strategy did not compromise disease control or survival, which remained poor and allowed more than half of the survivors to retain their larynx.

Patients who are prone to high surgical or medical risks can be treated with chemoradiation or radiation. The management of metastatic disease is discussed under "Palliative Chemotherapy" in this chapter.

Nasal Cavity and Paranasal Sinuses

Carcinomas of the nasal cavity and sinuses are rare entities, and include squamous cancers, melanomas, esthesioneuroblastoma, and sinonasal undifferentiated carcinoma (SNUC). Non-Hodgkin's lymphomas, plasmacytomas, sarcomas, adenoid cystic carcinoma, and other histologies may also present in the nasal cavity and 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 1.6.

Carcinomas of the nasal cavity and paranasal sinuses are usually detected in patients in advanced stages because of the relatively silent tumor location. Symptoms may include facial swelling, nasals stuffiness, pain, or epistaxis. Such patients should be evaluated by a multidisciplinary team experienced in tumors of the nasal cavities and sinuses. If feasible, surgery is the preferred primary management, but reports of good outcomes with the use surgery followed by adjuvant radiation with or without

chemotherapy have been published. Hypopituitarism may be a complication of radiation treatment. Local recurrence is common for epithelial tumors, while distant metastases are less common for these tumors.

Cancer of Unknown Primary Site (of the Head and Neck)

The workup of a patient with a neck mass is shown in Figure 1.3. Nasopharyngeal, oropharyngeal, and hypopharyngeal origins are most common. PET/CT together with biopsies reveals the origin of most of these cancers. In <10% of cases, a primary tumor is not found, and the term "cancer of unknown primary site" is used. Cervical lymph node involvement (except supraclavicular) by squamous carcinoma usually indicates a head and neck primary tumor. Unknown primary tumors of the head and neck are usually treated with neck dissection and radiation or concurrent chemoradiotherapy as for NP or OP cancers. The prognosis is roughly equivalent to cancers with the same N (nodal) status. For patients treated by surgery and/or concurrent chemoradiotherapy, 5-year survivals of 75% to 87% have been reported.

Salivary Gland Cancer

Salivary gland cancers make up about 3% of all head and neck cancers diagnosed in the United States yearly. Tobacco and alcohol consumption are not risk factors, except possibly in women. Ionizing radiation and certain occupational exposures (e.g., in workers in rubber and automotive industries, wood workers, and farm workers) have been associated with the development of salivary gland cancer.

The salivary glands are classified as major (parotid, submandibular, and sublingual) and minor (distributed along upper aerodigestive tract, predominantly in the oral and nasal cavities and the paranasal sinuses). About 75% of parotid gland neoplasms are benign, whereas about 75% of submandibular, sublingual, and minor salivary gland tumors are malignant.

Most salivary gland tumors are benign, and the most common histology is pleomorphic adenoma, characterized by slow growth and few symptoms, and is most frequently seen in the parotid gland. The most common presentation of benign salivary gland tumors is asymptomatic swelling of the lip, the parotid, or the submandibular or the sublingual gland. Persistent pain or neurologic involvement (mucosal or tongue numbness and facial nerve weakness) suggests malignant disease. The benign salivary gland tumors are listed in Table 1.7.

The 2005 WHO classification recognizes 24 histologic subtypes of salivary gland cancers. The most common type of malignant salivary gland cancer arising from the major salivary gland is mucoepidermoid carcinoma, followed by squamous carcinoma, acinic cell, adenoid cystic, and adenocarcinoma not otherwise specified. In the minor salivary glands, mucoepidermoid cell cancer is again the most common, followed by adenoid cystic carcinoma and adenocarcinoma not otherwise specified. Salivary duct carcinoma represents a subtype of adenocarcinoma that resembles ductal carcinoma of the breast histologically, but generally has an aggressive natural history. The clinical characteristics and prognosis of specific malignant salivary gland tumors are shown in Table 1.8.

Surgery is the mainstay of treatment for all localized stages of salivary gland tumors. Postoperative radiation is indicated for localized tumors of high-grade histology that are large, with close or positive margins, and/or positive regional lymph nodes. Radiation is the primary treatment for unresectable tumors. The role of chemotherapy is limited to the management of locally recurrent, unresectable

Table 1.7 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 Selected Salivary Gland Malignant Tumors: Clinical Characteristics and Prognosis

Histology	Clinical Characteristics	Prognosis
Mucoepidermoid carcinoma	Most common malignant tumor in major salivary glands; most common in parotid glands (32%) Low grade: local problems, 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	Low grade: 76–95% 5-y survival High grade: 30–50% 5-y survival
Adenocarcinoma	16% of parotid and 9% of submandibular malignant tumors Grade correlates with survival	76–85% 5-y survival 34–71% 10-y survival
Squamous cell carcinoma	Uncommon: 7% of parotid gland and 10% of submandibular gland malignant tumors 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	24% 5-y survival 18% 10-y survival
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	82% 5-y survival 68% 10-y survival
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	5-y survival: 50–90% 10-y survival: 30–67% 15-y survival: 25%
Malignant mixed tumor	14% of parotid gland and 12% of submandibular gland cancers May originate in previous pleomorphic adenoma Lymph node involvement in 25% of cases; 26–32% of patients develop metastases	5-y survival: 31–65% 10 y; 23–30%

disease or distant metastatic disease. Lung and bone are the most frequent sites for distant metastatic disease. There is no established standard chemotherapy for salivary gland cancer. Regimens employing cisplatin, carboplatin, anthracyclines, taxanes, cyclophosphamide, and 5-FU result in transient responses in 14% to 30% of patients with adenocarcinoma or mucoepidermoid carcinoma, but the effect on survival is unknown.

Molecular characterization of salivary gland tumors has revealed some characteristic molecular alterations. In 50% to 70% of mucoepidermoid cancers, a translocation t(11;19)(q21;p13) creates a fusion protein product of MEC translocated 1 (MECT) with mastermind-like gene family (MAML2) that interrupts NOTCH signaling. The presence of this fusion correlates with low-grade histology and improved prognosis. In about half of adenoid cystic carcinomas, t(6;9)(q22-23;p23-24) results in a fusion of MYB and NFIB, and portends a worse prognosis, as does del(1p32-p36). A new subtype of salivary gland cancer, mammary analog secretory carcinoma, is characterized by t(12;15)(p13;q25), fusing the ETV6 and NTRK3 genes. Other molecular characteristics of salivary tumors have been evaluated. EGFR has been found to be expressed or overexpressed in mucoepidermoid and salivary duct cancers, but activating mutations and high-level amplifications appear to be rare. Expression of HER2 with amplification appears to occur in about 30% of salivary duct cancers, and the majority of these cancers appear to express androgen receptors. PTEN abnormalities and activating mutations of PIK3CA have also been described in salivary gland cancers. Thus far, trials of targeted agents have not developed a clear signal of which salivary tumors may respond to a particular targeted therapy, even when the target is present. Targeted therapies, particularly inhibitors of EGFR, VEGF or its receptors, and Her-2/neu, have been tested in phase 2 clinical trials. Larger trials or trials incorporating molecular eligibility criteria are needed to confirm the activity of these new agents against salivary gland cancers either alone, or in combination. Exploratory studies of assigning treatments based on molecular abnormalities of a particular patient's tumor have shown intriguing results (response or prolonged time to progression). Patients with good performance status should be encouraged to enter clinical trials.

OTHER HEAD AND NECK TUMORS

Sarcoma

Soft tissue sarcomas of the head and neck account for only about 2% of all head and neck malignancies in adults. Of head and neck sarcomas, approximately 70% are seen in adults and 30% are in children. These tumors are heterogeneous and can present in any head and neck site, commonly as a submucosal or subcutaneous painless mass. In the hypopharynx and NP, the presenting symptoms may be cranial nerve abnormalities or airway or swallowing difficulties. As in sarcomas at other sites, grade is an important prognostic indicator. High-grade, aggressive tumors such as malignant fibrous histiocytoma, angiosarcoma, osteogenic sarcoma, neurofibrosarcoma, and soft part sarcomas tend to be locally aggressive and spread along neurovascular structures, fascia, and bone. Distant spread is typically to the lungs, but can less commonly involve other sites. In contrast to soft tissue sarcomas in other locations, in the head and neck region, local disease tends to have a greater impact on survival than does distant metastatic disease. This is likely because of the region's tight anatomical constraints, which limit the ability to achieve the wide resection margins typically required for local control of soft tissue sarcomas. Regional nodal disease is possible with some histologic types of sarcoma, but is much less common than with squamous cell carcinoma. Sarcomas may also arise after radiation therapy, but this is very uncommon in the head and neck region. The prognosis for these secondary sarcomas may be worse than for primary sarcomas.

Initial evaluation and workup is similar to that for a squamous cell carcinoma at the same site with some key differences. MRI is likely to be more useful in defining the extent of disease for treatment planning. In addition, if sarcoma is suspected, biopsy should be performed carefully with meticulous hemostasis, since the risk of seeding the biopsy tract or any biopsy-related ecchymosis is higher with soft tissue sarcomas.

Treatment depends on stage, age of the patient, tumor type, location, and size. Rhabdomyosarcomas should be treated under the current cooperative group trial. For bone and other soft tissue sarcomas, en bloc resection with wide (>1 cm) margins is the goal, but may not be possible because of the proximity of vital structures. Elective neck radiation is not necessary because the incidence of occult positive lymph nodes is low. Given the infiltrative nature of soft tissue sarcomas, there should be a low threshold for including adjuvant radiation and/or brachytherapy to improve local control, even in low-grade sarcomas. Postoperative chemotherapy is generally advised for most osteosarcomas, and may provide a local control benefit for soft tissue sarcomas as well. Such patients should be referred to clinical trials when possible. Overall survival rate approaches 60% for patients with sarcomas of the head and neck.

Melanoma

Most cutaneous head and neck melanomas occur on the face, scalp or neck. Superficial spreading melanoma is most common, followed by nodular melanoma. The principles of staging and treatment of cutaneous melanoma of the head and neck are similar to those for cutaneous melanomas elsewhere on the body. Elective neck dissection may be considered, and superficial parotidectomy may be needed due to nodes in the parotid. Sentinel lymph node dissection requires expertise due to the complexity of lymph drainage in the head/neck region, and the possibility of sentinel nodes in the parotid gland, with risk of facial nerve injury on dissection.

Mucosal melanomas represent less than 1% of all melanomas. The peak age of diagnosis is 60 to 80 years. In SEER data from 1987 to 2009, 452 mucosal melanomas of the head and neck were reported. The majority occurred in the nasal cavity, paranasal sinuses and middle ear (73%), while fewer occurred in the oral cavity, oropharynx, NP, or salivary gland (27%). Sinonasal lesions may present with epistaxis and nasal obstruction, while oral cavity lesions are usually flat and pigmented. Because of the rarity of these tumors, most literature reports consist of small numbers of cases treated over several decades. Primary treatment is usually surgery, and adjuvant radiation therapy may improve local control, without effect on survival. Local recurrence and metastases are common. Five-year survival is about 25% for these diseases. The National Comprehensive Cancer Network (NCCN) has recently published guidelines for diagnosis, workup, treatment, and follow-up of mucosal melanomas.

Molecular profiling has demonstrated mutations in NRAS and KIT, amplification of RREB1, and loss of MYB, P16INK4a, and PTEN. Fewer patients with mucosal melanoma appear to have BRAF mutations, compared with patients with cutaneous melanoma. There have been reports of responses of mucosal melanomas to ipilumumab, as well as to targeted agents when the target is present (imatinib, c-kit), and studies employing treatment guided by molecular profiling are being performed.

Targeted Therapies and Future Directions

EGFR is overexpressed in most head and neck squamous cancers, and therapies targeting this receptor and its downstream pathways have been the subject of most extensive investigation. Increased expression of EGFR correlates with poorer prognosis in this cancer. EGFR targeted therapy with the humanized antibody cetuximab in combination with radiotherapy has been approved by the U.S. Food and Drug Administration for treatment of head and neck cancer. However, the small improvement in response of radiation with cetuximab over radiotherapy alone, and the activity of EGFR targeted therapies alone (approximately 10% response rate) suggest that EGFR is a sole driver of a relatively small subset of head and neck squamous cancers. Several mechanisms of resistance to EGFR-targeted agents have been described in head and neck squamous cancers and other tumors. Amplification or mutation of PI3K catalytic subunit in ~30% and activation of PI3K-mTOR in >70% of head and neck squamous cancers has been reported. Preclinical and clinical activity of mTOR inhibitors has been observed, and several mTOR inhibitors are under clinical investigation at National Institutes of Health (NIH) and elsewhere. Activation of the NF-κB pathway is important in head and neck squamous cancer cell survival and reported in over 70% of these cancers. While proteasome inhibitors target NF-κB, they demonstrated limited activity alone or in combination with chemotherapies or reirradiation. They were also found to antagonize the clinical therapeutic effects of cetuximab or radiotherapy, by inhibiting degradation of EGFR. STAT3 is another important cell survival pathway, for which oligonucleotide decoys have

demonstrated activity in pilot studies, and for which identification of small molecule inhibitors remains an important objective. Other targets under investigation include PI3K-mTOR, MET, IGF-1R, and heat shock protein 90 inhibitors. IMRT has reduced toxicities of chemoradiation such as xerostomia and dysphagia, and other treatments that ameliorate these side effects are also under study. For supportive care, a recent pilot NIH gene therapy study demonstrated the feasibility of using adenoviral transfer of the aquaporin gene to temporarily restore salivary flow. A follow-up trial with adeno-associated virus is in the planning stages. Molecular characterization of tumors is a promising field made possible by high capacity sequencing that will likely lead to individualized treatment and prevention approaches. The NIH Cancer Genome Atlas report for genetic and pathway alterations in head and neck cancer is forthcoming.

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REVIEW QUESTIONS

1. A 47-year-old man presents with a neck mass and sore throat. He has a 2-year history of smoking 1 pack per day in college, but has not smoked since, and drinks one to two glasses of wine per week. He has been married for 15 years. He works as a financial consultant. Examination shows a 2 cm level II node on the left neck, and fiberoptic examination shows a mass in the left tonsil. Biopsy shows squamous carcinoma and staining for p16 is positive. PET/CT shows a 2.5 cm mass in the left tonsil, as well as 1 cm and 2 cm nodes in the left neck at level II, and a 1 cm node in the left neck at level III. He is staged as T_2 N_{2b} M_0 stage IVA.
Recommendations for treatment could include the following:

- **A.** Surgery followed by radiation therapy
- **B.** Definitive concurrent cisplatin and radiation
- **C.** Treatment on a clinical trial for HPV+ head and neck cancer
- **D.** Chemotherapy with cisplatin, fluorouracil, and paclitaxel
- **E.** A, B, or C

2. A 21-year-old woman presents with a sore tongue. Examination shows a 2.5 cm raised, tender mass on the lateral left oral tongue. She is a nonsmoker. Her family history includes a brother who died of leukemia as a child. She is married and has a 19-month-old daughter. She works part time in the county library. Biopsy of the tongue lesion showed squamous cell carcinoma. PET/CT shows only the 2.5 cm tongue mass; there is no lymph node positivity on the scan.
Which of the following is TRUE?

- **A.** Second primary head and neck tumors are a significant cause of morbidity and mortality. She should be followed up carefully for additional primary tumors
- **B.** She should receive radiation and concomitant cetuximab for organ preservation
- **C.** Consideration should be given to the possibility of an inherited abnormality in DNA repair
- **D.** She should receive local excision only and close follow-up
- **E.** A and C

3. A 58-year-old man who emigrated from southern China 10 years ago is evaluated for a 3-month history of an enlarging neck mass. Neck examination reveals two firm lymph nodes: a 4 cm left level III node and a 2 cm left supraclavicular lymph node. Fiberoptic endoscopy reveals a mass in the left NP. Biopsy revealed WHO type III nasopharyngeal carcinoma. Contrast-enhanced

(*continued*)

CT shows a 4.5 cm left level III lymph node, a 2.4 cm left supraclavicular node, as well as a mass localized to the NP with parapharyngeal extension. These were the only regions to show FDG uptake on PET/CT.

Which of the following is TRUE?

A. Surgical resection of the primary tumor with left neck dissection followed as needed by chemoradiation is the treatment of choice

B. This represents one of a minority of head and neck cancers in which a strong association with EBV has not been established

C. The recommended treatment is concurrent cisplatin chemotherapy and radiation followed by adjuvant cisplatin and 5-FU chemotherapy

D. With this stage and grade of disease, 5-year overall survival is typically about 20%

E. Both C and D

4. A 62-year-old woman presented with a 2 cm oropharyngeal squamous cell carcinoma (base of tongue) with spread to a 6 cm lymph node spanning left levels II and III. She began treatment with concurrent cisplatin and radiation. She developed oral candidiasis in her fourth week of treatment. She also experienced mucositis and throat pain with attendant anorexia and weight loss that required percutaneous feeding tube placement and narcotic pain medications. She is being seen for her end-of-treatment visit today and her weight has stabilized. She continues to use narcotics regularly for throat pain and mucositis.

Which of the following is TRUE?

A. Prophylactic anticandida treatment should be initiated for all such patients beginning concurrent chemoradiation.

B. Her percutaneous feeding tube should be scheduled for removal within the 1 to 2 months following treatment completion.

C. Any necessary dental extractions should be carried out as soon as acute toxicities of treatment subside after treatment is complete.

D. Should she have persistent xerostomia after treatment, cholinergic agonists may be considered.

E. After definitive chemoradiation, neck dissection for this patient is ill advised.

5. A 68-year-old man with an 80-pack-year smoking history and a history of alcohol intake consisting of 12 beers on most weekends presents with a stage IVA squamous carcinoma of the glottic larynx (T_3 N_{2c} M_0). His weight is 68 kg and height is 66″. His performance status is good, and he has no other medical problems except mild emphysema. He lives with his wife of 42 years and is retired from a machining company where he worked for 35 years. His past history includes military service in Vietnam, with exposure to Agent Orange. Which is the best treatment choice for this patient?

A. Cisplatin with concurrent radiation

B. Radiation as definitive treatment

C. Surgery followed by postoperative concurrent cisplatin and radiation if nodal extracapsular extension of disease or positive margins on pathological examination.

D. Cetuximab and concurrent cisplatin-based chemotherapy and radiation.

E. A or C.

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SECTION Two

Thorax

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 both men and women in the United States and worldwide.
- An estimated 226,160 new cases of lung and bronchus cancer (116,470 in men and 109,690 in women) were diagnosed in 2012 in the United States, resulting in 160,340 deaths (87,750 in men, 72,590 in women).
- More than 70% of patients are diagnosed with advanced disease that is not amenable to curative therapy.
- The 5-year relative survival rate for lung cancer is approximately 18.5%, reflecting a slow but steady improvement from 13.7% in the 1970s.
- Stage at diagnosis accounts for the most marked variation in prognosis. Patient characteristics associated with poorer prognosis include older age, male gender, and African American heritage.
- In the United States, as many women now die from lung cancer as die from breast, uterine, and cervical cancers combined. The increase in lung cancer risk among women reflects changes in smoking habits during the twentieth century. By 1987, lung cancer had surpassed breast cancer as the leading cause of cancer death in women as a result of an increase in the prevalence of female smokers.
- Rates of cigarette smoking have declined in the United States in the last 10 years, but developing nations are now seeing an alarming increase in smoking rates.

ETIOLOGY AND RISK FACTORS

- The vast majority 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 3,000 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 6,000 to 36,000 cases of lung cancer each year. The decay of radium 226 produces substances that emit α-particles, which may cause cell damage. Residential 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 less well understood than for any other of the common forms of solid tumors in human. 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 in both men and women in the United States. Tumors are classically peripheral and arise from surface epithelium or bronchial mucosal glands. Histologic examination reveals gland formation, papillary structures, or mucin production. 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.
  - Bronchioloalveolar carcinoma (BAC), a noninvasive subtype of adenocarcinoma, occurs more frequently in women and nonsmokers, and is associated with bilateral, multifocal pulmonary involvement, a lesser tendency for extrathoracic metastases, and a better survival rate than similar-stage NSCLC.
- A revised multidisciplinary classification of lung adenocarcinoma recommends discontinuing the use of the term BAC and instead introduced new categories such as adenocarcinoma in situ (AIS—small solitary adenocarcinomas with pure lepidic growth) and minimally invasive adenocarcinoma (MIA—small solitary adenocarcinomas with predominant lepidic growth and ≤5 mm invasion).
  - Squamous cell carcinoma accounts for approximately 25% of NSCLCs 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. Histologic examination reveals visible keratinization, with prominent desmosomes and intercellular bridges.
- Large cell carcinoma is the least common subtype of lung cancer, accounting for approximately 10% of all NSCLCs.

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) and 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 (Table 2.1). 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 NSCLCs.
  - 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 silencing of the RB gene and tumor progression. RB gene mutations occur in 15% of NSCLCs.
  - The human epidermal growth factor receptor (HER) family are a group of four trans-membrane tyrosine kinase receptors: epidermal growth factor receptor (EGFR, ErbB1, 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. Resistance to EGFR TKI may result from acquired mutations, most commonly the EGFR T790M point mutation (50% of cases of acquired resistance), in EGFR tyrosine kinase domain.
  - 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 trans-membrane tyrosine kinase and promotes survival and proliferation. Mutations in EGFR and KRAS are, in

Table 2.1 Frequency of Common Molecular Alterations in NSCLC

Description	Percentage
KRAS mutations	15–25
EGFR mutations	10–35
PTEN mutations	4–8
ALK rearrangement	3–7
HER2 mutations	2–4
PIK3CA mutations	1–3
AKT mutations	1–3
BRAF mutations	1–3
NRAS mutations	1
MEK1 mutations	1
RET rearrangement	1
ROS rearrangement	1

general, mutually exclusive and KRAS mutations confer primary resistance to EGFR TKIs. The RAS oncogene can be activated either by a point mutation or by overexpression. KRAS mutations are found with greater frequency in patients with adenocarcinoma histology (approximately 15% to 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 fusion with a variety of partner genes, most commonly EML4, results in its dimerization and constitutive kinase activity which leads to activation of cellular pathways involved in cell growth and proliferation. Approximately 3% to 7% of NSCLCs harbor ALK fusions. ALK fusions are more common in younger patients, never or light smokers, and patients with adenocarcinoma histology with signet ring or acinar histology and in most cases are mutually exclusive of EGFR and KRAS mutations. ALK fusions predict sensitivity to crizotinib, an ALK/MET TKI.

LUNG CANCER SCREENING

- Randomized trials of screening with chest radiography with or without sputum cytology have shown no reduction in lung cancer–related mortality.
- Low-dose computed tomography (CT) screening may benefit individuals at an increased risk for lung cancer. The potential harms of screening and the generalizability of results are unclear.
  - The National Lung Screening Trial (NLST), a randomized trial, compared annual screening by low-dose chest CT scanning 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: $n = 53{,}454$). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI 6.8 to 26.7; $P = 0.004$). The rate of death from any cause was reduced in the low-dose CT group, compared with the radiography group by 6.7% (95% CI 1.2 to 13.6; $P = 0.02$).

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 usually delayed.
- Clinical signs and symptoms of lung cancer are outlined in Table 2.2.

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.
- ^{18}F-fluorodeoxyglucose-positron emission tomography ("FDG-PET") is used to evaluate single pulmonary nodules (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 BAC. 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.

Table 2.2 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's 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

- Observation may be reasonable in a low-risk individual (<40 years old and has never smoked) with a negative FDG-PET and a stable lesion measuring <2 cm. Reimaging with regular CT scans and follow-up clinic appointments are recommended.

Suspected Lung Cancer

- Full history and physical examination are recommended, followed by complete blood count and chemistry tests, chest x-ray, and 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. Routine imaging of the brain in asymptomatic patients is controversial.
- 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.
- 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.
- Preresection forced expiratory volume per second (FEV1) should be ≥2 L for pneumonectomy, 1 L for lobectomy, or 0.6 L for segmentectomy.
- Preresection 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. Median overall survival for patients with pathologic stages IA, IB, IIA, IIB, IIIA, IIIB, and IV are 119, 81, 49, 31, 22, 13, and 17 months, respectively.
- The seventh edition of the *TNM Classification of Malignant Tumours* (UICC) was adopted by the American Joint Committee on Cancer (AJCC) in 2010. A summary of the TNM classification, stage grouping, and anatomical drawing can be found at http://www.cancerstaging.org/staging/posters/lung12x15.pdf. In stages I and II, disease is limited to one lung and does not involve the mediastinum or more distant sites. Involvement in stage III is heterogeneous and ranges from a tumor of size ≤ 2 cm with metastasis in ipsilateral mediastinal and/or subcarinal lymph node (T1a, N2-stage IIIA) to a tumor of any size with local invasion or a separate nodule in a different ipsilateral lobe with metastasis in contralateral mediastinal or hilar nodes (T4, N3-stage IIIB). Stage IV includes tumor involvement in a contralateral lobe and presence of malignant pleural (or pericardial) effusions or distant metastases.

TREATMENT

Stages I and II

- Stage I and stage II NSCLCs are considered early-stage disease. These two stages combined account for 25% to 30% of all lung cancers.
- Five-year survival rates are 58% to 73% for stage I and 36% to 46% for stage II.
- Surgical resection is the recommended treatment for patients with stage I and stage II NSCLCs. In patients who are medically fit for surgical resection, lobectomy or greater resection is recommended rather than sublobar resections (wedge or segmentectomy).
- Video-assisted thoracopic surgery (VATS) is an acceptable alternative to open thoracotomy.
- Intraoperative systematic mediastinal lymph node sampling or dissection is recommended for accurate pathologic staging.
- Even with complete resection, approximately half of these patients eventually experience relapse after resection, with a two- to three-fold higher proportion of distant metastases over local recurrences.
  - In selected patients who undergo complete surgical resection, several large trials have demonstrated a statistically significant survival benefit from cisplatin-based adjuvant chemotherapy (IALT, ANITA, JBR 10).
  - The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis which used individual patient data (n = 4,584) from five trials with a median follow-up of 5.2 years found that adjuvant cisplatin-based chemotherapy was associated with a an decrease in absolute risk of death of 5.4 % at 5 years compared with no chemotherapy (hazard ratio [HR] 0.89; 95% CI 0.82 to 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 overall survival benefit varied considerably by stage of disease, with potential harm seen in stage IA (HR 1.40; 95% CI 0.95 to 2.06), a trend toward benefit in stage IB (HR 0.93; 95% CI 0.78 to 1.10), and clear benefit in stage II (HR 0.83; 95% CI 0.73 to 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 large size (more than 4 cm), poor differentiation, vascular invasion, visceral involvement, and suboptimal resection.
- Current evidence suggests that postoperative radiotherapy is associated with decreased survival for patients with stage I (N0) and stage II (N1) NSCLCs. However, most meta-analyses included several older studies that used radiotherapy methods that are inferior to current methods.
- If surgery is contraindicated in early-stage NSCLC, radiotherapy can be an effective means of local control. In clinical studies, accelerated radiotherapy (54 Gy in 12 days) was associated with better 4-year survival than conventional radiotherapy (60 Gy in 6 weeks). Stereotactic body radiation therapy (SBRT), which delivers a high dose to a target volume and spares surrounding normal tissues, may be an option for patients with primary tumors of size <5 cm and in whom surgery is contraindicated.

Stage IIIA

- Stage IIIA (N2) NSCLC is a therapeutically challenging and controversial subset of lung cancer, with a 5-year survival rate of only 24%.
- 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 heterogeneous nature of stage IIIA disease.
- Clinically N0 or N1 patients 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 are 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 1,867 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 the investigator's choice). After a median 56-month follow-up, the overall survival rate was significantly higher in the chemotherapy group (HR 0.86), with a 5-year survival 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.
  - 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 survival of stage IIIA patients in the chemotherapy arm was significantly greater at 42% versus 26% in the observation arm ($P = 0.013$).
- Postoperative radiation therapy (PORT), while reducing local recurrence, does not improve survival, may be detrimental, and is not recommended as standard of care. Advocates of radiotherapy have emphasized that there are several differences between the treatment administered in several trials included in this meta-analysis and current practices in the United States.
  - The PORT meta-analysis (Meta-Analysis Trialist Group) of 2,128 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; $P = 0.001$).
- Evidence has yet to be established substantiating the benefit of adding adjuvant radiotherapy to adjuvant chemotherapy in fully resected stage IIIA patients.
- Individuals with clinically apparent (bulky) N2 disease or N2 disease found at mediastinoscopy prior to thoracotomy should not undergo upfront surgery based on the poor results of primary resection for bulky stage IIIA disease. Selected patients with nonbulky N2 disease, defined as a single N2 positive node less than 2 cm, may be considered for surgical resection followed by adjuvant therapy. However, thorough discussion regarding lack of data illustrating optimal treatment in this setting is needed.
- 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 to 1.04).
- Two clinical trials (European Organization for Research and Treatment of Cancer 08941 and North American Intergroup 0196) showed no significant difference in overall survival between patients with bulky stage IIIA NSCLC treated with neoadjuvant chemotherapy then surgery versus definitive chemoradiation alone (no surgery).

- The use of concurrent chemotherapy/radiotherapy versus sequential treatment has been addressed in numerous trials. At present, for patients with bulky N2 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

- 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. Anticipated 5-year survival for most patients with stage IIIB disease is 3% to 7%.
- Optimal treatment depends on extent of disease, age of patient, comorbidities, performance status (PS), and weight loss.
- Stage IIIB lung cancers are not amenable to curative surgical resection unless they are highly selected.
- For patients with stage IIIB disease with PS of 0 to 1, and minimal weight loss ($<$5%), platinum-based combination chemoradiotherapy followed by chemotherapy is recommended.
- The most common chemotherapeutic agents used concurrently with radiotherapy are etoposide, vinblastine, and paclitaxel in conjunction with cisplatin or carboplatin. No randomized phase III trials of concurrent chemoradiotherapy have shown the superiority of one chemotherapy regimen over another.
- Studies have shown that induction chemotherapy followed by concurrent chemoradiotherapy is not superior to initial treatment with concurrent therapy. It is uncertain how many cycles of chemotherapy are optimal in the treatment of patients with stage IIIB disease. The American Society of Clinical Oncology (ASCO) guidelines recommend two to four cycles of platinum-based chemotherapy, two of which should be administered concurrently with thoracic radiotherapy.

Stage IV or Recurrent Disease

- Prognosis for patients with advanced-stage NSCLC is poor. Best supportive care produces median survival rates of 16 to 17 weeks and 1-year survival rates of 10% to 15%. Addition of chemotherapy improves 1-year survival to $>$35%.
- Subsets of patients with stage IIIB disease who are treated as though they have stage IV disease include those with advanced ipsilateral supraclavicular adenopathy, and those whose intrathoracic disease is not amenable to combined treatment modalities.
- Therapy options for patients with advanced or metastatic disease includes chemotherapy or targeted therapy as these are shown to improve quality of life and reduce symptoms from disease burden. However, chemotherapy 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.
- Chemotherapeutic regimens can be divided into first-line, maintenance, second-line, and third-line settings.

First-Line Therapy

- Several factors have to be considered in choice of first-line treatment for metastatic or recurrent NSCLC: age, PS, and comorbidities of the patient, and molecular abnormalities and histology of the tumor.
- Patients with tumors harboring EGFR-sensitizing mutations should receive an EGFR TKI. In such patients, several studies have shown the efficacy of erlotinib and gefitinib, oral small molecule inhibitors which compete with ATP for binding to the EGFR receptor tyrosine-kinase domain.
  - The IPASS trial which randomized previously untreated patients with NSCLC who were likely to have EGFR mutations based on clinical criteria (n = 1,217) (Asian, adenocarcinoma histology, never or former light smokers) to receive gefi tinib (250 mg PO qd) or chemotherapy found superior response rates (43.0% vs. 32.2%) and PFS (12-month progression-free rate 25 vs. 7%) with gefitinib. The most common adverse reactions with EGFR TKIs are skin rash and diarrhea.
- Patients with tumors harboring ALK translocations, as detected by an approved ALK break-apart fluorescence in situ hybridization FISH test, should receive crizotinib, an oral selective small molecule inhibitor of the catalytic activity of ALK fusion protein among others.
  - In an expanded cohort phase I trial, crizotinib resulted in overall response rates of over 50% in previously treated patients with advanced NSCLC positive for ALK translocation.
- Patients harboring neither EGFR mutations nor ALK translocation should receive standard chemotherapy. Four to six cycles of platinum-based doublets prolongs survival and improves symptom control and is the standard of care for patients with recurrent or metastatic NSCLC and good PS. However, no single regimen has demonstrated superiority in patients with advanced NSCLC and treatment decisions should be based on benefit versus toxicity.
  - An ECOG study which randomized 1,207 patients to a reference regimen of cisplatin and paclitaxel or to one of three experimental regimens: cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel found comparable efficacy for all four regimens. This trial yielded an objective response rate of 19%, with a median survival of 7.9 months, a 1-year survival rate of 33%, and a 2-year survival rate of 11%.
- Histology is an important determinant of the choice of chemotherapy agent. A phase III trial comparing pemetrexed/cisplatin to cisplatin/gemcitabine in 1,700 advanced/metastatic patients in the first-line setting found OS between both treatment arms to be the same. However, subset analysis for 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).
- 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 histology advanced/metastatic disease in combination with chemotherapy as first-line treatment.
  - ECOG 4599 which randomized selected patients with nonsquamous NSCLC (n = 878) to chemotherapy (carboplatin/paclitaxel) alone or with bevacizumab 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%). 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 our 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 whether the lack of OS benefit is secondary to differences in chemotherapy between the two trials.
- Cetuximab is a monoclonal antibody that binds to the EGFR. It may be considered only for highly selected patients with PS of 0 to 1.
  - The phase III FLEX trial randomized patients with EGFR-expressing advanced NSCLC to cetuximab plus cisplatin/vinorelbine versus cisplatin/vinorelbine alone. Patients received a maximum of

6 cycles every 3 weeks. Cetuximab was administered until progression or unacceptable toxicity. A small, yet significant OS benefit, regardless of histology, was seen: median OS of 11.3 months for cetuximab arm versus 10.1 months in the control arm.
  - Cetuximab was further evaluated in the first-line setting in the BMS099 trial comparing paclitaxel or docetaxel plus carboplatin with randomization to receive cetuximab versus placebo, which was continued until disease progression or unacceptable toxicity. No differences in response, PFS, or OS were seen.
- Addition of a third chemotherapeutic agent to platinum-based doublets has failed to show a superior survival benefit; response rates improved only at the cost of substantially increased toxicity.

Maintenance Chemotherapy

- 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 quality of life.
- 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 cetuximab may all be chosen as continuation maintenance options.
  - The PARAMOUNT trial, a 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 to 0.81; $P = 0.00025$).
  - The phase III, IFCT-GFPC 0502 trial randomized patients to maintenance gemcitabine, erlotinib, or observation after lack of progression on cisplatin/gemitabine as upfront therapy. A significant improvement in PFS was observed for the gemcitabine maintenance (HR 0.51; 95% CI 0.39 to 0.66). Gemcitabine may be used in patients with squamous histology for continuation maintenance.
  - Both cetuximab (FLEX trial) and bevacizumab (ECOG 4599) (discussed above) demonstrated PFS benefit to the continuation of these therapies after nonprogression on upfront chemotherapy. Cetuximab may be used as continuation maintenance in patients with squamous cell histology unlike bevacizumab.
- Pemetrexed, docetaxel, and erlotinib are chemotherapeutic 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 to 0.61; $P < 0.0001$) but also OS (13.4 vs. 10.6 months; HR 0.79; 95% CI 0.65 to 0.95; $P = 0.012$) compared to placebo, respectively.
  - Erlotinib switch maintenance has been studied after nonprogression on platinum-based chemotherapy. PFS was significantly longer for the erlotinib arm compared to placebo, regardless of EGFR mutational status (12.3 vs. 11.1 weeks; $P < 0.0001$). However, patients with EGFR mutations were the ones who benefited the most from maintenance erlotinib.
  - In patients with squamous histology docetaxel maintenance may be considered.
- 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 Therapy

- 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 quality of life in advanced NSCLC; therefore, patients with a PS of 0 to 2 should be offered further treatment following progression.
- Approved agents for treatment of locally advanced or metastatic NSCLC after one prior therapy are docetaxel, pemetrexed (in nonsquamous histology), and erlotinib.

- 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 overall survival with docetaxel (median 7.5 months 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 months vs. 7.9 months for docetaxel) but with significantly fewer side effects.
- BR 21, a randomized (2:1), double blind, placebo-controlled trial of patients advanced NSCLC after failure of one or two chemotherapy regimens ($n = 731$), demonstrated improved OS with erlotinib (150 mg PO qd) (6.7 months vs. 4.3 months for placebo).

Third-Line Therapy

- Erlotinib is also an approved agent in the third-line setting. If disease progression occurs after second-line or third-line chemotherapy, it is recommended that patients with a PS of 0 to 2 be enrolled in a clinical trial or treated with best supportive care.

REVIEW QUESTIONS

1. A 70-year-old otherwise healthy former smoker presents with persistent cough and hemoptysis of 2-month duration. Further workup reveals a 3 cm cavitating hilar mass, multiple bilateral parenchymal lung nodules, and a 2 cm hypodense lesion in the right hepatic lobe. Biopsies of the lung and liver masses are consistent with squamous cell lung carcinoma. Tumor molecular analysis shows the absence of EGFR, KRAS mutations, and ALK fusion. MRI brain shows no evidence of metastatic disease. Which of the following combinations would be the best choice for first-line chemotherapy?

A. Cisplatin and gemcitabine
B. Cisplatin and pemetrexed
C. Carboplatin, paclitaxel, and bevacizumab
D. Carboplatin, pemetrexed, and bevacizumab

2. Based on available data, which of the following is true regarding screening for lung cancer in a 54-year-old man with 20 pack-year history of smoking who quit 3 years ago?

A. Annual low-dose CT screening is expected to result in a reduction in lung cancer–related mortality
B. Annual low-dose CT screening is expected to result in a reduction in all-cause mortality
C. Chest x-ray and sputum cytology are expected to result in a reduction in lung cancer–related mortality
D. Chest x-ray and sputum cytology are expected to result in a reduction in all-cause mortality
E. None of the above

3. A 70-year-old otherwise healthy woman came to medical attention with long-standing cough. CT scan showed a 4 cm left hilar mass and right hilar lymphadenopathy. The patient underwent bronchoscopy, right video-assisted thoracic surgery, wedge biopsy, and cervical mediastinoscopy with biopsy. Pathology showed lung adenocarcinoma with involvement of right hilar lymph nodes. Tissue is inadequate for molecular analyses. Which of the following is the best treatment option?

A. Surgical resection of the primary mass and lymph nodes followed by adjuvant chemoradiation
B. Concurrent chemotherapy and radiation
C. Neoadjuvant chemotherapy followed by surgery
D. Sequential chemotherapy and radiation

Suggested Readings

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3

Small Cell Lung Cancer

Jarushka Naidoo and Oscar S. Breathnach

EPIDEMIOLOGY

Small cell carcinomas are a biologically aggressive subset of neuroendocrine tumors (NETs) that most commonly originate in the lung. These cancers constitute approximately 15% to 20% of all lung carcinomas, the incidence of which is decreasing worldwide. Small cell lung cancer (SCLC) is a disease of the smoking population. Multimodality therapy in SCLC improves survival in patients who exhibit a response to combination chemotherapy. SCLC is highly responsive to chemotherapy, but unfortunately exhibits a high rate of relapse and thus poor prognosis.

PATHOLOGY

The 1999 WHO International Association for the Study of Lung Cancer (IASCLC) classifies SCLC into three groups:

1. Classical small cell carcinoma
2. Large cell neuroendocrine tumor
3. Combination of small cell carcinoma, with areas of non–small cell lung carcinoma (NSCLC)

SCLC is characterized by poor differentiation, elevated mitotic rate, and a high proliferation index as per the World Health Organisation classification (WHO). Cellular morphology under light microscopy shows small round blue cells with scant cytoplasm, fine granular chromatin, and indistinct nucleoli.

Immunohistochemical stains indicating the presence of small cell carcinoma include:

- Keratin
- Tissue transcription factor-1 (TTF-1)
- Epithelial membrane antigen

Immunohistochemical markers of neuroendocrine differentiation include:

- Synaptophysin
- Chromogranin
- Neuron-specific enolase

Thirty percent of SCLC biopsies can contain NSCLC, thus leading to the hypothesis that lung carcinoma originates from a pluripotent stem cell. NSCLC can co-express the above markers in up to 10% of cases, and lead to diagnostic challenges.

GENETIC ABNORMALITIES

The most commonly observed genetic mutations in SCLC include

- p53 (75% to 95% SCLCs)
- 10q and 9p loss of heterozygosity (PTEN site)
- 3p deletion (loss of tumor suppressor genes)
- Loss of Rb genes (60% of SCLCs)
- Telomerase enzyme activity is present in 90% of SCLCs. Telomerase functions to stabilize telomere length and resultant cellular immortality. This enzyme is usually present in cells with the ability to divide indefinitely, such as hematopoietic cells and basal epidermoid cells.
- C-kit and phosphorylated C-kit (80% to 90% of SCLCs)
- Kras and p16 mutations are uncommon

CLINICAL PRESENTATION

Seventy percent of SCLCs are metastatic at diagnosis. Patients can either present with symptoms related to the primary tumor or sites of metastatic disease. SCLCs are classically central in location, and present with symptoms such as cough, shortness of breath, or signs of post obstructive infection. Commonest sites of metastasis include the liver, adrenal glands, bone, and brain, and can cause clinical symptoms of bone pain, weight loss, general physical decline, and neurologic symptoms. SCLC is associated with a number of clinical syndromes caused by the production of paraneoplastic antibodies. These syndromes, termed "paraneoplastic syndromes," confer a poor prognosis, and include:

- Eaton-Lambert myasthenic syndrome (anti-Hu antibodies against voltage-gated calcium channels)
- Syndrome of inappropriate antidiuretic hormone (ADH excess)
- Ectopic ACTH production (Cushing's syndrome)
- Ectopic parathyroid hormone production
- Sensory neuropathy
- Paraneoplastic encephalomyelitis

The presence of antibodies can be tested in the blood to diagnose the above syndromes. Weight loss is also postulated to be a paraneoplastic phenomenon.

STAGING

Two staging systems exist for SCLC:

1. *Veteran's Administration Lung Group*

- This group divides SCLC into two stages: Limited stage and extensive stage.
- Limited stage (LS) SCLC is defined as disease that is encompassed safely into one radiation field. This usually involves disease confined to one hemithorax. Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy usually do not preclude a diagnosis of limited stage disease.
- Extensive stage (ES) disease is SCLC that has spread outside one of hemithorax, contralateral mediastinal lymph nodes, and ipsilateral supraclavicular lymph nodes. This usually refers to patients with distant metastases, or a cytologically confirmed malignant pleural or pericardial effusion.
- LS SCLC is usually treated with combined chemotherapy and thoracic radiotherapy, with curative intent.
- ES SCLC is not curable, and is thus treated with palliative chemotherapy alone.

2. *International Association for Lung Cancer*

- This consists of a TNM-based staging system.
- Patients without distant metastatic disease are treated as limited stage disease.

Staging workup usually consists of the following:

- History and physical examination
- CT thorax/abdomen (including adrenal glands)
- CT or MRI brain
- +/− Isotope bone scan

IMAGING

CT or MRI brain scans are important as 10% to 15% of SCLCs have brain metastases at presentation, and early detection and treatment have been shown to improve both patient morbidity and mortality.

The use of positron emission tomography (PET) in the staging of SCLC is a controversial topic. Two studies by Fischer et al. demonstrated that PET/CT had a sensitivity and specificity of 93% and 100% compared to 79% and 100% with standard staging. The rate of upstaging from LS to ES SCLC ranged from 0% to 33% in seven studies, with sample sizes of 4 to 63 patients. The main impact of PET/CT was noted in cases of unsuspected lymph node metastases where a change in the treatment volume of thoracic radiotherapy occurred. PET or PET/CT has not demonstrated improved assessment of treatment response compared to conventional imaging, and has not been shown to assist in prognostication of SCLC. However, studies investigating these questions have been small.

PROGNOSTIC FACTORS

Adverse prognostic factors include

- Poor performance status (PS) (Eastern Cooperative Oncology Group PS [ECOG PS] = 3 to 4)
- Weight loss
- High disease burden (high LDH levels)

Favorable prognostic factors in limited stage disease include

- Female gender
- Normal LDH
- Stage I disease

Favorable prognostic factors in metastatic disease include

- One metastatic site
- Normal LDH

SURVIVAL

Median overall survival (OS) for treated LS SCLC is 15 to 20 months, and treated ES SCLC is 8 to 13 months. Median OS for untreated extensive stage disease is 6 weeks. The 2-year survival for LS SCLC is 20% to 40% and <5% for ES SCLC. The median survival of patients with platinum-refractory or resistant disease is 7 and 30 weeks.

TREATMENT

Limited Stage SCLC

LS SCLC is treated with combined chemotherapy and thoracic radiotherapy. SCLC is an extremely chemosensitive tumor, and combination therapy produces 80% to 90% response rates, and 50% to 60% CR rates.

Chemotherapy

The most commonly used chemotherapy consists of a combination of cisplatin and etoposide (EP or PE regimen) due to high response rates and adequate tolerability. Carboplatin can be substituted for cisplatin in patients with a borderline ECOG PS (2 to 3). However, due to an increased risk of myelosuppression, cisplatin is preferred to carboplatin in LS SCLC, unless cisplatin is contraindicated or poorly tolerated.

Thoracic Radiotherapy

Patients treated with chemotherapy alone for LS SCLC have an 80% rate of local recurrence. Thoracic radiotherapy improves OS and reduces the rate of local recurrence. A meta-analysis of thoracic radiotherapy in LS SCLC showed an increase in the rate of local control by 23% (24% to 47%) and a 5% absolute improvement in OS at 2 years (15% to 20.5%).

Thoracic radiotherapy includes all gross tumor volume present on post chemotherapy planning radiologic investigations, and nodal regions present on prechemotherapy staging. Standard treatment consists of single daily fractions of 1.5 to 2.0 Gy 5 days per week for a 6-week period. Accelerated hyperfractionation consists of an increased number of fractions delivered in a shorter time period. These regimens are associated with increased toxicity. A hyperfractionated schedule of 45 Gy, delivered over a period of 3 weeks twice daily, has shown superior survival outcomes, and is the current standard of care. The CALGB 30610 trial aims to compare such a schedule with traditional longer schedules in a head-to-head comparison.

Thoracic radiotherapy can be concurrent, sequential, or have alternating patterns of delivery. Concurrent and alternating patterns have shown improved survival compared to sequential treatment, but at an increased rate of toxicity (pneumonitis, myelosuppression, esophagitis). Patients who receive different chemotherapy regimens to standard EP do not benefit from early radiotherapy. A recent phase III trial investigated the use of standard chemoradiotherapy with cisplatin and etoposide versus daily cisplatin 6 mg/m^2/day plus etoposide, and showed higher rates of toxicity, with no difference in local control or OS. Early thoracic radiotherapy delivered concurrently with cycle 1 or 2 of the standard 3-weekly platin-based chemotherapy is the current gold standard.

Extensive Stage SCLC

The chemotherapeutic regimens commonly used in SCLC include (Table 3.1)

- Platinum compounds (cisplatin, carboplatin)
- Podophyllotoxins (etoposide, teniposide)
- Camptothecins (irinotecan, topotecan)
- Alkylating agents (ifosfamide, cyclophosphamide)
- Anthracyclines (doxorubicin, epirubicin, amrubicin)
- Taxanes (paclitaxel, docetaxel)
- Vinca alkaloids (vincristine)
- Gemcitabine

Standard treatment for ES SCLC is palliative chemotherapy. In patients of adequate ECOG PS (>2) the EP regimen is the standard of care. Cisplatin-based treatment has demonstrated superior response rates and OS in some subgroups. A recent meta-analysis of carboplatin versus cisplatin-based chemotherapy in ES SCLC and poor prognosis LS SCLC demonstrated noninferiority of carboplatin-based regimens in terms of response and survival. Significant hematologic toxicity was noted with carboplatin, and gastrointestinal, ototoxicity, and nephrotoxicity were seen with cisplatin. These factors impact the choice of therapy. Multiple trials have explored the possible substitution of etoposide for irinotecan in ES SCLC. A phase III Japanese trial showed higher response rates (84% vs. 66%) and longer median OS (12.8 months vs. 9.4 months) when compared to EP. The IRIS trial compared EP to carboplatin–irinotecan (CI) and showed a higher response rate and improved median survival favoring the irinotecan arm (8.5 months vs. 7.1 months).

The Elderly

Forty percent of patients with SCLC are over the age of 70 years. Combination chemotherapy is associated with higher rates of toxicity in patients with poorer PS and organ reserve. However, elderly patients

Table 3.1 Chemotherapy Regimens for Small Cell Lung Cancer

Regimen	Dose	Duration
EP (cisplatin-containing)		
Cisplatin	60 mg/m^2	Q4 weekly × 4–6 cycles
Etoposide	120 mg/m^2 IV days 1-3 OR 100 mg/m^2 day 1-3	
EP (carboplatin-containing)		
Carboplatin	AUC 6	Q4 weekly × 4–6 cycles
Etoposide	100 mg/m^2 days 1–3	
EP (3 weekly)		
Cisplatin	25 mg/m^2 IV days 1–3	Q3 weekly × 4–6 cycles
Etoposide	80 mg/m^2 days 1–3	
EP (3 weekly)		
Cisplatin	80 mg/m^2 day 1	Q3 weekly × 4–6 cycles
Etoposide	80 mg/m^2 days 1–3	
CI		
Cisplatin	60 mg/m^2 day 1	Q4 weekly × 4 cycles
Irinotecan	60 mg/m^2 IV days 1, 8, 15	
CAV		
Cyclophosphamide	1,000 mg/m^2 IV day 1	Q3 weekly × 4–6 cycles
Doxorubicin	45 mg/m^2 IV day 1	
Vincristine	1 mg/m^2 IV day 1	
CAE		
Cyclophosphamide	1,000 mg.m^2 IV day 1	Q3 weekly × 4–6 cycles
Doxorubicin	45 mg/m^2 IV day 1	
Etoposide	50 mg/m^2 IV days 1–3	
CAVE		
Cyclophosphamide	1,000 mg/m^2 IV day 1	Q3 weekly × 4–6 cycles
Doxorubicin	50 mg/m^2 IV day 1	
Vincristine	1.5 mg/m^2 IV day 1	
Etoposide	60 mg/m^2 IV days 1–5	
IC		
Irinotecan	175 mg/m^2 day 1	Q3 weekly × 4 cycles
Carboplatin	AUC 4	
Topotecan	1.5 mg/m^2 days 1–5	Q3 weekly × 4 cycles
	1.25–1.5 mg/m^2 days 1–3	Q3 weekly × 4 cycles

AUC, area under the curve; po, post operative.

who are able to tolerate multimodality therapy benefit from this approach. Elderly patients with a poor PS, who are unable to receive standard combined therapy for LS SCLC, may derive palliative and survival benefit from two cycles of chemotherapy with sequential radiotherapy.

Relapsed/Refractory SCLC

Relapsed SCLC is recurrent disease more than 3 months post completion of first-line therapy. Refractory disease refers to recurrent disease during first-line therapy, or within 3 months of treatment completion. Eighty percent of patients with SCLC and nearly all patients with ES SCLC will relapse after first-line therapy. The treatment of relapsed/refractory disease consists of palliative chemotherapy.

Common chemotherapeutic agents used are mentioned above, and are usually given as single agents, with an average response rate of 10% to 25%. The current recommended second-line

therapy is single agent topotecan, which when compared to best supportive care in a registration randomized trial, was found to improve both quality of life and survival. Oral and intravenous topotecan shows similar response rates. Topotecan can be used in both the relapsed and refractory settings, with response rates of 11% to 31% and 2% to 7% respectively. A phase III trial comparing CAV (cyclophosphamide, doxorubicin, and vincristine) to topotecan in second line showed similar response rates (18% vs. 24%) and median survival (25 weeks vs. 24.7 weeks). Topotecan was associated with higher rates of thrombocytopenia and anemia, but had improved symptom control and less neutropenia compared to CAV. Risk factors for myelosuppression with topotecan include poorer PS, prior radiotherapy, extensive prior chemotherapy, prior platinum therapy, and renal impairment.

The median OS of relapsed, treated SCLC is 2 to 6 months. For patients with a longer disease-free interval and adequate PS, a rechallenge of initial chemotherapy regimen is reasonable. Response rates for irinotecan are similar to topotecan in patients with sensitive disease (30%) and refractory disease (<10%), with a median survival of 5 to 7 months. Single agent amrubicin has shown promising activity in refractory SCLC, with an overall response rate of 21.3%, median PFS of 3.2 months, and OS of 6 months, with an acceptable toxicity profile.

Surgery

SCLC presents rarely as an isolated lesion (<5% of cases). Patients with stage I SCLC (T1-2NO) can be treated with complete resection (lobectomy + mediastinal lymph node dissection), followed by adjuvant chemotherapy or chemoradiotherapy if mediastinal lymph node stage is negative or positive respectively. This approach yields a 43% to 53% 5-year survival rate. These recommendations are based on retrospective data and single institution studies. Two randomized trials in 1966 and 1994 investigated the role of surgery in SCLC, and did not support the role of surgery as the primary treatment of an isolated or recurrent lesion. These studies were done prior to the use of modern imaging techniques that would likely upstage many of these patients. A randomized trial of stage I SCLC to surgery versus combined chemoradiotherapy has not yet been done, but would be required to answer this clinical question. Adjuvant surgery after first-line chemotherapy (carboplatin/VP16 +/− ifosfamide) with or without radiotherapy was investigated prospectively in 23 patients with stage I to IIIA SCLC. In this study, only patients with a CR or pathologic stage I demonstrated a benefit in terms of local relapse and OS.

Prophylactic Cranial Irradiation

The incidence of brain metastases in SCLC at 2 years is 80%. Brain metastases represent an area of significant morbidity and mortality in SCLC. Prophylactic cranial irradiation (PCI) consists of 5 to 7 fractions of whole-brain radiotherapy delivered to prevent the onset of symptomatic brain metastases. Each treatment consists of 1.5 to 2.0 Gy per fraction. Higher doses (>3.0 Gy), concurrent chemotherapy, and high total radiotherapy doses have been associated with late neurologic toxicity. In LS SCLC, two meta-analyses demonstrated a 25% reduction in the cumulative incidence of brain metastases at 3 years (23% to 58%) and an improvement in 3-year OS with PCI (20.1% vs. 15.3%). In ES SCLC, the NEJM published an EORTC trial that showed those patients who exhibited either a partial or complete response to combination chemotherapy, benefitted from PCI. PCI reduced the incidence of symptomatic brain metastases from 40% to 15% at 1 year, and improved 1-year OS from 13% to 27%. PCI was well tolerated, with the commonest toxicities consisting of headache, nausea, and fatigue. PCI is not recommended for patients with a poor ECOG PS (3 to 4), multiple comorbidities, or impaired cognitive function. PCI is not given concurrently with chemoradiotherapy due to potentially cumulative neurotoxicity.

New Therapeutic Directions

Multiple strategies have been employed to try and improve response rates and survival in SCLC. These include additional agents, dose escalation, dose dense therapies, targeted therapies, and prognostic/predictive biomarkers.

Additional Agents

First Line A recent phase III trial of carboplatin/pemetrexed versus standard EP in first-line ES SCLC demonstrated inferior PFS and OS in the experimental arm. The addition of bevacizumab to standard EP improves PFS but demonstrated no OS benefit. Two phase III trials demonstrated a lack of benefit with the addition of paclitaxel to EP in ES SCLC, with an increase in treatment-related mortality in the experimental arm (6.5% vs. 2.4%). The addition of cyclophosphamide and epirubicin to EP showed an improvement in response rate and a minor improvement in survival, with a significant increase in hematologic toxicity. Ipilumumab, a CTLA4 inhibitor licensed in the treatment of metastatic malignant melanoma, was investigated in a three arm phase II study in first-line ES SCLC. Ipilumumab was administered either in a phased or concurrent basis with carboplatin/paclitaxel, and assessed by PFS, irPFS (immune-related), BORR (best overall response rate), irBORR, survival, and safety. Phased ipilumumab showed an improvement in irPFS, irBORR, and OS. Further studies with this drug are awaited.

Second Line Combination therapy with paclitaxel and carboplatin, doxorubicin, gemcitabine, cisplatin, and ifosfamide has yielded response rates of 25% to 75.3% in the phase II setting. Carboplatin and paclitaxel showed a response rate of 73% and would require further study. Five phase II trials investigated the combination of gemcitabine and irinotecan in the relapsed setting, with response rates ranging from 10% to 50%, and different conclusions reached in terms of therapeutic benefit. Combinations of gemcitabine with vinorelbine or irinotecan did not show any clinical benefit. Ifosfamide has been shown to improve OS and response rate in one trial, but this was not observed in subsequent validation studies. Picoplatin is a cisplatin analog that has shown preclinical activity in phase II studies in platinum-resistant and platinum-sensitive SCLC. It aims to overcome platinum resistance and in the phase II setting for relapsed/refractory disease demonstrated a 15% response rate and 30% disease control rate. The results of a registration trial are awaited.

Maintenance Therapy Maintenance therapy beyond 4 to 6 cycles of chemotherapy has shown a modest benefit in terms of response rate, but no improvement in survival, and significantly worse toxicity. This was demonstrated by Giacconne et al. with 5 versus 12 cycles of CDE (cyclophosphamide, doxorubicin, and etoposide), and Ettinger et al. with CAV and CAV–HEM (alternating with hexamethylamine, etoposide, and methotrexate) in complete responders.

Dose Escalation/Dose Dense Therapy

Increasing the administered dose or reducing the interval between doses achieves higher response rates, but not necessarily a survival advantage in SCLC. One trial that demonstrated an improvement in OS in LS SCLC stratified patients between standard dose PCDE (cisplatin, cyclophosphamide, doxorubicin, etoposide) versus high-dose PCDE (HD-PCDE), which uses 20% higher drug doses on cycle 1. HD-PCDE demonstrated improved response rates (67% vs. 54%) and improvements in 2- and 5-year OS (42% vs. 20% and 26% vs. 8%). Growth factor support with GCSF or GM-CSF was used to support the delivery of higher drug doses. Meta-analyses of dose intensity in trials using CAV/CAE/EP showed small but statistically insignificant improvements in OS in ES SCLC.

Targeted Therapy

Biologic agents targeting novel therapeutic pathways in SCLC include anti-VEGF therapies (bevacizumab), Mtor inhibitors (temsirolimus), tyrosine kinase inhibitors (imatinib and vandetanib), matrix metalloproteinase inhibitors, and antisense oligonucleotide olibmersen. More recently, the use of oral dasatinib, a SRC inhibitor, was found to have no minimal clinical activity in the phase II CALGB 30602 study. The proteosome inhibitor bortezemib showed some activity, and future trials are investigating its use with topotecan in the relapsed/refractory setting. Hypoxia-targeting agent tirapazamine (TPZ) was investigated in a phase II study in combination with cisplatin/etoposide and thoracic radiotherapy in LS SCLC. TPZ demonstrated an improvement in median survival to 22 months, compared to 17 months in the seminal INT-0096 trial that established combined chemoradiotherapy as standard of care on LS SCLC. However, a trial of TPZ in head and neck cancer was terminated early secondary to increased rates of grade 3/4 esophagitis. Further studies to confirm the role of TPZ, and similar agents are awaited.

Biomarkers

ERCC1 (excision repair cross-complementing-1) is a molecular marker that has been shown to predict response to platinum-based chemotherapy in non–small cell lung cancer. High ERCC1 expression by IHC and RT-PCR has been shown by a number of trials to be prognostic in LS SCLC. However, it has not been shown to be predictive of response to therapy. Whole-genome and haplotype analyses have demonstrated that GSS, ABCC2, and XRCC1 single-nucleotide polymorphisms (SNPs) involved in glutathione metabolism and DNA repair pathways are prognostic in SCLC. Clinical applications for these findings are limited by the different methods of evaluating ERCC expression, and the need for further validation studies. Circulating tumor cells (CTCs) and circulating tumor cell clusters or microemboli (CTMs) have been studied as potential prognostic and pharmacodynamic biomarkers in SCLC. One study has shown that CTC number and reduction after one cycle of chemotherapy are independent prognostic markers. Further studies regarding the clinical utility of these tools are required.

FOLLOW-UP/SURVEILLANCE

NCCN (National Cancer Control Network) and other national and organizational guidelines recommend the following algorithms for post treatment follow-up:

1. LS SCLC
   - History and physical examination every 3 to 4 months within years 1 to 2 post treatment
   - History and physical examination 6 monthly within years 3 to 5 post treatment, annually thereafter
   - Chest imaging at the time of history and physical examination (x-ray or CT)
2. ES SCLC
   - 3 to 6 monthly CT thorax/abdomen year 1 post treatment
   - 3 to 6 monthly chest x-ray years 2 to 5 post treatment
   - 3 to 6 monthly history and physical examination by clinician

Focused radiologic and laboratory investigations should be carried out depending on the clinical signs/symptoms of the patient at the time of consultation.

REVIEW QUESTIONS

A 56-year-old male presents with a 2-week history of shortness of breath and hemoptysis. A routine CXR reveals a 4 cm right hilar mass with associated ipsilateral hilar lymphadenopathy. A CT of the thorax, abdomen, and pelvis does not reveal any distant metastases. A bronchoscopy and biopsy reveal small cell carcinoma of the lung.

1. What immunohistochemical staining pattern would be consistent with the above diagnosis?
   - **A.** TTF1 positive, CK 7 positive, keratin positive, chromogranin positive, synaptophysin positive
   - **B.** TTF1 negative, CK 7 negative, keratin negative, chromogranin negative, synaptophysin negative
   - **C.** TTF1 negative, CK 7 negative, keratin positive, chromogranin positive, synaptophysin positive
   - **D.** TTF1 positive, CK 7 negative, keratin negative, chromogranin positive, synaptophysin positive

2. What other staging investigation should this patient receive?
   - **A.** PET/CT
   - **B.** CT or MRI brain
   - **C.** Mediastinoscopy
   - **D.** Bone marrow aspiration and trephine

3. What stage is this patient's disease?
   - **A.** Stage I
   - **B.** Stage IV
   - **C.** Limited stage
   - **D.** Extensive stage
4. What treatment would you advise for this gentleman's small cell lung carcinoma
   - **A.** Carboplatin AUC 6 day 1 and Etoposide 100 mg/m^2 days 1, 2, 3 q 3 weekly $\times$ 6
   - **B.** Cisplatin 60 mg/m^2 day 1 and Etoposide 100 mg/m^2 days 1, 2, 3 q 3 weekly $\times$ 6
   - **C.** Cisplatin 25 mg/m^2 days 1, 2, 3 and Etoposide 100 mg/m^2 days 1, 2, 3 q 3 weekly $\times$ 4 with concurrent thoracic radiotherapy
   - **D.** Carboplatin AUC 5 day 1 and Etoposide 100 mg/m^2 days 1, 2, 3 q 3 weekly $\times$ 4 with sequential thoracic radiotherapy
5. This patient's CT brain is negative for metastases. Would your treatment plan for this patient include prophylactic cranial irradiation?
   - **A.** Yes
   - **B.** No
   - **C.** Maybe

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SECTION Three

Digestive System

4

Esophageal Cancer

Mark K. Doherty and Gregory D. Leonard

Esophageal cancer is the ninth most commonly occurring cancer worldwide and the sixth most common cause of cancer mortality. It is highly curable in its earliest stages; however, it usually presents with advanced disease. Recent years have seen many advances in the management of esophageal cancer including optimization of neoadjuvant strategies, nonsurgical treatment options in early-stage disease, and the introduction of biologics agents to the management of advanced disease.

EPIDEMIOLOGY

United States

- Esophageal cancer was estimated to account for 1% of all malignancies and 6% of all gastrointestinal malignancies in 2012. The age-adjusted incidence from 2000 to 2009 is 4.6 cases per 100,000 population (http://seer.cancer.gov/csr/1975_2009).
- Approximately 17,460 new cases and 15,010 deaths were estimated for 2012.
- The median age at diagnosis is 69 years. This cancer rarely occurs in patients younger than 25 years.
- Esophageal cancer is two to four times more frequent in men than in women. Siewert type 1 tumors (adenocarcinoma [ADC]) are eight to nine times more common in men than in women.
- Rates of occurrence of esophageal cancer are approximately threefold higher among blacks than among whites.
- Squamous cell carcinoma (SCC) is more common in black men; ADC is more common in white men.
- Five-year relative survival rates were 5% from 1975 to 1977, 10% from 1987 to 1989, and 19% from 2001 to 2007.

Rest of the World

- There are approximately 500,000 cases of esophageal cancer in the world, but there is marked geographic variation. Regions with clusters of high rates include China (e.g., Linxian), Iran, France, and South Africa.

- In the 1970s, approximately 90% of esophageal cancers were SCCs. The incidence of ADCs has increased dramatically and currently accounts for approximately 60% to 70% of new cases—a rate of acceleration greater than that of any other cancer in the United States.

ETIOLOGY

Adenocarcinoma

- Barrett's esophagus
- Obesity
- Gastroesophageal reflux disease (GERD), which can be caused by obesity and might result in Barrett's esophagus

Squamous Cell Carcinoma

- Tobacco
- Alcohol
- Predisposing conditions:
  - Tylosis (SCC)
  - Achalasia
  - Esophageal diverticula and webs (SCC)
  - Plummer-Vinson syndrome
  - Human papillomavirus (HPV)
  - Celiac disease
- Less significant causes include environmental exposure and dietary factors.

BARRETT'S ESOPHAGUS

Barrett's esophagus, perhaps as a result of GERD, is the most important risk factor (100 times risk increase over other factors) for ADC.

Screening recommendations (no randomized trial data for surveillance practices) are as follows:

- For no dysplasia, endoscopy every 3 to 5 years
- For low-grade dysplasia, endoscopy every 6 months for 12 months and then yearly
- For high-grade dysplasia, 3-monthly endoscopy, esophagectomy, endomucosal resection, photodynamic therapy (PDT), or other ablative therapies

CLINICAL PRESENTATION

The most common clinical presentations of esophageal cancer are listed in Table 4.1 and are usually related to local compression or infiltration symptoms or generalized malaise and anorexia.

Table 4.1 Clinical Presentation of Esophageal Cancer

Symptoms	Patients with Symptoms (%)
Dysphagia (solids usually before liquids)	80–96
Weight loss	42–46
Odynophagia	≤50
Epigastric or retrosternal pain	≤20
Cough or hoarseness	≤5
Tracheoesophageal fistula	1–13

The classic triad for presentation of esophageal cancer is as follows:

- Asthenia
- Anorexia
- Analgesia (for dysphagia)

DIAGNOSIS

- Symptoms
  - Dysphagia or odynophagia
  - Hematemesis
  - Dyspepsia
  - Hoarseness
  - Dyspnea
  - Anorexia
- Signs (usually late presentation)
  - Horner syndrome
  - Left supraclavicular lymphadenopathy (Virchow's node)
  - Cachexia
  - Hepatomegaly
  - Bone metastases (rare, but paraneoplastic hypercalcemia can occur)
- Upper gastrointestinal endoscopy
  - This diagnostic procedure is the gold standard. The combination of endoscopic biopsies and brush cytology has an accuracy of greater than 90% in making a tissue diagnosis of esophageal cancer.
- Barium contrast radiography
  - This diagnostic procedure can document contour and motility abnormalities and unexpected airway fistula and may be useful when the entire esophagus has not been visualized endoscopically. However, a tissue diagnosis is needed for definitive diagnosis.

PATHOLOGY

- Most newly diagnosed patients have ADC, but there are contrasting reports on their relative prognosis. Less than 1% of esophageal tumors are lymphoma, melanoma, carcinosarcoma, or small cell carcinoma.
- Fifty percent of tumors arise in the lower one-third of the esophagus, 25% arise in the upper esophagus, and 25% of tumors occur in the middle one-third of the esophagus.

STAGING

The American Joint Commission for Cancer (AJCC) has designated staging of cancer by TNM classification, which defines the anatomic extent of disease. The most recent edition of this staging system proposes a distinction between T4a and T4b tumors—those that invade other structures but are resectable or unresectable, respectively. Other changes include staging based on histology and tumor grade, as well as N-staging based on the number of affected locoregional lymph nodes.

The Siewert classification subclassifies gastroesophageal junction tumors into three types according to their anatomic location: type I are distal esophagus tumors, type II are cardia tumors, and type III are subcardia gastric tumors.

Staging workup can include the following:

- Computerized tomography (CT) scan: CT scan of the chest and abdomen can demonstrate evidence of spread of tumors to lymph nodes or distant metastases to the liver (35%), lungs (20%), bone (9%), and adrenals (5%). CT scan may underestimate the depth of tumor invasion and peri-esophageal lymph node involvement in up to 50% of cases. Magnetic resonance imaging (MRI) provides similar results to CT.
- Endoscopic ultrasound (EUS): EUS may be helpful when metastases are not detected by CT or other imaging modalities. EUS is the optimal technique for locoregional staging. A meta-analysis demonstrated greater than 71% sensitivity in staging preoperative depth of invasion (T) and greater than 60% sensitivity for locoregional lymph nodes (N); specificity was greater than 67% and greater than 40%, respectively.
- Positron emission tomography (PET)/CT: PET/CT is useful when CT is negative for metastatic disease, and can change management of the disease in 25% to 40% of patients. It has limited utility in establishing T stage, and EUS is superior in establishing N stage, but PET/CT has a greater sensitivity for detecting distant metastatic disease than CT alone. PET/CT is currently being investigated for use in tailoring treatment based on metabolic response in the CALGB 80302 study.
- Bronchoscopy is required in tumors less than 25 cm from the incisors to exclude invasion of the posterior membranous trachea or tracheoesophageal fistula.
- Laparoscopy is sometimes performed for staging of EGJ tumors without evidence of metastatic disease, to rule out peritoneal dissemination.

TREATMENT

Surgery

- Surgery alone remains a recognized treatment for esophageal cancer with resectable local or locoregional disease. In 1993, surgery was used as a component of treatment in 34% of patients. Surgery alone was used in 18% of patients. In recent years, the improved survival seen with combined modality treatment has meant that surgery alone is generally only considered for patients with very early stage disease (T1-2N0M0).
- Endomucosal resection (EMR) with ablation is considered definitive treatment for patients with early T1a tumors, and may provide staging information for tumors with more advanced T stage.
- Recent improvements in staging techniques and patient selection have improved surgical morbidity and mortality. Operative mortality rates are now less than 5%. Surgical expertise is a major contributor to survival, with better outcomes in high-volume centers. Resection is possible in approximately 50% of patients. Five-year survival in patients with surgical resection is 5% to 25%.
- Surgical principles include a wide resection of the primary tumor with the goal of an R0 resection (no residual tumor), including more than 5 cm resection margins plus regional lymphadenectomy. Intraoperative frozen section can assess residual disease, which, if present, is considered an R1 (microscopic tumor) or R2 (macroscopic tumor) resection.
- In general, patients with cervical carcinoma of the esophagus (above the aortic arch) are not considered candidates for surgical resection; chemoradiation is favored in these patients. Other indicators of unresectable disease include T4 tumors or extensive nodal disease. Medical unresectability (due to comorbidities or poor performance status) is another common reason for patients not proceeding to esophagectomy.
- Surgical approaches include the following:
  - Transthoracic resection: En bloc esophagectomy requires laparotomy and thoracotomy, for example, total thoracic or transthoracic (Lewis) procedures. A three-field lymph node dissection (extended lymphadenectomy) includes superior mediastinum and cervical lymphadenectomy. It is the treatment of choice in Japan, but is associated with increased toxicity and has a questionable survival advantage.

- Transhiatal esophagectomy: This includes laparotomy and cervical anastomosis. This technique avoids thoracotomy.

Chemoradiotherapy (Combined-Modality Approach)

Although no large prospective randomized trials have directly compared primary chemoradiation with surgery, definitive chemoradiation for locoregional carcinoma of the esophagus is considered an alternative to surgery.

Inoperable Disease

Definitive Chemoradiotherapy

- The Radiation Therapy Oncology Group (RTOG) 85-01 trial demonstrated a survival advantage (14 vs. 9 months median survival and 27% vs. 0% 5-year survival) in favor of chemoradiotherapy over radiotherapy alone. The study used a regimen of cisplatin and short-course infusional 5-FU in combination with 50 Gy radiotherapy, compared with 64 Gy radiotherapy alone. A number of randomized trials of chemoradiotherapy versus radiotherapy alone have failed to duplicate the results of RTOG 85-01; however, a Cochrane review has confirmed the superiority of chemoradiotherapy versus radiotherapy in fit, motivated patients.
- The cisplatin/fluorouracil regimen used in the RTOG study carries significant toxicity, and alternative regimens have been sought to allow for effective treatment with better safety profiles. The recently presented phase III PRODIGE-5/ACCORD-17 study demonstrated similar survival in patients treated with a fluorouracil/oxaliplatin (FOLFOX) regimen to those treated with the RTOG regimen, but with lower rates of death from toxicity (1.1% vs. 6.4%) or within 15 days from chemotherapy (1.1% vs. 3.2%).

Operable Disease

Definitive Chemoradiotherapy Direct comparisons of chemoradiotherapy versus surgery in resectable esophageal cancer are limited and the optimal approach is controversial. Two trials have provided evidence to support a nonsurgical approach in some patients:

- In the first trial, patients with locally advanced but resectable squamous tumors were treated with chemoradiotherapy, and patients with at least a partial response were randomized to continued chemoradiotherapy or surgery. There was an improvement in local control rates (64% vs. 41% at 2 years), but no difference in overall survival, and early mortality and length of hospital stay were less in the chemoradiotherapy arm (12.8% vs. 3.5%, $P = 0.03$)
- The second trial randomized patients with locally advanced squamous tumors to either definitive chemoradiotherapy or chemoradiotherapy (lower doses of radiation) and surgery. There was no significant difference in survival outcomes (17.7 vs. 19.3 months, respectively) between the two groups of patients.

Radiation dose escalation has not proved to be beneficial. A trial examining this approach was closed after an interim analysis indicated that there would be no advantage with higher doses of radiation.

Neoadjuvant Chemoradiotherapy (Trimodality Approach)

- The rationale for preoperative chemoradiotherapy was first studied by Leichman et al. in 21 patients with SCC. The patients were treated with 30 Gy of radiation and with two cycles of concurrent 5-fluorouracil (5-FU) and cisplatin. An additional 20 Gy of radiation was given postoperatively when a residual tumor was seen at surgery. The pathologic complete response was 37%, with a median survival of 18 months.
- A number of prospective randomized phase 3 trials have addressed the issue of whether preoperative chemoradiotherapy offers any benefit over surgery alone. Much debate exists over interpretation of these trials.
  - Walsh et al. demonstrated a significant benefit in median survival (16 vs. 11 months; $P = 0.01$) and 3-year survival (32% vs. 6%; $P = 0.01$) for patients receiving preoperative chemoradiotherapy). However, limitations of this trial include poor surgical outcome, small numbers of patients studied, and the fact all patients had ADC.

  - The Cancer and Leukemia Group B (CALGB) 9781 was a prospective randomized Intergroup trial of trimodality therapy versus surgery in 56 patients with stage I to III esophageal cancer. Median survival was 4.48 years versus 1.79 years ($P = 0.002$) in favor of trimodality therapy.
  - The CROSS trial is the most recent study to investigate this issue. A preoperative regimen of weekly paclitaxel and carboplatin in combination with 41.4 Gy radiotherapy was compared with surgery alone. The neoadjuvant therapy was well tolerated. There was a higher rate of R0 resections in those who received preoperative treatment (92% vs. 69%), and a 29% complete response rate was observed. This translated to a survival benefit for those treated with the preoperative chemoradiotherapy (3-year survival 58% vs. 44%; HR 0.66; $P = 0.003$).
- In a meta-analysis of 12 randomized trials, the benefit of chemotherapy and surgery was observed over surgery alone. Overall survival in individual patient data from nine trials showed an absolute benefit of 4% (increased from 16% to 20%). The disease-free survival over 5 years showed an absolute benefit of 4% (increased from 6% to 10%). This meta-analysis showed a small but significant benefit for neoadjuvant chemotherapy over surgery alone ($P = 0.03$).
- Neoadjuvant chemoradiation has shown a trend toward superiority versus neoadjuvant chemotherapy alone in patients with locally advanced but resectable tumors. In one randomized trial that failed to meet accrual goals, patients received chemotherapy followed by surgery or chemotherapy followed by chemoradiation for 3 weeks, followed by surgery. A complete resection was possible in 77% versus 85% in arms A and B, respectively. Complete histologic response was 2.5% with chemotherapy and 17% after chemoradiation ($P = 0.06$). The median survival was 21.2 versus 32.8 months, and 3-year survival was 27% versus 43%, respectively ($P = 0.14$).
- A meta-analysis in 2007 clarified the benefits of neoadjuvant chemoradiation or chemotherapy versus surgery alone. The absolute difference in survival between neoadjuvant chemoradiation versus surgery alone was 13%, while absolute difference in survival between neoadjuvant chemotherapy versus surgery alone was 7% ($P = 0.05$).

Adjuvant Chemoradiotherapy There are few data available on the use of postoperative chemoradiotherapy in esophageal cancer.

- An Intergroup trial found a statistically significant survival advantage for postoperative chemoradiotherapy compared to surgery alone in gastroesophageal and gastric cancers. A recent CALGB study investigated the use of more intensive chemotherapy (ECF) given before and after postoperative radiotherapy with 5-FU, but found no improvement in survival compared with the 5-FU regimen used in the Intergroup trial. Based on these data, adjuvant chemoradiotherapy is an option for ADC tumors of the lower esophagus, though most clinicians favor preoperative treatment. It is possible that the survival benefit associated with the use of chemoradiotherapy results from reductions in local recurrences and thus compensates for inadequate surgery (only 10% of patients had the recommended D2 resection). The results of the CRITICS trial comparing postoperative ECC chemotherapy to postoperative cisplatin/capecitabine-based chemoradiotherapy are awaited.

Radiation Therapy

Radiation therapy alone is generally considered palliative and is used in patients who are unable to tolerate chemoradiotherapy. No prospective randomized trials of preoperative or postoperative single-modality radiotherapy have demonstrated a survival benefit in patients, although retrospective data do suggest benefit in those with node-positive tumors.

Chemotherapy

- Single-agent chemotherapy demonstrates response rates of 15% to 25%. Combination chemotherapy response rates are 25% to 45%.
- Cisplatin with 5-FU is a regimen for both combined-modality therapy in locoregional disease and systemic therapy for palliation.
- SCC may be more sensitive to chemotherapy, but there is no difference in long-term outcome between SCC and ADC.

Operable Disease

Adjuvant Chemotherapy

- The poor survival, even for patients with clinically localized carcinoma of the esophagus, suggests that occult metastases are present at diagnosis, thereby providing the impetus to add systemic therapy early during patient management.
- In the two largest trials examining preoperative chemotherapy, the Intergroup (INT 0113) trial showed no survival benefit, whereas the Medical Research Council (MRC) trial demonstrated a 3-month median survival advantage for chemotherapy over surgery alone.
- The following differences in the two studies may have contributed to their different outcomes:
  - Chemotherapy was of longer duration and was with higher doses in INT 0113. This therapy may have been detrimental by delaying access to surgery and causing more toxicity.
  - Surgery was performed in only 80% of the patients in the chemotherapy arm in INT 0113 compared to 92% in the MRC trial. Outcome for surgery alone was poor in the MRC trial, thereby possibly exaggerating the benefits of chemotherapy.
  - Radiation therapy off protocol (equally distributed between treatment arms) was available in the MRC trial.
  - A larger sample size in the MRC trial may have facilitated detection of a statistically significant result.
- One Japanese study suggests that neoadjuvant chemotherapy is highly superior to adjuvant chemotherapy (HR 0.64; $P = 0.014$).
- The MRC MAGIC trial published in 2006 assessed the use of perioperative epirubicin, cisplatin, and 5-FU (ECF) chemotherapy or surgery alone in esophagogastric adenocarcinoma. In 503 patients, 15% had esophagogastric cancer and 11% had esophageal cancer. Patients treated with chemotherapy had increased progression-free survival (HR 0.66; $P < 0.001$) and resectability rates, and a benefit in overall survival (HR 0.75; $P = 0.009$). As a result of this study, many patients with EGJ adenocarcinoma are treated with this approach.

Inoperable Disease

Palliative Chemotherapy Systemic therapy may be beneficial in patients with locally advanced or metastatic disease. Most data are extrapolated from trials in gastric cancer (see below).

Palliative Treatment

- Palliative options can be split into local or systemic options.
- Local therapies include external beam and brachytherapy radiation. This approach can palliate dysphagia in approximately 80% of patients. PDT has also been approved by the U.S. Food and Drug Administration (FDA) for this indication. For rapid palliation, laser or balloon dilatation and stenting is recommended. The placement of a gastrostomy or jejunostomy tube may improve the patient's nutritional status.
- The systemic chemotherapy options in esophageal cancer are improving.
- Most data on chemotherapy in advanced esophageal cancer are extrapolated from trials in gastric cancer that often include gastroesophageal tumors.
- Cisplatin combined with 5-FU is a commonly used regimen, but this did not demonstrate a statistically significant benefit over cisplatin alone when tested in a randomized trial of patients with advanced SCC of the esophagus 5-FU with either oxaliplatin or irinotecan have shown equivalence to the cisplatin and 5-FU combination in studies of advanced esophagogastric cancer, and may have more favorable toxicity profiles.
- Docetaxel, cisplatin, and 5-FU (DCF) were also compared to cisplatin and 5-fluorouracil (CF). Time to disease progression improved from 3.7 months to 5.2 months, and median overall survival improved from 8.5 months to 10.2 months ($P = 0.0053$) in patients receiving DCF compared to those receiving CF. DCF in this trial had significant toxicity and doses have been altered in similar regimens.
- The REAL-2 trial evaluated capecitabine and oxaliplatin as alternatives to cisplatin and fluorouracil. In a two-by-two design, patients were randomly assigned to ECF (epirubicin/cisplatin/5-fluorouracil),

ECX (epirubicin/cisplatin/capecitabine), EOF (epirubicin/oxaliplatin/5-fluorouracil), EOX (epirubicin/oxaliplatin/capecitabine). The median survival time was 9.9, 9.9, 9.3, and 11.2 months, respectively. Overall survival was highest with EOX ($P = 0.02$). EOX is now a standard of care in many institutions.

- S1 in combination with cisplatin, or with docetaxel, showed superiority compared to S1 in Asian studies. The FLAGS study in a western population showed equivalence of S1 cisplatin and 5-FU cisplatin in this setting.

New targeted therapies have been investigated in esophagogastric cancer with varying success:

- Trastuzumab has improved survival in combination with chemo. The ToGA trial demonstrated an improvement in response rate (47% vs. 35%) and survival (13.8 vs. 11 months) for patients with HER2-overexpressing tumors treated with trastuzumab in combination with cisplatin/5-FU chemotherapy compared with chemotherapy alone.
- EGFR inhibitors have not improved survival in combination with chemotherapy. In the REAL-3 study, panitumumab was used in combination with epirubicin, oxaliplatin, and capecitabine, and showed inferior survival to the same chemotherapy given alone (8.8 vs. 11.3 months). The panitumumab-containing arm used lower doses of chemotherapy which may account for the poor outcome in this group. A recent study investigating cetuximab in combination with capecitabine and cisplatin in this population showed similarly inferior survival (9.4 vs. 10.7 months).
- Antiangiogenesis therapy has shown some promise. The AVAGAST study evaluated the use of the anti-VEGF antibody bevacizumab in esophagogastric cancer, in combination with capecitabine and cisplatin. The addition of bevacizumab to chemotherapy improved response rates (46% vs. 37%), and progression-free survival (6.7 vs. 5.3 months), but failed to demonstrate an improvement in overall survival. Subgroup analysis suggested a benefit for patients enrolled in America. These results are provocative but further studies are required to define patients that may derive benefit from bevacizumab.
- Second-line therapy using docetaxel or irinotecan or the biologic agents ramucirumab or gefitinib have also improved survival compared to best supportive care.
- The validated approaches for treating patients with esophageal cancer are given by stage in Table 4.2.

Table 4.2 Stage, Distribution, Treatment, and Survival of Esophageal Cancers in the United States

Stage	Distribution (%)	Treatment
Very early stage (T1a)	5	Endomucosal resection and ablation, or esophagectomy
Early stage T1b, T2	5	Esophagectomy, or consider neoadjuvant CRT for T2
T2, T3 resectable	30	Neoadjuvant CRT Neoadjuvant CT Esophagectomy Definitive CRT (preferred for cervical tumors) Consider adjuvant therapy if no neoadjuvant treatment given Consider perioperative chemotherapy for GEJ or lower esophageal ADC
Locally advanced unresectable	35	Definitive CRT
Metastatic	25	Best supportive care/palliation *Local:* Radiation therapy or brachytherapy Intraluminal intubation or dilatation Laser or endocoagulation Photodynamic therapy

	Combination chemotherapy: CF (cisplatin, 5-fluorouracil or capecitabine) EOX (epirubicin, oxaliplatin, capecitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) FOLFIRI (5-fluorouracil, irinotecan) FOLFOX (5-FU, oxaliplatin) Trastuzumab with cisplatin/5-FU if HER2 overexpressing

ADC, adenocarcinoma; GE, gastroesophageal; 5-FU, 5-fluorouracil; CRT, chemoradiotherapy

FOLLOW-UP FOR PATIENTS WITH LOCOREGIONAL DISEASE

There is no standard surveillance scheme.

- History and physical examination, complete blood count (CBC), urea, electrolytes, and liver function tests are recommended every 4 months for 1 year, every 6 months for 2 years, and then annually (www.nccn.org).
- Chest radiograph should be obtained as indicated.
- CT scans of the chest/abdomen should be obtained as clinically indicated.
- Upper gastrointestinal endoscopy should be performed as clinically indicated.

REVIEW QUESTIONS

1. A 65-year-old white male patient is referred to the oncology clinic after upper endoscopy has revealed a visible tumor at 30 cm in his esophagus. Pathologic examination of a biopsy from the tumor is consistent with a moderately differentiated adenocarcinoma. Computed tomography of his chest and abdomen shows thickening of the thoracic esophagus, but no evidence of metastatic disease. The patient has no major medical comorbidities, and has only mild dysphagia. The next most appropriate staging investigation for this patient would be
   A. Laparoscopy
   B. Endoscopic ultrasound
   C. Positron emission tomography
   D. Bronchoscopy
   E. Barium swallow
2. A 75-year-old female patient, with a history of chronic obstructive airways disease, is investigated for dysphagia, weight loss, and chest pain. She is found to have a SCC of her upper thoracic esophagus, staged as T3N1 by endoscopic ultrasound. Whole-body PET/CT shows thickening of her esophagus with surrounding FDG-avid lymph nodes, but no evidence of distant metastatic disease. What treatment modality would be the optimal choice for this patient?
   A. Esophagectomy
   B. Neoadjuvant chemotherapy followed by esophagectomy
   C. Esophagectomy followed by adjuvant chemoradiotherapy
   D. Definitive chemoradiotherapy
   E. Palliative chemotherapy
3. A 70-year-old male is admitted with progressive dysphagia, weight loss, and dyspepsia. He is found to have a large tumor at his esophago-gastric junction, which is causing partial obstruction. Computed tomography of his chest and abdomen shows thickening of his distal esophagus, as well as multiple low attenuation lesions in his liver, consistent with metastatic disease. Pathologic examination of the endoscopic biopsy reveals a moderately differentiated adenocarcinoma.

(*continued*)

He has an ECOG performance status of 1, and palliative chemotherapy with cisplatin and fluorouracil is planned. What further molecular marker can be used to guide this patient's treatment?

A. Immunohistochemistry (IHC) for VEGFR
B. IHC for EGFR
C. EGFR mutational analysis
D. IHC and fluorescent in situ hybridization for HER2
E. IHC for ERCC1

Suggested Readings

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5

Gastric Cancers

Ellie E. Chan and Thomas J. George, Jr.

EPIDEMIOLOGY

Worldwide, gastric carcinoma represents the third or 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. The incidence of cancer of the distal half of the stomach has been decreasing in the United States since the 1930s. However, over the last two decades, the incidence of cancer of the cardia and gastroesophageal junction (GEJ) has been rapidly rising, particularly in patients younger than 40 years. There were 21,320 new cases and 10,540 deaths from gastric carcinoma in the United States in 2012.

RISK FACTORS

- Average age at onset is fifth decade
- 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% to 20% incidence), partial gastrectomy for benign disease, *Helicobacter pylori* infection (especially childhood exposure—three- to fivefold increase), Ménétrier's 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
- 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 with the rising incidence of Barrett's 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 age 50, 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's lymphomas (NHL), 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 receptors *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, particularly of the transforming growth factor-β type II receptor, with subsequent growth-inhibition deregulation
- 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

- Epidermal growth factor receptor overexpression, specifically *Her2/neu* and *erbB-2/erbB-3* especially in intestinal forms
- Epstein-Barr viral genomes are detected
- *Ras* mutations are rarely reported (less than 10%) in contrast to other gastrointestinal cancers

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 should prompt endoscopic evaluation.

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's 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 form 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 TNM classification. In the 2010 AJCC 7th 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 muscolaris propria (T2), subserosa (T3), and serosa (T4a) are considered resectable, whereas invasion of adjacent structures (T4b) is not. The nodal stage relates to the 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 outcome 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 y (%)**	**10 y (%)**	**Median (mo)**
IA	82	68	ND
IB	69	60	151
IIA	60	43	102
IIB	42	32	48
IIIA	28	18	28
IIIB	18	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 preoperative 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.
- Computerized 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 (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 epidermal growth factor 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 alone does not improve survival following resection. In addition to complete surgical resection, either postoperative adjuvant chemoradiotherapy (chemoRT) or perioperative polychemotherapy appear 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 and overall survival when compared to no adjuvant treatment. Similarly, the use of polychemotherapy pre- and postoperatively can increase disease-free and overall survival compared to observation.

In advanced gastric cancer, chemotherapy enhances quality of life and prolongs survival when compared with the best supportive care. There are numerous therapeutic options in this setting without a clear standard of 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. However, there is a pressing need for assessing new agents, both cytotoxic and molecularly targeted, in the advanced and adjuvant settings.

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 (TG), extent of lymph node dissection, and palliative surgery.

Subtotal versus TG Subtotal gastrectomy (SG) may be performed for proximal cardia or distal lesions, provided that the fundus or cardioesophageal junction is not involved (Fig. 5.1). 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 (Fig. 5.2).

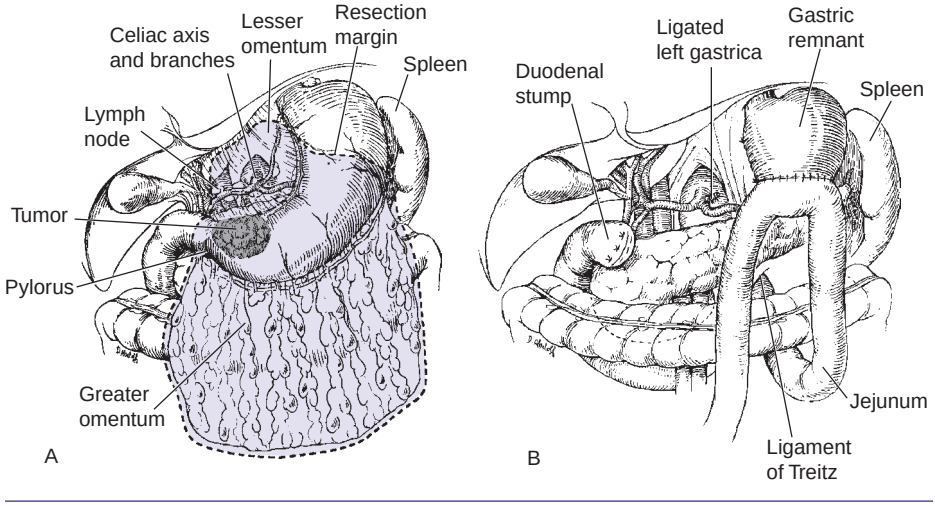

FIGURE 5.1 Subtotal gastrectomy.

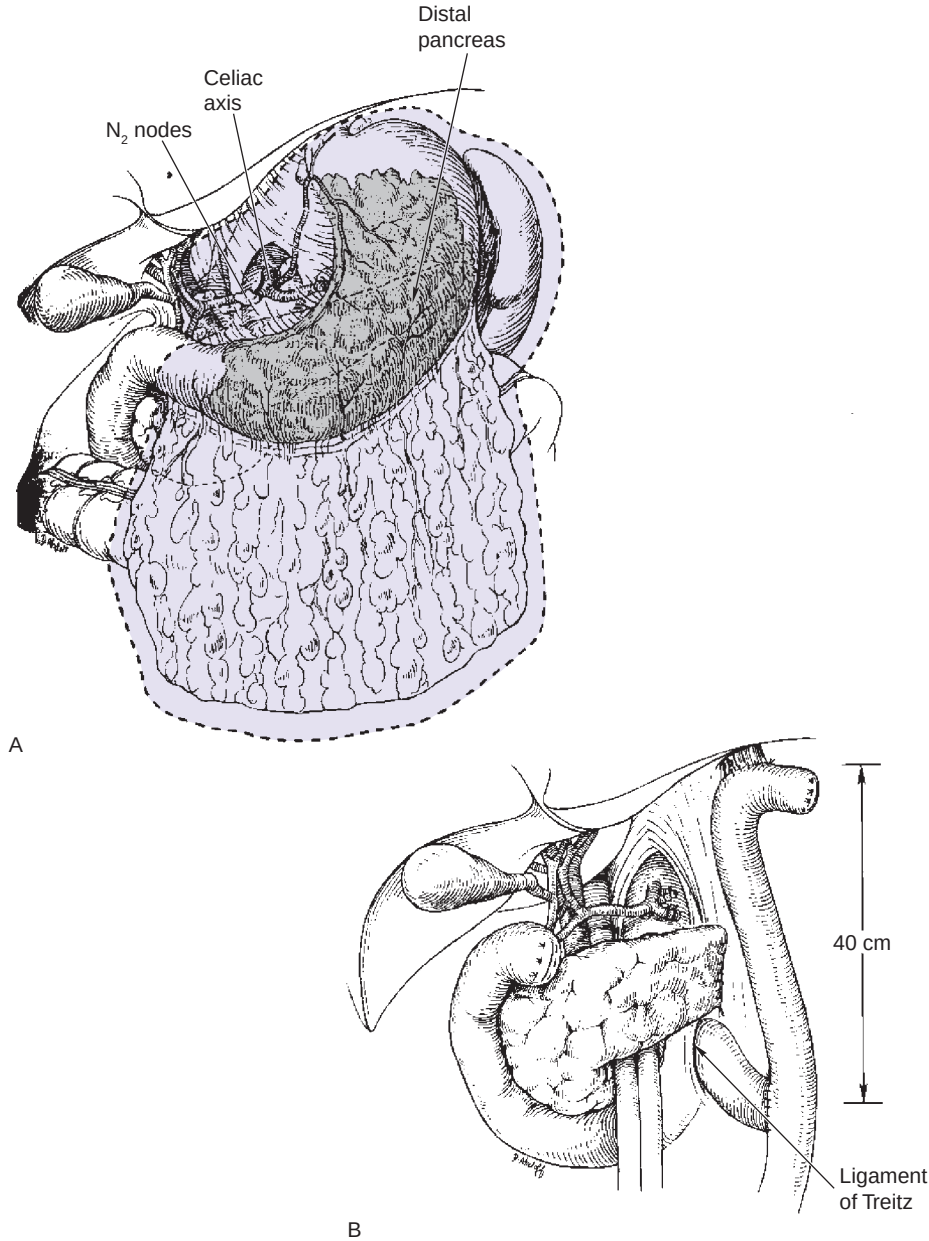

FIGURE 5.2 Total gastrectomy.

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

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 portahepatis

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

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.

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. Radiotherapy (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 overall survival 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 (GITSG) 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 in both 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 (i.e., 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 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 ($P = 0.006$). Both 3-year overall survival (50% vs. 41%; $P = 0.006$) and relapse-free survival (48% vs. 31%; $P < 0.0001$) favored adjuvant chemoRT. Although treatment-related mortality was 1% in this study, only 65% of patients completed all therapies as planned and many had inadequate lymph node resections (54% D0). After 10-year median follow-up, persistent benefit in overall survival (HR 1.32; 95% CI 1.10 to 1.60; $P = 0.0046$) and relapse-free survival (HR 1.51; 95% CI 1.25 to 1.83; $P = 0.001$) 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 overall survival (80% vs. 70%; $P = 0.002$) and relapse-free survival (72% vs. 60%; $P = 0.002$) advantage in favor of adjuvant chemotherapy. At 5-year follow-up, the improved overall survival 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 to IV nonmetastatic gastric cancer; 503 patients were stratified according to surgeon, tumor site, and performance status. Perioperative chemotherapy improved 5-year overall survival (36% vs. 23%; $P = 0.009$) 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%; $P = 0.03$), had smaller tumors (median 3 vs. 5 cm; $P < 0.001$), had T1/T2 stage tumors (52% vs. 37%; $P = 0.002$), and had N1/N2 stage disease (84% vs. 71%; $P = 0.01$). 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 to 0.95; $P = 0.02$) and disease-free survival (34% vs. 19%; HR 0.65; 95% CI 0.48 to 0.89; $P = 0.003$) was improved in the polychemotherapy arm. Curative resection rate was significantly improved with perioperative polychemotherapy (84% vs. 73%; $P = 0.04$) with similar postoperative morbidity in the two groups. In Europe, perioperative polychemotherapy is considered a standard of care.

Postoperative ChemoRT 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 to 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-year follow-up, no significant difference in locoregional recurrences (8.3% in chemo alone vs. 4.8% in chemoRT; $P = 0.3533$) or distant metastases (24.6% in chemo vs. 20.4% in chemoRT; $P = 0.5568$) 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 disease-free survival in those with node-positive disease (HR 0.68; 95% CI 0.47 to 0.99; $P = 0.047$), 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 has been planned.

CALGB 80101, 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 overall survival was not significantly better with ECF at 3 years (52% vs. 50%). The primary tumor location did not impact treatment outcome.

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 agent, 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.

Palliative Surgery and 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 requires 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% to 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.

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 most commonly used in the United States.

Newer Chemotherapy Agents Newer chemotherapeutic agents, including irinotecan, docetaxel, paclitaxel, and alternative platinums and fluoropyrimidines, have shown promising activity as single

Table 5.3 Single-Agent Cytotoxic Chemotherapy 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

Table 5.4 Randomized Studies of Combination Chemotherapy in Advanced Gastric Cancer

Treatment Arms	Patients (*n*)	RR (%)	Median Survival
FAMTX vs. FAM	213	41 vs. 9[a]	42 vs. 29 wk[a]
PELF vs. FAM	147	43 vs. 15[a]	35 vs. 23 wk
FAMTX vs. EAP	60	33 vs. 20	7.3 vs. 6.1 mo
ECF vs. FAMTX	274	45 vs. 21[a]	8.9 vs. 5.7 mo[a]
DCF vs. CF	445	37 vs. 25[a]	9.2 vs. 8.6 mo[a]
EOX vs. ECF	488	48 vs. 40	11.2 vs. 9.9 mo[a]
Cis/S-1 vs. Cis/5-FU	1,053	29 vs. 32	8.6 vs. 7.9 mo

[a]Difference is statistically significant.
RR, response rate; FAMTX, 5-FU, doxorubicin, and methotrexate; FAM, 5-FU, doxorubicin, mitomycin-C; PELF, cisplatin, epidoxorubicin, leucovorin, 5-FU with glutathione and filgrastim; EAP, etoposide, doxorubicin, cisplatin; ECF, epirubicin, cisplatin and 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; DCF, docetaxel, cisplatin, 5-FU; CF, cisplatin, 5-FU.
S-1; oral fluoropyrimidine, cisplatin, 5-FU.

agents and are being 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%; $P = 0.01$), time to progression (5.6 vs. 3.7 months; $P < 0.001$), and median survival (9.2 vs. 8.6 months; $P = 0.02$) 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 ($n = 1{,}053$) with advanced gastric or GEJ adenocarcinoma were randomized to either cisplatin/S-1 or cisplatin/infusional 5-FU. The median overall survival (8.6 vs. 7.9 months; $P = 0.20$), overall response rate (29.1% vs. 31.9%; $P = 0.40$), median duration of response (6.5 vs. 5.8 months; $P = 0.08$), and treatment-related deaths (2.5% vs. 4.9%; $P < 0.05$) 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; 1,002 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 progression-free survival were nearly identical between the groups, with the EOX regimen showing superiority in overall survival over ECF (11.2 vs. 9.9 months; $P = 0.02$).

Table 5.5 Efficacy Data on Selected Targeted Therapy Use in Advanced Gastric Cancer

Target	Treatment	Patients (*n*)	Response Rate (%)	Median Survival (mo)
EGFR	Cetuximab + 5-FU/irinotecan	34	44	16
	Cetuximab + 5-FU/oxaliplatin	46	65	9.5
	Cetuximab + FUFIRI	49	42	16.6
	Cetuximab + XELOX	44	52	11.5
	Cetuximab + docetaxel/cisplatin	72	41	9
	Erlotinib	68	9	6.7
	Gefitinib	36	3	5.5
HER2	Trastuzumab + cisplatin/5-FU	298	47	13.8
	Lapatinib	47	7	5
VEGF	Bevacizumab + cisplatin/irinotecan	35	65	12.3
	Bevacizumab + cis/capecitabine	387	46	12.2
	Bevacizumab + docetaxel/cis/5-FU	44	67	16.8
	Sunitinib	76	3	5.8
	Sorafenib + docetaxel/cisplatin	44	41	13.6

Cis, cisplatin; 5-FU, 5-fluorouracil; FUFIRI, 5-FU, folinic acid, irinotecan; XELOX, capecitabine, oxaliplatin.

Biologic/Targeted Agents

New biologic therapies aimed to inhibit or modulate targets of aberrant signal transduction in gastric cancer have been actively investigated. Inhibition of angiogenesis, vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) pathways are an early focus of clinical testing (Table 5.5).

Epidermal Growth Factor Receptor-2 (HER2)

Overexpression of EGF receptor (EGFR)-2 (HER2) is seen in approximately 7% to 22% of esophageogastric 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 (i.e., "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 cancers 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 overall survival (13.8 vs. 11.1 months; HR 0·74; 95% CI 0·60 to 0·91; $P = 0.0046$) in those receiving trastuzumab. The toxicities between the two arms were comparable. Subgroup analysis demonstrated that patients with HER2 IHC 3+ scores derived the greatest benefit from targeted therapy (HR 0.66; 95% CI 0.50 to 0.87). This trial established a new standard of care for advanced HER2-overexpressing esophagogastric tumors.

Epidermal Growth Factor Receptor

Overexpression of epidermal growth factor receptor (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 most extensively 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 (Table 5.5). 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 progression-free survival 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 (i.e., erlotinib and gefitinib) showed very limited activity in multiple phase II trials. Dual inhibitors of both HER2 and EGFR (i.e., lapatinib) are also under investigation. 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 vascular endothelial growth factor (VEGF) in gastric cancer is associated with a poor prognosis. A monoclonal antibody against VEGF, bevacizumab, has 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 overall survival, the benefit was not sustained in the global, phase III AVAGAST study. The study randomized 774 patients to cisplatin/fluoropyrimidine combination chemotherapy with or without bevacizumab. Response rate (46% vs. 37%; $P = 0.0315$) and progression-free survival (6.7 vs. 5.3 months; $P = 0.0037$) were both improved with bevacizumab; however, there was no improvement in overall survival (12.2 vs. 10.1 months; $P = 0.1002$). Bevacizumab is currently under investigation in combination with doublet or triplet chemotherapy in the perioperative setting in gastric or esophagogastric cancer. Alternate antiangiogenetic inhibitors using small molecule inhibitors are also under active investigation.

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

- 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
- Postoperative chemoRT is recommended for patients with at least stage IB disease.
- Perioperative polychemotherapy could also be considered for patients who present with at least a T2 lesion preoperatively.

Stage III Gastric Cancer

- Radical surgery: Curative resection procedures are confined to patients who do not have extensive nodal involvement at the time of surgical exploration.
- 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 without Distant Metastases (M0)

Neoadjuvant polychemotherapy can be considered to improve resectability. Radical surgery is performed if possible, either followed by postoperative chemoRT or perioperative polychemotherapy.

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. Balancing the risks to benefits of therapy in any individual patient is recommended.

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 for clinical trials or practice at an experienced center.

POSTSURGICAL FOLLOW-UP

- Follow-up in patients after complete surgical resection should include routine history and physical examination, with liver function tests and CEA measurements being performed.
- Evaluation intervals of every 3 to 6 months for the first 3 years and 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 1,000 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's 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's and Burkitt's-like lymphomas. 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 last 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, fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) 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

The 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 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 on the 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% to 50%) and confined to the stomach (70% to 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 disease-free survival. Radiation therapy (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). Overall survivals 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's and Burkitt's-like lymphomas 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 (i.e., highly effective antiretroviral therapy for AIDS).

REVIEW QUESTIONS

1. A 62-year-old man presented to his PCP with abdominal pain, nausea, early satiety, night sweats, and weight loss over the past 3 months. His past medical history includes hypertension, hypothyroidism, and chronic gastritis. Physical examination was unremarkable and laboratory studies including and CT scans were unremarkable. Upper endoscopy showed gastric mucosal erythema and nodularity. The biopsy showed the presence of dense diffuse infiltrate of centrocyte like cells in lamina propria with prominent lymphoepithelial lesions. *H. pylori* was positive. EUS did not reveal regional lymphadenopathy. What is the best next step before considering the treatment?

- **A.** Chemotherapy and radiation
- **B.** Bone scan
- **C.** Surgery consultation
- **D.** Florescence in situ hybridization for t(11:18) translocation
- **E.** Intraoperative radiotherapy

2. A 56-year-old woman was referred to you by her PCP. She has a history of peptic ulcer disease and had undergone partial gastrectomy 5 years ago for peptic ulcer perforation. She does not have symptoms of PUD currently. She has good appetite and stable weight. She wanted to know if she would need screening for gastric cancer as she heard that partial gastrectomy is one of the risk factors for gastric cancer. Which one of the following statements is TRUE?

- **A.** Because of the high risk of gastric cancer in patients after partial gastrectomy, the recommendation is to perform surveillance upper endoscopy 5 years after partial gastrectomy.
- **B.** There are no sufficient data to recommend surveillance endoscopy after partial gastrectomy for nonmalignant disorders.
- **C.** The risk of gastric stump cancer is threefold higher than general population 5 years after partial gastrectomy.
- **D.** Because of the low overall incidence of gastric cancer in the United States, upper endoscopy is not recommended, regardless of risks.
- **E.** Continued acid suppression from the PUD treatment is protective for gastric cancer.

3. A 65-year-old man presented to ER with worsening fatigue, shortness of breath, and black stool for 3 days. He noticed a few pounds' weight loss and intermittent epigastric discomfort associated with food for a few months. He has no other major medical problems and has not seen a doctor for many years. Physical examination revealed a thin male with left supraclavicular lymphadenopathy. Other system examinations were unremarkable. Laboratory studies showed microcytic anemia (Hgb = 7.2) and positive heme occult blood in stool. LFT showed

elevated AST (90), ALT (75), and alkaline phosphatase (230). EGD revealed nonbleeding ulcer at the gastric antrum with biopsy consistent with gastric adenocarcinoma. CT chest/abdomen/pelvis showed multiple liver lesions with perigastric and celiac lymphadenopathy. CEA was 38. He felt better after blood transfusion and Hgb improved appropriately. He has some limitations in doing strenuous activities but is ambulatory and can do daily activities without problems. Medical oncology was consulted to discuss the treatment options. Which of the following would you next recommend?

A. Radiation therapy
B. Palliative care alone
C. Trastuzumab in combination with chemotherapy if HER2 overexpressing
D. Chemotherapy and radiation
E. Chemotherapy in combination with bevacizumab

4. A 58-year-old woman was recently diagnosed with gastric adenocarcinoma of the distal stomach and underwent SG 4 weeks ago. She presented to your clinic today to discuss further treatment options. Pathology showed a tumor invading the subserosal connective tissue without invading the visceral peritoneum or adjacent structure and 0/16 lymph nodes were positive with clear margins and without lymphovascular or perineural involvement. She has no other medical problems and was previously healthy until the diagnosis of gastric cancer. She is recovering well from surgery. Physical examination revealed a well-appearing female, healing abdominal surgical wound with unremarkable examination otherwise. What is the optimal adjuvant treatment option for her?

A. Repeat resection with more extensive lymph node retrieval (D2)
B. Infusional fluoropyrimidine for 1 year
C. 6 months of ECF (epirubicin, cisplatin, 5-FU) postoperative polychemotherapy
D. 5-FU/leucovorin before, during, and after radiation therapy
E. Observation

5. A 53-year-old man presented with anorexia, epigastric discomfort, and early satiety for 3 months. He did not have significant medical problems and the symptoms were initially thought to be due to acid reflux related to his stressful job. The symptoms did not improve with PPI use. Physical examination was unremarkable and laboratory studies were within normal limits. Upper endoscopy was pursued which showed a 5-cm fungating nonbleeding mass in the gastric body. Subsequent EUS showed a tumor invading the muscularis propria with multiple enlarged perigastric lymph nodes. PET/CT showed no other occult sites of disease. The patient wishes to get the most aggressive treatment that would provide the best chance of cure. What would you recommend?

A. Surgery followed by adjuvant radiation
B. Neoadjuvant concurrent chemoradiation with cisplatin/5-FU regimen
C. Perioperative polychemotherapy with ECF (epirubicin, cisplatin, 5-FU)
D. Perioperative chemotherapy including bevacizumab
E. Palliative care

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6

Biliary Tract Cancer

Nilay A. Shah and Jon Cardinal

Carcinomas of the biliary tract include those cancers arising in either the gallbladder or the bile duct. There will be an estimated 10,130 new cases of gallbladder and biliary tract cancers (excluding intrahepatic biliary tract cancer) in 2013 with 3,230 expected deaths resulting from these cancers. Gallbladder cancer is the most common biliary tract cancer, occurring nearly twice as often as cholangiocarcinomas. While the term cholangiocarcinoma was initially used to designate tumors of the intrahepatic bile ducts; it is now taken to refer to the entire spectrum of tumors arising in the intrahepatic, perihilar, and distal bile ducts. The epidemiology, clinical features, staging, and surgical treatment are distinct for carcinomas arising in the gallbladder and bile duct, therefore, these are describe separately. The palliative treatment options are similar and are discussed together at the end of the chapter.

CARCINOMA OF THE GALLBLADDER

Epidemiology

- Carcinoma of the gallbladder is the fifth most common GI malignancy.
- Women are affected two to six times more commonly than men and whites have a 50% greater incidence compared to black individuals.
- There is a prominent geographic variation in the incidence of gallbladder cancer. High rates are seen among Native Americans and in South American countries (particularly Chile). There is increased incidence in India, Pakistan, Japan, and Koreas as well. 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 1.2 per 100,000 population in the United States.
- The mean age at diagnosis is 65 years.

Etiology

- Cholelithiasis (gallstones): A history of gallstones appears to be one of the strongest risk factors for gallbladder cancer. Seventy to 90% of patients will have gallstones, whereas only 0.5% to 3% of patients with gallstones develop gallbladder cancer. 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 malignancy potential and therefore are an indication for cholecystectomy.
- The anamolous pancreaticobiliary 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:

- Pain (82%)
- Weight loss (72%)
- Anorexia (74%)
- Nausea or vomiting (68%)
- Mass in the right upper quadrant (65%)
- Jaundice (44%)
- Abdominal distension (30%)
- Pruritus (20%)
- Incidental (15% to 20%)
- Courvoisier's law states that if the gallbladder is enlarged and if the patient has painless jaundice, the cause is unlikely to be gallstones

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.

- Of the three clinical scenarios listed above, the first is the most common with the majority of gallbladder cancers being diagnosed as an incidental finding during exploration of presumed benign disease. 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.
- Endoscopic ultrasound (EUS) is more accurate than transabdominal ultrasound; it is useful in the differential diagnosis of polyps and in preoperative staging. EUS can accurately assess the depth of tumor invasion as well as define regional lymph node involvement.
- Triple-phase computerized tomography (CT) scan (liver protocol), which includes a noncontrasted 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 is distinguishing benign from malignant polyps.
- Cholangiography: Magnetic resonance cholangiopancreatography (MRCP) is preferred to endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiopancreatography

because it is a noninvasive modality. MRCP can provide information regarding the extent of disease and is able to differentiate a benign from malignant lesion/polyp. Furthermore, ERCP and PTC do not provide appropriate visualization of the gallbladder.

- Positron emission tomography (PET) scan's role in the diagnosis of gallbladder cancer remains unclear at this time; however, it may be useful in detecting distant metastatic disease in patients previously determined to have resectable disease.
- Laboratory studies are generally not diagnostic. Elevated serum bilirubin or alkaline phosphatase can indicate a bile duct obstruction. Tumor markers such as carcinoembryonic antigen (CEA) or CA 19-9 can be elevated. CEA is specific for gallbladder cancer, but lacks sensitivity, whereas CA 19-9 has sensitivity and specificity that can approach 75%.

Pathology

- Adenocarcinoma accounts for close to 85% of cases. It is subcharacterized 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 developed by Nevin in 1976 is still widely used; however, the preferred classification scheme in the United States is the TNM staging system of the American Joint Committee on Cancer (AJCC).

- The AJCC TNM staging classification was recently updated in 2010. Please refer to the seventh edition of the Staging Manual for details. The Nevin staging, which is more commonly used in Europe, is provided in Table 6.1.
- 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. Stage 0, I, and II tumors are potentially resectable with curative intent. Stage T3 tumors and above are generally considered difficult to resect.
- Patients noted to have T1a lesions may be observed post–simple cholecystectomy as long-term survival approaches 100%.

Table 6.1 Nevin Staging System for Gallbladder Cancer

Stage	Description
I	Intramucosal only
II	Extends to muscularis
III	Extends through serosa
IV	Transmural involvement and cystic lymph nodes are involved
V	Direct extension to liver or distant metastases

- Controversy exists about the proper management of patients with T1b lesions as some series show only a 50% 1-year survival following simple cholecystectomy, while others report cure rates of 90% to 100% at 5 years. It is generally agreed, however, that medically fit patients with T1b lesions should undergo extended cholecystectomy.
- Patients with T2 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 strongly correlates 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.
- However, biopsy should be avoided in patients who are surgical candidates are gallbladder cancer notoriously seeds biopsy tracks and can easily seed the peritoneal cavity.

Radiation

- In patients with unresectable tumors, available data suggest that tumor control is rarely achieved with RT.
- 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. In 2003, however, Jarnigan and colleagues 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.

Chemotherapy and Palliation

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

Survival

The various aspects of survival following treatment of gallbladder cancers according to stage are given in Table 6.2.

Table 6.2 Treatment and 5-Year Survival of Gallbladder Cancers According to Stage

TNM Stage	Treatment	Median Survival	5-Y Survival (%)
I	Simple cholecystectomy Radical cholecystectomy	19 mo	60–100
II	Radical cholecystectomy +/– Radiation therapy (not standard)	7 mo	10–20
III	Radical cholecystectomy +/– Radiation therapy (not standard)	4 mo	5
IV	Palliation with stent placement Surgery or radiation or chemotherapy or combination of these	2 mo	0

CARCINOMA OF THE BILE DUCTS (CHOLANGIOCARCINOMA)

Epidemiology

- Cholangiocarcinomas arise from the epithelial cells of either intrahepatic or extrahepatic bile ducts.
- Cholangiocarcinoma accounts for 3% of all GI malignancies. The reported incidence within the Unites States is one to two cases per 100,000 population.
- For some unclear reasons the incidence of intrahepatic cholangiocarcinoma has been steadily rising over the past two decades, while rates of extrahepatic cholangiocarcinomas have been declining.
- Incidence typically increases with age. 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 significantly earlier.
- In contrast to gallbladder cancer, cholangiocarcinomas are more common in males.
- Cholangiocarcinomas are subdivided into proximal extrahepatic (perihilar or Klatskin tumor; 50% to 60%), distal extrahepatic (20% to 25%), intrahepatic (peripheral tumor; 20% to 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 recently. 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 blocked.

- Extrahepatic cholangiocarcinoma usually presents with symptoms and signs of cholestasis (icterus, pale stools, dark urine, and 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

Making a diagnosis of cholangiocarcinoma preoperatively can be challenging. The diagnosis is frequently based on the clinical scenario, serology, and radiographic findings but without histologic confirmation. This is an important issue because up to 33% of patients with imaging and symptoms suggestive of cholangiocarcinoma will have benign disease. Such a diagnosis in the absence of tissue should be made only after efforts are taken to prove the diagnosis by use of cytologic or pathologic evaluation.

- A cholestatic serologic picture may be seen as previously described. 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. CEA level $>$ 5.2 ng/mL had a sensitivity and specificity of 68% and 82%, respectively. Some tumors produce low levels or no CA 19-9. In one series, a level $>$180 units/mL had a sensitivity of 67%; however, the specificity was 98%.
- Ultrasonography is the first-line investigation for suspected cholangiocarcinoma, usually to confirm biliary duct dilatation, localize the site of obstruction, and to 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 is considered a safer alternative to ERCP or PTC. MRCP provides excellent imaging of the intrahepatic and extrahepatic bile ducts and can create three dimensional imaging of the biliary tree and the vascular structures. 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, ERCP and/or PTC offer both diagnostic and therapeutic value in the workup and management of biliary obstruction; however, the diagnostic yield on cytology obtained from biliary brushings is notoriously suspect with sensitivities and specificities of roughly 50% being the norm.
- EUS may be useful in visualizing the extent of tumor and lymph node involvement of distal bile duct lesions. Its role in proximal bile duct lesions is less clear.
- PET scan is used to identify metastatic disease which could alter surgical management.

Pathology

- Adenocarcinomas account for 90% to 95% of tumors. The remainder is squamous cell carcinomas. They are graded as well, moderately and poorly differentiated, and are further divided into sclerosing, nodular, and papillary subtypes. Patients with papillary tumors present with earlier disease and have the highest resectability and cure rates; however, they are unfortunately the least common of the three subtypes.
- Immunohistochemical staining with cytokeratins 7 and 20 can help differentiate intrahepatic cholangiocarcinoma (CK7+, CK20−, CDX2−) from colorectal metastatic lesion (CDX2+, CK20+).

Staging

- The AJCC has developed the staging systems for cholangiocarcinomas. The TNM staging system is primarily based upon the extent of ductal involvement by the tumor.
- Previously, intrahepatic cholangiocarcinomas were staged identical to hepatocellular carcinoma. In the seventh edition of the AJCC Staging Manual, however, there is a new staging system independent of the one used for HCC. This revised system was validated by a study showing improved survival predictability correlating with the new TNM system.

Table 6.3 The Bismuth-Corlette Classification of Perihilar Tumors

Type	Description
I	Tumors below the confluence of left and right hepatic ducts
II	Tumors reaching the confluence but not involving the left or right hepatic ducts
III	Tumors occluding the common hepatic duct and either the right or left hepatic duct
IV	Tumors that are multicentric or that involve the confluence of the right and left hepatic ducts

- The seventh 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 seventh 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 (Table 6.3).

Treatment

Surgery

Except in the case of distal common bile duct cancer, cholangiocarcinoma is a disease that, when managed surgically, often times requires major hepatic resection (segmentectomy, anatomic lobectomy, 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, steatosis/steatohepatitis) as well as any acute insults, which in the case of cholangiocarcinoma often times involves cholestasis. The former issues can limit the extent of resection that can safely be performed, while the latter often times 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 1 cm 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 re-resection versus chemoradiation options.
- The role of routine nodal dissection in the management of intrahepatic cholangiocarcinoma is debated, although it is agreed upon that lymph node status dose carry prognostic significance.
- In 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.

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 6.4).
- For patients with hilar cholangiocarcinoma, bile duct resection alone 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.
- Liver transplantation is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma and can only be recommended in highly select patients when combined with an intensive pretransplant regimen of chemo/radiation therapy.

Locoregional Therapies

- The role of local therapy (radiofrequency or cryoablation) in the management of intrahepatic cholangiocarcinoma is limited due to the often-large-size and multicentric nature of the tumor(s) at the time of their discovery.
- Regional approaches to intrahepatic cholangiocarcinoma are viable alternatives in cases where surgical resection is not possible. The approach with the most robust experience to date involves transarterial chemoembolization (TACE) with gemcitabine in combination with cisplatin, oxaliplatin, or mitomycin C. Selective internal radiation therapy (SIRT or Y90) is an option that lacks long-term follow-up data.

Adjuvant Chemotherapy and Chemoradiation

- The role of adjuvant therapy remains poorly defined. Due to the low incidence of biliary tract cancers, most trials represent single institution phase II trials. A large retrospective analysis using the SEER database revealed 2,325 patients in the surgical cohort from 1992 to 2002, of which only 17% received adjuvant chemoradiation.
- A phase III trial evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer. Fifty percent of these patients had gallbladder cancer of cholangiocarcinoma and they were randomly assigned to either 5-FU/mitomycin C or a control arm. Analysis revealed that adjuvant chemotherapy resulted in a significant improvement in the 5-year survival of only those patients with gallbladder cancer.

Table 6.4 Treatment and Survival of Cholangiocarcinomas According to Location

Location	Treatment	Median Survival	5-Y Survival (%)
Extrahepatic (hilar)	Type I + II: en bloc resection of extrahepatic bile ducts, gallbladder, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy Type III: as above plus right/left hepatectomy Type IV: as above plus extended right/left hepatectomy	12–24 mo	9–18
Extrahepatic (distal)	Pancreaticoduodenectomy	12–24 mo	20–30
Intrahepatic	Resect involved segments or lobe of liver	18–30 mo	10–45

- Recommendations for fluoropyrimidine-based or gemcitabine-based chemotherapy or fluoropyrimidine-based chemoradiotherapy generally represent an extrapolation of data from studies in patients with advanced disease.
- No consensus recommendations for adjuvant therapy in individuals with intrahepatic cholangiocarcinoma and negative surgical margins with no involved lymph nodes.

Chemotherapy in Advanced-Stage Disease

- In patients with unresectable locally advanced disease or resected disease with positive margins there have been reports of improved survival with chemotherapy or combined-modality chemoradiotherapy. This survival benefit was first suggested in a trial comparing 5-FU, leucovorin, and etoposide to best supportive care.
- Definitive evidence from phase III studies to support this practice, however, remains lacking.
- A number of chemotherapy combinations as well as single agents have been evaluated in clinical studies. Examples of combinations that have demonstrated activity in phase II trials include gemcitabine and cisplatin, gemcitabine and capecitabine, gemcitabine and oxaliplatin, capecitabine and oxaliplatin, capecitabine and cisplatin, and 5-FU and cisplatin.
- Of the combinations listed above, the combination of gemcitabine with a platinum-based agent had the greatest benefit. A most recent study demonstrated that this combination significantly improved overall survival (11.7 months vs. 8.1 months) and progression-free survival (8.0 months vs. 5.0 months) compared to gemcitabine alone. Based on this study, gemcitabine and cisplatin are considered to be the standard of care.

Chemoradiation in Advanced Disease

- In locally advanced disease, radiation with or without chemotherapy may ameliorate painful symptoms and contribute toward biliary decompression and may even improve overall survival.
- The most extensively investigated and hence recommended agents to be used concurrently with radiation therapy have been 5-FU and capecitabine. Gemcitabine is not recommended for concurrent chemoradiation therapy.
- Treatments should be restricted to individuals without evidence of metastatic disease.

Targeted Therapy

- A phase 2 study has shown erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor, to have efficacy in a small study of previously treated and chemo-naive patients with biliary cancer.
- Erlotinib plus bevacizumab combination was addressed in a phase II study with 53 patients with advanced biliary tract cancer. Combination therapy resulted in a median response duration of 8.4 months, a median time to progression of 4.4 months, and a medial overall survival of 9.9 months. Stable disease was documented in 51%. Randomized trials will be needed for further evaluation of these agents in combination.
- GEMOX plus bevacizumab, GEMOX plus erlotinib, GEMOX plus cetuximab: These combinations of therapy were recently shown to be effective in separate phase II trials. They will need to be compared to GEMOX alone to determine the significance of the targeted therapy compared to the toxicity profile associated with them.

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).
- Photodynamic therapy is another option for patients with locally advanced inoperable disease. This involves injecting a porphyrin photosensitizer and then endoscopically applying light to the tumor. Although the data are derived from small studies to support this practice, the survival benefit derived

from photodynamic therapy appears impressive with one report showing an improvement in median survival of 14 months.

- Celiac plexus blockade may also ameliorate symptoms of pain in the patient with inoperable disease.

REVIEW QUESTIONS

1. A 53-year-old woman with a history of hypertension and hypothyroidism presented to the ER with complaints of right upper quadrant discomfort for the past 3 to 4 days. The pain is nonradiating and is described as dull in nature. She stated there was no correlation with her diet; however, the patient does admit to a decreased appetite over the past 2 weeks. She also noted an unintentional 12 lb weight loss over this same period of time. She is afebrile. Physical examination reveals tenderness to the right upper quadrant, no jaundice and ascites noted. Labs: WBC 8.6 thou/μL, hemoglobin 14.4 g/dL, Platelet count was 232 thou/mL, AST 28 units/L, ALT 41 units/L, total bilirubin 1.1 mg/dL, and alkaline phosphatase was 77 units/L. RUQ ultrasound revealed a thickened gallbladder wall. No evidence of cholelithiasis. The bile duct diameter was estimated to be 6 mm. The patient was initially sent home with a short course of antibiotics, however returned within 48 hours with worsening pain and persistent nausea. CT abdomen and pelvis was nonrevealing. MRCP revealed a small polyp within the posterior aspect of the gallbladder wall. The patient underwent a cholecystectomy the following morning. Few gallstones were noted within the gallbladder. A small polyp was seen at the posterior aspect of the gallbladder wall. Pathology revealed a well-differentiated adenocarcinoma consistent with gallbladder cancer. The tumor invaded the lamina propria; however, there was no evidence of muscle layer involvement. Tumor margins were negative. On review of prior CT scan, no lymph nodes were noted within the abdomen or pelvis. What is the next best step in the management of this patient?

A. Initiate chemotherapeutic treatment with gemcitabine/cisplatin
B. Observation
C. Intraoperative staging with possible extended cholecystectomy
D. Hospice discussion with patient and family

2. A 66-year-old man with no significant medical history is admitted to the hospital with right upper quadrant pain, low-grade fevers and worsening jaundice for the past 3 to 4 weeks. On further discussion, the patient states he has unintentionally lost 10 lbs over the same time period; however, he believes he has likely lost approximately 30 lbs over the past 3 months. Temperature: 37.9° C. Physical examination revealed a significantly jaundiced male who appeared to be in mild distress secondary to pain. No masses were appreciated in the abdomen or right upper quadrant in particular; however, the patient did display increased tenderness to palpation over the right upper quadrant and mid epigastric region. The remainder of the physical examination was unremarkable. Blood work revealed abnormal liver function tests. Alkaline phosphatase was elevated to 381 units/L. Total bilirubin was 7.2 mg/dL with direct bilirubin 6.6 mg/dL. AST and ALT were both at the upper limits of normal levels. WBC was mildly elevated to 12.0 thou/μL with a normal differential. CEA and CA 19-9 were normal. AFP was normal. RUQ units/S revealed the common bile duct to be dilated to 1.8 cm. There was no direct evidence of cholelithiasis. CT scan of the chest, abdomen, and pelvis confirmed the common bile duct dilatation but also revealed a distal ductal mass as the likely source of the obstruction. Imaging also revealed diffuse abdominal lymphadenopathy. An ERCP was performed and brush cytology from the distal portion of the common bile duct was consistent with a poorly differentiated adenocarcinoma. During laparoscopic staging, the tumor appeared to involve the head of the pancreas as well as the gallbladder. It also appeared to be wrapped around the base of the celiac axis. The tumor at this time was determined to be unresectable. A biliary stent was placed for symptomatic control. What is the next best step in the management of this patient?

A. Surveillance
B. Initiate single agent chemotherapy with gemcitabine
C. Begin combination chemotherapy with gemcitabine and cisplatin
D. Neoadjuvant chemoradiation with gemcitabine

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7

Primary Cancers of the Liver

Midhun Malla and David P. Cosgrove

Primary liver cancers arise predominantly from the parenchymal liver cells or hepatocytes (90%) and are called hepatocellular carcinoma (HCC). The incidence of HCC continues to increase rapidly in the United States, with rates increasing fastest in men. Research on vaccinations for hepatitis B and their use have impacted the development of HCC in many regions of the world.

EPIDEMIOLOGY

- In the United States, the incidence of clinically significant metastatic carcinoma to the liver is approximately 20 times more common than primary liver cancer.
- Based on November 2011 SEER data submission, the HCC incidence for all races was 11.6 (9.9) per 100,000 men and 3.9 (3.5) per 100,000 women (http://seer.cancer.gov/statfacts/html/livibd.html).
  - HCC incidence in the United States has increased during the past two decades, possibly due to a large pool of people with long-standing chronic hepatitis C, combined with a large influx of immigrants from East Asia and other geographic areas with high endemic rates of hepatitis B viral infection.
  - The incidence of HCC in the United States is expected to continue to rise as a consequence of high hepatitis C infection rates between 1960 and 1990 and the average 20- to 30-year lag time between virus acquisition and the development of cirrhosis and carcinoma.
- There are approximately 20,000 patients diagnosed with HCC annually, accounting for less than 2% of all malignancies in the United States. HCC results in between 250,000 and 1 million deaths globally per annum.
- There is marked geographic variation in the incidence of HCC, with the highest incidences occurring in sub-Saharan Africa and Asia. Over 40% of all cases of HCC occur in the People's Republic of China.
- Men are affected more than twice as often as women (mean 3.7:1). The mean age at diagnosis is between 50 and 60 years. Although not fully understood, the differences in sex distribution are thought to be due to variations in hepatitis carrier states, exposure to environmental toxins, and the trophic effect of androgens.

ETIOLOGY

- Cirrhosis is present in 80% of patients with HCC. Therefore, risk factors for cirrhosis are also risk factors for HCC.
- Hepatitis B virus (HBV) accounts for around 55% of HCC cases in the world. In HBV carriers without cirrhosis, the risk is 0.02% to 0.03% in Caucasians and 0.4% to 0.6% per year in Asians. In those with

cirrhosis, the risk is 2.2% and 3.7%, respectively, in Caucasians and Asians. The risk of HCC is much greater in patients with high serum levels of HBV DNA compared with those who have low levels (<10,000 copies/mL).

- Hepatitis C virus (HCV) infection accounts for 30% to 50% of HCC in the United States. It has been estimated that HCV accounts for 27% of cirrhosis and 25% of HCC cases worldwide. In contrast to HBV infection, HCC in patients with hepatitis C occurs almost exclusively in those with cirrhosis.
- HCV-induced HCC correlates well with the degree of inflammation and necrosis and seems to be caused by inflammation rather than specific oncogene activation. In contrast, hepatitis B–related HCC does not correlate well with inflammation, and there appear to be specific oncogenes induced by the virus that result in an increased risk of HCC.
- Alcoholic cirrhosis accounts for 15% of HCC in the United States.
- Hemochromatosis (HH), hereditary tyrosinemia, and autoimmune chronic active hepatitis are other causes of cirrhosis and are associated with a significant risk for developing HCC. In all, 3% to 27% of patients with long-standing HH develop HCC.
- There is less convincing evidence for the risk of developing HCC from aflatoxin B_1 (chemical product of *Aspergillus*), androgenic steroids, thorotrast (radiology contrast agent), oral contraceptives, and nonalcoholic fatty liver disease (NAFLD). Furthermore, they are probably not important independent etiologic factors but rather may contribute to HCC development in individuals with other risk factors.
- In patients with diabetes mellitus, HCC risk is increased by approximately 2.5 times. However, associations between diabetes and HCC should be interpreted with caution. In many cases, the onset of glucose intolerance results from the development of cirrhosis, so "diabetes" in this context may be a surrogate for cirrhosis, which increases the risk of HCC. In addition, many patients with diabetes also have NAFLD, which has also been associated with an increased risk of HCC. It is likely that NAFLD causes HCC via cirrhosis, although the exact pathogenesis has not yet been determined. One study found that HCC in NAFLD was associated with obesity, diabetes, hypertension, and male sex.

CLINICAL FEATURES

The most common symptoms or signs of HCC are as follows:

- Pain (91%)
- Weight loss (35%)
- Vomiting (8%)
- Hepatomegaly (89%)
- Abdominal swelling (43%)
- Jaundice (7% to 41%)

The physical findings in patients with HCC tend to reflect the underlying liver disease rather than be specific for the malignancy—ascites, jaundice, splenomegaly, or other manifestations of decompensated cirrhosis.

Patterns of metastatic spread—the majority of metastases in HCC remain confined to the liver. Extrahepatic spread is present in only 5% to 15% of cases at diagnosis and is typically seen in patients with advanced stage primary tumors (>5 cm, macrovascular invasion). The most common sites of extrahepatic disease include lung, bone, lymph nodes, and adrenal gland.

DIAGNOSIS

The diagnosis of HCC is often suspected in a patient with underlying liver disease (i.e., cirrhosis, chronic viral hepatitis), who develops a rising serum α-fetoprotein (AFP) level.

Recommendations for diagnosis of HCC have been issued in a guideline from the American Association for the Study of Liver Diseases (AASLD).

- Nodules found on ultrasound surveillance that are smaller than 1 cm should be followed with ultrasound at intervals of 3 to 6 months. If there has been no growth over a period of up to 2 years, one can revert to routine surveillance.
- Nodules larger than 1 cm in diameter should be evaluated with four-phase multidetector computed tomography (CT) scan or dynamic contrast-enhanced magnetic resonance imaging (MRI). If the appearances are typical of HCC (i.e., hypervascular in the arterial phase with washout in the portal venous or delayed phase), no further investigation is required. If the characteristics are not typical for HCC (and do not suggest hemangioma), one of the two strategies is acceptable: either a second study (CT or MRI, whichever was not performed) or a biopsy.
- Biopsies of small lesions should be evaluated by expert pathologists. Tissue that is not clearly HCC should be stained with all available markers, including CD34, CK7, glypican 3, HSP-70, and glutamine synthetase, to improve diagnostic accuracy.
- If the biopsy is negative for HCC, patients should be followed by ultrasound or CT scanning at 3- to 6-month intervals until the nodule disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC, a repeat biopsy is recommended.

Serum Markers

The most commonly used marker for HCC is the serum Alfa-fetoprotein(AFP).

It is generally accepted that serum levels greater than 400 μg/L (normal in most laboratories is between 10 and 20 μg/L) in a high-risk patient is diagnostic of HCC. However, HCC is often diagnosed at a lower AFP level in patients undergoing screening, as not all tumors secrete AFP, and serum concentrations are normal in up to 40% of small HCCs, especially where alcohol is the etiologic factor. AFP levels are normal in the majority of patients with fibrolamellar carcinoma, a variant of HCC.

Because of the limitations of serum AFP measurements, several other serologic markers (such as des-gamma-carboxy prothrombin and Lens culinaris agglutinin-reactive AFP) used alone or in combination with the serum AFP have been evaluated for diagnosis or for determining prognosis in patients with HCC.

Imaging Studies

The imaging tests most commonly used for the diagnosis of HCC are ultrasound, CT, MRI, and angiography. A classic appearance on one of these imaging modalities combined with an elevated serum AFP concentration in the appropriate clinical setting is usually sufficient for establishing the diagnosis of HCC.

The place of positron emission tomography (PET) scanning (fluorodeoxyglucose [FDG] PET) in the diagnostic and staging evaluation of HCC remains uncertain; however, PET has a greater sensitivity for detection of distant metastases than other imaging modalities, including CT scan, bone scan, and MRI. However, sensitivity is limited for lesions ≤1 cm and false-positive results are also problematic.

PATHOLOGY

- HCC is the most common type of primary liver cancer. It accounts for 80% to 90% of primary cancers of the liver. The next most common is cholangiocarcinoma (10% to 20%).
- Other much rarer causes include hepatoblastoma, hemangiosarcoma, and angiosarcoma. There are many histologic subtypes of HCC, including trabecular, pseudoglandular or acinar, compact, scirrhous, clear cell, and fibrolamellar.
- Fibrolamellar carcinoma is a histologic variant accounting for 1% of HCC. It occurs more commonly in women, is not associated with cirrhosis, and has a better prognosis than HCC.

STAGING

- The four most commonly used staging systems are the TNM system of the American Joint Committee on Cancer (AJCC), the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, and the Cancer of the Liver Italian Program (CLIP) score. To best assess the prognosis of HCC patients, it is recommended that the staging system take into account tumor stage, liver function, and physical status. Currently, the BCLC system is the only staging system that accomplishes these aims (Fig. 7.1). The TNM staging system has been criticized because it does not evaluate the underlying liver disease, which is clearly a major prognostic factor in HCC patients, regardless of tumor stage. The T portion of the TNM system focuses on both tumor size and vascular invasion by the primary tumor, with delineation of stages I, II, and III based purely on these factors. This does reflect the natural history of HCC in which survival is often predicated on the degree of liver involvement rather than widespread extrahepatic disease, but the underlying liver function is just as critical in determining prognosis in many of these patients and is not incorporated into this anatomic system.

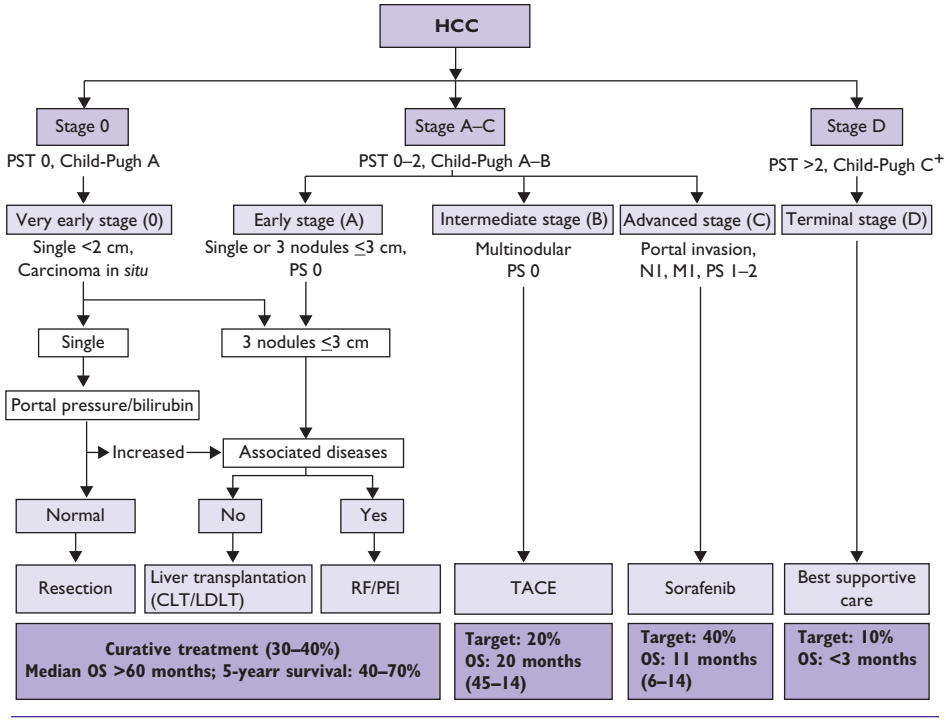

FIGURE 7.1 Barcelona Clinic Liver Cancer (BCLC) HCC staging classification. The classification includes an algorithmic treatment recommendation and outlines the approximate percentage of patients likely diagnosed within each stage in a Western population, as well as their estimated survival with the relevant treatment modalities. HCC, hepatocellular carcinoma; PST, ECOG performance status; CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; RF, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; OS, overall survival. (Adapted from Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208-1236. With permission of John Wiley and Sons, Inc.)

Table 7.1 Child-Pugh Scoring System

Chemical and Biochemical Parameters	Score Attributed to Each Parameter		
	1	2	3
Encephalopathy	None	1–2	3–4
Ascites	None	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time prolonged (s)	1–4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
Bilirubin (mg/dL)	1–2	2–3	>3

Class A, 5–6 points; Class B, 7–9 points; Class C, 10–15 points. These grades correlate with 1- and 2-year patient survival—grade A: 100% and 85%; grade B: 80% and 60%; and grade C: 45% and 35%.

- The BCLC staging classification comprises four stages that are based upon the extent of the primary lesion, performance status, the presence of constitutional symptoms, vascular invasion and extrahepatic spread, and Okuda stage. It provides broad, algorithmic treatment recommendations based upon these four stages, a feature that has led to some criticism by expert groups, who feel that treatment planning should be more patient-centered. Although in at least two comparative studies the BCLC system outperformed other prognostic models in patients undergoing surgical therapy, several larger series show that other systems can outperform BCLC, and still other studies show that treatment outside of BCLC guidelines positively impacts outcomes in select patients.

The consensus of the American Hepato-Pancreato-Biliary Association (updated in 2010) reasserts the need to use different systems in different patients. Their consensus statement recommends the use of the TNM system to predict the outcome following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery.

- The Child-Pugh grading system has been incorporated into the management of HCC because it evaluates the status of the underlying liver function and influences treatment (Table 7.1).

TREATMENT

Surgery

- Surgery remains the only possibility for cure in HCC, but it is applicable to only 5% of US population.
- The treatment of HCC is determined by two factors: tumor extent and the severity of the underlying hepatic parenchymal disease.
- Partial hepatectomy: Only 13% to 35% are surgical candidates. Small tumors have the best outcomes. Recurrence is most commonly seen in the remnant liver. Repeat hepatectomy is possible in 10% to 29% of patients. Operative mortality is <5%, but is higher in the presence of cirrhosis. Long-term relapse-free survival rates average 40% or better, and 5-year survival rates as high as 90% are reported in carefully selected patients.
  - Postoperative morbidity and mortality are related to the extent of operative resection.
  - Major postoperative complications include bile leak and pleural effusion.
- Total hepatectomy and liver transplantation: Transplantation is indicated in patients with severe cirrhosis or where extensive resection leaving minimal liver reserve is required.
- Orthotopic liver transplantation (OLT) is a suitable option for unresectable patients who have a solitary HCC ≤5 cm in diameter or up to three separate lesions none of which is larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases (the Milan/Mazzaferro criteria). Based on these criteria, 4-year survival was reported as 75% to 85%.

- Survival outcomes may be further improved by living donor transplantation, although this remains controversial.
- Disadvantages of transplantation are the expense, the lack of specialty centers performing operations, and the lack of donor livers.

POSTTREATMENT SURVEILLANCE

Even patients who have a good response to treatment are at risk for disease recurrence and second primary HCC. Guidelines from the National Comprehensive Cancer Network (NCCN) suggest the following posttreatment surveillance after resection:

a) Imaging every 3 to 6 months for 2 years, and then annually.
b) Assay of serum AFP, if initially elevated, every 3 months for 2 years then every 6 months.
c) In addition, all patients with the underlying liver disease should be monitored and treated appropriately.

Ablative Techniques

- Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation.
- Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are equally effective for tumors <2 cm. However, the necrotic effect of RFA is more predictable in all tumor sizes and its efficacy is clearly superior to that of ethanol injection in larger tumors. PEI is now less commonly used because it is uncomfortable and requires more treatment sessions than RFA, and in addition, it can be difficult to visualize the limits of the lesion on ultrasound because of the bubbles formed during the alcohol injection.
- The main drawbacks of RFA are its higher cost, limited efficacy in lesions adjacent to major blood vessels, and the higher rate (up to 10%) of adverse events (pleural effusion and peritoneal bleeding).
- The recurrence rate after ablation is as high as for resection. Some recurrences will occur in the vicinity of the treated nodule and are due to the presence of microscopic satellites not included in the ablation zone.
- Cryotherapy is also safe and more effective than RFA for larger tumors, but is less suited to a percutaneous approach.
- Hepatic artery chemoembolization (transarterial chemoembolization [TACE]) is based on the principle that $>80\%$ of the blood supply to tumors is from the hepatic artery, which supplies only 20% to 30% of normal liver parenchyma. Ligation or embolization of the hepatic artery can induce temporary tumor responses, and when combined with chemotherapy (TACE) may be more efficacious, although data are conflicting. The efficacy of TACE has been shown in a number of meta-analyses, revealing superior progression-free survival (PFS) when compared with best supportive care in locally advanced HCC.
- Indications of TACE:

  a) Treatment of large unresectable HCCs not suitable for local ablation.
  b) In patients awaiting OLT to reduce the rate of dropout because of local tumor progression.

  Benefit in any of these settings is highly dependent upon case mix, including tumor-related factors and the severity of preexisting liver dysfunction.

- The best candidates for TACE are patients with unresectable lesions without vascular invasion or extrahepatic spread and preserved liver function (i.e., Child-Pugh A or B cirrhosis).
- Conventional TACE using doxorubicin (50 to 75 mg/m^2) was directly compared with TACE with drug-eluting beads (DEBs) (150 mg doxorubicin per procedure) in a randomized trial of 212 patients with Child-Pugh A/B cirrhosis and unresectable HCC. The DEB group had higher rates of objective response at 6 months (52 versus 44 but the difference was not statistically significant), and significantly lower rates of serious hepatobiliary toxicity and doxorubicin-related side effects. DEBs may be preferred, although long-term outcomes using this technique are not available.

- Absolute contraindications to TACE include the complete absence of hepatopetal blood flow (portal vein thrombosis), encephalopathy, biliary obstruction, and Child-Pugh C cirrhosis.

Radiation

- HCC is a radiosensitive tumor, but it is located in an extremely radiosensitive organ. Normal liver can only tolerate about 20 Gy. The major drawbacks with radiotherapy (RT) are the poor radiation tolerance of normal liver and difficulty with tumor localization. However, safe and effective doses can be given to palliate pain.
- With the development of three-dimensional conformal radiation techniques, more precisely targeted RT (intensity-modulated RT and image-guided approaches, including stereotactic body radiotherapy [SBRT]) can be more safely delivered to the tumor-bearing parts of the liver with less liver toxicity. However, there are no studies demonstrating an impact on survival as yet.
- SBRT seems most applicable to patients with relatively small HCCs who are either inoperable or who refuse operation. It is unclear whether SBRT is a more effective or less toxic approach than RFA in these patients. Where available, proton beam irradiation may be a reasonable approach for patients with a large HCC and associated portal vein thrombus.
- Selective internal irradiation: For example, iodine-131 (131I)-labeled lipiodol or yttrium-90 (^{90}Y)-tagged glass microspheres are delivered selectively to the tumor via the hepatic artery. Early reports suggest that this procedure is safe and induces objective responses in patients with unresectable HCC. However, there are no studies demonstrating an impact on survival and no consensus as to the optimal use of this therapy.
- There is obvious overlap with eligibility for TACE; it is not yet clear how to choose one technique over the other.
- One clinical scenario in which radioembolization may be preferred over TACE is in patients who are otherwise eligible for TACE but who have a branch/lobar portal vein thrombosis.

Chemotherapy

- Systemic therapy is appropriate for patients with advanced unresectable disease who are unsuitable for locoregional therapy. Hepatocellular cancer has been considered to be a relatively chemotherapy-refractory tumor. This may be in part due to the high rate of expression of drug resistance genes, including P-glycoprotein, glutathione-S-transferase, heat shock proteins, and mutations in p53.
- Single-agent chemotherapy has demonstrated response rates of approximately 15% to 30%, which increases to 20% to 35% with combination therapy. Cisplatin and anthracycline combinations have been studied most extensively, but there is no reference regimen for this disease. Despite objective responses that are occasionally complete, median survival in all of these studies has been short (4 to 11 months), with the exception of those in which resection/transplantation is attempted after chemotherapy.
- Interferon-α (IFN-α) and chemoimmunotherapy: Combinations of chemotherapy with IFN-α have failed to show consistent responses in three randomized controlled trials conducted so far.
- The PIAF regimen (intravenous cisplatin, recombinant IFN-α2b, doxorubicin, and 5-fluorouracil) demonstrated a 50% objective response rate in 50 patients with unresectable disease from Hong Kong, but failed to show superiority versus doxorubicin. Hence, the place of the PIAF regimen in the treatment of unresectable HCC remains uncertain.

Molecularly Targeted Therapy

- Sorafenib (a multikinase inhibitor with antiangiogenic, proapoptotic properties) was well tolerated and the first agent to demonstrate a statistically significant improvement in overall survival (OS) for patients with advanced HCC when compared with placebo/supportive care. The OS was significantly longer in the sorafenib-treated patients (10.7 versus 7.9 months; HR = 0.69; $P = 0.0006$), as was the time to progression (5.5 versus 2.8 months; HR = 0.58; $P = 0.000007$). This effect is clinically

meaningful and established sorafenib as first-line treatment for patients with advanced HCC. Diarrhea and hand–foot skin reaction were the most significantly noted grade 3 or grade 4 side effects in this study.

- Sorafenib is also associated with potentially fatal liver toxicity, characterized predominantly by hepatocellular pattern of liver damage, with significant increases in liver transaminases.
- Sorafenib has also demonstrated encouraging results in combination with doxorubicin. There are ongoing clinical trials to assess this approach in terms of survival. Despite the approval of sorafenib in this disease, no other molecularly targeted agent has proven effective in subsequent studies. Agents that have been assessed in this setting include the following:
  - Bevacizumab (Avastin, a monoclonal antibody [MoAb] directed against vascular endothelial growth factor) has only modest single-agent activity in HCC. Efficacy was shown in a phase 2 trial in patients with nonmetastatic HCC, but it is not considered a standard of care at this time. Bevacizumab has also been assessed in combination with a variety of chemotherapeutic agents, including gemcitabine and oxaliplatin (GEMOX), and capecitabine and oxaliplatin (CAPOX). There have been early signals of efficacy, but no phase 3 data are yet available, and use should be restricted to the context of ongoing clinical trials.
  - Sunitinib is an orally active multikinase inhibitor that targets a variety of angiogenic proteins in addition to vascular endothelial growth factor receptor (VEGFR), including platelet-derived growth factor receptors, KIT, RET, and FLT3. Despite an efficacy signal in a phase 2 study, a randomized phase 3 study revealed decreased activity and increased toxicity in comparison with sorafenib in initial systemic treatment of advanced HCC.
  - Brivanib is a potent and selective inhibitor of VEGFR and fibroblast growth factor. It revealed promising activity in second-line therapy for advanced HCC, but a pivotal phase 3 trial proved negative.
  - Erlotinib (Tarceva), a small molecule inhibitor with specificity for EGFR, thought to be an important initiator of intracellular signaling in HCC, has shown limited activity in clinical trials so far.
  - Cetuximab (Erbitux) is an MoAb that binds to EGFR, but has not evidenced any single-agent activity in HCC.
  - Everolimus (Afinitor) is a mammalian target of rapamycin inhibitor, which showed promise as a single agent in a large phase 2 trial for second line therapy of advanced HCC, but the recent phase 3 registration study did not meet its endpoint of improved survival after sorafenib failure.
  - Tivantinib is a selective inhibitor of the mesenchymal–epithelial transition receptor and has shown promising activity in a phase 1 study in HCC patients—late phase trials are currently accruing.

HEPATOCELLULAR CARCINOMA SCREENING

- Patients at high risk for developing HCC should be entered into surveillance programs incorporating liver ultrasonography every 6 months. The surveillance interval does not need to be shortened for patients at higher risk for HCC.
  - Patients said to be at high risk are Asian male hepatitis B carriers over age 40, Asian female hepatitis B carriers over age 50, hepatitis B carriers with a family history of HCC, sub-Saharan Africans with hepatitis B, African-Americans with hepatitis B, cirrhotic hepatitis B carriers, patients with all-cause cirrhosis.
  - Patients on a liver transplant waiting list should also be screened for HCC. Development of HCC beyond the Milan/Mazzaferro criteria will make these patients ineligible for liver transplant. If HCC is detected at an early stage in these patients, exception points may be awarded, resulting in an expedited liver transplant.
- IFN-α reduces the onset of liver damage and its progression to cirrhosis in 10% to 30% of patients with chronic hepatitis B.
- Statin use has been associated with a lower risk of HCC among patients with HBV. This was demonstrated in a population-based study from China that included 33,413 patients with HBV57.

REVIEW QUESTIONS

1. A 57-year-old man with a known history of hepatitis C and cirrhosis reports to the ER with progressive right upper quadrant pain, abdominal swelling, and fatigue. Ultrasound reveals a 4 cm lesion in segment 7 of the liver and ascites. Laboratory data reveal a normal bilirubin, low albumin (2.8 g/dL), low platelets (68,000/mm^3), and normal creatinine (1.1 mg/dL). He is admitted for ascites management. Serum AFP is elevated at 420 ng/mL. Liver MRI is performed and reveals a hypervascular 3.9 cm solitary lesion in segment 7, with washout on the venous phase, and background cirrhosis. There is splenomegaly and radiographic evidence of portal hypertension, but no overt portal vein clot. What is the appropriate next step in management?

A. Core needle biopsy of segment 7 liver lesion
B. PET scan for further staging
C. Liver resection
D. Refer for liver transplant workup

2. A 48-year-old man with a long history of hepatitis B, but no overt cirrhosis is referred to a tertiary care hospital with a new diagnosis of HCC. He presented with multifocal, hypervascular liver masses, portal lymphadenopathy, and an adrenal lesion. Serum AFP was mildly elevated at 45 ng/mL, and a biopsy of one of the masses confirmed poorly differentiated HCC. His performance status is ECOG 1. What is the most appropriate initial therapy for this patient?

A. Refer to hospice
B. Initiate sorafenib therapy
C. Debulking surgery
D. Refer for TACE and possible liver transplant workup

3. A 52-year-old woman with a long history of diabetes mellitus, obesity, and hypercholesterolemia is diagnosed with multifocal HCC at an outside hospital. The HCC is biopsy confirmed, and her underlying liver revealed significant fatty infiltration on pathologic assessment. She is advised to undertake first-line therapy with sorafenib, but presents to your multidisciplinary clinic for a second opinion. Staging workup confirms five discrete nodules, involving both right and left lobes of the liver, with the largest measuring 6 cm in maximal diameter, and background steatohepatitis. There are no extrahepatic lesions on her imaging studies. Child-Pugh score is A on today's assessment, and ECOG performance status is 0. What is the appropriate first-line treatment for this patient?

A. Sorafenib
B. TACE/TAE
C. Clinical trial of systemic chemotherapy
D. Liver resection

4. A 60-year-old man, with a history of hepatitis B, was recently diagnosed with a solitary 8 cm HCC in segment 7 of his liver. He had preserved liver function and minimal medical comorbidities, and so was advised to undergo liver resection after his staging workup revealed no evidence of extrahepatic disease. His surgery is successful, with final pathology revealing an 8.2 cm moderately differentiated HCC with segmental portal venous invasion. His margins are clear and three portal lymph nodes revealed no evidence on nodal disease. He comes to see you in the clinic to discuss adjuvant therapy. What would you recommend?

A. Adjuvant XRT to the tumor bed
B. Adjuvant sorafenib therapy for 1 year
C. No adjuvant therapy, surveillance only
D. Refer for liver transplant workup

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8

Colorectal Cancer

Jennifer M. Duff and Thomas J. George, Jr.

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.
- Nearly 142820 new cases of CRC (72% colon; 28% rectal) were diagnosed in 2013 in the United States, and one-third will die as a result of the disease.
- The lifetime risk of developing CRC for both men and women is 5%.
- Surgery will cure almost 50% of all diagnosed patients; however, 40% to 50% of newly diagnosed CRC cases will eventually develop metastatic 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 (2.3% decrease from 1998 to 2004) as a result of prevention and early detection of disease through effective screening programs and effective adjuvant therapies.

RISK FACTORS

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

- Age: More than 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 more common in African Americans than in whites, and mortality is nearly 45% 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: Two prospective cohort studies show a 1.5-fold increased risk of CRC in people that have a high body mass index (BMI) compared to that in normal.

- 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.
- Micronutrient deficiency: Selenium and vitamins E and D deficiency may increase the risk of cancer. The role of folate remains unclear.
- Inflammatory bowel disease: Ulcerative colitis increases the risk by 7- to 11-fold, especially with the duration of colitis (8 to 12 years) and with the detection of dysplasia. Crohn's disease is associated with a twofold increased risk of CRC.
- 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 U.S. 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 cancer, 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 age 60. 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's syndrome: Associated with desmoid tumors, osteomas, lipomas, and fibromas of the mesentery or abdominal wall.
- Turcot's syndrome: Involves tumors (esp. medulloblastoma) of the central nervous system.
- Peutz–Jeghers syndrome: Includes non-neoplastic hamartomatous polyps throughout the gastrointestinal tract and perioral melanin pigmentation.
- Juvenile polyposis: Associated with hamartomas in colon, small bowel, and stomach.

Hereditary Nonpolyposis Colorectal Cancer

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

- 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 (e.g., *hMSH2*, *hMLH1*, *hPMS1*, 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 15% to 20% of sporadic colon cancers.

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 American Cancer Society and US Preventative Service Task Force screening guidelines (Table 8.1) are the most widely cited. Starting at age 50, both men and women should discuss the full range of testing options with their physician. 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 inflammatory bowel disease, should be tested earlier and possibly more often.

Virtual Colonoscopy

A virtual colonoscopy, or computerized tomographic colonography, is an emerging technology in which a spiral computerized tomography (CT) scan of the colon is obtained and three-dimensional images are created and reviewed by a radiologist. Specificity for detection of large polyps and cancer appear reasonable, but there is a wide range of sensitivities reported despite improved experience by providers and consistent technology. Patients still require bowel preparation and colonic distension as well as ingestion of oral contrast. Detected abnormalities require investigation with endoscopy.

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is not useful for general CRC screening purposes. CEA has a low sensitivity whereby approximately 60% of cancers are missed. It is routinely recommended in surveillance programs after cancer has been confirmed.

Table 8.1 Recommended Colorectal Cancer Screening Guidelines for Asymptomatic Average-Risk Individuals

Beginning at Age 50, All Patients Should Have *One* of the Screening Options Listed Below.	
Test	**Frequency**
FOBT (every 3 y) plus flexible sigmoidoscopy (every 5 y)	Ongoing
Fecal occult blood test (gFOBT) or fecal immunochemical test (FIT)	Every year
Colonoscopy[a]	Every 10 y
Flexible sigmoidoscopy[b]	Every 5 y
Double-contrast barium enema[b]	Every 5 y
CT colonography (virtual colonoscopy)[b]	Every 5 y

[a]Colonoscopy should be done if the FOBT shows blood in the stool, if sigmoidoscopy results show a polyp, or if double-contrast barium enema studies show anything abnormal. If possible, all polyps should be completely removed during the colonoscopy.

[b]These studies are not endorsed by the USPSTF recommendations.

Composite of American Cancer Society and US Preventative Services Task Force Guidelines. Data from American Cancer Society Guidelines for the Early Detection of Cancer. http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer. Accessed December 29, 2012.

K-*ras* Detection

The K-*ras* gene is mutated in 30% to 50% of CRCs, and the detection in stool represents a potentially powerful screening strategy. This is currently an active area of clinical investigation.

PATHOPHYSIOLOGY

More than 90% of CRCs are adenocarcinomas, the focus of this chapter. Other primary cancers of the colon and rectum include Kaposi's sarcoma, non-Hodgkin's lymphomas, small cell carcinoma, and carcinoid tumors. Although uncommon, metastases to the large bowel include melanoma, ovarian, and gastric cancer. Anatomic location and symptoms at presentation are the primary differences between right colon, left colon, and rectal adenocarcinomas.

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 (i.e., DCC) and the gene deleted in pancreatic 4 (i.e., DPC4).

Colon carcinogenesis also occurs as a consequence of defects in the DNA mismatch–repair system. The loss of *hMLH1* and *hMSH2*, predominantly, in sporadic cancers leads to accelerated accumulation of additions or deletions in DNA. This MSI 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

- Abdominal pain, typically intermittent, and vague
- Weight loss
- Bowel changes for left-sided colon and rectal cancers, including constipation, decreased stool caliber (pencil stools), and tenesmus
- Early satiety
- Fatigue
- Bowel obstruction, perforation, acute, or chronic bleeding, or liver metastasis, all of which contribute to symptom development
- Unusual presentations include deep venous thrombosis, *Streptococcus bovis* bacteremia or endocarditis, and nephrotic-range proteinuria
- Clinical findings include iron-deficiency anemia, weight loss, electrolyte abnormalities, and liver enzyme elevations

Diagnostic Evaluation

- Endoscopic studies provide histologic information, potential therapeutic intervention, and overall greater sensitivity, and specificity.
- 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 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% to 87%) than for detecting nodal involvement (45% to 73%) or the extent of local invasion (~50%). CT scanning is very sensitive for detection of malignant pelvic lymph nodes in rectal cancer as any perirectal adenopathy is presumed to be malignant, since benign adenopathy is not typically seen in this area.
- 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 perirectal adenopathy.
- PET scanning adds little over conventional imaging in the initial staging and diagnosis of CRC in the absence of abnormalities seen on CT scan.
- Endoscopic rectal ultrasound (EUS) is a valuable tool in the preoperative evaluation of rectal cancer, with high accuracy of determining the extent of the primary tumor (63% to 95%) and perirectal nodal status (63% to 82%).

STAGING

The seventh edition of the American Joint Committee on Cancer Staging for CRC uses the 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 staging remains the most important determinant of prognosis (Table 8.2) with similar outcomes for both colon and rectal cancers in the modern era. Other prognostic variables that have been proposed to be associated with an unfavorable outcome include

- Advanced age of patient
- High tumor grade
- High CEA level
- Bowel obstruction or perforation at presentation
- Several biochemical and molecular markers such as elevated thymidylate synthase, p53 mutations, or loss of heterozygosity of chromosome 18q (DCC gene) may be associated with a worse prognosis. MSI caused by a defective DNA mismatch–repair system (e.g., altered *MLH1*, *MSH2*; associated with Lynch Syndrome) is associated with an improved outcome for patients with node-negative disease

MANAGEMENT ALGORITHM

Surgery

- For colon cancers, the primary curative intervention requires en bloc extirpation 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.

Table 8.2 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.

- 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) 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 (LAR) versus an abdominoperineal resection (APR). The latter generates a permanent colostomy. For highly selected very early-stage rectal cancer cases, transanal endoscopic microsurgery may be a reasonable option.
- Surgical intervention is indicated if polypectomy pathology reveals muscularis mucosal 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 disease-free survival (DFS) have been reported in retrospective series of patients with T4 lesions or perforations, nodal disease, and subtotal resections, who have been treated with 5,000 to 5,400 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.
- In contrast, RT is routinely utilized in rectal cancers to reduce local recurrence and improve resectability.

Pivotal Adjuvant Chemotherapy Studies for Colon Cancer

Intergroup 0035

This large Intergroup trial of 5-fluorouracil (5-FU) and levamisole (Lev) is of historic importance because it reported a 41% reduction in the relapse rate and a 33% decrease in overall cancer mortality. 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.

Intergroup 0089

Intergroup 0089 randomized 3,759 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.

The 5-year DFS and overall survival (OS) for each of the four arms in the study were as follows:

- 5-FU + Lev for 12 months; DFS = 56%, OS = 63%
- 5-FU + high-dose LV (Roswell Park) for 8 months; DFS = 60%, OS = 66%
- 5-FU + low-dose LV (Mayo) for 6 months; DFS = 60%, OS = 66%
- 5-FU + LV + Lev; DFS = 60%, OS = 67%

X-ACT

Utilization of an oral fluoropyrimidine (capecitabine) was evaluated in patients with stage III disease. Capecitabine (1,250 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 arm was noninferior and demonstrated a trend toward superiority in DFS (64% vs. 60%; HR 0.87; 95% CI 0.75 to 1.00; $P = 0.0526$). Toxicity was improved 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 demonstrated equivalency to the conventional 5-year OS benchmark and serves as an acceptable endpoint.

MOSAIC

In Europe, 2,219 patients with stage II (40%) and III (60%) disease 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 to 0.92; $P = 0.002$). 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 to 0.97; $P = 0.023$). 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, with only 0.7% being associated with fever. Anticipated grade 3 peripheral neuropathy or paresthesias were observed (12%) which almost entirely resolved 2 years later (0.7%).

NSABP C-07

The addition of oxaliplatin to three cycles of adjuvant Roswell Park 5-FU with LV (FLOX) was evaluated in 2,407 stage II (30%) and III (70%) patients. The combination improved 3-year DFS (76.1% vs. 71.8%; HR 0.80; 95% CI 0.69 to 0.93; $P = 0.003$). Grade 3 diarrhea (38%) and peripheral neuropathy (8%) were significantly worse with FLOX without any difference in treatment-related mortality. MOSAIC and C-07 established doublet adjuvant chemotherapy with fluoropyrimidine and oxaliplatin 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 89803 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 3,500 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 not recommended in the adjuvant setting.

Adjuvant Biologics

Both cetuximab (cmab) and bevacizumab (bev) are biologic-targeted agents (see the metastatic CRC section) that have been shown to improve outcomes when combined with chemotherapy in metastatic CRC and have 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. Results 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 to 1.49; $P = 0.08$), 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 ≥70.

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 the duration of the 6 months of chemotherapy and then for an additional 6 months beyond (total of 1 year of biologic therapy). mFOLFOX plus bev did not significantly improve 3-year DFS compared to mFOLFOX (77.4% vs. 75.5%; HR 0.89; 95% CI 0.76 to 1.04; $P = 0.15$). 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 disappears 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 3,451 patients with high-risk stage II (17%) or stage III colon cancer to either FOLFOX4, FOLFOX4 plus bev, or XELOX 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 to 1.57; $P = 0.02$), and XELOX plus bev versus FOLFOX4 (HR 1.15; 95% CI 0.93 to 1.42; $P = 0.21$) suggesting a potential detriment.

Adjuvant Chemotherapy Regimens for Colon Cancer

Based on these studies, 6 months of adjuvant chemotherapy is recommended for patients with stage III colon cancer. Several acceptable options exist (Table 8.3), with combination regimens offering increased

Table 8.3 Acceptable Adjuvant Chemotherapy Regimens for Stage III Colon Cancer

Name	Regimen and Dose	Repeated (d)	Total Cycles
Mayo Clinic	LV 20 mg/m²/d IV followed by 5-FU 425 mg/m²/d IV days 1–5	28	6
Roswell Park	LV 500 mg/m² IV followed by 5-FU 500 mg/m² IV weekly × 6	8 wk	3–4
Capecitabine	1,250 mg/m² PO twice daily × 14 d	21	8
FOLFOX4	Oxaliplatin 85 mg/m² IV on day 1 followed by LV 200 mg/m²/d IV on days 1 and 2 followed by 5-FU 400 mg/m²/d IV on days 1 and 2 followed by 5-FU 600 mg/m²/d CIVI for 22 h on days 1 and 2	14	12
FOLFOX6	Oxaliplatin 85–100 mg/m² IV on day 1 followed by LV 400 mg/m²/d IV on day 1 followed by 5-FU 400 mg/m²/d IV on day 1 followed by 5-FU 2,400 mg/m² CIVI for 46 h	14	12
FLOX	LV 500 mg/m² IV followed by 5-FU 500 mg/m² IV on days 1, 8, 15, 22, 29, 36 and Oxaliplatin 85 mg/m² IV on days 1, 15, and 29	8 wk	3

There is no role for biologic-targeted therapy or irinotecan-containing regimens in the adjuvant setting at this time.

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

efficacy and toxicity. The use of irinotecan or biologic-targeted therapies in the adjuvant setting is not recommended. Adjuvant chemotherapy should be started within 8 weeks of surgery, if at all possible, with data supporting a delay beyond 2 months may compromise the effectiveness of adjuvant treatment.

Fluoropyrimidines

Reasonable options include 5-FU with LV via the Mayo Clinic or Roswell Park regimen or capecitabine. The toxicity profile of the regimens differs. Myelosuppression and oral mucositis are more common with the daily Mayo Clinic regimen, whereas diarrhea may be more severe with the weekly Roswell Park schedule. Cryotherapy with ice held in the mouth during the 5-FU infusion may help lessen the mucositis associated with the therapy. HFS and diarrhea are primary toxicities of capecitabine.

Oxaliplatin Combinations

Increased efficacy as well as toxicity is seen with the addition of oxaliplatin to either bolus or infusional 5-FU and LV. FOLFOX6 represents a modification to FOLFOX4, which omits the day 2 bolus 5-FU and LV and gives more continuously infused 5-FU over 46 hours, and appears to have activity equivalent to that of FOLFOX4 in the advanced disease setting. It has been incorporated into numerous adjuvant clinical trials given the improved ease of administration.

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:

- The National Surgical Adjuvant Breast and Bowel Project (NSABP) summary of protocols (C-01 to C-04) of 1,565 patients with stage II disease reported a 32% relative reduction in mortality (cumulative odds, 0.68; 95% CI 0.50 to 0.92; $P = 0.01$). 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%; $P = 0.217$) in 1,020 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 (SEER) database and identified 3,700 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 3,239 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 to 0.91; $P = 0.001$) and death (HR 0.82; 95% CI 0.70 to 0.95; $P = 0.008$) 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 to 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 (e.g., 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 defects in the mismatch–repair system (Lynch Syndrome). When these occur at a high frequency (MSI-high) in node-negative colon cancer, it portends a favorable

prognosis. There is controversy as to whether MSI-high 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.

- A commercially available and validated microarray gene expression profile (Oncotype Dx™; Genomic Health, Inc) examines formalin-fixed paraffin-embedded tissue samples from resected colon cancer. Using an 18-gene signature, and excluding patients with MSI-high tumors, a recurrence score can be generated for an individual patient with stage II disease that classify them as low risk (score less than 30; recurrence risk 12%), intermediate risk (score 30 to 40; risk 18%), or high risk (score $\geq$41; risk 22%). Several other expression profiles are also currently under development or validation.

Perioperative 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).

Intergroup 0114

A four-arm study of 1,695 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 chemotherapy in combination with 5,040 cGy of external beam RT (4,500 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.

NCCTG

Both DFS and OS advantages were observed in patients receiving continuous infusion of 5-FU during RT when 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.

German Rectal Cancer Study Group

The benefit of delivering chemoRT in a preoperative (neoadjuvant) fashion was evaluated 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%; $P = 0.006$), but no difference in 5-year OS. Both acute toxic effects (27% vs. 40%; $P = 0.001$) and long-term toxicities (14% vs. 24%; $P = 0.01$) were less common with neoadjuvant treatment. Preoperative chemoRT followed by surgical resection with postoperative 5-FU-based chemotherapy represents a standard for patients with rectal cancer.

NSABP R-04

This phase III, 2×2 noninferiority trial evaluated the substitution of oral capecitabine for infusional 5-FU as well as the intensification of radiosensitization by adding oxaliplatin in stage II and III rectal carcinoma. Over 1,500 patients were randomized into one of four neoadjuvant chemoRT arms. There was no increase in grade 3 to 4 diarrhea with capecitabine versus 5-FU alone, but the addition of oxaliplatin did significantly increase the risk of grade 3 to 4 diarrhea (6.6% vs. 15.4%; $P < 0.0001$). Both fluoropyrimidine alone arms had similar rates of pathologic complete responses, surgical downstaging, and sphincter sparing surgeries, suggesting that capecitabine has similar efficacy to infusional 5-FU. The primary endpoint of local-regional relapse and other survival data is anticipated shortly after press. Additional European studies have also demonstrated similar outcomes for using capecitabine as a substitute for infusional 5-FU in rectal cancer patients without benefit from intensification by adding oxaliplatin.
"Attempts to identify novel radiosensitizers with companion biomarkers for rectal cancer are ongoing."

Combined-Modality Options for Rectal Cancer

1. Neoadjuvant therapy (chemoRT):
   - Continuous infusion 5-FU (1,000 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 OR oral capecitabine 825 mg/m^2 twice daily given Monday through Friday on days of RT concurrent with external beam RT given in 180 cGy fractions to a total dose of 5,040 cGy
2. Followed by surgery adhering to total mesorectal excision standards
3. Adjuvant systemic therapy for 4 months upon recovery from surgery:
   - 5-FU bolus (500 mg/m^2/day) on days 1 to 5 repeated every 28 days for four cycles. Given the previously discussed data for adjuvant chemotherapy regimens in colon cancer, several different regimens (see Table 8.3) may also be considered in select cases as components of the systemic adjuvant chemotherapy phase of therapy in rectal cancer

FOLLOW-UP AFTER ADJUVANT 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 extirpation, 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 COLORECTAL CANCER

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 2 years 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.

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 3 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.

Oxaliplatin

Oxaliplatin is an agent that differs structurally from other platinums in its 1,2-diaminocyclohexane (DACH) 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 (i.e., peripheral neuropathy, laryngopharyngeal dysesthesias, and cold hypersensitivities), oxaliplatin lacks the emetogenic and nephrogenic toxicities of cisplatin.

Oxaliplatin was initially approved for second-line therapy in metastatic CRC based on a study comparing FOLFOX4 with oxaliplatin alone and with infusional or bolus 5-FU and LV. In this study, response rate, time to progression, and relief of tumor-related symptoms were improved with FOLFOX4, when compared to the other treatment arms. Despite the improved time to progression, the OS difference was not statistically significant (9.8 vs. 8.7 and 8.1 months, respectively).

The North Central Cancer Treatment Group (NCCTG-9741) conducted a trial comparing first-line FOLFOX4 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 FOLFOX4 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 are 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 ($P = 0.99$). Similar survival is observed in patients receiving either sequence and both are acceptable first-line therapies for advanced disease.

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 suggest that irinotecan should not be utilized with bolus 5-FU (i.e., IFL) due to excessive treatment-related mortality.

Irinotecan obtained FDA approval based on a study comparing IFL to the 5-FU bolus Mayo Clinic regimen. A higher response rate (39% vs. 21%; $P = 0.0001$) and OS (14.8 vs. 12.6 months; $P = 0.042$) were observed favoring IFL.

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.

Infusional 5-FU with biweekly irinotecan offered improvements in response (35% vs. 22%; $P < 0.005$), median survival (17.4 vs. 14.1 months; $P = 0.031$), and quality of life over 5-FU.

Neutropenia was equivalent to that found in the weekly irinotecan regimen, although febrile neutropenia and diarrhea were markedly reduced.

As monotherapy, irinotecan every 3 weeks produced responses in 13.7% of patients and stable disease in another 44% of cases. In patients who are refractory to 5-FU, a median survival of 10.5 months was reported. Administration of weekly irinotecan alone has also been reported by Pitot et al. In patients receiving 5-FU earlier, a 13% response rate and an 7.7 median response duration were observed.

Anti-VEGF Therapies

Bevacizumab is a recombinant humanized antivascular endothelial cell growth factor (VEGF) monoclonal antibody with amino acid sequence similarity of 97% to that of human IgG1. Bev blocks VEGF-induced angiogenesis with a high affinity for VEGF, preventing it from binding to VEGF receptors. One of the initial trials with bev in untreated CRC patients combined bev with weekly bolus 5-FU and LV. Interestingly, a 40% response rate and 21.5-month median survival was observed. The major toxicities included arterial thrombosis (13 patients with three treatment discontinuations and one patient death), proteinuria, and hypertension. Updated toxicity data reveal that full-dose anticoagulation can be administered with bev and that there is no increased risk of deep venous thrombus formation. When added to IFL, bev increased the response rate (45% vs. 35%; $P = 0.004$) and had a longer median survival (20.3 vs. 15.6 months; $P < 0.001$). When added to FOLFOX in the second-line setting, response rates are again increased (23% vs. 9%; $P < 0.001$) along with OS (12.9 vs. 10.8 months; $P = 0.0011$). Bev has been approved by the FDA for the treatment of patients with advanced CRC in combination with any intravenous 5-FU-based regimen. The optimal duration of treatment remains controversial but continuation of anti-VEGF therapy through lines of sequential therapy may provide a slight improvement in disease control.

Ziv-aflibercept is a fully humanized recombinant fusion protein that blocks angiogenesis by binding to VEGFA, VEGFB, 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 1,226 metastatic patients with CRC after an oxaliplatin-based regimen to second-line therapy with FOLFIRI plus ziv-aflibercept or placebo. Median survival of FOLFIRI plus ziv-aflibercept was statistically superior to FOLFIRI (13.5 vs. 12 months; HR 0.87; 95% CI 0.713 to 0.937; $P = 0.0032$) as was progression-free survival (6.9 vs. 4.7 months; $P < 0.0001$).

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; $P = 0.0052$).

Antiepidermal 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 metastatic CRC. Importantly, tumor EGFR positivity by immunohistochemistry staining does not correlate with treatment response; however, K-*ras*, and likely 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-*ras* (40%) and B-*raf* (6%) have high concordance between primary and metastatic CRC tumors (in excess of 90%), with recommendations for testing these at the time of metastatic diagnosis. Of note, B-*raf* mutation also appears to be prognostic with a more aggressive clinical course, shortened progression-free intervals, and overall reduced survival. Commercial testing for both mutations is available.

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 survival has been consistently noted with agents in this class with investigation underway to prospectively test the dose-to-rash response relationship.

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%; $P = 0.0074$) and time to progression (4.1 vs. 1.5 months; $P < 0.0001$) 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 1,217 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 to 0.99; $P = 0.048$) 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 this mutation is 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 to 0.66; $P < 0.0001$), although no OS advantage was noted. This agent also has data supporting improvements in PFS when combined with FOLFIRI in the second-line treatment.

CHEMOTHERAPY REGIMENS FOR METASTATIC CRC

See Tables 8.3 and 8.4. Investigations into the optimal timing, role of maintenance therapy, and sequence of treatment combinations both with and without EGFR and VEGF inhibition continue.

Table 8.4 Select Chemotherapy Regimens for Advanced Colorectal Cancer[a]

Name	Regimen and Dose	Repeated (d)
XELOX	Oxaliplatin 100–130 mg/m^2 IV on day 1 Capecitabine 850 mg/m^2 PO twice daily on days 1–14	21
Irinotecan	300–350 mg/m^2 IV	21
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 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 2,400 mg/m^2 CIVI for 46 hours	14
Bevacizumab[b]	5 mg/kg IV on day 1	14
Ziv-aflibercept	4 mg/kg IV on day 1	14
Cetuximab[c,d]	400 mg/m^2 IV on day 1 followed by 250 mg/m^2 IV weekly thereafter	weekly
Panitumumab[d]	6 mg/kg IV on day 1	14
Regorafenib	160 mg PO once daily for 21 d	28

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

[a]These are in addition to those presented in Table 8.3.

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

[c]Alone or in combination with irinotecan-based regimens

[d]Only indicated for patients with K-*ras* and/or B-*raf* wild-type tumors.

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 (i.e., 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%; $P = 0.06$). 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 to 34.8) for the entire cohort. 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 FOLFOX4 chemotherapy pre- and postresection compared to surgery alone. However, attention must be paid to the potential hepatotoxicity and surgical complications from prolonged perioperative chemotherapy. Importantly, systemic chemotherapy fails to sterilize hepatic metastases, even if radiographic complete response is noted. The role of targeted therapies in the perioperative setting is an area of active investigation.

REVIEW QUESTIONS

1. A 64-year-old woman complains of fatigue and 10 lb weight loss over the last 4 months. She denies any cough or abdominal pain, but reports occasional bright red blood per rectum after a bowel movement that she attributes to hemorrhoids. She is otherwise healthy and family history is noncontributory. She is a lifelong nonsmoker but has not seen a physician in 10 years. Her physical examination is unremarkable, except for some external nonbleeding hemorrhoids noted on digital rectal examination. Her lab tests including the comprehensive metabolic panel are within normal limits. A complete blood count shows hemoglobin 10.2 g/dL, mean corpuscular volume (MCV) of 73 fL, platelets 600,000/μL, and normal WBC count and differential. What is the next best test that should be performed?
   - **A.** Mammogram
   - **B.** Bone marrow biopsy
   - **C.** Colonoscopy
   - **D.** Positron emission tomography (PET) scan
   - **E.** Stool fecal occult blood test (FOBT or FIT)
2. A 43-year-old male presents with 2 months of intermittent dark-colored stools and shortness of breath with exertion. His personal medical history is unremarkable. His father was diagnosed with colon cancer at age 55, his paternal uncle died from colon cancer at age 52, and his sister

(*continued*)

had endometrial cancer at age 48. He has a microcytic anemia. Esophagogastricduodenoscopy is unremarkable. Colonoscopy reveals a 3 cm, friable, lesion on the right side of the colon near the hepatic flexure; there are no polyps noted on examination. A biopsy confirms poorly differentiated adenocarcinoma. Which of the following genetic deficiencies is most likely present?

A. BRCA 1 gene
B. APC gene
C. STK11 gene
D. CDH1 (E-cadherin) gene
E. DNA mismatch–repair gene

3. A 61-year-old male underwent surgical resection 4 weeks ago with end-to-end anastomosis for a sigmoid colon adenocarcinoma. The tumor was 2.5 cm across and extended into the muscularis propria, margins were negative. Fifteen lymph nodes were resected; four were positive for adenocarcinoma. A CT scan of the chest, abdomen, and pelvis showed no evidence of distant metastatic disease. He has healed well and is referred to oncology. Which of the following treatment is recommended after surgery?

A. Additional resection with removal of more lymph nodes
B. Adjuvant chemotherapy with a fluoropyrimidine-based regimen followed by radiation to the surgical bed
C. Adjuvant chemotherapy with a fluoropyrimidine-based regimen
D. Adjuvant RT to the surgical bed
E. No further treatment indicated

4. A 58-year-old male is evaluated for several months of fatigue, abdominal pain, lower back tenderness, and 25 lb unintentional weight loss. Examination is notable for tender hepatomegaly and no focal neurologic deficits. Laboratory tests reveal a total bilirubin 3 mg/dL, direct bilirubin 2.2 mg/dL, AST 72 units/L, ALT 65 units/L, alkaline phosphatase 212 units/L, creatinine 0.8 mg/dL. CEA is elevated at 478. A CT chest, abdomen, and pelvis shows multiple, hypodense lesions in the right and left hepatic lobes; small, bilateral pulmonary nodules; and scattered destructive lesions in the lumbar vertebrae. A biopsy of a liver lesion confirms poorly differentiated adenocarcinoma, CK20 positive, CK7 negative, CDX2 positive, supporting the diagnosis of a colorectal malignancy. A mutational analysis confirms wild-type K-*ras*. He is offered palliative chemotherapy for metastatic colon cancer. Which is NOT an approved biologic agent for this patient's metastatic colon cancer?

A. Bevacizumab
B. Rituximab
C. Panitumumab
D. Cetuximab
E. Regorafenib

5. A 54-year-old woman complains of difficulty passing stool and rectal fullness for 2 months. Her medical history is otherwise negative. Her heme-occult stool test is positive. A colonoscopy shows a 4 cm rectal mass located 8 cm from the anal verge, and biopsy confirms adenocarcinoma. An endoscopic ultrasound shows the lesion penetrates through the muscularis propria and four regional lymph nodes are involved. A CT of chest, abdomen, and pelvis does not reveal any overt distant metastases. What is the recommended treatment for her rectal cancer?

A. Surgical resection followed by adjuvant chemotherapy and radiation
B. Neoadjuvant combined chemotherapy and radiation followed by surgical resection
C. Definitive chemotherapy and radiation therapy
D. Neoadjuvant combined chemotherapy and radiation, surgical resection, then postoperative chemotherapy
E. Transanal mucosal resection of cancer

Suggested Readings

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9

Pancreatic Cancer

Austin Duffy, Christopher Ryan Heery, and Tim F. Greten

EPIDEMIOLOGY

- In 2012, an estimated 43,920 new cases of pancreatic cancer were diagnosed with 37,390 individuals dying from this disease.
- Pancreatic cancer remains the fourth leading cause of cancer death in the United States.
- There is a slight male predominance (1.3:1) and a variation in risk according to both race and family history. African Americans are at a higher risk for developing pancreatic cancer and have higher mortality rates. It is estimated that between 3% and 16% of cases have a familial component.
- Cigarette smoking is perhaps the most important environmental risk factor. The risk decreases following cessation. Other risk factors are chronic pancreatitis, heavy alcohol intake, diabetes, obesity, and physical inactivity. Data regarding diet type and intake of coffee or NSAID medication are inconclusive.
- The peak incidence of pancreatic cancer occurs in the seventh and eight decades of life.

Pathophysiology

The pancreas performs both endocrine and exocrine functions. Most pancreatic malignancies arise from the ductal epithelium of the exocrine pancreas. K-*ras* mutations are present in over 90% of pancreatic cancer, a molecular event which is believed to occur early in tumorigenesis. Other frequent molecular findings comprise loss of the tumor suppressor genes DPC4 and p16. Other primary pancreatic tumors are listed in Table 9.1. Intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms follow a more indolent course in general. Patients with IPMN are at increased risk of developing invasive adenocarcinoma and may also be at risk for the development of extra-pancreatic malignancies.

Clinical Features

- The majority of pancreatic ductal adenocarcinomas arise from the head of the pancreas, frequently presenting with biliary obstruction and jaundice necessitating stent placement. Pain caused by localized disease is classically described as mid to upper back pain resulting from tumor invasion of the celiac and mesenteric plexi. This can be palliated effectively by celiac axis block.
- Many patients develop some degree of pancreatic insufficiency leading to fat malabsorption and require replacement with exogenous enzymes at mealtime. Anorexia and weight loss are perhaps the most frequent symptoms in pancreatic cancer and nutritional support and supplementation is extremely important. Small bowel obstruction can occur with bulky head of pancreas tumors, often requiring surgical bypass. Glucose intolerance is also a frequent development.

Table 9.1 Primary Pancreatic Tumors

Type	Incidence
Exocrine carcinoma of pancreas	95%
Ductal adenocarcinoma	85–90%
IPMN with invasive component	2–3%
Mucinous cystic neoplasms with invasive component	1%
Pancreaticoblastoma	<1%
Solid and pseudopapillary neoplasm	<1%
Acinar cell	<1%
Mixed (e.g., acinar-endocrine)	–
Endocrine/islet cell carcinoma	5%
Gastrinoma	
Insulinoma	
VIPoma	
Glucagonoma	
Nonfunctional	

STAGING

The American Joint Committee for Cancer/International Union Against Cancer (AJCC/UICC) staging classification of pancreatic cancer is the most widely used staging system. The practical importance of accurate staging is to discriminate between three categories: (1) operable or potentially operable disease; (2) inoperable but localized disease; and (3) metastatic disease. It is noted that in pancreatic cancer—unlike other solid tumors—stage III disease is by definition inoperable.

DIAGNOSIS

- Screening tests: There are no approved screening tests for pancreatic cancer.
- Tumor markers: CA 19-9 is the most useful and frequently measured tumor marker. However, it is relatively nonspecific, being elevated in the presence of jaundice and other upper GI cancers. In addition, between 10% and 30% of patients will never manifest an elevation in this marker. The CA 19-9 may have utility for surveillance following surgery or in the setting of advanced disease; however, changes or trends during treatment are complimentary to management and should not be used to alter therapy.
- Imaging techniques: Imaging techniques include chest radiographs, triphasic abdominal computerized tomography (CT) (with oral water contrast for enhanced imaging), ultrasound, endoscopic retrograde cholepancreatography (ERCP), and endoscopic ultrasound (EUS).
- EUS is excellent for tumor and nodal staging, and also for detecting the presence of portal vein invasion, although it is operator dependent. A major advantage of EUS is the ability to perform fine-needle aspiration (FNA). Hepatic lesions can also be visualized and potentially sampled.
- Pathologic diagnosis may be achieved with ERCP, laparoscopy, peritoneal cytology, or CT-guided biopsy.

MANAGEMENT

For the management of patients with pancreatic cancer the most important considerations relate to both the tumor stage and performance status of the patient. Following either surgical or radiological staging, the patient's disease can be deemed (1) resectable or potentially resectable; (2) locally advanced, inoperable; or (3) metastatic.

Resectable Disease

Surgical removal of locally confined disease is the only realistic curative option. Even in that circumstance, however, the relapse rate is high such that surgical resection (with adjuvant chemotherapy) is viewed by many as deferring rather than eliminating recurrence. Less than 20% of patients with pancreatic cancer have disease that is considered resectable at diagnosis, meaning that the tumor is confined to the pancreas and not encasing the celiac axis or SMA and, at many institutions, not involving the superior mesenteric vein–portal vein confluence. A Whipple or modified, pylorus-sparing procedure is the surgical procedure of choice for pancreatic head tumors. The stomach (distal third), gallbladder, cystic and common bile ducts, duodenum, and proximal jejunum are resected, with resultant pancreatico-, choledocho-, and gastrojejunostomy. The peripancreatic, superior mesenteric, and hepatoduodenal lymph nodes are also staged. Pathologic review of the surgical margins must include assessment of the retroperitoneal margin (space directly adjacent to the proximal 3 to 4 cm of the SMA) by inking the margin and sectioning the tumor perpendicular to the margin. For tumors in the tail of the pancreas, distal pancreatectomy is performed.

Adjuvant chemotherapy: The current standard of care adjuvant chemotherapy for pancreatic cancer consists of either 5-fluorouracil (5-FU) or gemcitabine for 6 months. The major studies which have led to this are as follows:

- The ESPAC-1 trial (Neoptolemos et al. 2004) evaluated four groups of postsurgical patients treated with (1) surgery alone, (2) chemotherapy alone, (3) chemoradiation alone, or (4) chemoradiation followed by chemotherapy. The chemotherapy consisted of 5-FU/leucovorin and the median survival was 20.1 months (95% CI 16.5 to 22.7 months) for those who received chemotherapy and 15.5 months (95% CI 13.0 to 17.7 months) for those who did not receive chemotherapy (HR for death 0.71). Two-year and 5-year survival estimates were 40% and 21%, respectively, among patients who received chemotherapy compared to 30% and 8%, respectively, among patients who received no chemotherapy.
- The RTOG 9704 trial compared gemcitabine and 5-FU in a 442 patient study, all of whom also received adjuvant 5-FU-based chemoradiation. There was a suggested benefit to gemcitabine for patients with tumors in the head of the pancreas for whom the median and 3-year survival was 20.5 months and 31% respectively compared to 16.9 months and 22% in the fluorouracil group (HR 0.82; 95% CI 0.65 to 1.03; $P = 0.09$).
- The CONKO-1 study was a straightforward comparison of gemcitabine versus observation. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.0% in the gemcitabine group versus 8.5% and 6.5% in the observation group, respectively. Gemcitabine significantly improved median overall survival (22.8 months vs. 20.2 months; $P = 0.005$). Estimated survival at 3 and 5 years was 36.5% and 21.0% for the gemcitabine-treated group compared to 19.5% and 9.0% for the observation group.
- The European Study Group for Pancreatic Cancer (ESPAC)-3 trial directly compared 5-FU and gemcitabine in resected disease and found that there was no difference in survival (23 months vs. 23.6 months; $P = 0.39$).

Adjuvant chemoradiation: The role of radiation postpancreatectomy is controversial given the systemic nature of the disease when it recurs. A potential role for radiation is argued for the high risk of locoregional recurrence and the attendant morbidity of this. The data are conflicting however and derive mainly from older studies:

- The Gastrointestinal Study Group (GITSG) trial randomized patients to chemoradiation with maintenance chemotherapy ($n = 21$) versus surgery alone ($n = 22$). The chemoradiation arm consisted of split-course 4,000 cGy radiation in combination with bolus 5-FU. The chemotherapy was subsequently administered for up to 2 additional years. A significantly prolonged median survival of 20 months for the patients treated with chemoradiation versus 11 months for controls was observed.
- The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 218 patients with pancreatic or ampullary tumors to adjuvant 5-FU-based chemoradiotherapy (but no maintenance chemotherapy) or surgery alone. Although there was a trend toward a survival benefit for the treatment arm with median survivals of 17 and 13 months in the treatment and observation groups, respectively, and 5-year survival estimates of 23% and 10%, respectively, this was not statistically significant.

– The design of the ESPAC-1 study, mentioned above, allowed for a comparison of patients who received adjuvant chemoradiation and those who did not. There was no benefit for those patients who underwent chemoradiation, and in fact chemoradiation appeared to be detrimental. The median survival was 15.9 months (95% CI 13.7 to 19.9) among the 145 patients who were assigned to chemoradiotherapy and 17.9 months (95% CI 14.8 to 23.6) among the 144 patients who were not assigned to receive chemoradiotherapy (HR for death 1.28; 95% CI 0.99 to 1.66; $P = 0.05$). Two-year and 5-year survival estimates were 29% and 10%, respectively, among patients who received chemoradiotherapy, and 41% and 20%, respectively, among those who did not receive chemoradiotherapy. There have been a number of criticisms of this conclusion, however, especially with regard to the quality control of the radiation delivered.

Locally Advanced Pancreatic Cancer

For disease that is clearly unresectable the major modality of treatment is systemic chemotherapy. The role of radiation therapy (RT) has grown increasingly controversial—as in the adjuvant setting—largely due to a fuller appreciation of the tendency in pancreatic cancer for early systemic progression. An important exception to this, however, is for patients who have pain related to the loco-regional extent of their disease and for whom a definite palliative benefit exists with the use of chemoradiation. The majority of studies evaluating systemic therapy in metastatic disease also include locally advanced, non-metastatic disease. The major studies evaluating chemoradiation in locally advanced pancreatic cancer (LAPC) are as follows:

– A number of small older clinical trials suggested a possible survival benefit for (5-FU-based) chemoradiation compared to radiotherapy alone in this patient population. For example, a trial by the GITSG suggested a benefit for chemoradiation plus chemotherapy compared to chemotherapy alone. The chemotherapy consisted of streptozocin, mitomycin, and 5-FU, and the 1-year survival benefit was 41% compared to 19%.
– In an attempt to address this question in the modern clinical trial era the FFCD–SFRO (Fédération Francophone de Cancérologie Digestive–Société Française de Radiothérapie Oncologique) performed a phase III study—the first for nearly 20 years to address this question—directly comparing chemotherapy and chemoradiation. In this study, 119 patients (of a planned 176) were randomized to undergo induction chemoradiation (with 5-FU 300 mg/m^2/24 h as a continuous infusion, days 1 to 5 every week and cisplatin, 20 mg/m^2/day, days 1 to 5 at weeks 1 and 5) followed by gemcitabine, or straight to chemotherapy with gemcitabine. The study was stopped prior to its full enrollment due to an inferior survival in the chemoradiation group (median survival 8.6 vs. 13 months; $P = 0.014$).
– Recently a similar study was presented comparing gemcitabine alone (1,000 mg/m^2 weekly $\times$ 3 every 4 weeks for seven cycles) to chemoradiation (RT 50.4 GY in 28 fractions plus gemcitabine 600 mg/m^2 weekly $\times$ 6) followed by five cycles of gemcitabine alone (1,000 mg/m^2 weekly $\times$ 3 every 4 weeks). The trial was stopped early due to slow accrual ($N = 74$, out of a planned 316). The median survivals were 9.2 months (95% CI 7.8 to 11.4) and 11.0 months (95% CI 8.4 to 15.5) for the two arms respectively ($P = 0.044$).
– The Groupe Coordinateur Multidisciplinaire en Oncologie (GERCOR) performed a retrospective analysis of 181 patients with locally advanced PAC who had been entered on prior prospective GERCOR studies and who had been offered chemoradiation (at the discretion of the investigator), but only if they had remained metastasis-free after a 3-month period. For those patients who were metastasis-free after initial chemotherapy, there was a survival advantage if they proceeded to chemoradiation compared to those who continued with chemotherapy alone (median OS 15.0 and 11.7 months, respectively; $P = 0.0009$). These data suggest that chemoradiation may offer a survival benefit in selected patients who have disease that remains localized after a test of time.

Metastatic Disease

The majority of patients present with advanced disease and for these patients systemic therapy is the major modality of treatment. Compared to best supportive care, chemotherapy has been shown to prolong survival in patients with advanced pancreatic cancer, a conclusion based on a meta-analysis of over 50 studies. The major consideration in the management of metastatic disease is the performance status

of the patient which has been shown in multiple studies and meta-analyses to be in itself a powerful predictor of outcome. While progress has been slow there have been a few developments of note and the narrative pertaining to these is as follows:

- Gemcitabine is a nucleoside analog whose cornerstone role in pancreatic cancer was established in 1997 following a phase III study which demonstrated an improvement in clinical benefit and survival (a secondary endpoint in the study) compared to 5-FU in patients with advanced pancreatic cancer who had received no prior treatment. More patients treated with gemcitabine had an improvement in clinical benefit response—a composite measure of clinical improvement based on three factors: pain, performance status, and weight change—compared to those treated with 5-FU. There were also (modest) gains in survival (median survival 5.65 vs. 4.41; $P = 0.0025$; and 1-year survival 18% vs. 2% in favor of gemcitabine).
- Following this, efforts focused on combining with other cytotoxics, the majority of which resulted in negative studies. A meta-analysis of randomized trials, however, has indicated a significant survival benefit for combination regimens when gemcitabine was either combined with platinum agents (HR 0.85; 95% CI 0.76 to 0.96; $P = 0.010$) or fluoropyrimidines (HR 0.90; 95% CI 0.81 to 0.99; $P = 0.030$). In a subgroup analysis patients with a good performance status appeared to benefit from cytotoxic combinations (HR = 0.76; 95% CI 0.67 to 0.87; $P < 0.0001$), whereas patients with a poor performance status seem to have no survival benefit from combination chemotherapy.
- The first trial to show a survival benefit for any combination therapy in pancreas cancer and which led to FDA approval of this combination in the front-line treatment of pancreas cancer in 2005 was a study by Moore et al., in which 569 patients with untreated locally advanced or metastatic pancreas cancer were randomized to receive gemcitabine with either erlotinib or placebo. There was a very modest but statistically significant improvement in progression-free (HR 0.77; 95% CI 0.64 to 0.92; $P = 0.004$) 1-year survival (23% vs. 17%; $P = 0.023$) and median overall survival (6.24 months vs. 5.91 months, HR 0.82; 95% CI 0.69 to 0.99; $P = 0.038$) favoring the erlotinib arm. As has been the experience with EGFR inhibitors in other cancer types, the occurrence of a rash was associated with an improved outcome. The median survival rates for patients with grade 0, 1, and 2+ rashes were 5.3, 5.8, and 10.5 months, respectively, suggesting that although the benefit for the entire cohort is small, a specific subpopulation of patients may benefit significantly from the addition of erlotinib.
- Recently the combination of gemcitabine with albumin-bound paclitaxel formulation demonstrated activity in phase II studies and preliminary phase III results have been reported to be positive for survival.
- In 2011 the standard of care initial management for patients with good performance status changed with the publication of a phase III trial comparing gemcitabine with an intensive polychemotherapy regimen combining oxaliplatin, irinotecan, and 5-FU/leucovorin (FOLFIRINOX). Although there was increased toxicity with the experimental regimen it was associated with an impressive response rate (31.6% vs. 9.4%) and survival advantage (11.1 vs. 6.8 months) compared with gemcitabine.

REVIEW QUESTIONS

1. A 62-year-old male presents to his physician following the onset of jaundice. A CT scan reveals a 3 cm mass in the head of the pancreas with no evidence of metastatic disease. After referral to a surgeon the patient undergoes a Whipple resection. Pathology reveals a moderately differentiated T3 adenocarcinoma of the pancreas. Zero of 14 lymph nodes showed evidence of malignancy. The patient is recovering well. Which statement is TRUE regarding further management?

A. Adjuvant chemotherapy is not indicated as the patient's lymph node resection was negative.

B. Adjuvant chemotherapy is indicated to improve quality of life but it has not been shown to prolong survival in randomized studies.

C. Adjuvant chemotherapy is indicated based on randomized studies showing a small survival benefit compared to placebo.

(*continued*)

2. The following is a standard of care treatment consideration for a newly diagnosed patient of good performance status with metastatic pancreatic cancer to the liver:
- **A.** Gemcitabine alone
- **B.** FOLFIRINOX
- **C.** Gemcitabine and erlotinib.
- **D.** All of the above

3. Which of following statements about Ca-199 is TRUE?
- **A.** Ca-199 is a useful screening tool in pancreatic cancer because it is noninvasive.
- **B.** Ca-199 is particularly useful in patients with jaundice who are suspected of having pancreatic cancer.
- **C.** A rising Ca-199 following surgery for pancreatic cancer should be treated with early chemotherapy in order to prolong survival, even if the CT scan is negative for metastatic disease.
- **D.** Ca-199 has been shown to have prognostic value in both the pre- and postoperative settings.

Suggested Readings

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10

Anal Cancer

Stephen Ko

In the United States, anal cancer represents a rare malignancy and accounts for 2.2% of all gastrointestinal malignancies; 6,230 new cases are diagnosed annually. The incidence has been increasing over the last four decades. The most significant risk factors are sexually transmitted viruses, tobacco smoking, and immunosuppression. Progress has been made over the years in the management of anal cancer. In the 1970s, treatment focused on abdomino-perineal resection (APR). Initially Nigro at Wayne State employed preoperative chemotherapy with 5-FU and mitomycin (MMC) with radiation therapy (30 Gy) to improve on local control. Complete pathologic responses were discovered and ushered in the concept of definitive chemoradiation, which continues to be the mainstay of therapy for localized anal canal cancer.

EPIDEMIOLOGY

The annual age-adjusted rates in the U.S. Surveillance, Epidemiology, and End Results (SEER) registry for 1994 to 2000 had risen to 1.59 per 100,000 for males and 1.84 for females. Cancers of the anus, anal canal, and anorectum are some of the few cancers that are more common in females than in males at nearly all ages. A potential reason for the rise in females may relate to the evolving sexual practices and association with anal HPV infections. Median age at diagnosis is 60 to 65. Advancing age is a risk factor for anal canal cancer. In certain populations such as men who have sex with other men (MSM) and homosexuals, the rate of anal cancer can be as high as 37 per 100,000.

ETIOLOGY AND RISK FACTORS

Several risk factors have been associated with the development of anal cancer:

1. Sexual activity
   a. 10 or more lifetime sexual partners
   b. receptive anal intercourse before the age of 30
   c. history of gonorrhea or syphilis or herpes simplex 2 or chlamydia
   d. history of cervical cancer
2. Human papillomavirus infection. Up to 93% of SCC of the anal canal has been associated with HPV infection. Women are more likely to have an HPV-associated anal cancer than men. Also HPV infection is more common in MSM. HPV 16 and 18 are the most frequently associated strains linked with anal cancer and account for 90% of anal cancers.

3. HIV infection. The effect of HIV infection on the incidence of anal cancer is not known with certainty. It is unknown whether HIV directly affects the pathogenesis or if the impact is through the interaction with HPV.
4. Cigarette Smoking. Case–control studies indicate increased risk in smokers and especially among current smokers.

PATHOLOGY

Anatomy

- The anal canal measures approximately 3 to 4 cm in length. It extends from the anal verge to the puborectalis muscle of the anorectal ring. The dentate line is situated within the anal canal and the histology separates depending on the location above or below the dentate line. Proximal to the dentate, the histology is columnar epithelium, and distal to the dentate, the histology becomes squamous cell epithelium.
- The anal margin has been arbitrarily defined as an area within 5 cm of the anal verge.
- Lymphatic nodal pathways. Drainage proximal to the dentate line follows the distal rectum to the internal iliac lymph nodes (pudendal, hypogastric, and obturator). Drainage from the perianal skin, anal verge, and the region distal to the dentate line follows the superficial inguinal lymph nodes with some flow to the femoral nodes and external iliac lymphatics.

HISTOLOGY

The anus comprises three different histologic types: (1) glandular, (2) transitional, and (3) squamous mucosa. Cancers arising from the transitional or squamous mucosa develop into squamous cell carcinomas.

The basaloid or transitional carcinomas (formerly known as cloacogenic or junctional tumors) develop from the transitional mucosa. Those cancers developing above the dentate line are nonkeratinizing squamous cell carcinomas versus those distal to the dentate line are keratinizing squamous cell carcinomas. Tumors arising from the glandular mucosa of the anal canal develop into adenocarcinomas.

Anal margin tumors develop within the hair-bearing skin distal to the transitional mucosa.

PRESENTATION

Rectal bleeding and anal discomfort are the two most common symptoms and occur in over half of the patients. Pruitus and discharge are other symptoms. Pain can be severe. Changes in bowel habits can be a presenting symptom, especially with proximal anal canal cancers. Patients may be asymptomatic as well.

WORKUP

Workup should include anoscope with biopsy (incisional), digital rectal examination (DRE), inguinal lymph node evaluation (biopsy or FNA of any suspicious lymph nodes), chest CT, abdominal/pelvic CT or MRI. Pelvic examination should be performed on women including screening for cervical cancer. Consider HIV testing and CD4 levels for patients at risk. Consider PET/CT, which may be helpful for diagnosis but may aid in radiation treatment planning. Full chemistries and CBC should be performed as well.

STAGING

Staging is based on the seventh edition of the American Joint Committee on Cancer (AJCC), which employs a TNM system for the staging of anal canal cancers. T stage is based partly upon the size of the primary lesion or the invasion of nearby structures such as the bladder, prostate, vagina, or urethra. The N stage is determined by the presence of perirectal, internal iliac, or inguinal lymph nodes. The M stage is based upon the presence or absence of distant metastases.

PROGNOSTIC FACTORS

- Tumor size. 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.
- Lymph nodes. The presence or absence of lymph nodes also has been shown to impact survival.
- Metastasis. The most significant prognostic risk factor for overall survival is the presence or absence of extrapelvic metastases.
- HIV status. High viral load and low CD4+ count in some series have predicted for survival and local control.
- Other: Hemoglobin levels ≤10 g/L and male gender have impacted prognosis in some studies.

TREATMENT

Surgery

Anal Canal Lesions

In the 1970s, surgical resection with an APR was considered standard of care. APR produced local control rates of 70%, and overall survival rates from 20% to 70% (average 50%). With inguinal lymph node involvement, some series showed 5-year survivals of 10% to 20%. After the 1974 publication by Nigro showing complete pathologic response in three patients treated with chemoradiation, anal cancer patients are rarely treated with upfront surgery, and definitive chemoradiation remains the current standard of care. APR is reserved for salvage after failure with definitive chemoradiation or reserved for management of radiation complications.

Surgery alone with local excision may be considered with small, localized T1N0M0 squamous cell carcinomas of the anal canal. Several small retrospective series have demonstrated good local control and 5-year survival with such an approach. The key to offering local excision is patient selection. Patients with small tumors <2 cm, well differentiated, and no involvement of the sphincter may be considered candidates. Otherwise, chemoradiation should be offered.

Anal Margin Lesions

Early anal margin cancers have traditionally been treated with local excision. Such lesions behave more like a skin cancer, although this concept has never been validated prospectively. Wide local excision has been reserved mostly for well-differentiated T1N0M0 lesions with good local control. In a retrospective review of 48 patients with SCCA of the anal margin were reviewed. Thirty-one patients underwent local excision, and 11 were treated by APR. Local excision provided satisfactory results with a 5-year survival of 88%. However, larger lesions T2 or > or N+ should be treated with definitive chemoradiation.

Radiation Therapy

Since the 1974 Nigro publication, radiation therapy has involved into the primary curative modality for the treatment of anal cancer. Radiation techniques also have evolved over time and varying types of radiation therapy have been used including external beam radiation therapy (3D and intensity-modulated radiation therapy [IMRT]), electrons, and brachytherapy.

Radiation alone has been used to treat early anal cancer (T1–T2N0M0) with relative success; most retrospective studies have demonstrated modest local control and 5-year survivals; however, not all studies show good local control with radiation alone. Tumors < 2 cm particularly appear to have better local control. NCCN guidelines, however, recommend combined modality for even small T1N0M0 squamous cell carcinomas of anal canal. For the very elderly or those with significant comorbidities, radiation alone may be a reasonable approach.

Combined Radiation Therapy and Chemotherapy

In 1972, Nigro at Wayne State developed the concept of treating anal cancer patients preoperatively in order to decrease APR failures. He employed the Nigro regimen, 5-FU 1,000 m^2 on days 1 to 4 and 29 to 32 and mitomycin-c 10 to 15 mg/m^2 and mitomycin-c on day 1, combined with moderate pelvic RT dose of 30 Gy. With the discovery of three pathologic complete responses after preoperative chemoradiation, the focus changed to preserving the sphincter using chemoradiation and reserving APR for salvage.

Since Nigro's original publication, definitive chemoradiation therapy has become the standard. Several retrospective series have demonstrated the success achieved with chemoradiation therapy in terms of local control and overall survival (Table 10.1).

Radiation Therapy Alone versus Combined-Modality Therapy

Two prospective randomized trials have been conducted that have compared radiation alone versus chemoradiation (Tables 10.2 and 10.3).

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial enrolled patients with T1–T4, N0–N3, M0–M1 anal cancer and small number of anal margins patients and demonstrated improved local control and colostomy-free survival (CFS) with combined modality treatment (CMT) but no statistical difference in overall survival. Even for early anal cancer patients (T1–T2N0M0), there appeared to be a benefit favoring CMT on multivariate analysis.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a similar trial comparing radiation alone to radiation with chemotherapy (5-FU and MMC), which also demonstrated an advantage toward CMT. This trial enrolled locally advanced anal canal cancer patients, T3–T4, N0–N3, M0. Again, CMT showed a statistically significant advantage for CMT in terms of local control, colostomy rate, and disease-free survival (DFS) but not for overall survival.

Thus, both the UKCCCR and EORTC trials established the principle that combined modality is superior to single modality radiation alone.

Table 10.1 Selected Chemoradiation Trials

Trial	No. of Patients	Eligible Patients	Median f/u	Radiation	Chemo	LF	OS
Cummings et al.	66	T1–T4, N0/N+	24 mo	48–50 Gy/ 24–25 fxs	5-FU/MMC or 5-FU	26/65 (40%)	64%
Doci et al.	56	T1–T3, N0 /N+	49 mo	54–60 Gy/ 30–33 fxs split-course	5-FU/MMC	12/49 (24%)	81%
Sischy et al.	76	T< 3 cm T≥ 3 cm	32 mo	40.8 Gy/ 4.5–5 wk	5-FU/MMC	4/26 (15%) 18/50 (36%)	85% at 3 y 68% at 3 y
Allal et al.	68	T1–T4, N0/N+	48 mo	50–55 Gy 30 Gy EBRT+ 20 Gy brachy	5-FU/MMC	22/68 (32%)	65%
Martenson et al.	50	T1–T4, N0/N+	N/A	50–53 Gy	5-FU/MMC	20%	58%

fx, fraction of radiation; f/u, follow-up.

Table 10.2 Randomized Phase III Trials—Design

Trial	No. of Patients	Eligible Patients	Design	Chemo	RT Details	Break/Gap	1° End-point
UKCCCR (1987–1994)	585	T1–T4, N0–N3 M0–M1	RT vs. CRT	MMC 12 mg/m^2 day 1, 5-FU 1,000 mg/m^2 days 1–4, 29–32	45 Gy/25#/33 d 6 wk gap 15 Gy boost	6 wk after 45 Gy	LF
RTOG-8704/ ECOG (1988–1991)	291	T1–T4 N0–N1 M0	5-FU/RT vs. 5-FU/MMC/RT (if biopsy is +, 5-FU/ CDDP + RT)	MMC 10 mg/m^2 days 1 and 29 5-FU 1,000 mg/m^2 days 1–4, 29–32	45–50.4 Gy/25–28# if biopsy is +, then 9 Gy boost	4- 6 wk after 45–50.4 Gy if biopsy is +	DFS
RTOG 98–11 (1998–2005)	644	T2–T4 N0–N3 M0	Neoadj CDDP/5-FU then CDDP/5-FU/RT vs. 5-FU/MMC/RT	Neoadj with CDDP 75 mg/m^2 5-FU 1,000 mg/m^2 days 1–4 then CRT 5-FU/CDDP vs. CRT with MMC 10 mg/m^2 days 1–4, 29–32 and 5-FU 1,000 mg/m^2 days 1–4, 29–32	45 Gy/25# over 5–6.5 wk T3/T4, N+, or T2 with residual- received a boost to 54–59 Gy	Max of 10 d gap for skin toxicity	DFS
ACCORD-03 (1999–2005)	307	T ≥ 4 cm or T < 4 cm and N1–N3M0	2 × 2 factorial; Arm A: Neoadj 5-FU/CDDP + Std RT Arm B: 5-FU/CDDP + HD RT Arm C: 5-FU/CDDP + Std RT Arm D: 5-FU/CDDP + HD RT	Neoadj chemo 5-FU 800 mg/m^2 days 1–4 and 29–32, CDDP 80 mg/m^2 days 1 and 29 CRT- 5-FU and CDDP –dose same as neoadj regimen	Arms A and B: 45 Gy/25# to pelvis + std dose boost of 15 Gy or brachy boost (BT) Arms C and D: 45 Gy/25# to pelvis + high-dose boost of 20–25 Gy or BT; 20 Gy boost for CR 25 Gy boost for minor PR; BT: given to tumors involving <½ of the anal canal circumference at diagnosis	3 wk after 45 Gy the std or HD boost was delivered	CFS
ACT II (2001–2008) abstract only	940	T1–T4 N0–N3 M0	2×2 factorial; CDDP/5-FU-CRT vs. MMC/5-FU-CRT then 4 wk later randomized to maintenance CDDP/5-FU or no maintenance	CDDP 60 mg/m^2 on d 1 and 29, 5-FU 1,000 mg/m^2 on d 1–4 and 29–32 CRT vs. MMC 12 mg/m^2 on d 1, 5-FU 100 mg/m^2 on d 1–4 and 29–32 CRT; maintenance chemo × 2 cycles = 5-FU 1,000 mg/m^2 and CDDP 60 mg/m^2	50.4 Gy/28#/38 d	None	RFS

UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; ACT, Anal Cancer Trial; RT, radiation therapy; 5-FU, 5-fluorouracil; MMC, mitomycin C; CDDP, cisplatin; CRT, chemoradiation; Std RT, standard dose radiation therapy; HD RT, high-dose radiation therapy; LF, local control; LRF, local-regional failure; DFS, disease-free survival; CFS, colostomy-free survival; RFS, relapse-free survival.

Adapted from Lim F, Glynne-Jones R. Chemotherapy/chemoradiation in anal cancer: a systematic review. *Cancer Treat Rev*. 2011;37:521.

Table 10.3 Randomized Phase III Trials—Results

Trial	No. of Patients	Eligible Patients	Median f/u	LFR	CR	OS	DFS/RFS	Colostomy Rate
UKCCCR (1987–1994)	585	T1–T4, N0–N3 M0–1	12 y	57%-RT 32%-CRT at 5 y $P < 0.0001$	30%-RT 39%-CRT at 6 wk post-therapy	53%-RT 58%-CRT at 5 y 34%-RT 41.5%-CRT at 10 y	38%-RT 56%-CRT DFS at 3 y 34%-RT 47%-CRT RFS at 5 y	37%-RT 47%-CRT CFS at 5 y
EORTC 22861 (1987-1994)	110	T3-T4 N0-N3 M0 or T1-T2 N1-N3 M0	42 mo	50%-RT 32%-CRT at 5 y $P = 0.02$	54%-RT 80%-CRT at 6 wk post-therapy	54%-RT 58%-CRT at 5 y $P = 0.17$	Not available but estimated improvement in DFS by 18% at 5 y	Estimated CFS improvement of 32% at 5 y
RTOG-8704/ ECOG (1988-1991)	291	T1-T4 N0-N1 M0	3 y	16% at 4 y	86%-5-FU 92.2%- MMC at 4-6 wk post-therapy	71%-5-FU 78.1%-MMC	51%-5-FU 73%-MMC $P = 0.0003$ DFS at 4 y	59%-5-FU 71%-MMC $P = 0.014$ CFS at 4 y 22%-5-FU 9%-MMC $P = 0.002$
RTOG 98-11 (1998-2005)	682	T1-T4, N0-N3 M0-1	Updated analysis as of February 27, 2011	71.9%-MMC 65%-CDDP at 5 y $P = 0.087$	30%-RT 39%-CRT at 6 wk post-therapy	78.3%-MMMC 70.7%-CDDP at 5 y $P = 0.026$	67.8%-MMC 57.8%-CDDP DFS at 5 y $P = 0.006$	71.9%-RT 65%-CRT CFS at 5 y $P = 0.05$
ACCORD-03 (1999-2005)	307	$T \geq 4$ cm or $T < 4$ cm and N1–N3M0	50 mo	A: 72% B: 87.6% C: 83.7% D: 78% at 5 y	A: 92% B: 97% C: 86% D: 94%	A/B: 74.5% C/D: 71% OS at 5 y $P = 0.81$ A/C: 71% B/D: 74% OS at 5 y $P = 0.43$	A: 63.8% B: 78.1% C: 66.8% D: 62.3% TFS at 3 y	A: 69.6% B: 82.4% C: 77.1% D: 72.7% CFS at 5 y
ACT II (2001–2008)	940	T1–T4 N0–N3 M0	3 y	11% MMC 13% CDDP	94% 5-FU/MMC/RT vs. 95% 5-FU/CDDP/RT 12 wk post-therapy	85% with maintenance 84% without maintenance OS at 3 y; $P =$ nonsig	75% MMC 75% CDDP DFS at 3 y; $P =$ nonsig	5% with maintenance 4% without maintenance; $P =$ nonsig

UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; ACT, Anal Cancer Trial; RT, radiation therapy; 5-FU, 5-fluorouracil; MMC, mitomycin C; CDDP, cisplatin; CRT, chemoradiation; Std RT, standard dose radiation therapy; HD RT, high-dose radiation therapy; LF, local control; LRF, local-regional failure; DFS, disease-free survival; CFS, colostomy-free survival; RFS, relapse-free survival; f/u, follow-up.

Adapted from Lim F, Glynne-Jones R. Chemotherapy/chemoradiation in anal cancer: a systematic review. *Cancer Treat Rev*. 2011;37:522.

Value of MMC in the Combined-Modality Regimen

Due to the hematologic toxicity of MMC in CMT, two prospective phase III trials (RTOG/ECOG 8704 and RTOG 98-11) have evaluated the importance of MMC (Tables 10.2 and 10.3).

RTOG/ECOG 8704 was the first randomized trial to evaluate prospectively the importance of MMC in CMT and compared 5-FU and MMC with RT (standard arm) versus 5-FU and RT (experimental arm). The primary endpoint was DFS. At 4 years, DFS was 73% for 5-FU and MMC compared to 51% for 5-FU. Colostomy rate was 22% with 5-FU vs. 9% with 5-FU, MMC ($P = 0.002$). Despite the higher toxicity of MMC, the authors concluded that MMC was still the preferred regimen, given the higher DFS and lower colostomy rate.

RTOG 98-11 was the second randomized trial to evaluate prospectively the role of MMC in CMT and compared 5-FU and MMC with concurrent radiotherapy (standard arm) versus induction 5-FU and CDDP followed by concurrent 5-FU and CDDP with radiotherapy (experimental arm). The primary endpoint was again DFS. With a median of 2.51 years, the initial report revealed no statistically significant difference in 5-year DFS (60% MMC vs. 54% CDDP), 5-year OS (75% MMC vs. 70% CDDP), 5-year local-regional control rates (25% MMC vs. 33% CDDP) or 5-year distant metastasis (DM) rates (15% MMC vs. 19% CDDP). The cumulative colostomy rate proved to be statistically significantly higher with CDDP, 19% vs. MMC, 10%.

However, the updated RTOG 98-11 examined the long-term impact of treatment on survival (DFS, OS, CFS), as well as colostomy failure (CF), and locoregional failure (LRF), and DM. With longer follow-up, 5-FU/MMC regimen produced statistically significant improvement in DFS and OS for RT + 5-FU/MMC vs. RT + 5-FU/CDDP (5-year DFS; 67.8% vs. 57.8%; $P = 0.006$; 5-year OS, 78.3% vs. 70.7%; $P = 0.026$). There was a trend toward statistical significance for CFS, LRF, and CF. Thus, the authors conclude that RT + 5-FU/MMC remains the preferred standard of care.

ACT III (abstract form only) addressed two questions: (1) whether substituting CDDP for MMC improves the complete response rate and (2) whether two cycles of maintenance chemotherapy (5-FU/CDDP) reduce recurrences. The randomization employed a 2 × 2 factorial, and patients were randomized to 5-FU/MMC with concurrent radiotherapy (standard arm) or CDDP/5-FU with concurrent radiotherapy. Patients were then randomized to receive either two cycles of maintenance chemotherapy (CDDP/5-FU) or no maintenance therapy. At a median follow-up of 3 years, the complete response rate was 94% for MMC and 95% for CDDP ($P = 0.53$). No statistically significant differences in terms of recurrence-free survival and overall survival were noted between the maintenance and the no maintenance arms. The authors again concluded that 5-FU/MMC with RT should remain the standard of care.

The data from ACT III and the updated RTOG 98-11 may seem to contradict one another: the CDDP arm in RTOG 98-11 appears to have a detrimental effect on DFS and OS, whereas the ACT III shows that CDDP may be at least equivalent to that of MMC. However, the trial designs were quite different. RTOG employed the use of neoadjuvant chemotherapy prior to the start of concurrent chemoradiotherapy. The prolongation of the overall treatment time may account for the inferior results of the CDDP arm. However, given the current data available, 5-FU/MMC should remain the standard of care.

Toxicity of Combined-Modality Therapy

Toxicity from CMT can be divided into acute and late effects. A variety of toxicity criteria have been employed in the different randomized trials, which makes analysis difficult (Table 10.4).

Acute Toxicity

Patients typically experience moderate to severe acute toxicities from the combination of both chemotherapy (5-FU and MMC) and radiation therapy. Side effects include nonhematologic toxicities (nausea/vomiting, abdominal pain, increased frequency of stool, diarrhea, skin irritation, fatigue, weight loss) and hematologic toxicities (neutropenia, thrombocytopenia, anemia).

Toxic deaths from CMT have ranged from 0% to 5%). In the UKCCCR study, 6/116 (2%) experienced toxic death, mostly due to septicemia. The EORTC trial reported on 1 toxic death out 110 patients. In the RTOG 8704 study, four patients (3%) experienced death in the MMC arm. More recently, there were no reported toxic deaths in both RTOG 98-11 and ACT II trials. The ACCORD 03 trial, a four-arm randomized trial, showed similar toxic deaths across all four arms (A = 1 [1%], B = 2 [2.6%], C = 3[3%], D = 1[1%]). No patient required an APR for acute toxicity in any of the arms during the induction phase or the concurrent chemoradiation phase.

Table 10.4 Randomized Phase III Trials: Acute Toxicity

Trial	No. of Patients	Eligible Patients	Median f/u	Chemo	Grade 3/4 Hematologic (%)	Grade 3/4 Nonheme (%)	Overall Grade 4 (%)	Overall Grade 5 (%)
UKCCCR (1987–1994)	292	T1–T4 N0–N3 M0	12 y	MMC 12 mg/m^2 day 1, 5-FU 1,000 mg/m^2 days 1–4, 29–32	N/A	N/A	>50%	2
EORTC 22861 (1987–1994)	51	T3–T4 N0–N3 M0 or T1–T2 N1–N3 M0	42 mo	MMC 15 mg/m^2 day 1 5-FU 750 mg/m^2 days 1–5, 29–33	N/A	N/A	1	1
RTOG-8704/ ECOG (1988–1991)	146	T1–T4 N0–N1 M0	3 y	MMC 10 mg/m^2 days 1 and 29 5-FU 1,000 mg/m^2 days 1–4, 29–32	N/A	N/A	23	3
RTOG 98–11 (1998–2005)	325 324	T2–T4 N0–N3 M0	Updated analysis as of February 27, 2011	Neoadj CDDP 75 mg/m^2 5-FU 1,000 mg/m^2 days 1–4 then CRT 5-FU/CDDP vs. CRT with MMC 10 mg/m^2 days 1–4, 29–32 and 5-FU 1,000 mg/m^2 days 1–4, 29–32	MMC 60% CDDP 42%	MMC 74% CDDP 74%	34 20	0 0
ACCORD-03 (1999–2005)	A/B 153 C/D 157	T ≥ 4 cm or T < 4 cm and N1–N3M0	50 mo	Neoadj chemo 5-FU 800 mg/m^2 days 1–4 and 29–32, CDDP 80 mg/m^2 days 1 and 29 CRT- 5-FU and CDDP –dose same as neoadj regimen	Arms A and B: 30.7% Arms C and D: 13%	Arms A and B: 18.8% Arms C and D: 18.5%	Arms A and B: 0.7% Arms C and D: 2%	0
ACT II (2001–2008) abstract only	471 469	T1–T4 N0–N3 M0	3 y	CDDP 60 mg/m^2 on days 1 and 29, 5-FU 1,000 mg/m^2 on days 1–4 and 29–32 CRT vs. MMC 12 mg/m^2 on days 1, 5-FU 100 mg/m^2 on days 1–4 and 29–32 CRT; maint. chemo × 2 cycles = 5-FU 1,000 mg/m^2 and CDDP 60 mg/m^2	25 MMC 13 CDDP	61 MMC 65 CDDP	N/A N/A	N/A N/A

UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; ACT, Anal Cancer Trial; RT, radiation therapy; 5-FU, 5-fluorouracil; MMC, mitomycin C; CDDP, cisplatin; CRT, chemoradiation; f/u, follow-up.

Adapted from Lim F, Glynne-Jones R. Chemotherapy/chemoradiation in anal cancer: a systematic review. *Cancer Treat Rev.* 2011;37:526.

Late Toxicity

Late effects have not been well documented within the randomized trials. Part of the challenge in evaluating late effects is the differing toxicity scales used in the various trials. Early toxicity criteria used in the randomized trials did not allow for characterizing radiation-induced side effects.

Both the early EORTC and UKCCCR did not demonstrate a difference in long-term complications between those receiving CMT vs. RT alone. RTOG 8704 similarly revealed no significance difference in long-term toxicity between RT-5-FU and RT and 5-FU/MMC, although two patients from each arm required stoma secondary to RT-related complications. In the RTOG 9811 update, the most common types of late grade 3 or 4 toxicity included skin, small/large intestine, subcutaneous tissue, or other. There did not appear to be a difference between the MMC or CDDP arms for grade 3/4 toxicity (13.1% vs. 10.7%; $P = 0.35$). In the ACCORD 03 trial, late toxicities were primarily of grade 1 or 2. However, nine patients experienced grade 4 toxicities including necrosis, fistula, bleeding, or pain of whom five were treated with an APR and four underwent colostomy alone.

Chemoradiation in HIV-Positive Patients

HIV-positive patients pose a particular treatment challenge due to their inability to tolerate CMT. Early reports indicated that some patients were receiving less than optimal therapy due to concerns for treatment toxicity. However, patients with a CD4 count of ≥200 can have excellent control of their disease with acceptable morbidity. Those with CD4 counts of <200, however, may require a modification in their treatment regimen such as omission of MMC or a reduction in the RT field and/or dose. UCSF analyzed 17 HIV-positive patients and documented CD4 counts. All nine patients with a CD4 count ≥ 200 had control of their disease. Four patients did require a treatment break of 2 weeks, but no hospitalizations occurred. Among the eight patients with CD4 counts < 200, four experienced lowered blood counts, intractable diarrhea, or moist desquamation. Four of eight ultimately required colostomies for either treatment-related toxicity or for salvage of their disease. Disease, though, was controlled in seven of eight patients. Thus, based on the UCSF experience with HIV-positive patients, one should consider modifying the treatment regimen particularly if CD4 counts are less than 200.

Dose of Radiation

Local-regional failures occur in 20% to 30% after definitive chemoradiation. Because of such local-regional failures, RTOG 92-08, a phase II, dose escalation trial was designed to escalate dose to 59.4 Gy, with a mandatory treatment break of 2 weeks after the initial 36 Gy. The initial study included 47 patients with a mandatory break. The update of RTOG 92-08 analyzed not only the original 47 patients with the mandatory break but also analyzed 20 additional patients who did not have a planned break. Both groups of patients showed no difference in OS or LRF when compared historically to patients on RTOG 87-04 MMC arm. The higher dose likely did not result in improved outcomes because of the treatment break, which may have allowed for tumor repopulation and/or repair of sublethal damage.

The ACCORD 03 trial evaluated both the value of treatment intensification by induction chemotherapy (two cycles of 5-FU and CDDP) and radiation dose escalation by incorporating a 20 to 25 Gy boost in patients with locally advanced anal cancer patients (T2 > 4 cm or T3–T4Nx or any T, N1–N3, M0). The trial was conducted as a factorial 2×2 study (A = ICT; B = ICT +HDRT; C = reference arm = pelvic RT 45 Gy per 25 fractions with two cycles of 5-FU-CDDP + boost of 15 Gy; D = HDRT). High-dose RT (HDRT) incorporated a boost of 20 to 25 Gy. Thus, arms A and C received 60 Gy total and arms B and D received 65 to 75 Gy total. There appeared to be no difference in their primary endpoint of CFS at 3 years, or in any secondary endpoints such as response rate, toxicity, local control, or overall survival.

Although controversy exists regarding the optimal dose, a reasonable approach is to treat between 55 to 59 Gy (RTOG 98-11) if 3D conformal radiation is being contemplated and 54 Gy if dose painting IMRT (DP IMRT) is being employed per RTOG 0529.

Intensity-Modulated Radiation Therapy

IMRT represents a specific radiation technique that requires specific hardware and software and most importantly technical expertise to deliver conformal radiation doses to target volumes and to limit dose to organs at risk (OAR) such as the intestine, rectum, bladder, skin, external genitalia, and bone.

One of the greatest challenges in treating anal cancer is the morbidity from the CMT, and IMRT provides a means to reduce acute toxicity and potentially long-term toxicity. In the future, dose escalation may be possible through IMRT.

Early, single institution, retrospective trials demonstrated encouraging results in reductions in acute toxicity with the use of IMRT (Table 10.5). A multi-institutional phase II trial, RTOG 0529, has confirmed prospectively the reduction in acute toxicities with this technology. The goal of RTOG 0529 was to reduce grade 2+ combined acute GI and GU adverse events of 5-FU and MMC combined with DP IMRT by at least 15% compared with the conventional RT/5-FU/MMC arm from RTOG 98-11. Eligible patients included 52 evaluable, T2–T4N0–N3M0 anal cancers. As the primary endpoint, 77% experienced grade 2+ GI/GU AEs (9811 77%). However, there was a significant reduction in acute grade 2+ hematologic, 73% (98,11 85%; $P = 0.032$), grade 3+ GI, 21% (9811 36%; $P = 0.0082$) and grade 3+ dermatologic, AEs 23% (98,11 49%; $P < 0.0001$) with DP IMRT. Real-time quality assurance was conducted and on pretreatment review found 81% initial plans required replanning due to errors in creating volumes properly. Thus, this trial demonstrated that acute toxicity can be reduced but requires intimate knowledge of anatomy for proper planning and proper delivery. A separate publication regarding the efficacy (2-year local-regional control) and late effects of IMRT is forthcoming. Until further analysis can be performed, IMRT cannot be considered the standard of care. Although if reduced toxicity (acute and long term) is confirmed along with comparable efficacy of conventional radiotherapy, IMRT will become standard practice.

If 3D conformal radiation techniques are employed, patients should receive treatment as per the RTOG 98-11 study. If IMRT is contemplated, the guidelines published by RTOG for contouring the anatomy for GI pelvic tumors should be referenced as well as the RTOG 0529 atlas.

Tumor Regression after Chemoradiation

After patients have completed definitive chemoradiation therapy, patients should be followed up clinically in 8 to 12 weeks after therapy. Cummings demonstrated that mean time for tumor regression was 3 months but regression of a tumor could occur up to 12 months. Thus, if there is persistent disease at 8 to 12 weeks, patients should be followed up closely (every month) to document regression. As long as there is documented regression on serial examinations, patients may continue to be monitored. However, at any point if there is progression, then biopsy followed by salvage APR should be considered.

TREATMENT OPTIONS ACCORDING TO STAGE

Stage 0

- Surgical resection is the treatment of choice for the lesions of the perianal area that does not involve the anal sphincter.

Stage I

- Small, well-differentiated tumors of the anal margin not involving the anal sphincter can be treated with wide local excision.
- All other stage I tumors of the anal margin and anal canal are treated with chemoradiation with 5-FU/MMC.
- Patients who cannot tolerate chemotherapy, such as the very elderly or those with multiple comorbid conditions, may be treated with radiation alone.
- Surgical salvage with APR is reserved for residual cancer in the anal canal after chemoradiation.

Stages II to IIIB

- Chemoradiation with 5-FU/MMC is the recommended initial approach.
- Patients who cannot tolerate chemotherapy may be treated with radiation alone.
- Surgical salvage with APR is reserved for residual disease in the anal canal after chemoradiation.

Table 10.5 Selective IMRT Results (Retrospective + 1 Prospective Trials)

Trial	Number of Patients	Eligible Patients	Median f/u	RT Details	Chemo	LC/CFS	OS	Grade 3/4 Heme (%)	Grade 3/4 Nonheme (%)
Milano et al. 2005	17	T2–T4 N0–N3 M0	20.3 mo	Median 54 Gy/1.8 Gy per fx; Mean 52.3 Gy	MMC 10 mg/m^2 days 1 and 29, 5-FU 1,000 mg/m^2 days 1–4, 29–32	82% LC at 2 y 82% CFS at 2 y	91% at 2 y	38 % gr 4 hematologic toxicity among pts receiving MMC	0
Salama et al. 2007	53	T1–T4 N0–N3 M0	14.5 mo	54 Gy	MMC 10 mg/m^2 days 1 and 22, 5-FU 1,000 mg/m^2 days 1–4, 22–5	83.9% LC at 18 mo 83.7%; CFS at 18 mo	93.4% at 18 mo	30.2% gr 4 leukopenia; 34% gr 4 neutropenia; 39.6% total gr 4	15.1 % gr 3 GI 37.7% gr 3 derm
Pepek et al. 2010	47	Stage I–IV	14 mo (19 mo for SCCA)	Median: 54 Gy/ 1.8 Gy per fx	MMC/5-FU (62%) Capecitabine (9%) None (11%)	90% LRC at 2 y; 82% CFS at 2 y	85% actuarial at 2 y	7% gr 4 leucopenia; 2% gr 4 thrombocytopenia; 18% gr 3 leukopenia; 4% gr 3 anemia	9% gr 3 diarrhea; 2% gr 3 each for N/V, urinary, dehydration
RTOG 0529 Kachnic et al. 2012	52	T2–T4 N0–N3 M0	50.4/ Gy/ 28 fxs for T2N0M0; 54 Gy/ 30 fxs for T3–T4/ N+	N/A	MMC 10 mg/m^2 days 1 and 29, 5-FU 1,000 mg/m^2 days 1–5, 29–33	N/A	N/A	30.8% gr 3 blood/bm; 26.9% gr 4 blood/bm	21% gr 3 GI; 23% gr 3 dermatologic; 1.9% gr 4 dermatologic 3.8% gr 4 pain; 21.1% gr 3 infection 1.9% gr 4 infection

fx, fraction of radiation; f/u, follow-up; gr, grade.

Stage IV

There are limited data regarding the treatment of metastatic disease given the overall rarity of the disease. There are no available phase III data and only very limited phase II prospective data are available. The most widely used regimen is cisplatin plus 5-FU, which is the recommended as first-line therapy by NCCN. Response rates have been as high as 50% to 66% and median survivals of 12 to 34.5 months. Clinical trials should be encouraged. Palliative efforts remain an important component of care.

PERSISTENT OR RECURRENT ANAL CANCER

Surgery with APR is considered the treatment of choice for either persistent or recurrent disease and 20% to 40% of patients may achieve long-term control. For persistent disease, RTOG 8704 treated 22 patients with a 9 Gy boost with 5-FU and CDDP as salvage. Ultimately, 12 of 22 remained disease-free after surgical intervention. Given the limited data, surgery should remain the standard for chemoradiation failures.

Follow-Up

There are no prospective data regarding the optimal follow-up regimen. NCCN suggests the following: DRE, anoscopy, inguinal node palpation every 3 to 6 months for 5 years. For T3–T4 or positive inguinal lymph nodes at diagnosis, one should consider chest/abd/pelvic imaging annually for 3 years.

Prognosis

The National Cancer Database has provided 5-year survival of anal canal carcinoma patients by stage for both squamous and nonsquamous histologies. The database is based on cases diagnosed from 1998 to 1999 and includes 3,598 cases.

For squamous cell histology, the 5-year survival is as follows: stage I = 71.4%, stage II = 63.5%, stage IIIA = 48.1%, stage IIIB = 43.2%, and stage IV = 20.9%. For nonsquamous histology, the 5-year survival is as follows: stage I = 59.1%, stage II = 52.9%, stage IIIA = 37.7%, stage IIIB = 24.4%, and stage IV = 7.4%. The prognosis shows a statistically worst survival stage for stage between squamous and nonsquamous cell histologies, except for stage IIIA.

REVIEW QUESTIONS

1. A 63-year-old female has been diagnosed with a clinical stage IIIA, T2N1M0 squamous cell carcinoma of the anal canal. The patient presented with mild rectal bleeding but otherwise is healthy and has a good performance status, ECOG 1. What is her best treatment option?
   A. Neoadjuvant CDDP + 5-FU followed by concurrent CDDP + 5-FU with RT
   B. Concurrent 5-FU + MMC with RT
   C. Concurrent 5-FU + MMC with RT + adj chemo (5-FU + CDDP)
   D. Concurrent 5-FU +RT
2. A 63-year-old female has been diagnosed with a clinical stage IIIA, T2N1M0 squamous cell carcinoma of the anal canal. The patient asked about her prognosis. What is her estimated 5-year overall survival?
   A. 75%
   B. 30%
   C. 50%
   D. 15%

3. A 44-year-old HIV+ male with a CD4 count of 630 was recently diagnosed with a clinical stage II, T3N0M0 squamous cell carcinoma of the anal canal. The patient is otherwise healthy with an ECOG of 0. What is his best treatment option?
   A. Radiation alone
   B. Radiation with 5-FU
   C. Chemotherapy alone with 5-FU and MMC
   D. 5-FU/MMC with radiation alone
4. A 55-year-old female who was diagnosed with a stage IIIB, T4N1M0 squamous cell carcinoma of the anal canal just completed definitive chemoradiation with 5-FU and MMC with 59 Gy of radiation (45 Gy to the pelvis + 14 Gy boost to the primary tumor). Ten weeks after completing therapy, a DRE is performed. A small nodule remains within the anal canal. What is the patient's best treatment option?
   A. immediate APR
   B. chemotherapy alone with 5-FU and CDDP
   C. 4-week reevaluation with repeat DRE, inguinal node palpation, and anoscope
   D. reirradiation
5. A 67-year-old female with a newly diagnosed, locally advanced squamous cell carcinoma of the anal canal is having a consultation with the radiation oncologist. He is a very fit individual and has a good performance status, ECOG 1. Among his many questions, he inquires what is his chance of dying from the therapy?
   A. 5% to 15%
   B. 0% to 5%
   C. 10% to 20%
   D. 20% to 30%

Suggested Readings

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11

Other Gastrointestinal Tumors

Joleen M. Hubbard

GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal stromal tumors (GISTs), a type of sarcoma, are the most common nonepithelial tumors of the gastrointestinal (GI) tract that arise from precursors of connective tissue cells. Most GI soft tissue neoplasms, previously classified as leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas, are presently classified as GIST on the basis of molecular and immunohistologic features. Approximately 80% to 85% of GIST tumors have a mutation in the proto-oncogene KIT, and 5% to 8% harbor a mutation in the platelet-derived growth factor receptor alpha (PDGFRa) gene (5% to 10%), both of which lead to ligand-independent signal transduction resulting in increased cell proliferation and inhibition of apoptosis. The development of targeted therapies, which inhibit KIT and PDGFRa, has revolutionized the treatment of GIST in both the adjuvant and advanced settings.

Epidemiology

The incidence of GIST is estimated to be approximately 10 to 15 cases per 1,000,000 persons in the United States; the median age at diagnosis is 55 to 65 years. There are no established risk factors for the development of GIST.

Pathology

GISTs are believed to originate from interstitial cells of Cajal. The majority of cases can be classified into two categories: spindle cell type (70%) and epitheliod type (20%). The spindle cell type has uniform eosinophilic spindle cells organized in short fascicles or in a short storiform growth pattern. The epitheliod cell type has round-shaped cells exhibiting eosinophilic or clear cytoplasm that tend to exhibit a nested growth pattern.

GISTs most commonly occur in the stomach (60%) or duodenum, followed by the small intestine (25%), rectum (5%), and esophagus (2%); 5% are found in the colon, mesentery, and retroperitoneum. Early-stage GIST typically manifests as a localized tumor (i.e., in the stomach). Approximately 10% to 20% of patients present with metastatic disease, predominantly in the liver or peritoneum.

Diagnosis

Approximately 85% of GISTs express KIT, a type 3 transmembrane receptor tyrosine kinase. It is the single most common tumor marker for GIST and is identified with anti-CD117 antibodies on immunohistochemistry. PDGFRA mutations are homologous to those responsible for KIT- and Flt-3L-independent kinase activation in other malignancies, including acute myeloid leukemia, mast cell

disorders, and seminomas. KIT and PDGFRA mutations and overexpression are usually mutually exclusive in GIST. Thirty-five percent of KIT wild-type GISTs have PDGFRA mutations. Mutations in both KIT and PDGFRA lead to dysregulation of downstream intracellular signaling processes involving protein kinases and transcription factors such as AKT, MAPK, and STATs (STAT1 and STAT3), which play a critical role in the development and progression of cancer.

Computerized tomography (CT) scans remain the standard for initial staging workup and evaluation of response to therapy. Positron emission tomography (PET) scans are reserved for early response assessment or to further characterize inconclusive results on morphologic imaging, such as when results of a CT are ambiguous or inconsistent with clinical findings.

Clinical Presentation

The clinical presentation of GIST depends on the location of the tumor and may include the following:

- Abdominal discomfort or pain
- Sense of abdominal fullness
- Nausea
- Vomiting
- GI bleeding
- Fatigue related to anemia

Prognostic Factors

The risk stratification for recurrence after resection is based on size, mitotic index, and location of the tumor. Gastric GISTs are associated with a better outcome than GISTs located in the small bowel or rectum. Tumors with >5 mitoses per 50 high power field (HPF) are also at higher risk for recurrence.

Mutations are a prognostic factor in GISTs. Patients with KIT mutations have a higher rate of relapse than patients with "wild-type" GIST. In addition, PDGFRA exon 18 mutations, typically found in the stomach, are associated with improved outcomes after resection.

Treatment

Surgery

Surgery is the primary treatment of choice for localized or potentially resectable GIST. Since GIST tumors rarely give rise to lymph node metastases, extensive lymph node dissection is not routinely required. Neoadjuvant therapy with imatinib may be considered if significant morbidity would result after an en bloc resection of a large tumor.

Approximately 60% of patients with operable GIST will be cured with surgery alone. Median time to recurrence after resection of primary high-risk GIST is about 2 years. Metastases can develop 10 to 15 or more years after primary surgery, necessitating long-term clinical follow-up. Metastases into the abdominal cavity or liver are more common than in lymph nodes and extremely rare in the lungs and other extra-abdominal locations.

Adjuvant Therapy

The need for adjuvant therapy is determined by risk stratification tools. The NIH risk stratification criteria (Table 11.1) categorizes risk into very low, low, intermediate, and highly based on size and mitotic rate per 50 HPF. Based on the degree of risk of GIST recurrence, the current management after surgical resection is observation, 1 year of imatinib or 3 years of imatinib.

Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that targets the c-KIT and PDGFa receptors. Imatinib became the standard of care after the resection of GISTs based on the results of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Z9001 study. In this phase III clinical trial, 708 patients were randomized in a double-blind fashion to 1 year of imatinib 400 mg daily or placebo following complete gross resection of a primary GIST measuring at least 3 centimeters and expressing KIT. Upon recurrence, treatment assignment was unblinded and patients were allowed to cross over to imatinib if they had been on placebo or increase the daily dose of imatanib to 800 mg if they were already receiving the drug. Recurrence-free survival (RFS) at 1 year, the primary

Table 11.1 The Prognostic Factors That Define Different Risk Groups for GISTs

Risk	Size (cm)	Mitotic Count (per 50 HPF)	5-Yr Survival[a] (%)
Very low	<2	<5	~70
Low	2–5	<5	
Intermediate	<5	6–10	~56
	5–10	<5	
High	>5	>5	~22
	>10	>Any mitotic rate	
	Any tumor	>10	

HPF, high-power field.
Note: Size represents the single largest dimension.
[a]15-month follow-up.
Adapted from Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Int J Surg Pathol.* 2002;10(2):81-89.

endpoint of the trial, was 98% in the imatinib arm versus 83% in the placebo arm ($P < 0.0001$). Overall survival (OS) was not statistically significant between the two arms, likely due to short-term follow-up and the ability to crossover from the placebo arm to the imatinib arm.

In the Z9001, approximately 50% of patients with tumors >10 cm had recurrences in the first 3 years. This finding prompted a European study randomizing patients with high-risk of recurrence to 12 versus 36 months of adjuvant imatinib. The 5-year RFS was 65.6% in the 3-year arm compared to 47.9% in the 1-year arm ($P < 0.0001$). OS at 5 years was 92.0% and 81.7% in the 3-year and 1-year arms respectively ($P = 0.02$).

Neoadjuvant Therapy

RTOG 0132/ACRIN 6665, a prospective phase 2 study, evaluated safety and efficacy of neoadjuvant imatinib mesylate (600 mg per day) for patients with primary GIST or the preoperative use of imatinib mesylate in patients with operable metastatic GIST. The trial continued post-op imatinib mesylate for 2 years. Early results among 63 patients, of whom 52 were analyzable, 30 patients with primary GIST (group A) and 22 with recurrent metastatic GIST (group B) showed response (RECIST) as follows: group A, 7% partial, 83% stable, 10% unknown; group B, 4.5% partial, 91% stable, 4.5% progression. Two-year PFS was 83% for group A and 77% for group B. Estimated OS was 93% for group A and 91% for group B. Complications of surgery and imatinib mesylate toxicity were minimal. This trial represents the first prospective report of pre-op imatinib mesylate in GIST. This approach is feasible, requires multidisciplinary consultations, and is not associated with notable postoperative complications.

Therapy for Unresectable Disease

Prior to the development of targeted therapy, the treatment options for metastatic GIST were extremely limited. GIST does not respond to conventional cytotoxic agents, with reported response rates to doxorubicin lower than 5%. Other commonly used chemotherapeutic agents yielded similarly poor responses in GIST. Kinase inhibitors have dramatically increased survival in GIST, with the median survival approaching 5 years.

Imatinib

Imatinib has been proven to be highly effective against GIST and has improved survival in metastatic GIST. Early results from clinical trials confirm the high activity of this novel treatment, with response rates of approximately 60% and arrest of tumor progression seen in more than 80% of patients, which results in fast relief of symptoms.

Imatinib is approved at a dose of 400 to 600 mg daily for GIST. Investigators have attempted to determine the most effective dose of imatinib in GIST patients. Two large international randomized

phase 3 trials compared the efficacy of two different doses of imatinib in GIST patients. The studies were designed similarly to be combined in a meta-analysis (MetaGIST). Patients were randomized to receive either 400 mg of imatinib once daily (with crossover to 800 mg per day with disease progression) or 400 mg twice daily (for a daily dose of 800 mg). Response rates (mostly partial response or stable disease) were similar between doses in both trials. In the individual trials and the meta-analysis, PFS was prolonged with the 800 mg dose, but OS was not different between dosages.

Among KIT mutations, 70% are found on exon 11, 10% on exon 9; exons 13 and 17 are rarely involved. In a subgroup analysis of the MetaGIST analysis, the higher dose of imatinib was associated with better PFS for patients with KIT exon 9 mutations, but again, the higher dose was not associated with improved OS. In addition, approximately 80% of patients eventually develop secondary mutations in KIT exons resulting in progressive disease. Therefore, the current recommendations are to initiate therapy at 400 mg daily, and to increase to 800 mg daily for nonresponders.

Treatment with imatinib is generally well tolerated, although most common toxicities include grade 1 or 2 adverse events—most commonly nausea, diarrhea, periorbital edema, muscle cramps, fatigue, headache, and dermatitis.

Sunitinib

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities. Sunitinib is approved for the treatment of patients with GIST after disease progression or intolerance to imatinib mesylate therapy. A double-blind placebo-controlled, multicenter, randomized phase 3 trial confirmed the efficacy and safety of sunitinib as second-line therapy in 312 patients with GIST showing disease progression or intolerance under imatinib mesylate therapy. Patients were randomized in a 2:1 ratio 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 arm and in the placebo arm were 8% and 0%, respectively. Median time to progression was significantly longer in the sunitinib arm (6.3 vs. 1.5 months). Fifty-nine patients in the placebo group crossed over to sunitinib therapy due to disease progression. Ten percent had subsequent partial responses, suggesting that the optimal therapeutic effect of sunitinib may be observed when it is administered in the early disease phase. Hypertension and asthenia are the most common side effects with sunitinib.

Regorafenib

Regorafenib, a novel multikinase inhibitor that targets several protein kinases involved in tumor angiogenesis (VEGFR1–3 and TEK), oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and the tumor micro environment (PDGFR and FGFR), was tested in a randomized phase III trial for patients with metastatic GIST who had progressed on imatinib and sunitinib. Median PFS was 4.8 months for regorafenib and 0.9 months for placebo (HR 0.27; 95% CI 0.19 to 0.39; $P < 0.0001$). OS was not significantly improved with regorafenib; however, crossover was allowed on the study. Common adverse events were hypertension, hand–foot skin reaction, and diarrhea.

Radiotherapy

The effectiveness of radiation therapy in treating GIST also has not been proven, and is typically reserved in rare circumstances for palliation of symptoms.

SMALL BOWEL ADENOCARCINOMA

Despite the fact the small intestine comprises over 90% of the intestinal surface area, small bowel adenocarcinoma (SBA) is actually a rare entity, accounting for <2% of all GI tumors. SBA accounts for approximately one-third of small bowel malignancies with the remaining histologies being neuroendocrine cancers (carcinoid), lymphoma, and GIST. The rarity of SBAs has limited research into the natural history, prognosis, and management of patients with this disease. Recent studies suggest SBA is more closely related to colorectal carcinoma than gastroesophageal cancers. Given the lack of clinical trial data to support treatment recommendations, SBAs are often managed similarly to colorectal cancers.

Epidemiology

Approximately 6,110 new cases of SBA and 1,100 deaths from the disease are reported annually in the United States. The incidence of adenocarcinoma is estimated to be 5.7 to 7.3 per million in the United States. Some studies have suggested the incidence of SBA is increasing, particularly in the duodenal region, which may be explained by the increased use of upper endoscopies. Although SBAs are only one-fiftieth as common as large bowel adenocarcinomas, they share a similar geographic distribution, with predominance in Western countries. In addition, they tend to co-occur in the same individuals, with an increased risk of SBA in survivors of colorectal cancer and vice versa.

Risk Factors

Genetic Predisposition

- Familial adenomatous polyposis: Patients with this condition develop multiple adenomas throughout the small bowel and colon, which may lead to adenocarcinomas. After the colon, the duodenum is the most common site of adenocarcinoma. A 1993 study from Johns Hopkins by Offerhaus et al. found that patients with familial adenomatous polyposis have a relative risk of more than 300 for duodenal adenocarcinoma but no elevated risk of gastric or nonduodenal small bowel cancer.
- Hereditary nonpolyposis colorectal cancer: Aside from colorectal carcinoma, patients with this genetic syndrome also develop endometrial, gastric, small bowel, upper urinary tract, and ovarian carcinomas. The lifetime risk of SBA in patients with hereditary nonpolyposis colorectal cancer is 1% to 4%, which is more than 100 times the risk in the general population. SBAs in persons with hereditary nonpolyposis colorectal cancer are distributed evenly throughout the small bowel. They occur at younger age and appear to have a better prognosis than sporadic small bowel cancers.

Predisposing Medical Conditions

- Crohn's disease: The relative risk of SBA is estimated to be between 15 and more than 100 in patients with Crohn's disease. Unlike most SBAs, Crohn-related tumors generally occur in the ileum, reflecting the distribution of Crohn's disease. The risk of adenocarcinoma does not begin until at least 10 years after the onset of Crohn's disease, and the adenocarcinoma typically occurs more than 20 years afterward.
- Celiac disease (nontropical sprue): Patients with celiac disease appear to be at increased risk of small bowel lymphoma and adenocarcinoma. A 2001 survey of adult celiac disease patients in the United States performed by Green et al. found a relative risk of 300 for the development of lymphoma and 67 for the development of adenocarcinoma. SBAs associated with celiac disease appear to have an increased incidence of defective DNA mismatch repair compared with those not associated with celiac disease, and are associated with an earlier stage at diagnosis and a better prognosis.
- Peutz-Jeghers syndrome: Hemminki has reported an approximately 18-fold increase in the incidence compared to that in the general population.

Pathology

Approximately 50% of SBAs arise in the duodenum, 30% in the jejunum, and 20% in the ileum. Similar to adenocarcinomas in the colon, those in the small bowel arise from premalignant adenomas. This occurs both sporadically and in the context of familial adenomatous polyposis.

Genetic analyses of sporadic SBAs suggest similarities and differences from the pathogenesis from colorectal carcinomas. Although K-ras mutation and p53 overexpression appear to be as common in SBA as in colorectal carcinoma, mutation of the APC tumor suppressor gene, which is characteristic of colorectal carcinoma, does not commonly occur in SBA. The SMAD4/DPC4 gene, which is often mutated in pancreatic and colorectal carcinomas, also appears to be inactivated in SBAs.

Most SBAs are solitary, sessile lesions, often appearing in association with adenomas. They are usually moderately well differentiated and are almost always positive for acid mucin. SBAs can be positive for carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), and p53. Expression of c-erbB-2, Ki-67, and tenascin has also been described. SBAs arising from the ileum may show staining with neuroendocrine markers.

Clinical Presentation

The clinical presentation of SBA depends on the location of the primary tumor, its growth pattern, and the extent of metastatic spread. In general, symptoms are initially nonspecific and include anemia, bleeding, abdominal pain, nausea, and vomiting, or obstruction and/or perforation in cases of locally advanced tumors. Because of a vague presentation of SBA, the time between initial development of symptoms and diagnosis is often relatively long, approximately 6 to 8 months, and contributes to the higher percentage of advanced cases at the time of diagnosis (in contrast to colorectal cancer). Common sites of metastases include locoregional lymph nodes, liver, lung, and the peritoneum.

Diagnosis

Lab Studies

- Complete blood count (CBC) may show mild anemia related to chronic blood loss.
- Liver function tests may reveal hyperbilirubinemia, which may be related to biliary obstruction from periampullary tumors. Elevated transaminase levels also may be found in the presence of liver metastases.
- CEA levels may be elevated. Although cases with elevation of CA 19-9, or CA 125 levels have been reported, no clear role for such tumor markers has been established for diagnosis.

Imaging Studies

- Plain abdominal x-ray films may reveal partial or complete small bowel obstruction.
- Upper GI series with small bowel follow through show abnormalities in 53% to 83% of patients with small bowel cancer.
- Small bowel enteroclysis studies are done with double-contrast barium enema, which has a sensitivity of 95%. However, it is difficult to perform as it requires a long tube to be inserted in the small bowel to instill air and contrast.
- Abdominal CT scan may elucidate the site and extent of local disease and the presence of liver metastases.

Other Tests

In those rare cases of bleeding due to a small bowel tumor, the diagnostic approach is the same for all cases of lower GI bleeding. In the case of negative upper and lower endoscopy, tagged red blood cell scan and angiography can be helpful in localizing the disease process. Capsule endoscopy has a better sensitivity and specificity and may identify an SBA during the workup for occult GI bleeding.

Procedures

- Upper GI endoscopy with small bowel enteroscopy (push enteroscopy) may identify and allow biopsy of lesions in the duodenum and jejunum. Push enteroscopy is difficult to perform. The endoscopes are long and difficult to manipulate. The procedure is lengthy.
- Colonoscopy with retrograde ileoscopy may be useful in identifying ileal tumors.
- Capsule endoscopy: This test is done with a capsule with dimensions of 11 × 26 mm that weighs 4 g. The capsule contains a small video camera, batteries, and a radiofrequency transmitter. The batteries last 8 hours. The capsule takes about 50,000 pictures as it passes through the GI system. The pictures are captured in a device that is strapped to the waist. The test was FDA approved for small bowel use in 2001. Cobrin et al. reported that 9% of cases of occult GI bleeding were caused by small bowel tumors.

Staging

SBAs are staged according to the tumor–node–metastasis (TNM) criteria, as used for colon cancer. Staging is based on the extent to which the tumor is present in the bowel wall, the regional nodal status, and the presence or absence of distant metastasis. In a recent SEER database study evaluating the incidence of SBAs, 11.8% presented with stage I, 30.1% with stage II, 26.0% with stage III, and 32.2% with stage IV disease.

Prognosis

Resectability is the key prognostic factor. Historically, the median survival of patients with localized, locally advanced, and metastatic disease is 50.1, 22.2, and 8.6 months, respectively. Factors associated with poor prognosis after surgical resection of SBAs included age greater than 55 years, duodenal location, T4 tumors, nodal or distant metastases, poorly differentiated tumor, and involved surgical margins. Despite the resemblance to colorectal cancer, the stage-adjusted prognoses for SBAs are inferior to colorectal cancer.

Treatment of Localized Disease

Surgery

Surgical resection provides the only hope of cure for patients with SBAs. This is possible in approximately two-thirds of patients. The remaining have unresectable disease as a result of extensive local disease or metastases to regional lymph nodes, the liver, or the peritoneum. Wide local excision is recommended on lesions in the distal duodenum, jejunum, or ileum. Patients with lesions in the proximal duodenum, including those in the periampullary region, should undergo pancreaticoduodenectomy, which now has an operative mortality rate of less than 5%. Ileal tumors are more likely to develop intestinal obstruction than jejunal tumors. Emergency surgery for these patients relieves the obstruction but precludes a complete and negative margin resection.

Adequate lymph node dissection appears to play an important role in the survival outcomes of patients with SBAs. In a large, retrospective study, Overman et al. found among all patients as much as a 28.8% decrease in 5-year cancer-specific survival for resected SBAs compared to large bowel cancers. However, if more complete nodal dissection is performed with surgical resection of SBA, survival rates are not as discrepant with those of colorectal cancer. Among patients with at least 8 lymph nodes examined, the cancer-specific survival for SBA was 80.3% for stage I, 69.9% for stage II, and 45.1% for stage III disease compared to 93.3%, 85.8%, and 63.6% for large bowel cancers respectively.

Adjuvant Therapy

There is not a clear survival benefit to adjuvant chemotherapy in SBA, but no prospective phase 2 or 3 trials have investigated this issue. In addition, retrospective studies regarding the use of adjuvant therapy in SBA have yielded mixed results. Regardless, the use of adjuvant chemotherapy utilization for patients with SBA has increased from 8.1% in 1985 to 23.8% in 2005, which may be a reflection of clinicians applying the adjuvant data from large bowel cancers to SBAs. Patients are often treated similarly to colon cancer adjuvant therapy recommendations with a fluoropyrimidine combined with oxaliplatin.

In a large, retrospective study, 75 patients who received either adjuvant chemotherapy ($n = 34$) or chemoradiation therapy ($n = 41$) were compared to patients with no adjuvant therapy. Patients who underwent adjuvant therapy, chemotherapy, or chemoradiation therapy had a median OS of 35.7 months and a 5-year OS of 39% versus 29.3 months and 36% for patients without adjuvant therapy, respectively ($P = 0.44$). Although these results were not statistically significant, they do warrant further study of adjuvant therapy for SBA.

Treatment of Metastatic Disease

Surgery

The role of surgical resection is limited to either palliative measures or prevention of bowel obstruction or bleeding in patients with metastatic SBA.

Chemotherapy

There is no clearly established front-line systemic treatment regimen for metastatic disease due to the difficulty of conducting a randomized clinical trial on such a rare disease. Patients with metastatic disease do gain a survival benefit with the use systemic chemotherapy. Retrospective studies have demonstrated patients with stage IV SBA have median OS of 12 to 15.5 months with the receipt of chemotherapy compared to 2 to 7.7 months without treatment.

Metastatic SBA is commonly treated with regimens used in colorectal cancer given their similarities in histology and clinical behavior. Two prospective phase II studies have shown that combination of a fluoropyrimidine with oxaliplatin is both effective and well tolerated. In the study reported by Overman et al.

of patients with metastatic or unresectable SBAs, the use of capecitabine and oxaliplatin (CAPOX) showed a median time to progression (TTP) of 11.3 months and a median OS of 20.4 months. Among the patients with metastatic disease only the median TTP was 9.4 months and median OS was 15.5 months.

The use of an oxaliplatin-based regimen for metastatic SBA is also supported by several retrospective studies. The largest of these studies from Japan included 132 patients with unresectable or recurrent SBA who received systemic chemotherapy with either fluoropyrimidine monotherapy, fluoropyrimidine plus cisplatin, fluoropyrimidine plus oxaliplatin, fluoropyrimidine plus irinotecan, or another regimen. Median OS was 13.9 months, 12.6 months, 22.2 months, 9.4 months, and 8.1 months respectively. This study suggests using a fluoropyrimidine combined with oxaliplatin may be associated with survival rates expected in metastatic colorectal cancer. A similar trend was seen in a retrospective study of 93 patients reported by the AGEO group, which reported median OS times of 13.5 months, 17.8 months, 10.6 months, and 9.3 months with the use of fluoropyrimidine monotherapy, fluoropyrimidine plus oxaliplatin, fluoropyrimidine plus irinotecan, and fluoropyrimidine plus cisplatin respectively.

Fluoropyrimidine plus irinotecan is another systemic therapy option for metastatic colorectal cancer and it has also been evaluated for used in SBAs. A small, retrospective study evaluated 28 patients who were treated with FOLFIRI after first-line therapy with a fluoropyrimidine plus a platinum agent. The response rate was 20%, and 52% of patients had disease control 52%. The median PFS was 3.2 months and OS was 10.5 months.

Follow-Up

Patients who have undergone surgical resection for localized disease should have a follow-up visit in the outpatient setting every 3 months to assess for symptoms or signs suggestive of recurrent disease.

- CBC and liver function test results may be checked periodically to identify anemia related to blood loss or abnormal liver enzymes related to hepatic metastases or biliary obstruction, respectively.
- Abdominal CT scan images should be obtained every 6 months to identify subclinical recurrent disease early, which may be amenable to repeat surgical resection.
- Patients with SBA should also undergo colorectal cancer screening (i.e., colonoscopy) because of the high risk of secondary malignancies.
- Patients with advanced metastatic disease may be treated with chemotherapy in an outpatient setting. They should also be observed for hematologic and other toxicity related to chemotherapy.

Complications

- Partial or complete small bowel obstruction may occur because of an obstructing intraluminal tumor. This may be treated either conservatively (i.e., nasogastric tube decompression and parenteral nutrition) or with surgery (i.e., small bowel resection or bypass).
- Intestinal bleeding is common with small bowel sarcomas and may require transfusion support and surgical intervention.
- Biliary obstruction may result from compression of the extrahepatic common bile duct by a periampullary or proximal duodenal tumor. Biliary stenting via endoscopic retrograde cholangiopancreatography or transhepatic biliary drainage may be performed if feasible.

REVIEW QUESTIONS

1. A 54-year-old male underwent surgical resection of a gastric mass found on upper endoscopy as part of a workup for anemia. Pathology revealed a 5.8 cm gastrointestinal stromal tumor with > 10 mitoses per 50 HPF. The next best step in management is

A. Observation
B. Adjuvant radiation therapy
C. Adjuvant chemotherapy with doxorubicin
D. Adjuvant imatinib for 1 year
E. Adjuvant imatinib for 3 years

2. A 67-year-old female presents with progressively worsening diffuse abdominal pain. CT scan reveals a lesion in the ileum as well as multiple peritoneal nodules. Biopsy of one of the peritoneal nodules is consistent with GIST carrying a mutation in exon 9. She was initiated on systemic therapy with imatinib at 400 mg daily and after 3-month repeat imaging showed progression of her disease. What is the next best step in management?

A. Increase the dose of imatinib to 400 mg twice daily
B. Discontinue imatinib and initiate therapy with regorafenib.
C. Discontinue imatinib and initiate therapy with sunitinib.
D. Discontinue imatinib and initiate therapy with doxorubicin plus ifosfamide

3. A 62-year-old male underwent emergent surgery for small bowel obstruction. Pathology reveals a moderately differentiated adenocarcinoma originating in the jejunum. Staging CT scan of the abdomen and pelvis reveals multiple lesions in the liver throughout both lobes of the liver. Biopsy of a liver lesion is also consistent with adenocarcinoma. On surgical consultation he is felt not to be a candidate for resection of the liver lesions. The patient is asymptomatic of the liver disease. What is the next best step in management?

A. Referral to hospice
B. Systemic therapy with 5-fluoruracil
C. Radiation therapy to the liver lesions
D. Systemic therapy with gemcitabine
E. Systemic therapy with a fluoropyrimidine and oxaliplatin

Suggested Readings

Gastrointestinal Stromal Tumor

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SECTION Four

Breast

12

Breast Cancer

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Breast cancer is the most common cancer among women worldwide and it accounts for 23% of all cancer diagnosed among women. It is also the most common cancer diagnosed in women in North America, and is second only to lung cancer as the leading cause of death from cancer in women. 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.

EPIDEMIOLOGY

- In the United States, in 2013, an estimated 232,340 women and 2,240 men will be diagnosed with breast cancer.
- In 2013, about 39,620 women and 410 men are expected to die from breast cancer in the United States.
  - About 1.5 million women will get a diagnosis of breast cancer worldwide and about half a million will die globally from breast cancer.
- A US woman's lifetime risk of developing breast cancer is one in eight.
- There are currently more than 2.9 million breast cancer survivors in the United States.

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.

Genetics

- About 5% to 10% of all women with breast cancer may have a specific mutation in single genes that are passed down in a family, and the most common mutations are those of the genes BRCA1 or BRCA2. Other genes implicated with breast cancer are PTEN, TP53, and CDH1.

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
Atypical lobular hyperplasia or atypical ductal hyperplasia
Prior breast biopsies
Long-term postmenopausal estrogen replacement
Early exposure to ionizing radiation

- Mutations of BRCA1 (chromosome 17q21) and BRCA2 (chromosome 13q12–13q13) are responsible for 85% of hereditary breast cancer.
- Specific mutations of BRCA1 and BRCA2 are more common in women of Ashkenazi Jewish ancestry.
- Overall prevalence of disease-related mutation is BRCA1 has been estimated at 1 in 300, while BRCA2 is 1 in 800.
- Mutations of BRCA1 or BRCA2 can be highly penetrant, with estimates of 45% to 84% lifetime risk for breast cancer, as well as an increased risk for contralateral breast cancer.
- Mutations in either gene also confer about 11% to 62% lifetime risk of developing ovarian cancer.
- See also Chapter 45.

Indications for Genetic Testing

Genetic testing is available commercially (Myriad Genetics). All patients should undergo genetic counseling before undergoing the test. 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 germ-line mutation of the BRCA1/2 genes. 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 BRCA1 or 2 genes that have been associated with an inherited risk of developing breast cancer.

As per NCCN guidelines (accessed January 2013), patients with breast cancer with one or more of the following should undergo further genetic risk evaluation:

- Early-age onset breast cancer
- Triple negative breast cancer (ER–, PR–, HER-2/neu-)
- ≥2 breast primaries in a single individual or two different individuals from the same side of the family
- ≥1 close blood relative (first-, second-, or third-degree relative) with breast cancer ≤50 years of age
- ≥2 close blood relatives with breast cancer and/or pancreatic cancer at *any* age
- Population at increased risk (i.e., women of Ashkenazi Jewish descent)
- Male breast cancer

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. Recommendations include the following:

- Breast self-examination training and education starting at age 18.
- Clinical breast examination every 6 to 12 months, starting at age 25.
- Annual mammogram and breast magnetic resonance imaging (MRI) starting at age 25 or earlier based on family history.
- Discuss options of bilateral prophylactic mastectomy on a case-by-case basis, since it could prevent breast cancer in 90% to 100%.

- Recommend bilateral salpingo-oophorectomy (BSO) ideally between the ages of 35 and 40 or after completion of child bearing. BSO alone will reduce breast cancer risk by 50% and prevents ovarian cancer by 95%.
- Patients who defer BSO may consider concurrent trans-vaginal ultrasound with CA-125 lab draw every 6 months starting at the age of 30 or 5 to 10 years prior to the earliest age of ovarian cancer in the family.

CHEMOPREVENTION

Risk Assessment

- The Gail model (http://www.nci.nih.gov) is a statistical model that calculates a woman's absolute risk of developing breast cancer by using the following criteria: age, age at menarche, age at first live birth, number of previous biopsies, history of atypical ductal hyperplasia (ADH), and number of first-degree relatives with breast cancer. This model is not intended to be used in patients with an existing history of invasive cancer, DCIS, or lobular carcinoma in situ (LCIS). The Gail model underestimates the risk of breast cancer in a person with hereditary breast cancer.

Prevention Studies

The National Surgical Adjuvant Breast and Bowel Project

- 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 who took tamoxifen at a dose of 20 mg daily for 5 years.
- Women eligible for this trial were at least 35 years old and were assessed to have an absolute risk of at least 1.67% over the period of 5 years using the Gail model or a pathologic diagnosis of LCIS.
- Use of tamoxifen for breast cancer should be individualized, and must 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 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 1.66%). The results of the study revealed that raloxifene was equivalent to tamoxifen in preventing invasive breast cancer (about a 50% reduction). Raloxifene did not reduce the risk of DCIS or LCIS unlike tamoxifen.

Raloxifene has a better side effect profile, which resulted in a lower incidence of uterine hyperplasia, hysterectomy, cataracts, and a lower rate of thromboembolic events. In postmenopausal patients, due to equal efficacy and better side effect profile, raloxifene 60 mg daily could be used instead of tamoxifen for breast cancer prevention.

Aromatase Inhibitors for Risk Reduction

The Arimidex, Tamoxifen alone, or in Combination Trial (ATAC Trial) showed a nonsignificant reduction in contralateral breast cancers in women treated with anastrozole alone when compared with tamoxifen ($P = 0.62$). A significant reduction ($P = 0.04$) was noted in contralateral breast cancers in a subset of women with hormone receptor-positive first cancers.

The Breast International Group (BIG) 1-98 trial compared postmenopausal women with early-stage breast cancer to those who underwent 5 years of therapy and found that risk of breast cancer recurrence was lower in women in the letrozole arm when compared to the tamoxifen arm.

The MAP.3 trial evaluated the role of exemestane in a risk reduction setting, randomizing women to either exemestane or placebo. A median follow-up of 3 years showed that exemestane reduced the relative incidence of breast cancers by 65% when compared to placebo. It was not associated with any significant serious side effects and only minimal changes in quality of life.

Summary

In premenopausal women with increased risk of breast cancer as per the Gail model 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. Exemestane can also be considered; however, the FDA has not approved exemestane in this setting at this time. Any risk reduction approach should be carefully decided after a detailed risk versus benefit discussion with the patient.

There are only limited data for chemoprevention in patients with BRCA mutation. One study showed that tamoxifencan reduces the risk by 62% compared to placebo; however, tamoxifen use was not associated with reduction in risk in those patients with a BRCA1 mutation. Clinical trials are addressing the role of AIs in breast cancer prevention in mutation carriers.

Screening Mammograms and MRI

- The National Cancer Institute, American Cancer Society, and American College of Radiology all recommend mammography for women aged 40 years and older.
- Women aged 40 years and older at an average risk of breast cancer should have mammograms every 1 to 2 years.
- Women who are at higher than average risk of breast cancer (those with a family history of breast cancer or with either the BRCA1 or the BRCA2 gene) should discuss with their health care providers about whether to have mammograms before the age of 40 and how often to have them.
- Mammograms should be continued regardless of a woman's age, as long as she does not have serious, chronic health problems such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, and moderate to severe dementia. 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.
- Screening mammograms help reduce death in patients between the ages of 40 and 70 years.
- Potential harm of screening includes false-negative and false-positive results, over diagnosis and overtreatment.
- There is considerable controversy among various experts regarding the risk and benefit screening mammogram, especially women between 40 and 50 years.

Digital Mammography

The diagnostic superiority of digital mammography was demonstrated in the Digital Mammographic Imaging Screening Trial (DMIST). This study concluded that pre- or perimenopausal women under the age of 50, or women at any age with dense breasts, had a more accurate detection of breast cancer with the digital mammogram. The amount of radiation exposure in digital mammograms is less than film mammograms.

Magnetic Resonance Imaging

Breast MRI has been shown to have a higher sensitivity than mammography. Specificity is however lower, which will result in more false positives and therefore more biopsies. In a high-risk population, MRI and mammogram (92.7%) have a higher sensitivity than mammogram and ultrasound combined (52%). In high-risk women, breast MRI is cost effective, specifically those women with BRCA gene mutations (along with untested first-degree relatives) and women whose lifetime risk of breast cancer exceeds 20%. Patients need to be carefully selected for additional screening with MRI. MRI is recommended in patients with prior radiation therapy who are ≥25 years of age, and women with a genetic predisposition for breast cancer starting at the age of 25.

CLINICAL FEATURES OF BREAST CANCER

Clinical features may include a breast lump, skin thickening or alteration, peau d'orange, dimpling of the skin, nipple inversion or crusting (Paget disease), unilateral nipple discharge, and new onset pain. Patients may instead present with signs and symptoms of metastatic disease.

DIAGNOSIS

1. History and physical examination
2. Bilateral mammogram (80% to 90% accuracy)
3. Biopsy: Any distinct mass should be considered for a biopsy, even if the mammograms are negative. The standard methods of diagnosis for palpable lesions are
   - Core-needle biopsy
   - Incisional or excisional biopsy

The options in nonpalpable breast lesions are
   - Ultrasound-guided core-needle biopsy
   - Stereotactic core-needle biopsy under mammographic localization
   - Needle localization under mammography, followed by surgical excision
   - MRI-guided biopsy
4. Laboratory studies
   - Complete blood count, liver function tests, and alkaline phosphatase level.
   - Routine use of breast cancer markers such as CA 27:29 and 15:3 is not recommended.
5. 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
6. Estrogen receptor/progesterone receptor (ER/PR) status should be done in all tumors (both invasive and noninvasive) and biopsies of metastatic or recurrent (patients those who relapsed) lesions.
   - As per the ASCO/CAP guidelines (2010) ER/PR is considered as positive if 1% of tumor cell nuclei are immunoreactive.
7. HER-2/neu- testing (as per ASCO/CAP Guidelines 2013)
   - Positive for HER-2/neu- is either IHC 3 + (defined as uniform intense membrane staining of more than 30% of invasive tumor cells) or FISH amplified (ratio of HER-2/neu- to CEP17 of more than 2.0 or average HER-2/neu- gene copy number more than six signals/nucleus for those test systems without an internal control probe).
   - Equivocal for HER-2/neu- is defined as either IHC 2 + or FISH ratio of <2 or average HER-2/neu- gene copy number of 4 to 6 signals/nucleus for test systems without an internal control probe.
   - Negative for HER-2/neu- is defined as either IHC 0–1 + or FISH ratio of less than <2 with an average HER-2/neu- gene copy number of less than 4 signals/nucleus for test systems without an internal control probe.
8. Indices of proliferation (e.g., 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.
9. Radiographic studies are performed on the basis of the findings of the history and physical examination and blood tests.

Appropriate imaging studies such as CAT scan, ultrasound, MRI, or CT/PET scan can be considered as per the clinical indications. They are not routinely recommended for all patients.

10. Breast MRI is indicated in the following (American College of Radiology Guidelines):
    - Evaluating the extent of disease in known cancer patients
      - Multifocal and multicentric disease
      - Pectoralis and chest wall involvement
      - Contralateral breast cancer
    - Evaluating response to neoadjuvant chemotherapy
    - Axillary adenopathy, primary unknown
    - Postlumpectomy for residual disease (close or positive margins)
    - Suspected recurrence of breast cancer
      - Inconclusive mammographic/clinical findings
      - Reconstruction with tissue flaps or implants
    - Lesion characterization
      - Inconclusive findings on mammogram, ultrasound, physical examination

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.

11. Positron emission tomography (PET) scan. PET scans are of low yield in patients with early (stage I and II) breast cancer. CT/PET scan may be useful in patients with locally advanced or metastatic breast cancer.

PATHOLOGY

Infiltrating or invasive ductal cancer is the most common breast cancer histologic type and comprises 70% to 80% of all cases (Table 12.2).

STAGING OF BREAST CANCER

For staging of breast cancer the American Joint Committee on Cancer (AJCC) manual, seventh edition, should be followed.

Prognostic Factors

Anatomic features such as tumor size and lymph node status are important prognostic features. But 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.
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 to 3 points) for features such as size, mitosis, and tubule formation. These scores are added and tumors are labeled low grade (3 to 5 points), intermediate grade (6 to 7 points), or high grade (8 to 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.
   - Inflammatory breast cancer is one of the most aggressive forms of breast cancer.
6. HER-2/neu- expression
   - HER-2/neu- overexpression is a poor prognostic marker and patients with HER-2/neu- overexpression are candidates for HER-2/neu-targeted therapies. Availability of effective HER-2/neu-targeted therapies has revolutionized the treatment and outcome of HER-2/neu-positive breast cancer. Because of targeted therapies, for all practical purposes, HER-2/neu- positivity can be considered as a good prognostic feature now. It is important to remember that patients with a FISH ratio between 2.0 and 2.2 were considered as HER-2/neu- positive and were eligible for treatment in the early adjuvant trastuzumab trials. So patients with FISH ratio more than 2 should be considered for treatment with HER-2/neu-targeted drugs, especially trastuzumab in adjuvant settings.
7. Gene expression profiles

- Oncotype DX is a diagnostic genomic assay based on RT-PCR on paraffin-embedded tissue (Fig. 12.1). 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. Patients are divided into low-risk, intermediate-risk, and high-risk groups on the basis of the expression of a panel of 21 genes. The recurrence score determined by this assay is found to be a better predictor of outcome than standard measures such as age, tumor size, and tumor grade. Studies have validated the role of Oncotype DX

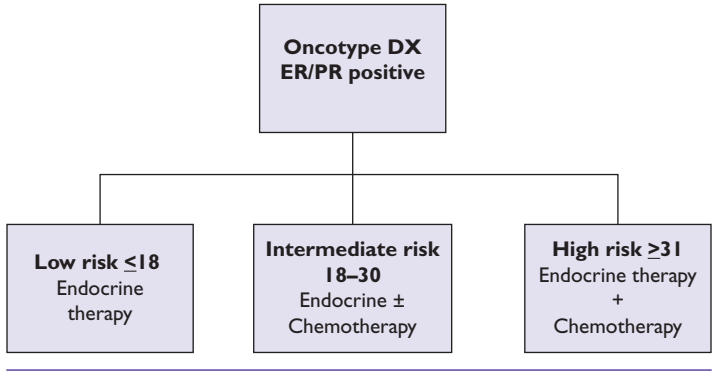

FIGURE 12.1 Oncotype DX assay.

Table 12.3 Systemic Treatment Recommendations Based upon Subtypes

Luminal A	Endocrine therapy alone
Luminal B (HER-2/neu- negative)	Endocrine +/– Chemo
Luminal B (HER-2/neu- positive)	Chemo + anti-HER-2/neu-drugs endocrine therapy
HER-2/neu- positive (nonluminal)	Chemo + anti-HER-2/neu-
Triple negative (ductal)	Chemotherapy
Special Biologic Subtypes	
Endocrine responsive (cribriform, tubular, and mucinous)	Endocrine therapy
Endocrine nonresponsive (medullary, adenoid, and metaplastic)	Chemotherapy

patients with node-positive and ER-positive tumors and it can be used in selected settings. It is being studied in DCIS also.

MammaPrint is a DNA microarray assay of 70 genes designed to predict the risk of recurrence of early-stage breast cancer. In February 2007, the FDA approved the use of MammaPrint in patients less than the age of 61, with a tumor size less than 5 cm and lymph node negative.

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).

- **Luminal subtypes**: Luminal A and luminal B, which 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% of cancers and they have the best prognosis. About 20% of breast cancers are of luminal B subtype and they have worse prognosis compared to luminal A.
- **HER-2/neu-enriched subtype** (previously the HER-2/neu-positive/ER-negative subtype): The HER-2/neu-enriched subtype comprises the majority of clinically HER-2/neu-positive breast cancers. It accounts for 10% to 15% of breast cancers. Not all HER-2/neu-positive tumors are HER-2/neu-enriched. About half of clinical HER-2/neu-positive breast cancers are HER-2/neu- enriched; the other half can include any molecular subtype including HER-2/neu-positive luminal subtypes.
- **ER-negative subtypes**: There are several ER-negative subtypes characterized by low expression of hormone receptor-related genes. These include the basal-like, claudin-low, interferon-rich, androgen receptor, and normal-like subtypes. They are mostly triple negative breast cancer and they have a more aggressive clinical course.

MANAGEMENT

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.

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.
- ADH is managed by close follow-up of patients.
- Clinical breast examination and mammogram are the preferred screening methods.
- Tamoxifen 20 mg PO for 5 years: The NSABP P-1 study showed 86% reduction in the risk of developing invasive breast cancer in patients who received tamoxifen.

- The NSABP P-2 study showed similar efficacy for raloxifene 60 mg daily for 5 years, but with fewer adverse effects. Hence, in postmenopausal patients, raloxifene could be considered as the preferred treatment option.

Lobular Carcinoma In Situ

- LCIS is not considered a form of cancer, but a marker of increased risk of developing invasive breast cancer.
- It is usually multicentric and bilateral.
- There is a 21% chance of developing breast cancer in patients within 15 years of developing LCIS.
- It is managed by close follow-up of patients.
- Patients can be followed up by clinical breast examination every 4 to 12 months, annual mammogram, and/or MRI.
- Tamoxifen or raloxifene (postmenopausal) may be used for prevention of breast cancer (56% reduction in risk as per the NSABP P-1 and P-2 studies).

Noninvasive Breast Cancer

Ductal Carcinoma In Situ

- The extensive use of mammograms has led to the diagnosis of ductal carcinoma in situ (DCIS) increasing over the last several years.
- Microcalcification or soft tissue abnormality is seen in the mammogram of DCIS.
- Comedocarcinoma has a poor prognosis.
- Noncomedocarcinoma includes micropapillary, papillary, solid, and cribriform carcinoma.

Treatment

- Lumpectomy followed by radiation treatment followed by tamoxifen for 5 years is the standard treatment option.

Other treatment options are

– Total mastectomy with or without tamoxifen
– In patients who previously had lumpectomy and radiation, tamoxifen reduced the risk of breast cancer recurrence (ipsilateral and contralateral; NSABP B-24). The benefit is limited only for patients with ER/PR-positive DCIS.
– The role of AIs in receptor-positive DCIS is being investigated in many clinical trials, some of which have closed for accrual (NSABP B-35). Another phase 3 clinical trial, the CRUK-IBIS-II-DCIS, is still accruing patients.
– NSABP B-43 is evaluating the role of trastuzumab in HER-2/neu-positive DCIS.

Invasive Breast Cancer

Breast cancer should be managed in a multidisciplinary approach with the input from the surgeon, medical oncologist, pathologist, radiologist, and radiation oncologist. 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

As per NSABP B-06 and EORTC 10801, no survival difference is seen in patients who are treated with modified radical mastectomy versus lumpectomy and radiation therapy (breast conservation therapy [BCT]). BCT is the preferred treatment for early-stage breast cancer.

As per NCCN guidelines contraindications for breast-conserving therapy requiring radiation therapy include

Absolute:

- Prior radiation therapy to the breast or chest wall
- Radiation therapy during pregnancy

- Diffuse suspicious or malignant-appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result
- Positive pathologic margin

Relative:

- Active connective tissue disease involving the skin (especially scleroderma and lupus).
- Tumors >5 cm.
- Focally positive margin.
- Women with a known or suspected genetic predisposition to breast cancer: May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast-conserving therapy. Prophylactic bilateral mastectomy for risk reduction may be considered.

Axillary Lymph Node Dissection

- Axillary lymph node dissection (ALND) primarily provides prognostic information. It has minimal therapeutic benefit, especially in clinically negative axilla.
- Among patients with clinically negative axillary lymph nodes, 30% will have positive histology after dissection.
- A complete axillary node dissection is associated with approximately 10% to 25% risk of lymphedema, which can be mild to severe.

Sentinel Node Biopsy

"The SLN is defined as any node that receives drainage directly from the primary tumor, therefore, allowing for more than one SLN." Injection of technetium-labeled sulfur colloid, vital blue dye, or both around the tumor, biopsy cavity, or in the subareolar area is taken up into the 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. Studies have shown a 97.5% to 100% concordance between SLN biopsy and complete ALND.

The ACOSOG Z 0011 clinical trial showed that there is no difference in overall survival (OS) and disease-free survival in doing a complete axillary node dissection in patients with clinical T1–T2 invasive breast cancer without palpable adenopathy and pathologic evidence of 1 to 2 SLNs-containing metastases. So in patients who meet the criteria for this trial, a complete axillary node dissection can be potentially avoided, even with a positive SNL metastasis.

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 stage I and IIA disease 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 stage IIB or III breast cancer and undergoing mastectomy, delayed reconstruction may be the more appropriate management option.

Reconstruction can be done in one of two ways: implant-based or an autologous tissue graft. Examples of autologous tissue grafts include TRAM (transverse rectus abdominis myocutaneous) flaps, the latissimus dorsi flap, and the DIEP (deep inferior epigastric perforator) flap. The latter is the preferred method as it is analogous to the TRAM flap; however, the rectus muscle is not raised to the breast site, thereby allowing quicker recovery of abdominal strength. The latissimus dorsi flap may be safer in patients who are obese or have compromised vasculature due to diabetes mellitus or smoking.

Radiotherapy

- 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. A boost 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 42.5 Gy

at 2.66 Gy per fraction to the whole breast. This treatment method has been demonstrated to provide comparable results following breast conserving surgery in patients with clear surgical margins and negative lymph nodes.

- RT is usually done after chemotherapy when systemic chemotherapy is indicated.
- Postmastectomy radiation treatment to the chest wall and supraclavicular lymph nodes 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 is being evaluated in more clinical trials. In selected patients, this should be discussed.

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. There are several APBI techniques currently under study; however, brachytherapy is the most widely used. Brachytherapy methods are designed to irradiate the tumor bed or cavity while sparing normal breast tissue. Patients should be selected according to published criteria since the whole breast is not treated. The standard dose for balloon catheter brachytherapy is 34 Gy in 10 fractions delivered twice daily.

Adjuvant Systemic Therapy

Adjuvant therapy decisions are made based upon the stage, nodal status, and tumor biology. Important tumor biologic factors are ER/PR, HER-2/neu-, tumor grade, and risk stratification based upon gene expression profiles (e.g., Oncotype DX or MammaPrint) (Fig. 12.2). Age, comorbid conditions, performance status, patient preference, risk–benefit discussion, and life expectancy should be incorporated in adjuvant treatment decision-making.

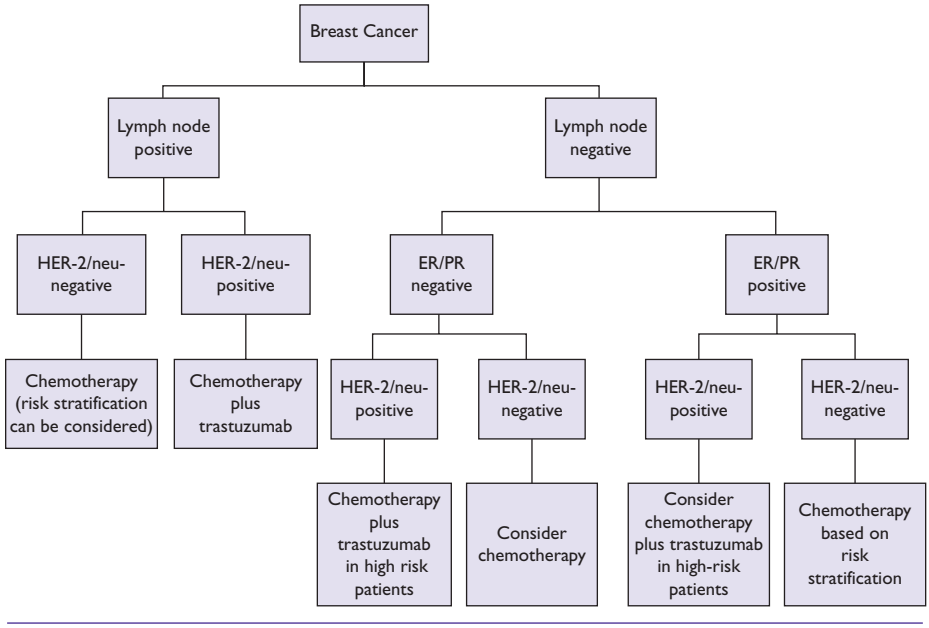

FIGURE 12.2 Algorithm for systemic adjuvant therapy.

General Principles of Adjuvant Therapy (Table 12.3)

1. All patients with breast cancer should be screened for potential clinical trials.
2. ER/PR-positive patients should be considered for antiestrogen therapy.
3. HER-2/neu-positive patients should be considered for HER-2/neu-targeted therapy.
4. Chemotherapy should be considered for the following patients:
   a. ER/PR-negative patients
   b. Triple negative patients
   c. HER-2/neu-positive patients
   d. Node-positive patients
   e. High-risk patients based upon Oncotype DX, MammaPrint, or other prognostic classification
   f. Patients under the age of 35 years

Adjuvant Therapy in HER-2/neu-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). There is no major difference in efficacy among the regimens.

Table 12.4 Non–Trastuzumab-Containing Combinations

Commonly Used Regimens

Dose-dense AC followed by paclitaxel chemotherapy
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
- Cycled every 14 d for 4 cycles
- Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day

Cycled every 14 d for 4 cycles (All cycles are with filgrastim support)

Dose-dense AC followed by weekly paclitaxel chemotherapy
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 d for 4 cycles

Followed by
- Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 wk

TC chemotherapy
- Docetaxel 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 d for 4 cycles

AC chemotherapy
- Doxorubicin 60 mg/m^2 IV day
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 d for 4 cycles

TAC chemotherapy
- Docetaxel 75 mg/m^2 IV day 1
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 d for 6 cycles (All cycles are with filgrastim support)

Other Regimens

FAC chemotherapy
- 5-Fluorouracil 500 mg/m^2 IV days 1 and 8 or days 1 and 4
- Doxorubicin 50 mg/m^2 IV day 1 (or by 72-h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 d for 6 cycles

CAF chemotherapy

(*Continued*)

Table 12.4 (Continued)

- Cyclophosphamide 100 mg/m^2 PO days 1–14
- Doxorubicin 30 mg/m^2 IV days 1 and 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 and 8

Cycled every 28 d for 6 cycles
CEF chemotherapy

- Cyclophosphamide 75 mg/m^2 PO days 1–14
- Epirubicin 60 mg/m^2 IV days 1 and 8
- 5-Fluorouracil 500 mg/m^2 IV days 1and 8

With cotrimoxazole support
Cycled every 28 d for 6 cycles
CMF chemotherapy

- Cyclophosphamide 100 mg/m^2 PO

days 1–14

- Methotrexate 40 mg/m^2 IV days 1 and 8
- 5-Fluorouracil 600 mg/m^2 IV days 1 and 8

Cycled every 28 d for 6 cycles
AC followed by docetaxel chemotherapy

- Doxorubicin 60 mg/m^2 IV on day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 d for 4 cycles
Followed by

- Docetaxel100 mg/m^2 IV on day 1

Cycled every 21 d for 4 cycles
EC chemotherapy

- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 830 mg/m^2 IV day 1

Cycled every 21 d for 8 cycles
FEC followed by docetaxel

- 5-Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 d for 3 cycles
Followed by

- Docetaxel 100 mg/m^2 IV day 1

Cycled every 21 d for 3 cycles
FEC followed by weekly aclitaxel

- 5-Fluorouracil 600mg/m^2 IV day 1
- Epirubicin 90 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 d for 4 cycles
Followed by

- 3 wk of no treatment

Followed by

- Paclitaxel100 mg/m^2 IV

Cycled every 21 d for 8 cycles
FAC followed by weekly paclitaxel

- 5-Fluorouracil 500 mg/m2 IV days 1 and 8 or days 1 and 4
- Doxorubicin 50 mg/m2 IV day 1 (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 d for 6 cycles
Followed by

- Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly

for 12 wk

Table 12.5 Trastuzumab-Containing Regimens

AC followed by T chemotherapy with trastuzumab
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 d for 4 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

TCH chemotherapy
- Docetaxel75 mg/m^2 IV day 1
- Carboplatin AUC 6 IV day 1

Cycled every 21 d for 6 cycles
With
- Trastuzumab 8 mg/kg IV day 1

Followed by
- Trastuzumab 6 mg/kg IV every 3 wk to complete 1 y of trastuzumab therapy

Dose-dense AC followed by paclitaxel chemotherapy
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 d for 4 cycles
Followed by
- Paclitaxel175 mg/m^2 by 3 h IV infusion day 1

Cycled every 14 d for 4 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

(Cardiac monitoring is recommended at baseline, 3, 6, and 9 mo)

Modified from NCCN guidelines 2013.

Adjuvant Therapy in HER-2/neu-Positive Patients (Table 12.5)

Incorporation of trastuzumab in the adjuvant therapy is the most important development in the treatment of breast cancer in the past 10 years. Many trastuzumab-containing regimens have been tested and all are equally effective. Clinical trials have shown more than 50% improvement in DFS and more than 30% improvement in OS for patients who received trastuzumab in an adjuvant setting. The major difference is in the cardiac toxicity. Non–anthracycline-containing regimen, such as TCH (BCIRG 006) and HERA trial (sequential herceptin), had less cardiac toxicity compared to other anthracycline-containing regimens.

Several ongoing clinical trials are evaluating the role of pertuzumab, ado-trastuzumab emtansine (TDM-1), lapatinib, and other HER-2/neu-targeted agents in adjuvant breast cancer treatment.

Neoadjuvant or Preoperative Chemotherapy

Neoadjuvantor preoperative chemotherapy can be considered for any patients with locally advanced breast cancer (IIB, IIIA, IIIB, IIIC), and inflammatory breast cancer. But in IIIA, IIIB, and IIIC, and inflammatory breast cancer it is the treatment of choice.

- Initial surgery is limited to biopsy to confirm the diagnosis and to identify the ER/PR, HER-2/neu-status, and other prognostic features.

- Preoperative evaluation of the breast mass by mammogram, ultrasound, or MRI is recommended.
- Potentially, the neoadjuvant chemotherapy can reduce the size of the primary tumor, so breast conserving surgery can be performed.
- HER-2/neu-negative patients:
  - Usually, a preoperative regimen contains an anthracycline and a taxane. Any adjuvant regimen can be used in a neoadjuvant setting.
  - One of the largest neoadjuvant clinical trials is the NSABP B-27 trial (four cycles of AC followed by docetaxel for four cycles given every 3 weeks).
- HER-2/neu-positive patients:
  - An M.D. Anderson study has shown that trastuzumab with paclitaxel for four cycles followed by FEC with trastuzumab for four cycles is highly active.
  - Any adjuvant trastuzumab regimen can be used in a neoadjuvant setting.
  - Several clinical trials have shown an advantage for combination of HER-2/neu-targeted agents such as pertuzumab (NEOSPHERE) or lapatinib (NEOALTO) with trastuzumab.

Adjuvant Endocrine Therapy

Unless there is a contraindication, endocrine therapy should be considered for all patients with ER-positive and/or PR-positive tumors. As per the Oxford overview analysis, tamoxifen can decrease mortality by about 30% recurrence by 50% in hormone receptor-positive patients (Fig. 12.3 and Table 12.6).

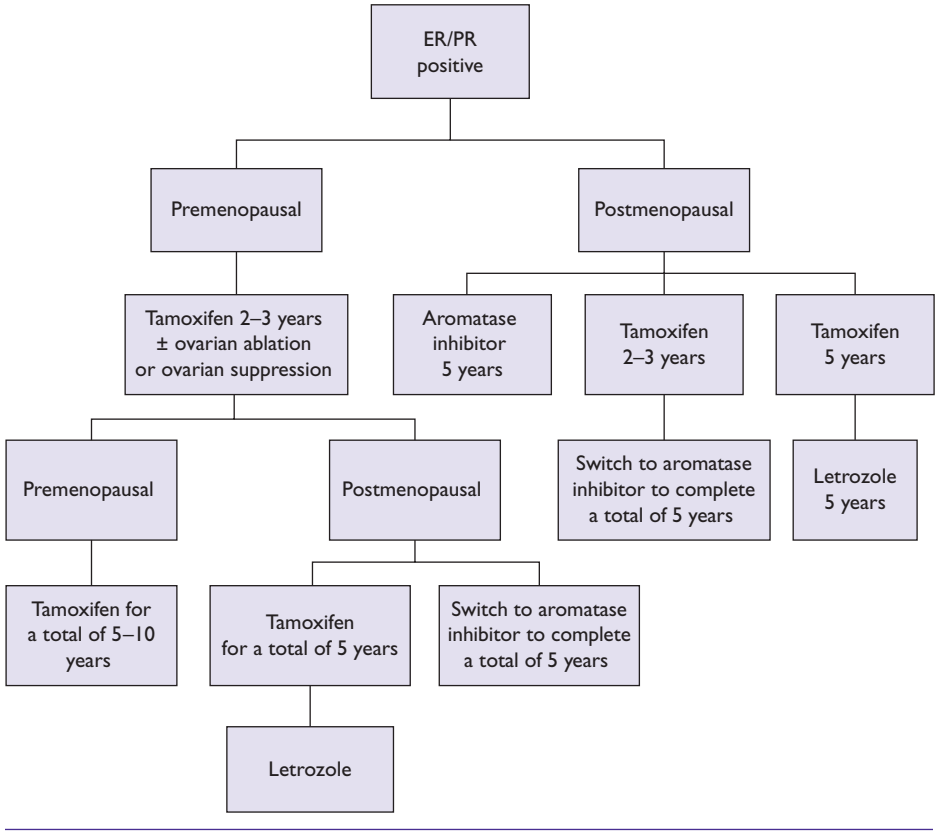

FIGURE 12.3 Adjuvant endocrine therapy.

Table 12.6 Endocrine Agents Used in Treatment of Breast Cancer

Selective estrogen-receptor modifier (SERM) with combined estrogen agonist and estrogen antagonist activity
Tamoxifen (Nolvadex, others), 20 mg/d PO
Toremifene (Fareston), 60 mg/d PO
Estrogen receptor downregulator
Fulvestrant 500 mg day 1, day 15 and then once a month intramuscular
Aromatase inhibitors
Anastrozole (Arimidex), 1 mg/d PO
Letrozole (Femara), 2.5 mg/d PO
Exemestane (Aromasin), 25 mg/d PO
LHRH agonist analog in premenopausal women
Leuprolide (Lupron Depot), 7.5 mg/dose i.m. monthly, or
Leuprolide (Lupron Depot), 22.5 mg/dose i.m. every 3 mo, or
Leuprolide (Lupron Depot), 30 mg/dose i.m. every 4 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
Used in patients who have tumors that express either ER or PR receptors or both receptors

LHRH, luteinizing hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; ER, estrogen receptor; PR, progesterone receptor.

Postmenopausal Women

Several large randomized studies have shown superiority of AIs over tamoxifen in adjuvant settings. If the patient has no contraindication, AIs are the preferred agents in postmenopausal patients. Anastrozole, letrozole, and exemestane are three third-generation AIs approved by the FDA for adjuvant use. The major side effects include arthralgia, ostopenia, osteoporosis, and fracture.

Anastrozole One of the largest adjuvant breast cancer trials, of comparing tamoxifen with anastrazole and combination of both anastrozole and tamoxifen (ATAC), has shown that anastrozole is superior to tamoxifen in improving DFS, reduction in contralateral breast cancer, and has a favorable side-effect profile. For postmenopausal patients, the recommended dose is anastrozole 1 mg PO daily for 5 years.

Letrozole BIG 1-98 showed a similar magnitude of improvement (like the ATAC trial) in DFS and a reduction of distant metastasis with letrozole. For postmenopausal patients, the recommended dose is letrozole 2.5 mg PO daily for 5 years.

Switching from Tamoxifen to an Aromatase Inhibitor 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).

The Italian Tamoxifen Anastrozole (ITA) trial, Austrian Breast Colorectal Study Group (ABCSG 8), and Arimidex, Noveldex (ARNO) study have shown an improvement in DFS and OS in patients who were initially treated with 2 to 3 years of tamoxifen and subsequently randomized to 2 to 3 years of anastrozole.

Extended Adjuvant 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 (extended adjuvant therapy). The NSABP B-42 clinical trial is looking at the role of extended use of AIs beyond 5 years.

Endocrine Therapy: Premenopausal Patients (Fig. 12.3)

Hormone receptor-positive, premenopausal patients are in general treated with tamoxifen. Combination of ovarian ablation or suppression with endocrine therapy (tamoxifen or aromatize inhibitors) is being investigated in many clinical trials.

Tamoxifen Tamoxifen is a selective estrogen-receptor modulator (SERM), 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, and endometrial cancer. Major adverse effects include a higher incidence of cerebrovascular accidents, thrombosis, endometrial cancer, hot flashes, mood changes, and weight gain.

In general, tamoxifen is recommended for 5 years. But a recent study (ATLAS) showed a continued benefit of tamoxifen for 10 years. In selected patients, tamoxifen should be considered for 10 years.

Ovarian Ablation or Ovarian Suppression

The Oxford overview and several studies have found that premenopausal patients who stopped having periods after completion of chemotherapy have better survival than those who continued to have periods. Ovarian ablation can be achieved by surgery, radiation, or with LHRH agonists (goserelin, triptorelin). The definite roles of ovarian suppression or ablation in patients who are receiving tamoxifen or AIs are not clear yet. Several ongoing phase 3 clinical trials using LHRH agonists (SOFT, TEXT, PERCHE) will answer this question.

BREAST CANCER IN PREGNANCY

- Breast cancer during pregnancy was thought to be more aggressive, but the overall poor outcome is likely related to the advanced stage at the time of diagnosis.
- Breast biopsy is safe in all stages of pregnancy and should be done for any mass concerning cancer.

Treatment

- Lumpectomy and axillary 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.
- No chemotherapeutic agent has been found to be completely safe during pregnancy.
- An anthracycline combined with cyclophosphamide (e.g., AC given every 3 weeks for four cycles) has been used safely in the adjuvant setting during the second or third trimesters.
- Chemotherapy should be scheduled to avoid neutropenia and thrombocytopenia at the time of delivery.
- Paclitaxel is teratogenic and should not be used during pregnancy.
- Tamoxifen is teratogenic and should not be used in pregnant women.
- Therapeutic abortion does not change the survival rate.

MALE BREAST CANCER

- Male breast cancer is uncommon.
- Risk factors are family history, BRCA2 germ-line mutation, Klinefelter syndrome, and radiation to the chest wall.

- Presence of gynecomastia is not a risk factor for breast cancer.
- It is first seen as a mass beneath the nipple or ulceration.
- The mean age of occurrence is 60 to 70 years.
- Eighty percent of male breast cancer is hormone-receptor positive.

Treatment

- Modified radical mastectomy.
- Lumpectomy is rarely done because it does not offer any cosmetic benefit.
- Systemic treatment with chemotherapy and endocrine therapy should follow the general guidelines for female patients.
- None of the adjuvant treatment modalities has been tested in a randomized clinical trial setting in men.

Phyllodes Tumor

A phyllodes tumor is clinically suspected when the tumor is growing rapidly and clinical and radiologic features suggestive of fibroadenoma. 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.

Paget Disease of the Nipple

Patients should be evaluated for any evidence of invasive or noninvasive breast cancer by appropriate imaging and biopsy. If the patient has only Paget disease of the nipple areolar complex (NAC), the patient can be treated with mastectomy with ALND or wide excision of the NAC and axillary node surgery with whole-breast radiation. Patients with invasive or noninvasive breast cancer should be managed appropriately.

METASTATIC BREAST CANCER (FIG. 12.4)

Principles of Treatment

1. Repeat biopsy to confirm the diagnosis of recurrent/metastatic breast cancer.
2. Strongly recommend to repeat all markers including ER/PR and HER-2/neu-.
3. All patients should be considered for clinical trials.
4. HER-2/neu-positive patients could be treated with HER-2/neu-targeted agents such as trastuzumab, ado-trastuzumab emtansine (TDM-1), pertuzumab, or lapatinib.
5. ER/PR-positive patients should be treated with antiestrogen therapy if they have nonvisceral disease or slow growing disease.
6. Combination chemotherapy regimens have not shown significant DFS or OS benefit, so patients should be treated with single, sequential agents if possible.
7. All patients with metastatic disease involving the bone should be considered for a bisphosphonates (zolendronic acid/pamidronate) or denosumab (RANK ligand inhibitor).
8. A detailed discussion of the comorbid conditions, performance status, patient preference, toxicities of the treatment, and risk versus benefit should be done with the patient.
9. Goal of treatment should be discussed in detail with the patient, since it is palliative for majority of the patients.

Targeted Therapy

Trastuzumab (Herceptin®)

This is a monoclonal antibody, which is found to be highly effective in metastatic and adjuvant breast cancer therapy. The dose is usually 4 mg/kg as a loading dose and 2 mg/kg weekly. It can also be given every 3 weeks, with a loading dose of 8 mg/kg followed by 6 mg/kg. The addition of 1 year of adjuvant trastuzumab improves DFS and OS among women with HER-2/neu-positive breast cancer. In general, trastuzumab is given in combination with chemotherapy in adjuvant and metastatic settings.

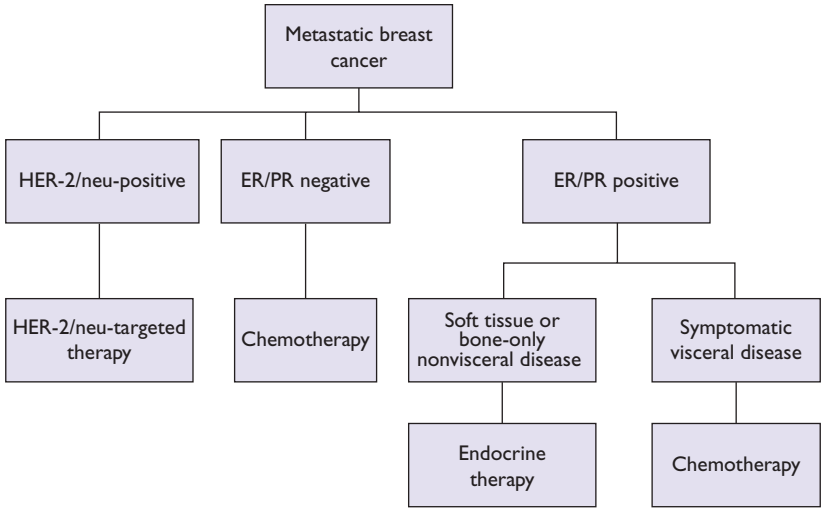

FIGURE 12.4 Algorithm for the management of metastatic breast cancer.

Trastuzumab is well tolerated; rarely it can cause infusion reaction and pulmonary toxicity. The major side effect from trastuzumab is cardiac toxicity when it is used with or after anthracyclines. With anthracycline-containing regimen, the congestive heart failure rate is about 2% to 4%. Nonanthracycline regimens such as TCH did not show increased cardiac toxicity. It is important to monitor cardiac function with an ECHO cardiogram or MUGA scan baseline and every 3 months, for patients who are receiving trastuzumab.

Ado-trastuzumab emtansine (Kadcyla®)

Ado-trastuzumab emtansine 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 HER-2/neu- receptors and the stable linker releases the cytotoxic agent only when the compound is internalized through receptor endocytosis. Ado-trastuzumab emtansine 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 3 EMILIA trial that compared trastuzumab emtansine with capecitabine plus lapatinib in advanced HER-2/neu-positive breast cancer showed a substantial improvement in progression-free survival (PFS) and OS with the conjugate.

The dose of ado-trastuzumab emtansine is 3.6 mg/kg IV every 3 weeks and it is extremely well tolerated in clinical trials.

Side effects include thrombocytopenia and liver function abnormalities. No significant increase in cardiomyopathy or peripheral neuropathy was seen. It is being evaluated in several clinical trials including neoadjuvant (NSABP B 50), adjuvant, and metastatic. Some of the trials are looking at the role of ado-trastuzumab emtansine in combination with pertuzumab.

Pertuzumab (Perjeta®)

Pertuzumab is a humanized monoclonal antibody that binds HER-2/neu- at a different epitope of the HER-2/neu- extracellular domain than that of trastuzumab. It prevents HER-2/neu- from dimerizing with HER3. Similar to trastuzumab, pertuzumab causes antibody-dependent, cell-mediated cytotoxicity. Since pertuzumab and trastuzumab bind to different HER-2/neu- epitopes and have complementary mechanisms of action, when pertuzumab is combined with trastuzumab, it provides a more comprehensive blockade of HER-2/neu- 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 HER-2/neu-positive metastatic breast cancer, it significantly prolonged progression-free survival. No additional cardiac toxicity was seen. The FDA-approved dose of pertuzumab was 840 mg, followed by 420 mg every 3 weeks.

Lapatinib (Tykerb®)

A potent, small molecule inhibitor of the HER1 and HER-2/neu- tyrosine kinases. 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. It is a dual tyrosine kinase inhibitor, which blocks both EGFR (HER1) and HER-2/neu- pathway intracellularly. The FDA-approved dose of lapatinib is 1,250 mg daily PO. The side effects include diarrhea and rash.

Other HER-2/neu-Targeted Agents

Many novel HER-2/neu-targeted agents are being tested for HER-2/neu-positive patients. Neratinib and afatinib are two active tyrosine kinase inhibitors in various phases of clinical trials.

Other Relevant Agents

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 (MRP1). 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 a 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.

Eribulin (Halaven®)

Eribulin mesylate is a nontaxane, tubulin- and microtubule-targeting chemotherapeutic agent binds directly with tubulin disrupting mitotic spindles and inhibits microtubule polymerization. A phase 3 study, which compared eribulin to treatment of physician's choice (TPC) in patients with locally recurrent or metastatic breast cancer with previous treatment with an anthracycline and taxane, 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.

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 a monotherapy for metastatic breast cancer. The FDA-approved dose is 1,250 mg/m^2 twice a day given

for 2 weeks and 1 week off, then repeating every 21 days. For practical purposes most clinicians use 1,000 mg/m^2 twice a day 2 weeks on 1 week off. The most common side effects are hand–foot syndrome and diarrhea. Patients should be educated about management of the hand–foot syndrome.

Faslodex (Faslodex®)

Fulvestrant (FASLODEX) is an ER antagonist (ER downregulator) and it is indicated in the treatment of hormone receptor-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.

Everolimus (Afinitor®)

The FDA approved everolimus tablets (Afinitor®) for the treatment of postmenopausal women with advanced hormone receptor-positive, HER-2/neu-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. A randomized study with everolimus 10 mg per day plus exemestane 25 mg per day showed improvement in PFS compared to placebo plus exemestane 25 mg per day. The most common adverse reactions in patients receiving everolimus plus exemestane were stomatitis, infections, rash, fatigue, diarrhea, hyperglycemia, and pneumonitis.

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 biphosphonates approved for bony metastatic disease.
- Osteonecrosis of the jaw (ONJ) is a very rare but a potential complication of long-term treatment with intravenous bisphosphonates.

Rank Ligand Inhibitor

Denosumab (XGEVA®) The receptor activator of nuclear factor-κB (RANK), the RANK ligand (RANKL), 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 RANKL, 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 osteonecrosis of the jaw is about 2.2% with denosumab. It does not have to be adjusted for renal impairment.

Central Nervous System Metastasis

Central nervous system (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.

The standard treatment for multiple brain lesions remains whole-brain radiation (WBR) for symptom control, with no improvement in survival. The therapy for a single-brain metastasis remains either surgery or radiosurgery (Gamma Knife), with conflicting information as to the benefit of prior WBR. Leptomeningeal metastasis is conventionally treated with intrathecal chemotherapy, and may provide short-term symptom control. The superiority of intrathecal versus systemic chemotherapy in leptomeningeal metastasis is controversial. About 30% of HER-2/neu-positive patients will develop brain metatastic disease, and lapatinib-containing regimen is an option in these patients.

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, although the survival advantage is not clear.

After lumpectomy:

- Mastectomy is the treatment of choice for patients who have only isolated breast cancer recurrence.

FOLLOW-UP FOR PATIENTS WITH OPERABLE BREAST CANCER (BASED ON ASCO GUIDELINES)

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 then annually.
2. Monthly breast self-examination.
3. Annual mammogram of the contralateral and ipsilateral (remaining breast after lumpectomy) breast.
4. Annual Papanicolaou smear and pelvic examinations in women who are taking, or who have taken, tamoxifen.
5. Blood tests including a complete blood count, liver function tests, and alkaline phosphatase levels are not routinely recommended.
   - Serum tumor markers (CA 27-29, and CA 15-3) are not recommended.
   - Bone scan and imaging of the chest, abdomen, pelvis, and brain or PET scans are not recommended routinely, but they are done if symptoms or laboratory abnormalities are present.
6. Rectal examination, occult blood testing, and skin examination must be performed annually or every 2 years.

REVIEW QUESTIONS

1. A 29-year-old white female of Irish ancestry was seen in the high-risk clinic. Her father was diagnosed with pancreatic cancer at the age of 45, her paternal grandmother was diagnosed with ovarian cancer at the age of 38, and her paternal aunt was diagnosed with breast cancer at the age of 48. There is no other family or personal history of breast cancer. In addition to genetic counseling and genetic testing, what is the next step?

A. Bilateral mastectomy and prophylactic oophorectomy
B. CT/PET scan for ovarian or pancreatic cancer screening
C. Breast MRI and pelvic ultrasound
D. CA 125 and CA 19-9
E. Wait for the genetic testing results to come before decide about the next step

2. A 55-year-old patient is seen in the medical oncology clinic after having a lumpectomy and sentinel lymph node dissection for an invasive ductal cancer. The tumor size is 1.8 cm and ER/PR strongly positive and HER-2/neu- negative. One of the two sentinel lymph nodes examined was positive for cancer. Her management options are

A. She should proceed with complete axillary node dissection, for local control, since one sentinel lymph node is positive.
B. She should get chemotherapy, because one node is positive.
C. May be a candidate for Oncotype, radiation therapy, and endocrine therapy, if she is in the low-risk group.
D. Since she has a lymph node involvement, she is not a candidate for Oncotype.

3. A 65-year-old patient with invasive ductal cancer had a left modified radical mastectomy and 2 lymph nodes were positive for invasive cancer. Her tumor size was 2.7 cm and she was staged as T2 N1 M0 (IIB). ER/PR was 90% to 100% positive and K1 67 was 5%. HER-2/neu- was negative by immunohistochemistry. She is in your office to discuss about adjuvant therapy options. She is otherwise very healthy.
   - **A.** Since she has a IIB tumor, strongly recommend chemotherapy with TC for four cycles.
   - **B.** Chemotherapy may not add much value to her treatment; her maximum benefit will be from endocrine therapy.
   - **C.** She should receive radiation therapy since she had a 2.7 cm tumor and one lymph node positive.
   - **D.** It is up to the patient to decide about her therapy since she is older than 65.
4. A 44-year-old school teacher was diagnosed with a stage IIB, ER/PR-negative and HER-2/neu-negative breast cancer in 2002. In 2007 the patient presented with chest pain and shortness of breath. Chest x-ray followed by a CT scan of the chest showed a 4 cm left lower lobe lesion, which was biopsied and was confirmed as breast cancer. The repeat ER/PR was negative, but HER-2/neu-testing by immunohistochemistry was 3+. The patient was started on multiple trastuzumab- and lapatinib-containing regimens. She continues to work and has an excellent cardiac function and ECOG performance status. The last restaging scan showed progression of the cancer compared to the previous scan. The patient clearly wishes to continue with the treatment. Her options are
   - **A.** Supportive care only, since she had multiple treatments in the past.
   - **B.** Pertuzumab, trastuzumab, and docetaxel as per the CLEOPATRA study.
   - **C.** Avoid HER-2/neu-targeted therapy, since it has worked in the past.
   - **D.** Ado-trastuzumab emtansine (TDM-1) is a very reasonable option for her.
   - **E.** Keep her on trastuzumab and change to different chemotherapy.
5. A 56-year-old woman with metastatic breast cancer, on treatment with exemestane and everolimus, presented to the walk-in clinic with new onset fever, cough, and shortness of breath. The chest x-ray showed diffuse patchy infiltrate. The patient's blood pressure was 134/86 mmHg and heart rate was 84 per minute. Her pulse oxymetry was 94% on room air. Her sites of metastatic disease were L4 and L5 lesions. The patient's last dose of zolendronic acid was about 3 weeks back. Her management options include
   - **A.** She has lymphangiatic spread of breast cancer, so consider stopping the current medicine and start her on chemotherapy.
   - **B.** It is everolimus-induced pneumonitis, so she should be immediately taken off the treatment and never put back on it again.
   - **C.** If it is only a grade 2 toxicity, we can interrupt the everolimus and restart at a lower dose, once the toxicity is improved to grade 1 or less.
   - **D.** She needs a bronchoscopy to confirm the diagnosis.

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Section Five

Genitourinary

13

Renal Cell Cancer

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Renal cell cancer (RCC), a term that includes a variety of cancers arising in the kidney, comprises several histologically, biologically, and clinically distinct entities. Surgical resection for localized disease and immunotherapy for metastatic disease have been the mainstays of therapy for RCC. However, recent advances in our understanding of the molecular mechanisms underlying individual subtypes of the disease have led to newer, more effective, targeted approaches to managing metastatic RCC.

EPIDEMIOLOGY

- An estimated 64,000 new cases of cancer arising in the kidney and renal pelvis were diagnosed in the United States in 2012, leading to more than 13,000 deaths.
- Incidence is higher in men, with a male:female ratio of 1.6:1.
- 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 has decreased during the same period by 0.4% per year in men and 0.6% in women.
- Largely a disease of adulthood, with a peak incidence after the fifth decade of life, RCC may also occur in children and infants.

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 Syndrome

- von Hippel-Lindau (VHL) syndrome 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), pancreatic neuroendocrine tumors, renal and pancreatic cysts, 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 germ line. Acquisition of a somatic "second hit" that inactivates the normal copy of VHL leads to tumor formation in the affected organ(s).

Hereditary Papillary RCC

- 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 germ-line 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 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-Dube Syndrome

- Affected individuals are at increased risk of developing cutaneous fibrofolliculomas, pulmonary cysts predisposing to the development of spontaneous pneumothoraces, and renal tumors.
- Several histologic types of renal tumors have been described in Birt-Hogg-Dube (BHD) syndrome, including chromophobe (34%), hybrid chromophobe-oncocytomas (50%), clear cell, 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 may function as a tumor suppressor.

Hereditary Leiomyomatosis and RCC

- 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.
- Sometimes described histologically as a type of papillary type 2 RCC; 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 germ-line mutation in the gene for 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 HIF1-α expression and downregulation of AMPK, a key cellular energy sensor.

Succinate Dehydrogenase and RCC

- Succinate dehydrogenase is a multiunit mitochondrial enzymatic complex that catalyzes the conversion of succinate to fumarate in the Krebs cycle.
- Germ-line mutations in the genes encoding SDHB, SDHC, and SDHD have been identified in patients with hereditary forms of kidney cancer. Patients with germ-line *SDHB* mutations are also at risk for developing pheochromocytomas and paragangliomas.
- Loss of SDH activity leads to impaired Krebs cycle function and leads to metabolic and biochemical alterations similar to that seen with FH inactivation.

Other Genes Associated with Hereditary Kidney Cancer

- Mutations in multiple genes involving the LKB1/TSC/mTOR are associated with familial forms of RCC.
- Mutations in the genes responsible for tuberous sclerosis complex (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.

PATHOLOGIC CLASSIFICATION

Based on histopathologic features, RCC is divided into the following subtypes:

- Clear cell RCC. The most common variety, comprising 70% to 80% 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.
- Collecting duct RCC. Rare (<1%) variant believed to originate in the collecting system. Medullary RCC, which 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. Represents approximately 3% to 5% of renal tumors. Lack distinct features of a particular subtype or variant.
- Renal tumors with sarcomatoid features do not comprise a separate entity. Instead, they represent localized or diffuse sarcomatoid differentiation of one of the subtypes of RCC. Generally associated with poor prognosis.

MOLECULAR MECHANISMS

Identifying familial kidney cancer syndromes 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

- Germ-line mutations in the *VHL* gene are the hallmark of VHL syndrome.
- The vast majority of patients with sporadic clear cell RCC show evidence of *VHL* inactivation in tumor tissue 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 (HIF).

- Increased intracellular HIF leads to transcriptional upregulation of several proangiogenic, 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 glut-1. This sequence of events appears to be important in the genesis and propagation of clear cell RCC.
- Several components of this pathway are 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 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 hereditary papillary RCC (HPRC).
- Activating somatic mutations in the tyrosine kinase domain of Met have also been identified in 10% to 15% of patients with sporadic papillary RCC. Duplication of chromosome 7, where genes for both MET and HGF are located, is seen more frequently in sporadic papillary tumors (approximately 70% in one series) and may represent an alternative mechanism for activation of the HGF/Met pathway.
- Agents targeting the MET pathway are currently being evaluated in patients with papillary RCC.

Type 2 Papillary RCC

- Includes tumors with papillary architecture but with features inconsistent with type 1 papillary tumors. Patients with HLRCC are at risk for developing renal tumors, which are sometimes described as type 2 papillary RCC.
- The underlying molecular defect in HLRCC-related tumors is 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.). While no sporadic counterpart for this tumor has been described, it is speculated that some sporadic type 2 tumors may be associated with impaired Krebs cycle activity.

Chromophobe RCC

- The precise biochemical aberrations underlying chromophobe RCC are being investigated; however, patients with BHD often present with chromophobe renal tumors.
- 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.

Other Subtypes

- Other histologic subtypes of RCC include (1) medullary RCC, seen almost exclusively in association with sickle cell trait, and (2) collecting duct RCC, which shares similarities with upper urinary tract tumors.
- 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, including elevated erythrocyte sedimentation rate, weight loss/cachexia, hypertension from increased renin, anemia, hypercalcemia (release of PTH-like substance), elevated alkaline phosphatase, polycythemia (increased erythropoietin), and Stauffer syndrome (reversible, nonmetastatic hepatic dysfunction that 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.
- Common sites of metastatic spread include lung (70% to 75%), lymph nodes (30% to 40%), bone (20% to 25%), liver (20% to 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 PT/PTT.
- CT scan of the abdomen and pelvis, with and without contrast, is standard for evaluating the renal mass and regional lymph nodes. If the CT scan suggests renal vein and/or inferior vena cava involvement, an 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 (TNM) staging system outlined by the American Joint Committee for 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 are metastases to regional lymph nodes, or the tumor extends into major veins or perinephric tissues but not the ipsilateral adrenal gland nor 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 are gaining 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 outcomes in patients treated with either cytokines or chemotherapeutic agents (Memorial Sloan-Kettering Cancer Center prognostic criteria) implicates the following features in poor outcome:
  - Poor performance status (Karnofsky PS <80)
  - Elevated LDH ($>1.5 \times$ upper limit of normal)

  - Elevated corrected calcium (>10 mg/dL)
  - Low hemoglobin (< lower limit of normal)
  - Absence of prior nephrectomy
- 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
- A similar prognostic scheme has been proposed for stratification of patients receiving agents targeting the VEGF and mTOR pathways, but remains to be independently validated.

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) is the treatment of choice. However, recent literature supports nephron-sparing procedures for tumors 4 to 7 cm in selected patients. Patients with primary tumors larger than 7 cm and disease localized to the kidney generally undergo a radical nephrectomy with curative intent.
- 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.

Adjuvant Therapy

Although a variety of agents such as cytokines and vaccines have been evaluated in the adjuvant setting, none has proved effective in reducing the risk of recurrence or improving long-term outcome. Ongoing adjuvant trials are evaluating the role of targeted therapeutic agents such as sunitinib, pazopanib, everolimus, and sorafenib in patients with high-risk disease following resection of the primary tumor.

TREATMENT OF METASTATIC RCC

Surgery

- In selected patients with isolated metastases, surgical resection may provide extended disease-free periods. Five-year survival rates of 30% to 50% have been reported in retrospective analyses using this approach.
- Cytoreductive nephrectomy preceding systemic cytokine therapy has been the subject of several studies. At least two randomized phase 3 trials have demonstrated a survival advantage in patients receiving interferon-alpha (IFN-α) following nephrectomy versus patients receiving IFN-α alone. Careful patient selection is key to the success of this approach, and patients with limited metastatic burden, favorable tumor kinetics, and good performance status are most likely to benefit. Cytoreductive nephrectomy as a prelude to antiangiogenic targeted therapies is currently under evaluation in randomized phase 3 trials.
- Cytoreductive nephrectomy can be performed for palliation of intractable hematuria and pain associated with RCC.

Systemic Therapy

- Conventional cytotoxic chemotherapy is ineffective in the vast majority of patients with metastatic RCC (approximately 5% to 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.
- Targeted agents directed against the VEGF/PDGF and mammalian target of rapamycin (mTOR) pathways have been evaluated in patients with metastatic RCC and have largely supplanted cytokines as standard first-line agents in the management of clear cell RCC (Table 13.1). The standard initial approach for most patients with metastatic clear cell RCC is treatment with small molecule inhibitors of angiogenesis, although cytokine-based therapy with interleukin (IL)-2 should be considered in selected patients.
- There are currently no standard treatments for non–clear cell variants, although several interesting mechanism-based approaches are under investigation.

VEGF Pathway Inhibitors

Upregulation of proangiogenic factors such as VEGF and PDGF is an important consequence of VHL inactivation and provides the basis for the efficacy of anti-VEGF agents in RCC. Several agents targeting the VEGF pathway are approved by the US FDA for the treatment of metastatic RCC.

Sunitinib

- An oral tyrosine kinase inhibitor with potent activity against VEGF receptor 2 (VEGFR-2) and PDGF receptor (PDGFR).
- Initial single-arm phase 2 studies demonstrated a remarkably high overall response rate of 30% to 40% in patients with cytokine-refractory disease. A randomized phase 3 study comparing sunitinib with IFN-α in previously untreated clear cell RCC patients has demonstrated a significantly higher response rate (47% vs. 12%), improved progression-free survival (PFS) (median 11 vs. 5 months), and superior overall survival (OS) (26.4 vs. 21.8 months) with sunitinib.
- Dosage is 50 mg per day over 4 weeks, followed by a 2-week rest period.
- Fairly well tolerated by the majority of patients. Common side effects include hypertension, fatigue, cutaneous side effects (rash, hand–foot syndrome), gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia, constipation), and cytopenia.
- Sunitinib is one of the most widely used first-line agents in metastatic clear cell RCC.

Pazopanib

- Oral angiogenesis inhibitor that targets VEGFR-1, -2, and -3. Approved in 2009 by the FDA for the treatment of advanced RCC.
- In a phase 3 trial of patients with advanced RCC with 0 or 1 prior cytokine treatment comparing pazopanib versus placebo, PFS was increased in the pazopanib group (9.2 months) compared to the placebo cohort (4.2 months). In subgroup analyses, the improvement in PFS was seen in both treatment naïve patients and those who had received prior cytokine therapy.
- Adverse reactions include diarrhea, hypertension, nausea, fatigue, and abdominal pain. Hepatotoxicity with elevated transaminases was seen, and a small number of deaths from hepatic failure were noted on study. Liver function testing should be performed while on therapy.
  - Although the adverse events seen with sunitinib and pazopanib are similar, head-to-head comparison in randomized studies suggested that pazopanib was better tolerated, with both patients and physicians indicating a preference for this agent over sunitinib based on better tolerability. Furthermore, in a phase 3 randomized study, the efficacy of pazopanib in clear cell RCC patients was shown to be noninferior to that seen with sunitinib.

Axitinib

- A highly selective oral tyrosine kinase inhibitor that targets VEGFR 1, 2, and 3. Approved by the FDA in 2012 for the treatment of advanced RCC in patients who had previously failed one prior systemic therapy.

Table 13.1 Key Studies of Targeted Agents in Metastatic Renal Cell Carcinoma

Agent(s)	Phase	Study Population	Number 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. 21.8**
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[b]	Randomized phase 3	Clear cell	233	**32% vs. 4%**	**11.1 vs. 2.8**	
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
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[b]	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

Bev, bevacizumab; IFN-α, interferon-alpha; NR, not reached; NA, Not available; OS, overall survival; PFS, progression-free survival; tem, temsirolimus.

[a]Statistically significant differences indicated in boldface type.

[b]Subgroup Analysis

- A phase 3 trial compared the efficacy of dose-escalated axitinib versus standard dose sorafenib following first-line treatment with either sunitinib, bevacizumab plus IFN-α, temsirolimus, or cytokine therapy. The PFS was 6.7 months in patients on axitinib versus 4.7 months in patients on sorafenib. In subgroup analysis the median PFS was consistently improved over the sorafenib group regardless of prior treatment, although the difference was more pronounced in patients who had received prior cytokine therapy.
- The agent appears to be fairly well tolerated. Adverse effects include hypertension, diarrhea, dysphonia, nausea, fatigue, and hand–foot syndrome.
  - Treatment-related hypertension has been proposed as a clinically evaluable pharmacodynamic marker in patients receiving axitinib as well as other agents targeting the VEGF pathway. Retrospective studies demonstrate a correlation between the occurrence of hypertension (thought to indicate adequate plasma levels of the agent and consequently optimal inhibition of the VEGF pathway) and outcome.
  - The effect of dose titration of axitinib on plasma levels of the agent and on treatment outcome is being currently evaluated in a phase 2 randomized study.

Bevacizumab

- A monoclonal antibody against VEGF-A, approved by the FDA in 2009 for the treatment of advanced RCC in combination with IFN-α.
- A randomized, three-arm phase 2 study comparing two different doses of bevacizumab (10 mg/kg and 3 mg/kg IV every 2 weeks) and placebo in cytokine-refractory patients showed a PFS advantage favoring the 10 mg/kg arm (4.8 vs. 2.5 months).
- Two multicenter randomized phase 3 studies with similar trial designs comparing IFN-α alone (9 million international units SC 3 times per week) versus the same dose of IFN-α plus bevacizumab (10 mg/kg IV every 2 weeks) showed superior PFS in the combination arm (5.4 vs. 10.2 months). These improvements in PFS did not appear to translate into significant OS benefits in either of these trials.
- Side effects include hypertension, headache, nosebleeds, headaches, and proteinuria and in some cases gastrointestinal perforation and difficulty with wound healing.

Sorafenib

- An oral tyrosine kinase inhibitor with activity against c-Raf, VEGFR-2, and PDGFR.
- A randomized phase 2 study showed significant improvement in PFS versus placebo (median 24 vs. 6 weeks) in patients with cytokine-refractory metastatic RCC. This finding was confirmed in a randomized phase 3 trial of sorafenib versus placebo (median PFS 5.5 vs. 2.8 months). OS was similar in the two groups (17.8 vs. 15.2 months) and may have been influenced by the trial's crossover design (patients progressing on placebo could cross over to the sorafenib arm).
- A randomized phase 2 study in metastatic, untreated clear cell RCC failed to demonstrate the drug's superiority over IFN-α.
- Typically administered at a dose of 400 mg twice a day. Adverse events are similar to those of sunitinib.
- Provides a reasonable option for patients who have failed sunitinib and/or other first-line agents.

mTOR Pathway Inhibitors

The mTOR inhibitors temsirolimus and everolimus are rapamycin analogs believed to act at least in part by downregulating mTOR-dependent translation of HIF.

Temsirolimus

- A prodrug of rapamycin-administered IV.
- The most convincing evidence for the activity of this drug in RCC comes from a randomized phase 3 trial of 626 patients with previously untreated high-risk metastatic RCC (defined as the presence of three or more poor prognostic criteria). All histologic subtypes of RCC were included in this trial. Patients were randomized to receive temsirolimus 25 mg IV per week or temsirolimus 15 mg

IV per week plus IFN-α (6 million international units 3 times per week) or IFN-α alone (18 million international units three times per week as tolerated). Single-agent temsirolimus was associated with significantly prolonged disease-free survival and OS compared to IFN-α alone (median OS 10.9 vs. 7.3 months). An exploratory subgroup analysis suggested that both patients with clear cell and those with non–clear cell RCC benefited from temsirolimus. The combined temsirolimus/IFN-α arm had superior disease-free survival compared to IFN-α alone, but there was no difference in OS between the two groups.

- Common adverse events include rash, fatigue, mucositis, hyperglycemia, hypercholesterolemia, and interstitial pneumonitis. Rapamycin analogs are also associated with a risk of immunosuppression.
- Single-agent temsirolimus is a reasonable first-line option for patients with poor-prognosis RCC.

Everolimus

- An oral rapamycin analog.
- In a randomized phase 3 trial of metastatic RCC patients who had progressed on front-line VEGF-targeted therapy, everolimus improved disease-free survival compared to placebo (4 vs. 1.9 months).
- Side effects are similar to those of temsirolimus.
- Both temsirolimus and everolimus are reasonable treatment options for patients who have progressed on sunitinib or other VEGF antagonists.

Cytokines

Until the advent of VEGF-targeted therapy, cytokines were the mainstay of treatment for metastatic clear cell RCC. High-dose IL-2 and IFN-α are the most studied agents in this class.

IL-2

Since the early 1980s, numerous studies have demonstrated the efficacy of IL-2 in patients with metastatic RCC.

- High-dose IL-2 (600,000 to 720,000 international units/kg every 8 hours as tolerated up to a maximum 15 doses) has shown an overall response rate of 15% to 20%, with complete responses in 7% to 9% of patients. Since only a small subset of patients appears to benefit from this agent, no survival advantage has been demonstrated in randomized trials. However, most complete responses were durable, with very few recurrences noted during long-term follow-up. IL-2 is FDA approved for treatment of RCC.
- Responses to IL-2 are best characterized in patients with clear cell histology; its role in other subtypes of RCC is unclear.
- The major limitation of IL-2 is toxicity associated with the high-dose regimen. A high incidence of serious and life-threatening but often reversible complications (notably vascular-leak syndrome, hypotension, multiorgan failure, etc.) occurred in early trials, with resultant mortality rates of 1% to 5%. However, further experience with IL-2 has led to better management of side effects. A report of over 800 patients treated at the National Cancer Institute reported no treatment-related mortality.
- IL-2 has been evaluated in combination with a variety of other modalities, including cellular therapy with lymphokine-activated killer cells and tumor-infiltrating lymphocytes, chemotherapy, interferon, etc. However, combining any of these therapies with high-dose IL-2 appears to provide no additional benefit.
- Lower doses of either IV or SC IL-2 have been evaluated to determine if toxicity could be reduced without compromising efficacy. At least two randomized trials have demonstrated that lower-dose IL-2 leads to fewer responses and, more importantly, a decline in durable complete responses.
- Despite the availability of newer, better tolerated, VEGF-targeted agents, high-dose IL-2 remains a reasonable first-line option for selected patients with metastatic clear cell RCC.

IFN-α

- The overall response rate in treatment-naïve RCC patients treated with recombinant IFN-α is approximately 15%.

- Administered SC in a variety of dosages (5 to 18 million international units) and regimens (three to five times per week).
- Limited long-term follow-up data; durable complete responses relatively rare.
- Common side effects include constitutional symptoms, gastrointestinal toxicity, elevated hepatic transaminases, and bone marrow suppression.
- Several studies evaluating combined IL-2 and IFN-α have demonstrated no survival benefit over single-agent cytokine therapy.
- Single-agent IFN-α has fallen out of favor due to associated toxicity and the availability of more effective agents.

Allogeneic Stem Cell Transplantation

- Investigated in metastatic RCC to test the hypothesis that this malignancy may be susceptible to alloimmune donor-mediated graft-versus-solid tumor effects.
- Several groups have reported overall response rates of up to 30% to 40%, including some durable complete responses following nonmyeloablative or reduced-intensity conditioning peripheral blood stem cell transplants.
- Transplant-related morbidity and mortality and the availability of HLA-matched donors are limitations to this current investigational approach.

PD-1/PD-1 L Inhibitors

- Activation of inhibitory T cell receptors such as Programmed Death-1 (PD-1) is believed to play a major role in mediating resistance of some tumors to immune surveillance.
- Inhibitors of PD-1 as well as one of its activating ligands, PDL-1, are currently undergoing clinical evaluation. In an early-phase clinical trial, these agents have shown promising activity in patients with clear cell RCC who have progressed on conventional therapy (overall response rate of 27% with many durable responses in one study).
- Further studies are expected to define the role of these agents in the management of clear cell RCC.

Non–Clear Cell RCC

- There are currently no standard systemic options of proven benefit for the treatment of patients with advanced RCC of non–clear cell histology.
- Retrospective analyses and small phase 2 trials indicate that inhibitors of the VEGF and mTOR pathways are associated with modest activity in some subtypes. A subgroup analysis of patients from the phase 3 ARCC trial suggested that patients with poor-risk, non–clear cell RCC had better outcomes when treated with temsirolimus compared to IFN-α. The efficacy of the oral mTOR inhibitor, everolimus, is currently being evaluated in a phase 2 study in patients with papillary RCC.
- 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 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 histologic/molecular variant.

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REVIEW QUESTIONS

1. In which of the following patients with metastatic RCC is cytoreductive nephrectomy most appropriate?
   - **A.** A 50-year-old male with an ECOG performance status of 0, a large 12 cm right renal mass, and four small pulmonary metastases
   - **B.** A 67-year-old female with an ECOG performance status of 0, a 7 cm left renal mass, retroperitoneal adenopathy, and hepatic metastases that have doubled in size over 4 weeks
   - **C.** An 81-year-old man with an asymptomatic 6 cm right renal mass, and multiple hepatic metastases who has declined sytemic therapy
   - **D.** A 72-year-old man with an ECOG performance status of 2, a 5 cm right renal mass, and mild dyspnea associated with numerous pulmonary metastases
2. Which of the following regarding IL-2 therapy for metastatic RCC is true?
   - **A.** IL-2 has demonstrable efficacy in clear cell as well as papillary RCC.
   - **B.** Randomized studies have demonstrated an OS benefit associated with high-dose IL-2.
   - **C.** Low-dose subcutaneous (SC) and high-dose intravenous (IV) IL-2 have comparable efficacy.
   - **D.** Durable complete responses are seen in a small proportion of patients receiving high-dose IL-2.
   - **E.** Newer formulations have led to better tolerability of high-dose IL-2.
3. A 68-year-old man undergoes a right radical nephrectomy for a 12 cm renal mass identified during evaluation of flank pain and unexplained weight loss. Histopathologic evaluation is consistent with clear cell RCC, Fuhrman grade III. Routine surveillance imaging 2 years later reveals multiple bilateral pulmonary nodules and three 2 to 3 cm liver masses. Biopsy of a liver lesion is consistent with clear cell RCC and he is referred to a medical oncologist for discussion of systemic therapy options. He has no symptoms attributable to metastatic disease, and his CBC and chemistry panel are normal. Reasonable treatment options, based on demonstration of clinical benefit in randomized phase 3 trials, include which of the following?
   - **A.** High-dose IL-2
   - **B.** Sunitinib
   - **C.** Axitinib
   - **D.** Temsirolimus
   - **E.** Everolimus
4. A 55-year-old woman is referred to you for further management of metastatic type 2 papillary RCC. She was initially diagnosed at the age of 54 when she underwent a left radical nephrectomy and retroperitoneal lymph node dissection for an 8 cm renal mass and associated regional lymphadenopathy. Complete staging evaluation at the time also revealed extensive mediastinal and hilar adenopathy and multiple bone lesions consistent with metastatic disease. She has received temsirolimus and sunitinib with disease progression following brief periods of stability with both agents. Which of the following statements best reflects available treatment options for this patient?
   - **A.** Foretinib and other antagonists of the MET pathway are associated with improved survival in this setting.
   - **B.** Treatment with axitinib should be considered as this agent has been shown to improve progression-free survival compared to sorafenib.
   - **C.** Everolimus has been shown to improve progression-free survival compared to sorafenib in patients with papillary RCC who have failed prior therapy with sunitinib.
   - **D.** There are no standard options of proven clinical benefit; appropriate clinical trials could be considered.
5. A 31-year-old man presents with a 4-week history of malaise and two to three episodes of gross hematuria. He has also noticed an unintentional weight loss of approximately 10 lb over the past 2 to 3 months. His family history is remarkable for kidney cancer in his mother. His physical examination is remarkable for several papular skin lesions, which are very sensitive to touch,

temperature changes. A CT of the chest, abdomen, and pelvis reveals a 10 cm left renal mass but is otherwise normal. He is offered a radical left nephrectomy by his urologist, but asks if the procedure can be deferred for at least 4 weeks as he is the sole caregiver for his 24-year-old sister who is undergoing a hysterectomy next week for removal of several large uterine fibroids. Which of the following statements about this patient's condition is most accurate?

A. This presentation is most consistent with hereditary papillary renal cell carcinoma and genetic evaluation will reveal a germ-line mutation in *MET.*

B. Imaging of the CNS in this patient and his sister will likely demonstrate the presence of hemangioblastomas.

C. He should undergo genetic counseling and should be evaluated for germ-line alterations in the *fumarate hydratase* gene.

D. His renal tumor will demonstrate loss of heterozygosity affecting the *VHL* gene.

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14

Prostate Cancer

Ravi A. Madan and William L. Dahut

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 2013 there will be an estimated 238,590 men diagnosed with CaP and 29,720 deaths from the disease.
- 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. Studies of Japanese immigrants to the United States show that the incidence of CaP increases after immigration.

RISK FACTORS

- Age: Risk increases progressively with age, with about 70% of cases in men over the age of 65.
- 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.

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.
- In the Prostate Cancer Prevention trial, finasteride was compared to placebo in more than 9,000 men. There was a reduction in the incidence of CaP from 24.8% in the placebo arm to 18.4% in the finasteride arm within 7 years ($P < 0.001$).
- In the REDUCE trial, 8,321 men randomized to receive either dutasteride or placebo. Again, there was a reduction in the incidence of CaP in the treatment arm by 22.8% over the 4-year study period ($P < 0.001$).

- Both of these therapies are approved for benign prostatic hyperplasia-related symptoms but are not approved for CaP prevention.
- Both of these prevention studies found an increase in the percentage of aggressive tumors (Gleason score 7 to 10) in patients treated with the respective 5-α reductase inhibitors compared to the placebo. Subsequent pathology reviews of prostatectomy specimens did not confirm this increase, indicating potential sampling bias in the biopsies, perhaps due to a preferential reduction in normal versus tumor tissue caused by the effect of the 5-α reductase inhibitors. Without a definitive explanation for these findings, enthusiasm to use these agents for prevention of CaP has been significantly diminished. Perhaps longer follow-up will provide additional data to better characterize these findings.

Selenium and Vitamin E Cancer Prevention Trial

- Retrospective data from two previous chemoprevention trials have suggested a preventive role for selenium and vitamin E supplementation. Selenium and Vitamin E Cancer Prevention Trial (SELECT) enrolled over 35,533 men at least 50 years old and found that selenium and vitamin E, alone or in combination, did not prevent CaP.

SCREENING

- Screening for CaP involves testing for levels of PSA and/or 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. Preliminary 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 or no screening, with 7 to 10 years of follow-up. One caveat is that a high number of patients (about 50%) in the control arm obtained PSA screening outside of the clinical trial.
- Preliminary data from the European study suggest that PSA screening was associated with a reduction in rate of death from CaP by 20% after a median follow-up of 9 years. However, 1,410 men would need to be screened and 48 additional cases of CaP would need to be treated to prevent one death from CaP. Final results for these studies are expected in the coming years and may provide more conclusive data.
- Despite the controversy, PSA screening in the United States is widespread. Most advocates recommend annual screening beginning at age 50 for average-risk men and at age 40 for African-American men and men with a family history of CaP.
  - 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.
- Frank discussions with patients about the risks and potential benefits of screening should be standard practice.

SIGNS AND SYMPTOMS

- With PSA screening now widely practiced 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. Men with regional disease occasionally have hematuria.

- Symptoms of metastatic disease include bone pain and weight loss; spinal cord compression is a rare but serious complication of metastatic disease.

WORKUP AND STAGING

Biopsy

- Abnormal PSA and/or DRE is followed by transrectal ultrasound with core biopsy (generally 10 to 12 cores). Historically, a PSA of >4 ng/mL was the threshold for biopsy, but recent 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.

Pathology

- Ninety-five percent of CaPs are adenocarcinomas. Adenocarcinoma arises in the peripheral zone of the prostate in approximately 70% of patients.
- Sarcoma, lymphoma, small cell carcinoma, and transitional carcinoma of the prostate are rare.
- Although visceral or osteolytic bone metastases are found in a few patients with metastatic adenocarcinoma of the prostate, careful pathologic examination should be performed to rule out a nonadenocarcinoma variant, as treatment regimens differ.
- 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 GS (range 2 to 10). There is no role in re-evaluating GS once treatment has begun.
- There is growing consensus that the highest GS is most predictive of clinical outcome. With current grading practices, scores <6 are very rare. A GS of 8 to 10 represents poorly differentiated CaP that is likely to be clinically aggressive.
- 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 (PIN), and perhaps proliferative inflammatory atrophy (PIA), are considered precursor lesions.

Baseline Evaluation

- In candidates for local treatment, a bone scan is indicated for patients with bone pain, T3 or T4, GS >7, or PSA >10 ng/mL. There is no clinical evidence that a baseline bone scan improves survival in patients with better prognostic factors.
- In candidates for surgery, computed tomography (CT) or magnetic resonance imaging (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 grade/score
- PSA level

- Number of cores and percentage of each core involved
- Age at diagnosis

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 (Fig. 14.1). 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 (RRP), perineal (RPP), or laparoscopic, with the latter often done with robotic assistance (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 to determine the potential to debulk 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.
- 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.

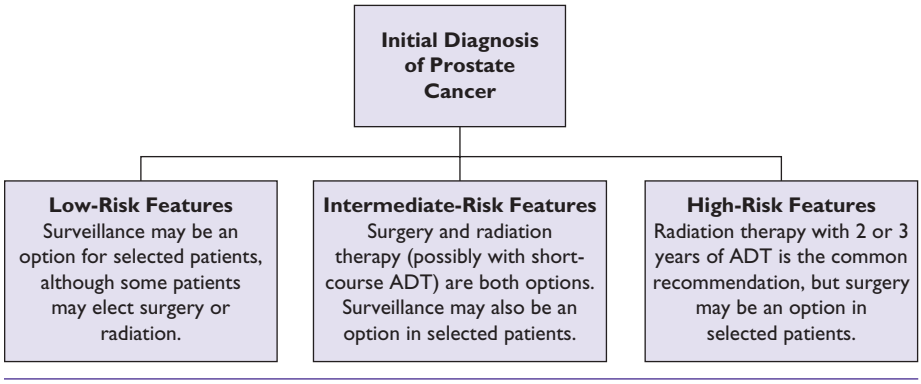

FIGURE 14.1 Treatment options for patients diagnosed with localized prostate therapy. RT can include EBRT or brachytherapy (generally reserved for select patients with intermediate- or low-risk disease), or a combination of the two in some high-risk cases.

Surgical Complications

- Immediate morbidity or mortality: 2%.
- Impotence: 35% to 60%.
- Urinary incontinence: 10% with frank incontinence; up to 60% require protective garments.
- Urinary structure.
- Fecal incontinence: retropubic approach, approximately 5%; perineal approach, 18%.
- 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.

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 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 on long-term outcomes for focal therapy. Thus, at most centers prostate focal therapies are largely performed as salvage procedures.

Radiation Therapy

External Beam RT

- External beam RT (EBRT) targets the whole prostate, frequently including a margin of extraprostatic tissue, seminal vesicles, and pelvic lymph nodes.
- Higher doses (≥78 Gy) given over approximately 8 weeks are associated with higher PSA control rates; however, survival data are not mature.
- 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.
- Unlike x-rays, which radiate beyond the target volume, proton beam irradiation focuses virtually all its energy within a very small area, thus theoretically minimizing damage to normal tissue.

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.

Table 14.1 Risk Categories for Posttherapy Prostate-Specific Antigen Failure

	Low	Intermediate	High
Stage	T1c, T2a	T2b	T2c
PSA	<10	10–20	>20
Gleason score	≤6	7	≥8
Qualifier	and	or	or

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.

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.

Salvage RT

For select patients with rising PSA after RP and a high likelihood of organ-confined local recurrence (e.g., PSA <1.5 and slowly rising), salvage RT may be considered. However, there are limited data on which to make recommendations.

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. Long-term clinical data including OS data from randomized trials are still pending. Nonetheless, some radiation oncologists are using this treatment combination in patients with high-risk disease.

Complications of RT

Acute

- Cystitis
- Proctitis/enteritis
- Fatigue

Long term

- Impotence
- Incontinence (3%)
- Frequent bowel movements (10% more than with RP)
- Urethral stricture (RT delayed 4 weeks after transurethral resection of the prostate)

COMPARISON OF PRIMARY TREATMENT MODALITIES

Comparing treatment modalities in terms of overall and disease-free survival is difficult because of differences in study design, patient selection, and treatment techniques.

- While there have been no satisfactory randomized trials comparing RT with RP, these approaches appear to have equivalent 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.
- Brachytherapy appears promising, although most studies have been conducted only in patients with early-stage, low-grade disease. One comparison of 3D conformational RT with ^{125}I implants in comparable patients concluded that these modalities had equivalent efficacy, with higher urinary complications in the brachytherapy group.

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 participation in clinical trials should be encouraged (Fig. 14.2). As previously mentioned salvage RT, salvage RP, or salvage focal therapy may be offered to select patients with local recurrence. ADT effectively lowers PSA and can be given intermittently to provide periods of normal testosterone. Based on preliminary results from randomized studies, CaP-specific outcomes with intermittent and continuous ADT appear to be similar. However, there are no data suggesting better survival with ADT than with no ADT. Recent data suggest that on average, men live about 14 years after biochemical failure. Thus a more conservative approach (e.g., treating

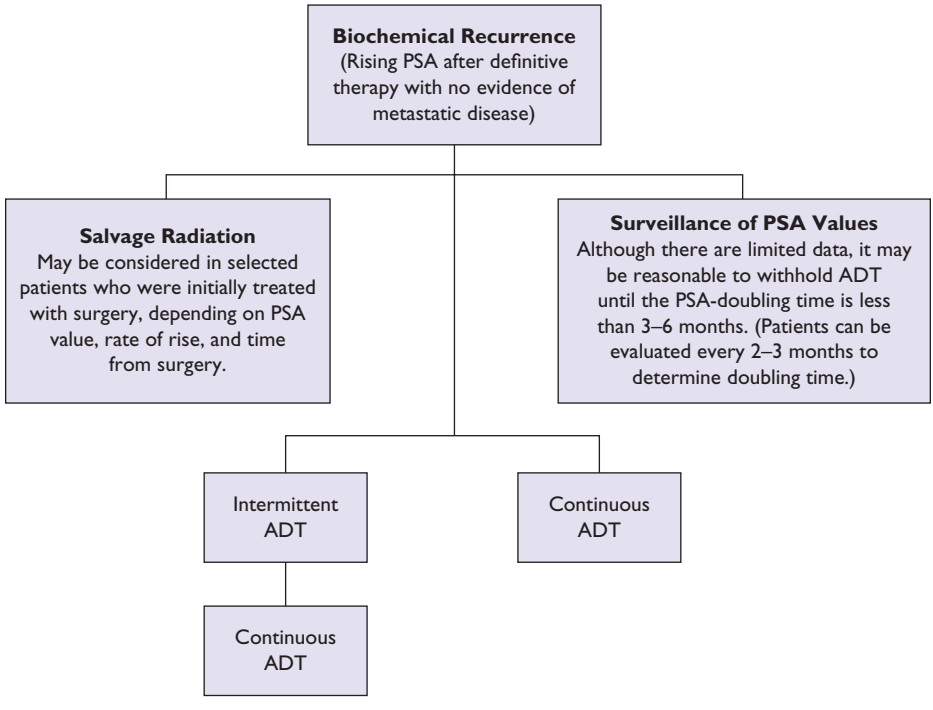

FIGURE 14.2 Treatment options for biochemical recurrence/nonmetastatic castration-sensitive prostate cancer. Continuous ADT employs repeated doses of GnRH agonists/antagonists to provide a constant testosterone suppression. Orchiectomy would also be an option. Intermittent ADT employs two or three doses of testosterone-lowering therapy, which are then discontinued if the PSA declines as expected. From there, PSA slowly recovers, lagging behind testosterone recovery. In selected patients, this approach can be used to alleviate some ADT toxicity. ADT is often reinstituted based on a PSA doubling time similar to the "surveillance of PSA" approach described in the figure.

when symptomatic) is a reasonable option for many men. Alternatively, using PSA-doubling time (i.e., less than 3 to 6 months) as a trigger to initiate ADT or intermittent ADT is frequently done in clinical practice; however, no randomized trials have prospectively evaluated this approach relative to continuous or delayed ADT based on doubling time.

TREATMENT OF SYSTEMIC DISEASE

Response Criteria: Using PSA, a Historical Perspective

Only 40% of patients with castration-resistant prostate cancer (CRPC), or progressing disease despite castrate levels of testosterone, have soft tissue disease. Therefore, PSA historically has been an important tumor marker for preliminary assessment of efficacy in proof-of-principle trials. PSA response rates (PRRs) are defined as percentage of patients with a PSA decline >50%, a traditionally used criterion. Because of differences in patient selection, it is difficult to compare clinical trials by PRRs alone. Many trials now include all PSA declines in a "waterfall plot." It is important to note that some agents (particularly cytostatic agents) may upregulate or downregulate PSA expression independent of their effect on cancer growth. Definitive studies historically have utilized skeletal-related events, palliation of symptoms, or OS for CRPC.

EVOLUTION OF RESPONSE CRITERIA IN METASTATIC DISEASE

The Prostate Cancer Working Group 2 and the Implications for Clinical Practice

- As the understanding of CaP has evolved in the last decade, in the context of new available therapies and greater experience with older therapies, a general consensus was generated by Prostate Cancer Working Group 2 (PSWG2) on determining response in clinical trials.
- Perhaps most importantly, PSA should not be used as the sole criteria to discontinue a therapy. Furthermore, the PSWG2 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.
- 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.
- In order to assess imaging, lymph nodes less than 2 cm in diameter are too small to be evaluated for response or progression of disease.
- 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 a 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 PCWG2 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 the sole criteria to determine when to discontinue a therapy.

ANDROGEN-DEPRIVATION THERAPY

- ADT is the mainstay of treatment for metastatic CaP (Table 14.2). However, as discussed previously, it has also been used to treat localized disease and in neoadjuvant and adjuvant settings with RT. CaP cells usually respond to hormonal manipulations that block the production of androgens, producing durable remissions and significant palliation. Duration of response ranges from 12 to 18 months, with 20% of patients having a complete biochemical response at 5 years. However, ultimately, CRPC cells emerge and lead to disease progression.

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 Angonists (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, gyecomastia, and osteoporosis
Androgen Receptor Antagonists (ARAs)		
Bicalutamide (Casodex)	50 mg PO daily	Nausea, breast tenderness, hepatotoxicity, hot flashes, loss of libido, and impotence
Flutamide (Eulexin)	250 mg PO three times per day	Diarrhea, nausea, breast tenderness, hepatotoxicity, loss of libido, and impotence
Nilutamide (Nilandron)	150 mg PO daily	Visual field changes (night blindness or abnormal adaptation to darkness), hepatotoxicity, impotence, loss of libido, hot flashes, nausea, disulfiram-like reaction, and pulmonary fibrosis (rare)
Androgen Biosynthesis Inhibitors		
Ketoconazole (Nizoral)	200 or 400 mg PO 3 times a day with hydrocortisone 20 mg PO in the morning and 10 mg in the evening. (Ketoconazole is absorbed at an acidic pH; therefore, the concomitant use of H_2 blockers, antacids, or proton pump inhibitors should be avoided.)	Adrenal insufficiency is limited with physiologic dosing of hydrocortisone. Other side effects include impotence, pruritus, nail changes, adrenal insufficiency, nausea, emesis, and hepatotoxicity. (Ketoconazole is a potent inhibitor of CYP3A4, and thus multiple drug interactions are possible so review of medications is important.)

(*Continued*)

Table 14.2 (Continued)

Abiraterone (Zytiga)	1,000 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		
Enzaluatmide	160 mg PO once daily	Hot flashes, diarrhea, peripheral edema, fatigue, arthralgia, and musculoskeletal pain. Limited risk of seizures (less than 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, myelosuppresion, cardiac toxicity, fever, fatigue, alopecia, nausea, diarrhea, infection, and hepatotoxicity
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.)

- Bilateral surgical castration and depot injections of GnRH agonists (e.g., 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; e.g., nilutamide, flutamide, and bicalutamide). However, this is controversial and provides little if any survival benefit.
- GnRH agonists initially increase gonadotropin, causing a transient (~14-day) increase in testosterone that can lead to tumor flare. A lower tumor volume reduces the risk of symptomatic 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. For high-risk patients, bilateral orchiectomy or ketoconazole can decrease testosterone more quickly.

- In patients initially treated with GnRH agonist or surgical castration alone, the addition of an ARA may produce PSA declines or symptomatic improvement in up to 40% of patients.
  - 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.
- Continuing testosterone suppression after patients develop 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 OF NONMETASTATIC CASTRATION-RESISTANT PROSTATE CANCER 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.
- For patients with a rising PSA but no evidence of metastatic disease ARAs can be added to ADT in order to provide a combined androgen blockade, which may delay disease progression or the development of metastasis, although clinical evidence supporting this is limited.
- Upon progression of disease with ARA and ADT, it is important to note that that up to 20% of patients treated with combined androgen blockade have a PSA decline of ≥50% upon discontinuation of oral ARA (range, 15% to 33%), although these declines generally last only 3 to 5 months. This proportion may be lower with shorter-term use 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% to 50%) will have PSA declines with second-line and even third-line antiandrogen therapy.
- Ketoconazole is a nonspecific inhibitor of secondary androgen production which may include both adrenal production and production of androgens by the tumor itself, a well-described mechanism of CaP resistance to castrate levels of testosterone. Ketoconazole can be combined with ADT to treat non-mCRPC, although ARAs are usually preferred because ARAs are better tolerated. When used, ketoconazole is combined with physiologic replacement of hydrocortisone to compensate for its impact on steroidgenesis within the adrenal glands which could lead to adrenal insufficiency.

TREATMENT FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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, and modern antiandrogen therapy, symptoms and pace of disease will likely dictate which treatments are most appropriate for each individual patient (Fig. 14.3).

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

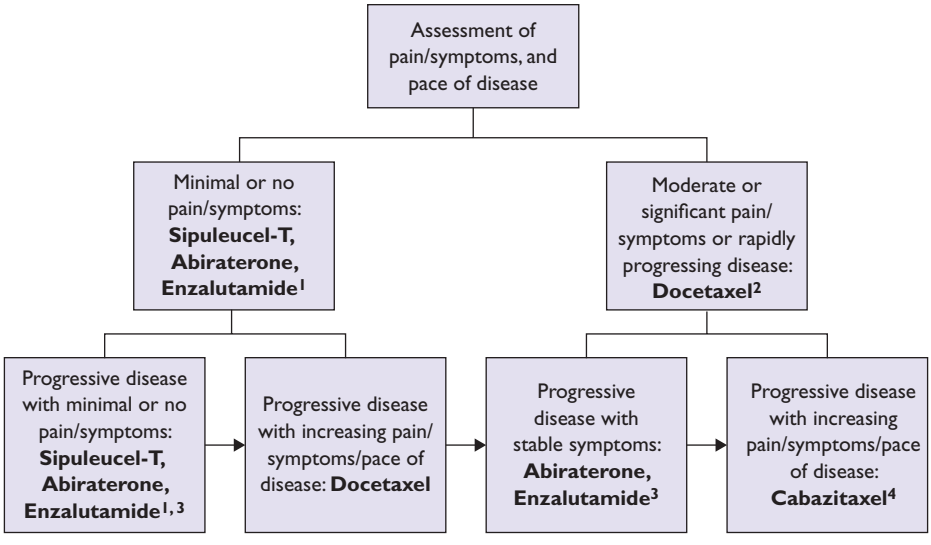

FIGURE 14.3 Suggested treatment approach for patients with metastatic castration-resistant prostate cancer. **(1)** Second-line antiandrogen therapies such as androgen receptor antagonists and ketoconazole could also be used. **(2)** Abiraterone or enzalutamide may also be an option in asymptomatic patients with rapid disease progression. **(3)** These agents may be given sequentially if there is disease progression after the initial treatment. **(4)** Radiopharmaceuticals could also have a role in patients with symptomatic disease.

cells are sent to a central processing facility where there 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; hazard ratio 0.77; $P = 0.02$), it does not change short-term disease progression or cause decreases in PSA in most patients. This is likely due to the characteristics of immune therapies that make them distinct from more cytotoxic treatments. 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 (Zytiga) 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 treated with chemotherapy relative to placebo (and has shown delayed progression in patient who have not been treated with 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 been shown to improve pain and quality of life in patients who have already received chemotherapy.

Androgen Receptor Inhibitor

- Enzaluatmide (Xtandi) 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.
- A phase 3 trial evaluated 1,199 mCRPC patients who had progressive disease on docetaxel, randomizing them 2:1 to enzalutamide 160 mg per day ($n = 800$) or placebo ($n = 399$). The OS-favored patients randomized to the enzalutamide arm 18.4 to 13.6 months. This 4.8 months' improvement in survival represented a 37% risk reduction in death (hazard ratio 0.63; 95% CI 0.53 to 0.75; $P < 0.001$), the largest relative and absolute improvement in OS in an appropriately powered phase 3 study in CaP. Median TTP based on radiographic findings was 8.3 versus 2.9 months (HR 0.40; $P < 0.001$).

CHEMOTHERAPY FOR mCRPC

In spite of the advent of new antiandrogen therapies for mCRPC, chemotherapy is still important.

- Docetaxel (Taxotere)
  - Improved median OS from 16.5 months (mitoxantrone/prednisone) to 18.9 months ($P = 0.0005$) and improved quality of life (functional assessment of cancer therapy-prostate, 22% vs. 13%; $P = 0.009$). 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.
  - Often used 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 (Jevtana)
  - This treatment became the second chemotherapy approved for CaP. A phase 3 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 improved time to progression 2.8 versus 1.4 months ($P < 0.0001$) but also met the primary endpoint of the trial by extending survival 15.1 versus 12.7 months ($P < 0.0001$).
  - 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.
  - Although the true role for cabzitaxel remains elusive, it would be appropriate to consider this treatment in patients who remain symptomatic but also with a good performance status after progression on docetaxel.
- 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 2 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 progression-free survival 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 (approximately 2% of patients).

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.
- Painful gynecomastia, often seen when ARAs are used alone, can be prevented with EBRT to the breasts (2 to 5 fractions) or may be treated with tamoxifen.
- 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 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.
- 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.
- The radioisotope strontium-89 (Metastron), a calcium analog that preferentially localizes in the tumor, can provide palliation for widespread metastases. Strontium relieves bone pain in up to 75% of cases, typically after 1 to 3 weeks of treatment and for several months thereafter. Toxicities include flare (15%), often associated with a later response, and a reversible thrombocytopenia (25%) that usually resolves within 3 months. Strontium can often be readministered. Samarium-153 lexidronam (Quadramet) is a newer radioisotope with treatment indications similar to those of strontium, but a shorter half-life and less marrow toxicity. Emerging data with α-particle emitting radium-223 (alpharadin) suggested minimal toxicity and a survival advantage in mCRPC. Its ultimate role in the treatment of mCRPC remains undefined.
- Bisphosphonates inhibit osteoclastic bone resorption and can decrease skeletal-related events in patients with advanced CRPC. 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 which is crucial in the function of osteoclasts, which play a vital role in bone resorption. Studies show that denosumab can also delay skeletal-related events in mCRPC. Furthermore, data have also indicated that denosumab can delay the development of metastasis in patients with non-mCRPC, although its clinical utility in delaying metastasis has not yet been established. Also, even though it is mechanistically different from bisphosphonates, there is a similar incidence of osteonecrosis of the jaw.

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 (e.g., 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 or orthopedic surgeons and/or radiation oncologists should be consulted soon after diagnosis.
- RT is the usual treatment modality, given as 3,000 cGy in 10 fractions to the involved vertebra and the two superior and two inferior vertebrae.
- Surgical resection of the vertebral body should be considered in the following instances:
  - The patient has had previous RT of the involved area or requires spinal stabilization.
  - The patient experiences progression despite treatment with steroids and RT.
  - RT facilities are not locally available.
  - The patient has a rapidly progressive neurologic deficit. A recent randomized trial showed that patients subjected to decompressive surgical resection followed by RT retained the ability to walk significantly longer than those treated with RT alone.

REVIEW QUESTIONS

1. A 56-year-old male with a PSA of 7.8 ng/dL has Gleason 4+3 adenocarcinoma of the prostate diagnosed on a biopsy. He elects to have a RP. After surgery, there are pathologic findings that indicate that adjuvant radiotherapy may be of benefit. Which of the following findings would not be an indication for adjuvant radiotherapy?
- **A.** Extracapsular extension
- **B.** Lymph node–positive disease
- **C.** Seminal vesicle involvement
- **D.** Positive surgical margins

2. A 72-year-old male with asymptomatic, nonmetastatic CaP has a rising PSA while on ADT. After a discussion of treatment options, the patient agrees to add bicalutamide, an ARA. The patient has a declining PSA for the following 12 months, but then his PSA starts to rise again. The PSA rise is confirmed 1 month after the initial rising value was seen. The patient has no new symptoms since starting the bicalutamide. What is the appropriate next step for this patient?
- **A.** Get an MRI to determine if the patient has metastatic disease.
- **B.** Initiate chemotherapy for mCRPC.
- **C.** Initiate abiraterone for non-mCRPC.
- **D.** Evaluate for a bicalutamide withdrawal effect 6 weeks after discontinuing bicalutamide.
- **E.** Consider switching from a GnRH agonist to a GnRH antagonist.

3. Which of the following patients would be an inappropriate patient for treatment with sipuleucel-T?
- **A.** A chemotherapy-naïve, mCRPC patient who takes occasional NSAIDs for rare pain symptoms
- **B.** A patient who completed docetaxel 6 months ago, but has slowly progressing disease and no pain while on treatment with enzalutamide
- **C.** A chemotherapy-naïve, mCRPC patient who has just completed treatment with abiraterone and has minimal symptoms
- **D.** A newly diagnosed, untreated patient with metastatic disease and minimal symptoms

4. Which of the following treatment strategies has been shown to delay the development of bone metastasis in a phase 3 trial?
- **A.** Zoledronic acid
- **B.** Denosumab

(*continued*)

C. Calcium/vitamin D
D. Cabozantinib
E. Alendronate

5. Which of the following statements about the use of docetaxel in CaP is accurate?
A. Docetaxel is no longer indicated in CaP because of the advent of abiraterone, enzalutamide, and sipuleucel-T.
B. Docetaxel with radiation in high-risk patients can enhance long-term outcomes.
C. Docetaxel is the most appropriate therapy for patients moderate to high levels of pain for castration-resistant, metastatic CaP.
D. Docetaxel is the most appropriate therapy for patients all patients with castration-resistant, metastatic CaP.
E. Docetaxel prior to surgery for high-risk CaP can improve survival.

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15

Bladder Cancer

Andrea B. Apolo and William L. Dahut

EPIDEMIOLOGY

It is estimated that 72,570 patients were diagnosed with bladder cancer in 2013 and that 15,210 died of the disease in the United States and more than 385,000 individuals are diagnosed with incident bladder cancer per year worldwide. There is a male:female ratio of 3:1, with a peak incidence of occurrence in the seventh decade of life, making bladder cancer the fourth and eighth most commonly diagnosed cancer in men and women, respectively.

ETIOLOGY

- Cigarette smoking: Smoking is the most common cause of bladder cancer, with smokers having twice the risk of developing bladder cancer compared to nonsmokers. Smoking explains a similar proportion of bladder cancer in both sexes, with population-attributable risks of 50% in men and 52% in women. There is an association between the duration and amount of cigarette smoking and the development of bladder cancer in both transitional and squamous histology.
- Occupational exposures: Occupational exposures to chemical carcinogens are associated with an increased risk of bladder cancer. Workers exposed to arylamines in the dye, paint, rubber, and leather industries are at increased risk.
- Analgesics: The abuse of analgesics, particularly phenacetin, is associated with an increased risk of urothelial cancers, especially in the renal pelvis.
- Treatment-related risks: Prior treatment with pelvic radiation and cyclophosphamide increases the risk of urothelial cancers.
- Chronic infections or inflammation: In endemic areas, chronic infection with *Schistosoma hematobium* predisposes patients to develop squamous cell cancer (SCC) of the bladder as a result of squamous metaplasia. Individuals with an ongoing source of inflammation (i.e., a spinal cord injury patient with an indwelling catheter) 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 tracts.
- Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, an autosomal dominant germline mutation in mismatch repair genes, predominantly MSH2 rather than in MSH1, increases the lifetime risk of urothelial carcinoma of the ureter and renal pelvis. Individuals with HNPCC develop upper urinary tract tumors at a younger age with an almost equal gender ratio compared to the general population.
- Thiazolidinediones such as pioglitazone and rosiglitazone indicated as second-line treatment of type 2 diabetes mellitus have been associated with an increase risk in bladder cancer. In June 2011, the U.S.

Food and Drug Administration (FDA) warned that use of pioglitazone (Actos) for more than 1 year may be associated with an increased risk of bladder cancer.
- Arsenic-contaminated drinking water: Epidemiologic studies provide solid evidence in favor of the carcinogenic risk of ingested arsenic and its association with bladder cancer.
- Aristolochic acid, which may be found in Chinese herbal remedies such as Fangchi, has been associated with urothelial carcinoma particularly upper tract tumors. Individuals who develop aristolochic acid-associated tumors tend to be younger and female.

PATHOLOGY

- The majority of urothelial carcinoma tumors originate in the bladder. Upper tract urothelial carcinoma tumors, including renal pelvis, ureter, and urethra, are less common and account for 5% to10% of all urothelial carcinomas.
- Urothelial carcinoma also known as transitional cell carcinoma (TCC) accounts for 90% to 95% of all bladder tumors in the United States. Other bladder cancer histologies include 5% SCC, 1 to 2% adenocarcinomas, and almost 1% small cell tumors. Urothelial tumors often have a mixture of divergent histologies that include 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 tumors. CIS increases the risk of subsequent invasive disease and recurrence, whether it occurs alone or in association with non–muscle-invasive bladder tumors.
- Patients with upper-tract urothelial tumors have a 20% to 40% incidence of synchronous or metachronous bladder cancer. Patients with bladder cancer have about a 1% to 4% incidence of synchronous or metachronous upper-tract tumor.

CLINICAL FEATURES

- Painless gross or microscopic hematuria occurs in about 85% of patients, and symptoms of bladder irritability are seen in 20% of patients.
- Patients with invasive disease may present with flank pain due to ureteral obstruction.
- Constitutional symptoms such as weight loss, abdominal pain, or bone pain may be present in patients with advanced disease.

SCREENING

Hematuria is the most commonly presenting symptom of patients with bladder cancer. Studies evaluating the role of screening for bladder cancer have examined the utility of conventional Hemastix® testing. 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 have been used, such as urine cytology or urine-based markers. Markers such as nuclear matrix protein 22, bladder tumor antigen, cytokeratins, and many others have widely variable sensitivity and specificity. Therefore, definitive diagnosis can be established only by cystoscopy and biopsy.

DIAGNOSIS AND STAGING WORKUP

- Diagnostic workup of a patient with suspected bladder cancer should begin with an office cystoscopy and urine cytology.
- If a bladder mass is detected, then the patient should undergo a transurethral resection of the bladder tumor (TURBT) for full primary tumor staging. The bladder tumor resection should include muscle

in the specimen to fully assess the depth of tumor invasion. The TURBT is performed with an examination under anesthesia (EUA).

- The EUA is an important part of clinical staging, allowing for the detection of locally advanced bladder cancer by assessing for invasion into adjacent organs, extravesical extension, and abdominal or pelvic sidewall extension.
- The upper tracts should also be evaluated with computerized tomography (CT) urography, ureteroscopy, retrograde pyelogram, intravenous pyelography (IVP), or MR urogram. In patients with a positive cytology and a normal cystoscopy, it is especially important to fully investigate the upper tracts. When CIS is detected, multiple random biopsies may be performed to assess the extent of involvement.
- In patients with high-grade and/or invasive tumors radiologic assessment should be performed with a CT of the chest abdomen and pelvis or MR of the abdomen and pelvis and CT of the chest to assess for local lymph node involvement, upper tract disease, and distant metastases.
- The value of FDG/PET CT for initial staging is still under investigation but appears to be a good adjunct (not a substitute) to anatomical imaging with a high-resolution CT or MR.
- A ^{99m}Tc bone scan is recommended for patients with elevated blood alkaline phosphatase level or bone pain.

Staging and Tumor Grading

- The staging of bladder cancer (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 (Fig. 15.1).
- Non–muscle-invasive bladder cancers are tumors that involve only the mucosa (Ta) or submucosa (T1) and flat CIS (Tis) and account for 70% of bladder cancers. Of the non–muscle-invasive bladder cancers, about 60% are Ta tumors, 30% are T1, and 10% are CIS. Most non–muscle-invasive bladder cancers recur within 6 to 12 months with the same stage, but 10% to 15% of patients may develop invasive or metastatic disease. Low-grade (grade 1 or 2, solitary) and lower stage (Ta) tumors have lower recurrence and progression rates than high-risk disease (T1, CIS, high grade [grade 3] or multifocal).
- Muscle-invasive bladder cancers are tumors that 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 the time of diagnosis.
- Muscle-invasive tumors that invade the abdominal or pelvic sidewall and are fixed or nonmobile during an EUA are staged as T4b tumors and are categorized as unresectable metastatic disease. Patients with node-positive disease have stage IV bladder cancer (see Fig. 15.1).
- In metastatic disease, the usual sites of metastases are pelvic lymph nodes, liver, lung, bone, adrenal glands, and intestine.

Tumor grade is a key prognostic factor in non–muscle-invasive tumors with regard to the potential risk of recurrence and progression. The 1973 World Health Organization (WHO) grading classification uses the designation for papilloma and grade 1, 2, 3 TCC. A revised grading classification was published in 2004 by WHO which added a new category for a tumor with particularly good prognosis; papillary urothelial neoplasm of low malignant potential. The designations were also changed from grade 1, 2, and 3 TCC to low-grade and high-grade urothelial carcinoma. Grade 2 lesions are now classified as either low or high-grade tumors. The 2004 WHO classification is potentially enhancing the prognostic significance of the pathologic grading categorizations of non–muscle-invasive urothelial tumors.

Table 15.1 Stage Grouping of Carcinoma of the Bladder by TNM Involvement

<table>
<tr><th></th><th>T1</th><th>T2</th><th>T3</th><th>T4a</th><th>T4b</th></tr>
<tr><td>N0</td><td>Stage I</td><td>Stage II</td><td colspan="2">Stage III</td><td rowspan="2"></td></tr>
<tr><td>N1–3</td><td colspan="4" rowspan="2">Stage IV</td></tr>
<tr><td>M1</td></tr>
</table>

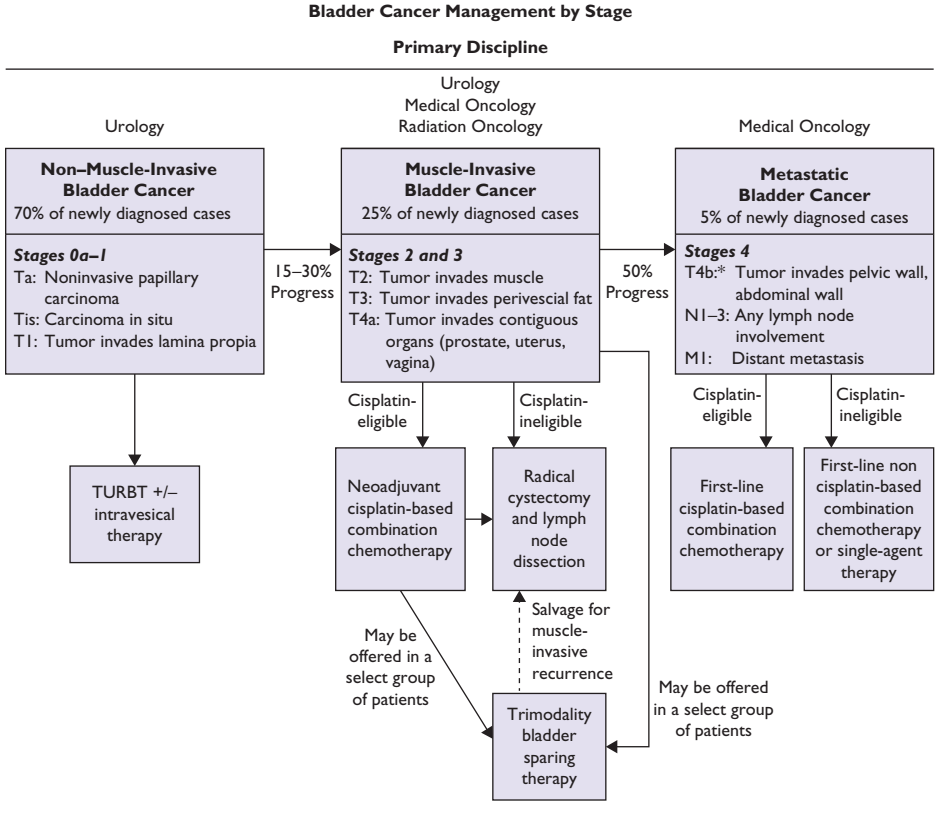

FIGURE 15.1 Treatment of bladder cancer by stage: The management of bladder cancer differs significantly depending on stage. This algorithm depicts the treatment of non–muscle-invasive, muscle-invasive and metastatic bladder cancer. *T4b, if tumor responds to systemic chemotherapy, consolidation with a radical cystectomy may be considered.

PROGNOSIS

- The major prognostic factors are tumor stage at the time of diagnosis and degree of tumor differentiation.
- Five-year survival rates for patients with non–muscle-invasive, muscle-invasive, and metastatic bladder cancer are 95%, 50%, and 6%, respectively. Median OS for non–muscle-invasive bladder cancer 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 these progress to a higher stage or grade. Significant variability in OS occurs in patients with metastatic urothelial cancer undergoing first-line treatment with chemotherapy. In order to better predict OS in these patients, Memorial Sloan-Kettering Cancer Center (MSKCC) developed a prognostic model using two pretreatment risk factors: Karnorfsky performance status (KPS) less than 80% or the presence of visceral metastases (liver, lung, or bone). Based on the MSKCC prognostic risk group model, patients with no risk factors had a median survival of 33 months; 1 risk factor, 13.4 months; and 2 risk factors, 9.3 months ($P = 0.0001$). There is now a new model modified by MSKCC

to include four pretreatment variable including visceral metastases, performance status, albumin, and hemoglobin. This new four-variable prognostic model for patients with metastatic urothelial carcinoma has a statistically significant superiority for predicting OS in patients with metastatic disease than the former two-variable model. The prognostic model can predict the survival probabilities at 1-, 2-, and 5-year and median OS in patients with metastatic urothelial carcinoma.

TREATMENT

Figure 15.1 shows an algorithm for treatment of bladder cancer.

Non–Muscle-Invasive Bladder Cancer

- *TURBT* remains the cornerstone of treatment for non–muscle-invasive disease, i.e., Ta, T1, and Tis bladder cancers. A second TURBT may be performed for high-grade tumors. In addition to observation after TURBT, intravesical therapy may be used. Close follow-up is recommended for high-risk tumors (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 used as an adjunct or prophylaxis after TURBT to lower the incidence of disease recurrence and/or progression. Intravesical chemotherapy is used for low-risk disease (low-grade Ta and T1) and intravesical bacillus Calmette-Guerin (BCG) therapy is recommended for high-risk disease (high-grade Ta, CIS, and high-grade T1). Intravesical chemotherapy: Chemotherapeutic agents used for intravesical instillation include thiotepa, doxorubicin, epirubicin, and 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 as the optimum delivery for intravesical chemotherapy, a meta-analysis showed one dose of cytotoxic chemotherapy reduced the risk of recurrence by 39%. Patients with low-grade solitary papillary tumors particularly benefited. Thus, in addition to observation after TURBT, an option for a low-grade, clinical stage Ta lesion would be administration of a single dose of intravesical chemotherapy within 24 hours of TURBT. Mitomycin C is the chemotherapy most often used. Immunotherapy with BCG has shown statistically significant clinical benefits, including induction of complete response (CR) in CIS (70% to 75%) and reduction of rates of recurrence in high-grade Ta of T1 (20% to 57%), but has shown no consistent reduction in tumor progression. Maintenance BCG has been shown to reduce recurrence, but optimal dose scheduling and duration have not been determined. A second induction of BCG therapy may be given, at 3-month follow-up, to recurrent/persistent tumors that responded to initial intravesical therapy. No more than two consecutive induction courses should be given. If disease recurs after two consecutive BCG inductions, then cystectomy is advised. Intravesical valrubicin is FDA approved for BCG-refractory patients who refuse or are intolerant of cystectomy. Other agents used in this population include gemcitabine and cotreatment with BCG and interferon α-2b.
- *Early radical cystectomy* indications include BCG-refractory CIS or high-grade lesions that recur after BCG immunotherapy. High-grade T1 and CIS lesions have a propensity to progress and even metastasize. Nonsurgical candidates may pursue a clinical trial with alternative therapies including chemoradiation.

Muscle-Invasive Bladder Cancer

- *Radical cystectomy* with bilateral pelvic lymph node dissection and distal ureterectomy is the standard therapy for muscle-invasive bladder cancer. In men, the surgery involves removal of the prostate gland, seminal vesicles, and proximal urethra. In women, it involves removal of the urethra, uterus, fallopian tubes, anterior vaginal wall and surrounding fascia.
- *Trimodality therapy with chemotherapy, radiotherapy, and TURBT*: Definitive chemoradiation is an alternative to radical cystectomy with the goal of bladder preservation. The two most common approaches include protocols developed at Mass General Hospital (MGH), the University of Paris, and the University of Erlangen. The MGH and University of Paris protocol patients undergo complete TURBT followed by an induction dose of chemoradiation therapy; the patients are then assessed for

response. Only patients who achieve a CR then undergo consolidative chemoradiotherapy for bladder preservation, whereas patients who do not achieve a CR are referred for radical cystectomy with curative intent. In the University of Erlangen protocol, patients receive upfront full-dose chemoradiotherapy and then are evaluated for therapeutic response; patients who do not achieve a CR then undergo radical cystectomy. Cisplatin is the most common radiosensitizer used in trimodality therapy; however, cisplatin is not ideal, since many bladder cancer patients who are referred for radiotherapy have impaired renal function or poor performance status. The combination of fluorouracil and mitomycin C is good alternative for patients who are not cisplatin candidates. Patients with multifocal disease, CIS, or hydronephrosis are not ideal candidates for definitive treatments with trimodality therapy. Combined chemotherapy with radiotherapy significantly improved locoregional control of bladder cancer, as compared with radiotherapy alone, without significant increase in adverse events.

- *Neoadjuvant cisplatin-based chemotherapy* prior to definitive therapy improves survival in bladder cancer patients with T2–T4a disease. The mature results of the Medical Research Council (MRC) and European Organization for the Treatment and Cure of Cancer (EORTC) trial of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) prior to definitive cystectomy or radiotherapy showed an absolute survival benefit of 6% and a relative reduction in the risk of death resulting from bladder cancer of 16% at 10 years in 976 randomized patients with muscle-invasive bladder cancer. A similar survival benefit was seen in a U.S. Intergroup trial (SWOG-8710) of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) randomized study. A meta-analysis of over 3,000 bladder cancer patients with muscle-invasive bladder cancer who received cisplatin-based neoadjuvant chemotherapy also showed a survival benefit of 6% and a 14% risk reduction in mortality at 5 years Bladder cancer patients that are cisplatin eligible should receive neoadjuvant chemotherapy prior to definitive therapy. In the United States, gemcitabine and cisplatin (GC) are frequently used in the neoadjuvant setting instead of MVAC or CMV. GC is equivalent to MVAC in the metastatic setting but has not been studied in a randomized trial in the neoadjuvant setting. Peri-operative therapies for cisplatin-ineligible patients are still under investigation. There are no data supporting the administration of noncisplatin-based neoadjuvant chemotherapy such as carboplatin combinations.
- *Adjuvant chemotherapy* data for cisplatin-based chemotherapy are less compelling, and this should not be used as a replacement for neoadjuvant chemotherapy. However, there are patients who benefit from cisplatin-based adjuvant chemotherapy, including patients who did not received neoadjuvant chemotherapy and have extensive disease found on radical cystectomy. Unfortunately, patients with bladder cancer are usually elderly and tend to have multiple comorbidities; therefore, delivering adjuvant chemotherapy to these patients after a radical cystectomy can be challenging.

Metastatic Bladder Cancer

First-Line Therapy (Tables 15.2 and 15.3)

- First-line therapy: MVAC, dose-dense MVAC (ddMVAC), and GC chemotherapy are standard of care chemotherapy regimens for metastatic urothelial carcinoma. MVAC is one of the most active chemotherapy regimens for the treatment of metastatic bladder cancer, with response rates between 40% and 72%. However, toxicities associated with this regimen limit its widespread use.
- GC have been shown to be equivalent to MVAC in OS, time to treatment failure, and response rates, but less toxic than MVAC.
- A randomized study in metastatic disease of standard MVAC versus ddMVAC showed that by eliminating days 15 and 22 of methotrexate and vinblastine the regimen could be completed faster, with less toxicity and better outcome.
- A randomized controlled study of ddMVAC versus ddGC showed that both regimens were comparable in terms of OS and progression-free survival, with a better toxicity profile in the ddGC group. However, this study halted randomization early due to poor accrual.
- Triplet chemotherapy combination regimens such as paclitaxel, cisplatin, and gemcitabine(PCG) may have increased response, but their impact on survival is unclear (see Table 15.2). When compared to standard GC, the PCG group had more febrile neutropenia (13.2% vs. 4.3%; $P < 0.001$). There are no data showing that carboplatin can be efficaciously substituted for cisplatin. Before it closed prematurely due to poor accrual, an ECOG phase 3 study comparing MVAC with carboplatin and

Table 15.2 Randomized Phase 3 Studies of Cisplatin-Based Chemotherapy in Metastatic Bladder Cancer

First Author, Year	Regimen	No. of Patients	Overall Response Rate (%)	Median Survival (mo)	*P* Value
Bamias, 2012	DD-MVAC vs. DD-gemcitabine/cisplatin	66 64	60 65	19 18	0.98
Bellmunt, 2012	Gemcitabine/cisplatin vs. gemcitabine/cisplatin/paclitaxel	314 312	44 56	12.7 15.8	0.075
Dreicer, 2004	MVAC vs. paclitaxel/carboplatin	44 41	40 28	14.2 13.8	0.41
Bamias, 2004	MVAC vs. docetaxel/cisplatin	109 111	54 37	14.2 9.3	0.025
Sternberg, 2001	MVAC vs. DD-MVAC	129 134	50 62	14.1 15.5	0.122
von der Maase, 2000	MVAC vs. gemcitabine/cisplatin	202 203	46 49	14.8 13.8	0.750
Loehrer, 1992	MVAC vs. cisplatin	120 126	39 12	12.5 8.2	<0.0002
Logothetis, 1990	MVAC vs. CISCA	55 55	65 46	12.6 10	<0.05

MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; CISCA, cyclophosphamide, cisplatin, doxorubicin; CMV, cisplatin, methotrexate, vinblastine; DD, dose dense.

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 ($P = 0.65$), with toxicity profiles favoring the carboplatin–paclitaxel arm. Therefore, carboplatin should be substituted for cisplatin only in patients deemed unfit for cisplatin.

Cisplatin Ineligible First Line

- Patients may be considered "unfit" for cisplatin if they have any one of the following: poor performance status, renal insufficiency, hearing loss, neuropathy, or class III heart failure.
- In patients unfit for cisplatin, a phase 2/3 randomized study examined gemcitabine and carboplatin versus M-CAVI (methotrexate, carboplatin, and vinblastine). The median OS was 9.3 months in the gemcitabine and carboplatin group versus 8.1 months in the M-CAVI group ($P = 0.64$). Severe toxicity was observed in 9.3% of gemcitabine and carboplatin arm versus 21.2% of the M-CAVI. These results demonstrated that there was no difference between these two carboplatin-based regimens related to survival outcome; however, there was more severe toxicity associated with the M-CAVI regimen.

Second-Line Therapy

- In the United States there is no FDA-approved therapy for bladder cancer patients after they progress from either cisplatin- or carboplatin-based first-line chemotherapy.
- In Europe, vinflunine is approved as second-line treatment in patients with metastatic bladder cancer based on a randomized phase 3 study of vinflunine plus best supportive care (BSC) versus BSC alone. In the intent-to-treat population, OS was not statistically significant ($P = 0.287$); however, multivariate cox analysis adjusted for prognostic factors did reveal a statistically significant difference in vinflunine plus BSC versus BSC alone. The median OS for vinflunine plus BSC was 6.9 months versus median OS for BSC alone at 4.3 months ($P = 0.040$).
- Response rates to chemotherapy in the second-line setting are low, ranging from 5% to 20%. Commonly used agents include single-agent taxanes or pemetrexed.

Table 15.3 Frequently Used Chemotherapy Regimens in Urothelial Carcinoma

Regimen	Dosing	Duration	Setting
Gemcitabine + cisplatin	Gemcitabine, 1,000 mg/m^2 IV days 1 and 8 Cisplatin, 70 mg/m^2 IV day 1	21 d	Neoadjuvant and first line
MVAC	Methotrexate, 30 mg/m^2 IV days 1, 15, and 22 Vinblastine, 3 mg/m^2 IV days 2, 15, and 22 Doxorubicin, 30 mg/m^2 IV day 2 Cisplatin, 70 mg/m^2 IV day 2	28 d	Neoadjuvant and first line
Dose-dense MVAC	Methotrexate, 30 mg/m^2 IV day 1 Vinblastine, 3 mg/m^2 IV day 2 Doxorubicin, 30 mg/m^2 IV day 2 Cisplatin, 70 mg/m^2 IV day 2 pegfilgrastim day 2	14 d	Neoadjuvant and first line
CMV	Methotrexate, 30 mg/m^2 IV days 1 and 8 Vinblastine, 4 mg/m^2 IV days 1 and 8 Cisplatin, 100 mg/m^2 IV infusion over 4 h on day 2, ≥12 h after methotrexate and vinblastine	21 d	Neoadjuvant and first line
Docetaxel and cisplatin	Docetaxel, 75 mg/m^2 slow IV infusion over 1 h day 1 Cisplatin, 75 mg/m^2 IV day 1	21 d	First line
Paclitaxel and carboplatin	Paclitaxel, 200 mg/m^2 IV infusion over 3 h day 1 Carboplatin AUC of 5 mg/mL/min IV after paclitaxel	21 d	Cisplatin ineligible first line
ITP	Ifosfamide, 1,500 mg/m^2/d IV days 1–3 Mesna, 300 mg/m^2 IV 30 min before ifosfamide, then 300 mg/m^2 IV 4 and 8 h after ifosfamide; 600 mg/m^2 p.o. 4 and 8 h after ifosfamide. Paclitaxel, 200 mg/m^2 IV infusion over 3 h day 1 Cisplatin, 70 mg/m^2 IV day 1 pegfilgrastim day 2	21 d	Nonurothelial carcinoma histology First line

MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; CMV, cisplatin, methotrexate, vinblastine; ITP, ifosfamide, paclitaxel, cisplatin; IV, intravenously.

REVIEW QUESTIONS

1. A 73-year-old woman presents with gross hematuria. Urine cytology is positive for malignant cells and CT is negative except for thickening of the bladder wall. The patient undergoes an EUA and bimanual assessment reveals no palpable masses but cystoscopy shows a 3 cm tumor over the dome of the bladder wall. The biopsy of this lesion shows high-grade muscle-invasive urothelial carcinoma. Which of the following is the most appropriate surgery?

(*continued*)

A. Partial cystectomy
B. Partial cystectomy and sentinel lymph node biopsy
C. Radical cystectomy and sentinel lymph node biopsy
D. Radical cystectomy and pelvic lymph node dissection, distal ureterectomy, and removal of the urethra, uterus, fallopian tubes, anterior vaginal wall, and surrounding fascia

2. A 70-year-old man is diagnosed with advanced bladder cancer with liver and bone involvement. He works as a construction worker and believes to have been exposed to asbestos in the past. He has a history of previous alcohol abuse, and a 50-pack-year history of smoking. His family history is significant for a brother who developed a germ cell tumor at the age of 30 years. Which of the following risk factors has been shown in clinical studies to have the highest association with the development of bladder cancer?
A. Asbestos exposure
B. Alcohol abuse
C. Brother with a germ cell tumor
D. Smoking history

3. A 66-year-old man undergoes a cystoscopy which reveals a 3 cm papillary tumor in the left lateral wall of the bladder as well as diffuse erythema of the remainder of the bladder wall. An EUA demonstrates a mobile bladder. Evaluation of the biopsy of the papillary lesion reveals high-grade papillary carcinoma, with no invasion. Biopsy of the erythematous areas reveals diffuse carcinoma *in situ*. Muscle is present in the biopsy specimen. Which of the following is the most appropriate therapy for this patient?
A. Intravesical BCG therapy
B. Cystectomy
C. Gemcitabine and Cisplatin chemotherapy
D. Intravesical gemcitabine therapy

4. A 72-year-old male smoker presents with intermittent painless gross hematuria and urinary frequency. Urine analysis is normal except for moderate red blood cells and trace white blood cells. Urine culture is negative. A course of antibiotics did not alleviate his symptoms. Complete blood count, electrolytes, and creatinine are normal. Prostate-specific antigen is 0.9. Which of the following would be the next appropriate diagnostic test?
A. Urine cytology and serum CEA
B. 18-Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
C. CT scan of the chest, abdomen, and pelvis
D. Urine cytology and cystoscopy

5. A 68-year-old man presents with gross hematuria. Urine cytology is positive for malignant cells. A cystoscopy reveals a 4 cm ulcerating bladder tumor. TURBT shows high-grade invasive urothelial carcinoma with muscle involvement. A CT scan demonstrates no masses or lymph nodes. He has renal impairment with a calculated creatinine clearance (CrCl) of 39 mg/dL. Which of the following treatments should be recommended?
A. Neoadjuvant chemotherapy with a non–cisplatin-containing regimens followed by radical cystectomy and pelvic lymph node dissection
B. Radical cystectomy and pelvic lymph node dissection
C. Radical cystectomy and pelvic lymph node dissection followed by adjuvant chemotherapy with a non–cisplatin-based regimen
D. Intravesical BCG therapy

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16

Testicular Carcinoma

Bamidele A. Adesunloye and Ravi A. Madan

Testicular carcinoma is the most common malignancy in men between the ages of 20 and 35, but represents only 1% of all malignancies in males. The disease is believed to originate from the malignant transformation of primordial germ cells that may occur early in embryonic development. As late as the 1970s, testicular carcinoma was generally fatal, but can now be cured in most cases. Effective treatment paradigms have been developed to help manage acute disease and follow-up. Given the high cure rate and the resulting improved life expectancy, special considerations must be given to the side effects of therapy, especially in early-stage disease where even conservative interventions yield a cure in over 98% of patients. Whatever the therapeutic intervention, all patients should be monitored closely in ensuing years for both recurrent disease and long-term sequelae of therapy.

CLINICAL FEATURES

Epidemiology

- It was estimated that in 2013 there would be 7920 new cases of testicular carcinoma and 370 deaths due to the disease in the United States.
- Testicular cancer accounts for 1% of all malignancies in men but the majority of cases occur between the ages of 20 to 35 years.
- There is significant variability in the incidence by ethnicity with Caucasians being five times more likely than African Americans to have testicular carcinoma.
- For unclear reasons, the incidence of testicular cancer has been increasing over the last four to five decades in most western countries. A few epidemiologic studies have attributed the increase in part to the birth cohort effect.
- Although the incidence of testicular cancer has increased over the past several decades, the peak of incidence has remained within the 25- to 29-year age group. Testicular cancer is rare after the age of 40.

Risk Factors

- Cryptorchidism: Cryptorchid testes, defined as maldescended testes located above the external inguinal ring, are associated with a two- to fourfold increase in the risk of testicular cancer with intra-abdominal testes having a higher risk than inguinal testes. There is also an increased risk in the normally descended contralateral testis.

The opinions expressed in this chapter represent those of the authors and do not necessarily represent official positions or opinions of the US government or of the U.S. Department of Health and Human Services.

- Second primary tumors: Synchronous or metachronous testicular carcinoma may occur in the contralateral testis in a few group of patients; 1% to 5% of patients have bilateral disease at presentation.
- Intratubular germ cell neoplasia: A premalignant condition seen in 90% of testicular carcinomas.
- Hereditary: Despite the overwhelming evidence of a strong familial component to the risk of testicular carcinoma, to date no definite oncogene has been identified. About 1.4% of patients with testicular carcinoma have a positive family history of the disease. A son of an affected father has a four- to six-fold increased risk while for a brother of an affected sibling the risk increases to 8 to 10-fold. The risk is reportedly greater than 70-fold in monozygotic twins.
- Chromosomal abnormalities: Klinefelter syndrome has been shown to be associated with increased risk of primary mediastinal germ cell tumors in a few case series and surveys. Similar studies have also suggested the possibility of an increased risk of testicular cancer with Down syndrome.
- Peutz-Jeghers syndrome: Although it is well established that females with Peutz-Jeghers syndrome have an increased risk of gonadal tumors, this association is less clear in males with the syndrome. However, functional Sertoli cell testicular tumors with feminization syndrome have been reported in some cases.
- HIV infection: The risk of seminomatous testicular tumors is considerably higher in HIV-infected men compared to age-matched HIV-negative men. There are also recent reports of non-Hodgkin lymphoma of the testicles in patients with HIV infection.
- Sarcoidosis: The likelihood of an association between sarcoidosis and testicular carcinoma has been proposed. The rationale behind this association is plausible given the chronic inflammation associated with sarcoidosis and impaired immune surveillance of tumor antigens.
- Testicular microlithiasis: Several retrospective studies have suggested a possible association between testicular microlithiasis and testicular cancer.
- Hypospadias: Analyses of data from Danish health registry have suggested a potential association between hypospadias and testicular tumor.

Presentation

- Asymptomatic testicular nodule or swelling (painful in 10% to 20% of patients)
- Feeling of testicular heaviness, dull ache, and/or hardness (up to 40% of patients)
- Disease at extragonadal site (5% to 10% of patients; symptoms vary with site):
  - Dyspnea, cough, or hemoptysis (pulmonary metastases)
  - Weight loss, anorexia, nausea, abdominal or back pain (retroperitoneal adenopathy)
  - Mass or swelling in neck (supraclavicular lymphadenopathy)
  - Superior vena cava syndrome due to mediastinal disease
- Rare presentations:
  - Urinary obstruction
  - Headaches, seizures, or other neurologic complaints due to brain metastases
  - Bone pain due to bone metastases
  - Gynecomastia due to elevated β-human chorionic gonadotropin (β-HCG).
  - Anti-Ma2-associated paraneoplastic encephalitis

DIFFERENTIAL DIAGNOSIS

- Epididymitis (initial diagnosis and treatment in 18% to 33% of testicular cancer patients)
- Orchitis, hydrocele, varicocele, or spermatocele
- Lymphoma or leukemia
- Metastasis from other tumors including melanoma or lung cancer
- Infectious diseases including tuberculosis and tertiary syphilis causing gumma

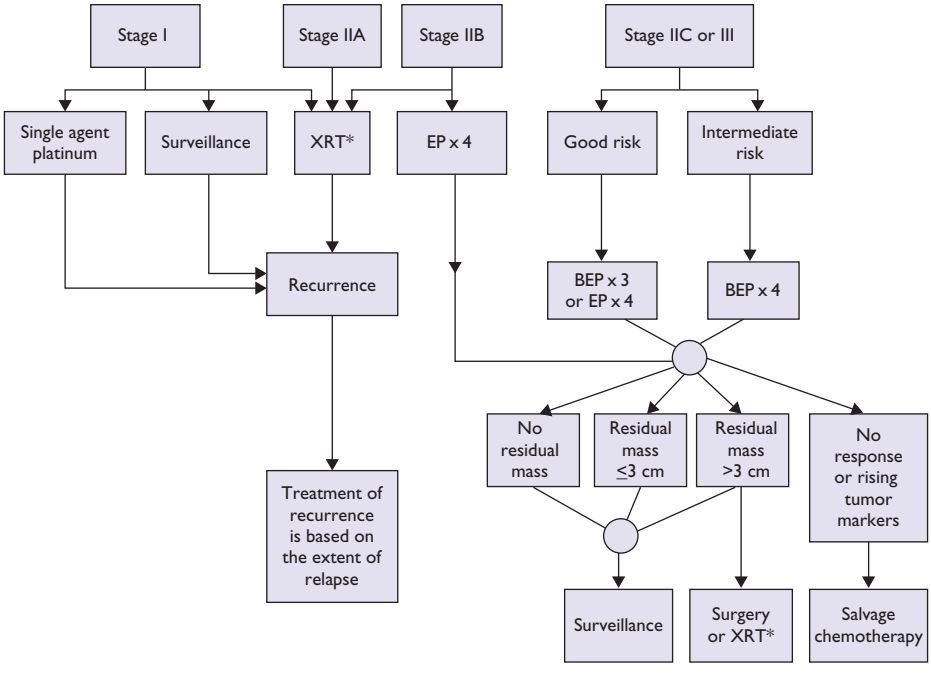

FIGURE 16.1 Adjuvant treatment options for seminoma. XRT*, radiation therapy to para-aortic lymph nodes; BEP, bleomycin, etoposide, and ciplatin; EP, etoposide, and cipaltin.

DIAGNOSIS

The initial evaluation of a suspicious testicular mass should include measurement of serum tumor markers, testicular ultrasound, and a chest x-ray. Subsequently, a radical inguinal orchietomy should be performed. Post-operatively, if germ cell tumor is confirmed, abdominopelvic CT scan should be done and the tumor markers should be repeated if they were elevated prior to orchiectomy. Chest CT and brain imaging should be done if indicated.

Goals

- Every testicular mass requires a timely workup to exclude testicular carcinoma.
- Histologic determination of tumor type and stage has prognostic and therapeutic significance.
- Testicular cancer is highly curable, with 5-year survival >95%.
- Long-term sequelae of therapy should be considered and minimized when possible.
- Orchiectomy is essential for diagnosis and local tumor control. Radical inguinal orchiectomy is preferred to scrotal orchiectomy, trans-scrotal biopsy, or fine-needle aspiration due to the risk of scrotal violation that may compromise patients' prognosis.

Laboratory

Serum α-Fetoprotein (AFP)

- A glycoprotein with a half-life of approximately 4 to 6 days
- Commonly produced by the fetal yolk sac, liver, and gastrointestinal tract

- Should not be elevated in serum of healthy men
- Not present in patients with pure seminoma. Elevated serum α-fetoprotein (AFP) levels indicate a nonseminomatous component to the patient's testicular cancer

Serum β-Human Chorionic Gonadotropin

- Secreted by syncytiotrophoblasts; half-life of 0.5 to 1.5 days
- Most commonly elevated tumor marker in patients with testicular cancer
- Present in choriocarcinomas; may be modestly elevated in pure seminomas
- High levels may lead to gynecomastia

Serum Lactate Dehydrogenase

- Nonspecific tumor marker in testicular cancer
- Elevated in 80% of metastatic seminomas and 60% of advanced nonseminomatous tumors
- Reflects overall tumor burden, tumor growth rate, and cellular proliferation

Imaging

- Ultrasound: Ultrasound detects the presence of testicular parenchymal abnormality in both testes.
- Chest x-ray: Posterior–anterior and lateral film evaluation for pulmonary metastases.
- Computerized tomography (CT): CT scans of chest, abdomen, and pelvis determine extragonadal metastasis and are the most effective modality for staging the disease.
- Magnetic resonance imaging (MRI): MRI may provide additional information if ultrasound is indeterminate. MRI of the brain is necessary only when there are symptoms involving the central nervous system (e.g., headache, neurologic deficit, seizure).
- Positron emission tomography (PET) scan: PET scans are not indicated in primary staging, but may have limited utility for characterizing residual masses. The routine use of PET scans has not been shown to improve outcome.

Pathology

Patients with testicular masses should have surgical exploration, with complete removal of the testis and spermatic cord through the inguinal ring. Although empirical evidence supporting this is weak, trans-scrotal testicular biopsy is not recommended due to the risk of local and nodal dissemination of tumor.

- Immunohistochemical staining can be used to distinguish the different histologic subtypes of testicular carcinoma.
- Historically, CD30 and cytokeratin staining have been used to distinguish embryonal carcinoma (positive for both markers) from pure seminoma.
- Modern immunostains have made it possible to increase the accuracy of this distinction. NANOG and OCT3/4 are expressed in seminoma and embryonal carcinoma while SOX2 is only expressed in embryonal carcinoma.
- Seminoma expresses c-kit, which is expressed by neither embryonal carcinoma nor yolk sac tumor.
- SALL4, a novel stem cell marker, stains nearly all subtypes of germ cell tumors, making it a very useful marker in confirming metastatic disease. It is particularly useful for identifying yolk sac tumor, which is strongly positive for SALL4 staining but negative for OCT4.
- Germ cell tumors are frequently aneuploid and display an array of histopathology (Table 16.1).
- 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 germ cell tumors compatible with X-linked inheritance, evidence suggests the presence of a susceptibility gene on chromosome Xq27.

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	
		Choriocarinomas	
Tumors of gonadal stroma	1–2	Leydig cell	
		Sertoli cell	
		Granulosa cell	
		Primitive gonadal structures	
Gonadoblastoma	1	Germ cell + stromal cell	

STAGING

Staging is in accordance with the American Joint Committee on Cancer tumor/node/metastasis (TNM) criteria.

- T classification is based on pathologic finding after radical orchiectomy, hence the pT nomenclature. pT0 means there is no evidence of disease. pTis refers to intratubular germ cell neoplasia or carcinoma in situ. pT1 is a disease that is limited to the testis and epididymis without lymphovascular invasion, although it may invade the tunica albuginea but not the tunica vaginalis. pT2 tumor is similar to pT1 but with lymphovascular invasion or the involvement of the tunica vaginalis. In pT3 tumor, there is invasion of the spermatic cord with or without lymphovascular invasion. Involvement of the scrotum with or without lymphovascular invasion is designated as pT4. pTx is used when the primary tumor cannot be assessed.
- N classification may be pathologic (pN) or clinical. When there is no regional lymph node involvement the N0 designation is used. N1 refers to metastasis in a lymph node mass that is $\leq$2 cm in greatest dimension. N2 is a lymph node metastasis or multiple lymph nodes metastases with any one mass $>$2 cm but $\leq$5 cm. Lymph node metastasis $>$5 cm is termed N3. If lymph node metastasis is ascertained pathologically after surgery, then the pN nomenclature is used. pN0 means that there is no evidence of lymph node involvement, while pN1 is similar to N1 except that the involvement of $\leq$5 lymph nodes with none $>$2 cm in greatest dimension is also considered pN1. Likewise, pN2 is similar to N2 but also include the involvement of more than 5 lymph nodes, none more than 5 cm or evidence of extranodal extension. pN3 has similar definition as N3. When the regional lymph nodes cannot be assessed the Nx or pNx designation is used.
- M classification is based on the extent of distant metastasis. M0 means there is no distant metastasis, while M1, which is further divided to M1a and M1b, signifies distant metastasis. M1a refers to nonregional nodal or pulmonary metastasis, while M1b indicates the presence of nonregional nodal and nonpulmonary metastases.
- Very unique to testicular germ cell tumors is the use of serum tumor markers in the staging process. S0 refers to normal serum levels of tumor markers. S1 means that the lactate dehydrogenase (LDH) is $<$1.5 times the upper limit of normal, β-HCG is $<$5,000 milli-international units/mL, and AFP is $<$1,000 ng/mL. S2 is used when the LDH is between 1.5 and 10 times the upper limit of normal, or β-HCG is between 5,000 and 50,000 milli-international units/mL, or AFP 1000 to 10,000 ng/mL. S3 refers to LDH $>$10 times the upper limit of normal, or β-HCG $>$50,000 milli-international units/mL, or AFP $>$10,000 ng/mL. Sx refers to tumor markers not available or not done.
- The TNM classification is then used in the anatomic stage grouping as follows:
  - Stage I: pT1-4, N0, M0, Sx/S0

- Stage IS: Any p T or Tx, N0, M0, S1-3
- Stage II: Any pT or Tx, N1-3, M0, Sx/S0-1
- Stage III: Any pT or Tx, any N, M1, Sx/S0-3

PROGNOSIS

- The prognosis is based on the International Consensus Risk Classification system that utilized postorchiectomy levels of tumor markers and the site of metastasis to predict the progression-free survival (PFS) and overall survival (OS) of patients with advanced testicular germ cell tumors (Table 16.2).
- The 5-year PFS and 5-year OS for disseminated seminomatous and nonseminomatous germ cell tumors are given in Table 16.3.

TREATMENT MODALITIES

A radical inguinal orchiectomy is the preferred surgical approach for all patients with a testicular mass. This is both diagnostic and therapeutic. Adjuvant therapy, which may include chemotherapy, radiotherapy, or further surgery, is tailored to the disease stage and histology. Due to the unique radiosensitivity

Table 16.2 International Consensus Risk Classification for Germ Cell Tumors

Prognosis	Nonseminoma	Seminoma
Good	Testis/retroperitoneal primary. No nonpulmonary visceral metastases. AFP <1,000 mg/mL; HCG <5,000 international units/L (1,000 mg/mL); LDH <1.5 × ULN (56% of all nonseminomas)	Any primary site. No nonpulmonary visceral metastases. Normal AFP; any concentration of HCG; any concentration of LDH (90% of all seminomas)
Intermediate	Testis/retroperitoneal primary. No nonpulmonary visceral metastases. AFP ≥1,000 and ≤10,000 ng/mL or HCG ≥5,000 milli-International units/milliliter (mIU/mL) and ≤50,000 international units/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 international units/L (10,000 ng/mL) or LDH >10 × ULN (16% of all nonseminomas)	No patients classified as poor prognosis

LDH, lactate dehydrogenase; HCG, human chorionic gonadotropin; AFP, α-fetoprotein; ULN, upper limit of normal; NL, normal limit.

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.

of seminomas, adjuvant radiation therapy is often employed. Patients should be counseled about sperm banking before the initiation of therapy. The need for aggressive therapy with early-stage disease is currently controversial.

Seminomas

Adjuvant treatment options for seminoma are outlined in Figure 16.1.

Stage I

- Orchiectomy is curative for most patients with stage I seminoma. With a recurrence rate of up to 20%, active surveillance is an option after surgery for patients who can comply with follow-up recommendations.
- When disease does recur, usually in the retroperitoneal lymph nodes, nearly all patients can be cured with radiation or chemotherapy.
- For patients who cannot comply with active surveillance, low-dose radiation therapy to regional lymph nodes after orchiectomy results in cure over 90% of the time.
- Chemotherapy with carboplatin is an alternative adjuvant treatment option. A single cycle of carboplatin has proven to be equivalent to radiation in producing a high rate of relapse-free survival (RFS) and OS at 4 years. It is also associated with a lower risk of second germ cell tumor.
- Regardless of initial therapy, over 98% of patients will ultimately be cured. Physicians and patients must discuss the short-term and long-term advantages and disadvantages of more aggressive therapies in this stage of disease. All patients must understand the need for frequent visits and imaging during follow-up.

Stage II

- For stage IIA/B, or nonbulky disease (lymph node mass <5 cm), radical inguinal orchiectomy followed by radiation therapy (30 Gy) to ipsilateral iliac and retroperitoneal lymph nodes results in cure 90% of the time.
- In selected cases where radiation is contraindicated, cisplatin-based chemotherapy may suffice. For stage IIC or bulky disease (lymph node mass >5 cm) cisplatin-based chemotherapy is the standard after radical orchiectomy.
- Patients with good risk stage IIC may be treated with three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP). Intermediate risk disease requires four cycles of BEP.
- There is no evidence that the combination of both radiation and chemotherapy increases RFS or OS.

Stage III

Stage III disease is usually still curable. Chemotherapy is required for patients following radical orchiectomy. Patients with good prognosis may be treated with three cycles of BEP; all other patients should be treated with four cycles of BEP.

Nonseminomas

Adjuvant treatment options for stage I, II, and III nonseminoma are outlined in Figures 16.2 and 16.3.

Stage I

- Stage I nonseminomatous disease (including tumors appearing to be seminomas but with elevated levels of serum AFP) is also highly curable, with several effective treatment options after radical orchiectomy.
- Retroperitoneal lymph node dissection (RPLND) has long been the mainstay of therapy in this disease and reports of cure are as high as 99%. After RPLND, 30% to 50% patients will be found to have pathologic stage II disease, although it is important to note that up to 10% of patients will have occult distant metastasis elsewhere (primarily in the lungs) that will not be detected by RPLND.
- While extremely effective, up to 70% of patients will be overtreated with RPLND and 10% may still require chemotherapy because of metastatic disease elsewhere. In patients with positive lymph nodes,

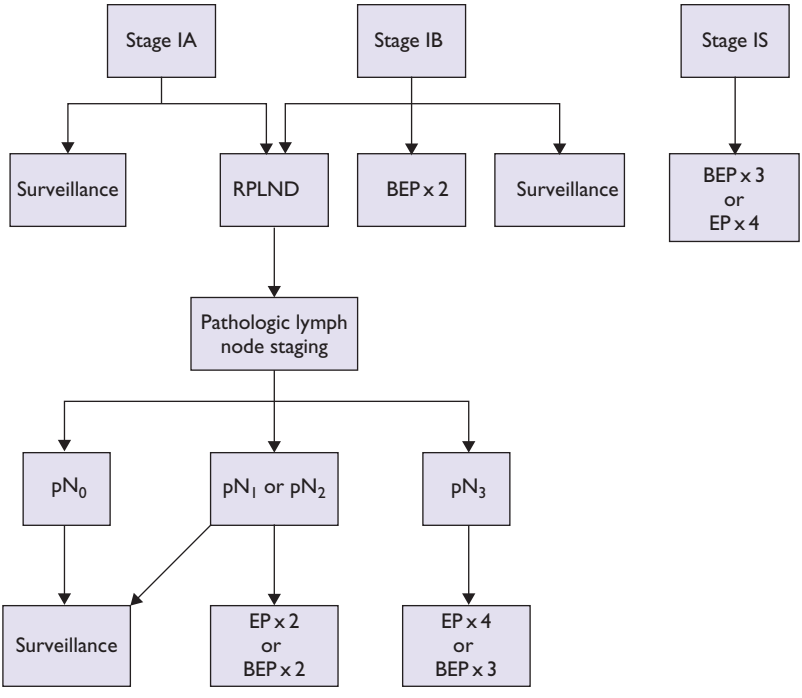

FIGURE 16.2 Adjuvant treatment options for stage I nonseminoma. RPLND, retroperitoneal lymph node dissection; BEP, bleomycin, etoposide, and ciplatin; EP, etoposide and ciplatin.

two cycles of adjuvant cisplatin-based chemotherapy reduce the risk of recurrence to <2%, although this could be considered an overtreatment.

- Adjuvant chemotherapy has been suggested after orchiectomy for stage I disease if there is evidence of lymphovascular invasion or if there is predominance of embryonal carcinoma histology. Active surveillance is again an option, with 30% of all patients expected to relapse (95% within 2 years; 99% within 4 years). Regardless of the time of recurrence, more than 95% of patients are still curable with salvage chemotherapy.
- Several factors must be considered before choosing active surveillance. These include the patient's level of anxiety, compliance, and access to a facility with experienced physicians, radiologists, and CT scanners to detect recurrence.

Stage II

- Stage IIA disease with lymph node mass ≤2 cm may be treated with RPLND after orchiectomy. If the nodal mass is completely resected and tumor markers return to normal levels, observation or two cycles of cisplatin-based chemotherapy may be considered. About 20% of patients may have disease relapse after RPLND alone, but over 95% may be still be cured with salvage chemotherapy.
- Platinum-based chemotherapy after RPLND may improve RFS in patients with lymphatic or venous invasion by tumor, although studies indicate equivalent cure rates for adjuvant chemotherapy versus chemotherapy at recurrence.
- If tumor markers do not decline after RPLND, it is indicative of residual disease and such patients should receive three to four cycles of cisplatin-based chemotherapy as systemic therapy.
- Patients with stage IIB/C tumors and nodal disease >2 cm should receive adjuvant cisplatin-based chemotherapy and residual mass after chemotherapy should be resected.

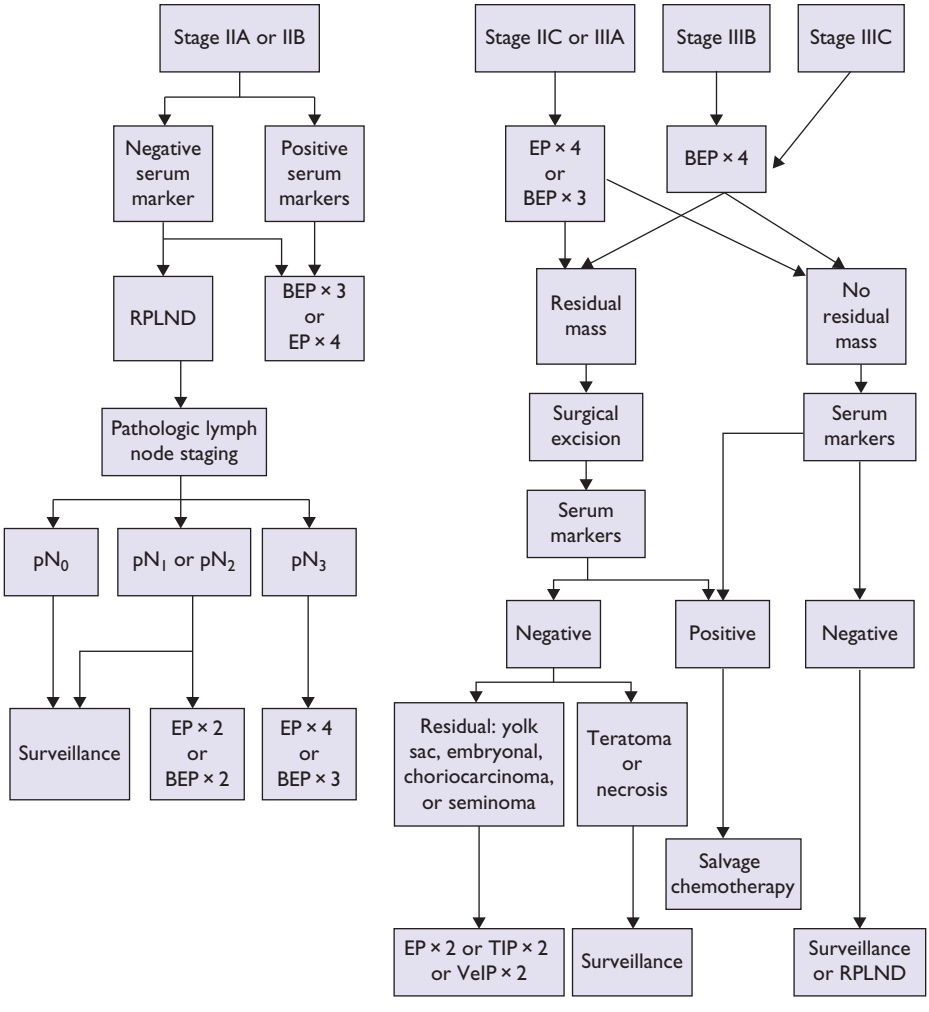

FIGURE 16.3 Adjuvant treatment options for stage II and III nonseminoma.

Stage III

- Just as in stages I and II, the goal of therapy in stage III testicular cancer is cure. Patients with good risk stage III should receive three cycles of BEP, while those with intermediate or poor risk stage III should receive four cycles of the same regimen.
- In patients with contraindications to bleomycin, four cycles of etoposide, ifosfamide, and cisplatin (VIP) are as effective as BEP but with more toxicity.
- Residual masses after chemotherapy should be resected. Patients with brain metastases should receive whole-brain radiation in conjunction with chemotherapy.

Chemotherapy Regimens

Commonly used chemotherapy regimens (Table 16.4) include BEP and EP. VIP and VeIP are used less often.

Table 16.4 Commonly Used Chemotherapeutic Agents and Regimens

Agent	Dose	Schedule
BEP	Bleomycin, 30 units IV weekly on days 1, 8, and 15 (can also be administered on days 2, 9, and 16) Etoposide, 100 mg/m^2 IV daily × 5 d Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	2 to 4 cycles administered at 21-d intervals
EP	Etoposide, 100 mg/m^2 IV daily × 5 d Platinol (cisplatin), 20 mg/m^2 IV daily × 5 d	4 cycles administered at 21-d intervals
VIP[a]	VePesid (etoposide), 75 mg/m^2 IV daily × 5 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	4 cycles administered at 21-d intervals
VeIP[b]	Velban (vinblastine), 0.11 mg/kg on days 1 and 2 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	3 to 4 cycles administered at 21-d intervals
TIP[b]	Taxol (paclitaxel), 175 mg/m^2 IV on day 1 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	4 cycles administered at 21-d intervals

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).

Salvage Therapy

- Salvage therapy is usually reserved for disease that has not had a durable response to primary chemotherapy with platinum-based regimen. Such patients may also be considered for a clinical trial especially if they have poor prognostic features.
- Conventional dose regimens incorporate ifosfamide and cisplatin with either vinblastine (VeIP) or paclitaxel (TIP).
- High-dose chemotherapy with autologous bone marrow or peripheral stem cell support is investigational and may represent a therapeutic option for selected patients.
- 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 3 studies (Table 16.7).
- In a large retrospective study, 5-year survival was 53% with HDT as the first salvage therapy.
- Cisplatin refractory germ cell tumors are less likely to have durable response to HDT as compared with tumors that are not refractory to cisplatin.
- HDT should be considered in patients with germ cell tumors that are refractory to primary chemotherapy or those that failed first-line conventional salvage chemotherapy.

Table 16.5 Surveillance Schedule for Seminoma

Year	H&P, CXR, Markers (Monthly Interval)	ABD/Pelvic CT (Monthly Interval)
Stages IA, IB (active surveillance)		
1–2	3–4	6
3–4	6–12	6–12 (annually from year 4)
5+	12	12 (no recommendations beyond year 5)
Stages IA, IB, IS (postradiation)[a]		
1–2	4	12
3–10	12	12 (up to year 3)
Stages IIA, IIB (postradiation)		
1	3	6–12 (years 1–2)
2–5	6	12 (from year 3)
6–10	12	
Stages IIB, IIC, III (postchemotherapy)		
1	2	3–6 (for RPLND) then if indicated
2	3	
3–4	6	

H&P, history and physical; CXR, chest x-ray; ABD, abdomen; CT, computed tomography.
Adapted from National Comprehensive Cancer Network (NCCN) guidelines. There is considerable interinstitutional variation in the standard of follow-up care, with little evidence that different schedules lead to different outcomes.
[a]Surveillance schedule for stages IA and IB (postchemotherapy) is similar.

Table 16.6 Surveillance Schedule for Seminoma

Year	H&P, CXR, Markers (Monthly Interval)	ABD/Pelvic CT (Monthly Interval)
Stages IA, IB		
	Surveillance only	
1	1–2	3–4
2	2	4–6
3	3	6–12
4	4	6–12
5	6	12
6+	12	12–24
	After complete response to chemotherapy and retroperitoneal lymph node dissection	
1	2–3	6
2	2–3	6–12
3	3–6	12
4	6	12
5	6–12	12
6+	12	As clinically indicated
	After retroperitoneal lymph node dissection only	
1	2–3	Baseline
2	2–3	As clinically indicated
3	3–6	As clinically indicated
4	6	As clinically indicated
5+	12	As clinically indicated

H&P, history and physical; CXR, chest x-ray; ABD, abdomen; CT, computed tomography.
Adapted from National Comprehensive Cancer Network (NCCN) guidelines. There is considerable interinstitutional variation in the standard of follow-up care, with little evidence that different schedules lead to different outcomes.

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	2 cycles given at 14-d 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	2 cycles given at 14-d interval. Leukapheresis on days 11–13
Ifosfamide 2,000 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	3 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.

Therapy-Related Toxicity

Complications of RPLND

- Surgical techniques have been refined over the years, but 1% to 2% of patients will have complications which can include bowel perforation, chylous ascites, lymphocele, vascular injuries, pancreatitis, and ejaculatory dysfunction or retrograde ejaculation.

Fertility

Although 70% to 80% of patients treated with chemotherapy may recover sperm production within 5 years, sperm banking should be discussed with all patients desiring to father children after therapy.

- At diagnosis, approximately 25% of patients have oligospermia, sperm abnormalities, or altered follicular stimulating hormone levels due in part to the association of testicular cancer with conditions such as cryptorchidism or testicular atrophy.
- 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

- Bleomycin may cause pneumonitis and pulmonary fibrosis, which may be fatal in up to 50% of patients.
- More frequently, asymptomatic decreases in pulmonary function resolve after completion of bleomycin therapy.
- Bleomycin should be discontinued if early signs of pulmonary toxicity develop or if there is a decline of ≥40% in diffusing capacity of lung for carbon monoxide (DLCO).
- Routine pulmonary function tests are rarely indicated and should be reserved for patients with signs and symptoms of pulmonary toxicity (e.g., dry rales on physical examination or dyspnea on exertion).
- Corticosteroids may be used to reduce lung inflammation if pulmonary toxicity occurs.
- Smokers treated with bleomycin should be particularly discouraged from tobacco use.
- Retrospective studies have suggested that low fraction of inspired oxygen and adequate intravascular volume management 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.
- 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 treated with cisplatin-based regimen. 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 patients with testicular cancer 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. Patients treated for testicular cancer with these agents reportedly have a 1.7-fold increase in their risk of developing a secondary malignancy.
- The increased risk of second malignancy may persist for up to 35 years after the completion of chemotherapy or radiotherapy for testicular carcinoma.
- Alkylating agents such as cisplatin may lead to a myelodysplastic syndrome within 5 to 7 years that can eventually progress to leukemia. Topoisomerase inhibitors such as 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.

REVIEW QUESTIONS

1. A 22-year-old man without significant medical history presented with right-sided chest pain. A chest radiograph showed a mass in the anterior mediastinum. Serum HCG and AFP levels were elevated but a thorough examination of the testicle was unrevealing. This patient likely has
- **A.** Seminoma
- **B.** Klinefelter syndrome
- **C.** Primary mediastinal B-cell lymphoma
- **D.** Thymoma
- **E.** Down syndrome

2. A 29-year-old man presented with a painless right testicular mass. His serum HCG was 10,000 milli-international units/mL and the AFP was 3 ng/mL. CT scan showed a retroperitoneal lymph node mass that measured 7 cm. Immunohistochemical staining of this tumor is likely to be positive for the following markers:
- **A.** CD30 and cytokeratin
- **B.** SOX2 and NANOG

C. CD117
D. CD30
E. OCT4 and SOX2

3. The patient in question 2 had right inguinal orchiectomy followed by four cycles of BEP. Thereafter, his serum tumor markers were in the normal range but there was a persistent 2 cm paraaortic lymph node mass. What is the best next course of action?
A. Surgical resection
B. Radiation therapy
C. Salvage chemotherapy
D. High-dose therapy with stem cell transplant
E. Surveillance

4. A 35-year-old man with cardiac arrhythmia has been on warfarin and amiodarone for several years. Recently, he was diagnosed with nonseminomatous germ cell tumor and he had radical left inguinal orchiectomy a few weeks ago. Preoperatively his AFP was 15,000 ng/mL, left ventricular ejection fraction was 55%, estimated glomerular filtration rate was 55, and DLCO was 50% of its value 6 months ago. He has been referred to you for adjuvant chemotherapy. What is the best treatment for this patient?
A. Four cycles of BEP
B. Three cycles of etoposide and carboplatin
C. Four cycles of EP
D. Four cycles of VeIP
E. Four cycles of VIP

5. A young executive of a thriving commercial firm has just been diagnosed with a poor-risk testicular germ cell tumor with lung metastases. He wants to know his chances for survival because he has two young children. You should tell him that
A. His 5-year OS is 99%.
B. His 5-year OS is 72%.
C. His 5-year OS is 48%.
D. He is more likely to die from the treatment than from the disease.
E. His survival cannot be determined until RPLND is performed.

6. Prior to treatment for testicular germ cell tumor all patients should
A. Have a pulmonary function test with DLCO
B. Be counseled about sperm banking
C. Have an echocardiogram
D. Have genetic testing
E. Receive corticosteroid to prevent bleomycin toxicity

7. The most common genetic abnormality in testicular germ cell tumor is
A. 47, XXY
B. Xq27
C. Increased copy number of 12p
D. SOX17
E. KIT

8. A 30-year-old man had a radical left inguinal orchiectomy for a nonseminomatous testicular germ cell tumor a few months ago. After four cycles of BEP there was a residual retroperitoneal lymph node mass. Excision of the mass was performed and there was evidence of yolk sac element. What will you recommend?
A. Close surveillance
B. Two cycle of EP
C. Three cycles of BEP
D. Four cycles of VIP
E. None of the above

Suggested Readings

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SECTION Six

Gynecologic

17

Ovarian Cancer

Jung-min Lee, Alexandre Buckley de Meritens, Dominic H. Moon, and Elise C. Kohn

BACKGROUND AND EPIDEMIOLOGY

- Ovarian cancer is the second most common gynecologic malignancy, the most common cause of gynecologic cancer death, and fifth leading cause of cancer death in women in the United States.
- In 2012, approximately 22,280 cases will be diagnosed, resulting in 15,500 deaths.
- The median age at diagnosis is 63, with ~70% of new diagnoses at or beyond 55 years of age.
- Lifetime risk of developing epithelial ovarian cancer (EOC) is approximately 1 in 70 (1.4%). It can be as high as 60% and 30% for patients with deleterious *BRCA1* and *BRCA2* mutation (*BRCA1/2*^{mut}), respectively.
- The majority of EOCs (~75%) are diagnosed at advanced stage (III/IV; Fig. 17.1).
- The EOC overall 5-year survival is 44%, with >70% of early-stage (I/II) patients alive at 5 years.

PATHOLOGY

- Epithelial histology accounts for 90% of all ovarian cancers. Serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas are EOC.
  - EOCs are moving into a two-type classification system:
    - Type I tumors include low-grade serous and endometrioid, mucinous, clear cell, and transitional cell carcinomas.
      - Type I tumors generally exhibit low-grade histopathologic features (with the exception of clear cell and endometrioid carcinomas) and appear to arise from well-defined ovarian precursor lesions. Low-grade serous and mucinous carcinomas can progress from their respective serous or mucinous cystadenomas and borderline or low malignant potential (LMP) counterparts.
      - Type I tumors may also develop from ectopic endometriosis to the ovary or peritoneal surface yielding clear cell and low-grade endometrioid carcinomas.

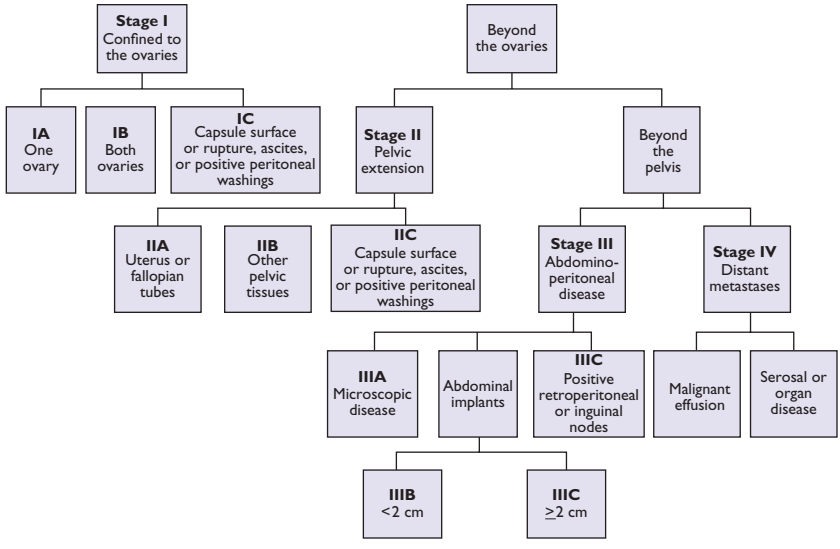

FIGURE 17.1 A flow chart for ovarian cancer FIGO staging. Patients are staged at diagnosis based on the extent of spread of the ovarian cancer. Correct staging is critical as it impacts treatment decisions.

- LMP neoplasms account for approximately 15% of EOC. They are defined by limited layers of stratified epithelial proliferation, without ovarian stromal invasion.
- Approximately 67% of low-grade serous cancers carry oncogenic mutations in *BRAF* and *KRAS*; these neoplasms may have an indolent course.
- Nearly 80% of mucinous ovarian cancers have KRAS mutations. If there is extension beyond the ovary, the appendix must be cleared of malignancy for a pathologic conclusion of mucinous carcinoma of the ovary.

- Type II tumors include high-grade serous carcinoma, high-grade endometrioid carcinomas, and undifferentiated carcinoma.
  - Type II tumor precursor lesions are hypothesized to be clonal expansions of transformed epithelial cells of the fallopian tube fimbria that spread to the ovaries.
  - Nearly all type II tumors are associated with abnormalities in *TP53*, with dysregulating mutations being most common.
  - Type II cancers are more aggressive and commonly disseminated within the abdominal cavity upon presentation.
  - High-grade serous ovarian, fallopian tube, and primary peritoneal carcinomas are now treated as a single clinical entity ("EOC").

- 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. 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
Patient characteristics
• Increasing age
• Personal history of breast cancer
Genetic factors
• Family history of ovarian cancer
• *BRCA1/2* mutations
• Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
Reproductive factors
• Nulligravity
• Early menarche
• Late menopause
• Infertility
• Polycystic ovarian syndrome
• Endometriosis
Environmental factors
• Obesity and high-fat diet (weak evidence)
• Talc exposure
• Cigarette smoking (for mucinous ovarian cancer)
Decreased Risk
Reproductive factors
• Use of oral contraceptives
• Pregnancy/multiparity
• Breastfeeding
Gynecologic surgery
• Salpingo-oophorectomy
• Tubal ligation

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 salpingo-oopherectomy (RRSO) has been shown to reduce the lifetime risk of ovarian/tubal/peritoneal cancer in high-risk women to less than 5%. RRSO is recommended for high-risk women, those with familial ovarian cancer syndromes and/or *BRCA1/2*^{mut}. Surgery is recommended after completion of childbearing and, where feasible, approximately 10 years earlier than the age of diagnosis of the youngest affected family member.
- RRSO has been shown to decrease the risk of breast cancer up to 50% in *BRCA1/2*^{mut} patients.
- RRSO is not recommended for women at average risk.

SCREENING

- 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.
  - Mounting evidence suggests that annual screening with transvaginal ultrasonography (TVU) and serum cancer antigen 125 (CA-125) does not reduce mortality. High false-positive rates leading to intervention are associated with subsequent harm, such as unnecessary surgical intervention.

- Women with a family history of breast/ovarian cancer should be offered genetic counseling. Refer to the NCI website for details: http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA

- Familial ovarian cancer syndrome patients and known *BRCA1/2*^{mut} carriers who have not undergone RRSO may be offered screening consisting of a pelvic examination, TVU, 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 first EOC diagnosis in the family. There are no data demonstrating survival benefit of screening high-risk patients.
- Women with high-risk families in whom deleterious mutations are not found (BRCA1/2, Lynch syndrome–associated genes) 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 EOC. It is elevated most commonly in serous histology.
  - 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 treatment and recurrence. It is neither approved nor recommended for screening.
  - The reliability of following CA-125 concentrations during molecularly targeted therapy 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 EOC recurrence and response to treatment. It is neither approved nor recommended for screening.

DIAGNOSIS AND EVALUATION

- EOC is not a silent disease. Symptoms are present, though nonspecific.
- Several studies suggest usefulness of a symptom index tool to identify women who may have EOC: new (within 1 year) and persistent (more than 12 times/month) pelvic/abdominal pain, increased abdominal size/bloating, difficulty eating/feeling full, and urinary urgency/frequency should trigger evaluation by a gynecologic oncologist.
- Stromal tumors can produce virilization, precocious puberty, amenorrhea, and/or postmenopausal bleeding, depending on patient age, and type and amount of ectopic hormone produced.
- The preoperative workup of a patient with a suspected ovarian malignancy is summarized in Table 17.2.
- Early referral to a gynecologic oncologist is recommended. The extent and quality of surgical debulking have important prognostic value and are an integral part of the upfront management of an EOC patient.

TREATMENT

Surgery

- Proper EOC diagnosis and staging require laparotomy with en bloc TAH/BSO tumor removal, abdominal fluid sampling, tumor debulking, and pathologic assessment of the abdomen, including

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
Labwork: full panels with added
CA-125 (consider HE4)
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.

diaphragms, paracolic gutters, and serosal surfaces. Unilateral salpingo-oophorectomy can be considered in women with stage I grade 1/2 tumors who wish to preserve fertility. Completion of salpingo-oopherectomy is recommended upon completion of child-bearing.

- The primary goal of EOC surgery is complete debulking. Data indicate better outcome for women undergoing surgical debulking by a gynecologic oncologist.
- Optimal debulking, defined as <1 cm maximal diameter residual disease, has positive prognostic value; no visible residual disease yields an even better prognosis.
- Stage I disease with favorable prognostic features (grade 1/2, stage IA/B, non–clear cell histology) can be treated by surgery alone.
- Complete primary debulking surgery (PDS) is still considered the gold standard in the United States. Neoadjuvant chemotherapy (NACT) followed by surgery or with interval debulking surgery yields similar overall survival (OS) to PDS.
- Second-look laparoscopy/laparotomy is no longer supported in the United States.

Initial Chemotherapy

- Stage IC disease with favorable prognostic features can be treated by surgery followed by limited course platinum-based chemotherapy (three cycles; GOG-157); six cycles are recommended for poor prognosis feature stage IC.
- The recommended standard of care adjuvant therapy for optimally debulked advanced stage III patients is a combination of IV paclitaxel and intraperitoneal (IP) cisplatin/paclitaxel chemotherapy. It is unclear if the benefit was due to the dose density, site of administration, or both factors.
- The standard of care NACT or adjuvant therapy for patients with suboptimally debulked stage III/any stage IV disease and patients who cannot tolerate IP chemotherapy is six cycles of IV carboplatin and IV paclitaxel every 21 days.
- NACT and adjuvant chemotherapy regimens are summarized in Table 17.3.
- The GOG 262 phase 3 trial evaluating the efficacy of dose dense weekly paclitaxel with carboplatin AUC 6 is maturing.
- Carboplatin and cisplatin are equally effective in the treatment of EOC; carboplatin has reduced renal, auditory, and neurotoxicity compared to cisplatin but greater and cumulative marrow effects (GOG-158).
- 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 IDMS method, FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing.

Table 17.3 Adjuvant Chemotherapy and Therapy for Recurrent Disease

Neoadjuvant or Adjuvant Chemotherapy		
Indication	***Treatment***	***Supporting Data***
Neoadjuvant chemotherapy (NACT), suboptimally debulked stage III/IV, patients who cannot tolerate IP therapy	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 for patients with bulky stage IIIC/IV EOC: OS HR = 0.98 (90% confidence interval [CI] 0.84–1.13; $P = 0.01$), PFS HR = 1.01 (90% CI 0.89–1.15)
Optimally debulked advanced stage III	IV paclitaxel at 135 mg/m^2 over 24 hours 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; $P = 0.05$); median OS 49.7 (IV) vs. 65.6 mo (IV/IP; $P = 0.03$)
Dose-dense weekly paclitaxel	Weekly paclitaxel at 80 mg/m^2 with carboplatin (AUC6)	Japanese GOG study: median PFS 28.0 (dose dense) vs. 17.2 mo (q3wk; $P = 0.0015$); OS at 3 y 72.1% (dose dense) vs. 65.1% (q3wk; $P = 0.03$)
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 currently approved in the United States. Approved by the EMA for high-risk EOC
Recurrent or Persistent Disease		
Indication	***Treatment***	***Supporting Data***
Platinum-sensitive disease	Platinum-based combination therapy (with pegylated liposomal doxorubicin, gemcitabine, or taxane)	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 are better than carboplatin alone; carboplatin/doxil is better tolerated and equivalent otherwise to carboplatin/paclitaxel
Platinum-resistant/ refractory disease	Single-agent chemotherapy: pegylated liposomal doxorubicin, topotecan, gemcitabine, taxotere, oral etoposide, weekly paclitaxel, hexamethylmelamine, and/or consideration of hormone ablation with letrozole/anastrazole or tamoxifen; experimental therapy	
Maintenance in recurrent disease	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 benefit for carbo/gemcitabine with maintenance bevacizumab (HR = 0.48; median PFS = 12.4 mo vs. 8.4 mo; $P < 0.0001$). Additional studies ongoing (GOG 213)

- Patients can demonstrate hypersensitivity to paclitaxel with the initial treatment 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.
- Platinum hypersensitivity is an anaphylactic, true allergic reaction and presents in later cycles (usually >6 to 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 PFS but may not improve OS (GOG218 and ICON7).
- A meta-analysis of six randomized maintenance trials confirmed no improvement in OS (HR 1.07; 95% CI 0.91 to 1.27; $N = 902$). This analysis did not include bevacizumab 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 a RCT comparing early treatment of relapse (increased CA-125 alone) versus observation until symptoms or physical examination trigger disease assessment (MRC OV05/EORTC 55955).
- Secondary cytoreduction surgery is recommended for women with recurrence-free intervals of ≥12 months. Value is being examined in an ongoing phase 3 trial (GOG-213).
- Patients with a progression-free interval of ≥6 months have platinum-sensitive disease. Second-line platinum-based therapy, single agent or combination, improves survival in women with platinum-sensitive disease (Table 17.3).
- Recurrence within 6 months of initial platinum-based chemotherapy is defined as platinum-resistant disease. Progression while on initial chemotherapy is platinum-refractory disease.
- Sequential single-agent chemotherapy is preferred for platinum-resistant/refractory patients, due to increased toxicity without sufficient evidence of increased benefit of combinations (Table 17.3). Cisplatin/gemcitabine is the one regimen with RCT-documented benefit.
- There has been increasing interest in the use of molecularly targeted agents:
  - Bevacizumab has modest activity in relapsed ovarian cancer, both platinum sensitive and platinum resistant, and ongoing studies are evaluating its use (OCEANS).
  - PARP inhibitors have demonstrated clinical activity in recurrent EOC in BRCA1/2^{mut} carriers in phase 1/2 studies.

Nonepithelial Ovarian Cancer

- Most patients with ovarian germ cell tumors are diagnosed with early-stage disease. Lymph node metastases are rare. Unilateral salpingo-oophorectomy, 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, distal bowel obstruction, 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).

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.
  - Occasionally, RT to a particular mass causing obstruction may be appropriate.

SUMMARY

- EOC is the most common cause of death among women with gynecologic malignancies and the fifth leading cause of cancer death in women in the United States.
- Limited disease with high-risk features and advanced disease need adjuvant paclitaxel/carboplatin.
- For women who experience a recurrence, the selection of therapy is commonly based upon response to initial platinum-based treatment.

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REVIEW QUESTIONS

1. The patient is a 54-year-old African-American woman who was diagnosed with stage IIIC high-grade serous ovarian 24 months ago. After an exploratory laparotomy resulted in successful resection of all gross disease, she received six cycles of intravenous paclitaxel/carboplatin with a resultant clinical complete remission. She now presents with a rising CA-125 (three successive monthly elevated values with the last value at 360). She is asymptomatic. A CT scan of the abdomen/pelvis shows no evidence of recurrent disease. Which of the following would you recommend at this point?
   - **A.** Observation
   - **B.** Exploratory laparotomy and secondary surgical cytoreduction
   - **C.** Insertion of an IP catheter and administration of IP cisplatin
   - **D.** Systemic chemotherapy with a carboplatin-based doublet
   - **E.** Systemic chemotherapy with an active agent to which she has not been previously exposed
2. A 40-year-old woman presents to her gynecologist because her sister, aged 42, was recently diagnosed with serous ovarian carcinoma and was found to carry a deleterious BRCA1 mutation. The patient reports a strong family history of both breast and ovarian cancer, also including her mother (breast cancer). Testing reveals that she also carries the deleterious BRCA1 mutation. She has completed her family, which of the following would you recommend?
   - **A.** Annual screening with transvaginal sonography and CA-125
   - **B.** Pelvic examination every 3 months
   - **C.** Annual screening with serum proteomic profiling
   - **D.** Risk-reducing salpingo-oophorectomy
   - **E.** Oral contraceptives
3. The patient is a 61-year-old Caucasian woman with increasing abdominal girth and discomfort beginning 3 months prior to seeing her gynecologist. The evaluation by the gynecologist revealed her to be in good health with no other significant problems. Physical examination observed a slightly distended abdomen and pelvic examination revealed a 6 cm mass in left adnexa. Laboratory data showed a CA-125 of 960. Computerized tomography of the abdomen showed a 7 cm mass involving the left ovary, ascites, and multiple scattered smaller masses throughout the abdomen. She underwent an exploratory laparotomy by a gynecologic oncologist with the identification of stage IIIC disease involving the peritoneal surface and omentum. At the conclusion of surgery, she had no gross disease remaining, and her CA-125 remained elevated, 34 units/mL, 4 weeks after surgery. Which of the following would be the best choice for treatment for this patient?
   - **A.** Paclitaxel/carboplatin for six cycles
   - **B.** IP chemotherapy with paclitaxel and carboplatin for six cycles
   - **C.** Docetaxel/carboplatin for six cycles
   - **D.** Gemcitabine/carboplatin for six cycles
   - **E.** Paclitaxel/carboplatin/bevacizumab for six cycles followed by maintenance bevacizumab until progression

Suggested Readings

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18

Endometrial Cancer

Anne M. Noonan and Christina M. Annunziata

EPIDEMIOLOGY

- Endometrial cancer is the most common pelvic gynecologic malignancy in women, and is the second most prevalent cancer among women comprising 6% of all cancers in women.
- In 2012, 47,130 new cases were projected. Since 2004, incidence rates of endometrial cancer have been stable in white women, but increasing in African-American women by 1.9% per year.
- One in 38 women will develop endometrial cancer in her lifetime.
- An estimated 8,010 deaths will occur in 2012 due to this malignancy, accounting for 3% of all cancer deaths in women.
- The mortality rate continues to decline, likely because of increased awareness of symptoms including abnormal vaginal bleeding.
- The incidence is 24.8 per 100,000 white women per year, compared to 21.8 per 100,000 African-American women per year.
- Although incidence is 1.14 times higher in white women than in African-American women, the 5-year survival rate is lower in African-American women than in white women (67% vs. 84%).
- Peak incidence is in the sixth and seventh decades of life; 7.5% of cases are diagnosed before the age of 44; 19% are diagnosed between the age of 45 and 54. The median age at diagnosis for cancer of the uterine corpus is 61 years.

RISK FACTORS

- Endogenous estrogen excess:
  - Polycystic ovary disease.
  - Anovulatory menstrual cycles.
  - Advanced liver disease.
  - Granulosa cell tumor of the ovary, or other estrogen-secreting tumors.
  - Obesity: Being overweight by 20 to 50 pounds increases risk threefold and being overweight by >50 pounds increases risk 10-fold. Each 5 kg/m^2 increase in BMI is associated with 30% to 60% increased risk of endometrial cancer.
- Endogenous prolonged estrogen exposure:
  - Early menarche and late menopause: Menopause in women older than 52 years increases risk by 2.4-fold.
  - Irregular menses, infertility, and nulliparity: 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.

- Exogenous unopposed estrogen sources:
  - Taking unopposed estrogens for 3 or more years is associated with a fivefold increased risk of invasive endometrial cancers.
  - Tamoxifen (TAM) acts as a weak estrogen, increasing the relative risk (RR) of developing endometrial cancer by twofold to eightfold depending on length of exposure to the drug.
- 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 consistent with hereditary nonpolyposis colorectal cancer (HNPCC) (Lynch II syndrome) is associated with a RR of 1.5 for development of endometrial cancer in the premenopausal years.
  - History of endometrial cancer in a first-degree relative increases risk threefold.
  - History of colorectal cancer in a first-degree relative increases risk of endometrial cancer twofold.

PROTECTIVE FACTORS

- Oral contraceptives:
  - There is a 50% decrease in RR when oral contraceptives that include a progestin are used for at least 12 months.
  - Protection lasts for at least 10 years after discontinuation of oral 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 appears to have a modest protective role. However, this is strongly outweighed by the significantly increased risk of lung cancer and other diseases.

DIAGNOSIS AND SCREENING

- Routine screening for endometrial cancer is not required in asymptomatic women, except those with HNPCC. Women with HNPCC have a 60% lifetime risk of endometrial cancer, and the disease occurs 10 to 20 years earlier than nonhereditary cancers. The American Cancer Society (ACS) recommends that women with HNPCC undergo annual endometrial biopsy after age 35.
- Women taking TAM should have a gynecologic evaluation according to the same guidelines for women not taking TAM.
- Endometrial biopsy is the preferred diagnostic test for symptomatic patients (vaginal bleeding or spotting).

Signs and Symptoms

- Abnormal vaginal bleeding is a common symptom of endometrial cancer, seen in approximately 90% of cases.
- Premenopausal women with prolonged and/or heavy menses or intermenstrual spotting should undergo endometrial biopsy.
- Ten percent of cases present with profuse serous or serosanguinous discharge.
- All postmenopausal women with vaginal bleeding should be evaluated for endometrial cancer (20% 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.
- Palpable, locally advanced tumor detected on pelvic examination is suggestive of endometrial cancer. Common distant sites of metastases include lung, inguinal and supraclavicular lymph nodes (LNs), liver, bones, brain, and vagina. Signs and symptoms of advanced disease, manifested in <10% of cases, include
  - Bowel obstruction
  - Jaundice
  - Ascites
  - Pain

Procedures

- Endocervical curettage and endometrial biopsy are well-tolerated outpatient procedures.
- Pap smear is of limited value (see the previous section).
- Fractional curettage under anesthesia involves scraping of the endocervical canal, followed by the uterine walls, in a set sequence. This is the standard procedure for the diagnosis of endometrial cancer in symptomatic women with negative or inadequate endometrial biopsy.
- Available data on transvaginal ultrasound suggest a direct correlation between endometrial stripe thickness, as seen on ultrasound, and subsequent risk of endometrial cancer. An endometrial stripe cutoff of <4 to 5 mm has been used as a diagnostic criterion; however, cases of endometrial cancer could occasionally be missed. Patients taking TAM tend to have thicker endometrium than women who do not take TAM. There is therefore no consensus on the cutoff thickness of endometrial stripe that would indicate a need for endometrial biopsy.

HISTOLOGY

Subtypes

Subtypes of endometrial cancer include endometrioid (75% to 80%), uterine papillary serous (5% to 10%), clear cell (1% to 5%), mucinous (1%), squamous cell (<1%), and uterine sarcoma (<10%). Endometrial carcinoma may also be divided into types 1 and 2, according to estrogen dependence:

- Type 1 (estrogen-related), the more common type of endometrial carcinoma, is associated with DM and obesity and tends to have better prognosis. Characteristics include the following:
  - Endometrioid histology
  - More differentiated (lower grade, higher progesterone receptor [PR] levels)
  - Less myometrial invasion (lower stage at presentation)
  - Younger patients
  - Genetic aberrations: Mutations in K-ras, β-catenin, PI3K, PTEN, ARID1A microsatellite instability, DNA mismatch repair defects
- Type 2 (unrelated to estrogen stimulation and endometrial hyperplasia):
  - Nonendometrioid histology (serous, clear cell)
  - Commonly associated with p53 mutations (serous), chromatin-remodeling and ubiquitin ligase complex genes (CHD4, FBXW7, and SPOP)
  - Aneuploid (grade 3)
  - Her2/neu overexpressed

Special Considerations

- Adenomatous hyperplasia is an estrogen-dependent lesion that could be seen along with type 1 but not type 2 endometrial carcinoma.

- Women with the serous subtype are at increased risk of developing a concurrent or subsequent breast cancer—breast cancer is diagnosed in 20% to 25% of patients with serous subtype compared to 3% with endometrioid subtype.

PRETHERAPY EVALUATION

- Physical examination.
- Routine blood and urine studies.
- Special laboratory tests: CA125 is elevated in about 20% of patients. CA125 >40 units/mL can predict extrauterine and/or LN metastasis. HE4 >70 pmol/L is a promising tool for preoperative evaluation and postoperative surveillance.
- Chest x-ray.
- Urinary imaging studies (IV pyelogram or renal scan), cystoscopy, and proctoscopy (very rarely done).
- Other imaging tests: Routine use of ultrasound, computerized tomography (CT) scan, and magnetic resonance imaging (MRI) are NOT routinely recommended, although MRI ± endorectal coil may improve the evaluation of myometrial and cervical invasion in medically inoperable patients; bone scan rarely yields useful information.
- Routine age-appropriate health maintenance: If HNPCC is suspected, colonoscopy should be performed before planning treatment.
- Evaluation of specific symptoms or physical examination findings as indicated.

STAGING

- Staging for endometrial carcinoma is surgical and is based on information from hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal cytology, and pelvic and periaortic LN dissection.
- Endometrial cancer distribution by stage:
  - Stage I: 70% to 75%
  - Stage II: 10% to 15%
  - Stage III: 5% to 10%
  - Stage IV: <5%

The 2009 FIGO staging system is as follows:

- IA: Tumor confined to the uterus, no or <½ myometrial invasion
- IB: Tumor confined to the uterus, >½ myometrial invasion
- II: Cervical stromal invasion, but not beyond uterus
- 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
- IVA: Tumor invasion bladder mucosa and/or bowel mucosa
- IVB: Distant metastases including abdominal metastases and/or inguinal LNs

PROGNOSTIC FACTORS

Uterine

- Histology—serous and clear cell have a worse prognosis; squamous and undifferentiated behave aggressively.
- Tumor hormone-receptor status: The presence and levels of estrogen receptor (ER)/PR are inversely proportional to histologic grade and are associated with longer survival.

- 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%
- Tumor size: Tumors >2 cm have worse prognosis.
- Vascular-space invasion: Rate of disease recurrence is approximately 25%.

Extrauterine

- Positive peritoneal cytology: 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.
- Older age is associated with worse prognosis.

MANAGEMENT

- Endometrial hyperplasia: Total abdominal hysterectomy (TAH) or BSO is the treatment of choice for patients with persistent endometrial hyperplasia after failure of adequate therapy with progestin.
- Endometrial carcinoma: Therapy should be individualized for endometrial carcinoma. However, the following guidelines may be generally employed:
  - Low risk: TAH/BSO (selected pelvic LN may be removed). This can be considered adequate for certain patients with:
    - Well-differentiated endometrioid histology tumors.
    - Negative peritoneal cytology. If no peritoneal fluid is found during surgery, peritoneal washing with normal saline should be done.
    - No vascular-space invasion.
    - <50% myometrial invasion.
- Intermediate risk: Radical TAH/BSO combined with para-aortic and selective pelvic LN sampling or dissection, and pelvic washings. If there are no medical or technical contraindications (e.g., morbid obesity), this should be done in patients with
  - Grade 1 or 2 tumors involving >50% of myometrium (stage IC)
  - Tumor presence in cervical isthmus (stage II)
  - Nonendometrioid histology
  - Visible or palpable LN enlargement
- High risk: Adjuvant therapy is recommended. Adjuvant radiation reduces the risk of local recurrence; adjuvant chemotherapy has shown a survival advantage (see the following section). Adjuvant therapy is recommended for patients with
  - Grade 2 or 3 with any myometrial invasion
  - Grade 2 with >50% myometrial invasion or cervical/vaginal involvement
  - Adnexal or pelvic metastasis
  - Lymphovascular-space involvement

Adjuvant Therapies

Chemotherapy

Adjuvant chemotherapy is recommended for women with advanced extrauterine disease. Regimens of choice include

- 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 G-CSF support.

- TC (paclitaxel 175 mg/m^2 and carboplatin AUC 5) for six cycles showed response rates ranging from 47% to 87%.

Chemotherapy has shown a survival advantage over whole abdominal irradiation (WAI) in advanced endometrial carcinoma (Trial GOG 122 by the Gynecologic Oncology Group).

- AP (doxorubicin 60 mg/m^2, cisplatin 50 mg/m^2 for seven cycles, plus one additional cycle of cisplatin alone) was compared to WAI (30 Gy in 20 fractions with a 15 Gy boost to pelvic and para-aortic nodes). Better progression-free and overall survival was seen in the chemotherapy arm.
- One randomized study of platinum-based chemotherapy in stage I uterine papillary serous carcinoma showed improvement in disease-free and overall survival.

Radiation Therapy

Radiation therapy (RT) may be used alone in women with high-risk cancer confined to the endometrium. It may be considered in patients with extrauterine disease confined to the pelvic LNs. RT reduces risk of local recurrence. RT is associated with early and late toxicity. Strategies include the following:

- Whole pelvic RT: 45 to 50 Gy external beam radiation (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 patient has undergone complete surgical staging to confirm that disease is confined to the uterus.
- WAI (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 to 25 Gy to a point A) and EBRT (40 to 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 periaortic LN sampling. This approach can provide 5-year disease-free survival of 70% to 80%.

Combined Chemotherapy and RT

- May decrease local recurrence rate, which can be as high as 50% with chemotherapy alone.
- To date studies of radiotherapy combined with chemotherapy have shown a benefit to progression-free survival but no definite increase in overall survival. GOG 249, GOG 258, and PORTEC III studies are currently under way to address the role of combined chemotherapy and radiotherapy in the management of endometrial cancer.

Special Considerations

- Low-risk, low-grade patients who still desire fertility can be managed with progestational agents such as levonorgestrel-releasing intrauterine system (e.g., 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 (e.g., 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 the subsequent text).

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 irradiation. Occasional long-term survival has been reported.
- Radiation: 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, irradiation may be curative if not previously administered.

Distant Metastasis: Systemic Therapy

Hormonal therapy produces responses in 15% to 30% of patients and is associated with survival twice as long as in nonresponders. On average, responses last for 1 year. Hormonal therapy is used for endoemetrioid histologies only (not for clear cell, serous, or carcinosarcoma). Tumor tissue should be checked for ER and PR levels, since hormone-receptor levels and degree of tumor differentiation correlate well with response. Hormonal therapy is preferred as first-line intervention for recurrent or metastatic endometrial cancer due to its lower toxicity profile and response rate similar to chemotherapy. Options include the following:

- Megestrol acetate (Megace), 160 to 320 mg daily, is the preferred initial regimen.
- Medroxyprogesterone acetate (Depo-Provera), 400 to 1,000 mg IM weekly for 6 weeks and then monthly.
- Oral medroxyprogesterone (Provera), 200 mg PO daily works equally well as 1,000 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 (e.g., anastrozole, letrozole) are currently being evaluated and to date have response rates of 10%.
- There is no role for hormonal therapy in the adjuvant setting to treat early-stage disease.

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
  - Response rates 17% to 28%; partial responses of short duration (<6 months); overall survival 9 to 12 months.
  - Options include doxorubicin, cisplatin, carboplatin, docetaxel, topotecan.
  - Paclitaxel may have a superior response rate of 27% to 37%.
- Combination chemotherapy
  - Response rates 36% to 67%; partial responses are short duration (4 to 8 months).
  - Overall survival not improved over single-agent therapy.
  - Combinations may include doxorubicin with cisplatin and/or cyclophosphamide; carboplatin with liposomal doxorubicin; cyclophosphamide, doxorubicin, and 5-FU.
  - Paclitaxel-containing regimens may improve response and progression-free intervals; overall survival 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 to 7, every 4 weeks).

Less well-studied treatment regimens have been proposed:

- Chemotherapy in conjunction with hormonal therapy
  - Response rates may be slightly higher than with either therapy alone.
  - Overall survival may also be improved.
- The addition of medroxyprogesterone (200 mg daily) to cyclophosphamide, doxorubicin, and 5-FU, followed by TAM 20 mg daily for 3 weeks was tested in a small clinical trial of 46 women. Overall survival was 14 months compared to 11 months with chemotherapy alone.
- Targeted agents:
  - Bevacizumab may be given in the recurrent setting following progression after cytotoxic chemotherapy. Trials are in progress looking at bevacizumab in combination with carboplatin and paclitaxel.
  - mTOR inhibitors such as temsirolimus are being investigated in phase 2 trials.

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.
- NCCN guidelines for posttherapy surveillance of endometrial cancer include:
  - History and physical examination, CA125 level, every 3 to 6 months for 2 years, then annually. Up to 70% of patients will report symptoms of vaginal bleeding, pain, cough, or weight loss.
  - Vaginal cytology every 6 months for 2 years, then annually.
  - CXR annually.
  - Genetic counseling or testing is advised in patients $<$55 years of age with a significant family history and/or pathologic features suggestive of Lynch syndrome, e.g., MSI-high.
  - A recent meta-analysis suggested that PET may be useful in the localization and detection of recurrent disease.

REVIEW QUESTIONS

1. A 56-year-old-female with a history of obesity and type II diabetes presents for follow-up 18 months after completion of surgery and for stage IIIC, grade 3 endometrioid endometrial cancer. The tumor was strongly ER and PR positive and lymphovascular space invasion was present. She also received adjuvant RT (50 Gy EBRT along with vaginal irradiation with vaginal cylinder to bring the vaginal surface dose to 90 Gy). On review of symptoms she complains of cough with mild shortness of breath on going up two flights of stairs, and 3 kg weight loss over the past 2 months. CXR reveals three lung nodules measuring between 1.2 and 2.3 cm—one on the left and two on the right. CT scan also shows a 1.4 cm para-aortic LN. She is in good health otherwise and is able to carry out all other activities of daily living. What is the most appropriate therapeutic option?
   A. External beam radiotherapy to lungs and para-aortic LNs
   B. Chemotherapy with 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 G-CSF support
   C. Medroxyprogesterone acetate 200 mg PO daily
   D. TAM 20 mg PO twice daily
   E. Bevacizumab 10 mg/kg IV every 2 weeks
2. A 40-year-old premenopausal woman with no significant comorbidities presents for her 6-month routine oncology follow-up. One year ago she underwent wide local excision for a stage II ER-positive, PR-positive, HER-2-negative ductal carcinoma of the breast. She completed chemotherapy and radiotherapy. Her menses returned postchemotherapy. She commenced TAM 20 mg

PO daily 6 months ago. She is concerned about the increased risk of uterine cancer while taking TAM and asks your advice about how she should be monitored for the occurrence of endometrial cancer. Which of the following is the *correct* advice for surveillance for endometrial cancer in patients taking TAM:

A. Annual transvaginal ultrasound while on TAM
B. Annual pelvic ultrasound and pelvic examination while on TAM
C. Screening hysteroscopy and biopsy every 2 years while on TAM
D. Annual pelvic examination and routine age-appropriate Papanicolaou smear with symptom-directed investigations should symptoms of endometrial cancer arise
E. MRI of pelvis every 2 years while on TAM

3. A 37-year-old woman presents to her primary care physician for routine health maintenance examination. Her father died from metastatic colon cancer at age 49. She reports that in the past year her brother aged 30 and a paternal cousin aged 33 were both diagnosed with colon cancer. She has seen a gastroenterologist and is scheduled for a screening colonoscopy. What further advice would you give her regarding her gynecologic health?

A. No additional gynecologic health screening is required beyond routine annual pelvic examination and age-appropriate Papanicolaou smear
B. She should immediately have a hysterectomy
C. Consultation with a genetic counselor is advised
D. Annual pelvic examination and endometrial biopsy after age 35
E. C and D

4. A 40-year-old African-American woman presents with a 3-week history of low back pain, abdominal swelling, serosanguinous vaginal discharge, and early satiety. CA125 is 120 units/L. Serum albumin is 2.5 mg/dL. CBC is normal. Serum chemistries reveal mildly elevated LFTs $<2\times$ upper limit of normal. CT scan shows a mass in the uterus, enlarged pelvic LNs, large volume ascites, peritoneal metastases, bilateral pleural effusions, and numerous liver lesions suspicious for metastases. She has a suboptimal debulking surgery including a TAH, BSO, omentectomy, pelvic and para-aortic LN dissection, and peritoneal stripping. Pathology reveals a grade 3 uterine papillary serous carcinoma. Peritoneal cytology is positive. Her disease is classified as FIGO stage IVB. What would you recommend next?

A. Clinical trial
B. Medroxyprogesterone acetate
C. Vaginal brachytherapy
D. Chemotherapy with cisplatin, irinotecan, and 5-FU
E. None of the above

Suggested Readings

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Cervical Cancer

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EPIDEMIOLOGY

- Worldwide, cervical cancer is the third most common cancer and the fourth leading cause of cancer death in women.
- In 2008, more than 529,800 new cases were diagnosed worldwide; an estimated 275,100 women die each year of this disease.
- In the United States, cervical cancer is the third most common cancer of the female reproductive tract, with more than 12,170 new cases and 4,220 deaths estimated in 2012.
- Introduction of Papanicolaou (Pap) smear screening has reduced the incidence and mortality of invasive cervical cancer by almost 75% over the last 50 years; however, 86% of cases occur in developing countries where screening may not be available.
- Cervical cancer incidence in the United States is decreasing but remains disproportionately high among subgroups of the population (Asians, African Americans, Latinos, Native Americans).
- In more developed areas, the cumulative risk of developing cervical cancer by age 75 is 0.9% and the mortality risk is 0.3%; in less developed areas, those risks are 1.9% and 1.1%, respectively.

RISK FACTORS

Human Papillomavirus

- Persistent human papillomavirus (HPV) infection is the most important factor in developing cervical cancer and greater than 99% of cervical cancers harbor HPV DNA.
- Approximately 40 distinct HPV types are known to infect the genital tract, and at least 15 types have been associated with cancer.
- HPV viruses of high oncogenic potential that are associated with cervical cancer include types 16, 18, 31, 33, 35, 45, 52, and 58. HPV types 16, 18, and 45 presented at a younger mean age than other HPV subtypes.
- HPV types 16 and 18 account for 70% of cervical cancer.
- 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.
- Prevalence of HPV in countries with high incidence of cervical cancer is 10% to 20% and in countries with lower incidence of cervical cancer is 5% to 10%.
- The oncogenic effect of the high-risk HPV subtypes appears to be mediated by E6 and E7 proteins, which have been shown to inactivate tumor-suppressor genes p53 and pRb, respectively. The subsequent loss of the cell-cycle regulatory mechanism leads to malignant transformation.

- Current clinical data show no evidence that determining whether an invasive cervical cancer harbors HPV influences clinical outcome or management. Therefore, routine HPV typing of cancers is not recommended except in clinical trials. For patients with cervical intraepithelial neoplasia (CIN), the presence of high-risk HPV serotypes increases the risk of invasive disease.

Demographic, Personal, or Sexual Risk Factors

- Risk of invasive cervical cancer is largely influenced by HPV exposure, vaccination, and screening as well as immune response to HPV infection.
- Demographic risk factors include race (higher in Hispanic/Latino, African American, and Native American women), lower socioeconomic status, and immigration from HPV high-prevalence or low-screening countries.
- 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 sex partners (RR is threefold with six or more partners compared to one partner), and a history of sexually transmitted infections.
- Among males with multiple sex partners (a known risk factor for HPV infection), penile circumcision appears to reduce the risk of cervical cancer for their female partners.
- Smoking increases the RR of squamous cell cervical cancer fourfold and has been shown to accelerate progression of dysplasia to invasive carcinoma twofold.
- Additional risk factors include multiparity (RR = 3.8), use of oral contraceptives for more than 5 years (RR of 1.90), and immunosuppression.
- Renal transplantation (RR = 5.7) and HIV infection (RR = 2.5) increase the risk of cervical cancer. (Cervical cancer is an indicator condition in the case definition of AIDS in HIV-positive women according to the 1993 Centers for Disease Control and Prevention criteria.)

SCREENING

- Joint national guidelines provide the following consensus screening recommendations:
  - Cervical cancer screening of women in the general population should begin no sooner than age 21.
  - Women aged 21 to 29 should be screened with cervical cytology alone every 3 years.
  - In women aged 30 to 65, cotesting with cervical cytology and HPV testing every 5 years is preferred. Continued screening with cervical cytology every 3 years is acceptable.
  - Screening should end at age 65 in women with negative prior screening and no history of CIN 2 or greater. Likewise, it should end in women who have had a (total) hysterectomy with removal of the cervix and no prior history of CIN 2 or greater.
- Cervical cytology should be described using the 2001 Bethesda System detailing specimen adequacy and interpretation.
- Interpretation is divided into nonmalignant findings and epithelial cell abnormalities including squamous and glandular abnormalities.
- Adenocarcinoma incidence has been increasing over past three 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

- Mild, moderate, and severe cervical dysplasias are categorized as CIN 1, 2, and 3, respectively.
- Mild-to-moderate dysplasias are more likely to regress than progress. Nevertheless, the rate of progression of mild dysplasia to severe dysplasia 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 carcinoma in situ (CIN 3) has a 30% probability of progression to invasive cancer within 30 years.

SIGNS AND SYMPTOMS

- CIN and early cervical cancer are often asymptomatic.
- In symptomatic patients, abnormal vaginal bleeding (i.e., 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 roots.
- Urinary or rectal symptoms (hematuria, rectal bleeding, etc.) may indicate bladder or rectal involvement.
- Persistent, unilateral, or bilateral leg edema may indicate lymphatic and venous blockage caused by extensive pelvic-wall 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 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 (may be colposcopically guided)
- Conization for subclinical tumor or after negative biopsy if malignancy is suspected
- Conization for microinvasive cancer to determine appropriate treatment
- Endocervical curettage for suspected endocervical lesions
- Cystoscopy and proctoscopy for symptoms concerning for bladder or rectal extension

Radiologic Studies

- Because of limits of low-resource countries, International Federation of Gynecology and Obstetrics (FIGO) limits imaging for staging purposes to chest x-ray, intravenous pyelography (IVP), and barium enema.
- When available for treatment planning purposes, recommended imaging may include CT or combined PET/CT and MRI.
- MRI is the best imaging modality for determining soft-tissue and parametrial involvement.
- CT or PET/CT is useful to evaluate nodal involvement and/or volume.

Laboratory Studies

- Complete blood count
- Blood chemistries
- Liver and renal function tests

HISTOLOGY

- Cervical carcinoma originates at the squamo-columnar junction, or transformation zone, of the cervix.

- Seventy-five percent to 80% of cervical cancers are of squamous cell histology; the remaining 20% to 25% are mostly adenocarcinomas or adenosquamous carcinomas.

STAGING

- Because the global burden of cervical cancer is in low-resource countries where abilities to surgically stage may be limited, cervical cancer is clinically staged according to the 2010 FIGO definitions and staging system. This system has been approved by the American Joint Committee on Cancer (AJCC) (see AJCC Cancer Staging Manual, seventh edition).
- Laparoscopy, lymphangiography, CT, MRI, and FDG-PET may be used for treatment planning.

PROGNOSTIC FACTORS

- Major prognostic factors are stage, nodal involvement, tumor volume, 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. The prognostic impact of squamous carcinoma versus adenocarcinoma remains controversial.
- Five-year survival based on extent of tumor at diagnosis:
  - Localized: 92%
  - Regional: 56%
  - Distant spread: 16.5%
  - Unstaged at diagnosis: 60%

MODE OF SPREAD

- Spread is usually orderly along lymphovascular planes into the parametria. It may extend to the vaginal mucosa or endomyometrium, or by direct extension into adjacent structures.
- Ovarian involvement by direct extension of cervical cancer is rare (0.5% of squamous cell carcinomas, 1.7% adenocarcinomas).
- Lymphatic spread most commonly involves pelvic and para-aortic lymph nodes.
- Hematogenous spread is typically a late occurrence but most commonly involves lung, liver, and bone.
- Risk of pelvic lymph node metastasis increases with increasing depth of tumor invasion and size, and presence of LVSI.

TREATMENT

(High-Grade Dysplasia/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 electrosurgical excision, cryotherapy, laser excision or ablation, surgical conization, or other surgical procedures.
- A one-step diagnostic and therapeutic option is the loop electrosurgical excision procedure (LEEP), which allows excision of the entire transformation zone of the cervix with a low-voltage diathermy loop.
- A cold-knife conization (CKC) excises the transformation zone with a scalpel, avoiding cautery artifact on the surgical margins. In the majority of situations, LEEP may be an acceptable alternative to CKC because it is a quick, outpatient procedure requiring only local anesthesia.
- When margin status will dictate the need for, and type of, additional therapy, as in cases of adenocarcinoma in situ or microinvasive squamous cell carcinoma, a CKC is preferred.

- Extrafascial (i.e., 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 Cervical Cancer

- Treatment in each stage may vary depending on the size of the tumor. Smaller tumors may be treated surgically or with radiation. Larger tumors are usually only treated with radiation.
- Results from five randomized phase 3 trials demonstrated an overall survival (OS) advantage for cisplatin-based chemotherapy given concurrently with radiation when compared to radiation-only therapy. These trials have demonstrated a 30% to 50% overall reduction in risk of death in patients with FIGO stage IB2 to IVA tumors and in patients with FIGO I to IIA tumors with poor prognostic factors (i.e., pelvic lymph node involvement, parametrial disease, and positive surgical margins) compared to radiation alone.
- Based on these data, the National Cancer Institute issued a clinical announcement stating that strong consideration should be given to adding chemotherapy to radiation therapy (RT) in the treatment of invasive cervical cancer.
- The most common regimen for concurrent chemotherapy is once-weekly cisplatin, 40 mg/m^2 IV (maximum 70 mg) for six cycles, concurrent with radiation. Alternatively, cisplatin with 5-FU given every 3 to 4 weeks during radiation is acceptable.

Stage IA1

- Prior to treatment, the most important variables include (1) the patient's fertility desires, (2) medical operability, and (3) presence of LVSI from the biopsy.
- For patients with no LVSI and negative 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, 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 chemoradiotherapy (whole pelvic radiation and brachytherapy)
- All options are equally effective but differ in associated morbidity and complications.
- For early-stage cervical cancers, primary surgery is often recommended rather than primary chemoradiation to avoid the long-term toxicities of radiation.
- Optimal choice depends on patient's age and childbearing plans, disease stage, current comorbidities, and presence of histologic characteristics associated with increased risk of recurrence.

Stage IB2 or IIA2 (Bulky Disease)

- General options for bulky disease include the following:
  - Definitive chemoradiotherapy (whole pelvic radiation and brachytherapy) is generally preferred.
  - 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.
- Concurrent radiation and cisplatin-based chemotherapy has been shown to improve patient survival.

Surgery

- Adjuvant hysterectomy after primary chemoradiation appears to improve pelvic control, but not OS and has increased morbidity. Postradiation (adjuvant) surgery 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.
- Laparoscopic and robotic approaches are associated with shortened recovery time, decreased hospital stay, and less blood loss. They are used routinely in many institutions with promising early outcome data.
- 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.

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 a modified radical hysterectomy should receive adjuvant chemoradiation treatment in the presence of risk factors (as 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 chemoradiation was associated with an improved PFS and OS.
- If definitive RT is chosen over radical hysterectomy, concurrent cisplatin-based chemotherapy should be administered.

Stages IIB, III, IV

- Patients with stage IIB to IVA (locally advanced) disease should be treated with tumor volume–directed radiation and concurrent cisplatin-based chemotherapy.
- Radiologic imaging (PET/CT) and potentially surgical staging (i.e., extraperitoneal or laparoscopic lymph node dissection) are recommended to assess nodal involvement to guide radiotherapy.
- Patients with IVA disease (bowel or bladder mucosal involvement) who are poor candidates for chemoradiation (i.e., acute or chronic pelvic inflammatory disease, coexistent pelvic mass) may be candidates for primary exenterative surgery.
- Patients who have distant metastasis (IVB disease) should receive systemic chemotherapy with or without individualized radiation.

Radiation Therapy

- For definitive treatment, pelvic external beam radiation therapy (EBRT) with intracavitary brachytherapy is routinely used.
- Higher doses of radiation can be delivered to the central primary tumor with the combination of EBRT and brachytherapy than with EBRT alone.
- 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 pelvic radiation.
- CT-based treatment planning is considered standard of care for EBRT.

- EBRT should cover the gross disease (vaginal margin 3 cm from tumor), parametria, uterosacral ligaments, and presacral, external/internal iliac, obturator nodes. For patients at high risk of nodal involvement, the radiation field should also cover common iliac nodes. If documented common iliac/para-aortic nodal involvement, extended field radiation up to the level of renal vessels is recommended.
- Both high-dose brachytherapy (isotope Iridium 192; rate 200 to 300 cGy per hour) and low-dose brachytherapy (isotope Cesium 137; rate 40 to 70 cGy per hour) are currently being used. The relative merits of each are under evaluation.
- 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 40 to 50 Gy, followed by 30 to 40 Gy to point A with brachytherapy for a total dose of 80 to 90 Gy to point A.
- Point A is located 2 cm cephalad and 2 cm lateral to the cervical OS. Anatomically, it correlates with the medial parametrium or lateral cervix, the point where the ureter and uterine artery cross.
- Depending on the extent of disease, a parametrial boost (10 to 15 Gy) with EBRT to a total dose of 60 Gy may be applied to point B (5 cm lateral to OS, corresponding to the pelvic-wall 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% to 90% in small-volume disease).
- A study by the Radiation Therapy Oncology Group (RTOG 79-20) showed a 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 analysis has shown that a total dose of $>$8,500 cGy intracavitary radiation to point A (advanced stage only), use of chemosensitizers, and overall treatment time of $<$8 weeks are associated with improved pelvic tumor control and survival in cervical cancer patients. Extending treatment time beyond 6 to 8 weeks can result in 0.5% to 1% decrease in recurrence-free survival for each day beyond treatment.

Palliative Chemotherapy

- No standard chemotherapy regimen has been shown to produce prolonged complete remissions.
- 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/taxol with cisplatin/taxol.
- 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%.
- Based on the above, cisplatin/paclitaxel and carboplatin/paclitaxel are the most commonly used regimens for metastatic and recurrent cervical cancer. Cisplatin/topotecan, cisplatin/gemcitabine or single-agent therapies are reasonable alternatives.
- The most active single agents include
  - Cisplatin (response rate 20% to 30%)
  - Carboplatin (response rate 15% to 28%)
  - Ifosfamide (response rate 15% to 33%)
  - Paclitaxel (response rate 17% to 25%)
- Other agents with activity include irinotecan, vinorelbine, gemcitabine, bevacizumab, docetaxel, 5-FU, mitomycin, topotecan, pemetrexed.
- The benefit of chemotherapy with or without radiation versus best supportive care in this patient population has not yet been established.

Special Considerations

- Recent studies have clearly demonstrated the deleterious effect of anemia on patients receiving RT. Hemoglobin $<$12 g/dL at the time of RT results in increased local recurrence and decreased survival.

However, the use of transfusions or erythropoietin-stimulating agents has not been associated with improved survival and is associated with their own risk of complications.

- Some patients with small-volume disease in para-aortic lymph nodes and controllable pelvic disease can potentially be cured. However, radiation is of little use in gross para-aortic disease because surrounding organs (bowel, kidney, spinal cord, etc.) cannot tolerate the high doses of radiation required. For this reason, removal of grossly involved nodes prior to radiotherapy is indicated.
- Toxicity from standard para-aortic lymph node radiation is greater than from pelvic radiation alone, but is seen mostly in patients with prior abdominopelvic surgery.
- Different surgical techniques affect the incidence of complications secondary to para-aortic lymph node radiation. For example, extraperitoneal lymph node sampling leads to fewer postradiation complications than transperitoneal sampling.
- Intensity-modulated radiation therapy (IMRT) is likely to reduce sequelae of extended field para-aortic nodal irradiation and is becoming more widely available. However, its utility in cervical cancer continues to be evaluated in several clinical trials.

Recurrent Disease

- A 10% to 20% recurrence rate has been reported following primary surgery or radiotherapy in patients with stage IB to IIA disease with negative nodes; up to 70% of patients with more advanced-stage disease with or without positive nodes exhibit recurrences.
- Majority of local/regional recurrences are symptomatic and 80% to 90% are detected within the first 2 years posttreatment.
- Favorable prognostic factors include localized, central pelvic recurrence, not fixed to the sidewall, disease-free interval >6 months, and size of tumor <3 cm.
- More than 90% of patients with distant recurrence will die of disease within 5 years.
- For early-stage disease, the predominant site of recurrence is local (vaginal apex) or regional (pelvic sidewall).
- Multiple studies have demonstrated the sites of recurrence as indicated:
  - Central (vaginal apex)—22% to 56%
  - Regional (pelvic sidewall)—28% to 37%
  - Distant metastasis—15% to 61%
- Patients with positive nodes, particularly para-aortic, at primary diagnosis have higher risk of distant metastasis than patients with negative nodes.
- No curative therapy is available for distant recurrent disease. However, local recurrence can potentially be treated with curative intent.
- Surgical resection of limited metastatic disease, such as in the lung, may result in prolonged clinical remission.
- For patients with recurrence in the pelvis after radical surgery, radiation combined with cisplatin has a 40% to 50% cure rate.
- Pelvic exenteration (resection of the bladder, rectum, vagina, uterus/cervix) is the preferred treatment for centrally located recurrent disease after radiation, with a 32% to 62% 5-year survival in select patients. Reconstructive procedures include continent urinary conduit, end-to-end rectosigmoid reanastomosis, and myocutaneous graft for a neovagina.
- High-dose intraoperative RT combined with surgical resection is offered by some centers for patients whose tumors extend close to the pelvic sidewalls.
- 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.
- Factors associated with higher likelihood of failure to cisplatin-based combination chemotherapy include
  - Black race
  - Performance status 1 or 2
  - Disease in the pelvis
  - Prior treatment with cisplatin
  - Recurrence within 1 year of diagnosis

- Chemotherapy-naive patients have a higher response rate than those exposed to chemotherapy as part of their initial treatment.

TREATMENT DURING PREGNANCY

- Cervical cancer is the most common gynecologic malignancy associated with pregnancy, ranging from 1 in 1,200 to 1 in 2,200 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 fetus's gestational age. 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.

TREATMENT OF HIV-POSITIVE PATIENTS

- HIV-infected women (or immunocompromised) should undergo cervical cancer screening twice in the first year after diagnosis and then annually.
- Each examination should include a thorough visual inspection of the anus, vulva, vagina, as well as the cervix.
- The American College of Obstetricians and Gynecologists and the Centers for Disease Control do not endorse HPV testing in the triage of HIV-infected patients. This conflicts with 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines, which endorse similar management of patients irrespective of HIV status.
- Treatment of preinvasive lesions and cervical cancer in HIV-positive patients is the same as in HIV-negative patients, though response to therapy is usually poorer.
- Incidence of CIN is four to five times higher in HIV-positive women compared to HIV-negative women with high-risk behaviors.
- Among HIV-infected women, rates of oncogenic HPV and high-grade CIN increase with diminished CD4 counts and higher HIV RNA levels.
- Women with HIV are more likely to have persistent HPV and CIN than uninfected women.
- Although anti-retroviral therapy has altered the natural history of HIV, its effect on HPV and HPV-associated neoplasia is less clear.

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 posttreatment, every 6 to 12 months for the following 3 years 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 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 of vaccination against HPV-16 and -18 to prevent high-grade CIN has been demonstrated in multiple studies since 2002. The Centers for Disease Control and Prevention now recommend that males and females aged 11 and 12 years be vaccinated. Vaccines may be administered as early as age 9 with catch up through age 26 in females and 21 in males (with "permissive use" through age 26). The vaccine is also recommended for gay, bisexual men, and men with compromised immune systems (including HIV) through age 26, if they did not get fully vaccinated when they were younger.

REVIEW QUESTIONS

1. A 35-year-old female has recently been diagnosed with cervical cancer. She is now in your office and after discussing her particular case, she asks about cervical cancer in the broader population. You tell her that all the following epidemiologic factors are true, EXCEPT:
   - **A.** Worldwide, cervical cancer is the fourth leading cause of cancer death in women.
   - **B.** Herpes simplex virus (HSV) is thought to be the causative agent in the majority of the cases.
   - **C.** Incidence of cervical cancer is higher in African American and Latino women compared to Caucasians in the United States.
   - **D.** During past 50 years, death rates from cervical cancer have decreased due to routine screening with Pap smears.
2. A 43-year-old patient is diagnosed with squamous cell cervical carcinoma after physical examination and cervical biopsy. All of the following risk factors are associated with metastatic disease EXCEPT:
   - **A.** Presence of microinvasion
   - **B.** Depth of invasion
   - **C.** Tumor size
   - **D.** Presence of LVSI
3. A 38-year-old patient presents with a 1-year history of bleeding after intercourse. She has not a Pap smear in 6 years. During a speculum examination, a 3 cm cervical lesion is seen and biopsied. The results of the biopsy show cervical adenocarcinoma. In regard to her staging all of the following are true EXCEPT:
   - **A.** If hydronephrosis was seen on CT scan, she would be stage IIIB.
   - **B.** MRI is the best imaging modality for determining soft-tissue and parametrial involvement.
   - **C.** Staging for cervical cancer is clinical, involving pelvic examination.
   - **D.** If enlarged lymph nodes were seen on CT scan, she would be at least a stage III.
4. A 51-year-old female with history of abnormal Pap smears presents with postcoital bleeding. On examination she has a 2 cm visible lesion on her cervix. A rectovaginal examination reveals no evidence of parametrial spread. After cervical biopsy and further evaluation she is diagnosed with stage IB1 squamous cervical cancer. The best treatment option for her includes
   - **A.** Simple hysterectomy
   - **B.** Radical hysterectomy with pelvic lymph node dissection or primary chemoradiation
   - **C.** Radical trachelectomy
   - **D.** Cervical conization

(*continued*)

5. A 42-year-old patient with stage IIIB cervical cancer develops a recurrence in her cervix less than 2 years from the completion of treatment. She had received primary chemoradiation at the time of her initial diagnosis. Current imaging shows a central pelvic tumor with no metastatic disease. The only treatment option that has a chance for cure in this setting is
   A. Chemotherapy with combined cisplatin and topotecan
   B. Chemotherapy with combined cisplatin and paclitaxel
   C. Referral back to radiation oncology for consideration of further radiation
   D. Referral to gynecologic oncology for consideration of pelvic exenteration

Suggested Readings

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20

Vulvar Cancer

Anne M. Noonan and Christina M. Annunziata

EPIDEMIOLOGY

- Vulvar cancer accounts for <5% of all female genital malignancies.
- A total of 4,490 new cases and 950 deaths from vulvar cancer were projected for 2012.
- It is most frequent in women in the seventh decade of life, but is occasionally diagnosed in women younger than 40 years.
- One in 368 women will be diagnosed with vulvar cancer during their lifetime (2.3 per 100,000 women per year in the United States).

ETIOLOGY AND RISK FACTORS

The etiology of vulvar cancer remains unclear, but potentially involves two distinct diseases associated with the following:

- Human papillomavirus (HPV) DNA, especially type 16
  - Can be detected in 80% of intraepithelial lesions
  - Found in 10% to 15% of invasive vulvar cancers (especially squamous cell)
- Chronic inflammation
  - Venereal or granulomatous lesions
  - Lichen sclerosus (coexists with up to 25% of vulvar cancers)
  - Squamous hyperplasia (hyperplastic dystrophy) or lichen simplex chronicus
  - Paget disease of the vulva (preinvasive)

Risk Factors

- Vulvar intraepithelial neoplasia (VIN), especially high grade (VIN III), increases the risk of development of invasive vulvar cancer.
- Other risk factors include prior history of cervical cancer, immunodeficiency disorders (e.g., HIV), and cigarette smoking.
- Classic risk factors such as hypertension, diabetes mellitus, and obesity are probably associated with aging and are not truly independent risk factors for this malignancy.

HISTOLOGY

- Squamous cell carcinomas (SCCs) constitute >90% of cases.
- Melanomas constitute <10% of cases.
- The remainder of tumor types include adenocarcinoma, basal cell carcinoma, verrucous carcinoma, sarcoma, clear cell carcinoma, and other rare tumors.

VULVAR SQUAMOUS CELL CARCINOMA

Vulvar SCC is commonly indolent, with slow extension and late metastases. Signs and symptoms in order of decreasing frequency are pruritus, mass, pain, bleeding, ulceration, dysuria, and discharge. Many patients are asymptomatic.

Diagnostic Workup

- Biopsy must include adequate tissue to determine histology and grade, depth of invasion, and stromal reaction present.
- Colposcopy using 5% acetic acid solution may be necessary to delineate suspected multifocal lesions.
- Cystoscopy, proctoscopy, chest x-ray, and intravenous urography should be performed as needed based on the extent of disease.
- Suspected bladder or rectal involvement must be biopsied.
- If invasive disease is present, detailed pelvic exam, CT, or MRI should be performed to assess deep and pelvic lymph nodes (LNs).

Indications for Excisional Biopsy of Vulvar Lesions

- Any gross lesion
- Red, white, dark brown, or black skin patches
- Areas firm to palpation
- Pruritic, tingling, or bleeding lesions
- Any nevi in the genital tract
- Enlarged or thickened areas of Bartholin glands, especially in postmenopausal women

Location and Metastatic Spread Pattern of Vulvar SCC

- Vulvar SCC is found on
  - The labia majora in 50% of cases
  - The labia minora in 15% to 20% of cases
  - The clitoris and perineum in rare cases
- Vulvar SCC tends to grow locally, with subsequent spread to inguinal, femoral, and pelvic LNs.
- Hematogenous spread rarely occurs without LN involvement.

Staging

- Vulvar cancer is a surgically staged disease. 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 (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes

- Stage III: Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinofemoral LNs
  - IIIA: (i) With one LN metastasis (≥5 mm), or (ii) 1 to 2 LN metastasis(es) (<5 mm)
  - IIIB: (i) With two or more LN metastases (≥5 mm), or (ii) three or more LN metastases (<5 mm)
  - IIIC: With positive nodes with extracapsular spread
- Stage IV: Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
  - IVA: Tumor invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguinofemoral LNs
  - IVB: Any distant metastasis including pelvic LNs

Prognosis and Survival

- Survival depends on stage, LN involvement, depth of invasion, structures involved, and tumor location.
- LN metastases are related to tumor size (>4 cm is associated with 30% to 50% rate of inguinofemoral metastases), clinical stage, and depth of invasion.
- Statistics based on the pathologic status of the inguinal LNs and the size of the primary lesion:
  - Lesions <2 cm in greatest dimension without LN involvement (stage I): 77% 5-year survival
  - Lesions of any size with unilateral LN (stage III): 31% 5-year survival

Management

Stage 0 (VIN)

Therapeutic options are based on individual patient need.

- Wide local excision, laser ablation, or both
- Skinning vulvectomy with or without grafting
- CO_2 laser total superficial vulvectomy
- Topical treatments include
  - 5-FU cream: response rate (RR) 40% to 75%
  - Five percent imiquimod: RR approximately 50% to 70%

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

- <1 mm invasion (stage IA): wide local excision
  - Excise down to inferior fascia of urogenital diaphragm.
  - Strive for 2 cm clear margins to minimize risk of local recurrence.
- >1 mm invasion (stage IB):
  - Modified radical vulvectomy with ipsilateral superficial inguinal lymphadenectomy for lesions located laterally.
  - Bilateral inguinofemoral node dissection for centrally located lesions.
  - Sentinel LN biopsy is an emerging technique in early-stage vulvar cancer and may obviate the need for full nodal dissections in many women.

Special Considerations

- Poor surgical candidates can be treated with radiation therapy, achieving long-term survival.
- Surgical complications include mortality (2% to 5%), wound breakdown or infection, sepsis, thromboembolism, chronic leg lymphedema (use of 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

- Modified radical vulvectomy and bilateral inguinofemoral lymphadenectomy can be used if ≥1 cm of negative margins can be achieved with preservation of midline structures.
- Adjuvant radiation therapy is recommended for women with more than one positive LN or surgical margins <1 cm.

Stage III

- Modified radical vulvectomy and bilateral inguinofemoral lymphadenectomy are standard.
- Adjuvant radiation therapy or chemoradiation is recommended for women with involved LNs, thick tumors (>5 mm), lymphovascular invasion, or close surgical margins <1 cm.

Stage IVA

- Radical vulvectomy and bilateral inguinofemoral lymphadenectomy 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 radiation therapy is recommended for women with more than one positive LN or surgical margins <1 cm.
- Neoadjuvant chemoradiation, with 5-FU or 5-FU plus cisplatin, may improve operability.

Special Considerations

- Management of positive groin nodes: One LN requires no further therapy. Two or more LNs can be treated with groin and pelvic radiation therapy, based on data from the GOG randomized trial in which improved survival was documented with this therapy compared to pelvic LN dissection.
- Suggested doses of localized adjuvant radiation are 45 to 50 Gy.
- Neoadjuvant chemoradiation can be used in stage III and IV disease to improve the operability of the tumor. Recent GOG trials have successfully used cisplatin and 5-FU concurrently with radiation.
- Patients with inoperable disease can achieve long-term survival with radical chemoradiation therapy.
- When radiation is given as primary definitive treatment, it is suggested that the addition of 5-FU with cisplatin or mitomycin C be considered.
- Radiation fraction size of ≤180 cGy has been proven to minimize the radiation complication rate (i.e., 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: No standard systemic chemotherapy is available for metastatic disease. These patients are appropriate candidates for clinical trials. Agents such as cisplatin, methotrexate, cyclophosphamide, bleomycin, and mitomycin C have shown a partial RR of only 10% to 15% and are of short duration (a few months). Trials evaluating the efficacy of paclitaxel in vulvar cancer are ongoing.
- Pelvic node metastasis or local recurrence can be treated with the following:
  - Wide local (re)excision with or without radiation (5-year survival of 56% if regional LNs are negative).
  - In cases with small, localized recurrence, radiation with or without 5-FU can be curative.
- Inguinal nodes can be subjected to radiation and surgery.

VERRUCOUS CARCINOMA

- Verrucous carcinoma is very rare and can be confused with condyloma acuminatum because of an exophytic growth pattern.
- It is locally destructive and rarely metastasizes.
- It is associated with HPV type 6.
- The main treatment is surgery. LN dissection is of questionable value unless LNs are obviously involved. Radiation therapy is contraindicated because it is ineffective and can potentially lead to more aggressive disease.

PAGET DISEASE

- Characterized by preinvasive lesions.
- Most frequent symptoms include pruritus, tenderness, or vulvar lesions (i.e., "red velvet," hyperemic, well-demarcated, thickened lesions with areas of induration and excoriation).
- Can be associated with underlying adenocarcinoma of the vulva (1% to 2%). Although Paget disease is histologically a preinvasive disease locally, it should be treated with radical wide local excision, as with other vulvar malignancies. Patients require radical excision, often with intraoperative frozen section confirmation of clear margins, because microscopic disease often extends beyond the gross visual margin observed by the operating surgeon.

MALIGNANT MELANOMA

- Malignant melanoma of the vulva is a rare tumor (5% of all melanoma cases).
- Most melanomas are located on the labia minora and clitoris.
- Prognosis depends on size of lesion and depth of invasion.
- Staging of malignant melanoma is the same as for skin melanoma.
- Suggested therapy is radical vulvectomy with inguinal and pelvic lymphadenectomy, although there is a current trend toward a more conservative approach. For most well-demarcated lesions, 2 cm margins are suggested for thin (up to 7 mm) lesions and 3 to 4 cm margins for thicker lesions.

BARTHOLIN GLAND

Adenocarcinoma

- Adenocarcinoma of the Bartholin gland is a very rare tumor (1% of all vulvar malignancies).
- Peak incidence is in women in their mid-60s.
- Enlargement of the Bartholin gland area in postmenopausal women requires evaluation for malignancy.
- Therapy includes radical vulvectomy with wide excision to achieve adequate margins and inguinal lymphadenectomy.

Adenoid Cystic Carcinoma

- Adenoid cystic carcinoma is a very rare tumor.
- It is characterized by frequent local recurrences and very slow progression.
- Recommended therapy is wide local excision with ipsilateral inguinal lymphadenectomy.

Basal Cell Carcinoma

- The natural history and therapeutic approach for basal cell carcinoma are similar to those for primary tumors seen in other sites (i.e., wide local excision).

REVIEW QUESTIONS

1. A 74-year-old woman presents to her primary care physician with an 18-month history of pruritus vulvae, difficulty with urination, and hard left inguinal mass. Pelvic examination reveals an erythematous ulcerating lesion on the labia majora extending on to the urethral orifice and labia minora bilaterally. On vaginal examination there is a hard mass palpable anteriorly. CT scan

(*continued*)

reveals extension into the lower posterior bladder and wall and involvement of the left inguinal and pelvic LNs. Biopsy of the vulvar lesion reveals a poorly differentiated SCC arising from the vulva. She has a history of depression and mild hypertension. What is the most appropriate treatment?

A. Tamoxifen
B. Pelvic exenteration
C. Chemoradiation to vulva and inguinal area followed by resection of any residual disease on the vulva
D. Vaginal brachytherapy
E. A and B

2. A 72-year-old female with a history of stage IVB SCC of the vulva treated 1 year ago with chemoradiation followed by resection of residual disease on the labia minora now presents to the ER with urinary retention, reduced appetite, and hard mass in the right lower abdomen. Serum chemistries and CBC are normal. Urethral catheterization is performed to relieve her urinary retention. On CT scan she has recurrence of her disease in the pelvis with involvement of the urethra causing a stricture and right-sided pelvic LN mass within the radiation port. She lives alone and was working as a secretary until her admission. She has no other significant comorbidities. What is the most appropriate next step?

A. Repeat external beam radiotherapy to the pelvis
B. Referral for a clinical trial
C. Carboplatin plus bevacizumab
D. Aromatase inhibitor
E. None of the above

3. A 69-year-old female with a history of stage I screen-detected ER- and PR-positive breast cancer treated 5 years ago with lumpectomy and adjuvant radiation therapy followed by 5 years of anastrozole presents for routine follow-up. On review of systems she reports a 6-month history of itching of the vulva. On examination there is a 0.5 cm erythematous raised lesion. Colposcopy and biopsy reveal VIN with no evidence of invasive disease. What is the most appropriate treatment?

A. Radical vulvectomy
B. Cisplatin 50 mg/m^2 IV every 3 weeks
C. No therapy. Observation only is required
D. Vaginal brachytherapy
E. Laser ablation

Suggested Readings

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SECTION SEVEN

Musculoskeletal

21

Sarcomas and Malignancies of the Bone

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EPIDEMIOLOGY

- Malignancies of the soft tissue (6.1%) and bones (4.7%) account for more than 10% of newly diagnosed cancers in children, adolescents, and young adults.
- Median age at diagnosis of rhabdomyosarcoma (RMS) is 5 years, with a male preponderance.
- Osteosarcomas account for approximately 60% of malignant bone tumors in the first two decades of life.
- Most of the remaining bone malignancies in children and adolescents are Ewing sarcomas and the histologically similar and genetically identical peripheral primitive neuroectodermal tumors (PNETs). Together, these tumors are often called the Ewing family of tumors (EFT).
- Identification of specific, recurrent genetic alterations in RMS and Ewing sarcoma has improved diagnosis by clarifying pathogenesis. Better supportive care and systematic application of effective multimodality treatment have dramatically improved survival during the last 30 years (Table 21.1).

RHABDOMYOSARCOMA

Clinical Presentation

RMS, which can occur in almost any anatomic site, is associated with development of a mass, along with signs and symptoms typically related to the anatomic location (Fig. 21.1):

- Orbit: proptosis
- Nasopharynx: nasal discharge and obstruction
- Basal skull and posterior orbit: cranial nerve palsies and visual loss
- Parameninges: headache and meningism

Table 21.1 Outcome of Therapy for Musculoskeletal Tumors of Childhood and Adolescence

Tumor Type	Commonly Used Chemotherapy Agents	Duration of Therapy (mo)	Long-Term Survival[a] (%)	Additional Treatment
Rhabdomyosarcoma				
Low-risk (patients with group I or II embryonal tumors at sites with favorable outcome or group III orbital tumors)	Vincristine, dactinomycin	8–12	90–95	Resection of primary tumor for all except orbital tumors; irradiation of group II or III tumors
Intermediate-risk	Vincristine, dactinomycin, cyclophosphamide	8–12	70–80	Irradiation of primary tumor and any metastases
High-risk (patients with metastases [group IV], except patients <10 y old who have embryonal tumors)	Vincristine, dactinomycin, cyclophosphamide; new agents; high-dose therapy with hematopoietic stem-cell transplantation	8–12	20	Irradiation of the primary tumor and all metastatic lesions
Osteosarcoma				
Localized to limb	Doxorubicin, high-dose methotrexate, ifosfamide, cisplatin	8–12	58–76	Surgery for control of tumor
Metastatic	Doxorubicin, methotrexate, ifosfamide, cisplatin	8–12	14–50	Resection of primary tumor and any metastases
Ewing sarcoma				
Localized	Vincristine, doxorubicin, cyclophosphamide, dactinomycin, etoposide-ifosfamide	8–12	50–70	Surgery, radiation, or both for local control of tumor
Metastatic	Vincristine, doxorubicin, cyclophosphamide, dactinomycin, etoposide-ifosfamide; high-dose therapy with hematopoietic stem-cell transplantation	8–12	19–30	Surgery, radiation, or both for local control of tumor

[a]Estimated progression- or relapse-free survival at 3–5 y.

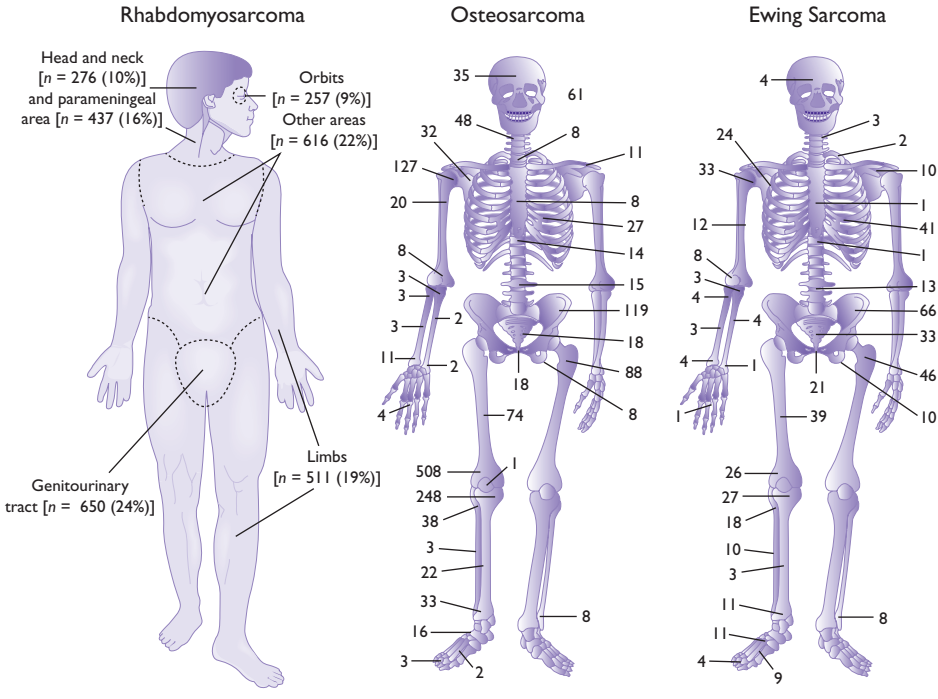

FIGURE 21.1 Primary sites of rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma, showing numbers of patients with primary tumors at specific sites.

- Vagina or uterus: vaginal polyp/discharge
- Bladder or prostate: urinary obstruction
- Male genitals: paratesticular scrotal mass

Pathophysiology

RMS is of mesenchymal origin and is characterized by myogenic differentiation. There are two main histologic subtypes, embryonal (80%) and alveolar (15% to 20%), with characteristic genetic differences (Table 21.2 and Fig. 21.2. Botryoid RMS and spindle cell sarcoma are both morphologic variants of embryonal RMS. Numerous environmental and genetic factors have been associated with an increased risk of RMS (Table 21.3).

Diagnosis

Radiologic

Comprehensive radiologic evaluation includes the following:

- **Tumor localization**
  - Computerized tomography (CT) and magnetic resonance imaging (MRI)
  - Positron emission tomography (PET)
- **Assessment of metastatic spread**
  - CT of chest/lungs
  - Technetium bone scan for bone or bone marrow involvement
  - PET

Table 21.2 Histologically Distinguished Subtypes of Rhabdomyosarcoma (RMS)

Embryonal RMS
Characteristic loss of heterogenicity (LOH) 11p15.5 (IGH-II gene)
Hyperdiploid DNA
Alveolar RMS
Characteristic translocations
PAX3/FKHR t(2,13)(q35;q14)
PAX7/FKHR t(1;13)(p36;q14)
Tetraploid DNA

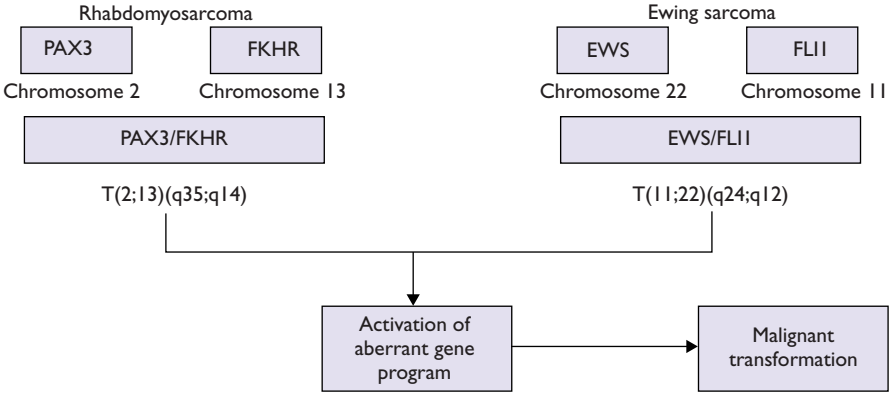

FIGURE 21.2 Molecular pathogenetic mechanisms in rhabdomyosarcoma and Ewing sarcoma.

Pathologic

Open biopsy is the preferred approach for tissue diagnosis and should be undertaken at an oncology center, where diagnostic material can be optimally used and the initial surgical approach can be determined by a multidisciplinary team responsible for the patient's subsequent treatment. Needle biopsy may restrict access to fresh and frozen tissue for cytogenetic and molecular genetic investigations.

1. Tumor characterization
   - Histopathology
     - Immunohistochemistry (desmin and myoD1)
   - Genetics
     - RT-PCR for presence of PAX/FKHR translocation
     - Cytogenetics
2. Metastatic spread
   - Cerebrospinal fluid PCR for PAX/FKHR translocation
   - Bone marrow aspirate cytology
   - Bone marrow biopsy for histochemistry and PCR

Treatment

The diversity of primary sites, distinctive surgical approaches and radiotherapies for each primary site, subsequent site-specific rehabilitation, and potential treatment-related sequelae (Table 21.4) underscore the importance of treating children and young adults with RMS in the context of a clinical trial at a major medical center that has appropriate experience in all therapeutic modalities.

Table 21.3 Risks Factors for Rhabdomyosarcoma in Children and Adolescents

Genetic
Familial cancer[a]
Germline mutant p53
Congenital abnormalities
Neurofibromatosis type I
Li-Fraumeni syndrome
Parental behaviors
Smoking
Use of recreational drugs
Prenatal consumption of alcohol
Chemical exposure at workplace

[a]Particularly breast cancer in a female relative.

Surgery

Local tumor control is the cornerstone of therapy, especially for patients with nonmetastatic disease. Primary tumor resection should be undertaken only if there is no evidence of lymph node or metastatic disease and if the tumor can be excised with good margins without functional impairment or mutilation. Surgery has minimal, if any, role in the primary management of orbital tumors and a limited role in local control of head and neck tumors. To achieve local control of pelvic tumors in very young children, the risks of radical surgery may be more acceptable than those of pelvic irradiation.

Radiotherapy

Radiotherapy after initial surgical resection or chemotherapy is recommended in the following instances:

- Completely resected tumor (clinical group I) with unfavorable histology (alveolar RMS)
- Microscopic residual disease (clinical group II: up to 4,100 cGy)
- Gross residual disease (clinical group III: up to 5,040 cGy)

Treatment Volume

- Volume is determined by extent of disease at diagnosis
- Radiation field should extend 2 cm beyond the tumor margin
- Whole-brain irradiation of 2,340 to 3,060 cGy for parameningeal disease with intracranial extension

Chemotherapy

Neoadjuvant combination, multiagent chemotherapy for extensive, primarily unresectable tumors is known to reduce the extent of subsequent surgery or radiotherapy. (Fig. 21.3 outlines this multidisciplinary approach for RMS.)

OSTEOSARCOMA

Osteosarcoma is a primary bone malignancy with peak incidence in the pubescent growth spurt (15 to 19 years) in the metaphyses of the most rapidly growing bones. Risk factors are listed in Table 21.5 and clinical presentation in Table 21.6.

Clinical Presentation

- Bone pain
- Swelling
- Mass in metaphyseal area of bone, most commonly femur or tibia

Table 21.4 Treatment Options, Local Control, and Potential Sequelae in Rhabdomyosarcoma

Tumor Site	Treatment Options	Local Control	Sterility	Renal Toxicity	On Growth	Esthetics
Orbit	Radical surgery, then VA ± C	++	–	–	±	±
	Biopsy, then radiation + V ± C	++	±	–	++	++
	Biopsy, then IVA/VAC	±	±	±	–	–
	No CR: radical surgery *or* radiation	–	–	–	++	++
		–	–	–	++	++
Paratesticular	Surgery + VA	±	–	–	–	–
	Surgery + VAC/IVA	++	±	±	–	–
Limbs	Surgery + VA	±	–	–	–	±
	Surgery + IVA	++	±	±	–	±
Vagina	IVA/VAC, then monitoring if CR	±	±	±	–	–
	IVA, then elective surgery or interstitial radiation	++	±	±	±	±
Bladder/prostate	Radical surgery, then IVA/VAC with/without selective radiation	++	±	±	±	±
	IVA/VAC, then local surgery	±	±	±	–	±
	No CR: radiation	±	–	–	–	–
Thorax/abdomen/pelvis	IVA/VAC, then radiation then IVA/VAC	–	++	±	±	±
	IVA/VAC, CR with/without surgery, then IVA/VAC	±	±	±	±	–
Parameningeal	IVA/VAC, then extensive early radiation, then IVA/VAC	++	±	±	++	–
	IVA/VAC, then delayed limited radiation, then IVA/VAC	±	±	±	±	–
Nonparameningeal head/neck	Radical surgery, then VA	++	–	–	–	++
	Biopsy, then IVA/VAC	±	±	±	–	–
	No CR: radiation *or* surgery	–	–	–	++	±
		–	–	–	–	±

A, actinomycin D; C, cyclophosphamide; CR, complete remission; I, ifosfamide; V, vincristine; ++, yes; ±, possible; –, no.

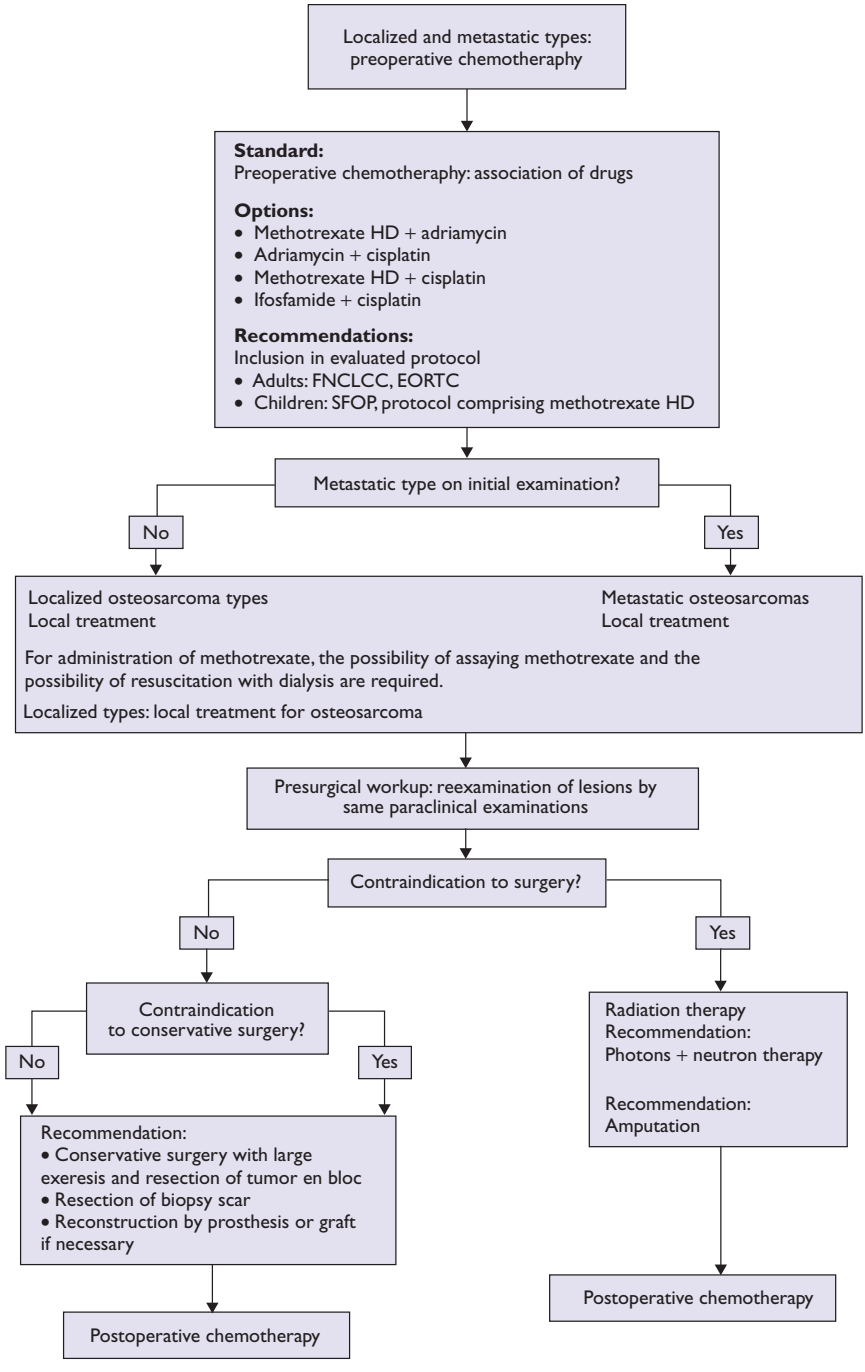

FIGURE 21.3 Treatment options for osteosarcoma.

Table 21.5 Risk Factors for Osteosarcoma

Familial cancer
Secondary osteosarcoma
Li-Fraumeni syndrome
Irradiated bones
Bilateral retinoblastoma (independent of therapy modality)
Loss of tumor-suppressor genes p53 and Rb (retinoblastoma)

Table 21.6 Clinical Presentation of Osteosarcoma and Ewing Family of Tumors (EFT)

Tumor Site	Radiographic Characteristics	Associated Signs
Osteosarcoma		
Metaphyseal bone	Periosteal elevation with new bone formation ("sunburst")	Soft-tissue swelling
EFT		
Diaphyseal/flat bones	Patchy bone destruction ("motheaten") Periosteal lamellation ("onion skin")	Soft-tissue swelling, pleural effusion

Diagnosis and Staging

Radiologic

- Tumor assessment: plain radiographs
  - Destruction of bone with consequent loss of normal trabeculae and appearance of radiolucent areas
  - New bone formation
  - Lytic or sclerotic appearance
  - "Sunburst sign": periosteal elevation from tumor penetrating cortical bone
- Extent of disease
  - MRI (T1-weighted) to assess primary tumor boundaries in entire long bone, including skip lesions
  - Technetium bone scan
  - PET
- Metastatic spread (15% to 20%)
  - Technetium bone scan
  - CT of chest/lungs
  - PET

Pathologic/Genetic

- Histologic diagnosis depends on the presence of frankly malignant sarcomatous stroma associated with the production of tumor osteoid. If the surgeon suspects a primary malignant bone lesion after history and physical and plain radiographs, it is highly recommended that an experienced orthopedic oncologist perform all invasive procedures, including biopsy.
- Ample fresh and frozen tissue should be available for various prognostic assays, including measurement of tumor DNA content, molecular genetic evaluations, and P-glycoprotein estimation. Serum lactate dehydrogenase (LDH), a significant prognostic factor, may be elevated in 30% of patients with no metastases.

Treatment

Most patients with osteosarcoma have subclinical micrometastases and thus require surgical ablation of the primary tumor (amputation or limb-sparing resection) plus chemotherapy for micrometastatic disease (Figs. 21.3 to 21.6).

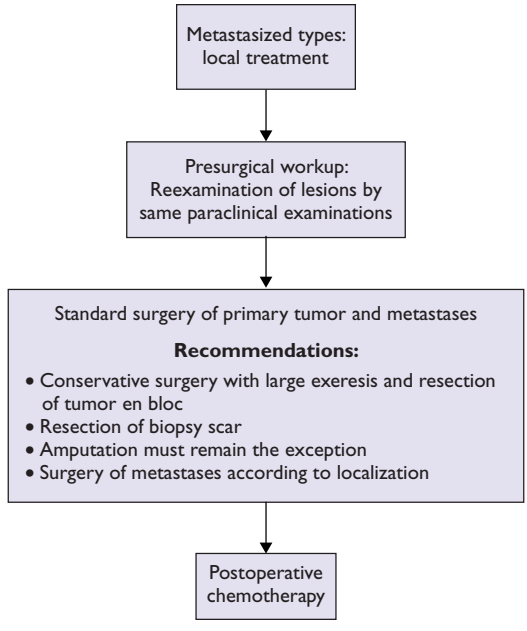

FIGURE 21.4 Treatment options for metastatic osteosarcoma.

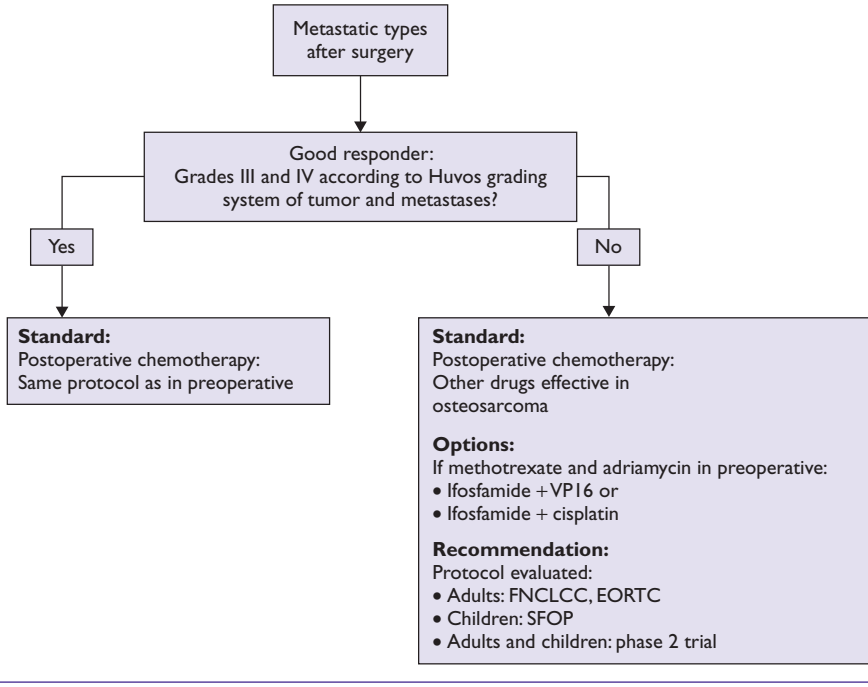

FIGURE 21.5 Treatment options for postoperative metastatic osteosarcoma.

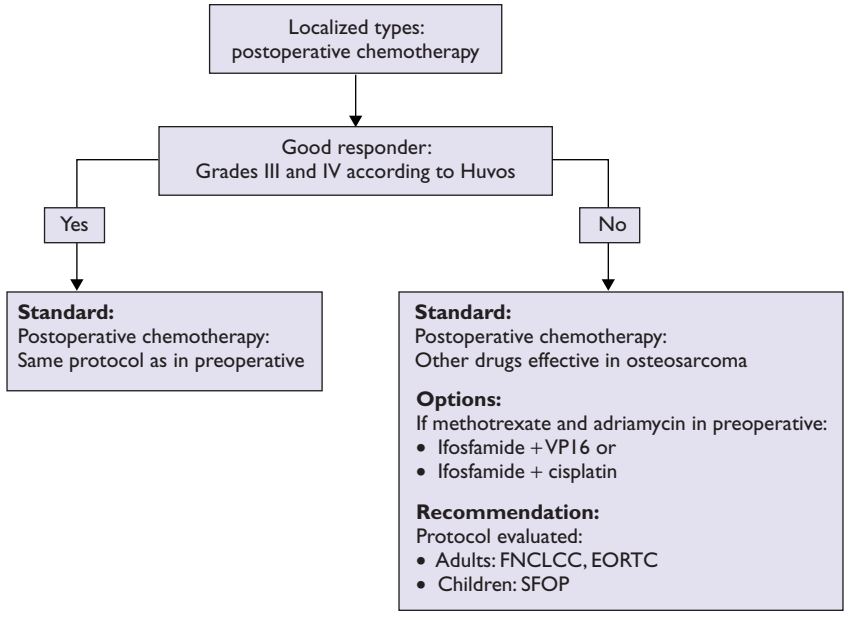

FIGURE 21.6 Treatment options for postoperative localized osteosarcoma.

Chemotherapy

- Neoadjuvant
  - Evaluation of bone marrow, cardiac, liver, and renal function
  - Initiated soon after completion of biopsy and staging studies
  - Duration: 9 to 12 weeks
- Adjuvant
  - Evaluation of extent of tumor necrosis in surgical specimen as predictor of disease-free and overall survival
  - Initiated soon after definitive surgery for primary tumor
  - Duration: 35 to 40 weeks

Surgery

Amputation and limb-sparing resection incorporate wide en bloc excision of the tumor and biopsy site through normal tissue planes, leaving a cuff of normal tissue around the periphery of the tumor. Limb-sparing surgery is now the preferred approach for 70% to 90% of patients with osteosarcoma due to improved functional outcome. Reconstruction involves allografts, customized endoprosthetic devices, modular endoprosthetic devices, or combinations of these methods. This approach requires a multidisciplinary team and close cooperation between the chemotherapist and orthopedic oncologist.

Follow-Up

Patients with osteosarcomas should have frequent radiographic monitoring for metastases for at least 5 years after completion of therapy. Most first recurrences appear asymptomatically in the lungs. Durable

salvage has been reported in 10% to 20% of such patients; thus, all patients with recurrent disease should be treated with curative intent.

EWING FAMILY OF TUMORS

- The EFT comprises Ewing sarcoma of the bone, PNETs, Askin-Rosai tumor (PNET of the chest wall), and extraosseous Ewing sarcoma. Studies using immunohistochemical markers, cytogenetics, and tissue culture indicate that these tumors all derive from the same primordial stem cell and are distinguished only by the degree of neural differentiation.
- Ewing sarcoma accounts for 10% to 15% of all malignant bone tumors, with peak incidence between 10 and 15 years of age.
- Incidence in African-American and Chinese populations is remarkably low.
- Nearly 12% of patients with Ewing sarcoma also have associated urogenital anomalies such as cryptorchidism, hypospadias, and ureteral duplication.

Clinical Presentation

- Persistent and increasing pain, local swelling, and functional impairment of affected area (see Table 21.6)
- Fever
- Associated neurologic symptoms, including paraplegia and peripheral nerve abnormalities
- Uncommon symptoms:
  - Lymph node involvement
  - Meningeal spread
  - Central nervous system disease

Diagnosis and Staging

Radiologic

1. Evaluation of primary tumor
   - CT and MRI of primary lesion
   - PET
2. Metastatic spread
   - CT of chest/lungs
   - Technetium bone scan for tumor extent and bone marrow involvement
   - PET

Approximately 20% of patients have visible metastases at diagnosis. Of these patients, about 50% have lung metastases and about 40% have multiple bone involvement and diffuse bone marrow involvement.

Biopsy and Laboratory Investigations

Open biopsy is preferred for tissue diagnosis. It should be undertaken at an oncology center where the diagnostic material can be optimally used and the initial surgical approach can be determined by a multidisciplinary team responsible for the patient's subsequent treatment. Needle biopsy may restrict access to fresh and frozen tissue for cytogenetic and molecular genetic investigations.

- Serology
  - LDH: prognostic indicator reflecting disease burden
- Histopathology
  - "Small blue round cell tumor"
  - Immunohistochemistry: NSE, vimentin, S-100, HBA-71

- Cytogenetics/molecular genetics
  - t(11;22)(q24;q12) translocation in 85% of tumors
  - RT-PCR of EWS/FLI-1 transcripts

The t(11;22)(q24;q12) translocation results in the formation of a chimeric gene between EWS (Ewing sarcoma gene), a novel putative RNA-binding gene located on chromosome 22q12, and FLI-1, a member of the erythroblastosis virus-transforming sequence family of transcription factors located on chromosome 11q24. It has been fully characterized at the molecular genetic level. RT-PCR of fusion transcripts from the tumor can identify patients with favorable prognosis.

Treatment

Most patients with apparently localized disease at diagnosis have subclinical micrometastases. Thus, a multidisciplinary approach including local disease control with surgery and/or radiation as well as systemic chemotherapy is indicated.

Surgery

Generally, surgery is the preferred approach for resectable tumors.

Radiotherapy

Radiotherapy is indicated for patients with no function-preserving surgical option or whose tumors have been excised with inadequate margins. Radiotherapy for EFT requires stringent planning and delivery by a team experienced in the treatment of this disease. Recommendations of the Intergroup Ewing Sarcoma Study (IESS) include the following:

- Gross residual disease: 4,500 cGy plus 1,080 cGy boost to the tumor site
- Microscopic residual disease: 4,500 cGy plus 5,400 cGy boost
- Pulmonary metastasis: whole-lung irradiation of 1,200 to 1,500 cGy even if complete resolution of pulmonary metastatic disease is possible with chemotherapy
- Metastasis to bone and soft tissues: 4,500 to 5,600 cGy

Chemotherapy

- The most effective agents are cyclophosphamide and doxorubicin, but vincristine and dactinomycin are also active. Recent dose-intensification studies of ifosfamide and etoposide have shown significant promise.
- Prognosis was poor before the advent of effective multiagent chemotherapy (5-year survival: 10% to 20% despite good local control) and is still dismal for patients with metastatic disease. A recent study reported a 3-year event-free survival of only 26.7% $\pm$ 13.2%.

FUTURE DIRECTIONS

Functional characterization of chromosomal translocations associated with RMS and Ewing sarcoma could elucidate the molecular pathogenesis of these tumors and lead to novel therapeutic strategies. Some current investigational approaches include

- Trabectedine, ET-743
- Cell-cycle signaling pathway inhibitors (i.e., IGF-1 receptor pathway and/or mTOR pathway)
- PARP inhibitors
- Epigenetic targeting (with HDAC inhibitors and others)
- Targeting of EWS-FLI with small molecules

REVIEW QUESTIONS

1. An 18-year-old girl presents with a several months' history of increasing calf swelling. An MRI shows a 7 cm tumor involving the fibula and extending into the surrounding soft tissues. A core needle biopsy is obtained. The histopathologic evaluation reveals a small blue round cell tumor. Ewing sarcoma is suspected. Which of the following is true? Ewing sarcoma
   A. Carries a characteristic translocation in the majority of cases which can be used for diagnosis
   B. Is related to RMS
   C. Is primarily treated with surgery
   D. Does not respond well to chemotherapy
2. A 50-year-old man is complaining of worsening right upper arm swelling over the last 2 to 3 months. Plain radiographs show a tumor involving the bone with periosteal reaction. A biopsy shows osteosarcoma. Which statement(s) is/are true?
   A. Osteosarcoma occurs in a bimodal age distribution.
   B. Osteosarcoma is primarily treated with chemotherapy.
   C. Osteosarcoma is curable with metastasectomy in selected cases.
   D. Osteosarcoma carries a disease specific translocation.
   E. A and C.
   F. B and D.
   G. All of the above.
3. A 22-year-old athlete is complaining of worsening pelvic pain. A muscle strain is suspected. Ibuprofen and cyclobenzaprin are prescribed without much improvement. Finally, a CT scan of the pelvis is ordered which shows an 8 cm tumor in the soft tissues along the pelvic wall. A biopsy shows alveolar RMS. Which statements about RMS are true?
   A. RMS occurs primarily in the bones.
   B. RMS requires multimodality therapy.
   C. RMS does not occur in infants.
   D. RMS may occur as a primary GU tumor.
   E. A and C.
   F. B and D.
   G. All of the above.

Suggested Readings

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SECTION Eight

Skin

22

Skin Cancers and Melanoma

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The skin is the largest organ of the human body that is embryologically derived from the neuroectoderm and the mesoderm to be organized into three layers namely epidermis, dermis, and subcutis. Cancer of the skin arises from the cell types of structures in all the three layers (Table 22.1). The direct exposure to sun's ultraviolet radiation and a wide variety of environmental carcinogens predisposes skin cells to genetic damage and increased risk of cancer. The 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 seventh leading type of cancer in men and women, respectively, in the United States.
- The estimated lifetime risk of developing melanoma in US whites is about 1 in 50.
- In the United States 76,250 new cases of melanoma were expected to be diagnosed in 2012, with projected deaths of 9,180.
- The incidence of melanoma is more than 10 times greater in whites than in blacks.
- The incidence of melanoma among US whites is over 20 cases per 100,000 population although some geographic areas have higher rates.
- The rate of increase 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 50 years of age, the incidence continues to climb at the fastest rate.
- Australia has the highest incidence of melanoma in the world, approximately 40 cases per 100,000 populations per year.

Table 22.1 Cell of Epidermis, Dermis, and Respective Tumor Types

Cells of Epidermis	Tumor-Type Incidence	Cells of Dermis	Tumor Type[a]
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 and angiosarcoma; lymphangioma
Langerhans cells	Histiocytosis X <1%	Lymphocytes	Non-Hodgkin lymphoma
Appendage cells	Appendageal tumors <1%	—	—

[a]Incidence of tumors in dermis <1% each type.

Etiology

- Ultraviolet rays: Exposure to sun's ultraviolet rays in the electromagnetic radiation spectrum is a major risk factor for melanoma development and is related to (Fig. 22.1)
  - Intermittent intense exposure
  - Exposure at a young age
  - Exposure in individuals with fair skin, blue eyes, blonde or red hair, propensity for sunburns, and inability to tan (poor tanners)
- Age: High incidence in young and middle-aged adults as well as in older subjects.
- Sex: Slightly more common in male subjects than in females.
- Ethnicity: Higher incidence in Northern than in Eastern and Southern Europeans.

Familial Melanoma

- About 5% to 10% of melanomas are familial and up to 40% have hereditary basis.
- A tumor suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A) is the most commonly mutated gene located on the short arm of chromosome 9.
- The protective effect of CDKN2A is mediated by encoded protein $p16^{INK4A}$.
- Other candidate genes in this category include cyclin-dependent kinase 4 and CDKN2A/p14 alternate reading frame CDKN2A/ARF.
- A high-risk variant of the α-melanocyte-stimulating hormone receptor gene (MC1R) located on chromosome 16q24 and associated with red hair and freckles confer 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 young age and family history of melanoma (mean age between 30 and 40)
  - 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
  - Dysplastic nevi locus of which resides on short arm of chromosome 1
  - Congenital nevi and acquired melanocytic nevi (Table 22.2)

Risk Factors for Melanoma

- Xeroderma pigmentosum
- Familial atypical mole melanoma syndrome (FAMMS)
- Advanced age and immune-suppressive states

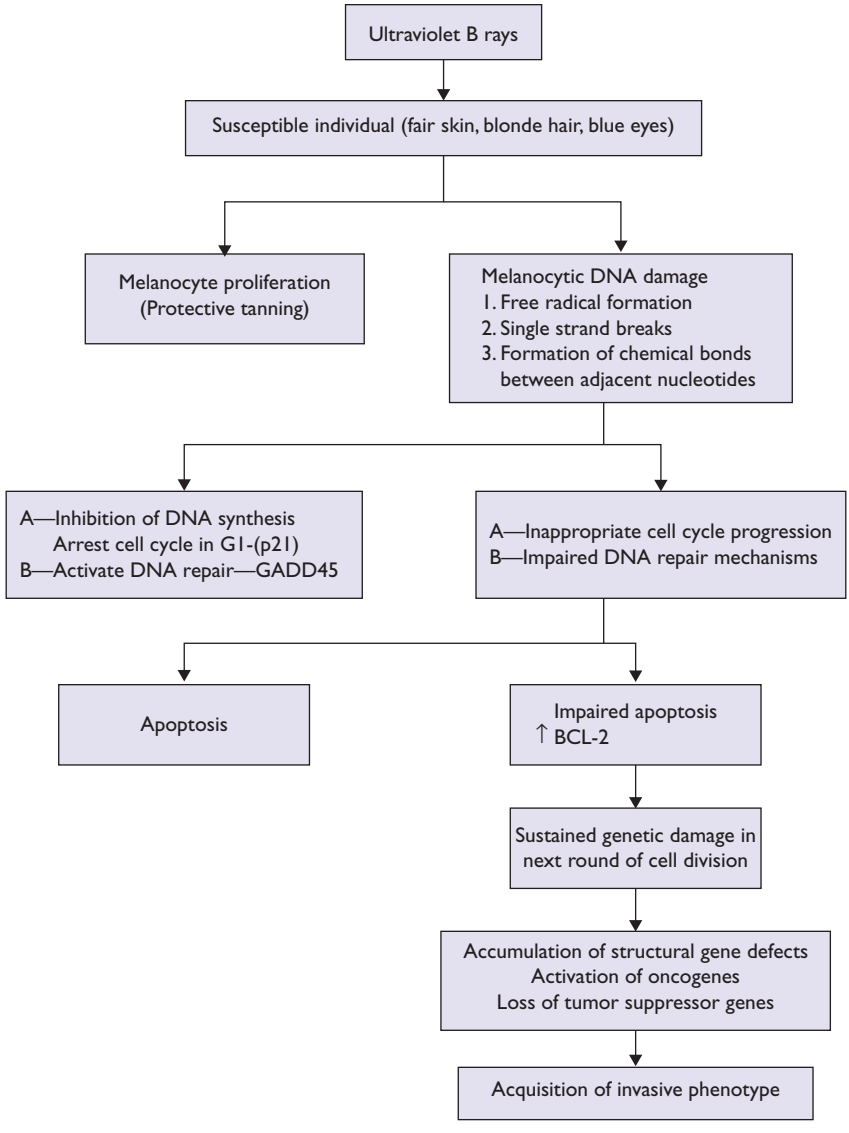

FIGURE 22.1 Model of ultraviolet B light-mediated pathogenesis of cutaneous melanoma.

- Sun exposure and sun-sensitive phenotype
- Melanoma in a first-degree relative and previous history of melanoma

Common Chromosomal Abnormalities in Melanoma

- Early chromosomal abnormalities:
  - Loss of 10q
  - Loss of 9p

Table 22.2 Differences between Acquired Melanocytic and Dysplastic Nevi

Acquired Melanocytic Nevus	Dysplastic Nevus
Develops in early childhood through fourth decade	Develops throughout life
<5 mm in diameter, sharp borders, evenly pigmented	6–8 mm in diameter, irregular borders, variegated pigment, and topographic asymmetry
Risk for melanoma development increases by 10-fold if more than 100 in number	Risk factor for melanoma development

- Late chromosomal abnormalities:
  - Deletion of 6q
  - Loss of terminal part of 1p
  - Duplication of chromosome 7
  - Deletion of 11q23

Clinical Features of Melanoma (abcde)

- Most cutaneous melanoma lesions are pigmented and display **a**symmetry, irregular **b**orders, variegate **c**olors with shades of brown, black or pink, white, red or blue, **d**iameter of at least 6 mm; progressive change in size, nodularity, ulceration, or bleeding with or without pain and or itching and **e**volving in size, shape, or color.
- Less than 1% of cutaneous melanomas lack pigment. These are called amelanotic melanomas and may pose diagnostic challenges.
- Cutaneous melanoma can occur anywhere in the body. Cutaneous melanoma is more common in the lower extremities in women, the trunk in men, and head and neck in the elderly subjects.

Pathologic Diagnosis of Cutaneous Melanoma

Melanoma In Situ

Biopsy of a suspicious skin lesion for melanoma reveals characteristic tumor cell morphology in the basal epidermal layer verified by the tumor cells staining of melanoma-specific antigens such as S-100, premelanosomal protein HMB-45, nerve growth factor receptor, tyrosinase-related protein-1 (MEL-5). Melanoma tumor cells stain positive for vimentin and negative for cytokeratin stains.

Invasive Melanoma

Tumor invasion into the dermis makes it an invasive melanoma quantified by two methods described by Clark et al. and Breslow see below. Additional histologic information provides important prognostic information and includes morphologic variants such as spindle cell morphology, ulceration, mitosis counted as number/mm^2, lymphocytic infiltration, regression if any, vascular invasion, perineural invasion, and solar elastosis (Table 22.3).

Clinicohistologic Types of Melanoma: Microstaging

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 (Fig. 22.2).

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 (Breslow thickness).

Table 22.3 Prognostic Factors of Melanoma

Good Prognostic Factors	Poor Prognostic Factors
Thin tumor (tumor ≤1 mm deep)	Thick tumor (tumor >1 mm deep), nodular tumor
No ulceration of tumor	Tumor ulceration present
No tumor cell mitosis	Tumor mitosis present
Absence of foci of regression and/or tumor satellites in the reticular dermis and subcutaneous fat	Presence of foci of regression and/or tumor satellites in reticular dermis and subcutaneous fat
Absence of vascular and/or lymphatic invasion	Presence of vascular and/or lymphatic invasion
Tumor involving an extremity	Tumor involving the trunk, head, and neck
Early stage (stages I and IIA)	Late stage at presentation (stages IIB, IIC, III, and IV)

Principles of American Joint Committee on Cancer Melanoma Staging

Melanoma is staged based on information derived from three key categories (**TNM**):

- (**T**) Tumor characteristics on microscopic examination
- (**N**) Nodes—status of the regional lymph node metastasis
- (**M**) Distant metastasis—either present or absent

In American Joint Committee on Cancer (AJCC) staging, melanoma is divided into four stages:

- Stage I—thin melanoma (subdivided into IA and IB)
- Stage II—deeper melanoma without lymph node metastasis (subdivided into IIA, IIB, and IIC)
- Stage III—melanoma spread to regional lymph nodes (subdivided into IIIA, IIIB, and IIIC)
- Stage IV—distant metastasis (subdivided into M1a, M1b, and M1c)

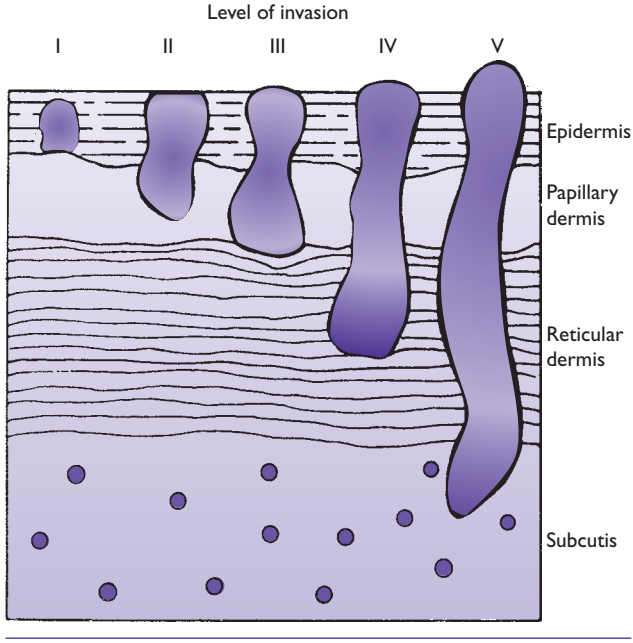

FIGURE 22.2 Schematic diagram of Clark levels of invasion.

Factors taken into consideration for subdividing each stage into subcategories A, B, or C include the following:

- Stages IA and IB: depth of invasion, ulceration, and mitosis
- Stages IIA, IIB, IIC: depth of invasion, presence or absence of ulceration
- Stages IIIA, IIIB, IIIC: Number of lymph node metastases, microscopic versus clinically palpable macroscopic lymph nodes, intralymphatic metastases (in transit metastasis) or satellites lesions (microscopic or macroscopic)
  - A sentinel lymph node biopsy procedure is prerequisite to identify occult lymph node metastasis when involved lymph nodes are not palpable on clinical examination. Only exception is melanoma 1or less than 1 mm in depth without ulceration or mitosis.
  - Immunohistochemical staining of melanoma-associated antigens is used to confirm morphologically identified cluster of few melanoma cells in the lymph node.
- Stage IV—M1a, M1b, M1c:
  - M1a—Metastasis to the distant lymph node and subcutaneous tissues
  - M1b—Lung metastasis
  - M1c—Non–lung visceral metastasis that includes liver, bone, brain, and other organs
  - Note: Serum enzyme lactate dehydrogenase if elevated upgrades M1a and M1b to M1c

Prediction of Patient Outcome Based on AJCC Melanoma Staging (Fig. 22.3)

- *Low risk:* Stages I and IIA (melanoma-specific mortality less than 25% at 20 years)
- *Medium to high risk:* Stages IIB, IIC, and III (melanoma-specific mortality between 55% and 75% at 20 years)
- *Poor risk:* Stage IV (melanoma-specific mortality more than 90% at 5 years)

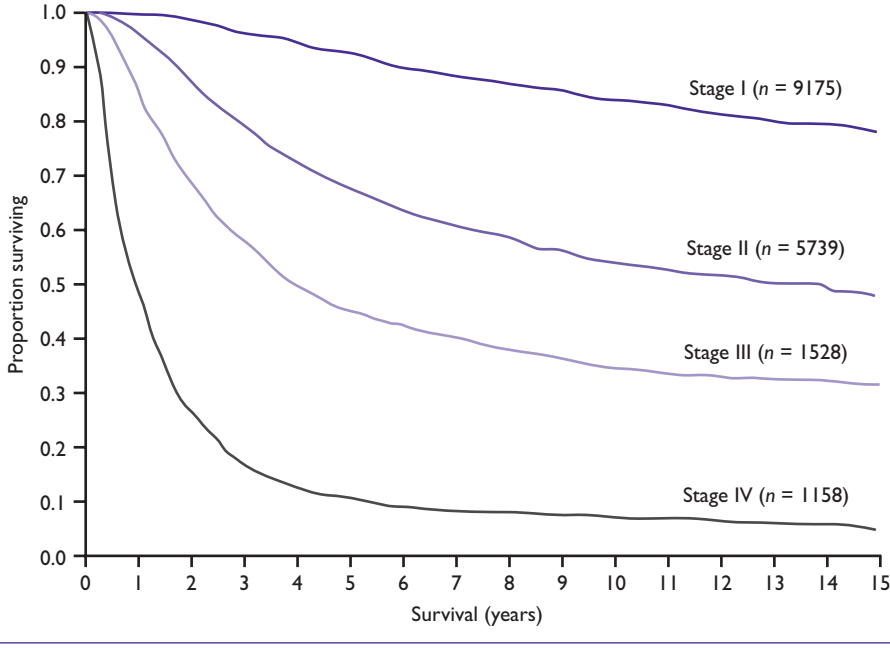

FIGURE 22.3 Relationship between the stage of melanoma and survival (20-year follow-up). (Kaplan-Meier survival curves adapted from Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199-6206.)

Cutaneous Melanoma: Prevention and Early Diagnosis

- Patient education: increasing awareness of melanoma as a serious cancer, its risk factors, self-skin examination (SSE), sun avoidance, light clothing, and effective use of sunscreens.
- Close surveillance: Total body skin examination (TBSE) performed by a dermatologist provides close surveillance to identify suspicious skin lesions for biopsy and early diagnosis.

Selected patients at high risk of melanoma might benefit from the following two techniques:

- Digital photography is used for tracking suspicious skin lesions over time in patients with multiple nevi or dysplastic nevus syndrome.
- Dermoscopy (epiluminescence microscopy), performed by a trained operator, utilizes either a dermatoscope or 10× ocular scope (microscope ocular eyepiece held upside down) to visualize a variety of structures and patterns in pigmented skin lesions that are not discernible to the naked eye. The procedure has a potential to improve diagnostic sensitivity.

Melanoma Management: General Surgical Treatment Principles

An algorithm for melanoma management is presented in Figure 22.4.

Principle: Complete surgical excision of primary melanoma confirmed by comprehensive histologic examination of the entire excised specimen forms the basis of surgical treatment.

Risk of local recurrence: Relates to completeness of resection of the primary tumor, but is not significantly associated with the extent of surgical margin of excision (Table 22.4).

Assessment of the Regional Lymph Node Metastasis and Lymph Node Dissection

Principle: The risk of melanoma metastasis to the regional lymph nodes is directly proportional to the depth of invasion (>1 mm deep), tumor ulceration, and mitosis. For invasive melanoma less than or equal to 1 mm in depth, the risk is increased if ulceration or mitosis is present.

Regional lymph node metastasis: Reflects aggressive tumor biology and depth of dermal invasion that if left untreated pose serious risk of spread to adjacent lymph nodes or to systemic organs.

Historically, complete excision of primary cutaneous melanoma is followed with elective, therapeutic, or delayed lymph node dissection from the respective basin.

- **Elective lymph node dissection:** Although clinically not palpable, all the lymph nodes are dissected from the respective basin because of concerns of melanoma metastasis.
- **Therapeutic lymph node dissection:** Is performed if the regional lymph nodes are enlarged and clinically palpable (suspected lymph node metastasis).
- **Delayed lymph node dissection:** Is performed when initially nonpalpable regional lymph nodes become palpable over a follow-up period (delayed metastasis).

Lymph node dissection is recommended only if regional lymph node metastasis is present and is avoided if lack of lymph node metastasis could be predicted by a reliable test.

Sentinel Node Biopsy

- Sentinel lymph node biopsy as a tool to detect regional lymph node metastasis.
- Characteristics of a sentinel lymph node:
  - First lymph node in the basin at greatest risk of metastasis.
  - Easily accessible and identified by lymphoscintigraphy.
  - Pathologic evaluation helps to detect occult melanoma lymph node metastasis.
- Surgical approach to obtain a sentinel lymph node: lymphoscintigraphy
  - Preoperative lymphoscintigraphy uses vital blue dye injected around cutaneous melanoma that provides a road map of the lymph node basin. Intraoperative lymphoscintigraphy uses radio colloid injection around the primary tumor, and a handheld device detects the radioactivity from the involved lymph node. The combination of vital blue dye and technetium-labeled sulfur colloid helps the surgeon navigate the identity of sentinel lymph node in the respective nodal basin for metastasis in 94% of cases.
- Implications of sentinel lymph node biopsy:

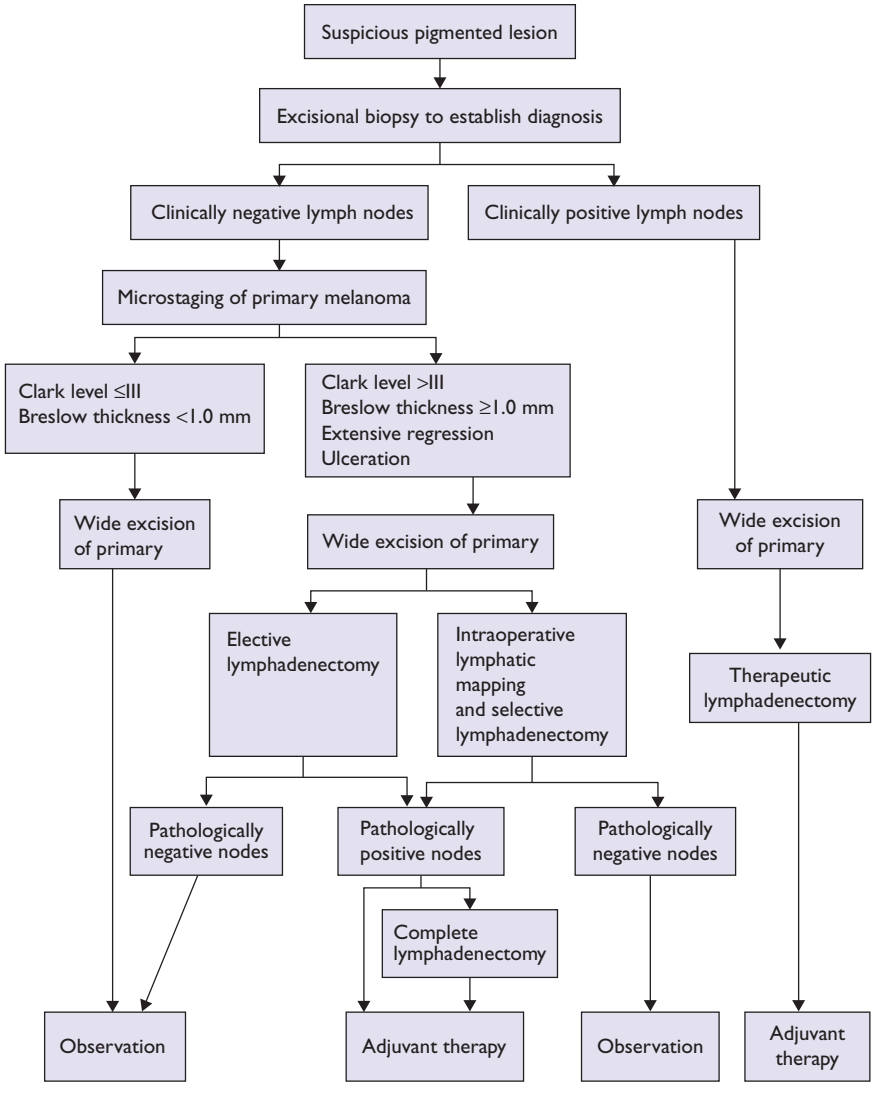

FIGURE 22.4 Algorithm for melanoma management.

Table 22.4 Recommended Margin of Surgical Excision Based upon Pathologic Stage of Primary Cutaneous Melanoma

Pathologic Stage	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

- Complete lymph node dissection is recommended only if sentinel lymph node is positive.
- A negative sentinel lymph node saves the patient morbidity of this procedure.
- Sentinel lymph node biopsy–guided information about the extent of lymph node metastasis helps in prognostication of primary melanoma and reduces the risk of local recurrence. Its impact on overall survival is not clear.
- In one study, immediate lymph node dissection after positive microscopic metastasis in the sentinel lymph node conferred survival advantage in a subset analysis.

Adjuvant Treatment of Melanoma in Patients at Risk of Recurrence after Surgery

Interferon alpha (IFN-α) Treatment Principle: There is a high rate of relapse of cutaneous melanoma (35% to 75%) among patients with AJCC melanoma stages IIB, IIC, and III after primary surgical treatment. Based on antiproliferative and immunomodulatory effects, prolonged use of IFN-α (high dose, low dose, intermediate dose for variable periods of time) has been extensively studied in large prospective randomized clinical trials as an adjuvant to primary surgery to assess benefit of reducing recurrences and improving survival (Table 22.5).

- IFN-α treatment conferred consistent relapse and disease-free survival benefit.
- Impact upon overall survival has been variable and less consistent.
- High-dose IFN-α is superior when compared to low-dose.
  - One month of high-dose intravenous IFN-α induction-only therapy is not sufficient and must be followed by the maintenance phase to confer any benefit.
  - Pegylated form of IFN-α (slow release) given subcutaneously once weekly for up to 5 years conferred relapse-free survival advantage without overall survival benefit.

Table 22.5 Use of Adjuvant IFN-α in Stage IIB, IIC, or III Cutaneous Melanoma

Study Group (Accrual)	Treatment Regimen
ECOG E 1684 (287 patients)	High-dose interferon treatment *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
ECOG E 1690 (642 patients)	High-dose IFN-α (as above) vs. low-dose interferon α-2b, (3 million units/m^2 SC, three times/wk for 104 wk (total dose/wk, 9 million units/m^2) vs. observation
ECOG E 1697 (1,444 patients)	IFN-α-2b: induction phase of high-dose interferon only of 4 wk as above vs. observation
UKCCCR study (674 patients)	IFN-α-2a, 3 million units/m^2 SC, three times/wk for 2 y or until recurrence of melanoma (total dose/wk, 9 million units/m^2) vs. observation
EORTC study 18952 (1,388 patients)	IFN-α-2b, 10 million units/m^2/dose SC 5 d/wk for 4 wk (total dose/wk, 50 million units/m^2), followed by IFN-α-2b, 10 million units/m^2 SC, three times/wk for 1 y (total dose/wk, 30 million units/m^2) vs. IFN-α-2b, 5 million units/m^2 SC, three times/wk for 2 y (total dose/wk, 15 million units/m^2) vs. observation

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee for Cancer; UKCCCR, The UK Coordinating Committee on Cancer Research; EORTC, European Organization for the Research and Treatment of Cancer; IV intravenous; SC, subcutaneous; vs., versus.

- The predominant toxicity of high-dose IFN-α severe flu-like symptoms, liver toxicity, and depression that adversely affect quality of life and may compromise the intended benefit of interferon therapy.
- The decision to use interferon in the adjuvant setting of cutaneous melanoma treatment should be based on the perceived relative merits of disease control, quality of life, and financial cost.

- Biochemotherapy as an adjuvant treatment of cutaneous melanoma after primary surgery did not confer survival advantage in one randomized phase 3 clinical trial.
- Ongoing clinical trials are evaluating the role of ipilimumab, an anti-CTLA antibody, and vemurafenib, an agent that targets BRAF mutation as adjuvant treatment of melanoma after primary surgery. Both of these agents have recently been approved for use in patients with metastatic melanoma.

Role of Radiation Therapy

- Pain relief of melanoma metastasis to the musculoskeletal region
- As an adjuvant treatment after the regional lymph node dissection:
  - In melanoma of the head and neck region
  - When lymph node metastases are bulky and/or involve four or more lymph nodes or exhibit extracapsular spread
  - Local recurrence of melanoma in a previously dissected lymph node basin
- After surgical resection of desmoplastic melanoma with neurotropism
- Brain metastasis of melanoma

Radiation therapy of brain metastasis of melanoma includes

- Whole-brain radiation if multiple and large size brain metastases are present
- Stereotactic brain radiation is preferred if small-sized or isolated or fewer (two to three) brain metastases are present

Results of the studies by Skibber et al. and others have suggested that external radiation to the brain after surgical resection of the solitary brain metastasis from malignant melanoma has survival benefits.

Isolated Limb Perfusion or Infusion as a Treatment of Melanoma

Principle: To deliver maximally tolerated chemotherapy doses 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 potentiate the tumoricidal effects of the chemotherapeutic agents that include melphalan (L-PAM), thiotepa, mechlorethamine with or without tumor necrosis factor (TNF-α), and IFNγ. This procedure provides palliative benefit to patients with in-transit metastasis of melanoma otherwise difficult to resect surgically or at high risk of recurrence after surgery (Table 22.6).

Isolated limb infusion: Is a simplified and minimally invasive procedure developed at the Sydney Melanoma Unit (SMU) intended to obtain the benefits of ILP without major disadvantages. It is a low-flow ILP procedure performed via percutaneous catheters without oxygenation.

Both the procedures provide local tumor control and pain relief with improvement of quality of life usually without impact on overall survival.

Table 22.6 Isolated Limb Perfusion in Melanoma

Advantages	Disadvantages
Provide local control of the disease	Expensive and invasive procedure that is available only at selected institutions
Help resolve local symptoms such as edema, ulceration, and bleeding	Procedure provides effective palliation of local symptoms but no survival benefit
Relieves pain	Potential complications of the procedure include ischemia of the limb, peripheral neuropathy, 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 two novel agents:

- Ipilimumab is a monoclonal antibody to CTLA-4 antigen on T lymphocytes that regulate T lymphocyte activation after an encounter with melanoma antigen.
- Vemurafenib is a targeted therapy that selectively blocks mutated BRAF in melanoma patients harboring BRAF mutation.
  Both of these agents have shown overall survival benefits to patients with metastatic melanoma and have unique toxicity profiles (see below).
- High-dose interleukin-2 (IL-2) (see below).
- Surgical resection of an accessible isolated metastatic lesion has a curative potential in about 25% of patients, while those who are not candidates for complete surgical resection of a metastatic lesion will require systemic treatment.
- Chemotherapy as a single agent, in combination, or with biologic agents (biochemotherapy) in patients with metastatic melanoma.
- Experimental therapies such as adaptive cell therapy and newer targeted therapies still remain promising options for selected patients with metastatic melanoma.

Chemotherapy of Metastatic Melanoma: Single-Agent Chemotherapy

- Dacarbazine is the only FDA-approved chemotherapeutic agent for melanoma treatment that has a response rate of about 10% to 20% without overall survival 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.
- In a recent phase 3 trial, nab-paclitaxel (abraxane) showed a statistically significant improvement in progression-free survival and a trend toward improved overall survival as compared to dacarbazine.

Combination Chemotherapy Regimens of Metastatic Melanoma (Table 22.7)

- M.D. Anderson regimen: cisplatin, vinblastine, dacarbazine (CVD)
- Dartmouth regimen: cisplatin, carmustine, dacarbazine, and tamoxifen (CBDT)

Table 22.7 Description of Combination Chemotherapy Regimens in Metastatic Melanoma

Chemotherapy Regimens	Treatment Description	Response Rates (%)
CVD (M.D. Anderson Cancer Center)	Cisplatin, 20 mg/m^2/d IV for 4 d (2, 3, 4, 5) (total dose/cycle, 80 mg/m^2) Vinblastine, 1.6 mg/m^2/d IV for 5 d (1, 2, 3, 4, 5) (total dose/cycle, 8 mg/m^2) Dacarbazine, 800 mg/m^2 IV on day 1 (total cycle dose 800 mg/m^2) cycle repeats every 21 d	21–48
CBDT (the Dartmouth regimen)	Cisplatin, 25 mg/m^2/d IV for 3 d (1, 2, 3) (total dose/cycle, 75 mg/m^2) Carmustine, 150 mg/m^2 IV day 1 (every odd-numbered cycle, i.e., every 43 d total dose every two cycles, 150 mg/m^2 Dacarbazine, 220 mg/m^2/d IV for 3 d (1, 2, 3) (total dose/cycle, 660 mg/m^2) Tamoxifen, 10 mg twice daily PO during the therapy Cycle repeated every 21 d	19–55

IV, intravenous; PO, per oral.

A phase 3 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.

Biologic Agents in the Treatment of Metastatic Melanoma: IFN-α

IFN-α is the first recombinant cytokine investigated in phase 1 and 2 clinical trials of patients with metastatic melanoma based on its antiproliferative and immunomodulatory effects.

- Initial studies showed response rates of about 15% in patients with metastatic melanoma.
- One-third of these responses were complete and durable.
- Responses could be observed up to 6 months after the therapy was initiated.
- Small volume disease and uninterrupted use resulted in pronounced responses.

Falkson et al. reported the outcome of patients with metastatic melanoma treated with either dacarbazine alone or a combination of dacarbazine and IFN-α-2b. The results indicated a response rate and median survival of 20% and 9.6 months, respectively, with dacarbazine alone compared to a response rate and median survival of 53% and 17.6 months, respectively, in patients receiving both these agents. These results could not be reproduced in subsequent randomized phase 3 studies.

Essentially, IFN-α is rarely used as primary therapy for metastatic melanoma.

IL-2 Based Therapy

- IL-2 is a T-cell growth factor produced primarily by T-helper cells upon antigen binding.
- Interacts with IL-2 receptors expressed on activated cytotoxic T lymphocytes (CTLs) and causes:
  - Increased production of other interleukins, IFN-γ, and TNF-α
  - Proliferation and differentiation of both B and T lymphocytes and cytotoxic cells
- Antitumor effects are mediated by its ability to stimulate proliferation of natural killer cells (NK cells), lymphokine-activated killer cells (LAKs), and CTLs.

The U.S. Food and Drug Administration (FDA) approved high-dose IL-2 for treatment of metastatic melanoma at 600,000 international units (The FDA approved the high dose IL-2 at 600,000 international units per kg) per kilogram body weight administered as a bolus over 15 minutes every 8 hours for a maximum of 14 doses on days 1 to 5 and 15 to 19. Imaging studies are repeated after two such courses to evaluate efficacy.

In patients responding to high-dose IL-2, the treatment is continued unless the patient has significant side effects or the physician decides to stop treatment for safety reasons.

- The overall response rate is about 16%, which includes a complete response rate of 6%.
- Responses are observed in all disease sites.
- Durable responses are achieved in those who achieved complete responses.
- Good baseline performance and chemo-naive status are predictive of response.
- A toxicity profile results from capillary leak syndrome that is dependent on dose, route, and duration of administration. Common toxicities are as follows:
  - High fever and fluid retention
  - Gastrointestinal system side effects (i.e., nausea, vomiting, and diarrhea)
  - Cardiovascular system side effects (i.e., hypotension or arrhythmias)
  - Pulmonary side effects (i.e., hypoxemia and pleural effusions)
  - Renal side effects (i.e., azotemia and renal failure)
  - Central nervous system side effects (i.e., confusion and delirium)
- Patients with active comorbidities involving heart, lung, kidney, and liver disease or those with untreated brain metastasis with vasogenic edema are at high risk of life-threatening complications and mortality related to capillary leak caused by high-dose IL-2 treatment emphasizing rigorous patient selection for treatment with this agent.
- High-dose IL-2 should only be administered by health care teams experienced in its use.
- Lower doses of IL-2 administered either subcutaneously or as a continuous intravenous infusion at 9 to 18 million international units/m^2/day for 4 to 5 days have been studied in patients not eligible for high-dose IL-2 treatment. Although total response rates as high as 20% have been reported, complete responses appear to be lower than those with high-dose IL-2.

Table 22.8 Biochemotherapy of Metastatic Melanoma

Biologic and Chemotherapeutic Agents	Response Rates
Cisplatin 20 mg/m^2 days 1, 2, 3, 4 Vinblastine 1.6 mg/m^2 days 1, 2, 3, 4 Dacarbazine, 800 mg/m^2 day 1 Recombinant IL-2, administered IV as continuous 24 h infusion at 9 MIU/m^2 days 1, 2, 3, 4 IFN-α2b, 5 MIU/m^2, SC days 1, 2, 3, 4, 5 Cycle repeated every 21 d	Overall response rate of 64% Complete response rate of 21% Partial response of 43%

MIU, million international units; IV, intravenous; SC, subcutaneous.

Combining Chemotherapy and Biologic Agents in Metastatic Melanoma Biochemotherapy: Rationale

- Preclinical studies suggest 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.
- There are no overlapping toxicity and cross-resistance.

Biochemotherapy: Built upon 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 (Table 22.8).

- The toxicity associated with biochemotherapy regimen and lack of reproducibility of survival benefit among investigators has dampened interest in its universal use.
- A recent meta-analysis of 18 clinical trials and a phase 3 randomized clinical trial comparing biochemotherapy to CVD chemotherapy in patients with stage IV melanoma confirmed high response rates (40% to 50%) and increased toxicity with biochemotherapy without overall survival advantage.

Principles of Immune-Based Therapy of Melanoma

- Melanoma is considered to be one of the best models of an immunogenic tumor attracting T lymphocyte infiltration at both the primary and metastatic sites representing the immune footprints.
- A number of well-defined melanoma antigens have been identified both at a protein and gene level that evoke a cellular immune-based antimelanoma response (Table 22.9).
- Antigen-specific CD8+ CTLs lead the antimelanoma response with critical help from CD4+ helper T cells and antigen-presenting cells (APCs).

Table 22.9 Melanoma-Associated Antigens, Peptides, and Presenting MHC Molecules

Melanoma Antigens	Peptides	Presenting MHC Molecules
MAGE-A1[a]	EADPTGHSY	HLA-A1 & 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
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 (CT) antigens; [c]mutated antigens.

Activation of CTLs against melanoma requires two signals:

- Signal 1 (CD8+ CTL priming): The melanoma antigen (peptide) is presented either by the tumor cell or by the APCs at their MHC class I or MHC class II molecules, respectively, to the T-cell receptor of CD8+ CTL or CD4+ T cells.
- Signal 2 (CD8+ CTL activation and proliferation): The antigen-primed CD8+ CTLs express CD28 molecules on their surface for engagement with costimulatory molecules B7.1 (CD80) and B7.2 (CD86) on the APCs resulting in CD8+ CTL activation and proliferation.

Activated CD8+ CTLs kill the tumor cells directly and by the elaboration of secreted cytokines such as TNF-α, IFNγ, granulocyte-macrophage colony stimulating factor (GMCSF), and IL-2 all helping shape the tumor microenvironment.

Immune-Based Treatment Strategies of Metastatic Melanoma: Two Approaches

- ***Specific immunity:*** Evoked by subcutaneous or intradermal 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). 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.
- ***Nonspecific immunity:*** Administration of biologic agents such as IL-2 and/or –IFN-α enhances antitumor immunity by activation and expansion of preexisting circulating melanoma antigen-specific CD8+ CTL precursors as well as NK cells (LAKs).

Tumor vaccines generate antimelanoma immune response. Based on our ability to successfully elicit melanoma-specific T-cell immune responses in mice and armed with a variety of tumor vaccines, a large number of phase 1, 2, and 3 clinical trials were completed. Although a proof of concept was demonstrated, generation of melanoma-specific T-cell activity did not consistently correlate with meaningful patient responses.

Failure to Generate Effective Antimelanoma Immunity in Patients: Immune Regulation Laboratory research showed that activated CD8+ CTL response to a tumor antigen (lysate or a vaccine) is highly regulated or held in check by a number of processes so as to prevent uncontrolled inflammation and body injury. These regulatory processes are due to factors intrinsic or extrinsic to the CD8+ CTLs.

- Intrinsic mechanisms that inhibit activated CD8+ CTLs:
  - CTL antigen 4: Activated T lymphocytes are downregulated by their own expression of an inhibitory molecule called CTL antigen 4. This molecule has higher affinity and successfully competes with CD28 for binding to costimulatory molecules CD80 and CD86 on APCs inhibiting its activity.
  - PD-1: Tumor expression of PD-1 ligand evokes CTL expression of PD-1 molecules. Interaction between these molecules leads to exhaustion and premature programmed cell death of activated CD8+ CTLs abrogating its activity.
- Extrinsic mechanisms that regulate activated CD8+ CTLs:
  - Regulatory T cells: CD8+ CTL responses are regulated by naturally occurring CD4+CD24+ T cells (nTreg) and those derived from CD4+ T cells that acquire inhibitory properties upon interaction with tumor antigens to negate CTL activity (induced Treg). The regulation of CD8+ CTLs by CD4 T cells is mediated by expression of a transcription factor foxP3.
  - Tumor factors: Include tumor secretion of inhibitory cytokines and molecules that negatively influence antimelanoma T-cell responses.
  - Downregulation of MHC class I molecules on both tumor cells and the APCs compromising effective antigen presentation to the T cells.

New FDA-Approved Immune-Based Therapy of Metastatic Melanoma Recognition that CTLA-4 antigen is the key inhibitory molecule expressed by antigen-activated CD8+ CTLs orchestrating downregulation of antitumor immunity led to successful targeting of this molecule for blockade to regain CD8+ CTL activity.

Ipilimumab is an IGG1 monoclonal antibody designed to block inhibitory CTLA-4 antigen on activated CD8+ CTLs that fulfilled its promise by effectively blocking the intended target. This strategy

showed promising antitumor activity in preclinical studies in mice bearing melanoma leading to successful human studies.

Two large randomized phase 3 clinical trials reported survival benefit of anti-CTLA-4 antibody ipilimumab in patients with previously treated or treatment naïve unresectable stage III and IV melanoma when compared with a glycoprotein 100 (gp100) peptide vaccine (Hodi et al. 2010) or dacarbazine (Robert et al.), respectively. In March 2011, this agent was approved by the U.S. FDA for the treatment of metastatic melanoma administered as an infusion at 3 mg/kg given every 3 weeks for four doses.

- Important facts about ipilimumab treatment of patients with metastatic melanoma:
  - The objective response is between 10% and 16% with a disease control rate (the proportion of patients with a partial or complete response or stable disease) of about 25% to 35%.
  - Responses are seen in previously untreated or treated patients including those with high-risk visceral metastasis and elevated serum levels of lactate dehydrogenase.
  - The onset of clinical benefit is slow and mediated by antigen-specific tumor infiltrating CD8+ CTLs consistent with the proposed mechanism.
  - Responses are sometimes preceded by transient tumor progression followed by continued tumor shrinkage beyond week 24 and lasting beyond 2 years.
  - In order to capture response patterns unique to immune therapy, immune-related response criteria (IRRC) are defined.
  - Reinduction therapy with ipilimumab at the time of disease progression can result in further benefit in a significant proportion of patients (reinduction is currently not FDA approved).
  - The effect on overall survival is independent of age, sex, baseline serum lactate dehydrogenase levels, metastasis stage, and previous treatment with IL-2 therapy.
  - The treatment is associated with autoimmune side effects due to cross-reactivity of antigen-specific CD8+ CTLs with normal tissues that often share these antigens. Such manifestations are referred to as immune-related adverse effects (irAEs).
  - irAEs may occur in up to 60% of patients, but high grades (3 and 4) occur in up to 10% to 15% cases.
  - The most common irAEs involve skin, gastrointestinal tract, liver, and endocrine organs although any organ can be affected requiring careful patient evaluation.
  - Clinical presentations include skin rashes of varying grades, nausea, abdominal pain, and diarrhea, or in severe cases colitis symptoms such as abdominal distension, blood in stools, and symptoms of intestinal obstruction or perforation.
  - Early diagnosis and prompt institution of immune-suppressive therapy with steroids or other agents are key to managing irAEs with slow taper over 3 to 4 weeks.
  - Responses and improved outcomes are sometimes more likely to occur in those who develop irAEs. Use of steroids to treat irAEs did not seem to decrease antitumor effects.
  - Majority of the irAEs usually occur about 3 to 4 weeks after the first ipilimumab infusion although in some cases it may occur earlier or later than this period. Skin manifestations of irAEs usually occur earlier and are first to appear followed by symptoms of toxicity in other organ system such as colon (colitis), liver (hepatitis) and endocrine organs (endocrinopathy) in that order (although any organ can be affected). 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.
  - Ipilimumab can safely be administered along with chemotherapeutic agents, vaccines, or biologic agents.

Targeted Therapy of Melanoma

- Targeted therapy of melanoma is based upon a precise understanding of the functional cellular genetic machinery generating critical signaling pathways for cellular growth signals from outside of the cells to the nucleus leading to transcription of key genes critical for cellular homeostasis controlling proliferation, differentiation, and cell death.
- The mitogen-activated protein (MAP) kinase pathway that consists of Ras/Raf/MEK/ERK signaling is a key signal cascade driving cell-cycle proliferation, differentiation, and survival.
- Mutations of the genes serving this pathway promote uncontrolled cell proliferation and increased survival leading to malignant progression of cancer.
- B-Raf is a serine/threonine kinase that occupies a central place in the MAP kinase pathway, mutations of which serve as a valuable therapeutic target for melanoma.

- Activating mutations in B-Raf (BRAF) were first described to occur in about 40% to 60% of cutaneous melanoma in 2002.
- About 90% of mutations in BRAF result in the substitution of glutamic acid for valine at codon 600 (BRAF V600E). Other BRAF mutations include V600K and V600D/V600R variants.
- Vemurafenib is a first-in-class, oral small molecule kinase inhibitor that selectively targets cells harboring BRAF mutations and recently been shown to have high response rates (50%), benefiting about 80% patients and improving survival compared to dacarbazine (Chapman et al. *NEJM*).
- Vemurafenib is now FDA approved for patients with metastatic or unresectable melanoma in the dose of 960 mg administered orally twice a day until disease progression or intolerance.
- Important facts about BRAF kinase inhibitor treatment of metastatic melanoma:
  - The survival benefit of vemurafenib was observed in each prespecified subgroup according to age, sex, performance status, tumor stage, serum levels of lactate dehydrogenase, and geographic region.
  - Unique toxicities include the development of squamous cell carcinomas in approximately 25% of patients along with photosensitivity and muscle pains. Other side effects include arthralgia, pruritis, fatigue, alopecia, diarrhea, and nausea.
  - About 38% of patients taking vemurafenib required dose modifications due to drug toxicity.
  - Acquired drug resistance to BRAF inhibitor agent frequently leads to treatment failures and is linked to upregulation of platelet-derived growth factor receptor beta (PDGFRβ) or mutated NRAS gene.
  - A second selective BRAF inhibitor dabrafenib has shown survival benefit in patients with metastatic melanoma carrying BRAF mutations. Of significance, the clinical benefit was extended to melanoma patients with brain metastasis of melanoma.
  - MEK is another therapeutic target in the MAPK pathway downstream of BRAF. Trametinib is an oral selective MEK inhibitor that improved progression-free survival and overall survival in patients with metastatic melanoma harboring BRAF mutation in a phase 3 randomized clinical trial.
  - Of interest, combining a MEK inhibitor (downstream of B-RAF in the MAP kinase pathway) with a B-RAF inhibitor may improve efficacy and at the same time reduce skin toxicity as reported in a recent randomized clinical trial.

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 22.10).
- Benign choroidal nevi are up to 5 mm and 1 mm in diameter and depth, respectively.
- Monosomy of chromosome 3 is a common cytogenetic abnormality and confers poor disease-free survival 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.

Table 22.10 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

- 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 hyperthermic isolated perfusion using melphalan.

A recent randomized trial evaluated the use of liver chemosaturation with melphalan using a specialized approach of isolating the liver using a system of catheters (PHP, percutaneous hepatic perfusion) in patients with melanoma (mostly uveal) metastasis to the liver. The trial showed high response rates and improved liver-specific progression-free survival.

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.

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 two major types of nonmelanoma skin cancers: basal cell carcinoma (BCC) and squamous cell carcinoma. Together they account for nearly 1 million cases in the United States per year. The immune system plays an important role in the pathogenesis of nonmelanoma skin cancers, as demonstrated clinically by their increased incidence in patients with immune-suppressed states, such as the aging population and transplant recipients. Histologically, the regressing nonmelanoma skin cancers show infiltration of the tumor by activated T cells and cytokines such as IFN-α, TNF-β, and IL-2.

Basal Cell Carcinoma

- BCCs are keratinocyte tumors most commonly diagnosed in people of European ancestry.
- Exposure to ultraviolet rays is the most important etiologic factor. Other causative factors include exposure to ionizing radiation and arsenic.
- BCC is the commonest cancer in the US white population over 50 years of age, accounting for 75% of 1 million new cases of nonmelanoma skin cancers.
- Usual location of BCC is the skin of the head and neck region (sun-exposed area).
- BCC is highly cured by surgery on most of the occasions and despite its high rate of occurrence, the death rate is extraordinarily low.
- When locally advanced or metastatic (rare occasions), local invasion can lead to tissue destruction that makes surgical treatment very difficult and outcomes very poor.

Clinical Presentations of BCC

- Typical presentation of BCC is a shiny pink translucent papule with telangiectasia.
- Nodular variant of BCC presents with central depression and rolled margins that may bleed from trauma and include pigmented types with brown to black pigment.
- Sclerosing or morphea-type BCC is yellowish, infiltrative tumor with indistinct borders often remaining undiagnosed for a long time. Management includes Mohs surgery.
- Hyperkeratotic-type carcinoma (less common) usually involves the head and neck area as multicentric ulcer and scar tissues or giant exophytic type or cystic type presenting as a blue–gray nodule on the face or as a sessile growth on the lower trunk.

BCC as a Heritable Disorder

- A rare familial presentation of BCC is called basal cell nevus syndrome (BCNS) also known as Gorlin syndrome characterized by high incidence of BCCs and medulloblastomas.

- The autosomal dominant inheritance of this syndrome is due to uncontrolled activation of the Hedgehog (Hh) signaling pathway.
- The genetic abnormality underlying this condition is linked to mutation of a gene called patched 1 (PTCH1) identified as a tumor suppressor gene and mapped to human chromosome 9q22.
- The mutations of genes PTCH1 and TP53 critical to BCC carcinogenesis are believed to be produced by exposure to UV radiation, elucidating the essential role of UV exposure in the causation of BCC.

Hedgehog Signaling Pathway and Targeted Therapy of BCC

- Hh signaling is a pivotal abnormality in all the BCCs resulting in uncontrolled proliferation of the basal cells and carcinogenesis.
- The Hh pathway is activated after binding of Hh ligand to the PATCHED 1 protein (PTCH1)—a tumor suppressor gene present on target cells.
- In the absence of excessive Hh ligand, the tumor-suppressive gene 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 result in transcription of gene important in proliferation and cell survival.
- Activity of SMO also leads to increasing transcription of Hh ligands GLI1 and GLI2 as well as decreasing PTCH1 expression constitutively activating the Hh signaling.

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 identifying agents that inhibit Hh signaling.

Plant alkaloid cyclopamin is the first well-studied Hh inhibitor (HHI) that when applied locally caused regression of BCC. Cyclopamin is a competitive inhibitor of SMO signaling, binding directly to the protein PTCH1 or SMO.

- Vismodegib is a first-in-class, small molecule inhibitor of SMO that is FDA approved for metastatic or locally advanced BCC at a dose of 150 mg given orally daily until disease progression or intolerable toxicity.
- A phase 1 study of vismodegib involving 33 patients with advanced BCC showed a 58% confirmed response rate and a median duration of response of 12.8 months.
- In a phase 2 study containing 33 patients with metastatic BCC and 63 patients with locally advanced basal cell carcinoma, vismodegib produced a response rate of 30% and 43%, respectively, with the median duration of response being 7.6 months.
- Common toxicity of vismodegib includes alopecia, dysgeusia (taste disturbance), muscle spasms, fatigue, and weight loss. Serious adverse events were reported in 25% of patients resulting in seven deaths.

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.
- The nodule may be ulcerated, and regional lymph nodes may be enlarged.

Squamous Cell Carcinoma of a Mucocutaneous Site

- Elderly men with chronic history of smoking, alcohol use, or chewing tobacco or betel nut.
- Common sites include mouth and lower lip.
- Lesions usually start as erosion or a nodule that ulcerates.
- Other sites of origin include 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

Detailed clinical history should include duration of the lesion, symptoms such as pain or itching, and recent changes of the surface in addition to the following:

- Chronic sun exposure and recreational and occupational history
- Radiation and arsenic exposure, chronic ulcer/burn scar, or osteomyelitis
- Ethnic background and type of skin

A complete skin examination includes

- Examination of scalp, ears, palms, soles, interdigital areas, and mucous membranes
- Evaluation of the extent of sun damage to skin (i.e., solar elastosis, scaling, erythema, telangiectasia, and solar lentigines)
- Assessment of the locoregional lymph nodes and distant metastases

An excisional or incisional tumor biopsy in small or large tumor, respectively, is obtained for histologic diagnosis. A shave biopsy with a scalpel may be used in noduloulcerative, cystic, or superficial type.

Treatment of Nonmelanoma Skin Cancer

Complete surgical resection with negative margins of at least 4 to 6 mm is recommended with lymph node resection if enlarged. Plastic surgery may be needed to close the defects produced by excision of the tumor.

Mohs Surgery

Mohs surgery allows excision of the tumor until the negative margins are achieved. It includes micrographic surgery that is guided by examination of a frozen section to ascertain complete resection.

Imiquimod is an FDA-approved agent for treatment of superficial BCC when used in cream form. The drug works via toll-like receptor agonistic activity and causes stimulation of innate and adaptive immune systems. 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 2,000 to 3,000 cGy penetrate up to 2 to 5 mm, where 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.

MERKEL CELL CARCINOMA

Merkel cell carcinoma 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 (APUD). Merkel cells are important for tactile sensations in lower animals and they function as a mechanoreceptor in humans.

Characteristics of Merkel Cell Tumors

- Occur in the elderly population with chronically sun-damaged areas of skin.
- Common sites include head and neck skin; less common sites are extremities and genitals.
- Present as 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.
- Recent identification of polyomaviral DNA integration in Merkel tumor cells indicates implication of polyomavirus in the pathogenesis of this tumor. Higher incidence of this tumor in the aging population may have clinical relevance to the aging immune system.
- Early spread occurs to locoregional lymph nodes and hematogenously to the distant sites.

Management of Merkel Cell Tumors

Management of Merkel cell tumors includes complete primary surgical excision with lymph node assessment by the sentinel lymph node procedure and lymph node dissection if necessary, as in cutaneous melanoma. Adjuvant radiation treatment is recommended in patients at high risk of local recurrence due to incomplete resection or larger tumor size (2 cm or more).

A metastatic Merkel cell tumor is managed with systemic chemotherapy. Effective chemotherapeutic agents include cisplatin, etoposide, adriamycin, cyclophosphamide, vincristine, and irinotecan. Although the tumor is responsive to chemotherapy, high recurrence rates lead to uniformly poor outcomes.

RARE TUMORS ARISING FROM THE SKIN

Rarely, skin appendageal tumors arise in the following locations:

- Hair follicle
- Arrector pili muscle
- Apocrine sweat gland
- Sebaceous gland

Most of these tumors are benign, and carcinomas are rare. The treatment principle of carcinomas includes complete surgical excision and lymph node assessment as in melanoma.

Dermatofibrosarcoma Protuberans

A rare fibrohistiocytic tumor arising in the skin and subcutaneous tissue of intermediate malignant potential demonstrating slow growth and consistent cytogenetic abnormality t(17;22) in more than 90% of patients, with the following characteristics:

- Common tumor sites include trunk and extremities.
- Frequent local recurrences occur after surgical resection.
- Low propensity to distant metastasis.

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 PDGFβ.

Recent reports suggest high response rates to imatinib mesylate. This potent and specific inhibitor of PDGFRβ is effectively used in neoadjuvant settings and in patients with recurrent disease.

REVIEW QUESTIONS

1. You are seeing a 44-year-old patient with newly diagnosed cutaneous melanoma of the upper extremity. The biopsy of the tumor shows the tumor to be 0.8 mm deep, Clark level III, ulceration absent, mitosis 0/mm^2. A chest x-ray is negative for metastasis and the serum level of lactate dehydrogenase is normal. Which of the following treatment recommendations is correct?
   A. Wide resection of the tumor with wide negative margins
   B. Wide resection of the tumor with negative margins followed by sentinel lymph node biopsy
   C. High-dose interferon treatment
   D. No further treatment
2. The independent prognostic factor(s) for melanoma is/are
   A. Clark level
   B. Tumor infiltrating lymphocytes, regression, and solar elastosis
   C. Depth of invasion in the dermis, presence of ulceration, mitosis, and older age
   D. Perineural invasion and vascular invasion

3. A 67-year-old Caucasian male is referred to you with a diagnosis of metastatic melanoma to the lung. He was found to have a 1.5 cm nodule on an annual chest x-ray by his primary care provider who confirmed it to be a metastasis from previously resected cutaneous melanoma of the upper back. The patient who has mild diabetes mellitus and well-controlled hypertension is otherwise asymptomatic. A whole-body PET study showed a PET avid lesion in the right upper lobe measuring about 1.5 cm ×1.5 cm with no other abnormalities. A brain MRI is negative for metastasis and a peripheral blood showed normal level of serum lactate dehydrogenase. What is the best option for treatment in this patient?
   A. Discuss with him treatment with high-dose IL-2.
   B. Discuss with him treatment with biochemotherapy.
   C. Arrange a repeat chest CT scan within 3 months.
   D. Refer him to a thoracic surgeon for resection of the lung metastasis.
4. A 35-year-old Caucasian woman is diagnosed with metastatic melanoma to the liver from a previously resected cutaneous melanoma of the right lower chest wall 3 years ago. The patient has lost about 20 pounds of weight in the last 4 weeks and is increasingly short of breath. On examination, the patient sits on a wheel chair with pain in the right upper abdomen. Clinical examination reveals an ill-looking individual with mild anemia and an enlarged liver of 7 cm below the costal margins. Whole-body CT scan showed multiple enhancing lesions in both the lobes of liver with right lower pleural effusion. The serum level of lactate dehydrogenase is 450 units/L (upper limit of normal is 175 units/L). A brain MRI is negative for metastasis, while the tumor tested for mutational analysis confirmed the presence of BRAF mutation V600E. What is the best treatment option for this patient?
   A. High-dose IL-2
   B. Intravenous administration of dacarbazine
   C. Ipilimumab treatment
   D. Start oral doses of vemurafenib at 960 mg twice a day
5. Which of the following skin cancers is associated with polyoma virus?
   A. BCC
   B. Squamous cell carcinoma
   C. Merkel cell tumor
   D. Cutaneous melanoma

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SECTION Nine

Hematologic Malignancies

23

Acute Leukemia

Aaron Cumpston and Michael Craig

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. Accumulation of the blasts within the bone marrow results in progressive hematopoietic failure, with associated infection, anemia, and thrombocytopenia. It is these complications that often prompt evaluation in newly diagnosed patients.

Acute leukemia continues to present a grave diagnosis because of its rapid clinical course. Patients 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 treatment difficult. Elderly or unwell patients who are given the best supportive care survive only for a few months.

The immature, clonally proliferating cells that form blasts may be derived from myeloid or lymphoid cell lines. Transformation of granulocyte, RBC, or platelet (myeloid) precursors results in acute myelogenous leukemia (AML). Acute lymphoblastic 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 2013 are 14,590 for AML and 6,070 for ALL.
- AML accounts for 10,370 deaths and ALL accounts for 1,430 deaths annually in the United States.
- The risk of developing AML increases with advanced age, the median age being 60 to 69.
- Seventy-five percent of newly diagnosed patients with AML are older than 60.
- ALL is more common in children; 60% to 70% of cases are found in patients younger than 20 years.

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

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia.

RISK FACTORS

Most patients will have no identifiable risk for developing leukemia. Table 23.1 lists the conditions that are identified with an increased risk for developing acute leukemia. Most studies have evaluated the relationship between the risk factors and AML. The conditions that are mostly associated with AML are chronic benzene exposure, exposure to ionizing radiation, and previous chemotherapy.

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. Usually, these are preceded by only a brief myelodysplastic state rapidly evolving to AML.
- Previous high-dose therapy with autologous transplant leads to a cumulative risk of 2.6% by 5 years, especially with total body irradiation (TBI)-containing regimens.

CLINICAL SIGNS AND SYMPTOMS

- Ineffective hematopoiesis: Results from marrow infiltration by the malignant cells
  - Anemia: pallor, fatigue, and shortness of breath
  - 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 leukemia (AML M5)
  - Granulocytic sarcoma: Localized tumor composed of blast cells; imparts poorer prognosis; occasionally extramedullary leukemia masses associated with 8;21 translocation
  - Liver, spleen, and lymph nodes: Common in ALL, occasionally in monocytic leukemia (AML M5)
  - Thymic mass: Present in 15% of ALL in adults
  - Testicular infiltration: Also a site of relapse for ALL
  - Retinal involvement: May occur in ALL
- Central nervous system (CNS) and meningeal involvement
  - 5% to 10% of cases at diagnosis, mainly ALL, inv(16) (French–American–British [FAB] M4Eo), and high blast count
  - Analysis and prophylaxis are given in ALL to decrease CNS relapse.
  - Symptoms: Headache and cranial nerve palsy, but mostly asymptomatic
- Disseminated intravascular coagulation (DIC) and bleeding
  - Very common with acute promyelocytic leukemia (APL); the mechanism is related to tissue factor release by granules and fibrinolysis; generally improves with all-trans retinoic acid (ATRA) of which early initiation is imperative.
  - Can be present in AML inv(16) or monocytic leukemia or can be related to sepsis.
- Leukostasis
  - Occurs with elevated blast count
  - Symptoms result from capillary plugging by leukemic cells.
  - Common signs: dyspnea, headache, confusion, and hypoxia
  - Initial treatment includes leukapheresis, aggressive hydration, and chemotherapy to rapidly lower the circulating blast percentage with drugs (e.g., oral hydroxyurea or intravenous cyclophosphamide).
  - Transfusions should be avoided because these may increase viscosity.
  - Leukapheresis is repeated daily in conjunction with chemotherapy until the blast count is $<$50,000.

DIAGNOSTIC EVALUATION

- History and physical examination are an essential part of diagnosis of acute leukemia.
- Complete blood count (CBC), differential and manual examination of peripheral smear, and peripheral blood flow cytometry are considered when circulating blasts are sufficiently abundant to establish a diagnosis.
- Coagulation tests include prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, and fibrinogen.
- Electrolytes with calcium, magnesium, phosphorus, and uric acid. Low glucose, potassium, and PO_2 (partial pressure of oxygen) can occur with delay in analysis of high blast count.
- Bone marrow biopsy and aspirate (with analysis for morphology), cytogenetics, flow cytometry, and cytochemical stains (Sudan black, myeloperoxidase, acid phosphatase, and specific and nonspecific esterase) are used for diagnosis.
- 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, cytomegalovirus, herpes simplex virus, human T-cell leukemia virus, 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 treatment with anthracyclines.
- Lumbar puncture: Performed when signs and symptoms of neurologic involvement are present. Low platelets should be corrected. The procedure may be performed after reduction of peripheral blast

count to avoid inoculation of blasts into uninvolved cerebrospinal fluid (CSF). Obtain cell count, opening pressure, and protein level, and submit cytocentrifuge specimen for cytology.
- Central venous access should be obtained. An implanted port-type catheter is not recommended. 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 testing of fluorescent in situ hybridization (FISH) assay for 15;17 translocation is performed when APL is suspected; and a BCR-ABL test is performed when CML in blast phase or ALL is suspected.
- Cytogenetic and gene mutation analysis of blasts will contribute dramatically to subsequent preferred management and prognosis.

INITIAL MANAGEMENT

The initial management of acute leukemia involves the following:

- Hydration with IV fluids (2 to 3 L/m^2 per day).
- Tumor lysis prophylaxis should be started.
- Blood product support suggestions for prophylactic transfusions are hemoglobin level <8 and platelet level $<10{,}000$. Platelet trigger threshold can be higher in the context of fever or bleeding ($<20{,}000$ suggested), cryoprecipitate can be used if fibrinogen level is <150, and fresh frozen plasma (FFP) can be used to correct significantly elevated levels of PT and PTT. Platelet trigger should be increased in APL patients to $<50{,}000$. The minimum "safe" platelet level required to prevent spontaneous hemorrhage is not known. Additional platelet optimization strategies include avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and clopidogrel-like agents.
- Blood products should be irradiated and a WBC filter (if CMV-negative blood inventory is not available) should be used in those patients who are future allogeneic transplant candidates.
- Fever and neutropenia require blood and urine cultures, followed by treatment with appropriate antibiotics (see Chapter 36), 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 is required.
- Suppression of menses: Medroxyprogesterone (Provera) 10 mg daily or twice daily.

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, phosphorus, and uric acid; with a resulting decrease in calcium.
- The patients should be initiated on allopurinol 300 mg twice daily for 3 days, followed by once daily until risk is resolved.
- For hydration, alkalinizing fluids (0.5 NS with 50 mEq sodium bicarbonate) could be considered to increase solubility of uric acid, minimizing intratubular precipitation. Caution should be taken since alkanizing the urine also promotes calcium–phosphate complex deposition, and considering the availability of uricolytic agents (rasburicase), alkalinization is typically not utilized.
- Rasburicase (Elitek) should be used if the patient has hyperuricemia and an elevated creatinine on presentation or has hyperuricemia uncontrolled with allopurinol. Prophylactic rasburicase is not necessary with proper uric acid monitoring, due to 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 38).

Table 23.2 The World Health Organization (WHO) and French–American–British (FAB) Classification of Acute Myeloid Leukemia

AML with recurrent genetic abnormalities
AML with t(8;21) (usually FAB M2)
AML with abnormal bone marrow eosinophils and inv(16) or t(16;16) (usually FAB M4Eo)
Acute promyelocytic leukemia with t(15;17) (FAB M3)
AML with 11q23 abnormalities
AML with multilineage dysplasia
Following MDS or myeloproliferative disorder
Without prior MDS but with dysplasia in 50% cells in two cell lines
AML and MDS, therapy related
Alkylating agent or radiation related
Topoisomerase II related
Others
AML not otherwise categorized
AML minimally differentiated (FAB M0)
AML without maturation (FAB M1)
AML with maturation (FAB M2)
Acute myelomonocytic leukemia (FAB M4)
Acute monocytic leukemia (FAB M5)
Acute erythroid leukemia (FAB M6)
Acute megakaryocytic leukemia (FAB M7)
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

AML, acute myelogenous leukemia; MDS, myelodysplasia.

CLASSIFICATION

Acute Myelogenous Leukemia

There are two current systems to classify AML. The most commonly used criterion is from the World Health Organization (WHO) and incorporates recurrent cytogenetic abnormalities and prognostic groups (Table 23.2). Marrow blasts should make up 20% of the nucleated cells within the aspirate unless t(8;21) or inv(16) is present. The FAB classification is also used and classifies AML into eight subtypes. 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, 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 in confirming the suspicion of this subtype requiring a specific induction therapy.

Acute Lymphoblastic Leukemia

The WHO classification of ALL divides the disease into precursor B-cell, precursor T-cell, and Burkitt-cell leukemia. Immunophenotyping of B-lineage ALL reveals lymphoid markers (CD19, CD20, CD10, TdT, and immunoglobulin). T-cell markers include TdT, CD2, CD3, CD4, CD5, and CD7. Burkitt-cell leukemia is characterized by a translocation between chromosome 8 (the *c-myc* gene) and chromosome 14 (immunoglobulin heavy chain), or chromosome 2 or 22 (light chain) regions.

Table 23.3 Cytogenetic Risk Groups in Treated Adult Acute Myelogenous Leukemia Cases

Favorable risk (5-y survival with therapy approximately 55%)
t(15;17)
inv(16), del(16q), t(16;16)
t(8;21) with or without complex karyotype and del(9q)
Standard risk (5-y survival with therapy approximately 25%)
No cytogenetic abnormality identified (i.e., normal)
All other cytogenetic abnormalities not associated with a specific prognosis
Poor risk (5-y survival with therapy approximately 5%)
−5, −7
inv(3) or t(3;3)
t(9;22)
11q23 (MLL) abnormalities, excluding t(9;11)
Three or more abnormalities
t(6;9)

PROGNOSTIC GROUPS

Acute Myelogenous Leukemia

Those patients who are older (>60 years) and those with an elevated blast count at diagnosis (>20,000) have a worse prognosis. Chemotherapy-related AML and prior history of myelodysplasia (MDS) impart a lower chance of obtaining complete remission (CR) and long-term survival. Table 23.3 illustrates the prognostic groups according to cytogenetics.

Acute Lymphoblastic Leukemia

As in AML, patients with ALL have a worse prognosis when presenting with advanced age or elevated WBC count. Burkitt-cell (mature B-cell) leukemia or lymphoma has an improved prognosis with intensive chemotherapy and CNS treatment; it usually has a translocation involving chromosome 8q24. Table 23.4 lists the prognostic groups according to cytogenetic analysis. The presence of t(9;22) (Philadelphia chromosome) is the most common abnormality in adults. It is present 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, and patients are recommended to undergo allogeneic transplantation if they are a suitable candidate in first CR.

TREATMENT

Acute Myelogenous Leukemia (Non–t(15;17) Acute Promyelocytic Leukemia)

The goal of induction chemotherapy is to obtain CR, which has been shown to correlate with improved survival. CR is the elimination of the malignant clone (marrow blasts <5%) and recovery

Table 23.4 Prognostic Groups in Adult Acute Lymphoblastic Leukemia

Poor Risk	Good Risk
t(9;22)	8q24 translocations
t(4;11)	t(12;21)
Hypodiploid	t(10;14)
t(1;19)	t(7;10)

Table 23.5 Standard Induction for Acute Myelogenous Leukemia

"7 + 3," 7 d of 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

of hematopoiesis (absolute neutrophil count [ANC] >1,000 and platelet count >100,000). 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 is essentially undetectable but will lead to relapse in weeks to months if more therapy is not administered. Additional intensive "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 CR. The general approach to induction chemotherapy for adults is shown in Table 23.5. Patients should be considered for clinical trials if available.

In general:

- Addition of high-dose cytarabine (HDAC) or etoposide has been evaluated in published regimens for induction that may benefit some patients younger than 60. These additions have not been demonstrated to be conclusively superior to 3 days of anthracycline and 7 days of cytarabine alone.
- Bone marrow aspiration should be repeated at approximately day 14. If significant residual blasts are present, induction chemotherapy should be repeated (consider "5 + 2" in Table 23.6). If significant disease is present (<50% reduction in disease volume), induction should be repeated or a change in the regimen to age-appropriate HDAC should be considered.
- Older (>60) patients may benefit from treatment. HDAC requires dose reduction due to CNS toxicity.
- Older patients or patients not fit for intensive induction chemotherapy (i.e., 7 + 3) may be candidates for therapy with azacitidine or decitabine. These hypomethylating agents have lower CR rates (approximately 20% to 30%) but are better tolerated than intensive therapies.

Supportive Care

- Infection is a major cause of morbidity and mortality. Prophylactic antibacterials (quinolones), antifungals (fluconazole or posaconazole), and antivirals (acyclovir) are typically given during these periods of prolonged neutropenia. Broad-spectrum antimicrobials are used for neutropenic fever (see Chapter 35).
- Growth factors such as granulocyte colony-stimulating factor (G-CSF) are associated with shortened length of neutropenia and are of demonstrated value in patients older than 55 years. Growth factors are not routinely recommended in younger patients but can be safely added if necessary. Initiation of G-CSF is delayed until after day 14, when bone marrow shows a satisfactory induction pattern. Growth factors may have the most benefit in those patients with infectious complications.
- Steroid eye drops are required during HDAC infusions to reduce risk of exfoliative keratitis.

Table 23.6 Consolidation of Acute Myelogenous 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 agent (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

Table 23.7 Treatment of Acute Promyelocytic Leukemia

Induction
ATRA + anthracycline (idarubicin or daunorubicin)
Addition of cytarabine should be considered in high-risk patients
Consolidation
ATRA + anthracycline × 3 cycles +/− cytarabine can be considered in high-risk patients
Or
Arsenic × 2 cycles followed by anthracycline × 2 cycles
Maintenance (2 y)
ATRA 45 mg/m^2 daily for 15 d q3mo
Mercaptopurine 50 mg/m^2 daily
MTX 15 mg/m^2 weekly

ATRA, all-trans retinoic acid; 6-MP, 6-mercaptopurine; MTX, methotrexate.

Acute Myelogenous Leukemia Consolidation, Non–t(15;17)

The consolidation options for those patients who enter CR are shown in Table 23.6. HDAC especially may benefit those patients with good-risk disease [t(8;21) or inv(16)]. These good-risk patients should not receive transplantation in CR1. Consolidation usually consists of four cycles (the minimum effective dose and number of cycles are not clear). Older patients do not seem to benefit from more than one to two consolidation cycles. Patients with preceding MDS or poor-risk cytogenetics should receive an allogeneic transplantation, if possible. Patients with standard-risk cytogenetics should be considered for an allogeneic transplant, especially if they have a matched sibling donor. Gene mutations may assist in the proper identification of standard-risk patients who would benefit from allogeneic transplant in CR1 (see the Allogeneic Transplant section).

Acute Promyelocytic Leukemia, 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 allowing abnormal accumulation within the marrow space. Because the characteristic translocation occurs in this subgroup of AML, therapy incorporates ATRA, which acts as a differentiating agent. Table 23.7 shows a treatment summary in APL.

- Therapy with ATRA should be started immediately upon suspicion of APL; therapy can be tailored pending genetic confirmation.
- Time to attain remission may be more than 30 days and a bone marrow biopsy is not performed on day 14.
- PCR should be followed for PML-RAR: Reinduction therapy should be considered if PCR is still positive postconsolidation; also, levels should be followed during the maintenance phase. A return of the transcript to positive heralds relapse.
- ATRA syndrome (retinoic acid 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 25% of patients during induction, with peak occurrences at 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 arsenic trioxide.
- 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.

- ATRA + arsenic trioxide is an alternative option for untreated patients unable to tolerate anthracyclines. Preliminary data show excellent outcomes with ATRA + arsenic when compared to standard anthracycline-containing regimens.

Relapsed Disease

- Arsenic trioxide 0.15 mg/kg/day 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.
  - Arsenic trioxide may be given as consolidation at a dose of 0.15 mg/kg/day, 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 Acute Myelogenous Leukemia

Relapse of AML after initial CR is very common (60% to 80% of all cases). Relapse occurring within 6 months of induction or a patient never attaining remission with induction (refractory disease) complicates many induction attempts. The prognosis for long-term survival in this subset of patients is very 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 HDAC.
  - Reinduction may be an option for those patients who relapse more than 6 to 12 months after 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 inhibitors may have activity (sorafenib, midostaurin, and quizartinib), but are currently investigational.
- 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 employed in many North American centers. The Larson regimen reported by Cancer and Leukemia Group B (CALGB) Study 9111, shown in Table 23.9, is also commonly employed. Other options based on the Hoelzer and Linker regimen are also available. Burkitt-cell leukemia (mature-B ALL, L3) can be treated with hyper-CVAD without maintenance therapy but requires aggressive CNS treatment to prevent relapse. Adolescent and young adult patients (age ≤40) with ALL should be treated with pediatric regimens.

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 (i.e., levofloxacin 500 mg daily, fluconazole 200 mg daily, and valacyclovir 500 mg daily).

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 days 1–3 (six doses)
Mesna 600 mg/m^2/d IV as continuous infusion days 1–3
Vincristine 2 mg IV days 4 and 11
Doxorubicin 50 mg/m^2 IV day 4
Dexamethasone 40 mg PO daily 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 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

G-CSF, granulocyte colony-stimulating factor; CNS, central nervous system; MTX, methotrexate.
[a]Dosing interval based on risk stratification (see text).
[b]Maintenance therapy is not given in Burkitt-cell leukemia/lymphoma.

Central Nervous System Disease

- 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 intrathecal (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 2,400 to 3,000 cGy) can also be considered, being aware of potential late-term cognitive toxicities.
- Prophylaxis decreases CNS relapse from 30% to <5%. The prophylactic chemotherapy schedule is dependent on the relapse risk.
- In the hyper-CVAD regimen, patients with high-risk disease (i.e., 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.

Table 23.9 The Larson Regimen

Course I: Induction (4 wk)
Cyclophosphamide 1,200 mg/m^2 IV day 1[a]
Daunorubicin 45 mg/m^2 IV days 1–3[a]
Vincristine 2 mg IV days 1, 8, 15, 22
Prednisone 60 mg/m^2/d PO days 1–21[a]
L-Asparaginase (*Escherichia coli*) 6,000 IU/m^2 SQ/IM days 5, 8, 11, 15, 18, 22
G-CSF 5 μg/kg/d SQ starting day 4
Course IIA (4 wk; repeat once for course IIB)
Methotrexate 15 mg intrathecal (IT) day 1
Cyclophosphamide 1,000 mg/m^2 IV day 1
6-Mercaptopurine 60 mg/m^2/d PO days 1–14
Cytarabine 75 mg/m^2/d SQ days 1–4 and 8–11
Vincristine 2 mg IV days 15 and 22 (two doses)
L-Asparaginase (*E. coli*) 6,000 IU/m^2 SQ/IM days 15, 18, 22, 25 (four doses)
G-CSF 5 μg/kg/d SQ starting day 2
Course III: CNS prophylaxis and interim maintenance (12 wk)
IT Methotrexate 15 mg days 1, 8, 15, 22, 29
Cranial irradiation 2,400 cGy (fractionated) days 1–12
6-Mercaptopurine 60 mg/m^2/d PO days 1–70
Methotrexate 20 mg/m^2 PO days 36, 43, 50, 57, 64
Course IV: Late intensification (8 wk)
Doxorubicin 30 mg/m^2 IV days 1, 8, 15
Vincristine 2 mg IV days 1, 8, 15
Dexamethasone 10 mg/m^2/d PO days 1–14
Cyclophosphamide 1,000 mg/m^2 IV day 29
6-Thioguanine 60 mg/m^2/d PO days 29–42
Cytarabine 75 mg/m^2/d SQ days 29–32 and 36–39
Course V: Prolonged maintenance (continue until 24 mo after diagnosis)
Vincristine 2 mg IV day 1 of every 4 wk
Prednisone 60 mg/m^2/d PO days 1–5 of every 4 wk
6-Mercaptopurine 60 mg/m^2/d PO days 1–28
Methotrexate 20 mg/m^2 PO days 1, 8, 15, 22

CNS, central nervous system.
[a]Dosage reductions for age >60 y: cyclophosphamide 800 mg/m^2 day 1, daunorubicin 30 mg/m^2 days 1–3, and prednisone 60 mg/m^2 days 1–7.

Relapsed Acute Lymphoblastic Leukemia

Marrow is the most common site of relapse, but relapse can occur in 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. Early relapse or refractory disease will require changing the treatment plan and evaluation for allogeneic transplantation. Several chemotherapy options are available, including

- HDAC with idarubicin, mitoxantrone, or fludarabine
- Methotrexate, vincristine, asparaginase (not PEG), steroids (MOAD)
- Imatinib, dasatinib, or nilotinib (if Ph positive)
- Hyper-CVAD, if not given initially
- Vinorelbine with mitoxantrone, fludarabine, steroids, or rituximab
- Nelarabine
- Clofarabine +/− cytarabine or cyclophosphamide
- Liposomal vincristine

- Investigational monoclonal antibody agents (blinatumomab, epratuzumab, inotuzumab, ozogamicin, etc.)

Use of Targeted Therapies in Acute Lymphoblastic Leukemia

1. Rituximab (Rituxan)
   - Anti-CD20 chimeric murine–human monoclonal antibody
   - Given in addition to the previously noted regimens in front-line treatment, if CD20+
2. Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib
   - Tyrosine kinase inhibitors targeting the Philadelphia chromosome [t(9;22)].
   - Imatinib should be considered in addition to previously noted regimens in front-line treatment, if Ph positive.
   - Role in maintenance therapy is unknown at this time, but could be considered.
   - May be used as treatment or palliation in patients unable to tolerate aggressive chemotherapy.
   - Choice of tyrosine kinase inhibitor agent should be selected based on BCR/ABL mutation analysis.

TRANSPLANTATION

Autologous Transplant

- Autologous transplant appears to have minimal benefit in acute leukemia in CR1.
- Autologous transplant could be considered for patients achieving CR2, without availability of an allogeneic donor.
- It may be performed in older patients (age >60).

Allogeneic Transplant

- 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.
- It is performed in the first CR or early in the course for those patients with poor-risk cytogenetics or transformation from MDS.
- Patients with good-risk AML [t(8;21), inv(16), or 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.
- Gene mutations may be able to help stratify intermediate-risk patients as poorer or more favorable outcome, assisting in the decision of the usefulness of transplantation in CR1. NPM1 and CEBPA mutations (without FLT3/ITD mutations) may have a good prognosis and may not benefit from transplant in CR1. FLT3 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.
- Nonmyeloablative transplantation is reasonable for those patients unable to proceed with ablative treatment secondary to age or comorbidities.
- BMT CTN 0901 currently ongoing evaluating the role of reduced-intensity conditioning compared to myeloablative preparative regimens for allogeneic transplant in patients with AML.

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 80% to 90% CR rate, and long-term disease-free survival is 60% to 70% in younger patients treated with HDAC. 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 where there are no cytogenetics that can guide therapy. In these patients, FLT3 mutations confer a poor prognosis. In patients who are FLT3 negative, NPM1 and CEBPA seem to be 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 Larson regimen, 85% obtained CR (39% older than 60 years). The hyper-CVAD course yielded a CR of 91% (79% for patients older than 60 years). Median duration of CR was 30 months with Larson regimen and was 33 months with hyper-CVAD. Five-year survival was approximately 40%.

REVIEW QUESTIONS

1. A 51-year-old man is newly diagnosed with AML with cytogenetics revealing a translocation (8;21). He has no other significant comorbidities and has a good performance status. What would be the most appropriate course of therapy for this patient?
   - **A.** Induction chemotherapy followed by four cycles of low-dose cytarabine therapy
   - **B.** Induction chemotherapy followed by four cycles of HDAC therapy
   - **C.** Induction chemotherapy followed by autologous hematopoietic cell transplant
   - **D.** Induction chemotherapy followed by allogeneic hematopoietic cell transplant
2. A 32-year-old female presents with bruising, fatigue, and persistent fevers for 2 weeks. Her WBC is 2,700, hemoglobin is 6.4, and platelets count is 16. Her fibrinogen is <70 and PT is elevated at 22 (INR 2.2). What should be the next step in the management of this patient?
   - **A.** Hydration and allopurinol
   - **B.** Urgent bone marrow biopsy and aspiration
   - **C.** Treatment with idarubicin or daunorubicin
   - **D.** Initiation of ATRA
3. A 59-year-old man is diagnosed with precurser B-cell ALL. He is found to be CD19 positive and CD20 negative. Cytogenetic analysis reveals a translocation 9;22 resulting in a BCR-ABL fusion gene. What targeted therapy should be added to his chemotherapeutic plan?
   - **A.** Rituximab
   - **B.** Imatinib
   - **C.** Alemtuzumab
   - **D.** Ofatumumab

Suggested Readings

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24

Chronic Lymphoid Leukemias

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Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the western world. Major advances in the management of CLL over the past decade resulting in an improved patient outcome include more accurate diagnostic techniques, validated prognostic studies, better supportive care, and improved treatment regimens. This chapter will focus on CLL and include information on two other chronic lymphoid malignancies, prolymphocytic leukemia (PLL) and hairy cell leukemia (HCL).

PRESENTATION AND DIAGNOSIS

The estimated incidence of CLL in the United States for 2012 was 16,060 cases. It tends to be a disease of the elderly, with a median age at diagnosis of 70 years. The disease affects men twice as more frequently than women. Although about half of the patients present with an asymptomatic lymphocytosis, symptoms typically associated with disease include recurrent infections and constitutional symptoms such as fatigue, weight loss, fevers, chills, and night sweats. Other clinical features include nontender lymphadenopathy, splenomegaly, autoimmune hemolytic anemia (AIHA), pure red cell aplasia, or immune-mediated thrombocytopenia.

According to guidelines published by the National Cancer Institute-Sponsored Working Group (NCI-WG), diagnostic criteria for CLL include the following:

- Absolute lymphocytosis ($\geq 5 \times 10^3/\mu L$), with a morphologically mature appearance, often with smudge cells.
- Monoclonal B-cell phenotype by flow cytometry: CD19, CD23, and CD5 with low levels of CD20 and surface immunoglobulin. Expression of CD38 and Zeta-associated protein-70 (ZAP-70) is not diagnostic for CLL, but has prognostic implications.
- 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. If a bone marrow biopsy is performed, the degree of lymphocytic involvement should be greater than 30% in order to confirm the diagnosis. 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 should be performed prior to and after treatment in order to evaluate for response.

Table 24.1 Staging and Prognosis of Chronic Lymphocytic Leukemia

Rai	Modified Rai	Criteria	Median Survival[a]
0	Low risk	Lymphocytosis only ($\geq 15 \times 10^3/\mu L$ in peripheral blood)	>10 y
1	Intermediate risk	Lymphocytosis with enlarged nodes	7 y
2	Intermediate risk	Lymphocytosis with increased splenic or hepatic size	
3	High risk	Lymphocytosis with anemia (Hgb ≤11 g/dL)	5 y
4	High risk	Lymphocytosis with thrombocytopenia ($\leq 100 \times 10^3/\mu L$)	

Hgb, hemoglobin.
[a]Survival as reported in the original publication.

STAGING AND PROGNOSIS

The most commonly used staging methods include the Rai, modified Rai, and the Binet staging systems. Prognosis based on the modified Rai staging system is outlined in Table 24.1. There are a number of prognostic factors for CLL. Those associated with an inferior outcome include the cytogenetic abnormalities detected by fluorescent in situ hybridization of deletion (del) 11q and del 17p, an elevated serum β-2-microglobulin level ≥4, unmutated immunoglobulin variable region heavy chain genes (IgVH), overexpression of the ZAP-70 >20%, expression of CD38 >30%, and advanced-stage disease. Trisomy 12 and normal cytogenetics are associated with an intermediate outcome, while del 13q is associated with a favorable outcome. The utility of these factors lies in prognosis and is usually not used to determine when to initiate treatment or the choice of regimen.

Computerized tomography (CT) is not required at diagnosis or for staging purposes, but may be useful to evaluate the presence of internal enlarged lymph nodes unable to be palpated by physical examination. Patients with clinical stage 0 disease, but stage I by CT, often behave more like the latter. Contrast-enhanced CT has a higher sensitivity of detecting CLL than PET/CT. At this time there is no role for positron emission tomography (PET) scanning in CLL, except to assess for a potential transformation to a high-grade lymphoma.

COMPLICATIONS

Patients with CLL can develop infections, high-grade transformation, and are at an increased risk for other malignancies. Hematologic complications include anemia or thrombocytopenia due to marrow involvement, treatment effect, splenic sequestration, AIHA, pure red cell aplasia, and immune-mediated thrombocytopenia. AIHA can be due to the CLL itself or to fludarabine, which is commonly used in the treatment of this disease. Pure red cell aplasia, although rare, is possibly caused by suppressor T cells. Cyclosporine may be effective with a reticulocyte response within a few weeks. Frequent infections, often sinopulmonary, are often related to immunosuppressive treatments, hypogammagobulinemia, inadequate humoral response, and impaired complement activation. Transformation to Richter syndrome (large B-cell lymphoma), PLL, ALL, and multiple myeloma occurs in 10% to 15% of cases. Patients are also at increased risk of developing other malignancies of sites such as the gastrointestinal tract, lung, and skin. Other chemotherapeutics, such as cyclophosphamide or chlorambucil, are associated with secondary malignancies such as AML and MDS.

TREATMENT

CLL often exhibits an indolent course, not requiring treatment at diagnosis. The indications for treatment of CLL per the NCI-Sponsored WG guidelines include the following:

- Significant and persistent fatigue
- Unintentional weight loss of ≥10% in previous 6 months
- Persistent fevers >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
- Autoimmune anemia or thrombocytopenia poorly responsive to steroids
- Progressive marrow failure with worsening or new anemia or thrombocytopenia
- Progressive splenomegaly (>6 cm below costal margin) or lymphadenopathy (>10 cm)
- Progressive lymphocytosis: Increase >50% in 2 months or doubling time <6 months

Chlorambucil was the mainstay of therapy for CLL until fludarabine (F) was found to be superior, with a survival advantage. Following demonstration of modest single-agent activity, combinations incorporating fludarabine with the chimeric anti-CD20 monoclonal antibody, rituximab (R) were developed with promising results. The combination of FR with or without cyclophosphamide (C) has demonstrated overall response rates (ORRs) of 90% to 95% (complete response [CR] 44% to 47%) with improved survival, and is a current standard of care for previously untreated CLL. The addition of cyclophosphamide appears to benefit the poor prognostic del 11q group; therefore, an alkylating agent should be incorporated into the treatment of these patients. Bendamustine was approved for the treatment of CLL based on superior response and progression-free survival (PFS) when compared to chlorambucil. A survival benefit was seen in patients who achieved a CR. The combination of bendamustine and rituximab (BR) in the front-line setting produced response rates similar to those previously reported with fludarabine-based regimens (ORR 88%, CR 23%), a more tolerable toxicity profile, and responses in traditionally poor-risk cytogenetic groups. The results of the GCLLSG CLL-10 study of BR versus FCR and the US Intergroup study of FR versus FCR versus FR followed by lenalidomide will help define the appropriate regimen for previously untreated patients. Chlorambucil alone or in combination with rituximab remains an option for patients who are unable to tolerate these regimens, producing responses in 31% to 37% with minimal toxicity. Single-agent rituximab is not recommended for CLL as it has minimal activity and a short duration of response.

In addition to rituximab, two other monoclonal antibodies are approved for the treatment of CLL. Alemtuzumab, a CD52 antibody, was approved based on results of a randomized phase III comparison to chlorambucil. In the front-line setting, alemtuzumab demonstrated an ORR of 83% (CR 24%) and median PFS of 14.6 months. Toxicities include severe opportunistic infections and infusion-related reactions, which are less severe with subcutaneous administration. Alemtuzumab is no longer commercially available. Ofatumumab is a CD20 antibody with a slightly different mechanism of action than rituximab. It was approved for fludarabine and alemtuzumab-refractory CLL based on an ORR of 58% (0% CR) and median OS of 14 months. Ofatumumab can be administered as a single agent or in combination with chemotherapy, but does not appear to provide an advantage over rituximab.

Despite the multiple effective treatment options for CLL, patients inevitably relapse and require additional therapy. Similar to indolent lymphomas, patients with relapsed CLL can be retreated with a prior regimen if a durable response was achieved. Selection of the optimal salvage treatment depends on age, performance status, prior treatment, adverse effects, duration of remission to prior therapy, and extent of disease. Options include purine nucleoside analogs, alkylating agents, monoclonal antibodies, stem cell transplantation, combination chemotherapy, and investigational treatments (Table 24.2). A number of biologic therapies have been designed to target the tumor microenvironment and intracellular signaling pathways that contribute to the pathogenesis of CLL. These include lenalidomide, an immunomodulatory agent, and several novel drugs that interfere with key pathways downstream from the activated B-cell receptor including ibrutinib (Bruton tyrosine kinase inhibitor), idelalisib (phosphatidylinositol 3-kinase inhibitor), and ABT-199 (selective BCL-2 inhibitor). At this time the only therapy that has been proven to be potentially curative in CLL is allogeneic stem cell transplantation. However,

Table 24.2 Therapy for Chronic Lymphocytic Leukemia

Therapy	Doses and Comments
Chlorambucil	40 mg/m² PO cycle 1 day 1 q4wk × 12 C; toxicity: myelosuppression 0.4 mg/kg with an increase to 0.8 mg/kg, q2 wk × 12 months
Fludarabine	25 mg/m² IV days 1–5 q4wk × 6 C; toxicity: myelosuppression, hemolytic anemia, and prolonged immunosuppression 40 mg/m² PO days 1–5 q4wks × 6 C
Bendamustine	100 mg/m² IV days 1–2 q4wk; toxicity: myelosuppression
Alemtuzumab	Escalated from 3 to 10 to 30 mg/d as tolerated, continue at 30 mg SC or IV three times a week for 12–16 wk; toxicity: infections and myelosuppression; prophylaxis for PCP and CMV
Rituximab	375 mg/m² IV qwk for 4 wk; toxicity: infusion reaction
Ofatumumab	300 mg IV wk 1, then 2,000 mg IV qwk for 7 wk, then 2,000 mg IV q4wk for 4 doses; toxicity: infusion reaction
Combination therapy	FR: fludarabine 25 mg/m² IV days 1–5, rituximab 375 mg/m² IV day 1; q4wk × 6 C FCR: cycle 1: fludarabine 25 mg/m² IV days 2–4, cyclophosphamide 250 mg/m² IV days 2–4, rituximab 375 mg/m² day 1; cycles 2–6: fludarabine 25 mg/m² IV days 1–3, cyclophosphamide 250 mg/m² IV days 1–3, rituximab 500 mg/m² day 1; q4wk × 6 C BR: front-line: bendamustine 90 mg/m² days 1–2, rituximab 375 mg/m² day 1 for cycle 1 and 500 mg/m² of cycles 2–6 BR: relapsed/refractory: bendamustine 70 mg/m² day 1, rituximab 375 mg/m² day 1 for cycle 1 and 500 mg/m² of cycles 2–6 R-Clb: Clb 8 mg/m²/day PO C 1–8 days 1–7, R 375 mg/m² cycle 3 day 1 and 500 mg/m² C 4–8 day 1 q4wk for a total of 8 C
Stem cell transplantation	Patients with multiple relapses; relapsed younger del 17p patients. Allogeneic transplantation with nonmyeloablative approaches allow older patients and patients with comorbidities to undergo transplant; toxicities: opportunistic infections and GVHD
Investigational	Lenalidomide, idelalisib, ibrutinib, ABT-199

CLL, chronic lymphocytic leukemia; PCP, pneumocystis jiveruci; CMV, cytomegalovirus; IV, intravenously; SC, subcutaneously; PO, by mouth; d, day; C, cycle; del, deletion.

this is often not an option for the elderly population that CLL typically affects or patients with multiple comorbidities.

While receiving therapy patients with white blood cell counts >50,000/μL and/or bulky disease should receive tumor lysis prophylaxis with allopurinol and aggressive hydration. Patients receiving bendamustine should not receive allopurinol, given the risk of severe rash and Stevens-Johnson syndrome. Antimicrobial prophylaxis against pneumocystis jiveruci, varicella zoster, and fungi should be considered for each patient based on their functional immune status.

OTHER CHRONIC LYMPHOID LEUKEMIAS

Other rare lymphoid malignancies include PLL (Table 24.3) and HCL (Table 24.4). PLL presents similarly to CLL, and can be of either T-cell or B-cell origin. PLL typically presents with >90% circulating prolymphocytes, whereas CLL has <55% prolymphocytes. PLL can occur de novo or rarely, from CLL, and has a poorer prognosis. HCL is a de novo process. It is highly treatable with cladribine, pentostatin, α-interferon, and rituximab.

Table 24.3 Prolymphocytic Leukemia

Clinical findings	Hepatosplenomegaly; very high lymphocyte count; patients with T-PLL may have pleural effusion and skin lesions
Clinical course	B-PLL: variable course; indolent in some, while others with anemia, thrombocytopenia, and a high lymphocyte count have a shorter survival T-PLL: more aggressive than B-PLL or CLL
Morphology	Large cells with abundant cytoplasm and prominent nucleolus within a convoluted nucleus with immature chromatin
Phenotypic features	B-PLL: surface expression of CD19, CD20, CD22, CD79a, FMC 7, bright IgM, and/or IgD; occasional ZAP-70, CD38, CD5, CD23, negative for CD11c, CD103, cyclin D1 T-PLL: surface expression of CD52, CD2, CD3, CD5, CD7, occasionally CD4 and/or CD8; rearrangement of the T-cell–receptor gene
Treatment	B-PLL: anecdotal reports of treatment with nucleoside analogs and monoclonal antibodies T-PLL: alemtuzumab, pentostatin, allogeneic stem cell transplantation for patients who achieve a CR and are eligible

CLL, chronic lymphocytic leukemia; B-PLL, B-cell prolymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia; sIg, surface immunoglobulin.

Table 24.4 Hairy Cell Leukemia

Clinical findings	Male predominance, pancytopenia, splenomegaly, B symptoms, infections Less often: lymphadenopathy, necrotizing vasculitis, lytic bone abnormalities, effusions
Morphology	Lymphocytes with cytoplasmic projections, TRAP-stain positive
Bone marrow	Aspiration frequently unsuccessful, "dry tap" secondary to fibrosis; marrow biopsy reveals "hairy" cells and classic "fried-egg" appearance
Immunology	CD11c, CD20, CD25, CD103, and CD123
Treatment indications	Symptomatic splenomegaly or lymphadenopathy, neutropenia ($<1.0 \times 10^9$/mL) with repeated infections, symptomatic anemia (Hgb <11 g/dL), bleeding due to thrombocytopenia ($<100 \times 10^9$/mL), constitutional symptoms
Treatment	*First-line* Cladribine: RR: 80–95%, dose: 0.1 mg/kg/d by CIV days 1–7 Pentostatin: RR: 75–80%, dose: 4 mg/m^2 IV q2wk for 3–6 mo *Relapsed/recurrent disease* Retreatment with nucleoside analogs Interferon-α; RR: 75–90%, dose: 2 million units/m^2 SC three times/wk Splenectomy is reserved for those with symptomatic splenomegaly, pancytopenia despite other chemotherapeutics, and as a temporizing measure in symptomatic pregnant women Rituximab RR: 24–80%, dose: 375 mg/m^2 IV qwk for four doses *Investigational* BL22, anti-CD22 monoclonal antibody linked to pseudomonas exotoxin A, RR 72% (CR 47%) in cladribine-refractory patients

TRAP, tartrate-resistant acid phosphatase; sIg, surface immunoglobulin; Hgb, hemoglobin; CIV, continuous intravenous infusion; RR, response rate; CR, complete response.

REVIEW QUESTIONS

1. An 83-year-old gentleman presents to the emergency department at the direction of his primary care physician who noted abnormalities in his blood work on routine evaluation. He denies any fevers, night sweats, infections, fatigue, or bleeding. His labs are notable for a hemoglobin of 10 g/dL, platelet count of 120 $\times$ 10^3/mm^3, and white blood cell count of 50 $\times$ 10^3/mm^3 with 60% lymphocytes. His chemistry profile is normal, and his peripheral smear is notable for several small mature lymphocytes and scattered smudge cells. You suspect a diagnosis of CLL. Which of the following characteristics are associated with a favorable prognosis?

A. Expression of CD38
B. Unmutated immunoglobulin variable region heavy chain
C. Trisomy 12
D. Del 13q

2. A 55-year-old female with Rai stage I CLL whom you have been following with a watch and wait strategy for 2 years presents for a follow-up with complaints of increasing fatigue over the past month. She has no other medical problems and her vital signs are normal. She denies any bleeding and has no evidence of bruising or hematomas on examination. Her labs are notable for a hemoglobin of 7 g/dL, platelet count of 140 $\times$ 10^3/mm^3, and white blood cell count of 75 $\times$ 10^3/mm^3 with 50% lymphocytes. Her chemistry profile is normal except for an elevated indirect bilirubin and a mild increase in the LDH. What is the most appropriate treatment for this patient at this time?

A. Transfusion of packed red blood cells
B. Fludarabine-based chemotherapy regimen
C. Corticosteroid therapy
D. Single-agent rituximab

3. After completing six cycles of fludarabine, cyclophosphamide, and rituximab, your 50-year-old male patient with Rai stage III CLL (trisomy 12 positive) achieves a complete remission. Five years after completing therapy he develops worsening anemia and thrombocytopenia. His labs are notable for a white blood cell count of 8 $\times$ 10^3/mm^3, hemoglobin of 8 g/dL, and platelet count of 90 $\times$ 10^3/mm^3. You perform a bone marrow biopsy for further investigation that reveals myelodysplastic syndrome. What is the most common cause of this complication in your patient?

A. Prior exposure to fludarabine
B. Prior exposure to cyclophosphamide
C. Prior exposure to rituximab
D. CLL which in itself is associated with other malignancies

Suggested Readings

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Chronic Myeloid Leukemia

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EPIDEMIOLOGY

Chronic myeloid leukemia accounts for 20% of newly diagnosed leukemia in adults, and was likely first described in Europe during the 1840s as reviewed by Geary and Deininger.[9] The incidence of chronic myeloid leukemia (CML) is 1 to 2 cases per 100,000, with a median age at diagnosis of 65 years, although the disease can be seen in all age groups. The average person's lifetime risk of being diagnosed with CML is about 1 in 625, and over half of cases are diagnosed in people 65 and older.

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)], characterized as the Philadelphia (Ph) chromosome, is the hallmark of CML. This translocation results in the transfer of the Ableson (ABL) gene on chromosome 9 to an area of chromosome 22 termed the breakpoint cluster region, resulting in the BCR-ABL fusion gene. This fusion gene results in the expression of the constitutively active protein tyrosine kinase, BCR-ABL1, which plays the major role in the pathogenesis of CML. The Ph chromosome is present in more than 90% of CML patients, and the majority express the 210 kDa oncoprotein, while less than 10% express either the 190 kDa oncoprotein. The different-molecular-weight isoforms are generated due to different breakpoints and mRNA splicing. It is likely that clonal evolution plays a role in blastic progression and the most common gross cytogenetic abnormalities associated with CML blast crisis include duplication of the Ph chromosome, trisomy 8, and isochromosome 17.

DIAGNOSIS AND CLINICAL FEATURES

Symptoms and Signs

- Frequently patients in chronic phase (CP) are asymptomatic.
- Fatigue
- Anorexia and weight loss
- Sweats and low-grade fever
- Left upper quadrant discomfort/early satiety associated with splenomegaly
- Dyspnea on exertion

Laboratory Features

The diagnosis of CML may be accomplished with peripheral blood. An elevated white blood cell count with a left shift, basophilia, and thrombocytosis in up to 50% of patients is suggestive of CML. Although identification of Ph chromosome on cytogenetic analysis or the detection of BCR-ABL fusion transcript by polymerase chain reaction (PCR) in peripheral blood can be done, a bone marrow aspiration and cytogenetic analysis are necessary for staging of the disease as well as to identify clonal evolution at the time of diagnosis or in the future. The absolute value of the transcript level is not important in staging but it is essential for subsequent evaluation of response.

Differential Diagnosis

- Leukoerythroblastic reaction in response to infection, inflammation, or malignancy
- Chronic myelomonocytic leukemia
- Atypical CML
- Idiopathic myelofibrosis
- Essential thrombocytosis
- Polycythemia vera

STAGING AND PROGNOSTIC FACTORS

CML normally progresses through three distinct clinical phases (Table 25.1), and while 90% of patients are diagnosed in the more indolent period termed chronic phase (CP), it is followed by an accelerated phase (AP), and then an aggressive blastic phase (BP). Often this progression is over years but the period between phases can be extremely variable. Twenty to 25% of patients can progress directly from CP to BP, which is characterized by ≥30% blasts in the bone marrow or peripheral blood, or the development of extramedullary disease outside of the spleen. Risk stratification scores are commonly used for patients in CP. The Sokal and Hasford risk scores are derived from patients treated with conventional chemotherapy or recombinant interferon alpha (rIFNα), and use clinical and laboratory features at diagnosis such as age, spleen size, platelet count, and blast percentage in peripheral blood (Table 25.2). The Sokal score has been shown to correlate with response to imatinib mesylate (IM), with event-free survival (EFS) and has been shown to be more consistently predictive of outcome. According to the 5-year data from the IRIS trial (International Randomized Study of Interferon vs. STI571),

Table 25.1 WHO Criteria for Chronic Myeloid Leukemia Stages

Stage	Features
Chronic phase	Blast cells in blood or marrow <10%
	Basophils in blood <20%
	Platelets >100 × 10^9/L
Accelerated phase	Blast cells in blood or marrow 10–19%
	Basophils in blood 20% or more
	Persistent thrombocytopenia unrelated to therapy
	Thrombocytosis unresponsive to therapy
	Progressive splenomegaly and increasing WBC count unresponsive to therapy
	Cytogenetic evidence of clonal evolution
Blastic phase	Blast cells in blood or bone marrow ≥20%
	Extramedullary blast proliferation
	Large foci or clusters of blasts in the bone marrow biopsy

From Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* 2002;100:2292-2302.

Table 25.2 Sokal and Hasford Risk Indexes

Risk Category	Risk Index	Median Survival
Sokal		
Low	<0.8	5 y
Intermediate	0.8–1.2	3.5 y
High	>1.2	2.5 y
Hasford		
Low	≤780	98 mo
Intermediate	781–1,480	65 mo
High	>1,480	42 mo

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.

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 ≥ 1,500 × 10^9/L) + 0.0584 × myeloblasts + 0.2039 (when basophils ≥3%) + 0.0413 × eosinophils (%)] × 1,000.

overall survival (OS) at 54 months was 94%, 88%, and 81% for low, intermediate, and high Sokal risk patients, respectively ($P < 0.01$). More recently the EUTOS score has been developed based on spleen size and basophils; however, its significance has not been determined. Additional cytogenetic abnormalities develop in over 80% of patients in the accelerated and blast crisis phases, most commonly trisomy 8, trisomy 19, duplication of the Ph chromosome, and isochromosome 17q. The appearance of clonal evolution confers a worse prognosis (Table 25.3).

TREATMENT

In the past treatment options for CML included conventional cytotoxic chemotherapy with hydroxyurea and busulfan, interferon α, with allogeneic hematopoietic stem cell transplantation being the only potentially curative option. In the last decade tyrosine kinase inhibitors (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 mainstay of CML therapy is now IM, and second-generation TKIs such as nilotinib and dasatinib, and more recently ponatinib. These newer agents can overcome genetic mutations that previously caused TKI resistance as well as lead to quicker and deeper molecular remission when compared to IM.[4] Omacetaxine, a subcutaneously bioavailable semisynthetic form of homoharringtonine, was recently approved for treatment in TKI-resistant patients.

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;

Table 25.3 Prognostic Factors

Disease phase at diagnosis
Prognostic scores in early disease phase (Hasford and Sokal risk indexes)
Cytogenetic changes during disease course
Degree and timing of hematologic, cytogenetic, and molecular response to treatment

From Baccarani M, Castagnetti F, Gugliotta G, Palandri F, Soverini S. Response definitions and European Leukemianet Management recommendations. *Best Pract Res Clin Hematol*. 2009;22:331–341.

however, it does not alter disease course. Allopurinol may be added to prevent tumor lysis syndrome when starting hydroxyurea.

Interferon

Recombinant IFNα-based regimens were the standard therapy for chronic-phase CML before the discovery of IM, and while effective and even curative in some patients, they had significant adverse effects that greatly impaired quality of life and adherence to treatment. Follow-up for large studies of rIFNα showed 9- or 10-year OS between 27% and 53%.

Tyrosine Kinase Inhibitors

Imatinib Mesylate

With the advent of IM, CML set the bar for how malignancy could be effectively treated with targeted therapy, and ushered in a new era of research in this field. IM is a phenylaminopyrimidine derivative that inhibits the BCR-ABL tyrosine kinase by competitive binding at the ATP-binding site. Although active in all phases of CML, the most durable responses are seen in newly diagnosed patients in CP. Results of the pivotal IRIS trial established the superiority of IM, and at 8-year follow-up, the estimated EFS was 81%, freedom from progression to CML-AP or CML-BP 92%, and OS 85%. When only CML-related deaths were considered, OS reached 93%. An estimated 7% of patients progressed to accelerated-phase CML or blast crisis. As a result, IM 400 mg daily was established as the standard of care for patients with newly diagnosed chronic-phase CML. The most common adverse events seen with IM are skin rash, muscle cramps, myelosuppression, diarrhea, and liver function test abnormalities.

The high rate of complete cytogenetic response with IM has shifted the goal of therapy to achieving molecular responses measured by PCR. Response criteria are summarized in Table 25.4. Duration of remission and survival are related to the depth of clinical response achieved. As more information has become available, the responses to TKI therapy have become the most important marker of overall prognosis. This makes molecular monitoring an essential component of CML management. More recently monitoring schema have become available that help to determine when a second-generation TKI would be appropriate as well as timing to refer for allogeneic stem cell transplant. If there is suboptimal response to IM, then the options remaining are to increase IM dose, change to a second-generation TKI, or proceed to allogeneic transplant. At this time there are no data favoring one option over another although the failure of IM predicts for poorer prognosis. Most experts would refer patients for stem cell transplant evaluation after suboptimal response to 2 TKIs. The response schema proposed by Baccarani et al. is summarized in Table 25.5.

Second-Generation Tyrosine Kinase Inhibitors

Second-generation TKIs include dasatinib, nilotinib, and bosutinib that are more potent than IM. Dasatinib is approved by the U.S. Food and Drug Administration. Presently there are experts who

Table 25.4 Response Criteria

Complete hematologic response (CHR)	WBC $< 10 \times 10^9$/L No immature granulocytes Less than 5% basophils, Platelets $<450\times 10^9$/L Spleen nonpalpable
Complete cytogenetic response (CCgR)	No Ph+ metaphases
Partial cytogenetic response (PCgR)	1–35% Ph+ metaphases
Minor cytogenetic response (mCgR)	36–65% Ph+ metaphases
Minimal cytogenetic response (minCgR)	66–94% Ph+ metaphases
No cytogenetic response (NoCgR)	≥95% Ph+ metaphases
Major molecular response (MMolR)	BCR-ABL:ABL ≤0.1% on the International scale
Complete molecular response (CMolR)	BCR-ABL transcript undetectable by RT-Q-PCR

Table 25.5 Definition of the response to treatment with IM, early chronic phase, frontline

	Warnings	Failure	Suboptimal Response	Optimal Response
Baseline	– Hematologic resistance to IM – Clonal abnormalities in Ph+ cells – Mutations			
3 Mo	Minimal CgR (Ph+ 66–95%)	– No CgR – New mutations	Minor CgR (Ph+ 36–65%)	At least PCgR (Ph+ <35%)
6 Mo	Minor CgR (Ph+ 36–65%)	– Minimal CgR (Ph+ 66–95%) – New mutations	PCgR (Ph+ 1−35%)	CCgR
12 Mo		– Less than PCgR (Ph+ >35%) – New mutations	Less than MMolR	MMolR

The response is assessed based on the time and the loss of hematologic, cytogenetic and molecular responses, and on the detection of BCR-ABL mutations.

From Baccarani M, Castagnetti F, Gugliotta G, Palandri F, Soverini S. Response definitions and European Leukemianet Management recommendations. *Best Pract Res Clin Hematol*. 2009;22:331–341.

would advocate starting therapy with a second-generation TKI as the rate of complete cytogenetic response is significantly improved, with rates of more than 90% and very low rates of transformation in the first 2 to 3 years, the years with the greatest risk of transformation. For patients who are diagnosed in AP or BP, a second-generation TKI followed by allogeneic transplant is the standard recommendation. There are several third-generation TKIs in the pipeline. These agents have activity against the BCR-ABL/T315I mutation that is mainly responsible for resistance to IM and second-generation TKIs. Recently ponatinib was approved by the FDA for use in patients failing second-generation TKIs or with the BCR-ABL/T315I mutation. As more information is gathered regarding mutational status, better decisions can be made on the optimal TKI selection for CP patients. Currently, mutational status is checked at the time of failure of initial TKI therapy; however, the argument can be made that ascertaining mutational status at diagnosis leads to a decreased rate of failure and hence a better durable response by choosing the right TKI while the disease is at its earliest stage. This is the topic of ongoing clinical trials.

Omacetaxine

Homoharringtonine is a natural alkaloid that is obtained from various Cephalotaxus species and its mechanism of action is through inhibition of protein synthesis and promotion of apoptosis. Its semisynthetic form, omacetaxine, has been shown to have benefit in IM-resistant CML as well as those patients who have the T315I mutation. In an open-label registration study, omacetaxine resulted in an overall hematologic response of 80% in CP patients, 45% in AP patients, and 13% in BP where all patients had failed at least 2 TKIs. The cytogenetic remission rate was 28% in CP patients with a median duration of response of >11 months. Its most frequent grade 3/4 toxicities were thrombocytopenia, neutropenia, anemia, and diarrhea. Ongoing studies will determine the activity of this agent in patients who have resistance to more than 1 TKI.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation has been shown as a potentially curative treatment for CML and is still the most viable treatment option for patients diagnosed in AP, in BP, or with known resistance mutations against TKIs. CML is a disease in which graft versus leukemia plays an important role and there are extensive reports of the use of donor lymphocyte infusions leading to durable complete

remissions. An analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) data reported outcomes on 2,444 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 a matched general population, these patients had a 2.5 times higher risk of death at 10 years due to complications such as organ failure, infection, graft versus host disease, relapsed disease, and secondary malignancies. However, mortality rates approached that of the general public at 15 years post–allogeneic transplant for those who survived. Goldman et al., J Clin Oncol. Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. 2010 Apr 10;28(11):1888-95. doi: 10.1200/JCO.2009.26.7757.

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 the recent past, advances with alternative donor sources have made it possible to offer transplants to minorities that previously were unable to find a matched unrelated donor. Interestingly, patients who were resistant to TKIs prior to transplant have been found to be responsive posttransplant and a number of studies continue to look into how to incorporate TKIs into the transplant paradigm.

Summary

IM 400 mg daily is the standard treatment for newly diagnosed chronic-phase CML, if mutational status is unknown. If IM fails or response is less than optimal, dose escalation of IM, second-generation TKIs, allogeneic stem cell transplantation, or a clinical trial with investigational agents are alternatives. For patients with known T315I mutations, ponatinib should be the TKI of choice. For patients who present with accelerated-phase CML, starting treatment with second-generation TKIs followed by allogeneic stem cell transplantation, or clinical trials can be considered. Allogeneic stem cell transplantation after second-generation TKIs and induction chemotherapy or clinical trials can be considered for patients diagnosed in BP.

REVIEW QUESTIONS

A 37-year-old Hispanic gentleman presents to his physician with 25 lb weight loss, profound fatigue, and lower extremity edema. On labs he was found to have a white blood cell count of 500 K/μL with a normal hemoglobin and platelet count, and on examination he had significant splenomegaly. He was started on hydroxyurea for cytoreduction and bone marrow biopsy was done. His bone marrow was consistent with CML in CP with no blasts, and cytogenetics showed Ph chromosome in 10 metaphases. His BCR-ABL quantitative PCR was 12.12%. After 3 months of therapy his PCR was stable, he had hematologic response with normal counts, and his next bone marrow biopsy revealed CML in CP with no blasts, and cytogenetics showed trisomy 8 in a Ph-negative clone in 10 metaphases and Ph chromosome in 10 metaphases. Mutation analysis reveals a new T315I mutation.

1. Based on the Baccarani score what would his response be characterized as?
   - **A.** Optimal
   - **B.** Suboptimal
   - **C.** Failure
2. What is the next step in management?
   - **A.** Switch to dasatinib and check PCR in 1 month; if rising, then double the dose of dasatinib.
   - **B.** Switch to ponatinib and check PCR in 3 months, and check another bone marrow in 1 month.
   - **C.** Admit to inpatient service and start cytotoxic chemotherapy with idarubicin and cytarabine and check for potential donors in order to proceed to allogeneic stem cell transplant.
   - **D.** Switch to ponatinib and check PCR in 1 month and check for potential donors in order to proceed to allogeneic stem cell transplant.

Suggested Readings

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26

Chronic Myeloproliferative Neoplasms

Yogen Saunthararajah

Chronic myeloproliferative neoplasms (MPNs) are clonal diseases 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):

1. Chronic myelogenous leukemia (CML), BCR-ABL positive
2. Chronic neutrophilic leukemia
3. Polycythemia vera (PV)
4. Primary myelofibrosis (MF)
5. Essential thrombocythemia (ET)
6. Chronic eosinophilic leukemia, not otherwise specified
7. Mastocytosis
8. MPNs, 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 MF. These three neoplasms share clinical characteristics, including propensities to thrombosis and hemorrhage, splenomegaly, debilitating systemic symptoms, cytopenias of some lineages, 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. Common biologic strands are revealed also by evolution of both PV and ET into MF 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. Inactivating mutations in *EZH2* (a polycomb repressor

Table 26.1 The 2008 World Health Organization Classification Scheme for Myeloid Neoplasms

1. Acute myeloid leukemia
2. Myelodysplastic syndrome (MDS)
3. Myeloproliferative neoplasms (MPN)
   - 3.1 Chronic myeloid leukemia
   - 3.2 Polycythemia vera
   - 3.3 Essential thrombocythemia
   - 3.4 Primary myelofibrosis
   - 3.5 Chronic neutrophilic leukemia
   - 3.6 Chronic eosinophilic leukemia
   - 3.7 Mast cell disease
   - 3.8 MPNs unclassifiable
4. MDS/MPN
   - 4.1 Chronic myelomonocytic leukemia
   - 4.2 Juvenile myelomonocytic leukemia
   - 4.3 Atypical chronic myeloid leukemia, BCR-ABL negative
   - 4.4 MDS/MPN unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of *PDGFRA, PDGFRB, or FGFR1*
   - 5.1 Myeloid neoplasms associated with *PDGFRA* rearrangement
   - 5.2 Myeloid neoplasms associated with *PDGFRB* rearrangement
   - 5.3 Myeloid neoplasms associated with *FGFR1* rearrangement (8p11 myeloproliferative syndrome)

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 MF, and interestingly, with transformation of PV or ET into MF. Thus, the improving knowledge regarding the molecular basis of MPNs is useful for diagnosis and prognosis (Table 26.2), and hopefully increasingly useful in guiding therapy. Testing for the *JAK2* V617F mutation by different techniques (PCR, restriction enzyme digestive pyrosequencing) is sensitive and specific, and readily available as a diagnostic tool.

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). Distinctive clinical features relate to these lineage changes and splenomegaly.

- Increased red blood cell (RBC) mass and thus viscosity in PV can produce symptoms such as 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.
- 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 be seen in MF but also in the other MPNs.

As outlined earlier, there is overlap in the molecular underpinnings of MPNs, and thus, not surprisingly, in clinical behaviors. Nonetheless, the various MPN classifications do have differing risks and prognoses; thus, the diagnostic approach prioritizes not mistakenly classifying an MPN into a category with less urgent prognostic or treatment implications. Accordingly, ET is diagnosed after excluding PV, and MF is diagnosed after excluding PV and ET (because marrow fibrosis can be a sequela of the other MPNs with their greater thrombo-hemorrhagic implications). CML should be ruled out by performing a fluorescence in situ hybridization (FISH) analysis for *BCR-ABL* in *JAK2* mutation-negative thrombocytosis or bone

Table 26.2 WHO Diagnostic Criteria for Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (MF)

	PV (Requires 2 Major and 1 Minor, or 1 Major and 2 Minor Criteria)	ET (Requires All 4 Criteria)	MF (Requires All 3 Major and 1 Minor Criteria)
Major criteria	– Hgb >18.5 g/dL (men) >16.5 g/dL (women) OR Hgb or Hct >99th percentile of reference range for age, sex OR altitude of residence OR Hgb >17 g/dL (men) or >15 g/dL (women) if associated with a sustained increase of >2 g/dL from baseline that cannot be attributed to correction of iron deficiency OR elevated red cell mass >25% above mean predicted value – Presence of *JAK2* mutation	– Sustained platelet count ≥450 × 10^9/L – Megakaryocyte proliferation with large and mature morphology; no granulocyte or erythroid proliferation. – Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasms – Presence of *JAK2* mutation OR in the absence of this mutation, no evidence of reactive thrombocytosis	– Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis, OR in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation, and often-decreased erythropoiesis – Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasms. – Presence of *JAK2* mutation or other clonal markers OR in the absence of clonal markers, no evidence marrow fibrosis that is secondary to some other cause such as infection, autoimmune disorder, etc.
Minor criteria	– Hypercellular for age with trilineage hyperproliferation – Subnormal serum EPO level – Endogenous erythroid colony growth		– Leukoerythroblastosis – Increased serum LDH – Anemia – Palpable splenomegaly

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 is recommended, 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 1,638 patients with PV, the 5-year event-free survival was 82%, with a relatively low risk of death

Table 26.3 Distinguishing Clinical Features of the Myeloproliferative Neoplasms

	CML	PV	ET	MF
Hematocrit	N or ↓	↑↑	N	↓
WBC count	↑↑↑	↑	N	↑ or ↓
Platelet count	↑ or ↓	↑	↑↑↑	↑ or
Splenomegaly	++++	+	+	++++
Cytogenetic abnormality	Ph chromosome	±	−	±
LAP score[a]	↓	↑↑	N or ↑	N or ↑
Marrow fibrosis	±	± or ↓	±	++++ (Dry tap)
Marrow cellularity	↑↑↑ Myeloid	↑↑	↑↑ Megakaryocytes	N or ↓
Basophils ≥2%	+	±	±	Usually +

CML, chronic myeloid leukemia; PV, polycythemia vera; ET, essential thrombocytopenia; MF, myelofibrosis; N, normal; WBC, white blood cell; LAP, leukocyte alkaline phosphatase; MPN, myeloproliferative neoplasm.
[a]See Chapter 25.

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 1,638 patients with PV prospectively followed in the 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%, respectively, at 10 and 20 years from diagnosis.
- 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 MF

Both PV and ET may progress to post-PV MF or post-ET MF, previously referred to as the spent phase, which clinically resembles primary MF and is characterized by progressive cytopenias, splenomegaly, and marrow fibrosis. The cumulative rate of transformation is 5% and 10% at 10 years 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. Surgery should be avoided in patients until a hematocrit <45% has been maintained for more than 2 months.
- In ET, age over 60 years and the presence of other cardiovascular risk factors (e.g., 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 $>2 \times 10^6/\mu L$ is a risk factor for hemorrhage (please also see recommendations regarding treatment).

TREATMENT

As a general principle, treatment for PV, ET, MF, or overlaps thereof is aimed at (i) alleviating the particular symptoms present in the individual patient (e.g., symptoms from splenomegaly, or symptoms from cytopenia) and (ii) anticipating and preventing potential life-threatening complications such as thrombosis or hemorrhage. Bone marrow transplantation is a potentially curative option that should be considered for some patients with MF. Following is a definition of risk categories and recommended treatments, with an overview provided in Table 26.4.

Polycythemia Vera

- Low risk: Age <60 years with no personal history of vascular events and who do not have additional risk factors for cardiovascular disease. Recommended treatment: phlebotomy alone with or without low-dose aspirin.
- Intermediate risk: Age <60 years with no personal history of vascular events and who do have additional cardiovascular risk factors. Recommended treatment: phlebotomy alone is adequate therapy; use of low-dose aspirin is encouraged.
- High risk: Age ≥60 years with a positive history of thrombosis. Recommended treatment: HU (with or without concomitant phlebotomy) and low-dose aspirin.

Maintaining a hematocrit <45% dramatically decreases the incidence of thrombotic complications. This is important, since in PV, 35% of initial thrombotic events are fatal. A randomized study of 518 patients with PV has shown that treatment with low-dose aspirin (100 mg per day) lowers the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table 26.4 Current Management Depending on Risk Stratification in PV, ET, and MF

Risk Category	PV	ET	MF age <50	MF age >50
Low	Low-dose aspirin + phlebotomy	Observation or low-dose aspirin	Individualize per predominant symptoms (e.g., anemia, splenomegaly, constitutional) Consider experimental drug therapy or allotransplant, especially in higher risk patients	Individualize per predominant symptoms (e.g., anemia, splenomegaly, constitutional) Consider experimental drug therapy or allotransplant, especially in higher risk patients
Intermediate		Low-dose aspirin		
High	Low-dose aspirin + phlebotomy + hydroxyurea	Low-dose aspirin + hydroxyurea		

PV, polycythemia vera; ET, essential thrombocytopenia; MF, myelofibrosis.

- Post-PV/ET MF: Options to alleviate cytopenia associated with massive splenomegaly include HU, IFN-α, and EPO (please see treatments for MF). Analgesia may be required for splenic infarct pain. It is difficult to treat cytopenia associated with marrow fibrosis and massive splenomegaly, since agents that reduce splenomegaly may not necessarily relieve cytopenia. Splenectomy can be followed by progressive hepatomegaly and can eventually transform to acute leukemia. In selected patients, allogeneic transplantation can be curative.
- Pruritus: Intractable pruritus responds to IFN-α in up to 81% of patients. In low-risk patients in whom IFN-α is not indicated, paroxetine, a selective serotonin reuptake inhibitor, can alleviate symptoms in most cases.
- Hyperuricemia: Allopurinol should be started before chemotherapy to decrease the risk of urate nephropathy (300 mg per day given orally; dose reduction needed in renal insufficiency).

Essential Thrombocythemia

- Low risk: Age <60 years, and no history of thrombosis, and platelet count $<1{,}000 \times 10^9$/L. Recommended treatment: observation or low-dose aspirin, especially if there are symptoms or cardiovascular risk factors (e.g., smoking). If platelet count is $\geq 1{,}000 \times 10^9$/L, clinically significant acquired von Willebrand syndrome (ristocetin cofactor activity $<30\%$) should be excluded before initiation of low-dose aspirin therapy.
- High risk: Age $\geq$ 60 years and/or a previous history of thrombosis. Recommended treatment: cytoreduction with HU and low-dose aspirin therapy.

Treatment in ET must consider the fact that life expectancy is nearly normal and that platelet reduction with HU may be associated with an increased risk for transformation to leukemia. Treatment is directed at preventing thrombosis and hemorrhage in those patients deemed to be at risk for these complications, because of an actual history of thrombosis, cardiovascular risk factors such as smoking or age more than 60 years, or a platelet count $>1{,}500 \times 10^9$/L. Increased WBC ($\geq 15 \times 10^9$/L) might be an additional risk factor for thrombosis.

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. 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. IFN-α can also effectively cause platelet cytoreduction. The therapeutic target platelet count in this trial was $<400 \times 10^9$/L. Plateletpheresis is used as an emergency therapy when ongoing thrombosis cannot be adequately managed with chemotherapy and antithrombotic agents.

Myelofibrosis

- Risk stratification by the Dynamic International Prognostic Scoring System Plus (DIPSS Plus): one point each for age >65 years, white blood cell count $>25 \times 10^9$/L, circulating blast cells $\geq 1\%$, presence of constitutional symptoms, unfavorable karyotype, platelet count $<100 \times 10^9$/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.

- Palliative therapy for MF is directed toward alleviating symptoms which are generally related to anemia, splenomegaly, or systemic symptoms such as severe fatigue.

Anemia: Androgens (e.g., danazol) combined with prednisone (prednisone is tapered after a few weeks), or thalidomide combined with prednisone, or erythropoietin replacement therapy in patients with inappropriately low erythropoietin levels can be considered, although results have been mixed. Transfusion needs may diminish after splenectomy (see below). Transfusion support (with iron chelation when indicated) may be necessary. Lenalidomide should be considered to treat MF with a 5q– chromosome abnormality. Experimental therapies that are being evaluated include pomalidomide and DNMT1-depleting drugs (5-azacytidine and decitabine).

Splenomegaly: Options include *JAK2* inhibitor (e.g., ruxolitinib), although the currently approved dosages may be unnecessarily high, and it may be appropriate to start with lower than standard dosages

with an escalation if necessary. The main cautions are potential for exacerbating cytopenia with associated risk for hemorrhage, and for rebound disease growth and inflammatory symptoms if the drugs are discontinued abruptly (dosage should be tapered off rather than abruptly discontinued). Lenalidomide should be considered to treat MF with a 5q– abnormality. HU can be considered, with dose modifications depending on cytopenias. Splenectomy is an option to alleviate pain and early satiety, depending on local surgical experience and thus surgical risk. Secondary hepatomegaly is a potential long-term complication of splenectomy. Increasing white blood cell counts and platelet counts after splenectomy may necessitate HU therapy. Experimental therapy options include IFN-α, pomalidomide, and DNMT1-depleting drugs.

- Curative therapy: Allogeneic transplantation should be considered for patients younger than 55 years who have MF.

Five-year survivals with a related or an unrelated matched transplant are 54% and 48%, respectively, as determined by the European Group for Blood and Marrow Transplantation (EBMT). A recommendation for transplantation is not clear-cut in asymptomatic patients without cytogenetic abnormalities and no cytopenia because the median survival in this group is >14 years with palliative therapy alone. 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.

REVIEW QUESTIONS

Mr. Jones is a 47-year-old active Caucasian male seen in the office of the internist Dr. Brown. His main complaint is increasing fatigue. He has noticed a decrease in his exercise tolerance, and a sense of fatigue that has been progressive in the 3 months preceding his visit to the clinic. He enjoys playing soccer, and usually participates in a "40 years and older" pick-up game every Saturday. For the past 2 months, he has not felt like playing.

Upon questioning, he states that he gets winded easily and feels fatigued after physical effort. It takes him longer to recover from effort than ever before. He denies any chest or abdominal pain and he has not had a change in his bowel habit or noticed any change in the color of his stool. His weight has not changed and his appetite remains good. He has not noticed blood in the toilet bowl after bowel movements. He has not experienced any recent colds, and he has not had recent cough, sore throat, fever, body ache, or headache. He denies night sweats, too. He has noticed some blood when rinsing after brushing his teeth, but, has noticed some bruises, although he wonders if these are from his soccer games. He has not had any bleeding from the nose.

He does not have any significant past medical history and initially he denied taking any medications. However, upon specific questioning regarding use of over-the-counter medications including pain medications, he mentions that he does use naproxen occasionally for pain and swelling in the knees after playing soccer. He has not used naproxen for more than 4 weeks.

He is a lawyer for a local law firm and has not had any unusual chemical exposures. He drinks alcohol only occasionally and in small amounts, and has not noticed swelling around the ankles, although his knees do swell after his soccer games, requiring use of postgame icel-packs. He did travel to Thailand 5 years ago, had a good time, and was not unwell during or after the trip.

He has two siblings, one of whom was born before the patient, "was deformed at birth," and died as an infant. His other sibling, a brother aged 44, is alive and well without medical problems.

On examination, he is a fit-appearing Caucasian male. Although alert, he does appear fatigued and is pale without icterus. Bruises are noted on his lower extremities. There was no palpable lymphadenopathy. A spleen tip is palpated 12 cm below the left costal margin in the mid-clavicular line. There was no palpable hepatomegaly.

(*continued*)

Labs

WBC	10.76	(4–11 K/μL)
RBC	1.82	(4.2–5.4 M/μL)
Hgb	7.3	(12–16 g/dL)
Hct	21	(37–47%)
MCV	105.2	(80–100 fL)
MCHC	34.9	(32–36%)
RDW-CV	12.4	(11.7–15%)
Platelets	70	(150–400 K/μL)
MPV	10.6	(7.3–11.1 fL)

1. What is the diagnosis, or what are the differential diagnoses, for Mr. Jones' condition?
   - **A.** MDS
   - **B.** MF
   - **C.** Post-PV MF
   - **D.** Post-ET MF
   - **E.** All of the above
2. What additional investigations are indicated to establish a definitive diagnosis?
   - **A.** Reticulocyte count and lactate dehydrogenase
   - **B.** Evaluation for *JAK2* V617F mutation
   - **C.** Bone marrow aspirate and biopsy for morphology and karyotype evaluation
   - **D.** FISH studies to detect the *BCR-ABL* fusion
   - **E.** All of the above
3. The *JAK2* V617 test was positive, and the bone marrow evaluation demonstrated an increase in reticulin fibrosis, and an increase in the myeloid:erythroid ratio, without an increase in megakaryocyte numbers. A 20q– chromosome abnormality was detected in 20 of 20 metaphases. Liver and renal function tests were normal. What are appropriate therapies for Mr. Jones?
   - **A.** Allogeneic stem cell transplant
   - **B.** *JAK2* inhibitor
   - **C.** HU
   - **D.** Erythropoietin
   - **E.** Iron supplements

Suggested Readings

1. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29(4):392-397.
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27

Multiple Myeloma

Preet Paul Singh and Shaji K. Kumar

Multiple myeloma (MM) is a neoplastic process 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 requires the presence of these clinical features and its attribution to clonal plasma cell proliferation. Newer active agents and autologous stem cell transplantation (ASCT) have led to outcome improvements, from a median survival of 3 years in the late 1990s to nearly 8 years currently, a metric that continues to improve.

EPIDEMIOLOGY

MM accounts for 1% of all cancers and about 10% of all hematologic malignancies. In 2012, 21,700 new cases and 10,710 deaths from MM were estimated in the United States. The annual age-adjusted incidence in the United States is approximately 4 to 5 per 100,000 and has remained stable over time. The median age at diagnosis is about 65 years and MM is slightly more common in men than in women (1.3:1). Incidence among African Americans is two- to threefold higher than that in Caucasians, whereas it is lower in Asians. The risk of developing MM is approximately 3.7-fold higher for persons with a first-degree relative of MM.

PATHOPHYSIOLOGY

MM is characterized by the proliferation and accumulation of clonal plasma cells in the bone marrow. Almost all patients with MM evolve from an underlying, asymptomatic monoclonal gammopathy of undetermined significance (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. Some patients may also develop an intermediate, more advanced stage referred to as smoldering multiple myeloma (SMM) that is defined clinically (Table 27.1). The risk of progression of SMM to symptomatic myeloma is about 10% per year over the first 5 years after diagnosis.

The clonal plasma cells in myeloma are characterized by significant genetic abnormalities, with the majority having one or more well-characterized abnormalities. Five recurrent translocations involving the heavy chain locus on chromosome 14 have been identified and are present in approximately 40% of all myeloma tumors. Trisomies of odd-numbered chromosomes are detected in nearly half of the patients, with monosomies or deletions of other chromosomes overlapping with these two sets of abnormalities. The clinical features of MM are a result of bone marrow infiltration by the malignant clone;

Table 27.1 International Myeloma Working Group Criteria for Diagnosis of Monoclonal Gammopathies

Disorder	Clonal Plasma Cells	Monoclonal (M) Protein	End-Organ Damage Due to the Plasma Cell Proliferative Process[a]
Monoclonal gammopathy of undetermined significance (MGUS)	<10% in bone marrow	<3 g/dL in serum	None
Smoldering (asymptomatic) multiple myeloma[b]	≥10% in bone marrow	≥3 g/dL in serum	None
Multiple myeloma	≥10% in bone marrow[c]	Present in serum and/or urine (any amount)	Present
Light chain myeloma	≥10% in bone marrow	Not detectable; elevated FLC with abnormal ratio	Present
Nonsecretory multiple myeloma	≥10% in bone marrow	None	Present
Solitary plasmacytoma	Present at site of solitary bony or extramedullary tumor; None in bone marrow	May or may not be present	None other than primary solitary lesion

[a]End-organ damage may include one or more of the following: hypercalcemia (serum calcium ≥11.5 mg/dL, renal insufficiency (serum creatinine >2 mg/dL or estimated creatinine clearance <40 mL/min), anemia (normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL), and bone lesions (lytic lesions, severe osteopenia, or pathologic fractures).

[b]A diagnosis of asymptomatic multiple myeloma would require the presence of ≥10% clonal plasma cells in bone marrow and/or M-protein in serum of ≥3 g/dL.

[c]Approximately 4% of patients may have fewer than 10% bone marrow plasma cells since marrow involvement may be focal, rather than diffuse. Repeat bone marrow biopsy may be considered in such patients but diagnosis of MM can be made, if other diagnostic criteria are fulfilled.

Adapted from International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749–757.

damage from high levels of immunoglobulins or free light chains (FLCs) 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, and light chain cast nephropathy. Other etiologies may include renal amyloidosis, light chain deposition disease, cryoglobulinemia, or drug-induced kidney injury. In some patients, 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 of nerve roots by paravertebral plasmacytoma or by fractured vertebral body. Peripheral neuropathy is a rare manifestation and, when present, is almost always secondary to 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. The criteria for diagnosis of monoclonal gammopathies proposed by the International Myeloma Working Group (IMWG) are shown in 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. In addition, for diagnosis and staging, these labs 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; serum protein electrophoresis (SPEP) and immunofixation (IFE); serum FLC assay; 24-hour urine protein electrophoresis (UPEP) and IFE; quantitative immunoglobulins; radiographic skeletal survey; and bone marrow aspirate and biopsy.

SPEP is useful in detecting and quantifying the presence of an intact 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, more importantly, determines its type (Fig. 27.1). SPEP and/or serum IFE is sometimes inadequate as approximately 15% of patients have only light chains (light chain myeloma), which may rapidly be cleared from the plasma to the urine. Hence, serum FLCs, UPEP, and/or urine IFE should be performed in all patients and are very useful in such patients.

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 FLC 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 include conventional karyotyping and fluorescent in situ hybridization (FISH) designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), hyperdiploidy, and deletion 17p for risk stratification. Gene expression profiling, when available, may also be considered for additional prognostic information.

Radiologic changes seen on a skeletal survey include punched-out lytic lesions, severe osteopenia or osteoporosis, and pathologic fractures. A nuclear medicine bone scan is not useful in MM because lytic lesions are not visualized on bone scans. Routine fluoro-deoxyglucose positron emission tomography/computed tomography (PET-CT) and magnetic resonance imaging (MRI) scans are not needed for every patient, but are indicated when symptomatic areas show no abnormality on a radiographic skeletal survey or when there is uncertainty about the true extent of bone disease on radiographs alone. Another indication where these scans should be utilized is when solitary plasmacytoma is suspected, to reliably rule out bony or extramedullary disease. Any patient with significant back pain should also undergo MRI of the spine to evaluate cord compression.

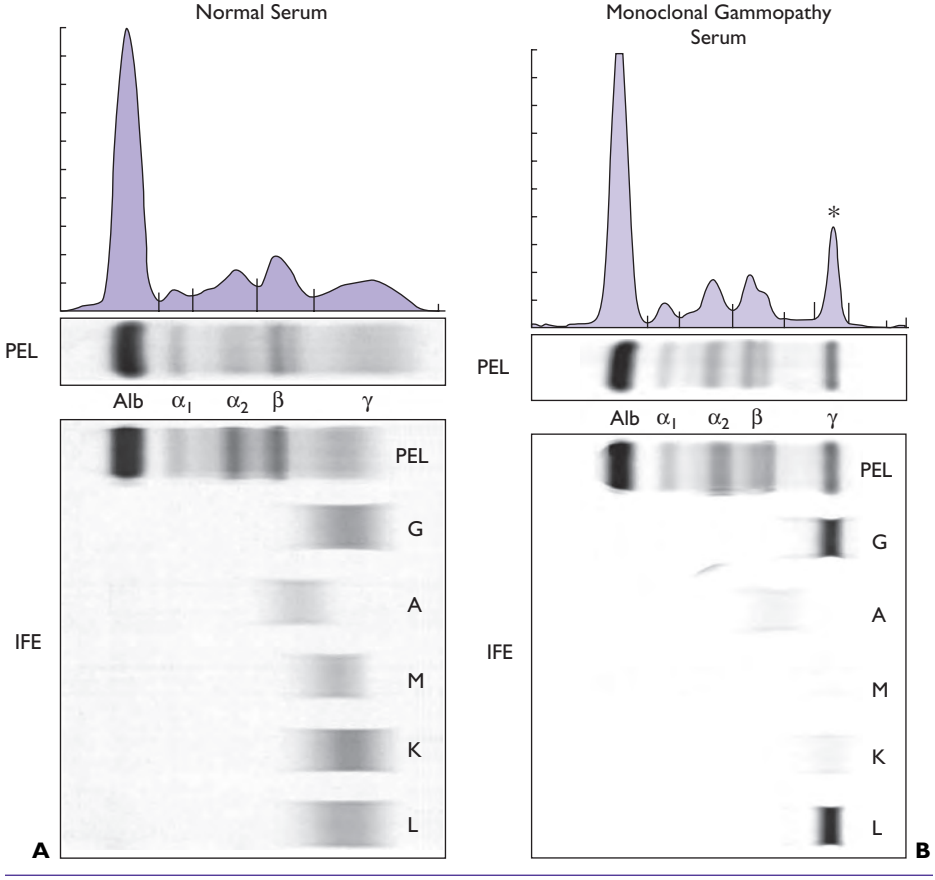

FIGURE 27.1 Electrophoretic pattern of (A) normal human serum and (B) immunoglobulin G (IgG lambda) multiple myeloma. Asterisk indicates M spike in the gamma region.

STAGING

Two main staging systems exist for MM that primarily reflect tumor burden: the International staging system (ISS) that is based on laboratory values and the Durie-Salmon staging system, predominantly a clinical system. Both of these provide prognostic information but are not helpful in making therapeutic choices. Of these, the ISS has become the preferred staging system because of its simplicity and lack of subjectivity (Table 27.2).

PROGNOSIS

Prognosis in myeloma depends on host factors (age, performance status, and comorbidities), stage, disease aggressiveness, and response to therapy. Other laboratory parameters such as hemoglobin concentration, creatinine, calcium, lactate dehydrogenase, immunoglobulin subtype, plasmablastic morphology, circulating plasma cells, and C-reactive protein have also been shown to be independent risk factors for survival in myeloma. A high plasma-cell–labeling index also strongly predicts poor

Table 27.2 International Staging System for Multiple Myeloma

Stage	Criteria	Percentage of Patients	Median Survival (mo)
I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL	28	62
II	Not fitting stage I or III Serum β_2-microglobulin 3.5–5.4 mg/L Serum albumin <3.5 g/dL	33	44
III	Serum β_2-microglobulin ≥5.5 mg/L	39	29

Adapted from Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol.* 2005;23(15):3412–3420.

prognosis, but this test is not commonly available. A risk stratification model based on independent molecular cytogenetic markers to assess disease aggressiveness has been found useful for both prognosis and therapeutic decision-making. Newly diagnosed patients can be stratified using these markers as having standard-, intermediate-, and high-risk disease based on the Mayo stratification for myeloma and risk-adapted therapy (mSMART) classification (Table 27.3). Median survival varies from 8 to 10 years for standard-risk patients versus 2 to 3 years for high-risk myeloma.

TREATMENT

General

Monoclonal Gammopathy of Undetermined Significance

Risk-stratification models have been proposed for progression of monoclonal gammopathy of undetermined significance (MGUS) and assist in detecting patients with higher risk of progression to myeloma. Patients with risk factors consisting of a serum M-protein >1.5 g/dL, IgA or IgM MGUS, and an abnormal serum FLC ratio have a risk of progression at 20 years of 58%; compared with 37% when two risk factors are present; 21% when one risk factor is present; and only 5% when none of the risk factors are present. Patients with MGUS should be monitored indefinitely without treatment because 20% to 25% of them will eventually progress to myeloma at a rate of approximately 1% per year. Patients should be followed with SPEP every 6 months, 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.

Table 27.3 Risk-Stratification of Multiple Myeloma

High Risk	Intermediate Risk	Standard Risk[a]
17p deletion	t(4;14)	Hyperdiploidy
t(14;16)	Deletion 13 or hypodiploidy by conventional karyotyping	t(11;14)[b]
t(14; 20)		t(6;14)
High-risk signature on gene expression profiling		

Based on FISH analysis unless specified.
[a]LDH >ULN and β-2 microglobulin >5.5 may indicate worse prognosis.
[b]t (11;14) may be associated with plasma cell leukemia.
Adapted from Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc.* 2009;84:1095-1110.

Smoldering (Asymptomatic) Multiple Myeloma

These patients should also be observed closely without therapy, but they have a higher risk of progression to myeloma than MGUS (10% per year vs. 1% per year). These patients should have SPEP, UPEP, complete blood count, and calcium and creatinine measurement 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. Patients with an abnormal FLC (involved to uninvolved) ratio of >100 have 72% risk of progression to MM in the first 2 years after diagnosis and should be monitored more closely. Currently, treatment is indicated only when there is evidence of progression to symptomatic disease, or as a part of clinical trial, although there is increasing thought that treating high risk patients early (before they develop symptomatic disease) may lead to better outcomes.

Solitary Plasmacytoma

These patients are treated with radiation therapy (solitary bone) and/or surgical removal (extraosseous plasmacytomas) of the affected area, followed by close monitoring of M-protein every 6 months because of the risk of developing MM.

Multiple Myeloma

To date, there is no clear curative therapy available for most MM patients and the "cure vs. control" debate is ongoing. In the past decade, the availability of novel highly active drugs such as thalidomide, bortezomib, and lenalidomide has significantly improved the outcome of patients with MM. More recently newer drugs like carfilzomib and pomalidomide have become available for management of relapsed disease. One approach is upfront aggressive multidrug treatment to achieve complete response (CR) versus a sequential disease control approach emphasizing quality of life and prolonged survival. Patients with high-risk disease have better long-term OS if they achieve a CR, justifying an aggressive strategy upfront. For standard-risk patients, achievement of CR does not affect OS and the goal of therapy is to improve quality of life, delay disease progression, and prolong survival. The treatment choice for symptomatic myeloma patients largely depends on eligibility for transplantation and risk stratification (Fig. 27.2). Eligible patients should always be considered for enrollment in clinical trials that evaluate novel treatment strategies. The proposed criteria by the IMWG for evaluating disease response and progression in myeloma patients are outlined in Table 27.4.

Initial Therapies

Induction Treatment for Patients Eligible for Transplantation

Infusional therapy with vincristine, doxorubicin, and dexamethasone (VAD) was commonly used for many years as an induction regimen prior to ASCT. However, VAD is no longer used as initial therapy since several novel drug combinations using thalidomide, bortezomib, or lenalidomide have been shown to be superior to VAD. A summary of these regimens is shown in Table 27.5.

Thalidomide-Dexamethasone This combination has been shown in randomized trials to have higher response rates and improved time to progression as compared to dexamethasone alone. Still, due to inferior activity and toxicity profile as compared to lenalidomide-based regimens, thalidomide-dexamethasone (TD) is not used as front-line therapy, except where lenalidomide may not be available. Thalidomide also has utility in patients with renal failure as no dose adjustments are needed and it can be safely combined with bortezomib. The combination of thalidomide, cyclophosphamide, and dexamethasone has been studied in phase 3 trials, and is an effective initial therapy. Patients are at high risk of developing venous thrombosis and should be on DVT prophylaxis with aspirin, low-molecular-weight heparin, or warfarin.

Lenalidomide-Based Regimens Lenalidomide is a safer and more effective analog of thalidomide, which in combination with dexamethasone has been superior to dexamethasone alone in randomized trials. Combination of lenalidomide with low-dose dexamethasone (40 mg once weekly) (Rd) is significantly less toxic and provides better OS as compared to combination with high-dose dexamethasone (RD). Long-term results suggest an excellent toxicity profile with prolonged therapy with this regimen. All patients should be given antithrombosis prophylaxis with aspirin. Low-molecular-weight heparin and warfarin

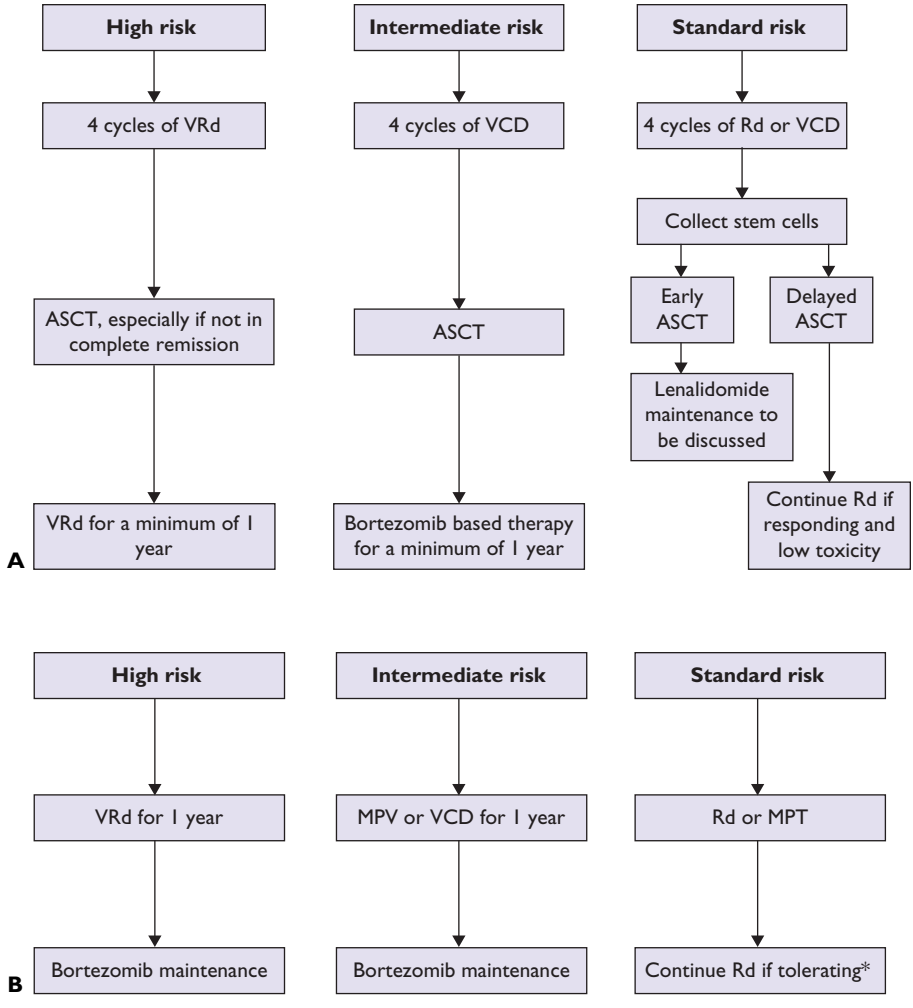

FIGURE 27.2 A suggested treatment algorithm for newly diagnosed multiple myeloma patients. Transplant eligible (A) and transplant ineligible (B). All patients should receive supportive care and must be considered for bisphosphonate treatment and clinical trials. (*Dexamethasone is usually discontinued after 12 months. ASCT, autologous stem cell transplantation; VRd, bortezomib, lenalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Rd, lenalidomide, dexamethasone; MPT, melphalan, prednisone, and thalidomide; MPV, melphalan, prednisone, and bortezomib; CR, complete response; VGPR, very good partial response.) (Adapted from Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc.* 2009;84:1095-1110; Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Oncol.* 2011;8:479-491.)

Table 27.4 International Myeloma Working Group Uniform Response Criteria

Response Subcategory	Response Criteria
Stringent complete response (sCR)	CR as defined below plus Normal free-light-chain (FLC) assay ratio plus Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
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
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 For nonsecretory myeloma, ≥50% decrease in the difference between involved and uninvolved FLC levels 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% If present at baseline, ≥50% reduction in the size of soft-tissue plasmacytomas
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)	≥25% increase from lowest response level in serum M-protein (absolute increase must be ≥0.5 g/dL) and/or ≥25% increase from lowest response level in urine M-protein (absolute increase must be ≥200 mg/24 h) and/or For nonsecretory myeloma, ≥25% increase from lowest response level in the difference between the involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) and/or ≥25% increase from lowest response level in bone marrow plasma cell percentage (absolute plasma cell percentage must be ≥10) and/or Development of new bone lesions or soft-tissue plasmacytomas or definite increase in the size of existing bone lesions or soft-tissue plasmacytomas and/or Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell disorder
Relapse from CR	Reappearance of serum or urine M-protein by immunofixation or electrophoresis and/or Development of ≥5% plasma cells in the bone marrow and/or Any other sign of progression (new plasmacytoma, lytic bone lesions, or hypercalcemia)

All response categories (sCR, CR, VGPR, PR) require two consecutive assessments made at any time before the institution of any new therapy. sCR, CR, VGPR, PR, and SD also require no known evidence of new or progressive bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy the response requirements. Bone marrow assessments need not be confirmed.

Adapted from Durie BG, Harousseau JL, Miguel JS, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.

Table 27.5 Responses to Induction Therapy for Transplant-Eligible Myeloma Patients

Regimen	OR (CR + PR)	CR + VGPR	Reference(s)
TD vs. dex	63% vs. 46%	44% vs. 16%	47,51
Lenalidomide + high-dose dex vs. high-dose dex	85% vs. 51%	79% vs. 26%	62
Lenalidomide + low-dose dex (Rd) vs. lenalidomide + high-dose dex (RD)	70% vs. 82%	42% vs. 52%	49
Bortezomib + dex vs. VAD	89% vs. 71%	50% vs. 24%	17
Bortezomib + TD vs. TD	93% vs. 80%	60% vs. 25%	7
Bortezomib + cyclophosphamide + dex (VCD)	90%	70%	52
Bortezomib + lenalidomide + dex (VRD)	100%	70%	20,53

OR, overall response; CR, complete response; PR, partial response; VGPR, very good partial response; dex, dexamethasone; Thal, thalidomide; TD, thalidomide and dexamethasone; TAD, thalidomide, doxorubicin, and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone.

should be used in patients at high risk of thrombosis. Lenalidomide has been combined with bortezomib as well as older drugs resulting in very active combinations both for initial therapy and for relapsed disease.

Bortezomib-Based Regimens Randomized trials have shown that bortezomib in combination with dexamethasone (VD) is superior to VAD as pretransplant induction therapy. Three drug combinations containing bortezomib such as combination with thalidomide and dexamethasone (VTD), cyclophosphamide and dexamethasone (VCD), and lenalidomide and dexamethasone (VRD) are highly active in newly diagnosed MM. VTD has been shown to be superior to TD and VD (Table 27.5). VCD is less expensive and better tolerated than VRD with similar activity in newly diagnosed patients. It also appears to overcome the poor prognosis associated with t(4;14) and hence is an excellent choice as front-line therapy for intermediate-risk patients. These three drug combinations have not been directly compared to Rd. Peripheral neuropathy is a significant adverse effect, which may occur early in the disease course with upfront bortezomib-containing regimens. Administering Bortezomib subcutaneously (as compared to intravenously) and on a once-weekly schedule significantly reduces the risk of neuropathy.

Certain regimens may also be preferable in specific clinical scenarios that are not uncommonly seen in MM patients. For patients at high risk of DVT and those with renal insufficiency, bortezomib-based regimens are favored, whereas for patients with history of peripheral neuropathy, Rd would be a preferred choice.

Autologous Stem Cell Transplantation

Two large randomized trials, the InterGroupe Francophone du Myelome 90 (IFM 90) trial and the Medical Research Council Myeloma VII Trial, demonstrated that high-dose therapy (HDT) followed by ASCT significantly improves response rate and overall survival by around 12 months compared to conventional chemotherapy in myeloma patients younger than 65 years with good performance status (Table 27.6). The IFM 95 randomized trial demonstrated that 200 mg/m^2 of melphalan is less toxic and at least as effective a conditioning regimen as total body irradiation of 8 Gy 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. Lenalidomide may impair peripheral blood stem cells in certain patients, so stem cell mobilization may require cyclophosphamide plus G-CSF or G-CSF and plerixafor in patients who have received prolonged lenalidomide therapy. Bortezomib does not appear to negatively impact stem cell mobilization.

Table 27.6 Results for Conventional Chemotherapy (CC) versus High-Dose Therapy (HDT) Followed by Autologous Stem Cell Transplantation (ASCT)

Treatment	OR (CR + PR)	CR	Median EFS/PFS	Median OS	Reference
CC vs. HDT (IFM 90)	57% vs. 81%	5% vs. 22%	18 vs. 28 mo	44 vs. 57 mo	3
CC vs. HDT (MRC7)	48% vs. 86%	8% vs. 44%	20 vs. 32 mo	42 vs. 54 mo	9

OR, overall response; CR, complete response; PR, partial response; IFM, InterGroupe Francophone du Myelome; CC, conventional chemotherapy; HDT, high-dose therapy; EFS, event-free survival; PFS, progression-free survival; OS, overall survival; MRC, Medical Research Council.

In a Spanish randomized trial (PETHEMA), patients responding to induction therapy had similar overall and progression-free survival with ASCT, suggesting that ASCT provides greatest benefit to the subgroup of patients that are refractory to induction therapy. Therefore, the timing of ASCT is based on patient preference and other conditions, including response to initial induction therapy. Although the benefit of ASCT in terms of event-free and overall survival is yet to be proven after induction therapy with novel agents, it is generally recommended as it has been shown to improve CR rates.

The IFM 94 trial and the Bologna 96 Clinical study from Italy established that double (tandem) transplantation is superior to single autologous transplantation and should be considered as a treatment option, especially for patients younger than 60 years who fail to achieve very good partial response (defined as >90% reduction in serum M-protein level) after first ASCT (Table 27.7).

Induction Treatment for Patients Not Eligible for Transplantation

Major options for newly diagnosed MM patients who are considered ineligible for ASCT due to age or other comorbidities include melphalan-based combinations or lenalidomide-dexamethasone (Rd). The duration of therapy is usually 9 to 18 months with the newer combinations as long as toxicity is acceptable. MP has been the standard treatment regimen for MM for more than 40 years. However, randomized trials have now shown that in patients aged ≥65 years, combination of MP with any of the new agents (thalidomide, bortezomib, and lenalidomide) is significantly superior to MP in terms of response rate, event-free survival, and overall survival, although increased toxicity with the newer regimens needs to be considered when choosing therapy (Tables 27.8 and 27.9). These new combinations of MPT, MPV, and MPR are now considered standard of care for elderly patients. Rd is probably a better-tolerated and safer option for elderly patients, with a response rate of 70% in patients older than 70 years that is comparable to MPT or MPV. MP alone may still be considered in elderly patients without access to Rd or are not candidates for MPT or MPV due to advanced age or significant comorbidities.

The preference for one regimen over the other may depend on the patient's comorbid conditions and other social factors. For patients at risk of DVT and in patients with renal insufficiency, MPV is preferred; for patients with history of peripheral neuropathy, MPL should be the choice; if costs are a concern, MPT is least expensive; if oral therapy is desired, MPT or MPR would be good choices.

Table 27.7 Results for Single versus Double Autologous Stem Cell Transplantation (ASCT)

Treatment	OR (CR + PR)	CR + VGPR/nCR	Median EFS	Median OS	TRM	Reference
Single vs. double ASCT (IFM 94)	84% vs. 88%	42% vs. 50%	25 vs. 30 mo	48 vs. 58 mo	4% vs. 6%	1
Single vs. double ASCT (Bologna 96)	n/a	33% vs. 47%	23 vs. 35 mo	65 vs. 71 mo	3% vs. 4%	8

OR, overall response; CR, complete response; PR, partial response; VGPR, very good partial response; nCR, near complete response; SCT, stem cell transplantation; EFS, event-free survival; OS, overall survival; TRM, treatment-related mortality.

Table 27.8 Responses to Induction Therapy in Newly Diagnosed Elderly Myeloma Patients

Regimen	OR (CR + P)	CR + VGPR	EFS/PFS/TTP	OS	Reference
MPT vs. MP	76% vs. 48%	28% vs. 7%	54% vs. 27% at 24 mo	80% vs. 64% at 36 mo	41
MPT vs. MP	76% vs. 35%	47% vs. 7%	28 vs. 18 mo	52 vs. 33 mo median OS	14
Bortezomib + MP (MPV) vs. MP	82% vs. 50%	45% vs. 10%	24 vs. 17 mo	83% vs. 70% at 24 mo	55
Lenalidomide + MP (MPL)	81%	48%	92% at 12 mo	100% at 12 mo	42

OR, overall response; CR, complete response; PR, partial response; VGPR, very good partial response; EFS, event-free survival; PFS, progression-free survival; TTP, time to progression; OS, overall survival; MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide.

Table 27.9 FDA-Approved Agents for Use in Relapsed and/or Refractory Multiple Myeloma

Regimen	Treatment Description	Cycle Duration	Response Rate
TD	Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 Thalidomide 200 mg/d PO daily at bedtime	28 d	63% in untreated patients
TAD	Thalidomide 200–400 mg/d PO daily at bedtime Doxorubicin 9 mg/m^2/d IV rapid infusion days 1–4 (total dose/cycle = 36 mg/m^2) Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 (total dose/cycle = 480 mg)	28 d	72% in untreated patients
Thal + VAD-doxil	Thalidomide 200 mg/d PO daily at bedtime Vincristine 2 mg IV bolus on day 1 Pegylated liposomal doxorubicin 40 mg/m^2 IV 60 min infusion day 1 Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 for cycle 1 and on days 1–4 for cycles 2–4	28 d	81% in untreated patients
MPT	Melphalan 0.25 mg/kg/d PO days 1–4 (use 0.20 mg/kg/d for patients aged above 75 y) Prednisone 2 mg/kg/d PO days 1–4 Thalidomide 100–200 mg/d PO days 1–28 at bedtime	28–42 d	76% in untreated patients
Bortezomib + dexamethasone	Bortezomib 1.3 mg/m^2/d IV on days 1, 4, 8, and 11 (total dose/cycle = 5.2 mg/m^2) Dexamethasone 40 mg/d PO on days 1–4 and 9–12 during cycles 1 and 2; and days 1–4 only during cycles 3 and 4	21 d	80% in untreated patients
Bortezomib + TD (VTD)	Bortezomib 1.3 mg/m^2/d IV on days 1, 4, 8, and 11 Thalidomide 200 mg/d PO daily at bedtime Dexamethasone 40 mg/d PO on days 1, 2, 4, 5, 8, 9, 11, and 12	21 d	93% in untreated patients

(*Continued*)

Table 27.9 (Continued)

Bortezomib + Pegylated liposomal doxorubicin	Bortezomib 1.3 mg/m^2/d IV on days 1, 4, 8, and 11 Pegylated liposomal doxorubicin 30 mg/m^2 IV 60 min infusion on day 4	21 d	44% in relapsed or refractory patients
MPV	Melphalan 9 mg/m^2/d PO days 1–4 Prednisone 60 mg/m^2/d PO days 1–4 Bortezomib 1.3 mg/m^2/d IV on days 1, 4, 8, 11, 22, 25, 29, and 32 for four cycles and on days 1, 8, 22, and 29 for five cycles	42 d	88% in untreated patients
Lenalidomide + high-dose dexamethasone	Lenalidomide 25 mg/d PO on days 1–21 Dexamethasone 40 mg/d PO on days 1–4, 9–12, and 17–20	28 d	82% in untreated patients
Lenalidomide + low-dose dexamethasone	Lenalidomide 25 mg/d PO on days 1–21 Dexamethasone 40 mg/d PO on days 1, 8, 15, and 22	28 d	70% in untreated patients
MPL	Melphalan 0.18 mg/kg/d PO on days 1–4 Prednisone 2 mg/kg/d PO on days 1–4 Lenalidomide 10 mg/d PO on days 1–21	28 d	81% in untreated patients
MP	Melphalan 10 mg/m^2/d PO days 1–4 (total dose/cycle = 40 mg/m^2) Prednisone 60 mg/m^2/d PO days 1–4 (total dose/cycle = 240 mg/m^2)	4–6 wk	53% in untreated patients
Pulse dexamethasone	Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 for odd cycles and days 1–4 for even cycles (total dose/cycle = 480 mg for odd cycles and 160 mg for even cycles)	28 d	43% in untreated patients
VAD	Vincristine 0.4 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 1.6 mg/m^2) Doxorubicin 9 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 36 mg/m^2) Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 for odd cycles and days 1–4 for even cycles	21 d	55–84% in untreated patients
CVAD	Cyclophosphamide 225 mg/m^2/dose IV every 12 h on days 1–4 (total dose/cycle = 1,800 mg/m^2) Vincristine 0.4 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 1.6 mg/m^2) Doxorubicin 9 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 36 mg/m^2) Dexamethasone 40 mg/d PO days 1–4, 9–12, and 17–20 for odd cycles and days 1–4 for even cycles	21 d	40% in relapsed or refractory patients

(*Continued*)

Table 27.9 (Continued)

DCEP	Dexamethasone 40 mg/d PO days 1–4 (total dose/cycle = 160 mg) Cyclophosphamide 400 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 1,600 mg/m^2) Etoposide 40 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 160 mg/m^2) Cisplatin 10 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 40 mg/m^2)	4–6 wk	41% in refractory patients
DTPACE	Dexamethasone 40 mg/d PO days 1–4 Thalidomide 400 mg/d PO daily at bedtime (continuous) Cisplatin 10 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 40 mg/m^2) Doxorubicin 10 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 40 mg/m^2) Cyclophosphamide 400 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 1,600 mg/m^2) Etoposide 40 mg/m^2/d continuous IV infusion days 1–4 (total dose/cycle = 160 mg/m^2)	4–6 wk	40% in refractory patients
Thalidomide	Thalidomide start at 200 mg/d PO daily at bedtime for 2 wk; increase dose by 200 mg every 2 wk to a maximum of 800 mg/d	Continuous	32% in refractory patients
HDT + AutoSCT	Conditioning regimen: Melphalan 200 mg/m^2 IV infusion over 30 min on day 2 (total dose/cycle = 200 mg/m^2) PBSC transplantation on day 0	N/A	>80% in untreated patients
Pamidronate	Pamidronate 90 mg IV infusion over 2 h (total dose/cycle = 90 mg)	Monthly	N/A
Zoledronic acid	Zoledronic acid 4 mg IV infusion over 15 min (total dose/cycle = 4 mg)	Monthly	N/A

Maintenance Therapy

Prior to the availability of novel agents, interferon or corticosteroids had shown little benefit when used as maintenance therapy in clinical trials and are no longer recommended.

Multiple trials have evaluated the role of thalidomide, lenalidomide, and bortezomib in post-ASCT maintenance therapy as well as in elderly patients after induction therapy. Thalidomide has shown PFS and OS improvement in two randomized trials. The feasibility and efficacy of lenalidomide as post-ASCT maintenance therapy have been shown in two recent placebo-controlled randomized trials. In both of these studies, PFS improvement was observed, although an increased number of second malignancies were noted in the lenalidomide arm. Bortezomib administered every 2 weeks as maintenance therapy has been shown to improve PFS and OS in myeloma patients as compared to thalidomide.

Even in elderly patients who are not transplant eligible, lenalidomide maintenance after induction with MPL showed improved PFS, especially in patients aged 65 to 75 years. Bortezomib as maintenance

therapy after bortezomib-based induction therapy (MPV or VTP) also showed improvement in CR rates, PFS with acceptable toxicity.

Maintenance treatment can be associated with significant side effects, and none of the drugs evaluated is currently approved for maintenance therapy. Potential benefits and risks should be carefully evaluated and treatment decisions should be individualized based on patient characteristics and preference. This could be particularly important for high-risk patients as well as those who fail to achieve VGPR after ASCT.

Supportive Measures

Bisphosphonates should be considered for all patients with evidence of lytic bone lesions and/or osteopenia. 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, pamidronate may be preferred due to the greater risk of development of osteonecrosis of the jaw with zoledronic acid. Bisphosphonate therapy should be continued for 2 years postdiagnosis as long as the disease is in remission.

Infection prophylaxis is crucial during induction therapy. All patients should receive antibacterial prophylaxis with single strength sulfamethoxazole/trimethoprim daily for 4 months. A quinolone or penicillin can be substituted for patients with sulfa allergy or when lenalidomide is used in the induction regimen. Herpes zoster prophylaxis with acyclovir 400 mg twice a day or valacyclovir 500 mg daily should be used in patients receiving bortezomib-containing regimens. For patients on long-term, high-intensity steroid treatment, *Pneumocystis jiroveci* prophylaxis with sulfamethoxazole/trimethoprim is recommended. Inhaled pentamidine monthly can be substituted for patients with sulfa allergy.

Other supportive measures in myeloma include adequate analgesia and/or local irradiation for bone pain, radiation or surgery for spinal cord compression, surgery for impending pathologic fractures, erythropoietin for anemia, treatment and prevention of hypercalcemia, avoidance of dehydration by a high fluid intake of approximately 3 L per day to maintain renal function, and dialysis if necessary. Intravenous immunoglobulin therapy may be beneficial for patients with recurrent life-threatening infections.

Prophylactic anticoagulation to decrease the risk of thrombotic complications is recommended for myeloma patients receiving thalidomide- or lenalidomide-based therapies. The IMWG recommends a prophylaxis strategy according to a risk-assessment model. Risk factors to be considered include obesity, history of venous thromboembolism, central venous catheter, infections, diabetes, cardiac disease, chronic renal disease, immobilization, surgery, inherited thrombophilia, eythropoietin usage, myeloma diagnosis per se, hyperviscosity, and therapy with high-dose dexamethasone, doxorubicin or multiagent chemotherapy in combination with thalidomide or lenalidomide. Patients with one risk factor should receive prophylaxis with aspirin (81 to 325 mg once daily). Low-molecular-weight heparin (equivalent to a dose of enoxaparin 40 mg per day) is recommended for patients with $\geq$2 risk factors. Warfarin targeting a therapeutic INR of 2 to 3 is an alternative to low-molecular-weight heparin.

REFRACTORY OR RELAPSED DISEASE

Almost all MM patients eventually relapse and are again treated with multidrug novel agent combinations. The remission duration in MM decreases with each subsequent line of therapy used. Patients with relapsed MM refractory to lenalidomide and bortezomib have a poor prognosis with median PFS and OS of 5 months and 9 months, respectively.

Novel agents that are FDA approved based on phase 3 trials for use in relapsed and/or refractory MM include single-agent bortezomib, bortezomib in combination with pegylated liposomal doxorubicin, and lenalidomide in combination with dexamethasone (Table 27.9). Other salvage regimens that have shown efficacy include thalidomide with or without dexamethasone, bortezomib in combination with dexamethasone, single-agent lenalidomide, high-dose pulse dexamethasone, VAD, cyclophosphamide-VAD, high-dose cyclophosphamide, DCEP, and DT-PACE or VDT-PACE.

Patients relapsing more than 6 months after primary induction therapy may be retreated with the initial regimen or other novel agent combinations (VRD or VTD). Patients who have had only one ASCT should be considered for a second ASCT as salvage therapy. Patients with indolent relapse can be often treated with bortezomib, lenalidomide, or alkylators plus low-dose corticosteroids. Patients with more aggressive relapse or plasma cell leukemia often require aggressive multiagent salvage chemotherapy like VCD, VRd, or VDT-PACE. Duration of therapy in relapsed disease is not standard and discontinuation may be considered to minimize toxicity if a stable disease plateau phase is achieved.

Pomalidomide, a novel immunomodulatory agent, and carfilzomib, a second-generation proteasome inhibitor, are two new drugs with efficacy in relapsed, refractory MM and should be considered for patients refractory to bortezomib and lenalidomide. In MM-002, a multicenter, randomized, open-label study, 221 patients with relapsed and refractory MM who were refractory to lenalidomide and bortezomib were randomized to receive pomalidomide alone or pomalidomide plus low-dose dexamethasone. The overall response rate was 7% in patients treated with pomalidomide alone, and 29% in pomalidomide plus low-dose dexamethasone arm. The median response duration was not evaluable in the pomalidomide alone arm and was 7.4 months in the pomalidomide plus low-dose dexamethasone arm. A multicenter, phase 3 randomized trial (MM-003) comparing pomalidomide plus low-dose dexamethasone (pomalidomide 4 mg on days 1 to 21 and dexamethasone 40 mg on days 1, 8, 15, and 22 in a 28-day cycle) versus high-dose dexamethasone (40 mg on days 1 to 4, 9 to 12, and 17 to 20 in a 28-day cycle) showed that PFS was significantly longer with the combination versus dexamethasone alone (median 15.7 vs. 8.0 weeks). Median duration of treatment was 12.4 weeks in the pomalidomide arm. Frequent grade 3/4 hematologic toxicities included neutropenia (42%), thrombocytopenia (21%), and febrile neutropenia (7%).

In the phase 2 study leading to accelerated FDA approval, single-agent carfilzomib was administered at a dose of 20 mg/m^2 intravenously twice weekly for 3 of 4 weeks in cycle 1, and if tolerated, then 27 mg/m^2. A total of 95% were refractory to their last therapy; 80% were refractory or intolerant to both bortezomib and lenalidomide. The overall response rate was 23.7% with median duration of response of 7.8 months. The median overall survival was 15.6 months. Fatigue, anemia, and nausea were seen in nearly half of the patients. Thrombocytopenia (39%) and peripheral neuropathy (12.4%) were other adverse events reported in the trial. Carfilzomib has also shown promise in newly diagnosed MM; further studies are ongoing. Currently both pomalidomide and carfilzomib are approved for the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.

Myeloablative as well as nonmyeloablative allogeneic stem cell transplantation may potentially benefit a small percentage of patients because of a powerful graft-versus-myeloma effect, however associated with high treatment-related mortality (TRM) of up to 50% and 10% to 20% respectively. The role of allogeneic transplantation remains controversial and largely investigational. Nevertheless, up to 50% of patients relapse following allogeneic transplantation; therefore, at present, this option is far from ideal for most patients.

REVIEW QUESTIONS

1. A 68-year-old lady is found to have IgA lambda M-spike of 3.1 g/dL on evaluation for lower back pain. Her hemoglobin is 12 g/dL, MCV 87 fL, and platelets 212 × 10^9/mm^3, and serum calcium and creatinine are normal. A skeletal survey reveals no lytic lesions. MRI pelvis and MRI lumbosacral spine are negative for bony deformities, but show a moderate disk bulge at L2 without neural impingement. Her bone marrow biopsy reveals 25% lambda restricted plasma cells. Congo red stain is negative. What is the most likely diagnosis?

A. Monoclonal gammopathy of uncertain significance
B. AL amyloidosis
C. SMM
D. MM

(*continued*)

2. A 60-year-old man with IgG kappa MM presents with modest renal insufficiency and bone pain. He is treated with thalidomide plus dexamethasone, but his urine M-spike continues to increase. After 2 months of therapy, he is re-evaluated and found to have hemoglobin of 8.7 g/dL and creatinine of 4.8 mg/dL. His serum calcium is normal. His urine M-spike has further increased. Which of the following treatment options is most appropriate at this time?

A. Bortezomib-based therapy
B. Lenalidomide-based therapy
C. Melphalan and prednisone
D. Increase thalidomide dose

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28

Non-Hodgkin Lymphoma

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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. The past two decades have seen significant therapeutic advancements as well as progress in our understanding of the genetic and molecular basis of the different NHL subtypes.

EPIDEMIOLOGY

NHL is the seventh most common adult malignancy in the United States, with 70,130 new cases expected to be diagnosed in 2012. 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. Although NHL occurs within all ethnic groups, it is most common in the Caucasian population. There is also 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.

There has long been speculation that certain environmental or lifestyle factors may contribute to the increased incidence of NHL. Although a variety of positive associations have been identified in recent years (i.e., exposure to organic solvents and hair dyes, smoking, BMI, high-fat diet, alcohol abstinence), these associations have generally been weak, inconsistent between studies, and confounded by various methodologic limitations. Consequently, the extent to which these external factors affect overall or subtype incidence rates remains unclear at this time, and further study is clearly warranted.

PATHOGENESIS AND MOLECULAR CHARACTERIZATION

The process of lymphomagenesis in NHL involves a complex interplay between genetic mutations that disrupt the normal cellular pathways of proliferation, differentiation, and apoptosis. These mutations lead to activation of proto-oncogenes and/or inactivation of tumor suppressor genes vital to the

Table 28.1 Molecular Characteristics of B-Cell Lymphomas

Histology	Cytogenetics	Oncogene/Protein
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Trisomy 12[a], 13q–, 11q–, 17p–	
Lymphoplasmacytoid lymphoma/ Waldenström macroglobulinemia	t(9;14)	PAX-5
Follicular[b]	t(14;18)	BCL-2
Marginal zone[c]	Trisomy 3, t(11;18)	
Mantle cell lymphoma	t(11;14)	BCL-1/cyclin D1
Diffuse large B cell[d]	t(14;18), 3q–, 17p–	BCL-2, BCL-6, P53
Primary mediastinal B-cell lymphoma	Gains 9p	REL gene, MAL gene overexpression
Lymphoblastic lymphoma/leukemia	t(9;22), t(12;21), t(1;19)	BCR/ABL, TEL/ AML1, PBX/E2A
Burkitt lymphoma	t(8;14), t(2;8), t(8;22)	C-MYC

[a]Trisomy 12 is seen in 30% of cases and abnormalities in 13q are present in 25% of patients.
[b]t(14;18) is present in 75–95% of FL.
[c]Cytogenetic abnormalities have been seen in extranodal MZ NHL.
[d]Bcl-2 rearrangements in up to 30% and Bcl-6 in up to 45% of cases of DLBCL.

maintenance of regulated cellular proliferation. Balanced chromosomal translocations, thought to serve as inciting events in lymphomagenesis in NHL, are identified in a substantial percentage of cases (Tables 28.1 and 28.2). The notable exception is chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), which is characterized by a predominance of partial chromosomal deletions (13q–, 11q–, 17p–) and a conspicuous absence of balanced translocations.

Disorders of the immune system, often in conjunction with chronic viral infection, are also heavily implicated in lymphomagenesis and are associated with increased risk of NHL. Significantly higher rates of NHL are seen in patients with congenital and acquired immunodeficiencies as well as diseases of immune dysregulation. Though most of these lymphomas are of B-cell lineage, there are notable

Table 28.2 Molecular Characteristics of T-Cell Lymphomas

Histology	Cytogenetics	Oncoprotein	TCR Gene Rearrangements
T-CLL/T-PLL	Inv14, Trisomy 8q	Bcl-3	+
Mycosis fungoides			+
Peripheral T-cell lymphoma unspecified	9p–, 5q–, 12q–		+
Angioimmunoblastic T-cell lymphoma[a]	Trisomy 3 or 5		+
ATL	HTLV-1 integration+		+
Enteropathy T cell			β+
Hepatosplenic			δγ+
Systemic ALCL[b,c]	t(2;5)	Alk	+
Precursor T-lymphoblastic lymphoma/leukemia	Variable t(7;9)	Tcl-4	Variable

TCR, T-cell receptor; CLL, chronic lymphocytic leukemia; PLL, prolymphocytic leukemia; ATL, adult T-cell lymphoma/leukemia; ALCL, anaplastic large cell lymphoma.
[a]TCR gene rearrangement is present in 75% and IgH in 10%.
[b]TCR gene rearrangement in 60% +.
[c]Alk, anaplastic lymphoma kinase.

exceptions such as enteropathy-associated T-cell lymphoma (EATL), which occurs most commonly in patients with gluten enteropathy, and hepatosplenic T-cell lymphoma (HSTCL), which occurs in patients with inflammatory bowel disease or post–solid organ transplantation.

Epstein-Barr virus (EBV) is implicated in the pathogenesis of many different subtypes of NHL that occur in the immunocompromised host. Within the HIV-infected population, EBV is strongly associated with primary CNS lymphoma (PCNSL) and plasmablastic lymphoma, oral type. It is also seen in immunodeficient patients with primary effusion lymphoma (PEL), plasmablastic lymphoma, and post-transplant lymphoproliferative disorder (PTLD). EBV is also pathogenically implicated in a number of NHL subtypes in immunocompetent patients. In many of these lymphomas, EBV is thought to drive lymphomagenesis by constitutively activating NF-κB and other cell signaling pathways, while in other lymphomas its pathogenic role remains unknown.

Various other infectious pathogens have also been implicated in the development of NHL subtypes, such as HHV-8 and HTLV-1. Marginal zone lymphoma (MZL) is known to be antigenically driven by both viral and bacterial pathogens, to include hepatitis C virus (HCV) in splenic and nodal MZL variants, *Helicobacter pylori* in gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and *Chlamydia psittaci* in ocular adnexal MALT lymphoma (OAML).

CLASSIFICATION

NHL is classified according to the 2008 update of the World Health Organization (WHO) classification system. 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 current classification system for NHL will continue to evolve as our knowledge of the genetic and molecular basis of these diseases continues to improve.

DIAGNOSIS

A properly evaluated and technically adequate excisional lymph node biopsy remains the gold standard for diagnosis of suspected lymphoma. In recent years, 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, multiple factors—including include perioperative risk, institutional experience with core-needle biopsy, and risk of possible delay in diagnosis—need to be considered when deciding upon the preferred approach to biopsy.

Diagnosis of NHL is achieved primarily through a combination of morphologic and immunohistochemical tissue analysis. Important additional studies for diagnostic confirmation and subclassification often include flow cytometry, cytogenetic analysis, and molecular studies. Testing for specific oncogenic chromosomal rearrangements or staining for overexpression of their corresponding oncoproteins can also be diagnostically useful in a number of NHL subtypes (see Tables 28.1 and 28.2).

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. In addition, the following tests should be performed:

- Complete blood count with differential
- Complete metabolic panel to include lactate dehydrogenase (LDH)

- Serologies for HIV, HBV, HCV (regardless of exposure history)
- CT scan of the chest, abdomen, and pelvis
- Whole-body FDG-PET scan (strongly consider for aggressive lymphomas, or if concern exists for extranodal disease)
- Bone marrow (BM) aspirate and biopsy
- Lumbar puncture with CSF cytology and flow cytometry (patients at increased risk for central nervous system [CNS] disease: BL, ALL, intravascular lymphoma, elevated LDH, multiple extranodal sites, or involvement of BM, testis, or paranasal sinuses)

The Ann Arbor staging system, originally designed for Hodgkin lymphoma, also has prognostic and predictive utility in NHL, and its use is considered standard for newly diagnosed cases (Table 28.3). Although this system is often of limited prognostic value due to the lack of contiguous orderly spread through lymph node regions, it nevertheless remains an integral component of the validated international prognostic indices for aggressive NHL (IPI) and follicular lymphoma (FLIPI).

Restaging for Response Evaluation

Upon completion of therapy, staging studies should be repeated (CT scan and BM biopsy if positive previously). In accordance with the Revised Response Criteria for Malignant Lymphoma, FDG-PET is also useful for the evaluation of residual masses at the completion of therapy. In cases of suspected disease relapse or refractoriness to initial therapy, repeat biopsy should be performed whenever possible, both to exclude nonmalignant causes of the abnormal imaging or findings in question and to evaluate for possible transformation of disease.

Table 28.3 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 (e.g., 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 paraaortic, 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.

PROGNOSTIC FEATURES

The International Prognostic Index (IPI) applies to untreated 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 to 1, 2, and 3, and 4 to 5 correspond to 5-year survivals of 73%, 51%, 43%, and 26%, respectively. A validated clinical prognostic index has also been applied to patients with untreated follicular lymphoma. The Follicular Lymphoma International Prognostic Index (FLIPI) is scored according to age, stage, serum LDH level, hemoglobin, and the number of nodal areas, and has been found to reliably predict survival. In recent years, gene expression profiling has emerged as a useful means of identifying molecularly distinct subclassifications of NHL, and is likely to either augment or supplant current prognostic and predictive tools in the future. At this time, however, this technology remains investigational and not readily applicable to standard practice.

MANAGEMENT

Indolent B-Cell Non-Hodgkin Lymphoma

Follicular Lymphoma

FL is the most common of the indolent lymphomas, constituting approximately 70% of cases. 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. Median survival is approximately 10 years. Histologic transformation to a more aggressive NHL subtype (typically DLBCL) occurs at an approximate cumulative rate of 3% per year. 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 is considered a variant of DLBCL for the purposes of treatment.

FL is generally considered to be an incurable malignancy. Patients with early-stage FL, however, may achieve prolonged remissions and long-term survival with radiation treatment alone. Multiple studies have reported a 15-year overall survival rate of approximately 50% in these patients, with few relapses reported after 10 years. For patients with asymptomatic advanced-stage FL, chemotherapy has not been shown to improve OS compared to watchful waiting. In recent years, the anti-CD20 monoclonal antibody, rituximab, has demonstrated both safety and efficacy in follicular lymphoma with response rates of up to 73% in previously untreated patients. However, there is not yet evidence of a survival benefit to rituximab in the first-line setting in asymptomatic patients, and this approach is still considered investigational. In therapy-naive patients with symptomatic advanced FL by the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, the addition of rituximab to chemotherapy is now considered the standard of care due to the significantly higher response rates and OS achieved over chemotherapy alone in multiple studies. Although no chemoimmunotherapy regimen has yet demonstrated superior survival over another, the combination of bendamustine and rituximab (BR), in an early report, demonstrated superior progression-free survival (PFS) and reduced toxicity compared to the combination of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) in patients with low-grade NHL (predominantly FL). Patients not able to tolerate chemotherapy may be given single-agent rituximab. Extended treatment with rituximab, or "maintenance" rituximab, has been shown to extend PFS, although no OS advantage has yet been demonstrated.

Patients with relapsed/refractory FL can be treated with combination chemoimmunotherapy, single-agent rituximab, or radioimmunotherapy. The latter involves the delivery of targeted radiotherapy to tumor tissue by conjugating an anti-CD20 antibody to a radioactive isotope. In a randomized trial of relapsed or refractory follicular or transformed lymphoma, the overall response rate was better with

ibritumomab tiuxetan than with rituximab (80% vs. 56%). However, a recently published phase III intergroup trial evaluating the role of radioimmunotherapy in newly diagnosed FL patients (R-CHOP versus CHOP followed by ^{131}Iodine tositumomab) demonstrated similar PFS and OS in both groups at median 5 years of follow-up. Further studies of radioimmunotherapy in FL should better define the true benefit and optimal use of this treatment modality.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SLL represents the less common lymphomatous/aleukemic phenotype of CLL and both diseases are considered to be biologically the same. Median age at diagnosis is 72, and many patients are asymptomatic at diagnosis. Similar to FL, treatment is only indicated for symptomatic disease.

CLL/SLL is a clinically heterogeneous disease, ranging from stability or slow progression for years without treatment (most commonly the 13q– variant) to rapidly progressive disease with a high degree of resistance to conventional therapy (17p– variant). Chemoimmunotherapy regimens containing fludarabine and rituximab are considered standard of care for first-line therapy. The OS benefit of adding rituximab to chemotherapy was recently demonstrated in the German CLL8 trial which randomized patients to fludarabine, cyclophosphamide, and rituximab (FCR) versus FC alone. FCR and FR are both acceptable first-line therapies; although rates of complete response and PFS seem to be superior with FCR, it is a more toxic regimen than FR and there has yet to be a proven survival benefit. In patients with the 11q deletion, however, recent data indicate that the inclusion of cyclophosphamide may overcome the adverse prognostic significance of this genetic lesion. In elderly patients and those unlikely to tolerate FCR, options include FR, "FCR-lite" (reduced doses of FC with higher doses of R), BR, lenalidomide, or alemtuzumab. In contrast to FL, single-agent rituximab does not possess sufficient activity to warrant its use in CLL/SLL.

For relapsed/refractory CLL/SLL, any of the aforementioned regimens or agents can be used. Additionally, the second-generation anti-CD20 monoclonal antibody, ofatumumab, was recently FDA approved for CLL/SLL refractory to fludarabine and alemtuzumab. Compared to rituximab, ofatumumab binds with higher affinity to CD20 and has a response rate of over 50% in these "double-refractory" CLL patients. Studies combining ofatumumab with chemotherapy are ongoing.

Allogeneic hematopoietic stem cell transplantation (HSCT) remains an option for relapsed/refractory CLL/SLL. There is evidence of a strong and durable graft-versus-leukemia effect in patients transplanted for this disease, making it the only CLL therapy capable of achieving cure. Given the substantial risks and morbidity associated with this approach, however, it is generally reserved for patients who have failed conventional therapy and those with relapsed high risk (17p–) or transformed disease.

Lymphoplasmacytoid Lymphoma/Waldenström Macroglobulinemia

This is an indolent but incurable lymphoma composed of mature plasmacytoid lymphocytes that produce monoclonal IgM. It primarily affects older patients and is most common in the Caucasian population. 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. Symptomatic disease occurs in approximately 60% of patients within 5 years after diagnosis.

Options for therapy include single-agent rituximab, chemoimmunotherapy regimens such as FR or BR, and rituximab combined with novel agents 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

These are indolent lymphomas, comprising approximately 10% of NHL, that occur primarily in extranodal MALT (EMZL or MALT lymphomas), and to a lesser extent within the spleen (splenic MZL)

and lymph nodes (nodal MZL). The majority of EMZL occurs within the gastrointestinal tract (most commonly the stomach), but can also occur in the parotid and salivary glands, thyroid, lungs, ocular adnexae, and breast, among others. Most patients present with localized disease, and 5-year survival is approximately 90%. EMZL is highly antigen driven, and a history of chronic infection such as *Helicobacter pylori*-associated gastritis in gastric MALT lymphoma or *Chlamydiphila psittaci* in ocular adnexae MALT lymphoma is common. With current antibiotic regimens, the majority of patients with early-stage gastric MALT lymphoma will achieve sustained remission with bacterial eradication alone. Likewise, recent data indicate that eradication of *C. psittaci* with doxycycline can induce clinical remission in a substantial percentage of patients with ocular adnexae MALT lymphoma. For patients with advanced or antibiotic-refractory disease, or those with MALT subtypes not associated with known infectious agents, therapeutic options include rituximab, chemoimmunotherapy regimens similar to those used in FL, and radiation.

Splenic MZL accounts for approximately 20% of MZL, and typically presents with splenomegaly and BM involvement. Five-year overall survival is approximately 80%. Splenectomy has been the historical standard of care; however, rituximab is increasingly being used as an alternative or adjunct to surgical therapy, and in a recent prospective trial, was shown to significantly improve disease-free survival compared to splenectomy. Similar to EMZL, splenic MZL can also be antigen driven; approximately one-third of cases are associated with the 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 less indolent than its extranodal or splenic counterparts, and 5-year overall survival is lower at just over 50%. Although it can also be associated with HCV, it is typically not associated with a known infectious etiology. The therapeutic approach for nodal MZL follows that of FL.

Aggressive B-Cell Non-Hodgkin Lymphoma

Diffuse Large B-Cell Lymphoma

DLBCL is the most common NHL subtype, accounting for approximately 30% of all cases. Although it is most commonly diagnosed in the seventh decade of life, DLBCL can occur at any age. DLBCL can occur either de novo or as a transformation from a more indolent NHL subtype. Gene expression profiling can classify most DLBCL into two molecularly distinct subtypes, germinal center B cell (GCB) and activated B cell (ABC), with the latter being less curable with standard therapies. Although novel agents targeting the B-cell receptor signaling pathway (such as ibrutinib, a first-in-class inhibitor of Bruton Tyrosine Kinase or BTK) are showing great promise in ABC-type DLBCL and may ultimately improve long-term outcomes in these patients, they have not been studied in the first-line setting and are not yet commercially available. Consequently, the GCB/ABC distinction cannot yet be used to guide choice of initial therapy for DLBCL.

Patients with both early-stage and advanced DLBCL are treated with systemic chemoimmunotherapy with curative intent. In multiple studies, R-CHOP given every 21 days (R-CHOP-21) has been shown to significantly improve response rates, PFS, and OS compared to CHOP alone in previously untreated patients with advanced disease, and consequently this regimen is now considered standard. The addition of IFRT to an abbreviated course of systemic therapy is considered an option in patients with early-stage DLBCL, although such an approach has failed to demonstrate survival benefit over chemoimmunotherapy alone and introduces the risk of long-term complications of radiation treatment. Likewise, the use of "dose-dense" R-CHOP with myeloid growth factor support (R-CHOP-14) has failed to demonstrate superiority over standard R-CHOP-21, with a trend toward increased toxicity. Dose intensity may still have a role in DLBCL, however, as the dose-intensive regimen of R-ACVBP recently demonstrated superior 3-year PFS and OS in untreated DLBCL patients aged 18 to 59 with low-intermediate IPI compared to R-CHOP. Although serious adverse events were more than twice as common with R-ACVBP, it nevertheless remains a promising regimen that can be considered for younger patients. Dose-adjusted (DA) EPOCH-R is another alternative regimen that has shown promising results in phase II trials and is currently being evaluated against R-CHOP-21 in the phase III setting. This regimen has a lower observed incidence of cardiac toxicity compared to R-CHOP and can be considered for patients in whom this is a concern.

Primary mediastinal B-cell lymphoma (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 and increased risks of cardiac disease and secondary tumors, particularly breast cancer in females. Recently, the DA-EPOCH-R regimen has demonstrated high efficacy in this disease, obviating the need for radiation in almost all patients.

Up to 10% of patients with DLBCL harbor t(8;14) with overexpression of MYC, and many of these patients are also positive for t(14;18) with overexpression of BCL2 (so-called "double-hit" lymphoma). Many of these tumors may fit into the WHO category of "B-cell lymphoma unclassifiable with features intermediate between BL and DLBCL." In several retrospective studies, these patients have demonstrated inferior outcomes with standard therapies. The optimal management of patients with "double-hit" lymphoma is currently unknown.

Primary CNS Lymphoma

PCNSL is a rare and aggressive lymphoma that is confined to the CNS (brain parenchyma, meninges, cranial nerves, eyes, spinal cord). It is of DLBCL histology in over 95% of cases, and can occur in both immunocompetent and immunocompromised patients. It most commonly affects the brain parenchyma, although there can be concomitant or isolated leptomeningeal involvement in approximately 20% of cases. 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 DLBCL chemoimmunotherapy regimens due to inability of the component agents to penetrate effectively through the blood–brain barrier. High-dose methotrexate (3 to 3.5 g/m^2) achieves therapeutic levels within the CSF and produces high response rates and 5-year OS of 20% to 40%. In a recent randomized trial, the addition of high-dose cytarabine to high-dose methotrexate improved both response rates and OS, and consequently this combination is now considered standard of care in medically fit patients. The role of radiotherapy as an adjunct to chemotherapy remains controversial, as it is associated with significant and sometimes disabling neurotoxicity. Patients not achieving CR to chemotherapy are generally offered WBRT. Studies assessing the utility of postchemotherapy WBRT in patients achieving CR to chemotherapy are ongoing.

Burkitt Lymphoma

BL is a highly aggressive but curable lymphoma, accounting for 1% to 2% of lymphomas in the United States. The majority of cases in the United States and Western countries are either sporadic or associated with immunodeficiency, typically affecting children and young adults and demonstrating EBV positivity in 30% to 50% of cases. Endemic BL, by contrast, is strongly associated with EBV infection and is highly prevalent in young children in equatorial Africa. 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 are also common. All variants of BL are characterized by acute clinical onset and rapid disease progression without therapy.

Dose-intensive multiagent chemotherapy regimens incorporating high-dose methotrexate, high-dose cytarabine, and intrathecal chemotherapy (CODOX-M/IVAC, hyper-CVAD) are commonly used to treat BL, with approximately 60% to 80% of patients achieving long-term survival. The addition of rituximab to intensive chemotherapy was recently shown to improve EFS and OS in a randomized trial of over 250 patients with HIV-negative BL, and is now considered standard in most BL regimens. Additionally, a recent study of DA-EPOCH-R in BL yielded an event-free survival (EFS) of 97% at a median follow-up of 57 months. A confirmatory multicenter study of this regimen in BL and MYC+ DLBCL is ongoing.

Mantle Cell Lymphoma

MCL is an incurable and variably aggressive lymphoma. Median age at diagnosis is 60, and the majority of those affected are men. Patients commonly present with advanced disease, splenomegaly, and involvement of the BM, peripheral blood, and GI tract. Virtually all cases of MCL harbor t(11;14) with resultant overexpression of cyclin D1, although a small minority of MCL can be negative for this translocation.

Although response rates to chemotherapy are high in MCL, remissions tend to be short-lived and historic median survival is approximately 3 to 6 years. The recently developed mantle cell IPI (MIPI) classifies patients into prognostic categories based upon age, performance status, LDH, and WBC count, and can aid in therapeutic decision making. Given that a subset of MCL behaves in an indolent manner, watchful waiting is a reasonable approach in asymptomatic patients with a low risk MIPI. For symptomatic patients or those with a high risk MIPI, therapeutic options include standard chemotherapy (R-CHOP, BR, DA-EPOCH-R) or dose-intensive chemotherapy such as R-hyper-CVAD; although the latter approach has recently yielded impressive results (7-year OS of 68%), it has also been associated with considerable toxicity, especially in older patients.

High-dose chemotherapy with autologous stem cell rescue (HDT/ASCR) in first remission has been studied and may extend PFS over chemotherapy alone. However, this approach has not yet been shown to improve survival. Nonmyeloablative allogeneic SCT is still considered investigational, although at this time it remains the only potentially curative option. Novel agents such as bortezomib, lenalidomide, and temsirolimus have recently demonstrated significant activity in relapsed/refractory MCL, and are currently being studied in combination with chemotherapy and with each other in the first-line setting.

T/NK-Cell NHL

The term "peripheral T-cell lymphoma" (PTCL) encompasses the various lymphomas derived from mature T and natural killer (NK) cells, whereas "lymphoblastic lymphoma" (LBL) refers to the lymphomatous manifestation of acute lymphoblastic leukemia, a disorder of precursor/immature lymphocytes (most commonly of T-cell origin) that is addressed elsewhere in this handbook. 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 relatively aggressive lymphomas with poor response rates to chemotherapy and poor OS relative to B-cell lymphomas. There are notable exceptions, however, such as 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.

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)

This subclassification includes all T-cell lymphomas not identified as clinicopathologically distinct by the WHO classification. They are generally aggressive lymphomas that affect men disproportionately, present with both nodal and extranodal diseases, and respond poorly to CHOP-like chemotherapy, with 5-year OS of approximately 30% to 40%. Dose-intensive regimens such as hyper-CVAD have not been shown to improve outcomes over CHOP. A recent study of upfront HDT/ASCT in PTCL demonstrated good results, with long-term PFS of 44%. Although this approach is promising, randomized studies to assess the true benefit of HDT/ASCR are needed.

Several novel agents have demonstrated activity in relapsed/refractory PTCL in recent years, and are currently being evaluated in combination with chemotherapy and in the first-line setting. These include the histone deacetylase inhibitor, romidepsin, and the novel antifolate, pralatrexate, which have both been recently FDA approved for relapsed/refractory PTCL. Other agents being studied include alemtuzumab, vorinostat, denileukin deftitox, lenalidomide, and bortezomib.

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, and patients typically present with diffuse lymphadenopathy, hepatosplenomegaly, extranodal involvement, systemic symptoms, rash, and hypergammaglobulinemia. Autoimmune phenomena, both hematologic and nonhematologic, are also common. Response rates to anthracycline-based chemotherapy are relatively poor, and 5-year OS is approximately 30%. High-dose chemotherapy with autologous stem cell rescue as first-line therapy for AITL is being studied; however, at this time the benefit of this approach remains unclear. Immunosuppressive therapy with cyclosporine has shown promising early results, and can be considered for select patients. Otherwise, the approach to treatment of AITL largely follows that of PTCL-NOS.

Anaplastic Large Cell Lymphoma

ALCL is a CD30-positive subtype of PTCL that encompasses two biologically distinct diseases: ALCL that overexpresses anaplastic lymphoma kinase (ALK), 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, with a 5-year OS of approximately 70% after anthracycline-based chemotherapy. ALK-negative ALCL has poorer outcomes, and the approach to therapy generally follows that of PTCL-NOS. Additionally, the anti-CD30 monoclonal antibody/cytotoxic conjugate, brentuximab vedotin, was recently FDA approved for relapsed/refractory ALCL after demonstrating a 57% CR rate. This promising agent is being further evaluated in combination with chemotherapy and in the first-line setting.

Primary cutaneous ALCL is a separate disease entity characterized by indolent behavior, predominantly dermatologic involvement, and excellent long-term survival. Additionally, a recent phenomenon of primary breast ALCL occurring in women with breast implants has been reported over the past decade. A recent FDA analysis concluded that breast implants are potentially associated with an increased relative risk, but still very low absolute risk, of primary breast ALCL.

NK/T-Cell Lymphomas

The two main subclassifications of NK/T-cell lymphoma are extranodal NK/T-cell lymphoma, nasal type (ENKL), 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 and nasal cavity, and palate, and can also affect the skin, gastrointestinal tract, and testis. Patients with disease confined to the nasal cavity can be successfully treated IFRT with or without chemotherapy, while those with extranasal disease and ANKL have a very poor prognosis. Encouraging results have recently been seen with L-asparaginase-based chemotherapy regimens, and further studies evaluating this agent in ENKL and ANKL are ongoing.

Hepatosplenic T-Cell Lymphoma

This is a rare and aggressive PTCL that typically affects young men and involves the liver, spleen, and BM. Histologic diagnosis can often be difficult to obtain. Prognosis is poor regardless of choice of therapy, with a 5-year OS of less than 10%. There is no standard of care, although most patients are treated with CHOP-like regimens with or without HDT/ASCR.

Enteropathy-Associated T-Cell Lymphoma

This is a rare and aggressive PTCL of the small intestine that typically affects older individuals with celiac disease, although many patients are diagnosed with EATL who have no known history of enteropathy. Patients typically present with abdominal pain and anorexia. Prognosis is poor, with a 5-year OS of 20% in patients treated with conventional chemotherapy. Although many patients are unable to tolerate multiagent chemotherapy, a recent study reported a 5-year OS of 60% in patients treated with chemotherapy followed by HDT/ASCR.

Cutaneous T-Cell Lymphoma/Mycosis Fungoides

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 MFCG 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 (TSEBT). Patients with more advanced disease are treated initially with

systemic therapies such as extracorporeal photopheresis (ECP), 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.

Treatment Approaches for Relapsed Aggressive Lymphomas

Treatment for relapsed aggressive DLBCL generally involves salvage chemotherapy followed by HDT/ASCR in fit patients who demonstrate chemosensitive disease. Commonly used salvage chemotherapy regimens include R-ICE, R-DHAP, R-ESHAP, and EPOCH-R. Patients with chemoresistant disease do not benefit from HDT/ASCR and should be enrolled into clinical trials, considered for allogeneic HSCT, or treated palliatively. Additionally, the results of the recently published CORAL study indicate that the benefit of HDT/ASCR 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 HDT/ASCR. This study also demonstrated a similarly poor 3-year EFS in patients who relapsed less than 12 months after initial diagnosis. Consequently, careful consideration of disease factors, as well as a frank discussion of treatment and available trial options, should precede referral for HDT/ASCR. Nontransplant candidates who are not eligible for a clinical trial can be treated palliatively with any of the aforementioned salvage regimens or with BR or lenalidomide.

The other aggressive B-cell lymphomas (MCL, BL) and the majority of aggressive T-cell lymphomas are rarely, if ever, cured with conventional salvage chemotherapy or HDT/ASCR, although studies of HDT/ASCR in relapsed PTCL have demonstrated a 5-year OS of approximately 40% and patients with ALK-positive ALCL can be cured with this approach. HDT/ASCR is considered an option in patients with PTCL who demonstrate chemosensitivity to salvage chemotherapy, although again careful consideration should be given to investigational therapies to include allogeneic HSCT.

REVIEW QUESTIONS

1. Which of the following statements are true concerning chromosomal abnormalities in NHL?
   - **A.** BL is associated with t(8;14), t(2;8), or t(8;22).
   - **B.** Virtually all cases of mantle cell lymphoma harbor t(11;14), leading to overexpression of bcl-2.
   - **C.** Cyclin D1 is overexpressed in the majority of follicular lymphoma and is associated with t(14;18).
   - **D.** Patients with anaplastic large cell lymphoma harboring t(2;5) have a worse prognosis than those without this translocation.
   - **E.** Patients with CLL/SLL harboring an 11q deletion have a relatively favorable prognosis compared to patients with normal cytogenetics.
2. Which of the following statements is false regarding the molecular biology of DLBCL?
   - **A.** Patients with ABC-DLBCL have inferior PFS and OS compared to those with GCB-DLBCL.
   - **B.** The NF-κB pathway is constitutively activated in GCB-ABCL.
   - **C.** PMBL has a molecular signature that is distinct from that of ABC- or GCB-DLBCL.
   - **D.** PCNSL is typically of DLBCL histology.
   - **E.** DLBCL cases that harbor both BCL-2 and MYC translocations constitute a highly aggressive subgroup that respond poorly to current therapies.
3. A 55-year-old man presents to his primary care physician with progressive fatigue and night sweats. Physical examination reveals cervical and axillary lymphadenopathy, and laboratory analysis is notable for a hemoglobin of 11 g/dL, serum LDH 1.5 × ULN, and normal renal and hepatic function. He is referred for excisional biopsy of an enlarged left cervical lymph node, which reveals DLBCL. Subsequent oncologic staging workup includes a BM aspiration/biopsy which reveals no evidence of large malignant lymphocytes, and a PET/CT scan which reveals hypermetabolic lymphadenopathy in the neck, axillae, hilum, and retroperitoneum, as well

(*continued*)

as multiple hypermetabolic lytic foci within non–weight-bearing bones. Serologic testing for chronic hepatitis and HIV are negative. MUGA scan demonstrates normal cardiac function. The patient has an ECOG performance status of 1, but does not wish to be referred for a clinical trial. Which of the following is the most appropriate approach to treating this patient?

A. R-CHOP-21 for six cycles followed by posttherapy PET/CT scan and BM biopsy.
B. R-CHOP-14 with filgrastim for six cycles followed by posttherapy PET/CT scan and BM biopsy.
C. R-CHOP-21 for six cycles followed by posttherapy CT scan and BM biopsy.
D. R-CHOP-21 for four cycles if PET/CT after cycle 2 demonstrates complete response.
E. R-hyper-CVAD for eight cycles, followed by posttherapy CT scan and BM biopsy.

4. A 50-year-old man with symptomatic stage III follicular lymphoma (histologic grade 2) is treated with six cycles of BR and obtains a complete remission. Two years later, he presents with worsening fatigue and frequent drenching night sweats. His examination reveals new anterior cervical and axillary lymphadenopathy and splenomegaly. Laboratory analysis reveals a hemoglobin of 9.5 g/dL, serum LDH 2 × the upper limit of normal, AST, and ALT 2× the upper limit of normal, and normal renal function. CT scan reveals multiple new enlarged cervical lymph nodes (2 cm maximal diameter), a 3 cm right axillary node, a 4 cm right external iliac node, splenomegaly (16 cm craniocaudal), and several enhancing foci within the liver (2 cm maximal diameter). Subsequent PET scan reveals moderate hypermetabolism (SUVs 5 to 10) within the cervical nodes and liver lesions, SUV of 14 within the right external iliac node, and SUV of 21 within the right axillary node. A surveillance CT scan performed 6 months ago revealed no abnormalities. What is the most appropriate next step?

A. Initiate salvage therapy for relapsed FL with R-CHOP.
B. Initiate salvage therapy for relapsed FL with ibritumomab tiutexan.
C. Initiate salvage therapy for relapsed FL with BR.
D. Obtain BM aspirate/biopsy.
E. Obtain BM aspirate/biopsy and excisional biopsy of the right axillary lymph node.

5. A 34-year-old woman presents to her primary care physician with progressive dyspnea on exertion and cough. Physical examination reveals mild facial plethora. Chest x-ray reveals mediastinal widening. Subsequent CT scan of the chest, abdomen, and pelvis is notable for a large mediastinal mass (13 cm in maximal diameter) compressing the SVC, and no other significant findings. Laboratory analysis reveals elevated LDH but is otherwise unremarkable. Tissue biopsy obtained via cervical mediastinoscopy reveals numerous large malignant lymphocytes in a sclerotic background that possess the following immunophenotype: CD20 strong+, CD23+, CD45+, CD79a+, Bcl6+, Mum1+, CD30 weak+, CD15–. What is the most likely diagnosis?

A. Hodgkin lymphoma
B. T-lymphoblastic lymphoma
C. PMBL
D. SLL
E. Mantle cell lymphoma

Suggested Readings

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29

Hodgkin Lymphoma

Mehdi Hamadani and Elaine S. Jaffe

EPIDEMIOLOGY

Hodgkin lymphoma (HL) is a common lymphoid malignancy, representing 11% of all lymphomas. Approximately 9,000 patients were diagnosed with HL in 2012 in the United States. Median age at the time of diagnosis is 38 years, with a bimodal age distribution in resource-rich countries, showing a first peak at 15 to 35 years and a second peak after the age of 50 years. The age-adjusted incidence rate of HL is 2.8 per 100,000 individuals per year. Unlike non-Hodgkin lymphoma, 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 less commonly than Caucasians.

ETIOLOGY AND RISK FACTORS

The cause of HL remains unknown.

- Epstein-Barr virus (EBV) has been postulated to play a role in the pathogenesis of classical HL (CHL) (particularly mixed cellularity and lymphocyte-depleted subtypes).
- Loss of immune surveillance in immunodeficiency states (e.g., HIV infection, allogeneic stem cell transplantation, and solid organ transplantation) may predispose to development of HL.
- Twofold increased risk of HL is seen in smokers.
- Family history of classical HL increases the risk to develop disease by threefold to ninefold. Identical twin sibling of a HL patient has a 99-fold higher risk of developing HL.

PATHOLOGY

HL is a neoplastic disease of B-cell origin. CHL is characterized by the presence of Reed-Sternberg (RS) cells and mononuclear variants, amidst an inflammatory background that is composed of lymphocytes, eosinophils, monocytes, and histiocytes. Nodular lymphocyte predominance HL (NLPHL) is characterized by LP cells in a background of lymphocytes and histiocytes but without other inflammatory cells.

RS and LP cells are derived from the follicular center B cells with clonally rearranged V heavy-chain genes. RS cells often exhibit two mirror-image nuclei (owl's eyes appearance) (Fig. 29.1). RS cells are positive for CD30 and CD15 and typically negative for CD20 and CD45, whereas LP cells more fully express a normal B-cell program.

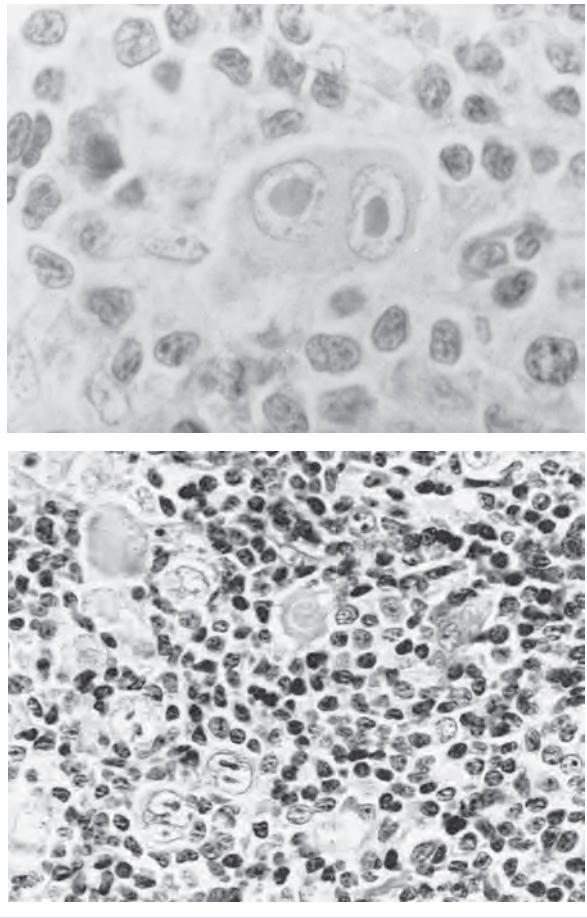

FIGURE 29.1 (A) Diagnostic Reed-Sternberg (RS) cell, seen in classic types of Hodgkin lymphomas (mixed cellularity, nodular sclerosis, lymphocyte depletion). (B) Variants of RS cells seen in nodular lymphocyte-predominant Hodgkin lymphomas: popcorn cells or L and H cells (lymphocytic or histiocytic predominance). RS cells of the classic type generally are not seen in a nodular lymphocyte-predominant Hodgkin lymphoma.

Pathologic Classification

The World Health Organization (WHO) classification divides HL into two main types (Table 29.1):

- CHL
  - CHL is characterized by the presence of RS cells in an inflammatory background and is divided into four histologic subtypes.
    - Nodular sclerosis HL
    - Mixed cellularity HL
    - Lymphocyte-rich HL
    - Lymphocyte-depleted HL
- NLPHL
  - NLPHL lacks RS cells but is characterized by LP cells, which are sometimes referred to as *popcorn cells*.

Table 29.2 summarizes the clinical and pathologic features of the disease subtypes.

Table 29.1 Immunophenotypic Features of Hodgkin Lymphoma

	Classical 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	Majority of cases positive	Negative

[a]Positive in rare cases.
[b]Present in up to 40% of the cases but usually expressed on minority of tumor cells with variable intensity.

CLINICAL FEATURES

- Lymphadenopathy: Most commonly above the diaphragm (cervical, axillary, or mediastinal). Enlarged nodes are not tender 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 lung, bone marrow, liver, and bones.
- 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

Table 29.2 Classification of Hodgkin Lymphoma

Pathologic Type	Pathologic Features	Clinical Features
Classical 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 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	No RS cells, but characterized by "popcorn" or LP 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

Table 29.3 Cotswolds Modified Ann Arbor Staging of Lymphoma

Stage I	Single lymph node region, lymphoid structure (e.g., 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 IV	Diffuse or disseminated involvement of one or more extranodal organs or tissue 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

Staging

The modified Ann Arbor staging of lymphoma is used to clinically stage HL (Table 29.3).

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. 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 (LDH) 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

- Chest radiograph.
- Computerized tomography (CT) scan of the chest, abdomen, and pelvis are required for staging. CT-scan of the neck may sometimes be needed.
- Positron emission tomography (PET) CT-scan.

Unilateral Bone Marrow Biopsy and Aspiration

Required in clinical stage IB, IIB, III, or IV.

Evaluation/Procedures for Specific Treatments and Counseling

- MUGA scan or echocardiography to evaluate left ventricular ejection fraction before anthracycline treatment.
- Pulmonary function tests (including DLCO) are recommended prior to bleomycin-containing treatment.
- Fertility counseling (to discuss sperm, ovarian tissue, and/or oocyte cryopreservation).
- Smoking cessation counseling.
- Vaccination (pneumococcal, hemophilus influenza, and meningococcal) prior to splenic irradiation is recommended.

MANAGEMENT

- HL is sensitive to radiation and many chemotherapeutic agents. All patients, regardless of stage, should be treated with a curative intent. 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, but 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 CXR) disease is widely practiced in North American centers; however, radiation consolidation may not be necessary in PET-negative bulky masses.

Principles of Chemotherapy

- The standard regimen for HL in North America is ABVD since it superseded MOPP regimen in the large randomized trial of the Cancer and Leukemia Group B (CALGB) in 1992 (Table 29.4). ABVD was associated with less myelosuppression and reduced risk of secondary leukemias and infertility compared to MOPP regimen. Growth factors are not required with ABVD. Treatment delay and/or dose reduction due to leukopenia is not recommended.
- The German Hodgkin Lymphoma Study Group (GHSG) developed the dose-escalated BEACOPP regimen and showed it to be superior to COPP-ABVD and standard-dose BEACOPP in advanced HL. However the significant associated toxicities of dose-escalated BEACOPP (3% rate of treatment-related death, 2% to 3% rate of secondary leukemias, and nearly universal infertility) has precluded its widespread use in North America. Dose-escalated BEACOPP is not recommended for elderly HL patients (≥60 years).
- Stanford V is a dose-intense 12-week regimen. Involved field radiation to macroscopic splenic disease and all lymph nodes measuring ≥ 5 cm in size is an integral part of Stanford V. The cumulative doses of doxorubicin and bleomycin in Stanford V are less than those in ABVD, with potentially less risk for cardiac and pulmonary toxicity. In the three randomized prospective trials (from Italy, United Kingdom, and United States) compared to ABVD, Stanford V had inferior complete remission rates and was associated with more hematologic and neurologic toxicity.

Chemotherapy regimens are described in Table 29.5.

Principles of Radiotherapy

- Radiation therapy for HL targets sites with either clinical disease (involved field or involved nodal) 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.

Table 29.4 CALGB Study Comparing Different Regimens in Hodgkin Lymphoma

Regimen	Complete Response Rate (%)	5-y Overall Survival Rate (%)
MOPP	67	66
ABVD	82	73
Alternating MOPP/ABVD	83	75

Table 29.5 Commonly Used Chemotherapy Regimens for Hodgkin Lymphoma

ABVD (every 28 d)	Doxorubicin 25 mg/m²/dose IV on days 1 and 15 Bleomycin 10 units/m²/dose IV on days 1 and 15 Vinblastine 6 mg/m²/dose IV on days 1 and 15 Dacarbazine (DTIC) 375 mg/m²/dose IV on days 1 and 15
Dose-escalated BEACOPP (every 3 wk)	Bleomycin 10 international units/m² IV on day 8 Etoposide (VP-16) 200 mg/m² IV on days 1–3 Doxorubicin (Adriamycin) 35 mg/m² on day 1 Cyclophosphamide (Cytoxan) 1,200 mg/m² on day 1 Vincristine 1.4 mg/m² (max 2 mg) on day 8 Procarbazine 100 mg/m² PO on days 1–7 Prednisone 40 mg/m² PO on days 1–14 Filgrastim (G-CSF) support is needed
Stanford V (every 4 wk) × three cycles (12 wk)	Nitrogen mustard 6 mg/m² IV day 1 Doxorubicin (Adriamycin) 25 mg/m² IV days1 and 15 Vinblastine 6 mg/m² IV days 1 and 15 Vincristine 1.4 mg/m² IV days 8 and 22 (maximum dose is 2 mg/dose). Bleomycin 5 units/m² IV days 8 and 22 Etoposide (VP-16) 60 mg/m² IV days 15 and 16 Prednisone 40 mg PO qod × 10 wk, then taper by 10 mg every other day between weeks 10 and 12 For patients older than 50, reduce vinblastine to 4 mg/m² and vincristine to 1 mg/m² in cycle 3

Treatment Response Evaluation

All patients (early and late stages) should receive interim restaging (after two and/or four cycles of chemotherapy) to evaluate the response to treatment. Restaging should be repeated 3 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 CHL should be treated with intent to cure. Poor risk factors have been identified in this subset of patients.

GHSG Unfavorable Prognostic Features for Early-Stage Disease (I and II)

Any of the following four features:

- Extranodal disease
- Bulky disease: A mass >10 cm in diameter or high mediastinal mass ratio (> one-third of maximum intrathoracic diameter)
- ESR >50 with no B symptoms, or >30 with B symptoms
- More than 2 nodal areas

Early-stage patients with bulky disease and stage IIB patients are best treated like advanced-stage (stage III/IV) disease. The remaining early-stage patients can be managed as following:

- Favorable early disease (by GHSG criteria): These patients are treated with ABVD × two cycles followed by 20 Gy of involved field radiation. The cure rate of these patients is >90%.
- Unfavorable early disease (by GHSG criteria): These patients are treated with ABVD × four cycles followed by 30 Gy of involved field radiation.
- An alternative for early-stage disease is chemotherapy with four to six cycles of ABVD alone without involved field radiation. This option is especially attractive for patients with abdomen only disease

and in young patients where involved field radiation to chest or axillae is associated with a high risk of subsequent second cancers (particularly breast cancer in young female patients) and premature coronary artery disease.
- 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)

Aggressive histology (e.g., mixed cellularity or lymphocyte-depleted) is more common among patients with advanced CHL. In North America, subjects with bulky stage I or II disease and those with stage IIB are managed like patients with advanced-stage (III/IV) disease.

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
- 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%).

Increased number of tumor-associated (CD68+) macrophages is strongly associated with shortened survival in patients with CHL. The 10-year survival of HL patients with <5% CD68+ macrophages in lymph node biopsy is 88%, compared to only 59% in those with >25% CD68+ cells.

The goal of treatment in advanced CHL should be curative. The primary treatment of advanced disease is chemotherapy. ABVD is the standard of care in North American centers. The recommended initial treatment is six cycles of ABVD. Nonbulky advanced-stage patients with a negative PET-CT at the end of chemotherapy do not need radiotherapy consolidation. 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 field RT. While not commonly used in North America, dose-escalated BEACOPP is an alternative option in younger patients with high-risk disease (e.g., ≥4 unfavorable factors). The recommended initial treatment is six cycles of BEACOPP. Stanford V is not recommended outside the setting of a clinical trial.

TREATMENT OF NODULAR LYMPHOCYTE–PREDOMINANT HODGKIN LYMPHOMA

The NLPHL subtype represents 5% of HL. Unlike CHL, NLPHL is strongly CD20 positive and typically behaves like an indolent non-Hodgkin lymphoma. 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 30 to 36 Gy of involved field radiation alone.
- Stages IA, IB, IIA, and IIB can be managed with a combined-modality approach (e.g., two to four cycles of ABVD or R-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 non-Hodgkin lymphomas such as CHOP, CVP, or dose-escalated EPOCH with rituximab (because of strong CD20 expression on LP 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 non-Hodgkin lymphomas.

Follow-up after Completion of Treatment

The purpose of follow-up is detection of disease relapse and late treatment-related complications.

- Clinical evaluation with CBC, ESR, chemistry panel every 3 months for 2 years, then every 6 months for 5 years
- CT of chest, abdomen, and pelvis should be done every 3 to 6 months for 3 years, then annually for up to 5 years. Surveillance PET-CT-scan is controversial because of high false-positive results.
- Annual influenza vaccination.
- TSH annually if neck RT was given (risk of hypothyroidism).
- Annual mammogram screening should start 8 to 10 years after 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 10 and 30 years. Breast self-exam should be encouraged.

LATE TREATMENT–RELATED COMPLICATIONS

- Hypothyroidism 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 G-CSF is used during treatment; hence G-CSF use is discouraged with ABVD.
- Cardiac toxicity secondary to anthracycline is uncommon (total cumulative anthracycline dose is not high). The risk for premature coronary artery disease and cerebrovascular accidents is increased after mediastinal and cervical RT, respectively.
- Lhermitte sign: It is an infrequent complication that can occur 6 to 12 weeks after neck RT and resolves spontaneously. Patients feel electric-like shock sensation radiating down the back and extremities when neck is flexed. This sign is attributed to transient spinal cord demyelinization.
- Capsulated organism infection (pneumococcal, meningococcal, and hemophilus) can occur in patients not vaccinated after splenic RT or splenectomy (rarely used now).

TREATMENT OF RELAPSED HODGKIN LYMPHOMA

- 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 without autologous transplantation can be very effective treatment.

Table 29.6 Salvage Chemotherapy Regimen for Hodgkin Lymphoma

ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin)
ICE (ifosfamide, carboplatin, and etoposide)
DHAP (dexamethasone, high-dose cytarabine, and cisplatin)
GND (gemcitabine, nevalbine, and doxil)
GCP (gemcitabine, cisplatin, and methylprednisolone)

- If conventional chemotherapy (with or without RT) was the primary treatment, salvage chemotherapy such as ICE, DHAP, ESHAP, and GND (Table 29.6) followed by autologous transplantation is curative for about 50% of the patients.
- Brentuximab vedotin, an antibody-drug conjugate, is an attractive option for HL patients relapsing after autologous transplantation, or ones who are not a candidate for autologous transplantation. The drug consists of an anti-CD30 chimeric monoclonal antibody; brentuximab, linked to the antimitotic agent; monomethyl auristatin E (MMAE). The antibody portion of the drug attaches to CD30 on the surface of HL cells, delivering MMAE which is exerts anti-HL activity.
- 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.

- NLPHL: Relapsed disease is best approached as an indolent lymphoma. Reasonable options include observation, rituximab alone or with chemotherapy, and/or RT.

Palliative Treatment

- Sequential single-agent chemotherapy such as gemcitabine, vinblastine, bendamustine, or lenalidomide.
- RT can be used to relieve pain or pressure symptoms of bulky masses.
- Investigational treatment is encouraged through enrollment in clinical trials.

Future Directions

- Interim-negative PET-CT (after two to three cycles of chemotherapy) is a strong predictor of an excellent outcome, and might be a useful tool to identify patients with a high likelihood of cure. Ongoing studies are using interim PET-CT to develop "tailored" therapies for individual patients. Trials are deescalating treatment length and intensity in good-risk patients with a negative interim PET-CT (e.g., omitting RT in early-stage patients, or treating with only two or four cycles of ABVD alone) to reduce the long-term treatment-related complications, while in the poor-risk patients who have a positive interim PET-CT, trials are examining the role of escalating therapy (e.g., switching from ABVD to dose-escalated BEACOPP).
- Recently completed trials (e.g., EORTC 20012 study) comparing ABVD against BEACOPP in patients with high IPS score advanced-stage disease, in the coming years, will clarify if these high-risk patients benefit from more aggressive approaches upfront.
- Phase III studies are being planned to combine brentuximab vedotin in a first-line setting to improve patient outcomes.

REVIEW QUESTIONS

1. A 19-year-old heterosexual, single African American male presented with a two-month history of right supraclavicular lymph node enlargement. He denied weight loss, night sweats, or unexplained fevers. Physical examination showed a 2 cm firm lymph node in the right supraclavicular fossa and a 3 cm lymph node in the right axilla. An excisional biopsy of the right axillary node was consistent with nodular sclerosis CHL. A PET/CT-scan showed hypermetabolic activity confined

to nonbulky right supraclavicular and right axillary nodal areas. His CBCs, differential, and chemistries were within normal limits. ESR was 22. Echocardiogram showed a left ventricular ejection fraction of 65% and pulmonary function tests showed normal spirometric parameters. What is the next best step in this patient's management before starting treatment?

A. Unilateral bone marrow aspiration and biopsy
B. Bilateral bone marrow aspiration and biopsy
C. Sperm banking
D. MRI brain with and without contrast
E. Infuse-A-port insertion

2. What is the best therapy option for the 19-year-old African American man in question 1?

A. Four cycles of ABVD followed by 30 Gy of involved field radiation therapy
B. Two cycles of ABVD followed by 20 Gy of involved field radiation therapy
C. Six cycles of chemotherapy with R-CHOP
D. Subtotal nodal radiation therapy
E. Four cycles of dose-escalated BEACOPP followed by 30 Gy of involved field radiation therapy

3. A 45-year-old schoolteacher with stage IIIA mixed cellularity CHL is undergoing first-line chemotherapy with ABVD. She is tolerating chemotherapy well. A PET/CT-scan performed after two cycles showed complete remission. She presents now to start cycle 4 of chemotherapy with ABVD. She reports no nausea, vomiting, or fevers with the previous cycle. Her blood work today showed normal hepatic and renal function. Blood counts showed an absolute neutrophil count (ANC) of 880/μL and platelet count of 145/μL. What is the best next step in management?

A. Delay chemotherapy until ANC >1,000/μL
B. Delay chemotherapy until ANC >1,000/μL and add growth factor support to the next cycle of chemotherapy
C. Continue ABVD without delay and add growth factor support
D. Continue ABVD without delay and without growth factor support
E. Continue ABVD with 25% dose reduction in doxorubicin and bleomycin

4. A 55-year-old man with advanced-stage nodular sclerosis CHL presented with new-onset right axillary lymph node enlargement. He was treated with six cycles of ABVD 3 years ago. An excisional biopsy of the right axillary node confirmed relapsed disease. A PET/CT-scan showed widespread hypermetabolic lymphadenopathy above and below the diaphragm. Bone marrow biopsy was negative. He goes on to achieve a second complete remission after three cycles of salvage chemotherapy with ICE. He has four siblings. You now recommend

A. High-dose therapy and autologous hematopoietic cell transplantation
B. Matched sibling allogeneic hematopoietic cell transplantation
C. Six cycles of ICE followed by watchful waiting
D. Six cycles of ICE followed by brentuximab vedotin maintenance therapy

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Hematopoietic Cell Transplantation

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The effective therapeutic implementation of hematopoietic cell transplantation (HCT) required the concerted efforts of several prominent investigators spanning the entire 20th century. Seminal work done predominantly on murine models identified the cellular basis of hematopoiesis and raised the possibility of human HCT in the first half of the 20th century. The latter half witnessed the successful, albeit with early setbacks and pessimism, 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).

HCT is an effective therapeutic option for patients with a wide range of malignant and benign conditions. Apart from matched related donor (MRD) allo-HCT and auto-HCT, patients may be offered allografts from unrelated donors (URD), HLA-mismatched, cord blood, or haploidentical donors. In recent years the application of HCT has broadened with the advent of reduced intensity conditioning (RIC) regimens. Although HCT may be associated with significant morbidity and mortality, 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 outcomes. A brief overview of autologous and allogeneic HCT is provided in this chapter, along with a discussion of the complications and their management.

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells (HSCs) reside within the bone marrow space (niche) 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, erythroid, and myeloid cell lines. True HSC are characterized by their unlimited self-renewal capacity, pluripotency, 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 $CD34^+$, $CD38^-$, $Thy\text{-}1^{low}$ 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. A unique property of the infused HSC is 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 graft

product has important ramifications on post-HCT outcomes and lower $CD34^+$ cell dose can be associated with a higher risk of graft failure, delayed engraftment and hematopoietic recovery, and 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. Bone marrow harvesting is the repeated aspiration of the marrow from the posterior iliac crest usually under general anesthesia to obtain the graft. The goal is to obtain $\geq 2 \times 10^8$/kg recipient body weight of mononuclear cells to allow safe engraftment. The maximum volume of marrow that may be safely removed at a given time is 20 mL/kg donor weight. The harvesting procedure is very well tolerated and the most common side effect is self-limiting local pain. Other adverse effects may include neuropathy, infection, and anemia (autologous red cell transfusion is considered in many centers). HCT with peripheral blood progenitor cells (PBPC) 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 hematologic disorders such as aplastic anemia.

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 very safe with no 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 more 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 who are often difficult to mobilize with G-CSF alone. In the setting of auto-HCT chemotherapy is sometimes used prior to G-CSF mobilization to obtain additional antineoplastic effects and the postchemotherapy recovery phase improves the PBPC yield.

PBPC grafts result in more rapid engraftment and hematopoietic recovery. Based on existing evidence PBPC is preferred over marrow HSCs in auto-HCT. It is more controversial in the setting of allo-HCT. Due to the 10- to 20-fold higher T lymphocytes present in the PB product, there is concern for increased GVHD. Results of early comparative studies in MRD allo-HCT suggest earlier engraftment, similar acute GVHD and relapse rates, and increased chronic GVHD in some but not all studies with PBPC. Results of a randomized trial in URD allo-HCT suggest increased chronic GVHD with PBPC, which is offset by delayed engraftment with marrow graft and no difference in relapse or survival. Registry studies have also suggested increased chronic GVHD in patients receiving PBPC allo-HCT for severe aplastic anemia. A risk-adapted approach is warranted in choosing the ideal graft source.

Umbilical Cord Blood

HSCs can be collected from umbilical cord blood (UCB) of placenta after delivery and cryopreserved. This represents an enriched source of HSC in a relative small volume of blood in comparison with bone marrow or PBPC and is readily available upon request. The presence of immunologically naïve immune cells allow for crossing HLA barriers without increasing the risk of GVHD. Graft rejection and delayed engraftment occur more frequently owing to lower number of nucleated cells in the infusate. However, the simultaneous use of two UCB (double UCB) units from different donors has shown to improve engraftment. Higher total nucleated cell doses and better degrees of HLA match are associated with improved transplant outcomes.

Haploidentical Donors

Half-matched relative donors are a readily available source for most patients. Early studies were associated with prohibitive GVHD in T-cell replete and graft rejection and infectious complications in T-cell–depleted allografts. Recent reports with the use of T-cell–replete marrow-derived HSC administered after RIC regimen and posttransplant high-dose cyclophosphamide (Cy) to kill allo-reactive T cells that would cause GVHD have shown encouraging results. An ongoing randomized trial compares allo-HCT outcomes with double UCB and haploidentical donors.

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.marrow.org, provides a more complete list. See Table 30.1 for common indications in adults. Some of the salient features are

- In a pediatric population (≤20 years), chief indications for auto-HCT are nonhematologic malignancies and for allo-HCT they are benign hematologic 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, myelodysplastic syndrome, and aplastic anemia are common indications for allo-HCT.
- Trends in HCT have changed over time with therapeutic advances. An important example is as follows: allo-HCT used to be the standard of care for chronic phase chronic myeloid leukemia (CML) but not so in the tyrosine kinase inhibitor era. Similarly, there are new promising results with the use of HCT for solid tumors such as renal cell carcinoma, neuroblastoma, or nonmalignant diseases such as sickle cell anemia, and autoimmune disorders.

Table 30.1 Common Indications for Hematopoietic Cell Transplantation in Adults

Diagnosis	Autologous HCT	Allogeneic HCT
Aplastic anemia	No	Yes
Acute lymphoid 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
Diffuse large B-cell lymphoma	Yes; 1st relapse/CR2 (chemosensitive)	Yes; >CR2, >2nd relapse, Ref
Follicular lymphoma	Yes; 1st relapse/CR2 (chemosensitive)	Yes; >CR2, >2nd relapse, Ref
Germ cell tumor (testicular)	Yes; Rel[a]	No
Hodgkin lymphoma	Yes; 1st relapse/CR2 (chemosensitive)	Yes; >CR2, >2nd 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

HCT, hematopoietic cell transplantation; CR, complete remission; Ph, Philadelphia chromosome; Rel, relapsed; Ref, refractory; TKI, tyrosine kinase inhibitor; CP, chronic phase.

[a]Either investigational or ideally considered as part of the clinical trial.

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.

- HLA typing of the patient and a search for an HLA-matched donor are required if an allogeneic transplant is being considered. Donor search is initiated with siblings as first choice, followed by URDs and alternative donors (UCB and haploidentical).
- 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 is considered more important than chronologic 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.
- Physical examination.
  - Thorough physical examination including evaluation of oral cavity and dentition
  - Neurologic evaluation to rule out central nervous system involvement, if indicated
  - Performance status evaluation
- Organ function analysis.
  - Complete blood count.
  - Renal function: Preferably a creatinine clearance >60 mL per minute, except in myeloma.
  - Hepatic function: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than twice the upper level of normal and bilirubin <2.00 μg/dL.
  - 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 hematopoietic cell transplantation-specific comorbidity index (HCT-CI) that can predict NRM based on patient factors may be used to risk-stratify patients.
- Infectious disease evaluation.
  - Cytomegalovirus (CMV), 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
- Pregnancy testing for all women of child-bearing age and consideration of referral to reproductive center for sperm banking or in vitro fertilization.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

The principle behind high-dose chemotherapy (HDT) is the administration of maximal tolerated doses of cytotoxic agents 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/HSCs to reconstitute the hematopoietic system. HDT regimens typically use combinations of cytotoxic agents with nonoverlapping organ toxicities. Commonly used regimens include (a) BEAM—carmustine + etoposide + cytarabine + melphalan (lymphoma), (b) CBV—Cy + carmustine + etoposide (lymphoma), and (c) single-agent melphalan 200 mg/m^2 (myeloma). HDT is considered in chemotherapy-sensitive tumors or as consolidation therapy for patients in remission

(Table 30.1). Overall it is well tolerated with 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:

- Rare infusional reactions may include bronchospasm, flushing, hypertension, or hypotension secondary to DMSO.
- Pancytopenia for 10 to 14 days with the predominant use of PBPC and G-CSF. Packed red cell (PRBC) and platelet transfusions may be required.
- 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 requiring continued prophylaxis beyond engraftment.
- Regimen-related toxicities may be (a) acute—infusional reaction (carmustine), hemorrhagic cystitis (Cy), hypotension (etoposide) or (b) delayed—pulmonary toxicity (carmustine, total body irradiation [TBI]), sinusoidal obstruction syndrome (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 HEMATOPOIETIC CELL TRANSPLANTATION

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 co-ordination 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 URD allo-HCT. All physicians may perform a free initial search for an HLA-matched URD in the NMDP, which maintains a registry of about 9 million potential donors and 145,000 UCB units. As of 2013, the NMDP can search over 16 million URD and 500,000 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 colonizing donor immune system to recognize and eradicate the malignant or abnormal stem cell clone, the so called graft-versus-tumor (GVT) effect. This immune effect is largely mediated by transplanted donor lymphocytes and is evidenced by the lower relapse rate of hematologic malignancies in patients who undergo allo-HCT than in those who undergo auto-HCT, as well as by an increased relapse rates 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 new evidence supports potential contribution from nonspecific cytokines (host and/or donor derived) and alloreactive natural killer (NK) cells (haploidentical allo-HCT).

Human Leukocyte Antigen 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 plays 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, and -DRB1 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 a less stringent match for HLA -A and -B (antigen level) and HLA -DRB1 (allele level) for UCB units.

Donor Types for Allogeneic Hematopoietic Cell Transplantation

Related Donor

In the United States, approximately 30% of patients will have an HLA-matched sibling and is the preferred donor source. The probability that a sibling pair is HLA matched is about 25%. The risk of GVHD is higher with increasing HLA disparity, and therefore, most transplant centers prefer a 6/6 or 5/6 HLA match (HLA -A, -B, -DRB1).

Syngeneic Donor

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 rates tend to be significantly higher.

Unrelated Donor

As discussed above the search for an appropriate HLA-matched URD is performed through NMDP. It typically takes 3 to 6 months 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 an HLA-identical URD, while it is more difficult for ethnic minorities owing to disparities in registered volunteers in the NMDP registry. The risk of GVHD and graft failure increases with HLA mismatch and NMDP requires at least a 6/8 match prior to approving a match. The presence of recipient HLA antibodies against the mismatched donor HLA molecules in the context of a mismatched URD transplant significantly increased the risk of graft failure. Therefore, recipients of mismatched transplants should be screened for the presence of donor-specific HLA antibodies (DSA). Recent data suggest high-resolution matched URD allo-HCT have similar outcomes to MRD allo-HCT.

Alternative Donors

Include UCB and haploidentical-related donors and have been discussed elsewhere in the chapter.

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.

- Donor HLA typing.
- ABO typing.
- History-relevant information of the donor: Any previous malignancy within 5 years, except nonmelanoma skin cancer, is considered an absolute exclusion criterion. Age, sex, and parity of the donor impact HCT outcomes, and though they 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 should be considered.
- Infection exposure: HIV, human T-lymphotropic virus (HTLV), hepatitis, CMV, HSV, and EBV serology.
- Pregnancy testing for women.

STAGES 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 or nonmyeloablative regimens (NMA) preserve immunosuppressive effects to aid donor engraftment with minimal or no myelosuppression.

Myeloablative Conditioning

The most commonly used myeloablative conditioning regimens incorporate high-dose Cy (120 mg/kg) in combination with TBI (usually 12 Gy) or busulfan (Bu). Both regimens are considered equally efficacious, except slight superiority of TBI in acute lymphoid leukemia (ALL). 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, and age and performance status of the patient. Early regimen-related toxicity includes mucositis, nausea, diarrhea, alopecia, pancytopenia, seizures (Bu), and SOS. Late effects include pulmonary toxicity, hypothyroidism, growth retardation, infertility, an increased risk of cardiovascular disease, and second malignancies (mostly related to TBI).

Nonmyeloablative/Reduced Intensity Conditioning

RIC or nonmyeloablative (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 ($\leq$2 Gy) or an alkylating agent such as Cy, Bu, or melphalan. While the division is somewhat arbitrary, RIC is intermediate between myeloablative and NMA regimens and is usually associated with cytopenias needing transfusion support. The advent of RIC/NMA regimens has broadened the applicability of allo-HCT to include older patients ($>$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 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

The 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 neutrophil count of $>0.5\times10^9$/L, usually occurring by day +21. Platelet engraftment usually lags behind granulocyte recovery and is usually defined platelet counts of at least $>20\times10^9$/L without transfusion for 7 days. Erythrocyte engraftment occurs much later and is characterized by independence from PRBC transfusions. Posttransplant cytopenias depend on the

conditioning regimen used, diagnosis and disease status, donor source, $CD34^+$ cell dose in the allograft, growth factors, and GVHD prophylaxis.

Posttransplant Postengraftment Phase

Even after myeloid engraftment occurs the recipient remains immunosuppressed due to GVHD prophylaxis/treatment and owing to delayed immune reconstitution, which may take up to 12 months 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.

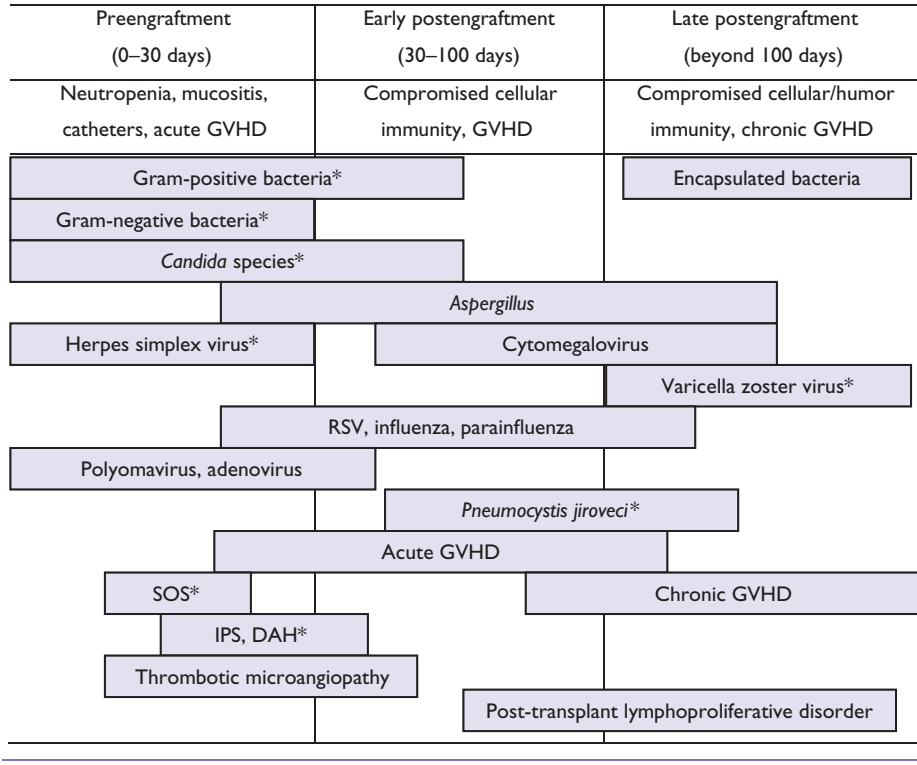

FIGURE 30.1 General timeline of complications after hematopoietic cell transplantation. All complications specific to allogeneic transplantation unless noted by asterisk, in which case they are also seen in autotransplant recipients. GVHD, graft-versus-host disease; RSV, respiratory syncitial virus; SOS, sinusoidal obstruction syndrome; IPS, idiopathic pulmonary syndrome; DAH, diffuse alveolar hemorrhage. (Modified from Cantor AB, Lazarus HM, Laport G. Cellular basis of hematopoiesis and stem cell transplantation. *American Society of Hematology—Self Assessment Program*. 4th ed. American Society of Hematology; 2010.)

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 may be primary (early) when no hematopoietic recovery is noted post-HCT by day +28 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 important approaches to the management of graft failure.

Infections

Infection remains a major cause of morbidity for patients undergoing HCT. Indwelling catheters are a common source of infections, and bacteremia and sepsis may occur during the neutropenic phase of HCT. Current approaches to minimize the risk of life-threatening infections include the use of prophylactic antimicrobial, antifungal, and antiviral agents, as well as aggressive screening and treatment for common transplantation-associated infections.

Cytomegalovirus

CMV infection most commonly occurs due to reactivation in seropositive patients or 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 greatest up to day +100. CMV pneumonia and colitis cause significant morbidity and mortality. In addition, it can cause febrile disease, hepatitis, and marrow suppression. Screening for viral reactivation is performed weekly after transplantation by measuring the CMV antigen levels or by polymerase chain reaction (PCR). Initial treatment is with intravenous ganciclovir ± 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 (i.e., become CMV-PCR+) significantly prevents the development of CMV disease and results in a substantial reduction in CMV-associated morbidity and mortality.

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, sinusitis, cellulitis, 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 agents.

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).

Sinusoidal Obstruction Syndrome (Formerly 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 Cy with higher dose TBI or ablative doses of Bu. The intravenous use and pharmacokinetic monitoring of Bu drug levels have dramatically reduced the incidence of SOS. Defibrotide, an investigational agent available through an expanded access trial in the United States for SOS, has shown promising results for treating this order.

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% to 20% 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. Use of recombinant factor VIIa has also been reported. Other causes such as CMV pneumonitis, circulatory overload (TACO), and transfusion-associated lung injury (TRALI) 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 alien and mount an immunologic attack resulting in GVHD. It is one of the chief treatment-related toxicities and impacts NRM significantly. Conventionally acute GVHD was defined to occur within day +100, and chronic GVHD beyond 100 days posttransplant. It is no longer true and the classification should be based on clinical features rather than time of onset.

Acute GVHD

Up 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. A commonly used staging system for acute GVHD is presented in Table 30.2. Risk factors for acute GVHD include degree of HLA mismatch, infections (CMV, VZV), URD or haploidentical donors, older patients, multiparous donor, older donors in URD transplants, sex-mismatched transplants (female donor → male recipients), and the use of intensive conditioning regimens.

Prevention of Acute Graft-versus-Host Disease Strategies to prevent acute GVHD have been established and are more effective than treating acute GVHD. Commonly employed strategies include

- Pharmacologic therapy: Combination therapy of nonspecific immunosuppressive agents (methotrexate, steroids) and T-cell–specific immunosuppressant (calcineurin inhibitors—cyclosporine and tacrolimus, mycophenolate mofetil) is 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.

Table 30.2 Staging System for Graft-versus-Host Disease

Level of Injury	Skin	Liver (Bilirubin)	Gut
1	Maculopapular rash <25% BSA	2–3 mg/dL	500–1,000 mL/d[a]
2	Maculopapular rash 25-50% BSA	3–6 mg/dL	1,000–1,500 mL/d
3	Generalized erythroderma	6–16 mg/dL	>1,500 mL/d
4	3 + Bullae or desquamation	>15 mg/dL	>2,000 mL/d, severe abdominal pain +/− ileus
Clinical Grade	**Skin**	**Liver**	**Gut**
I	1 or 2	None	None
II	1–3	1	1
III	2 or 3	2 or 3	2 or 3
IV	2–4	2–4	2–4

[a]Milliliters per day of liquid stool.
BSA, body surface area.

- T-cell depletion: Achieved by (a) ex vivo separation by CD34+ selection or the use of monoclonal antibodies to remove T cells or (b) in vivo T-cell depletion with the use of monoclonal antibodies such as ATG or alemtuzumab or the administration of posttransplant Cy. Though effective in reducing GVHD, these maneuvers may increase relapse rates and infections due to late immune reconstitution.

Treatment of Acute Graft-versus-Host Disease Frontline treatment for clinically significant (grades II–IV) acute GVHD is methylprednisolone at a dose of 2 mg/kg/day and calcineurin inhibitors should be continued or restarted. For those not responding or with partial response mycophenolate is usually added. Additional agents (azathioprine, daclizumab, photopheresis, ATG, infliximab) are used with variable success. Steroid refractory acute GVHD portends very poor prognosis. Prophylactic antifungal therapy against *Aspergillus* should be considered in those on corticosteroid treatment.

Chronic GVHD

Use of PBPC allografts, URD, and prior history of acute GVHD are risk factors. It presents with variable and multisystem organ involvement, and clinical manifestations may resemble autoimmune disorders (i.e., 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 (e.g., penicillin) and antifungal agents. Other potentially useful agents include thalidomide, mycophenolate mofetil, imatinib mesylate, pentostatin, rituximab, photopheresis, Psoralen ultraviolet radiation (skin GVHD), and possibly interleukin-2 administration.

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 the worst prognosis. Immunosuppression is typically withdrawn to enhance the GVT effect and, in some cases, DLI is administered. This 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 very high risk of NRM.

SURVIVORSHIP

It is estimated that there are over 125,000 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 as follows:

- Auto-HCT survivors are at risk for lung dysfunction, cardiovascular diseases, and secondary myelodysplasia/AML.
- Major complications afflicting allo-HCT survivors include chronic GVHD; infections; organ dysfunction involving pulmonary, cardiovascular, endocrine, and immune systems; secondary myelodysplasia/AML; and solid organ malignancies. In addition, the pediatric population is at risk for growth retardation.
- Immunizations are recommended for auto-HCT patients at 1 year and after withdrawal of immunosuppressive agents for allo-HCT. Long-term antibiotic prophylaxis is needed for patients receiving prolonged treatment for chronic GVHD.
- Recommended screening and preventive measures for survivors have been established (see the reference list). This includes routine hemogram, hepatic, and renal function tests, endocrine screening (lipid panel, vitamin D, and thyroid panel), immunologic studies, and other studies (echocardiogram, pulmonary function tests, age-appropriate cancer screening, ophthalmologic evaluation, and bone densitometry).

CONCLUSION

HCT has evolved into an effective therapeutic option for a broad range of disease entities. The improved safety profile of the procedure and the increasing availability of donor sources have led to an increase in the number of transplants performed each year. There have been improvements in survival, less acute complications, and improved awareness and treatment of chronic complications. The number of patients who benefit from this procedure will likely increase as future transplantation strategies continue to evolve, minimizing adverse effects and expanding the stem cell source, while maximizing the beneficial effects donor immune–mediated GVT effects.

REVIEW QUESTIONS

1. A 36-year-old Caucasian female with no siblings was diagnosed with AML with normal cytogenetics. She received standard "3 + 7" induction chemotherapy and entered complete remission and completed four cycles of consolidation therapy. Six months later she presents with peripheral blasts and bone marrow evaluation confirms relapse. Apart from admitting the patient for reinduction chemotherapy and supportive care, what other step should be initiated at this time?
   - **A.** Consider high-dose therapy and autologous HCT.
   - **B.** HLA type the patient and run a preliminary search for URD allogeneic HCT.
   - **C.** HLA type the patient, but defer allogeneic HCT for next relapse.
   - **D.** Do nothing; allogeneic HCT is not a treatment option for this patient.
2. A 55-year-old male with relapsed Hodgkin lymphoma underwent high-dose therapy with BEAM (carmustine + etoposide + cytarabine + melphalan) followed by autologous PBPC infusion. Hematopoietic recovery occurred by day +14 and he was discharged from the transplant center by day +25. He reports to your clinic on day +48 with 3-day onset of progressive dyspnea and dry cough. His current medications include trimethoprim-sulfamethoxazole and acyclovir. On examination his pulse is 110, BP 108/70, respiratory rate 34, and pulse-oximetry reads 88% on room air. Chest x-ray shows nonspecific interstitial markings. What should be the next step in his management?
   - **A.** Initiate the patient on intravenous azithromycin and ceftriaxone.
   - **B.** Stop trimethoprim-sulfamethoxazole and start the patient on inhaled pentamidine.
   - **C.** Start IV ganciclovir and immunoglobulin.
   - **D.** Obtain a pulmonary function test and start the patient on steroid therapy.
3. You are evaluating the 40-year-old HLA-matched brother of a patient with AML with complex cytogenetics in CR1. The potential donor is in good health, has no medical complaints, and is not on any medications except a history of basal cell carcinoma that was resected 3 years ago. When counseling the patient regarding PBPC collection, which of the following statements is accurate?
   - **A.** The history of basal cell carcinoma rules him out as a donor for allogeneic HCT.
   - **B.** The procedure consists of giving a single-dose Cy followed by growth factors for mobilization and progenitor cell collection by apheresis.
   - **C.** The procedure is well tolerated with the most common side effect being self-limiting bone pain and a very rare risk of splenic rupture.
   - **D.** The history of AML in his sibling (recipient) increases significantly the risk of future AML in the brother and so he cannot serve as a donor.
4. A 50-year-old woman with history of CML underwent mismatched URD PBPC allogeneic HCT 16 days ago after Cy and Bu conditioning. She had myeloid engraftment on day +12. She complains of diffuse abdominal pain that is more prominent in the right upper quadrant.

Her stool output is documented as 150 mL of liquid stool over the last 24 hours. Volume status shows that she is 3 L positive with a weight gain of 2.5 kg compared to the day before. Blood work shows hyperbilirubinemia (3 mg/dL), stable hemogram, creatinine 1.1, and normal peripheral smear. What is the most likely diagnosis?

A. SOS
B. Acute GVHD
C. Hepato-splenic candidiasis
D. Thrombotic microangiopathy

Suggested Readings

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9. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(3):348-371.

Invaluable Web Resources for Further Reading

10. American Society of Blood and Marrow Transplantation. www.asbmt.org
11. Center for International Blood and Marrow Transplantation. www.cibmtr.org
12. National Marrow Donor Program. www.marrow.org

SECTION Ten

Other Malignancies

31

Carcinoma of Unknown Primary

Hung T. Khong

DEFINITION

Carcinoma of unknown primary (CUP) is defined as the detection of one or more metastatic tumors for which standardized evaluation, including history and physical examination, routine blood work, urinalysis, chest x-ray, computed tomography (CT) scan, and histologic evaluation, fails to identify the primary site.

EPIDEMIOLOGY

- Incidence: 2% to 4% of all diagnosed oncologic cases in the United States are CUP.
- Gender: Male-to-female ratio is approximately 1:1.
- Age: Highest incidence is in the sixth decade of life.

CLINICAL FEATURES AND PROGNOSIS

Clinical Features

- At presentation, most patients (97%) complain of symptoms at metastatic site(s). Common presenting sites and common metastatic sites are listed in Tables 31.1 and 31.2.
- Nonspecific constitutional symptoms also are common, such as anorexia, weight loss, and fatigue.
- At diagnosis, more than 50% of patients have multiple sites (more than two) of metastatic involvement.

Prognosis

- In general, the median survival time of patients with CUP is 6 to 9 months.
- Less than 20% of patients survive at 1 year and less than 10% at 5 years.

Table 31.1 Common Presenting Sites

Site	%	Range (%)
Lymph node	26	14–37
Lung	17	16–19
Bone	15	13–30
Liver	11	4–19
Brain	8	7–10
Pleura	7	2–12
Skin	5	0–22
Peritoneum	4	1–6

In each patient, the metastatic site that was apparent or symptomatic first was the only one counted. Data were collected from three series involving a total of 611 patients.

Table 31.2 Common Metastatic Sites

Site	%	Range (%)
Lymph nodes	41	20–42
Liver	34	33–43
Bone	29	29
Lung	27	26–31
Pleura	11	11–12
Peritoneum	9	
Brain	6	6
Adrenal gland	6	4–6
Skin	4	
Bone marrow	3	

All principal metastatic sites in each patient were counted. Data were collected from two series involving a total of 1,051 patients. Data reported from subspecialty practices were excluded.

Poor prognostic factors include the following:

- Male gender
- Adenocarcinoma histology
- Increasing number of involved organ sites
- Hepatic or adrenal involvement
- Supraclavicular lymphadenopathy

Advantageous prognostic factors include the following:

- Nonsupraclavicular lymphadenopathy
- Neuroendocrine histology
- A study of 1,000 patients (from the M.D. Anderson Cancer Center) revealed several prognostic subgroups. Some of these are shown in Table 31.3.

DIAGNOSIS

- The recommended initial evaluation is listed in Table 31.4.
- Generous tissue samples should be obtained at the first biopsy.
- Accurate pathologic evaluation is critical.

Table 31.3 Median Survival in Some Prognostic Subgroups

Median Survival Time (mo)			
40 1 or 2 metastatic organ sites, nonadenocarcinoma, and no involvement of liver, bone, adrenal, or pleura	24 Liver mets and neuroendocrine histology	5 Liver mets, not neuroendocrine histology, and age >61.5 y	5 Adrenal mets

mets, metastasis.
Note: The median survival for all patients in this study was 11 mo.

Table 31.4 Initial Evaluation

Complete H&P (attention to breast and pelvic examination in women; prostate and testicular examination in men; and head/neck and rectal examination in all patients)
CBC
Chemistry profiles
Urinalysis
Stool testing for occult blood
CXR
Symptom directed endoscopy
Consider PET scan in the initial workup for squamous cell and cervical nodes

H&P, history and physical examination; CBC, complete blood count; CXR, chest x-ray.

Table 31.5 Immunoperoxidase Staining in the Differential Diagnosis of Carcinoma of Unknown Primary Site

		Immunoperoxidase Stains			
Tumor Type	**Cytokeratin**	**Leukocyte Common Antigen**	**S100 Protein, HMB 45**	**Neuron-Specific Enolase, Chromogranin**	**Vimentin Desmin**
Carcinoma	+	−	−	±	−
Lymphoma	−	+	−	−	−
Melanoma	−	−	+	±	−
Sarcoma	−	−	−	−	+
Neuroendocrine	+	−	−	+	−

HMB, β-hydroxy β-methylbutyrate monohydrate.

- Light microscopic examination.
- Immunoperoxidase staining (IPS) should be performed in all CUP cases of poorly differentiated carcinomas (PDCs). Table 31.5 lists some immunoperoxidase stains that are most useful. In addition, some other useful markers are thyroid transcription factor (TTF-1) which is positive in lung and thyroid cancer; WT-1 which is positive in epithelioid mesothelioma, and serous ovarian cancer.
- Electron microscopy should be considered if the tumor cannot be identified by IPS.
- Most common primary sites are listed in Table 31.6.

Table 31.6 Primary Sites (Diagnosed During Life or at Autopsy)

Primary Sites	%
Lung	23.7
Pancreas	21.1
Ovary	6.4
Kidney	5.5
Colorectal	5.3
Gastric	4.6
Liver	4.3
Prostate	4.1
Breast	3.4
Adrenal	2.2
Thyroid	2.2
Urinary tract/bladder	1.9
Esophagus	1.5
Lymphoma	1.5
Gall bladder/biliary tree	1.2
Testicular germ cell	1
Mesothelioma	0.5
Uterus	0.3
Others	9.3
Total	100

Data were collected from nine series involving a total of 1,453 patients with CUP. A diagnosis was made either during life or at autopsy in 582 patients. Head/neck primary and data from subspecialty practices have been excluded in the calculation (to avoid artifactual representation of certain cancers such as the high rates of pancreatic primary reported by clinics specializing in gastrointestinal malignancy).

- Gene and protein microarray technologies have emerged as valuable tools in the diagnosis of CUP. Three assays that are commercially available in the United States are the bioTheranostics CancerTYPE ID, a 92-gene RT-qPCR that provides a molecular classification of 39 tumor types in metastatic cancer with 85% sensitivity and more than 99% specificity; Pathwork Tissue of Origin Test, a 2000-gene microarray that identifies 15 origin sites, with 89% sensitivity and 99% specificity; and Rosetta miRview mets, a 48 microRNAs RT-qPCR, with 85% to 90% sensitivity and 99% specificity.

WELL-DIFFERENTIATED OR MODERATELY DIFFERENTIATED ADENOCARCINOMA OF UNKNOWN PRIMARY

Clinical Features

- Accounts for about 60% of CUP cases, typically affecting elderly patients.
- Metastatic tumors at multiple sites.
- Poor performance status (PS) at diagnosis.
- Common metastatic sites: lymph nodes, liver, lung, and bone.
- Most common primary sites identified: the lung and pancreas (45%) (see Table 31.6).
- Poor prognosis (median survival of 3 to 4 months).
- Primary site is rarely found (<15% before death); an exhaustive search is not indicated.

Further Workup

Additional studies that should be performed include prostate-specific antigen (PSA) serum level and/or IPS for men, and mammography, serum CA 15-3, serum CA 125, and estrogen receptor/progesterone

receptor (ER/PR) (IPS) for women. CT scan of the abdomen can identify a primary site in approximately 30% of cases. In patients with CUP who have metastatic adenocarcinoma to the axillary lymph nodes and a negative mammogram, breast magnetic resonance imaging (MRI) detected a primary breast cancer in 9 of 12 (75%) patients in one study and in 19 (86%) of 22 patients in another study.

Treatment

- Most cases (90%) of well-differentiated or moderately differentiated adenocarcinoma of unknown primary show low response rates (RRs) and few complete responses with systemic chemotherapy.
- Patients in this group have a poor prognosis.
- The empiric chemotherapy for CUP is discussed in Table 31.7.
- The various subsets of patients with different types of CUP who can be treated are discussed in the following sections.

Peritoneal Carcinomatosis in Women

- Typical of ovarian cancer.
- Occasionally associated with cancers from the gastrointestinal (GI) tract or breast.

Table 31.7 Empiric Chemotherapy for Carcinoma of Unknown Primary

Regimen	Treatment Description	Cycle
Adenocarcinoma		
Paclitaxel, carboplatin	200 mg/m²/3 h IV day 1 AUC 6 day 1	21 d
Paclitaxel, carboplatin, etoposide	200 mg/m²/1 h IV day 1 AUC 6 day 1 50 mg/d PO alternating with 100 mg/d PO days 1–10	21 d
Docetaxel, carboplatin	65 mg/m² IV day 1 AUC 6 day 1	21 d
Gemcitabine, cisplatin	1,250 mg/m² IV days 1 and 8 100 mg/m² IV day 1	21 d
Gemcitabine, docetaxel	1,000 mg/m² IV days 1 and 8 75 mg/m² IV day 8	21 d
Squamous cell carcinoma		
Paclitaxel, cisplatin, 5-FU	175 mg/m²/3 h IV day 1 100 mg/m² IV day 2 500 mg/m²/d continuous infusion over 120 h	21 d
Docetaxel, cisplatin, 5-FU	75 mg/m² IV day 1 75 mg/m² IV day 1 750 mg/m²/d continuous infusion days 1–5	21 d
Neuroendocrine tumor		
Paclitaxel, carboplatin, etoposide	200 mg/m²/1 h IV day 1 AUC 6 day 1 50 mg/d PO alternating with 100 mg/d PO days 1–10	21 d
Cisplatin, etoposide	45 mg/m² IV days 2 and 3 100 mg/m² IV days 1 and 3	28 d
Cisplatin, etoposide	60–80 mg/m² IV day 1 100–120 mg/m² IV days 1 and 3	21–28 d
Carboplatin, etoposide	AUC 5 day 1 100 mg/m² IV days 1–3	28 d
Temozolomide	100–200 mg/m² PO days 1–5	28 d
Temozolomide, thalidomide	150 mg/m² PO days 1–7 and days 15–21 50–400 mg PO daily	28 d

IV, intravenous; AUC, area under the curve; PO, by mouth.
Adapted from the National Comprehensive Cancer Network. *Pract Guidelines Oncol.* 2011;9(12).

- Serum CA125 level is often elevated.
- Treatment is the same as for stage III ovarian cancer (laparotomy with surgical cytoreduction, followed by platinum-based combination chemotherapy) (see Chapter 17). It should be noted that about 20% of patients have complete remission and 16% have prolonged disease-free survival.

Women with Axillary Lymph Node Metastases

- Suggests breast cancer.
- ER/PR and Her-2/neu should be checked.
- Occult breast primary is found in 55% to 75% of cases.
- Axillary node metastases in women should be treated in the same manner as stage II or III breast cancer.
- Modified radical mastectomy has been recommended.
- Alternatively, radiation therapy (XRT) to the breast can be performed after axillary node dissection.
- Adjuvant systemic chemotherapy should also be considered (see Chapter 17).
- Patients with metastatic sites in addition to axillary nodes should be treated for metastatic breast cancer (see Chapter 12).

Men with Elevated Prostate-Specific Antigen or Osteoblastic Bone Metastasis

- If the PSA serum level or tumor staining is positive, a regimen of hormonal therapy similar to that used for metastatic prostate cancer (Chapter 14) should be started.
- If osteoblastic bone metastases are present, empiric hormonal therapy should be started regardless of the PSA levels.

Patients with a Single Metastatic Site

- Surgical excision and/or XRT should be performed.

POORLY DIFFERENTIATED CARCINOMA/ADENOCARCINOMA OF UNKNOWN PRIMARY

- PDC and poorly differentiated adenocarcinoma (PDA) account for 30% of CUP (PDC accounts for two-thirds of cases and PDA accounts for one-third).
- Patients with PDC and PDA show poor response to fluorouracil-based chemotherapy and exhibit a short survival.
- Some patients have neoplasms that are highly responsive to platinating agent–based combination chemotherapeutic treatments. Some long-term survivors and cures have been described for both PDC and PDA.

Clinical Features

- Younger median age (about 40 years).
- Rapid progression of symptoms.
- Evidence of rapid tumor growth.
- Most common sites of metastatic involvement (50% of cases): lymph nodes, mediastinum, and retroperitoneum.

Pathologic Evaluation

- IPS is useful in the pathologic evaluation of PDC and PDA.
- Electron microscopic evaluation should be performed if tumor cannot be identified by IPS.

Further Workup

- Additional workup should include CT scan of chest, abdomen, and pelvis, and serum β-human chorionic gonadotropin (β-HCG), and α-fetoprotein (AFP).

Treatment

1. Extragonadal germ cell cancer syndrome
   - This syndrome is commonly found in young men.
   - These are predominantly midline tumors (mediastinum or retroperitoneum).
   - The syndrome is characterized by elevated levels of β-HCG, AFP, or both.
   - This syndrome should be treated in the same manner as a germ cell tumor (Chapter 16).
2. Poorly differentiated neuroendocrine carcinoma
   - These carcinomas are high-grade tumors.
   - They are characterized by multiple metastatic sites.
   - The carcinomas are highly responsive to cisplatin-based chemotherapy.
   - The overall RR for combination chemotherapy was 71% (33 of 46 patients), with a complete response in 28% (13 of 46 patients); 17% of patients (8 of 46 patients) showed durable disease-free survival.
   - Patients in this group should be treated with a regimen of combination chemotherapy including a platinating agent and etoposide (see Table 31.7). It should be noted that other patients with PDC or PDA should receive an empiric therapy of platinating agent–based chemotherapy (see Table 31.7). (In a prospective study of 220 patients, the overall RR was 62%, with a complete RR of 26%. Thirteen percent of patients were considered cured.)

POORLY DIFFERENTIATED MALIGNANT NEOPLASMS OF UNKNOWN PRIMARY

- Found in 5% of all patients with CUP.
- A specialized pathologic study found 35% to 65% of the malignant neoplasms to be lymphomas; carcinomas accounted for most of the remaining cases. Less than 15% of the neoplasms are melanoma and sarcoma.

SQUAMOUS CELL CARCINOMA OF UNKNOWN PRIMARY

- Account for 5% of all patients with CUP.

Cervical Node Involvement

High Cervical Node(s)

- Workup and treatment of squamous cell CUP in the high cervical nodes are the same as those for primary head and neck cancer (see Chapter 1). PET scan may help identify the primary site in this setting.
- High long-term survival rates (30% to 70%) have been reported after local treatment.
- The role of chemotherapy is undetermined. However, concurrent chemoradiation is an option in patients with extracapsular spread or N2 or N3 disease.

Low Cervical or Supraclavicular Node(s)

- Histology can be squamous, adenocarcinoma, or poorly differentiated tumors.
- Poorer prognosis (particularly for adenocarcinoma histology) is because lung and GI tract are frequent primary sites.
- If no other sites of disease are found, a few patients (10% to 15%) will have a long-term disease-free survival with aggressive local therapy (surgery and/or XRT).
- The role of chemotherapy is undetermined.

Inguinal Lymph Node(s)

- A primary site in the genital or anorectal areas is often identified in most patients.
- Curative therapy is available for some of these patients.
- If no primary is found, surgical node dissection (with or without XRT) can offer long-term survival.

REVIEW QUESTIONS

1. A 47-year-old man with chest pain is found to have mediastinal nodes. Biopsy of one of the enlarged nodes reveals adenocarcinoma. The most appropriate evaluation at this point is
   - **A.** CT chest, abdomen, and pelvis
   - **B.** β-hCG and AFP
   - **C.** PSA
   - **D.** C
   - **E.** A, B, and C
2. Further workups do not reveal the site of origin and PSA, β-hCG, and AFP were not elevated in the patient described in question 1. Which of the following choices BEST described the next approach:
   - **A.** Treat as poor-risk germ cell tumor
   - **B.** Testicular ultrasound
   - **C.** Treat as non–small cell lung cancer
   - **D.** A and C
   - **E.** A and B
3. A 54-year-old woman presents with an enlarged node in her left groin. Biopsy revealed squamous cell carcinoma. CT scans show no evidence of disease elsewhere. Which of the following is FALSE?
   - **A.** A primary site in the anogenital areas is most likely.
   - **B.** If there is no primary site found, surgical node dissection should be performed.
   - **C.** The patient has good prognosis.
   - **D.** The patient may be cured with locoregional therapy.
   - **E.** All of the above.

Suggested Readings

1. Abbruzzese JL, Abbruzzese MC, Hess KR, et al. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J Clin Oncol.* 1994;12:1272-1280.
2. Bugat R, Bataillard A, Lesimple T, et al. Summary of the standards, options and recommendations for the management of patients with carcinoma of unknown primary site (2002). *Br J Cancer.* 2003;89(suppl 1):S59-S66.
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32

Central Nervous System Tumors

Christopher Ryan Heery and Teri Kreisl

Tumors within the central nervous system (CNS) are most commonly due to metastatic spread from other primary tumor sites. This chapter will focus mainly on primary CNS tumors that vary significantly in histology, epidemiology, and management.

Secondary CNS lesions (metastatic from other sites) will also be discussed. Brain metastases often occur late in the disease course and are a poor prognostic indicator. Because patients may be severely symptomatic from other sites of disease, these lesions may not be detected until autopsy in many patients with metastatic cancer. Improved imaging techniques (MRI and CT) have allowed enhanced differential diagnosis based on radiographic features and location combined with patient age (Table 32.1), but a definitive diagnosis is dependent on biopsy and histolopathologic analysis.

PRIMARY BRAIN TUMORS

Epidemiology

- Primary brain tumors comprise 1.4% of all cancers.
- In 2012, American Cancer Society estimates that 22,910 primary CNS tumors will be diagnosed, resulting in 13,700 deaths (approximately 2.4% of all cancer deaths).
- According to the Surveillance, Epidemiology, and End Results (SEER) registry for 2005 to 2009, the age-adjusted incidence of primary malignancies of the brain and CNS is 6.5 cases per 100,000 persons per year.
- There is a bimodal distribution of incidence, with peaks under 20 years (13.0% of cases) and over 65 (35.2% of cases).
- Median age at diagnosis is 57, overall; if no tumor is found by the age of 4 (tumors which may have been present at birth), the risk of a primary brain tumor appears to increase with age.
- CNS tumors are the most prevalent solid tumors in childhood, comprising 27% of all cancer diagnoses in children (second to leukemia which is 33%). Brain tumors are the most frequent cancer-related cause of death in children aged $<$15 years and men aged 20 to 39.
- The majority (80%) of all primary brain tumor-related deaths occur in patients aged $>$59 years.
- The most common CNS tumors are derived from glial precursors.
- The risk of brain tumors increases for patients with type 1 neurofibromatosis (NF1).

Clinical Diagnosis

The most common symptoms in order of decreasing frequency are

- Headache
- Seizure
- Cognitive/personality changes

Table 32.1 Brain Tumor Case Incidence per 100,000 by Type and Age of Patient

	Age (y)							
Histology	0–19	20–34	35–44	45–54	55–64	65–74	75–84	85+
Astrocytoma								
Pilocytic	0.80	0.24	0.12	0.09	0.08	0.07	0.07	–
Diffuse	0.27	0.49	0.64	0.64	0.84	1.14	1.28	0.71
Anaplastic	0.08	0.26	0.35	0.43	0.67	0.92	0.96	0.40
GBM	0.14	0.39	1.21	3.66	8.16	13.21	14.64	8.96
Oligoastrocytoma	0.03	0.28	0.35	0.28	0.26	0.23	0.16	–
Oligodendroglioma	0.06	0.32	0.49	0.42	0.33	0.25	0.18	0.07
Anaplastic oligodendroglioma	0.01	0.09	0.17	0.18	0.22	0.19	0.14	–
Ependymoma	0.27	0.36	0.49	0.58	0.59	0.55	0.37	0.11
Meningioma	0.14	1.27	4.31	8.41	14.02	24.26	35.06	44.90

Based on data from the Central Brain Tumor Registry of the United States, published by Dolecek TA, Propp JM, Stroup NE, Kruchko C. *Neuro Oncol*. 2012;14(suppl 5):v1-v49.

- Focal weakness
- Nausea/vomiting
- Speech abnormalities
- Altered consciousness

The most common signs in order of decreasing frequency are

- Hemiparesis
- Cranial nerve palsies
- Papilledema
- Cognitive dysfunction
- Sensory deficits
- Hemiparesthesia
- Hemianopia
- Dysphasia

Acute Complications

Because the skull's rigidity does not allow for intracranial expansion, brain lesions can result in structural displacement and life-threatening consequences. Following the path of least resistance, increased intracranial pressure (ICP) may cause tentorial or foramen magnum herniation, causing significant neurologic signs (Table 32.2).

Types of Primary Brain Tumors

Gliomas

Gliomas account for approximately 65% of all intracranial tumors (range 46% to 85% in various databases), with age-related incidence by histologic subtype. Table 32.3 shows the prevalence of the pathologic subtypes of gliomas in relation to other more common primary brain tumors.

There are four major types of gliomas, based on their presumed glial cell of origin:

- Astrocytoma (glioblastoma multiforme [GBM], anaplastic astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, pilomyxoid astrocytoma, pilocytic astrocytoma, giant cell astrocytoma)
- Oligodendroglioma (anaplastic oligodendroglioma, oligodendroglioma)
- Mixed glioma (anaplastic oligoastrocytoma, oligoastrocytoma)
- Ependymoma (anaplastic ependymoma, ependymoma, subependymoma, myxopapillary ependymoma)

Table 32.2 Signs of Severe Increased Intracranial Pressure and Brain Herniation

Tentorial/Temporal Lobe Herniation	Cerebellar/Foramen Magnum Herniation
Pupillary dilation	Head tilt
Ptosis	Stiff neck
Ipsilateral/contralateral hemiplegia	Neck paresthesias
Homonymous hemianopia	Tonic tensor spasms of limbs and body
Midbrain syndrome	Coma
Coma with rising blood pressure/bradycardia	Respiratory arrest

Table 32.3 Prevalence of Gliomas by Pathologic Subtype

Subtype of Glioma	Prevalence (%)
Glioblastoma	55
Astrocytoma	20.5
Ependymoma	6
Medulloblastoma	6
Oligodendroglioma	5
Choroid plexus papilloma	2
Colloid cyst	2

Table 32.4 Grading of Gliomas by Subtype

	Astrocytoma	Oligodendroglioma	Mixed Glioma	Ependymoma
Grade I	Pilocytoic, giant cell			Subependymoma, myxopapillary ependymoma
Grade 2	Diffuse, pilomyxoid, pleomorphic, xanthoastrocytoma	Oligodendroglioma	Oligoastrocyoma	Ependymoma
Grade 3	Anaplastic astrocytoma	Anaplastic oligodendroglioma	Anaplastic oligoastrocytoma	Anaplastic ependymoma
Grade 4	Glioblastoma, giant cell glioblastoma, gliosarcoma			

Grading The World Health Organization's pathologic grading system, generally accepted by neuropathologists since 1993 (most recently updated in 2007), determines the grade (level of aggressiveness) of each histologic subtype of tumor (Table 32.4) based on the following features:

- Cellular atypia
- Mitotic activity
- Degree of cellularity
- Endothelial proliferation
- Degree of necrosis and/or microvascular proliferation

Molecular Genetics Patterns of genetic abnormalities have been identified in various glioma subtypes (Table 32.5). Secondary or progressive gliomas often demonstrate mutations of p53, but they seldom show amplification of epidermal growth factor receptor (EGFR). By contrast, primary (de novo) GBMs

Table 32.5 Molecular Genetics of Gliomas

Genetic Alteration	Primary (De Novo) GBM (90%)	Secondary GBM (10%)
IDH1 mutation	Absent	>95% (indicates progression from grade 2 astrocytoma)
LOH10p	50%	Rare, possibly never
LOH 19q	~5%	~30–50%
LOH10q	~70%	~70%
PTEN mutation (10q23.3)	25%	Uncommon, <5%
EGFR amplification	~35–45%	Uncommon, 0–6.5%
TP53 mutation	~20–35%	~60–85%

GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; LOH, loss of heterozygosity; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; RB, retinoblastoma.
% Represents the percentage of tumors that will express this genetic alteration.
Based on data from Ohgaki H et al. *Cancer Res*. 2004;64:6892-6899; Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res*. 2013; 19(4): 764-772.

usually lack p53 mutations and contain an amplified EGFR. IDH (isocitrate dehydrogenase) mutations appear to be pathognemonic for secondary GBM diagnosis by current definitions of the two entities, which indicate common precursor events for all secondary GBMs.

Glioblastoma Multiforme (WHO Grade IV Astrocytoma)

- The most common adult primary brain tumor, accounting for about half of all gliomas and 10% to 15% of all intracranial tumors.
- Peak incidence is at 45 to 65 years; overall incidence is 2 to 3/100,000; male-to-female ratio is 3:2; median survival is around 3 months if untreated, approximately 12 to 15 months with standard therapy (discussed below).
- More likely to cross the corpus callosum than other types of brain tumors.
- Development may occur de novo (primary) or after progression from a lower-grade precursor lesion (secondary).

Imaging Characteristics

- Heterogeneous hypointense or isointense mass on CT or T1-weighted MRI.
- Heterogeneously contrast-enhancing mass, often the presence of necrosis visible.
- Hypervascular appearance.
- Rare calcifications (more common in oligodendroglial tumors).
- MR spectroscopy is increasingly used to distinguish tumor from other processes visualized on MRI.
- Gliosarcoma, a variant, has a mesenchymal component and a greater tendency for dural invasion.
- GBMs are characteristically infiltrative within brain parenchyma but rarely show extracerebral metastasis.
- High-grade tumors (by definition, GBM) are commonly hypermetabolic on FDG PET.
- Single-photon emission-computed tomography (SPECT) and MR cerebral perfusion imaging may distinguish radiation necrosis (hypovascular) from tumor recurrence (hypervascular).

Differential Diagnosis

- Brain metastasis
- Cerebral abscess
- Demyelinating/inflammatory process (i.e., multiple sclerosis)
- Radiation necrosis

Treatment

First Line

- Maximal surgical debulking is of primary importance after diagnosis is established (not ideal if primary CNS lymphoma is suspected). The degree of resection is a strong prognostic factor.
- The landmark study, which established the standard of care for upfront therapy, was a randomized phase 3 trial by the EORTC-NCIC (European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada Clinical Trials Group), reported by Stupp et al. in the *New England Journal of Medicine* in 2005.
- This study randomized 573 patients between August 2000 and March 2002 to radiotherapy (focal, 60 Gy in 2 Gy fractions given 5 days per week over 6 weeks) alone or in combination with temozolomide (75 mg/m^2, PO 7 days per week during concurrent chemotherapy, then 150 to 200 mg/m^2 PO days 1 to 5 of 28-day cycles for up to six cycles). Patients were stratified according to performance status, previous surgical intervention (yes/no and % resected), and treatment center.
- Concurrent chemotherapy and radiotherapy resulted in an improved median overall survival (OS) (14.6 months) compared with radiotherapy alone (12.1 months). The 2-year survival rate also favored the combination arm (26.5% vs. 10.4%) with minimal additional toxicity.
- An analysis of the tumor tissue identified methylation of the MGMT promoter as an excellent indicator of response and prognosis with temozolomide. In the combined group, patients with MGMT promoter methylation had a median OS of 23.4 months compared with 12.6 months for the patients without promoter methylation.
- Gliadel wafers (3.8% carmustine) are also FDA-approved for newly diagnosed GBM, which are placed locally into the tumor bed during surgery, followed by radiotherapy for newly diagnosed GBM (increased median OS by 2.1 months vs. radiotherapy alone). This approach carries an increased risk of CNS leakage (can cause increased infections and increased need for use of steroids to treat swelling).

Second-Line or Other Agents

- Bevacizumab (Avastin, monocolonal antibody against circulating VEGF) given 10 mg/kg IV over 30 to 90 minutes every 2 weeks—capable of inducing significant tumor responses in phase 2 studies for recurrent GBM.
- Other standard agents used to treat malignant gliomas are generally alkylating agents and include irinotecan, carboplatin, procarbazine, etoposide, carmustine, and lomustine.
- Other promising strategies using inhibitors of the EGFR, PDGFR, ras, and mTOR (mammalian target of rapamycin) signal transduction pathways are being studied. Additional treatment strategies currently under investigation include therapeutic gene transfer and immunotherapeutic approaches.

Prognosis

- See Table 32.6—based on several Radiation Therapy Oncology Group trials.

Astrocytoma and Anaplastic Astrocytoma

Low-Grade Diffuse Astrocytoma Low-grade diffuse astrocytomas are categorized as grade 2 and account for approximately 5% of primary brain tumors. They occur mostly in the cerebral hemispheres, but may also occur in the brain stem. Median age at diagnosis is 35 to 45.

Imaging characteristics on MRI are most commonly as follows:

- A nonenhancing lesion on T1-weighted images after contrast
- A well-delineated hyperintense lesion with little edema/mass effect on T2-weighted images
- Difficult to distinguish from nonmalignant infarct/cerebritis/demyelination
- Rare calcifications

Treatment

- Maximal surgical debulking is recommended in all cases that can be performed safely except in the case of small, asymptomatic lesions, which may be observed radiographically until resection is required.
- "High-risk" patients (two or more of age $>$ 40, KPS $<$ 70, tumor dimension $>$ 6 cm, tumor crossing midline, preoperative neurologic deficit) are usually recommended to receive postoperative

Table 32.6 Median Survival in Malignant Glioma

Tumor Type	Patient Status	Median Survival (mo)
Anaplastic astrocytoma	<50 y, normal mental status	40–60
	>50 y, KPS >70, symptoms >3 mo	40–60
	<50 y, abnormal mental status	11–18
	>50 y, symptoms <3 mo	11–18
Glioblastoma	MGMT promoter methylated	18–33
	MGMT promoter unmethylated	11–14
	Complete resection	16–23
	Partial resection	12–16
	Biopsy only	8–14
	>50 y	12–15
	<50 y, KPS >70	15–22
	>50 y, KPS <70 or abnormal mental status	11–18

KPS, Karnofsky performance status.

radiotherapy (54 Gy, based on the EORTC study indicating equivalent efficacy with improved safety compared with 60 Gy). Low-risk patients (those not meeting criteria for high risk) may be considered for observation alone.

- RTOG 98-02 is a prospective randomized clinical trial in low-grade gliomas evaluating the use of chemotherapy. It randomized patients with astrocytoma, oligodendroglioma, or oligoastrocytomas, stratified by age, histology, performance status, and extent of resection, to RT alone or in combination with PCV (procarbazine, CCNU, and vincristine) chemotherapy. The addition of chemotherapy improved median PFS, but not OS, but in the subset of patients who survived >2 years, median OS was significantly improved, as was PFS. This finding indicates a delayed benefit for chemotherapy and indicates that it might be most beneficial for the patients with best prognosis.
- Pilocytic astrocytomas, a subset of low-grade astrocytomas, are the most common pediatric astrocytic tumors and virtually the only type curable with complete surgical resection.

Prognosis The number of poor prognostic factors influences prognosis for a given patient: age, location (resectablity influenced by surrounding structures), size, and characteristics (size, enhancement on MRI) of the tumor as well as its molecular profile (IDH mutation, 1p and/or 19q mutations, which confer improved prognosis). These were combined in a recursive partitioning analysis (RPA), which separated patient characteristics into prognostic signs and then used those signs to separate patients into RPA classes (I to VI initially) with lower numbers having improved prognosis. These classes have been slightly modified over the years, but are still an excellent prognostic tool for any patient with a newly diagnosed glioma.

As surgical techniques improve, overall prognosis improves because the patients with the worst outcomes do much better with excellent resections. Prognosis of a given patient is strongly influenced by the surgical expertise, and difficult cases should be referred to centers of excellence when possible for best outcomes.

Median survival for all patients:

- Five years: 65% to 85%
- Ten years: 25% to 50%

High-Grade Diffuse (Anaplastic) Astrocytoma High-grade diffuse astrocytomas are categorized as grade 3 and account for approximately 5% of primary brain tumors. Age at diagnosis is most commonly 35 to 55. They are distinguished from low-grade diffuse astrocytomas by increased mitoses. They have a high propensity for transforming into GBM. Survival is 2 to 5 years.

Treatment

- Treat essentially identically to GBM.
- Maximal surgical debulking with or without carmustine (BCNU) wafer implantation when possible followed by adjuvant therapy (concurrent metronomic temozolomide plus radiotherapy followed by temozolomide as discussed in GBM treatment).

Oligodendroglioma and Oligoastrocytoma (Mixed Glioma)

These diffuse cerebral tumors often appear with prominent areas of calcification on CT scan. They account for 5% to 10% of all gliomas and may have a better prognosis than astrocytomas. Like astrocytomas, low-grade oligodendrogliomas may progress to a higher grade.

Treatment

- For all grades, when safe to do so, a maximal surgical resection is the initial step in management, allowing confirmation of tumor grade and the use of more directed therapy as needed.
- When only subtotal resection is available or surgery cannot be undertaken at all, patients are treated depending on risk stratification as they would be in the adjuvant setting after maximal resection.
- High-risk patients (2 or more of the following risk factors: >40 years, KPS <70, tumor >6 cm, tumor crossing midline, more than minor neurologic symptoms preoperatively, one or no deletions of 1p and 19q, or IDH not mutated) are usually treated with adjuvant radiotherapy and, in many centers, chemotherapy (a randomized trial is evaluating the role of RT alone or in combination with PCV chemotherapy; temozolomide).
- Low-risk patients (with 1 or less high-risk feature) may be observed at patient preference, but are commonly treated with RT adjuvantly. Chemotherapy may also be considered depending on the likelihood of chemosensitivity of the tumor (may be dependent on the presence of codeletion of 1p and 19q).
- Radiation therapy has been the treatment of choice for low-grade progressive and anaplastic oligodendrogliomas. However, chemotherapy with PCV or temozolomide is occasionally used as neoadjuvant therapy to delay radiation therapy with its potential long-term neurotoxicity.

Ependymoma

Ependymomas comprise a spectrum of tumors ranging from aggressive childhood intraventricular tumors to low-grade adult spinal cord lesions. Typical locations are on the ventricular surface and the filum terminale.

Epidemiology

- Ependymomas account for 2% to 10% of all CNS neoplasms.
- Seventy-five percent of ependymomas are low grade.
- Fifty percent occur before the age of 5 years.
- Intracranial tumors are 60% infratentorial, 40% supratentorial, with 50% intraventricular.
- Overall incidence of spinal seeding is approximately 7% to 15.7% for high-grade infratentorial lesions and increases with uncontrolled primary lesions.
- Highly variable biologic behavior despite pathologic appearance.

Imaging

CT and MRI are highly suggestive of the presence of ependymoma (e.g., calcified mass on the fourth ventricle) but are not diagnostic.

Treatment

- Complete resection can be curative. Subtotal resection benefit is not clearly defined, but is often a standard practice prior to radiotherapy as mainstay of treatment.
- When complete surgical resection is achieved, CSF analysis and MRI of the spine are commonly performed to rule out evidence of spinal seeding.

- Observation and limited-field adjuvant radiation therapy are reasonable options for low-grade ependymomas with no evidence of metastases.
- Subtotal resection with no evidence of metastases should have limited field radiotherapy in the setting of tumor progression.
- If recurrence occurs and radiotherapy has been previously employed, chemotherapeutic options are quite limited with poor response rates. Options include single-agent or doublet platinum regimens, etoposide, nitrosurea, and bevacizumab. Clinical trials should also be considered or best supportive care when radiotherapy is not an option. Craniospinal irradiation is warranted for evidence of diffuse seeding by cerebrospinal fluid (CSF), cytologic or radiographic studies, or for anaplastic ependymomas.

Prognosis

- Five-year survival
  - Low-grade tumors: 60% to 80%
  - Anaplastic ependymoma: 10% to 47%
- Long-term survival
  - Surgery alone: 17% to 27%.
  - Surgery plus radiation: 40% to 87%.
  - Age is a dominant prognostic factor. Infants do poorly.

CHOROID PLEXUS TUMORS (NONGLIOMAS)

Choroid plexus tumors occur mostly in ventricles; in adults, occurrence is predominantly in the fourth ventricle. Tumors range from aggressive supratentorial childhood tumors to benign cerebellopontine angle tumors of adulthood. An association with Li-Fraumeni syndrome and von Hippel-Lindau syndrome has been described.

Diagnosis

- Signs of increased ICP.
- Focal findings of the fourth ventricle (ataxia and nystagmus).
- Anaplastic histologic changes warrant CSF examination for increased risk of disseminated disease.

Treatment

Surgery

- Complete resection is the goal of surgery.

Radiation Therapy/Chemotherapy

Given the rarity of these tumors, there are few prospective studies to evaluate a uniform approach. Radiation therapy, in conjunction with chemotherapy, has shown some benefit. Combinations of doxorubicin, cyclophosphamide, vincristine, and nitrosoureas have been used, as well as intraventricular methotrexate and cytarabine, but there have been no studies to evaluate these approaches.

MEDULLOBLASTOMA

Medulloblastoma is a malignant, small, blue, round cell tumor of the CNS.

Epidemiology

- Medulloblastoma comprises 25% of all pediatric tumors.
- Found predominantly in the posterior fossa in children; uncommon in adults.
- Thirty percent to 50% of medulloblastomas have isochromosome 17q.
- Associated with Gorlin syndrome and Turcot syndrome.

Clinical Presentation

- The most common presenting symptoms are signs of increased ICP and cerebellar and bulbar signs.
- At diagnosis, 5% to 25% of patients have CSF dissemination.
- Less than 10% of patients exhibit systemic metastasis, commonly in bone.
- Forty percent of patients have brain stem infiltration.

Risk Stratification

- Average risk: Localized disease at diagnosis; total or near-total resection
- High risk: Disseminated disease at diagnosis and/or partial resection

Imaging

Typically, CT or MRI reveals a contrast-enhancing posterior fossa midline lesion, most frequently arising from the cerebellar vermis.

Staging

- Based on the modified Chang staging system.
- Tumors are evaluated according to size, local extension, and presence of metastasis.
- CSF and spinal axis should be evaluated for metastasis with lumbar puncture and contrast-enhanced MRI.

Treatment

- Surgical resection.
- Radiation therapy involves postoperative 35 Gy radiation to the whole brain, with 15 to 20 Gy boost to posterior fossa. Average-risk patients may be cured with radiation alone.
- Ongoing studies are investigating the possibility of further reducing craniospinal radiation to 18 Gy in combination with local irradiation and adjuvant chemotherapy.
- Children with localized disease have shown an OS of >81% when treated with 23.4 Gy irradiation to the craniospinal axis, supplemented by 32.4 Gy local irradiation, followed by eight cycles of the following adjuvant chemotherapy regimen:
  - Vincristine 1.5 mg/m^2 IV weekly *plus*
  - CCNU 75 mg/m^2 PO on day 0 *plus*
  - Cisplatin 75 mg/m^2 IV on day 1

Results of this combination therapy were equivalent to

  - Cisplatin 75 mg m^2 IV on day 0 *plus*
  - Vincristine 1.5 mg/m^2 IV weekly *plus*
  - Cyclophosphamide 1,000 mg/m^2 IV over 60 minutes on days 21 and 22
- Small nonrandomized trials with select patients suggest that a small percentage (<20%) of patients who relapse after primary treatment can be successfully retreated and remain disease-free for >5 years with high-dose chemotherapy and stem cell support.

Prognosis

Disseminated disease is the most important prognostic factor. Other important factors are age (worse in children aged <3 years) and extent of resection (controversial).

Progression-free survival after chemotherapy and radiation is as follows:

- High-risk patients: 40% to 60%
- Average-risk patients: 65% to 91%

MENINGIOMAS

Meningiomas comprise up to 39% of primary CNS tumors. They are usually benign.

Genetics

- Monosomy 22, with frequent mutation of the *NF2* gene on 22q.
- Malignant meningiomas frequently show loss of 1p, 10, and 14q.
- Female sex, ionizing irradiation, *NF2*, and breast carcinoma are predisposing factors.

Clinical Presentation

Meningiomas commonly present in the parasagittal region, cerebral convexity, and sphenoidal ridge. Signs and symptoms include seizures, hemiparesis, visual field loss, and other focal findings.

Imaging

- A uniformly enhancing lesion on contrast-enhanced MRI, sometimes observed with a "dural tail."
- Isodense and isointense on unenhanced CT and MRI scans, respectively, and can display calvarial hyperostosis adjacent to lesion.

Treatment

Surgery

- Treatment goal is complete resection.
- Recurrence rate after complete resection is about 1% to 2% per year. Quality of resection and dural margins removed (1 cm is standard) predict lower recurrence rates.

Radiotherapy

- Radiation: Consider for incompletely resected or inoperable meningiomas, and WHO grade 3.

Chemotherapy

There is no effective drug for treatment of meningiomas. Despite having estrogen and/or progesterone receptors, meningiomas are generally nonresponsive to hormonal therapy with agents such as tamoxifen. Although a small phase 2 trial suggested that the antiprogestin RU-486 had antimeningioma activity, a subsequent large randomized trial of RU-486 versus placebo for locally unresectable meningiomas showed no benefit for the drug compared to placebo. Other regimens studied with little success include interferon and hydroxyurea.

PRIMARY CNS LYMPHOMA

- Intracerebral lymphoma most frequently presents as parenchymal lymphoma, but may be found in other anatomic sites such as the eye, meninges, or ependymal nodules.
- Primary CNS lymphoma accounts for 3% to 4% of all primary brain tumors, but up to one-quarter of HIV-associated lymphomas. Its prevalence in AIDS patients has declined with improved retroviral therapy.
- For unknown reasons, there has been a 10-fold increase in the last few decades in incidence of this tumor in immunocompetent patients, from 0.3/100,000 to 3/100,000. This increase has leveled off since 1995.
- Histologically indistinguishable from other systemic lymphomas. Usually most similar to diffuse large B-cell lymphoma. Rare to have concurrent systemic lymphoma (3% to 5%).

Risk Factors

- HIV/AIDS
- Immunosuppression for organ transplantation
- Autoimmune disease
- Congenital immunodeficiencies such as Wiscott-Aldrich syndrome
- Epstein-Barr virus (EBV) infection

Clinical Presentation

- Symptoms of intracranial mass (headaches and signs of increased ICP).
- Frontal lobe is most commonly involved, often with multiple lesions. Personality changes and decreased alertness are common. Basal ganglia and corpus callosum are also common sites.
- Large lesions (>2 cm) are common, variably circumscribed and multiple shapes may occur.
- Multifocal disease: 42% leptomeningeal, 15% occular seeding at diagnosis

Diagnosis and Staging

Tissue diagnosis is paramount, except when EBV DNA is evident in the CSF of an AIDS patient, combined with hypermetabolic lesion on PET or SPECT imaging. Can be diagnosed with needle biopsy, but excisional biopsy is best, as it is for lymphoma diagnosis in general. Staging studies should include the following:

- MRI of brain with gadolinium
- Lumbar puncture for CSF cytology
- Ophthalmologic evaluation with slit lamp
- Bone marrow biopsy
- Complete physical and blood work (including liver function tests)
- Consider MRI spine if symptomatic
- CT chest, abdomen, and pelvis

Treatment

Many primary CNS lymphomas may initially shrink or disappear in the presence of corticosteroids. When primary CNS lymphoma is in the differential, steroids should be withheld, if possible, until tissue diagnosis is confirmed. A ring-enhancing lesion that "disappears" after starting steroids is strongly suggestive of CNS lymphoma, although other infectious diseases (i.e., toxoplasmosis) and inflammatory/demyelinating diseases (i.e., multiple sclerosis) must be considered.

Surgery

Surgery has no role in therapy, but is used to confirm diagnosis.

Radiotherapy

Whole-brain radiotherapy (WBRT) yields 80% to 90% radiographic complete response. Common dosage is 40 to 50 Gy to the entire brain and meninges (C2 radiation). More extensive radiotherapy (including the spine or focal boosts to the area of greatest involvement) does not convey improved outcomes. Median survival is 12 to 18 months.

Chemotherapy

- The standard agents (adriamycin, cyclophosphamide, vincristine, prednisone, and rituximab) used for similar histologic systemic lymphomas (DLBCL) are not effective probably due to poor blood–brain barrier penetration.
- Methotrexate (high-dose) is the most active agent in CNS lymphoma. Studies suggest that preradiation chemotherapy with high-dose methotrexate significantly increased median survival (range: 30 to 60 months) and led to many long-term survivors.
- The role of radiotherapy for patients who have complete response to chemotherapy is unknown.
- The potential for long-term treatment-induced neurocognitive toxicity is considerably greater for patients receiving combined-modality treatment, especially when WBRT precedes high-dose methotrexate.
- Treatment is poorly tolerated in patients aged ≥60 years. Single-agent methotrexate should be the treatment of choice for these patients unless contraindicated.
- The two most widely utilized treatment regimens for primary CNS lymphoma are the New Approaches to Brain Tumor Therapy (NABTT) regimen and the Memorial Sloan-Kettering Cancer Center (MSKCC) regimen, as outlined in Table 32.7.

Table 32.7 Two Chemotherapy Regimens for Primary Brain Lymphoma

	Treatment	Results
NABTT regimen[a]	High-dose methotrexate 8 g/m^2 every 2 wk, with leucovorin rescue to maximal response; delayed radiotherapy until tumor progression	22 patients treated; overall response rate 74%; median progression-free survival 12.8 mo; median overall survival 22.8 + mo; no reported delayed severe neurologic toxicity
MSKCC regimen[b]	Five cycles of methotrexate 2.5 g/m^2, vincristine 1.4 mg/m^2 with maximum dose at 2.8 mg (2 m^2), procarbazine 100 mg/m^2/day for 7 days (cycle 1, 3, 5), and intraventricular methotrexate 12 mg followed by whole-brain radiotherapy to 45 Gy	102 patients treated; 94% response to preradiation chemotherapy; median progression-free survival 24 mo; overall survival 3.9 mo; 15% of patients experienced severe delayed neurologic toxicity

[a]New Approaches to Brain Tumor Therapy.
[b]Memorial Sloan-Kettering Cancer Center.
Based on data from DeAngelis LM, Seiferheld W, Schold SC, et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol.* 2002;20(24):4643-4648.

PINEAL REGION TUMORS

Clinical Presentation

Because the pineal region is close to the center of the brain, symptoms are generally related to increased ICP and ocular pathway cranial nerve palsies:

- Obstructive hydrocephalus (headache, nausea, vomiting, and lethargy)
- Cranial nerve palsies (diplopia and upward-gaze paralysis)
- Elevated levels of serum tumor markers α-fetoprotein, α-human chorionic gonadotropin, and placental alkaline phosphatase

Differential Diagnosis

- Germ cell tumors (most common, ~50% germinoma, others: teratoma, choriocarcinoma, endodermal sinus tumor, embryonal carcinoma)
- Pineal parenchymal tumor (or pineal cyst)
- Meningioma
- Tectal astrocytoma

Diagnosis

- If suspicious for germ cell tumor, serum and CSF tumor markers should be checked (AFP, β-HCG, and LDH).
- Because of the differential, biopsy is indicated. Open is preferred to ensure adequate tissue.

Imaging

- Germinomas are usually isointense and homogeneous on T1-weighted images on MRI.
- Teratomas and nongerminomas tend to appear heterogenous with more invasive features. Choriocarcinoma may have indications of prior hemorrhage.

Treatment

- Germinomas—surgery not indicated, primarily treated with radiotherapy (40 Gy + 15 Gy boost). Craniospinal radiotherapy is indicated if CSF seeding is found.

- Nongerminomas—radical resection teratomas and residual masses may be required due to mixed histology. For nongerminomas, chemotherapy with radiotherapy is recommended, with etoposide and cisplatin as the main drugs.
- Others—primarily surgically treated, radiotherapy may be employed based on histology.

METASTATIC BRAIN TUMORS

Epidemiology

- Brain metastases are the most prevalent intracranial malignancy. Estimated incidence in the United States is 80,000 to 170,000 cases per year, compared to approximately 23,000 newly diagnosed primary brain tumors, highlighting the importance of proper diagnosis and management of this disease.
- An estimated 25% of adults and 6% to 10% of children with systemic cancer will develop symptomatic brain metastases.
- The most common tumors to metastasize to the brain are lung, breast, melanoma, testicular, choriocarcinoma, and renal cancers.

Clinical Presentation

Common presenting signs and symptoms of brain metastasis include

- Hemiparesis
- Change in mental status
- Gait ataxia
- Sensory loss/change
- Papilledema
- Headache
- Focal deficit
- Seizure
- Speech disturbance

Differential Diagnosis

- Primary brain tumors
- Abscess
- Demyelination
- Cerebral infarction
- Cerebral hemorrhage
- Progressive multifocal leukoencephalopathy
- Radiation necrosis

The false-positive rate for single brain metastasis may be as high as 30%. Nonmetastatic brain lesions are equally divided between primary brain tumors and infections. Meningioma must be considered in patients with primary breast cancer with a dural-based brain lesion because the prevalence of this primary brain tumor increases in breast cancer.

IMAGING

Contrast-enhanced MRI is the diagnostic imaging modality of choice. Features that favor MRI diagnosis of brain metastasis include the following:

- Multiple lesions
- Location at gray/white matter junction
- High ratio of vasogenic edema to tumor size

- If imaging indicates that metastatic CNS lesion is likely and primary is unknown, CT chest, abdomen, and pelvis should be performed to identify primary disease.

Treatment

Symptomatic Therapy

- To reduce symptoms including vasogenic edema, SIADH, and neurologic impairment, a loading dose of dexamethasone 10 mg followed by 4 mg four times per day can be given.
- Symptomatic improvement should be seen within 24 to 72 hours.
- Imaging studies may not show a decrease of cerebral edema for up to 1 week.
- Steroid use should be tapered after completion of irradiation or earlier if cerebral edema is minimal.

Seizure Management

- Because infratentorial metastases have a very low risk of seizures, anticonvulsant therapy is usually not indicated.
- In patients with supratentorial brain metastasis and no surgery or prior seizures, prophylactic anticonvulsant therapy is not routinely recommended. Generally, antiseizure medication is started only after seizure activity has occurred or for a short term after a patient has undergone craniotomy with prior history of ictal events.
- Close monitoring is advised because dexamethasone and phenytoin mutually increase the clearance of phenytoin, and an increasing number of reports suggest a correlation between Stevens-Johnson syndrome and palliative whole-brain irradiation in patients taking phenytoin.
- Because phenytoin (like most older antiepileptic drugs) induces hepatic cytochrome P450 isoenzymes, thereby considerably altering the metabolism and pharmacology of agents such as paclitaxel and irinotecan, some physicians are initiating seizure prophylaxis with newer agents that do not induce hepatic enzymes, such as levetiracetam, lamotrigine, or topiramate.

Surgery

Before recommending surgical resection, the following factors should be considered:

- Interval between diagnosis of primary cancer and finding of brain metastasis
- Type of primary cancer
- Extent of systemic disease
- Number and location of cerebral metastases
- Patient's neurologic status

Several controlled studies suggest a benefit for surgery combined with WBRT (described below in the Radiation Therapy section) for patients with single brain metastasis and stable extracranial disease. The benefit of resection of multiple brain metastases with therapeutic intent has not been established. For patients with multiple brain metastases, the role of surgery is generally limited to the following:

- Large, symptomatic, or life-threatening lesions
- Tissue diagnosis in unknown primary
- Differentiation of metastasis from primary brain tumor (e.g., meningioma)

Radiation Therapy

- Considered first-line therapy for brain metastasis in addition to surgery when suitable.
- WBRT increases median survival to 3 to 6 months from about 1 month.
- A randomized study conducted by Patchell and colleagues in 48 patients demonstrated superiority of surgery followed by WBRT compared with WBRT alone in OS (40 vs. 15 weeks, $P < 0.01$) as well as functional independence, and local recurrence for patients with single metastasis and KPS >70.
- The same group also randomized 95 patients between surgery alone or in combination with WBRT and found a significant decrease in tumor recurrence, and likelihood of neurologic deficit–related death. There was no difference in OS, however.
- Overall response rate is 64% to 85%.
- Fractionation schedule: From 20 to 40 Gy in 5 to 20 fractions.

- Most common schedule: 30 Gy in 10 fractions over 2 weeks (5 days per week) or 37.5 Gy in 15 fractions over 3 weeks.
- For patients with good prognosis, more prolonged fractionation, such as 40 Gy in 2 Gy fractions, may reduce long-term morbidity. For patients with poor performance status and prognosis, a shorter course of 20 Gy in five fractions is a reasonable option.
- For patients with reasonable systemic disease control and a limited number of lesions that are not considered resectable, stereotactic radiosurgery (SRS) can be considered, due to improved toxicity profile compared with WBRT.
- SRS followed by WBRT may be considered for patients with limited but unresectable lesions who otherwise have reasonable control of systemic disease, based on a subset analysis of RTOG 9508 which demonstrated a survival advantage in patients randomized to SRS plus WBRT (compared with WBRT alone) who had only one metastatic lesion.
- Approximately 50% of patients with brain metastases die from progressive neurologic disease; the rest die from progressive systemic disease.

Late Toxicities Dementia is common in patients receiving a total dose of >30 Gy, as a delayed effect and is considered a reasonable risk in patients with anticipated longer survivals. Recommended dose is 40 to 45 Gy in 1 to 2 Gy fractions.

Radiosurgery Indications include

- Young age
- Good performance status
- Limited extracranial disease
- Oligometastases; up to three lesions <3.5 cm
- Recurrent brain metastasis after whole-brain irradiation

Adverse prognostic indicators include

- Poor performance status
- Progressive systemic disease
- Infratentorial location

Interstitial Brachytherapy There is presently no indication for interstitial brachytherapy.

Chemotherapy

- In select malignancies, brain metastases may respond to systemic treatment of the underlying cancer. This is dependent on the primary tumor and drug treatment available.
- In breast cancer, regimens of combined chemotherapeutic agents are generally directed at the systemic disease. Responses have been seen in 50% to 70% of cases, and there appears to be a survival advantage in patients who respond. Common breast cancer regimens include
  - Cyclophosphamide/5-fluorouracil/cisplatin (CFP)
  - Cyclophosphamide/methotrexate/5-fluorouracil (CMF)
  - Doxorubicin (adriamycin)/cyclophosphamide (AC)
- In small cell lung cancer, regimens including etoposide and platinating agents have been used. Overall response rates for primary brain metastasis approach 76%. Response rates decrease to 43% on CNS relapse.
- Active targeted therapies, such as erlotinib in NSCLC and vemurafenib in melanoma, have demonstrated surprisingly high response rates in patients with appropriate disease for these treatments (EGFR and V600E mutations, respectively).

Prognosis

Median survival is 2.3 to 7.1 months depending on prognostic indicators (Table 32.8) that include

- Karnofsky performance status >70
- Age <65 years
- Controlled primary disease
- No extracranial metastasis

Table 32.8 Prognostic Indicators and Median Survival in Metastatic Brain Tumors

RPA Class	Median Survival (mo)
Class I (KPS ≥ 70, age <65, systemic control)	6–8
Class II (KPS ≥ 70 and age ≥65 or uncontrolled primary at any age)	3–5
Class III (KPS <70)	2–4

Source: Derived from multiple validation series of RTOG RPA classes.

REVIEW QUESTIONS

1. A 37-year-old male presents to the emergency room with headaches that have been bothering him for about 3 weeks. They are worse when he is in bed. A CT scan of his head shows a mass-occupying lesion in the right-frontal lobe that appears heterogeneously enhancing. An MRI is performed that indicates a hypervascular appearance. He is seen by a neurosurgeon and undergoes a resection and pathology reveals a GBM. Which of the following features, if present, indicates a poor prognosis in this patient?
   A. Age <50
   B. MGMT promoter unmethylated
   C. Had a gross total resection
   D. KPS 90 prior to surgery
   E. All of the above

2. A 47-year-old woman with metastatic breast cancer was diagnosed originally with stage IIIa disease 2.5 years ago. Her tumor did not express ER, PR, or Her2 by IHC. After initial surgery, chemotherapy, and radiation, she had no evidence of disease. However, about 2 years later, she developed cough that did not go away. A CT of the CAP revealed metastatic disease in the lungs and liver. She was started on single-agent chemotherapy and had a partial response. She presents today to your clinic for follow-up and reports new numbness and weakness in her right hand. That is her only symptom of neurologic dysfunction. An MRI of the brain reveals a single brain metastasis. What of the following would you like to do next?
   A. Refer to radiation oncology for WBRT
   B. Refer to hospice
   C. Refer to neurosurgery for consideration of resection of solitary brain lesion
   D. Refer to neurosurgery and radiation oncology for resection followed by WBRT

3. A 63-year-old man, in otherwise excellent health, trips over his grandchild's toy and hits his head. He is taken to the ER as a precaution and a CT scan of his head demonstrates a uniformly enhancing lesion near the skull in the right occipital area. He reports no neurologic deficit, and a complete neurologic examination reveals no abnormality. An MRI demonstrates a uniformly enhancing lesion on T1 with no evidence of peri-tumor edema. A stereotactic biopsy of the lesion confirms the diagnosis of meningioma, low grade. What would you recommend next?
   A. Radiotherapy to the lesion
   B. WBRT
   C. Surgical resection
   D. Observation
   E. Surgical resection followed by radiotherapy to the tumor cavity

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33

Endocrine Tumors

Ann W. Gramza

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 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

- Thyroid carcinoma
- Parathyroid carcinoma
- Adrenocortical carcinoma (ACC)
- Pheochromocytoma
- Carcinoid tumors
- Pancreatic neuroendocrine tumors (NETs).

THYROID CARCINOMA

General

Epidemiology

- Thyroid cancer is the most common endocrine malignancy, and now the fifth most common cancer in women.
- The incidence has been increasing for the past three decades, with a current estimate of more than 56,000 men and women to be diagnosed with thyroid cancer in 2012. The increase in incidence extends to both men and women.
- Mortality has also been rising for the past two decades. The precise reasons for the increase in incidence and mortality are unknown.
- The ratio of female to male patients is approximately 3:1.

Risk Factors

- The best-established risk factor for thyroid cancer is exposure to ionizing radiation during childhood.
- A family history of thyroid cancer and history of a benign thyroid condition such as goiter or nodule also confer an increased risk of thyroid cancer.

Table 33.1 Hereditary Endocrine Cancer Syndromes

Familial Syndrome	Associated Malignancies	Gene Mutated
Multiple endocrine neoplasias (MEN)		
MEN 1	**Carcinoids, pancreatic neuroendocrine tumors (gastrinomas, insulinomas)**, pituitary tumors, parathyroid adenomas	*MEN 1*
MEN 2	**Medullary thyroid cancer, pheochromocytoma**	*RET*
Neurofibromatosis 1	**Carcinoids, pheochromocytomas, pancreatic neuroendocrine tumors,** gastrointestinal stromal tumors (GIST), paragangliomas	*NF1*
von Hippel-Lindau	**Pheochromocytomas, pancreatic neuroendocrine tumors**, hemangioblastomas, retinal angiomas, renal cell carcinomas, endolymphatic sac tumors, and epididymal papillary cystadenomas	*VHL*
Li-Fraumeni	**Adrenocortical cancer**, breast cancer, sarcoma, leukemia, brain tumors	*TP53*
Beckwith-Wiedemann	**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	**Follicular thyroid cancer,** breast cancer, endometrial carcinoma	*PTEN*
Peutz-Jeghers	**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*

Prognosis

- Prognosis varies by thyroid cancer subtype, but the overall 5-year relative survival is nearly 98%. This is because more than 80% of cases are papillary thyroid cancer (PTC), the subtype with the best survival.

Differentiated Thyroid Cancer: Papillary, Follicular, Hurthle Cell

- More than 90% of all thyroid cancers are a subtype of differentiated thyroid cancer (DTC).
- PTC is the most common subtype (80% to 85%).
- PTC is generally unilateral, but may be multifocal within a lobe. Variants include tall cell, columnar, and diffuse sclerosing.
- PTC metastasizes primarily via lymphatic invasion; vascular invasion is uncommon.
- Genetic alterations involved in the MAPK signaling pathway are found in at least 75% of PTC cases. *BRAF*^{V600E} mutation is found in approximately 45% of PTCs, while *RET* rearrangements are found in approximately 25% Activating point mutations in the *RAS* oncogenes occur in approximately 10% of cases.
- 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 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.
- Hurthle cell cancer (HCC) 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 TSH and thyroid ultrasound. 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 scan 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, and may allow a more conservative approach for those who would otherwise undergo a diagnostic surgical procedure.
- 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 ≤45 years old, 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 thyroid, or for patients with history of prior exposure to ionizing radiation to 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.
- 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.

Adjuvant Therapy

- Treatment with radioiodine (I-131, 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.
- 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.

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; Hurthle 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	

Targeted Therapy/Chemotherapy

- Patients with advanced disease that is refractory to I-131 and unresectable should participate in a clinical trial when possible. These patients are often treated with a small molecule VEGFR inhibitor (off label) based on phase II studies that have shown responses and clinical benefit. Traditional systemic chemotherapy has largely been ineffective. Isolated metastases can be treated with external beam radiotherapy.

Medullary Thyroid Cancer

- Medullary thyroid cancer (MTC) is a calcitonin-secreting tumor of the parafollicular (C) cells occurring either sporadically (75% of cases) or as a part of hereditary syndrome (25% of cases). The hereditary syndromes are the multiple endocrine neoplasia type 2 syndromes (MEN 2A or 2B) and familial medullary thyroid cancer (FMTC) (see Table 33.3).

Table 33.3 Syndromes of Multiple Endocrine Neoplasias

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 2A (Sipple syndrome)
Medullary thyroid cancer
Pheochromocytomas
Primary hyperparathyroidism (parathyroid hyperplasia)
MEN 2B
Medullary thyroid cancer
Pheochromocytomas
Multiple mucosal neuroma
Marfanoid body habitus
Megacolon

- MEN 2 and FMTC are autosomal dominant syndromes caused by germline *RET* oncogene mutations. Somatic *RET* mutations also occur in approximately 50% of sporadic MTC.
- MTC represents 3% to 5% of all thyroid cancer cases.
- Sporadic tumors tend to be solitary, whereas familial tumors tend to be bilateral and multifocal.

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 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 CEA 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.
- Patients with advanced, progressing, or symptomatic residual or recurrent disease not appropriate for surgery or radiation therapy should be considered for systemic therapy.
- Both vandetanib and cabozantinib have recently been approved by the US FDA for the treatment of advanced MTC based on improvement in progression-free survival in phase III trials. No improvement in overall survival has been demonstrated; therefore, patients with indolent disease should consider observation until their disease becomes necessary to treat. See Table 33.4 for vandetanib and cabozantinib dosing.
- Traditional systemic chemotherapy has largely been ineffective.

Anaplastic Thyroid Cancer

- 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.

Other Thyroid Cancers

- Primary thyroid lymphoma
- Metastasis to the thyroid

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.

Table 33.4 Systemic Therapy Regimens for Advanced or Metastatic Endocrine Cancers

Regimen	Malignancy
Vandetanib 300 mg orally daily	Medullary thyroid cancer
Cabozantinib 140 mg orally daily	Medullary thyroid cancer
Cyclophosphamide 750 mg/m^2 day 1, Vincristine 1.4 mg/m^2 day 1, Dacarbazine 600 mg/m^2 day 1, and Dacarbazine 600 mg/m^2 day 2, every 21–28 d	Malignant pheochromocytoma[a]
Sunitinib 37.5 mg orally daily	Pancreatic neuroendocrine tumors, Malignant pheochromocytoma[a]
Everolimus 10 mg orally daily	Pancreatic neuroendocrine tumors, carcinoid
Octreotide 150–250 μg SC TID or depot 20 mg IM every 4 weeks	Pancreatic neuroendocrine tumors, carcinoid
Depot octreotide 30 mg IM every 28 d and Everolimus 10 mg daily	Pancreatic neuroendocrine tumors, carcinoid
Streptozocin 500 mg/m^2/d IV days 1–5 and 5-Fluoruracil 400 mg/m^2/d IV days 1–5 every 6 weeks	Pancreatic neuroendocrine tumors, carcinoid[a]
Streptozocin 500 mg/m^2/d IV days 1–5 and Doxorubicin 50 mg/m^2 IV days 1, 22 every 6 weeks	Pancreatic neuroendocrine tumors, carcinoid[a]
Capecitabine 750 mg/m^2 twice daily on days 1–14 plus temozolomide 200 mg/m^2 daily on days 10–14	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 days 2, 3, and 4), Doxorubicin (40 mg/m^2 IV day 1), and Cisplatin (40 mg/m^2 IV days 3 and 4) every 4 weeks	Adrenocortical carcinoma

[a]Limited phase II data.

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 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 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.

ADRENOCORTICAL CARCINOMA

Epidemiology

- ACC is a rare malignancy arising from the adrenal cortex, with 1 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.
- Most cases are sporadic, but it can be a component of a hereditary syndrome (Li-Fraumeni, Beckwith-Wiedemann) (see 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.
- 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 and not laparoscopically.

Adjuvant Therapy

- Adjuvant mitotane may improve survival for patients with stage I to III disease who have undergone a complete resection. 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 overall survival.
- Combination chemotherapy with mitotane plus etoposide, doxorubicin, and cisplatin demonstrated better rates of response and disease-free survival than mitotane plus streptozotocin in patients with advanced disease.
- Radiofrequency ablation may also be implemented for local control or metastases in patients with unresectable disease.
- See Table 33.4 for detailed chemotherapy regimens.

Prognosis

- 5-year survival rate: 38% to 60%.
- Prognosis is better in children.
- Common sites of distant metastasis are liver, lung, lymph nodes, and bone.

PHEOCHROMOCYTOMA

Epidemiology

- Catecholamine-secreting tumor of the adrenal medulla chromaffin cells with an incidence of <1 per 100,000 person-years.
- Up to 25% of cases are associated with a familial genetic syndrome such as MEN 2 or von Hippel-Lindau disease (see Table 33.1).
- Found in <0.2% of patients with hypertension.

Clinical Presentation

- The classic triad of symptoms includes headache, sweating, and tachycardia. Clinical features of pheochromocytomas are summarized in Table 33.5.

Table 33.5 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

- Pheochromocytomas are generally indolent, with morbidity and mortality related to the tumors' secretory products.
- Approximately 10% of pheochromocytomas are bilateral, with occurrence more frequent in familial syndromes.
- Approximately 10% of pheochromocytomas are extra-adrenal; these tumors are more likely to be malignant.
- Less than 10% are malignant; metastasis is most common in lung, brain, and bone.

Diagnosis

- Measurement of 24-hour urinary-fractionated metanephrines is the most specific tool for diagnosis of pheochromocytoma.
- 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 pheochromocytoma.
- CT and MRI are equally sensitive diagnostic tools for pheochromocytoma.
- Labeled metaiodobenzylguanidine (^{131}I-MIBG), which is structurally similar to norepinephrine, is taken up and concentrated in adrenergic tissue. It is highly sensitive and specific for malignant tumors and familial syndromes, but is inferior to bone scan for detecting bone metastases.
- Vascular invasion and extension into the cortex may be seen with both benign and malignant tumors.
- The only absolute criterion for malignancy is the presence of secondary tumors in sites where chromaffin cells do not usually exist.

Treatment

Surgery

- Surgery is the mainstay of treatment and should be considered for primary, recurrent, and metastatic disease.
- Appropriate preoperative evaluation and $\alpha \pm \beta$-blockade are required to minimize risk of hypertensive crisis.
- Laparoscopy is acceptable if imaging reveals no obvious tumor invasion or metastases.

Radiation

- Radiation has a limited role in the treatment of pheochromocytoma, 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.

Chemotherapy/Targeted Therapy

- In a small study (14 patients) with metastatic, malignant pheochromocytoma, the combination of cyclophosphamide, vincristine, and dacarbazine had a biochemical response of 79%, with a 57% reduction in measurable disease and median duration of response >20 months.
- Responses have also been reported with the targeted agent sunitinib.
- See Table 33.4 for detailed chemotherapy regimens.

NEUROENDOCRINE TUMORS

NETs are cancers of the interface between the endocrine system and the nervous system. These rare tumors are distinguished from most other solid tumors by their ability to secrete biologically active molecules that can produce systemic syndromes. The 2010 WHO classification separates NETs into well-differentiated and poorly differentiated based on tumor grade, mitotic count, and Ki-67 proliferation index. The most common types of NETs are carcinoid tumors and pancreatic NETs, both of which are typically well differentiated.

Carcinoid Tumors

- Incidence in the United States is approximately 2 per 100,000 individuals.
- Carcinoids 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 liver.
- Features of foregut, midgut, and hindgut carcinoids are outlined in Table 33.6.

Table 33.6 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 such as octreotide. Octreotide has also demonstrated antitumor activity, potentially improving time to progression.
- Carcinoids are resistant to most chemotherapeutic agents. Active agents include 5-fluorouracil, capecitabine, streptozocin, doxorubicin, and interferon. Chemotherapy is typically reserved for patients who are progressing with no other treatment options. See Table 33.4 for detailed systemic therapy regimens.
- Radiation therapy is for palliation only.

Pancreatic Neuroendocrine Tumors

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 malignant. They are associated with familial syndromes in up to 25% of cases (see 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 *MEN1* 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: >1,000 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, somatostatin analogs (e.g., octreotide), and tumor embolization.
- Both sunitinib and everolimus were approved for the treatment of progressive, well-differentiated pancreatic NETs. Approval was based on improved progression-free survival.
- Cytotoxic chemotherapy can also be used for metastatic disease. Active chemotherapeutic agents include streptozotocin, doxorubicin, temozolomide, 5-fluoruracil, and dacarbazine.

- See Table 33.4 for detailed chemotherapy regimens.
- For those patients with liver metastases, liver-directed therapies such as embolization, radiofrequency ablation, and cryosurgery are options.

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.
- Patients with recurrent disease that includes liver metastases can be treated with surgical resection (when possible) or liver-directed therapy such as chemoembolization or radiofrequency ablation.
- Refractory hypoglycemia can be treated with oral diazoxide, which inhibits pancreatic secretion of insulin and stimulates release of catecholamine and glucose from the liver.
- Both sunitinib and everolimus have been approved for the treatment of progressive, well-differentiated pancreatic NETs. Approval was based on improved progression-free survival.
- Cytotoxic chemotherapy can also be used for metastatic disease. Active chemotherapeutic agents include streptozotocin, doxorubicin, temozolomide, 5-fluoruracil, and dacarbazine.
- See Table 33.4 for detailed chemotherapy regimens.

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 somatostatin analogs, which decrease VIP secretion. Interferon-α can also be used.
- Patients with recurrent disease that includes liver metastases can be treated with surgical resection (when possible) or liver-directed therapy such as chemoembolization or radiofrequency ablation.
- Both sunitinib and everolimus have been approved for the treatment of progressive, well-differentiated pancreatic NETs. Approval was based on improved progression-free survival. See Table 33.4 for detailed chemotherapy regimens.

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, somatostatin analogs, 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.

REVIEW QUESTIONS

1. A 36-year-old woman is found to have a 3 cm thyroid mass, enlarged neck lymph nodes, and multiple subcentimeter bilateral pulmonary nodules. Subsequent biopsies of both a lung nodule and the thyroid mass revealed PTC. What is the appropriate next step in this patient's management?
- **A.** Diagnostic radioactive iodine whole-body scan to evaluate sites of disease
- **B.** Total thyroidectomy and lymphadenectomy
- **C.** Radioactive iodine treatment
- **D.** Doxorubicin-based combination chemotherapy
- **E.** Clinical trial with a kinase inhibitor

2. A 23-year-old male with a history of MEN2A and MTC presents for follow-up. He was originally diagnosed 5 years ago when a thyroid mass was noted incidentally following a car accident. He subsequently underwent a total thyroidectomy with central and right neck dissections. Today, his review of systems is negative. On physical examination, his neck is notable for well-healed surgical scars and no palpable nodules or lymph nodes. The rest of the examination is unremarkable. Laboratory studies reveal normal serum chemistries, CBC, and TSH. His calcitonin from today is 93 and has been stable since his thyroidectomy. Which of the following is the most appropriate next step in his management?
- **A.** Radioactive iodine whole-body scan and treatment with radioactive iodine if the scan is positive for disease.
- **B.** Contrast-enhanced CT or MRI of the neck, chest, and abdomen with liver protocol for initial staging followed by treatment with vandetanib 300 mg daily. Repeat calcitonin in 2 to 3 months.
- **C.** Contrast-enhanced CT or MRI of the neck, chest, and abdomen with liver protocol for staging. If imaging is negative, repeat serum calcitonin in 6 months.
- **D.** Treat his neck with external beam radiotherapy.
- **E.** Increase his levothyroxine dose to suppress TSH to <0.1. Repeat his calcitonin and TSH levels in 6 weeks.

3. A 50-year-old female with a history of ACC presents for consultation regarding further management. She underwent resection 1 year ago, and now presents with left flank pain, weight gain, weakness, and uncontrolled hypertension. She is found to have a 7.5 cm mass in the left renal fossa and multiple lesions consistent with metastatic disease. A CT-guided biopsy confirms ACC recurrence. She is judged unresectable. Of the treatment options listed, which should be started immediately?
- **A.** Streptozocin
- **B.** Combination chemotherapy with cisplatin, doxorubicin, and etoposide
- **C.** Sunitinib
- **D.** Mitotane
- **E.** Hydrocortisone

4. A 55-year-old male presents with severe abdominal pain and diarrhea. Evaluation by EGD reveals a 1 cm duodenal ulcer, and biopsies are negative for *Helicobacter pylori*. A serum gastrin level is elevated at 1,300 pg/mL. What is the next appropriate step in his evaluation?

A. Octreotide scan
B. Secretin stimulation test
C. EUS
D. CT scan of the abdomen
E. ^{131}I-MIBG scan

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SECTION Eleven

Supportive Care

34

Hematopoietic Growth Factors

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BACKGROUND

- Hematologic toxicity (leukopenia, anemia, and thrombocytopenia) is the most common side effect of chemotherapy. 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), the 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. Its labeled clinical indication for its administration is

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%). Although no nomogram exists to calculate this risk, factors to consider when 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 a patient's risk factors including

- Age above 65
- 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 2,607 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.

Secondary Prophylaxis

The guidelines recommend administering CSFs to patients who had FN or dose-limiting neutropenic event that could otherwise impact planned dose of chemotherapy from a prior cycle of chemotherapy when no CSFs were given. Dose reduction and treatment delay are reasonable alternatives in the palliative setting.

Neutropenic Fever

Routine adjunctive use of CSFs for treatment of 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

- Age above 65
- Expected prolonged (more than 10 days)
- Profound (<100/μL) neutropenia
- Sepsis syndrome
- Hospitalization at the time of the development of fever
- Pneumonia
- Invasive fungal infection
- Uncontrolled primary disease

A multicenter randomized trial demonstrated that therapeutic G-CSF shortened hospital stay (median, 5 days versus 7 days; $P = 0.015$), antibiotic therapy (median, 5 days versus 6 days; $P = 0.013$), and duration of grade IV neutropenia (median, 2 days versus 3 days; $P = 0.0004$), in 210 solid tumor patients

with FN, and at least one high-risk feature. Cochrane meta-analysis of 1,518 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 cells (PBSCs) and to shorten the duration of neutropenia after cytoreduction and autologous PBSC transplantation. Postautotransplantation 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.

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 been shown to have a favorable effect on remission rate, duration, or survival. Use of G-CSF after completion of consolidation chemotherapy seems to have a more profound shortening of neutropenia duration and infection rate, with no effect on complete response duration or overall survival. Recent Cochrane meta-analysis including 5,256 AML patients in 19 trials reported that the addition of CSFs did not alter all-cause mortality in the short and long term. The administration of CSFs did not affect the occurrence of episodes of neutropenic fever, bacteremias, or invasive fungal infections. Currently, there are insufficient data 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 effects 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 the 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.

G-CSF

- 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.

GM-CSF

- 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.

DOSING

- Recommended dosing of CSFs is listed in Table 34.1.
- In chemotherapy patients, a transient increase in neutrophil count is typically observed in the first 1 to 2 days after initiation of CSFs. Treatment should continue until post–nadir 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-α and darbepoetin-α. Darbepoetin-α has a half-life around three times longer than that of epoetin-α; 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 9,353 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 different 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

Table 34.1 Growth Factors for Transplant or Nonmyeloid Cancer Patients Only: FDA-Approved Dosing and Indications

Drug	Dosing	Indications
Filgrastim (Neupogen)	5 μg/kg SC daily 24 h after completion of chemotherapy until ANC reaches 2,000– 3,000/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 1,500/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-α (Epogen; Procrit)	Start at 150 units/kg SC TIW or 40,000 U SC weekly Escalate dose to 300 units/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	Chemotherapy-induced anemia
Darbepoetin-α (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 post–nadir 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 wk; SC, subcutaneously; TIW, three times per week.

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 earlier 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 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 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 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.

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 units/L). Combining ESAs and G-CSF in MDS patients has resulted in improved response rates.
- Other reported uses include multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, β-thalassemia, radiation therapy, rheumatoid arthritis, paroxysmal nocturnal hemoglobulinuria, Castleman disease, congestive heart failure, critical illnesses, hepatitis C (in patients treated with interferon-α and ribarvirin), 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 to 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, pruritis, 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 $\leq$100 units/L are more likely to respond to ESAs than those with levels $>$100 units/L.

PLATELET GROWTH FACTORS

- Thrombocytopenia can be a life-threatening consequence of antineoplastic treatments. Platelet transfusions are required to prevent or mitigate hemorrhagic complications. 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 (e.g., 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. At present, formal guidelines for the use of thrombopoietic growth factors are under development.
- 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.
- Recombinant thrombopoietins (TPOs) are no longer being developed because of antibody production. TPO mimetics (TPO receptor agonists) are currently under investigation.

REVIEW QUESTIONS

1. Which of the following benefits of ESA has been consistently demonstrated in RCTs and meta-analyses?
   - **a.** Reduced requirement for blood transfusion
   - **b.** Decrease in symptoms related to anemia
   - **c.** Decreased mortality in cancer patients
   - **d.** Decreased cardiac complications related to anemia
   - **e.** Improved quality of life
2. Among the following clinical scenarios, which patient is the best candidate for ESA if the goal is to reduce the need for blood transfusions?
   - **a.** A 55-year-old female with stage II breast cancer on adjuvant chemotherapy with asymptomatic Hb of 10 g/dL.
   - **b.** A 60-year-old female with metastatic breast cancer on palliative chemotherapy with symptomatic anemia of Hb 8 g/dL.
   - **c.** A 55-year-old male with metastatic prostate cancer on palliative chemotherapy with asymptomatic anemia of Hb 9 g/dL.
   - **d.** A 50-year-old female with stage III breast cancer on dose dense adjuvant chemotherapy with asymptomatic Hb level of 10.5 g/dL.
   - **e.** None of the above.
3. Which of the following clinical cases LEAST justifies the use of G-CSF?
   - **a.** A 50-year-old male on the 12th cycle of FOLFIRI with bevacizumab for metastatic colon cancer presents with FN with ANC 220. He has no other complaints.
   - **b.** A 49-year-old female with stage II triple negative breast cancer is coming to receive cycle 3 of dose dense AC-T. A prior cycle without G-CSF support was complicated by prolonged FN.
   - **c.** A 40-year-old female with cervical cancer with history of extensive pelvic radiation presents with fever and ANC of 90. Otherwise, the patient has no complaints.
   - **d.** A 69-year-old male with metastatic non–small cell lung cancer presents on cycle 3 of cisplatin and vinorelbine presents with FN and increased productive cough and shortness of breath.
   - **e.** A 69-year-old male presenting to start induction chemotherapy with Docetaxel, cisplatin, and 5-fluorouracil for unresectable hypopharyngeal carcinoma.
4. Which of the following is the TRUE statement about the evidence concerning CSFs?
   - **a.** A dose-dense chemotherapy regimen supported by pegfilgrastim showed superior clinical benefit, compared with the regimen supported by filgrastim in elderly patients with aggressive lymphoma.
   - **b.** Meta-analysis of lymphoma clinical trials showed that CSF as a primary prophylaxis reduced the risk of neutropenia, FN and infection, but no benefit in overall survival.
   - **c.** Meta-analysis clinical trials of G-CSF for chemotherapy-induced FN showed that CSFs reduced the hospital stay, time to neutrophil recovery, and infection-related mortality.
   - **d.** ASCO 2006 update guideline recommends that the use of CSFs when the risk of FN is approximately 40%.
   - **e.** Meta-analysis of randomized controlled trials that evaluated the addition of CSFs during and following chemotherapy in patients with AML showed that CSF decreases the occurrence of bacteremia and invasive fungal infection but produces no difference in all-cause mortality.

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35

Infectious Complications in Oncology

Mauricio Burotto Pichún, Sarah Read, and Juan C. Gea-Banacloche

FEVER

- Fever is the most common sign of infection, and a very usual 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 IN THE NEUTROPENIC CANCER PATIENT

- Neutropenia, the most important risk factor for bacterial infection in cancer patients, is defined as an absolute neutrophil count (ANC) $<500/mm^3$, or ANC $\leq 1{,}000/mm^3$, 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* (Fig. 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 (see below).
- 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. 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 to 7, depending on the study) the frequency of invasive fungal infection is high enough that it is standard practice to add empirical antifungal

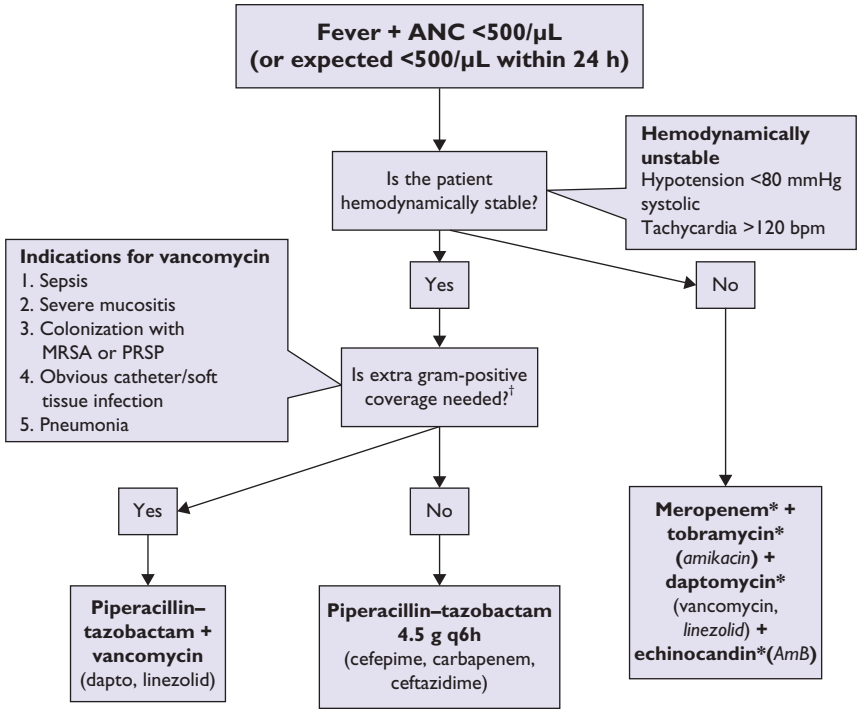

FIGURE 35.1 Approach to patients with fever and neutropenia without clinically or microbiologically documented infection. The choice between piperacillin–tazobactam (shown here emphasizing the higher dose required in neutropenic patients), cefepime, imipenem, meropenem, and ceftazidime will vary between 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*.

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 used may vary with the clinical situation and the preexistent use of antifungal prophylaxis, but there are good data supporting the empirical addition of amphotericin B (deoxycholate or liposomal), voriconazole, and caspofungin. It is indicated to look for invasive fungal infection by blood cultures (including fungal blood cultures) and computed tomography (CT) of chest and 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. In this situation, both breakthrough bacterial and fungal infections are possible. The management includes changing

or adding antibiotics and antifungals plus diagnostic studies as outlined above. Drug-resistant bacteria are increasing, for example, extended-spectrum beta-lactamase-producing (ESBL) gram-negative bacilli, vancomycin-resistant enterococcus (VRE), carbapenemase-producing *Klebsiella* (KPC). The specific bacteria vary depending on the institution, and their prevalence may play a role in determining the optimal choice of antibiotics (both as initial regimen and as "rescue" regimen for recrudescent fever).

- 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 (e.g., 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, blood and urine cultures, and chest x-ray should be obtained.
- Blood cultures: Two sets of blood cultures are more sensitive than a single set for the diagnosis of bacteremia. 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. A differential time to positivity of 2 hours or more (i.e., 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.
- 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 their potential for faster progression and higher morbidity, the emphasis is on coverage of enteric gram-negative bacilli and *Pseudomonas*. This may be achieved by using single agents 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 the aforementioned 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
- Effective antibiotic combinations include one of the aforementioned β-lactams plus an aminoglycoside (choice based on local resistance) or colistin. Ciprofloxacin may 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 polymixin B are being used more frequently with the increasing prevalence of KPC and multiresistant *Acinetobacter baumannii*.

Role of Vancomycin and Other Agents with Gram-Positive Coverage

Vancomycin should be part of the initial empirical regimen under the following circumstances:

- Severe sepsis or septic shock
- Pneumonia
- Soft tissue infection (cellulitis, necrotizing fasciitis)
- Clinically suspected catheter-related infections (not the mere presence of an intravascular device)
- Severe mucositis or other risk factors for infection with *Streptococcus mitis* (use of prophylaxis with fluoroquinolones, high-dose Ara-C, use of H_2 blockers)
- Known colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or penicillin-resistant *Streptococcus pneumoniae* (PRSP)

Addition of vancomycin to the initial regimen:

- Adding vancomycin to the initial regimen because of persistent fever alone does not improve the outcome and is not recommended.
- Positive blood cultures for 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 (gram-positive cocci in pairs and short chains suggest enterococcus or *S. pneumoniae*, gram-positive cocci in clusters suggest *Staphylococcus*).
- It is not known at this time whether linezolid or daptomycin should be used empirically in patients known to be colonized with VRE, nor whether screening cultures result in improved outcomes.
- In the case of documented VRE infection, the choice between daptomycin, linezolid, and quinupristn–dalfopristin is not based on clinical outcome data, but on theoretical considerations and local resistance patterns.

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 (e.g., AML induction therapy), as well as patients with symptoms or signs of clinical instability or with significant comorbidities (e.g., COPD, heart failure). Low-risk patients do not exhibit any high-risk factors and their neutropenia is expected to be short lived. These patients could be considered for outpatient antibiotic treatment.
- A quantitative risk assessment, the Multinational Association for Supportive Care in Cancer (MASCC) 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 chronic obstructive pulmonary disease (4), solid tumor *or* no previous fungal infection (4), absence of dehydration (3), outpatient status (3), and age $<$60 years (2) and the points are added up. Patients with a score of $\geq$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 in to 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: >70 years old, 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 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 the course of neutropenia.
- Specific modifications are dictated by specific clinical syndromes (Table 35.1) 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 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 should be added empirically for neutropenic patients in the following circumstances:

- Severe sepsis or septic shock: it may be caused by *Candida*; amphotericin or an echinocandin should be added.
- 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/day IV.
- A lipid formulation of amphotericin B such as liposomal amphotericin B (Ambisome) or amphotericin B lipid complex (Abelcet), 3 to 5 mg/kg/day IV.
- Voriconazole, 6 mg/kg IV every 12 hours for 24 hours followed by 4 mg/kg IV every 12 hours.
- Caspofungin, 70 mg IV loading dose followed by 50 mg IV daily.

For persistent fever, these four options 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. Some authorities have suggested to start antifungal agents only when there is ancillary evidence of fungal infection besides the fever (e.g., positive serologic tests like galactomannan and/or ß-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.

Table 35.1 Specific Infectious Disease Syndromes in Oncology Patients and Approach to Diagnosis and 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 (e.g., ceftazidime, cefepime, and 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, *S. 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*, *S. pyogenes*, gram-negative bacilli (e.g., *Pseudomonas*), VZV, HSV, *Candida* For vesicular lesions, scrape base for DFA for VZV and culture or PCR for HSV	Ecthyma gangrenosum: coverage of *Pseudomonas* (e.g., ceftazidime, cefepime, ciprofloxacin) Infections with *S. pyogenes*: treat aggressively with penicillin G, clindamycin, IVIG, and surgical debridement Perianal cellulitis: broad-spectrum coverage including anaerobes (e.g., imipenem) VZV, HSV: acyclovir
Sinusitis	Evaluate with CT scan and examination by otolaryngologist Tissue should be biopsied if there is suspicion of fungal infection or no response to antibiotic therapy after 72 h Pathogens: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, gram-negative bacilli (e.g., *Pseudomonas*), fungi including agents of mucormycosis (Mucorales)	Nonneutropenic: levofloxacin or amoxicillin/clavulanate Neutropenic: broad-spectrum coverage including *Pseudomonas* (e.g., carbapenem, cefepime) and consider fungal coverage (e.g., amphotericin B, voriconazole)
Pulmonary infections	CT scan and BAL should be performed early Pneumonias in any cancer patient are often caused by	For all patients, ensure adequate coverage of community-acquired pneumonia including *Legionella* (e.g., newer generation fluoroquinolone)

(*Continued*)

Table 35.1 Specific Infectious Disease Syndromes in Oncology Patients and Approach to Diagnosis and Management (Continued)

	gram-negative bacilli and *S. aureus* as well as community-acquired pneumonia pathogens: *S. pneumoniae*, *H. influenzae*, *Legionella* spp, and *Chlamydia pneumoniae*	Neutropenic: coverage of *S. pneumonia, S. aureus*, and *Pseudomonas* (e.g., newer generation fluoroquinolone and ceftazidime and vancomycin); add antifungal coverage if pneumonia develops on antibiotics (e.g., amphotericin B, voriconazole)
	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* Mycobacteria should also be considered, particularly in patients with previous exposure	Cell-mediated immunodeficiency: consider coverage of *Pneumocystis* with TMP/SMX, CMV with ganciclovir, and *Nocardia* with TMP/SMX
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	*C. difficile*: metronidazole or vancomycin if refractory
	Diarrhea is most commonly caused by *C. difficile* (send toxin assay) but can also be caused by *Salmonella*, *Shigella*, *Aeromonas*, *E. coli*, *Campylobacter*, viruses, parasites, etc.	Neutropenic enterocolitis: broad-spectrum coverage including *Pseudomonas* and anaerobes (e.g., 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*, *N. 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) Brain abscesses may be confused with tumor	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

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; VZV, varicella zoster virus.

It should be noted that posaconazole (a new broad-spectrum antifungal agent given as 200 mg PO every 8 hours with food) has shown very good activity as antifungal prophylaxis, but has no role in the acute management of presumptive fungal infection, because therapeutic levels are not achieved for 5 to 7 days after starting.

Duration of Antibiotic Therapy

- Documented bacterial infection: Antibiotics should be continued for the amount of time standard for that infection or until resolution of neutropenia, whichever is longer.
- Uncomplicated fever and neutropenia of uncertain etiology: Antibiotics should be continued until the fever has resolved and the ANC is above 500 for 24 hours.
- If no infection was documented and the patient became afebrile on antibiotics, but the neutropenia persists, it is acceptable to complete 2 weeks of treatment. At that point one may discontinue the antibiotics and observe. Alternatively, it is acceptable to resume fluoroquinolone prophylaxis until marrow recovery.
- 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; 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 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 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 (see Table 35.1).

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, and the source of the infection should be sought.

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. Intravascular devices should be removed. 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 to rule out endocarditis.
- Oxacillin and nafcillin are the drugs 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 as long as there is no pulmonary involvement.
- Bacteremia with viridans group streptococci may cause overwhelming infection with sepsis and acute respiratory distress syndrome (ARDS) 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).
- Risk factors for viridans group streptococci bacteremia include severe mucositis (particularly following treatment with cytarabine), active oral infection, and prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) or a fluoroquinolone.
- Enterococci often cause bacteremia in debilitated patients who have had prolonged hospitalization and have been on broad-spectrum antibiotics.
- VRE are 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). There is no evidence at this time whether empirical treatment with these agents should be initiated in febrile neutropenic patients with known VRE colonization.

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. *Propionibacterium* is almost always a contaminant, but it can cause infection of Ommaya reservoirs.

Gram-Negative Bacteremia

- Gram-negative bacteria in the blood should never be considered contaminants and should be treated immediately.
- Depending on the preliminary result from the Microbiology lab (variable from one laboratory to another), preliminary information may be nonexistent or may be specific enough (e.g., "enteric-like" or "*Pseudomonas*-like" gram-negative bacillus, to guide antibiotic choice), 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 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 these have practical importance, as they may carry an inducible β-lactamase that may result in treatment failure with third-generation cephalosporins like ceftazidime. Carbapenems, fluoroquinolones, and piperacillin–tazobactam 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.
- KPC pneumoniae and other enterobacteriaceae resistant to carbapenems are becoming more prevalent and have caused institutional outbreaks with high mortality. There are no comparative data, and the treatment usually involves combination or several drugs including colistin, tigecycline, and gentamicin. In vitro data suggest that the addition of doripenem may result in synergistic antibacterial activity.
- *P. aeruginosa* is one of the most lethal agents of gram-negative bacteremia in the neutropenic patient. Combination therapy should be started to 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 or who have intravascular catheters; TMP/SMX is the treatment of choice. For the allergic patient, ticarcillin–clavulanate or moxifloxacin may be effective.
- *Acinetobacter baumannii* bacteremia is frequently associated with infected intravascular catheters in cancer patients and is often resistant to multiple antibiotics, including imipenem–cilastatin. Ampicillin–sulbactam, tigecyclin, or colistin may be effective, but consultation with an infectious diseases specialist should be sought.

Fungemia

- *Candida* species cause most cases of fungemia in cancer patients. The frequency of non-*albicans* candidemia is increasing, probably as a consequence of the widespread use of fluconazole prophylaxis.
- 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.
- All 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 (e.g., AIDS, alemtuzumab use, allogeneic bone marrow transplantation) *C. neoformans*, always resistant to echinocandins, should be considered. In neutropenic patients, *Fusarium, Paecilomyces*, 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 blood cultures (or a positive catheter-tip culture) *and* evidence that the catheter is the source of the bacteremia. The most easily 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 culture bottles is higher. Of note, this definition makes mandatory to draw blood cultures from the catheter as well as directly from a vein via a peripheral stick.

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.
- 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 if an organism is identified.
- Septic thrombophlebitis also necessitates catheter removal, and anticoagulation can be considered. Surgical drainage is occasionally necessary.
- Catheter-related bloodstream infections caused by coagulase-negative *Staphylococcus* or gram-negative bacilli should be 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 (e.g., 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 (refractory thrombocytopenia, 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.

- 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 bacteremia due to other gram-negative bacilli. Antibiotic therapy with coverage of *Pseudomonas* should be initiated and early surgical involvement for possible debridement 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 (DFA) testing to diagnose VZV and for shell–vial culture or PCR to diagnose 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 debridement as needed and antibiotic therapy with penicillin G and clindamycin, as well as, in the case of shock, IV immunoglobulin (IVIG).
- Perianal cellulitis may develop in neutropenic patients. Antibiotic therapy should include gram-negative and anaerobic coverage (e.g., imipenem–cilastatin or meropenem 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, CRC) and tyrosine kinase inhibitor (TKI) like erlotinib (lung cancer) and sorafenib (renal cancer, HCC).
- 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.
- Sinusitis in immunocompromised hosts 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 are appropriate. Biopsy should be obtained if there is any suspicion of fungal infection (e.g., 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, the treatment of choice for aspergillosis) are increasingly recognized. When patients have been receiving voriconazole prophylaxis, the relative frequency of mucormycosis increases.
- If fungal sinusitis is confirmed, treatment is with surgical debridement and antifungal treatment, which should be started at maximum dosing:
  - Amphotericin B 1 to 1.5 mg/kg/day.
  - Lipid formulation of amphotericin B 5 to 7.5 mg/kg/day.
  - 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 requires 5 to 7 days to achieve therapeutic levels and is only available as an oral formulation with poor absorption. It should never be used to treat an infection that can progress quickly (like fungal sinusitis during neutropenia) but it can be a possible treatment alternative once the diagnosis is established and the disease stabilized by another agent.

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 agent for *Legionella* and other agents of community-acquired pneumonia (e.g., newer generation fluoroquinolone like levofloxacin or moxifloxacin, or macrolide like azithromycin in addition to ceftazidime).
- CT scan and bronchoscopy for BAL should be performed early, particularly if there is no prompt improvement.
- 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.

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.
- 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 ß-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.
- There are molds that do not produce either galactomannan or ß-D-glucan (e.g., mucor, rhizopus). This means that a negative test *does not* rule out invasive fungal infection.
- Positive serum galactomannan and ß-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. Other options include:
  - High-dose lipid formulation of amphotericin B (5 mg/kg/day).
  - Amphotericin B (1 to 1.5 mg/kg/day).
  - Caspofungin (70 mg loading dose followed by 50 mg/day IV) has been approved for patients with invasive aspergillosis who are unresponsive to or intolerant of amphotericin B.
- Mucorales (previously known as zygomycetes) such as *Rhizopus*, *Mucor*, and *Cunninghamella* species are less common causes of pulmonary infection in neutropenic patients. They are voriconazole resistant but have variable susceptibility to posaconazole. 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 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 an infectious diseases specialist is strongly advised.

Pulmonary Infiltrates in Patients with 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*. 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. *Pneumocystis* pneumonia (PCP) may have a more indolent presentation in HIV-infected patients and stem cell transplant recipients.
- 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 (prednisone should be added if the pO_2 is $<$70 mmHg).
- In TMP/SMX-allergic/intolerant patients, alternatives for serious disease include IV pentamidine, and for moderate disease dapsone–trimethoprim, 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.
- Diagnosis is made from material obtained at bronchoscopy, either by pathology or culture.
- Treatment is with TMP/SMX, which is given for 6 months. Depending on the species, imipenem–cilastatin + amikacin may also be used.

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.
- The effect of antiviral treatment on the outcome of these viral respiratory infections is unclear. Anecdotal successes reported in case reports and case series have not been reproduced in controlled trials. 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 (SPAG-2) via a face mask, ideally inside a scavenging tent to prevent environmental contamination or intermittently (2 g inhaled every 8 hours). Some experts recommend adding intravenous immunoglobulin (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. Control of this infection, however, seems to be mainly related to the recovery of adenovirus-specific immunity.

- CMV pneumonitis 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. CMV pneumonia after day 100 is becoming more common and should be considered in patients with a history of previous CMV reactivation.
- CMV reactivation and disease have also been rarely observed in patients with HTLV-I associated adult T-cell leukemia/lymphoma and in patients treated with alemtuzumab.
- After allogeneic stem cell transplant, the presence of CMV in the BAL by culture is considered sufficient to establish the diagnosis. In other settings, tissue is required. Of note, identifying CMV in the BAL only by PCR is not diagnostic of CMV pneumonitis.
- Treatment of CMV pneumonia is with ganciclovir 5 mg/kg IV every 12 hours with IVIG 500 mg/kg every 48 hours for 3 weeks. Foscarnet (90 mg/kg every 12 hours) may be substituted for ganciclovir.
- Human herpes virus-6 (HHV-6), VZV, and (very rarely) HSV have also been associated with pneumonitis in the immunocompromised patient.

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. If the infection is less severe, valacyclovir 1,000 mg PO every 12 hours or famciclovir 500 mg PO every 12 hours can be used.
- Candidiasis can be treated locally with clotrimazole troches 10 mg dissolved in the mouth 5×/day, 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 (e.g., ceftazidime + vancomycin or piperacillin–tazobactam or imipenem or meropenem).
- CMV can also cause esophagitis.

Diarrhea

- *Clostridium 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 assays 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.
- Treatment for mild/moderate cases is with metronidazole 250 mg PO four times a day or 500 mg PO three times a day. The antiparasitic agent itazoxanide (500 mg PO twice a day) may offer similar efficacy. In severe and/or refractory cases, vancomycin 125 to 250 mg PO four times a day should be used. Fidaxomicin 200 mg PO twice daily was as effective as oral vancomycin in a randomized clinical trial. Metronidazole can be given IV if patients are unable to tolerate oral therapy or have ileus. 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.
- Recurrent infection after metronidazole therapy should be treated with a longer course of metronidazole before oral vancomycin therapy is initiated.

- Bacteria such as *E. coli, Salmonella*, *Shigella*, *Aeromonas*, and *Campylobacter* species, as well as parasites and viruses, are less common causes of diarrhea in cancer patients. Stool should be sent for culture of bacterial pathogens and examined for ova and parasites. Specific therapy should be directed against recovered pathogens when indicated.

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.
- 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* (e.g., 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 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.
- Stable patients can be treated empirically without biopsy if suspicion is high. Blood cultures are typically negative. If the diagnosis is in question, a liver biopsy is recommended. 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 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, and young age.
- Lamivudine prophylaxis is recommended, 100 mg daily beginning 1 week prior to chemotherapy and for 8 weeks after completion of treatment.

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 per day for 1 to 2 weeks is the treatment of choice. In the case of non-*albicans* candiduria, another -azole or amphotericin should be used. Caspofungin is minimally present in the urine, and there is no clinical experience in this setting.

Central Nervous System Infections

- Changes in mentation or level of consciousness, headache, 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 also 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/day or amphotericin B 0.5 to 0.7 mg/kg/day in combination with flucytosine 37.5 mg/kg every 6 hours for 2 weeks. If the patient improves (afebrile, cultures negative), therapy can be 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 CSF and should be treated with acyclovir 10 mg/kg IV every 8 hours. Potential clinical indications for empirical HSV treatment include predominance 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 and has been associated with rituximab and mycophenolate mofetil (MMF).
- 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 plus vancomycin plus metronidazole plus voriconazole.

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 EBV 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-EGFR) is associated with acneiform rash and secondary bacterial infection.

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 may increase the frequency of gram-positive infections and 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 valacyclovir 500 mg PO once or twice daily or acyclovir 250 mg/m^2 IV every 12 hours or 800 mg PO twice daily.

CMV

- Prophylactic ganciclovir can reduce the incidence of CMV disease, but its use is limited by myelosuppressive toxicity. Valganciclovir (the prodrug of ganciclovir) is also effective, but it seems to result in a higher frequency of myelosuppression.
- Patients who have undergone allogeneic stem cell transplant should be monitored for CMV replication by following CMV antigenemia or PCR weekly.
- If positive, patients 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 (a) foscarnet 60 to 90 mg/kg IV every 12 hours for 14 days followed by 90 mg/kg daily, (b) valganciclovir 900 mg IV every 12 hours for 14 days followed by 900 mg daily, or (c) 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).

Pneumocystis jirovecii Pneumonia Prophylaxis

- Prophylaxis against *Pneumocystis* is generally administered to patients during the 6-month poststem 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 treatments include (a) dapsone 100 mg PO daily (rule out G6PDH deficiency before using dapsone), (b) inhaled pentamidine 300 mg every 4 weeks, or (c) atovaquone 1,500 mg daily.

Antifungal Prophylaxis

- Fluconazole 400 mg PO/IV daily has been the regimen of choice. Of note, fluconazole has no activity against molds like *Aspergillus*.

- An alternative regimen is itraconazole 200 mg IV every 12 hours for 2 days followed by 200 mg IV daily for 12 days followed by 200 mg PO every 12 hours, but this is frequently limited by gastrointestinal toxicity.
- Posaconazole 200 mg PO three times a day has been shown to be more effective than fluconazole/itraconazole in patients with prolonged neutropenia. It may also result in less cases of aspergillosis in patients receiving corticosteroids for graft-versus-host disease. It is reasonable to choose posaconazole when the risk of mold infection is considered significant.
- Prophylaxis should be continued until 100 days posttransplant and until immunosuppressants have been discontinued.
- Use of fluconazole has led to increased frequency of fluconazole-resistant infections such as *Candida tropicalis*, *C. parapsilosis*, and *C. krusei*.

REVIEW QUESTIONS

1. A 26-year-old woman with AML in second remission is undergoing allogeneic stem cell transplantation. On day +7 after an allogeneic BMT, she started with fever (38.6°C). The patient is hemodynamically stable. The physical examination reveals ulcers and redness in mouth and pharyngeal area. There is *no* erythema or tenderness around her right Hickman catheter exit site or tunnel. The rest of physical examination is unremarkable. The ANC is 0.07 (70/μL). Which of the following is the best answer regarding the recommended management?

A. Obtain blood cultures and start oral antibiotics because this is a low-risk patient.
B. Obtain blood cultures and start IV cefepime.
C. Start vancomycin and cefepime because the patient has a central line that may be the source of the fever.
D. Obtain blood cultures, and start cefepime and vancomycin, imipenem or meropenem because the patient has mucositis.
E. Obtain blood cultures and observe for 1 hour to be sure that the fever is real.

2. The patient was started on cefepime but the fever persisted and after 48 hours her blood pressure dropped from 130/80 to 90/65, and her heart rate was 130. Blood cultures came positive for coagulase-negative *Staphylococcus* (one out of six bottles). A report from a previous hospitalization stated that the patient was colonized with VRE and that she had had a UTI 3 months prior caused by an ESBL-producing Klebsiella pneumoniae. What is the best approach at this time?

A. Add empirical antifungal treatment with amphotericin B.
B. Add an antibiotic with VRE coverage to enterococcus (e.g., linezolid) and remove the catheter.
C. Add vancomycin to the cefepime, and do not remove the catheter.
D. Add vancomycin to the cefepime, and remove the catheter.
E. Change antibiotics to meropenem and daptomycin IV and add an echinocandin as empirical antifungal.

3. Cultures were positive for ESBL-producing Klebsiella pneumoniae. The patient's blood pressure and heart rate recovered with the new antibiotic regimen and fluid resuscitation, but the fever never went away for more than 24 hours. Five days later the patient continues to be febrile and neutropenic. The blood pressure is stable. What do you think is the best strategy at this point?

A. Maintain same antimicrobial agents until the ANC more than 0.5, unless there is further hemodynamic instability.
B. Stop daptomycin because VRE was never found in the blood and continue with meropenem.
C. Get a CT scan of the chest looking for signs of fungal infection.
D. Get a CT scan of the chest and sinuses to look for signs of fungal infection and start amphotericin B.
E. Discontinue the meropenem to test for β-lactam-induced drug fever.

4. A patient with non-Hodgkin lymphoma will be treated with the combination of CHOP chemotherapy and rituximab mAb. Which of the following test has to be done before starting this treatment?

A. PPD
B. Galactomannan
C. Hepatitis B serology
D. Hepatitis C serology

Suggested Readings

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36

Oncologic Emergencies and Paraneoplastic Syndromes

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SPINAL CORD COMPRESSION

- Spinal cord compression (SCC) is an oncologic emergency, as delay in recognition and therapy can cause irreversible loss of neurologic function.
- SCC is diagnosed in more than 30% of all patients with disseminated cancer, and roughly 5% to 10% of all patients experience cord dysfunction.
- SCC most often involves the thoracic spine (60%), followed by the lumbosacral spine (30%) and cervical spine (10%).

Etiology

- The three most common underlying cancer diagnoses associated with SCC are lung cancer (24.9%), prostate cancer (16.2%), and multiple myeloma (11.1%). The highest cancer-specific incidence rates are seen in patients with multiple myeloma (15%), Hodgkin and non-Hodgkin lymphomas (13.9%), and prostate cancer (5.5%).
- Hematogenous seeding of tumor to vertebral bodies is the most common cause of spinal metastases, followed by direct extension and cerebrospinal fluid spread.
- SCC, infrequently, is the first sign of malignancy.

Clinical Manifestations

- Pain is usually the first symptom of SCC, often worse with recumbency. Over time, pain may develop a radicular quality.
- Muscle weakness.
- Sensory loss.
- Bladder and bowel dysfunction.
- Ataxia.
- Thorough physical examination should be performed including percussion of the spinal column, evaluation for motor and sensory deficits including pinprick testing, straight-leg raising, and rectal examination.

Diagnostic Imaging

- Magnetic resonance imaging (MRI) of the entire thecal sac is the preferred modality for initial evaluation of a patient with suspected SCC. Advantages of MRI include ability to define adjacent soft

tissues and bone, avoids the need for lumbar or cervical puncture as required with myelography, and can safely be performed in patients with brain metastases, thrombocytopenia, or coagulopathy. MRI without contrast may be preferred in patients with renal failure with a creatinine clearance of less than 60 mL per minute.

- Computerized tomography (CT) myelography is less often used since the widespread utilization of MRI. CT myelogram and MRI have roughly equivalent sensitivity and specificity. CT myelography may be preferred in patients with mechanical valves, pacemakers, paramagnetic implants, and shrapnel; patients with significant pain since MRI requires the patient to lie still; patients requiring CSF analysis to rule out leptomeningeal metastases.
- Other imaging modalities include CT, conventional spinal radiographs, and bone scan; however, none are reliable enough to replace either MRI or myelography.

Differential Diagnosis

- Musculoskeletal disease
- Spinal epidural abscess
- Metastatic disease with vertebral metastases without cord compression and leptomeningeal metastases
- Radiation myelopathy from prior radiation to the spine

Treatment of Spinal Cord Compression

- The goals of treatment for SCC include pain control, preservation, or improvement of neurologic function and avoidance of complications from tumor growth.
- The most important prognostic factor for regaining ambulation after treatment of SCC is pretreatment neurologic status.
- Begin treatment with a "loading" dose of dexamethasone, 10 mg intravenously (IV), followed by 4 mg IV infusion 6 hours later and every 6 hours thereafter. In a trial comparing dexamethasone bolus of 10 mg or 100 mg IV, both followed by 16 mg daily orally had no differences in pain control or neurologic outcome. Cochrane meta-analysis concluded that higher initial steroid doses were not associated with better outcomes, but increased the incidence of serious adverse events related to glucocorticoid side effects.
- Surgical and radiation oncology consultation(s) are immediately required after diagnosis, and further therapy is decided on the basis of clinical signs and symptoms, availability of histologic diagnosis, spinal stability, and previous therapies.
- In a study with symptomatic patients with SCC caused by metastatic tumors other than lymphoma, initial debulking surgery followed by radiation resulted in 4 times longer duration of maintained ambulation after treatment, and 3 times higher chance of regaining ambulation for nonambulatory patients, than that with radiation alone. In addition, patients who receive combined-modality therapy achieve superior pain control and bladder continence. Patients treated with radiation therapy alone require more steroids and narcotics and are less likely to maintain continence.
- Patients with spinal instability even in the absence of clinical signs and symptoms should undergo surgery unless otherwise contraindicated.
- Radiotherapy (RT) may be used to treat radiosensitive tumors (breast, prostate, lymphoma, multiple myeloma, and neuroblastoma) in asymptomatic individuals and in those who are symptomatic but are poor surgical candidates. Standard radiation dosages range from 2,500 to 4,000 cGy delivered in 10 to 20 fractions. In patients with relatively short life expectancy, a short course of external beam RT (one fraction of 8 Gy) produces similar palliation. Stereotactic body radiotherapy (SBRT) with a single 24 Gy fraction has also been found to give excellent tumor control, even in patients with relatively radioresistant tumors such as melanoma and renal cell cancer.
- Chemotherapy may be considered first-line therapy for patients with chemosensitive malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, germ cell neoplasms, and breast and prostate cancer) and in individuals who are not candidates for radiation or surgery. Chemotherapy may be an attractive option since it can also treat tumor deposits elsewhere in the body.

SUPERIOR VENA CAVA SYNDROME

- Superior vena cava (SVC) syndrome can occur in any condition that obstructs blood flow through the SVC. This commonly occurs as a manifestation of either primary or metastatic malignancy (extrinsic), thrombosis associated with malignancy or central venous access devices (intrinsic), or combination of both.
- SVC syndrome can result in interstitial edema of the head and neck, which may narrow the laryngeal lumen causing airway compromise, and cause cerebral edema leading to cerebral ischemia, herniation, and death.

Etiology

- SVC syndrome is caused by an intrathoracic malignancy in 60% to 85% of cases and SVC obstruction if often a presenting symptom of a previously undiagnosed tumor.
- Small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). SVC syndrome occurs in 10% of SCLC cases at presentation; however, NSCLC is a more frequent cause because of higher incidence.
- Non-Hodgkin lymphoma, especially diffuse large cell lymphoma, primary mediastinal large B-cell lymphoma, or lymphoblastic lymphoma in the anterior mediastinum. Hodgkin lymphoma is rarely a cause of SVC syndrome.
- Other malignant tumors include thymoma, primary mediastinal germ cell neoplasms, mesothelioma, and solid tumors with mediastinal lymph node metastases (e.g., breast cancer).
- Nonmalignant disorders include thrombosis (commonly related to indwelling intravascular devices), fibrosing mediastinitis (commonly associated with fungal infections), and postradiation fibrosis.

Clinical Manifestations

- Clinical symptoms may occur acutely or gradually.
- Dyspnea is the most common symptom.
- Other symptoms include facial swelling or head fullness, arm swelling, cough, chest pain, or dysphagia.
- Physical examination findings frequently include facial edema and venous distension of the neck and chest wall. Facial plethora, arm edema, and cyanosis are less frequent.

Diagnostic Imaging

- Contrast-enhanced CT is the most useful imaging study as it can define the extent of venous blockage and identify the underlying cause of venous obstruction.
- Chest radiograph is often abnormal and common findings include mediastinal widening and pleural effusion.
- Venography is considered the gold standard for identifying SVC obstruction; however, it does not identify the cause of obstruction unless thrombosis is the sole etiology.
- Magnetic resonance venography is another modality useful for patients with contrast dye allergy.
- Radiocontrast or other injections into veins of the affected extremity are not recommended because of the risk of extravasation.

Treatment

- Treatment of SVC syndrome depends upon the underlying etiology, extent of disease, pace of symptoms progression, and overall prognosis which is linked to the type of malignancy.
- Current guidelines suggest obtaining accurate histologic diagnosis prior to starting therapy, and consider upfront use of endovascular stents in symptomatic patients to provide more rapid relief than can be achieved with RT. RT may obscure the histologic diagnosis. Most malignancies causing SVC syndrome can be identified with minimally invasive techniques including sputum cytology, pleural fluid cytology, bone marrow biopsies, and biopsy of lymph nodes. Bronchoscopy, mediastinoscopy, video-assisted thoracoscopy, and thoracotomy may be required in certain cases.

- Exceptions to above guidelines are patients with respiratory compromise (e.g., stridor due to central airway obstruction or severe laryngeal edema) or those with coma from cerebral edema. These patients require immediate stent placement and RT.
- Supportive care measures include elevation of the head of the bed, supplemental oxygen, and bed rest.
- Glucocorticoids are effective in reversing symptoms due to SVC syndrome caused by steroid-responsive malignancies such as lymphoma or thymoma. For patients undergoing RT for laryngeal edema, steroids are commonly given to reduce swelling.
- Use of loop diurects may provide transient, symptomatic relief of edema.
- Chemotherapy is the treatment of choice for patients with SCLC, NHL, or germ cell cancer (and possibly breast cancer) presenting with symptomatic SVC syndrome.
- Therapy of choice for NSCLC presenting with SVC syndrome includes endovascular stent placement and radiation therapy.
- Anticoagulant or thrombolytic therapy may be indicated for caval thrombosis and catheter-associated thrombosis.
- Surgery is rarely performed in malignant causes of SVC syndrome and most often reserved for nonmalignant causes. One possible exception is malignant thymoma and thymic carcinoma.

HYPERCALCEMIA

Etiology

Hypercalcemia occurs in about 20% to 30% of all cancers and over 30% of all patients with hypercalcemia have an underlying malignancy (Table 36.1).

Clinical Signs and Symptoms

- Symptoms of hypercalcemia depend on the rapidity of onset of hypercalcemia. Patients with chronic hypercalcemia may tolerate levels well in excess of 14 mg/dL without any apparent symptoms.

Table 36.1 Etiology for Hypercalcemia of Malignancy

Humoral hypercalcemia of malignancy
Squamous cell cancer (lung, head and neck, esophagus, cervix)
Renal cell carcinoma
Ovarian
Breast
Endometrial
T-cell lymphoma
Bone metastasis
Breast cancer
Lymphoma
Multiple myeloma
Calitriol mediated
Hodgkin and non-Hodgkin lymphoma
Ectopic parathyroid production
Parathyroid
Ovary
Lung

- Signs and symptoms include
  - Dehydration, weakness, fatigue, and pruritus.
  - CNS changes (i.e., hyporeflexia, mental status changes, seizure, coma, and proximal myopathy) and GI or genitourinary tract (GI: weight loss, nausea/vomiting, constipation, ileus, polyuria, polydipsia, azotemia, dyspepsia, and pancreatitis).
  - Cardiac symptoms: Bradycardia, short-QT interval, wide T wave, prolonged PR interval, arrhythmias, and cardiac arrest.

Diagnosis

- A diagnosis of hypercalcemia is primarily made from serum levels of calcium (Table 36.2). Testing of ionized calcium may be indicated in some settings.
- The calcium concentration [Ca] usually changes by 0.8 mg/dL for every 1.0 g/dL change in plasma albumin concentration.
- Formula for corrected serum calcium concentration:
  - (mg/dL) = serum Ca (measured) + 0.8 × [4- serum albumin concentration (g/dL)]
- In hypercalcemia of malignancy, serum intact parathormone (iPTH) level is low or undetectable.

General Principles of Treatment

- Unfortunately, hypercalcemia most often occurs in advanced stages of disease and in patients who have progressed through available standard chemotherapy. In patients with solid tumor primary cancers, survival is often <6 months after hypercalcemia is diagnosed.
- Any symptomatic patient with hypercalcemia, regardless of absolute serum calcium level, should be treated for correction of the hypercalcemia.
- Symptomatic patients with severely elevated calcium levels often require profound fluid volume replacement, which makes outpatient therapy impractical and unsafe.
- Mild asymptomatic hypercalcemia with serum calcium concentration in the range of 11 to 12 mg/dL should be treated, when there is associated hypercalciuria, because of the risk of nephrolithiasis and nephrocalcinosis.

Practical Management

- Immediate administration of isotonic saline (1 to 2 L over 1 hour followed by 300 to 400 mL per hour, unless the patient has heart failure or renal failure) to increase renal blood flow and calcium excretion.
- Once rehydration is complete and urinary output is optimized, the need for bisphosphonate administration should be assumed.
- IV zoledronic acid (4 mg IV, infused over at least 15 minutes) is commonly used in malignancy-induced hypercalcemia. Usually a single dose is adequate, when used to treat hypercalcemia.
- Bisphosphonate administration is well tolerated by patients except for occasional IV site irritation and fever during infusion. Its onset of action is within 24 to 48 hours of administration; the maximal effect may not be achieved until 72 hours after treatment.
- Dose should only be repeated after at least 7 days.
- The ASCO guidelines for bisphosphonate use in myeloma recommend that for zoledronic acid,
  - Creatinine clearance >60 mL per minute; no dosing changes are required.
  - Creatinine clearance >30 mL per minute and <60 mL per minute; dose should be reduced (follow package insert).
  - Creatinine clearance <30 mL per minute contraindicated.

Table 36.2 Classification of Hypercalcemia Based on Serum Levels of Calcium

Mild	Moderate	Severe
>10.5 mg/dL to <12 mg/dL	12 to 13.5 mg/dL	>13.5 mg/dL

- Denosumab inhibits osteoclast development, activation, and survival by preventing the receptor activator of nuclear factor-kappa B ligand and has been used to treat bisphosphonate refractory hypercalcemia. In meta-analysis of over 5,000 patients there was an increased incidence of hypocalcemia in the denosumab group; grade 3 or 4 laboratory abnormalities for hypocalcemia were 88 (3.1%) for the denosumab group and 38 (1.3%) for the zoledronic acid group. In addition, denosumab is safe to be used in patients with renal failure and could be effective in bisphosphonate refractory patients.
- Denosumab should be the preferred agent in patients with creatinine clearance <30 mL per minute.
- Depending on clinical urgency, dental evaluation must be obtained before bisphosphonates are initiated to prevent osteonecrosis of the jaw.
- Osteonecrosis of the jaw is a potentially devastating complication of bisphosphonate and RANKL inhibitor use, and is associated with poor dentition. Among bisphosphonates use, jaw osteonecrosis rates are higher among myeloma patients. Patients with multiple myeloma had a rate 4.5 times that of patients with breast cancer in one study.
- Corticosteroids can be considered in select patients and is often effective. These tumors include lymphoma, leukemia, myeloma (prednisone, 40 to −100 mg per day), and breast cancers (prednisone, 15 to 30 mg per day) during hormonal therapy.
- Calcitonin has a rapid onset of action (within 4 hours) and is often useful in severe and symptomatic hypercalcemia until the more slowly acting agents become effective (e.g., zoledronic acid, pamidronate, and gallium nitrate).
- Salmon calcitonin is initially given at 4 units per kg (body weight) SC or IM every 12 hours. If response is not satisfactory after 1 to 2 days, the dosage may be increased to 8 units per kg SC or IM every 12 hours. If response is still not adequate after a 1- to 2-day trial at the higher dose, the dosing interval should be decreased to 8 units per kg SC or IM every 6 hours. Although many patients initially will respond to calcitonin, tachyphylaxis often develops rapidly, which renders patients refractory to its hypocalcemic effect.
- Hemodialysis should be considered, in addition to the other treatments listed for hypercalcemia, in patients who have serum calcium level in the range of 18 to 20 mg/dL and/or in those who have neurologic symptoms but are hemodynamically stable.
- Galium nitrate and mithramycin have been found to be useful in the treatment of malignancy associated hypercalcemia.
- Treatment of hypercalcemia of malignancy is summarized in Table 36.3.

Table 36.3 Treatment of Hypercalcemia of Malignancy

First-line medications	
Hydration	
Immediate	Isotonic saline (1–2 L over 1 h)
Maintenance	300–400 mL/h, unless the patient has heart failure or renal failure, until calcium normalizes
Bisphosphonates (caution with renal impairment—refer to package insert)	
Zoledronic acid	4 mg IV, infused over at least 15 minutes
Pamidronate	60 or 90 mg IV, in 500 mL 0.9% caline or 5% dextrose in water, infused over 2–4 h
RANKL inhibitors (preferred with renal failure)	
Denosumab	120 mg SC
Second-line medications	
Glucocorticoids	Prednisone 60 mg PO daily for 10 d
Calcitonin	4–8 international units/kg SC or IM every 12 h
Phosphate replacement (if serum phosphorus ≤3.0 mg/dL)	
250 mg Neutrophos orally 4 times daily until serum phosphorus >3 mg/dL	

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) occurs when cellular disruption results in life-threatening lactic acidosis, with concomitant hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Etiology

- Tumor lysis can occur before the start of treatment (primary TLS) or more commonly after the administration of highly effective therapy (secondary TLS). The risk of developing TLS depends on multiple factors such as disease burden and preexisting nephropathy. In one study, for AML patients, tumor lysis was the major cause of death in 2% of cases.

Clinical Setting, Signs, and Symptoms

- TLS typically occurs in patients with acute leukemias (AML and ALL) with high white cell count, though it can also occur in patients with lymphomas (particularly Burkitt lymphoma) and solid tumors that are sensitive to therapy.
- TLS can be classified as laboratory TLS and clinical TLS. Laboratory TLS is defined as two or more abnormal values of uric acid, potassium, phosphorus, or calcium at presentation or a 25% change from baseline.
- Clinical TLS is defined as laboratory TLS accompanied with seizures, cardiac arrythmias, renal dysfunction, or sudden death.
- These criteria must be met 3 days before and up to 7 days after the initiation of therapy.
- Clinical index of suspicion should be high, as onset of TLS could be insidious. Cardiac arrhythmias may result from the severe hyperkalemia or hypocalcemia that accompanies the TLS. Hypocalcemia can result in tetany, whereas hyperphosphatemia and hyperuricemia can result in acute renal failure (ARF).

Management

Main Principles

- Identification of high-risk patients with initiation of preventive therapy.
- Early recognition of metabolic and renal complications with prompt supportive care, including hemodialysis.

Prevention and Treatment (Table 36.4)

- Preventive measures include the identification of individuals at risk; 24 to 48 hours of vigorous pre-treatment volume expansion (3,000 mL/m^2/day), use of pretherapeutic allopurinol (300 to 600 mg, PO q day), and vigilant metabolic monitoring (every 3- to 4-hour laboratory tests) after institution of therapy. These actions are the hallmarks of TLS prevention and management. Elevated levels of lactate dehydrogenase (LDH), uric acid, or creatinine at presentation identify a particularly high-risk patient.
- Rasburicase is a recombinant urate oxidase that catalyzes enzymatic oxidation of poorly soluble uric acid into an inactive and more soluble metabolite (allantoin). It can be given as a single dose between 3 mg and 7.5 mg. The manufacturer suggested dose is 0.2 mg/kg as an IV infusion over 30 minutes. Usually a single dose is adequate, though as per the manufacturer up to five doses can be administered.
- Rasburicase enzymatically degrades uric acid in blood samples left at room temperature. Blood should be collected in prechilled tubes containing heparin, transported in an ice bath, and assayed within 4 hours.
- Rasburicase should not be administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Table 36.4 Prevention and Treatment of Tumor Lysis Syndrome

Metabolic Abnormality	Value or Change from Baseline	Clinical Features	Management
Hyperkalemia	>6.0 mmol/L or 25% increase	Muscle cramps Paresthesia Dysrhythmias	Calcium gluconate 100–200 mg/kg slow IV infusion Sodium bicarb 1–2 mEq/kg IV push Insulin 0.1 unit/kg with dextrose 25% 2 mL/kg Polystyrene sulfonate 1 g/kg
Hypocalcemia	<7 mg/dL or 25% decrease	Muscle cramps Tetany	Calcium gluconate 50–100 mg/kg slow with EKG monitoring
Hyperphosphatemia	>2.1 mmol/L for children or >1.45 mmol/L for adults or 25% increase	Lethargy Seizures Nausea Vomiting Diarrhea	
Hyperuricemia	8 mg/dL or 25% increase	Acute renal failure	IV normal saline at 150–200 mL/h Allopurinol 300 mg PO daily Rasburicase 3–6 mg as an intravenous infusion over 30 min. Usually one dose is adequate

HYPERPHOSPHATEMIA

- In mild hyperphosphatemia, dietary phosphate is restricted to 0.6 to 0.9 g per day, and an oral phosphate binder such as calcium carbonate is added. Severe hyperphosphatemia with symptomatic hypocalcemia can be life-threatening.
- The hyperphosphatemia usually resolves within 6 to 12 hours if renal function is intact.
- Phosphate excretion can be increased by saline infusion, although this can further reduce the serum calcium concentration by dilution.
- Phosphate excretion can also be increased by administration of acetazolamide (15 mg/kg every 3 to 4 hours).
- Hemodialysis is often indicated in patients with symptomatic hypocalcemia, particularly if renal function is impaired.

HYPOCALCEMIA

- The most appropriate treatment of hypocalcemia, in the absence of hypomagnesemia, is IV calcium, at a dose of 100 to 200 mg of elemental calcium (1 to 2 g of calcium gluconate) in 10 to 20 minutes.
- Such infusions do not raise the serum calcium concentration for more than 2 to 3 hours and, therefore, should be followed by a slow infusion of 10% calcium gluconate (90 mg of elemental calcium per 10 mL ampule) at the rate of 0.5 to 1.5 mg/kg IV per hour.
- Calcium chloride, 10% (272 mg of elemental calcium per 10 mL ampule), can also be used, with 5 to 10 mL given initially IV slowly over 10 minutes or diluted in 100 mL of 5% dextrose in water and infused over 20 minutes. This dosage should be repeated as often as every 20 minutes if the patient is symptomatic. Serum calcium levels should be monitored every 4 to 6 hours and hypomagnesemia be corrected as needed.

- Primary management of the hyperphosphatemia is critical to minimize metastatic deposition of insoluble calcium phosphate. Hemodialysis is almost always required by this time.

HYPERKALEMIA

- Psuedohyperkalemia can occur in the setting of extreme hyperleukocytosis, most commonly with chronic lymphocytic leukemia. This has been attributed to use of vacuum tubes and pneumatic tube transport, which may directly lyse the fragile malignant WBCs, releasing potassium. Aspiration of blood gently into a syringe without shaking and gently transporting the sample to the laboratory might correct the artifact.
- If the patient is asymptomatic, with a plasma potassium concentration of 6.5 mEq/L and with an ECG that does not manifest signs of hyperkalemia, then withhold potassium and initiate the administration of cation exchange resins.
- If the patient is symptomatic, with peripheral neuromuscular weakness, electrocardiographic signs of hyperkalemia, or plasma potassium concentration above 7 mEq/L, consider calcium gluconate, 10% solution, 10 mL IV given over 2 to 5 minutes (dose can be repeated after 5 minutes if electrocardiographic changes persist), followed by glucose with insulin, sodium bicarbonate, or a nebulized β-agonist. Prepare for hemodialysis.
- Measures to reduce serum potassium level:
  - Regular insulin, 10 units plus 50% glucose, 50 mL IV as a bolus (onset 15 to 60 minutes; duration 4 to 6 hours), followed by glucose infusion to prevent hypoglycemia. Insulin along with glucose lowers the potassium level by driving it into the cell.
  - Adrenergic β2-agonist, such as nebulized albuterol, 10 to 20 mg in 4 mL normal saline, inhaled over 10 minutes (onset 15 to 30 minutes; duration 2 to 4 hours), is effective in reducing serum potassium concentration. Adrenergic β2-agonists induce hypokalemia by stimulating the transport of potassium into skeletal muscle.
  - Sodium bicarbonate, at the dose of 45 mEq (1 ampule of a 7.5% sodium bicarbonate solution), is infused slowly over 5 minutes (onset 30 to 60 minutes; duration several hours); this dose can be repeated in 30 minutes if necessary. This also temporarily drives the potassium inside the cell.
  - Kayexalate, orally or rectally, 15 to 50 g in 50 to 100 mL of 20% sorbitol solution, is repeated every 3 to 4 hours, as needed, for up to 5 times per day (onset, 1 to 3 hours, duration of several hours).
  - Minimize administration of drugs that can cause or potentiate hyperkalemia (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], β-blockers, angiotensin-converting enzyme [ACE] inhibitors, and potassium-sparing diuretics).

HYPERURICEMIA AND RENAL FAILURE

- Hyperuricemic ARF following chemotherapy may be avoided by (a) prechemotherapeutic identification of patients at risk for developing TLS and (b) administration of allopurinol at doses of 600 to 900 mg every day, starting several days before chemotherapy, with tapering doses to maintain uric acid levels of <7 mg/dL.
- The therapy for hyperuricemic ARF before chemotherapy consists of administering allopurinol (if it has not already been given) and attempting to wash out the obstructing uric acid crystals by a loop diuretic and by fluids. Sodium bicarbonate should not be given at this time because it is difficult to raise the urine pH in this setting. Hemodialysis to remove the excess circulating uric acid should be used in patients in whom a diuresis cannot be induced.
- Rasburicase can be used at 3 to 7.5 mg as a single dose for the rapid correction of hyperuricemia. It can also be used prophylactically, prior to the initiation of definitive therapy to underlying malignancy, for high-risk tumors, that is, ALL and AML.
- Hyperuricemic ARF following chemotherapy is usually refractory to conservative intervention (hydration, diuretics, etc.), and patients require hemodialysis for supportive therapy and renal recovery.

REVIEW QUESTIONS

1. A 62-year-old male recently diagnosed with IgA kappa multiple myeloma presents with new onset pain in his lower back, muscle weakness, and sensory loss along his lower extremities. His symptoms are consistent with SCC. All of the following statements are accurate about SCC except for
   - **A.** SCC most often involves the lumbosacral spine.
   - **B.** The three most common underlying cancer diagnoses associated with SCC are lung cancer, breast cancer, and multiple myeloma.
   - **C.** Pain is usually the first symptom of SCC, often worse with recumbency.
   - **D.** MRI of the entire thecal sac is the preferred modality for initial evaluation of a patient with suspected SCC.
   - **E.** The most important prognostic factor for regaining ambulation after treatment of SCC is pretreatment neurologic status.

2. A 29-year-old man presents with new onset dyspnea and dysphagia. On physical examination, he has left-sided facial edema and venous distension of the neck and chest wall. He does not have stridor or mental status changes. CT with contrast of the neck and chest reveals bilateral cervical lymphadenopathy, a 10 cm anterior mediastinal mass compressing the SVC. What is the next best step?
   - **A.** Immediate radiation oncology consult for RT to the affected area.
   - **B.** Start the patient on glucocorticoids and chemotherapy.
   - **C.** Consider thrombolytic therapy and subsequent anticoagulation.
   - **D.** Endovascular stenting followed by excisional biopsy of the cervical lymph node.

3. An 83-year-old man presents to the emergency room with 1-week history of generalized weakness and progressive change in mental status. He was found confused at his apartment, by his son. He has a history of diabetes and renal failure, which is well controlled. Labs in the emergency room show serum calcium of 14 mg/dL. His albumin is 3 mg/dL. Serum creatinine is 3 mg/dL. Chest x-ray shows a left upper lobe mass lesion.
   Which of the following statements is/are correct?
   - **A.** He should receive an immediate dose of zolendronic acid 4 mg, given over 15 minutes.
   - **B.** He should be adequately hydrated prior to giving zolendronic acid.
   - **C.** Denosumab might be a better alternative, to correct his hypercalcemia.
   - **D.** His calcium levels should be closely monitored, if he is treated with denosumab to assess for hypocalcemia.
   - **E.** Osteonecrosis of jaw seldom occurs with denosumab.
   - **F.** A and B.
   - **G.** B and D.
   - **H.** B, C, and D.

4. A 34-year-old man is being treated with chemotherapy for acute myeloid leukemia. You are called to evaluate the patient, late at night, as he has become somnolent and is not waking up. At presentation, 24 hours ago his white blood cell count (WBC) was 160,000/L with 80% myeloblasts; the hemoglobin was 7.5 g/dL, and platelet count was 10,000/L. His electrolytes and renal function are normal. His uric acid is 11.0 mg/dL, and LDH is 1,000 international units/L (normal, 100 to 250 international units/L). His phosphate levels are 2 mmol/L.
   Which of the following statements is/are true?
   - **A.** A diagnosis of TLS has to be considered.
   - **B.** Rasburicase is a synthetic urate oxidase agonist that is indicated for the treatment of hyperuricemia in patients with TLS.
   - **C.** A single dose of rasburicase between 3 and 7.5 mg has been shown to be as effective as weight-based dosing.
   - **D.** Blood samples have to be collected in prechilled tubes and transported on ice to avoid spuriously low values of uric acid in patients being treated with rasburicase.
   - **E.** For patients suspected to have or at high risk for TLS, hydration with 4 to 5 L of IV fluids, 48 hours before induction chemotherapy, and maintaining a urine output of at least 80 to 100 mL/m^2 per hour is indicated.
   - **F.** All the above.

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37

Psychopharmacologic Management in Oncology

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Psychiatric syndromes, predominantly depression and anxiety, occur commonly in patients with cancer, and, if misdiagnosed or poorly managed, can have profoundly negative effects on optimal oncologic care. The comprehensive psychiatric care of patients with cancer includes psychosocial, behavioral, and psychoeducational interventions as well as appropriate pharmacologic and psychotherapeutic treatment. This chapter focuses on the psychopharmacologic management of the major psychiatric syndromes encountered in the oncology setting and includes information on specialist referral. The chapter concludes with specific recommendations for psychopharmacologic management in pediatric oncology.

CONSIDERATIONS PRIOR TO PRESCRIBING PSYCHOPHARMACOLOGIC AGENTS

- Psychiatric symptoms are often manifestations of an underlying medical disorder or complications of its treatment (Table 37.1). For example, specific malignancies (e.g., lung, breast, renal, melanoma) are prone to metastasize to the central nervous system (CNS). In addition, advanced cancer can result in metabolic CNS insults that precipitate psychiatric symptoms. For those patients whose psychiatric symptoms fail to respond to psychopharmacologic treatment, CNS involvement should be reconsidered, even in malignancies that do not commonly metastasize to the brain.
- Medically ill patients are particularly susceptible to CNS adverse effects of medications. Specific examples of medications associated with mood, cognitive, and behavioral symptoms include the following: corticosteroids, interleukin-2, interferon-α, opiates, benzodiazepines (BZDs), and dopamine-blocking antiemetics (e.g., prochlorperazine, metoclopramide, and promethazine). For patients who develop psychiatric symptoms after treatment with such agents, it is often more prudent to lower the dose or discontinue the use of a currently prescribed medication than introduce yet another agent (i.e., a psychotropic) in an attempt to combat the adverse effect as it may exacerbate the psychiatric symptoms.
- Polypharmacy is unavoidable in patients with cancer; however, most clinically significant interactions with psychotropic agents are predictable and can be avoided by choosing alternative agents or by making dose adjustments. The use of monoamine oxidase inhibitors (MAOIs) with either meperidine (Demerol) or selective serotonin reuptake inhibitors (SSRIs) can be life-threatening by causing

Table 37.1 Medical Conditions Associated with Anxiety and Depression

Neoplasms	Cardiovascular
Brain tumors	Ischemic heart disease
Head/neck cancer	Arrhythmias
Pancreatic cancer	Congestive heart failure
Lung cancer	Stroke
Lymphoma	
Leukemia	Metabolic
Insulinoma	Electrolyte disturbances
	Uremia
Endocrinologic	
Thyroid ↑↓	Vitamin B_{12} or folate deficiency
Cushing syndrome	
Adrenal ↑↓	Other
Hypopituitarism	Substance abuse and withdrawal
Pheochromocytoma	Pain (uncontrolled)
	Hematologic (e.g., anemia)
Medication related	Sexual dysfunction
Interferon-α	
Corticosteroids	
Interleukin-2	
Dopamine-blocking antiemetics	

serotonin syndrome. Serotonin syndrome classically includes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, but patients can also demonstrate a broad range of clinical signs and symptoms. Supportive care remains the mainstay of treatment. Up-to-date drug interaction resources can be found at several internet websites (e.g., http://medicine.iupui.edu/flockhart/).

- Inadequate pain control frequently induces symptoms of anxiety, irritability, or depression. It is essential to have pain well controlled so that the appropriate psychiatric diagnosis and treatment can proceed (see Chapter 37). One note of caution in this regard concerns the use of SSRIs and tricyclic antidepressants (TCAs), which are occasionally used in combination to treat neuropathic pain. Some SSRIs (e.g., fluoxetine, paroxetine) inhibit the metabolism of TCAs, which can in turn prolong the corrected QT (QTc) interval.

COMMON PSYCHIATRIC SYNDROMES IN THE ONCOLOGY SETTING

Adjustment Disorder

This is a time-limited, maladaptive reaction to a specific stressor that typically involves symptoms of depression, anxiety, or behavioral changes and impairs psychosocial functioning. The diagnostic criteria include the onset of symptoms within 3 months of the stressor but the duration of symptoms is no more than 6 months.

Management

The initial treatment approach includes crisis intervention and brief psychotherapy. Time-limited symptom management with medications may be indicated. For example, anxiety, tearfulness, and insomnia are frequent reactions to the diagnosis of a new or recurrent malignancy. Short-term treatment of these symptoms with BZDs (e.g., lorazepam and clonazepam) is appropriate, effective, and rarely associated with the development of abuse or dependence. Short-term use of non-BZD sleep agents (e.g., zolpidem, eszopiclone) is also commonplace in clinical practice (Table 37.2).

Table 37.2 Commonly Used Hypnotic Agents

Generic	Brand	Dose Range	Half-Life
Eszopiclone	Lunesta	1–3 PO	Short
Zalepon	Sonata	5–20 PO	Short
Zolpidem	Ambien	2.5–10 PO	Short
	Ambien CR	6.25–12.5 PO	Extended Release

Major Depression

Major depression and subsyndromal depressive disorders are common in patients with cancer. Prevalence rates vary between 5% and 50% depending on how depression is defined, whether study samples are drawn from outpatient clinics or hospital wards and the type of cancer involved. Untreated depression has been correlated with poor adherence with medical care, increased pain and disability, and a greater likelihood of considering euthanasia and physician-assisted suicide. Recent studies suggest that depression is also associated with increased mortality in patients with cancer.

A frequent diagnostic task in the oncology setting is differentiating symptoms of major depression from those symptoms that are caused by the underlying cancer or its treatment. Patients with cancer, especially those with advanced disease who are undergoing chemotherapy, are more likely to experience fatigue, anorexia, weight loss, and insomnia, whether a major depression is present or absent. Our practice is to institute empiric trials of antidepressants using a targeted symptom-reduction approach. In questionable cases, a personal or family history of depression and the presence of symptoms of excessive guilt, poor self-esteem, anhedonia, and ruminative thinking strengthen the argument for a medication trial. Furthermore, because the number of well-tolerated, safe, and effective antidepressants has grown, we have lowered our threshold for treating subsyndromal depression in the oncology setting.

Because patients with cancer have an increased risk of suicide compared with the general population, particular attention should be paid to symptoms of hopelessness, helplessness, suicidal ideation, and intense anxiety (Table 37.3). Cancer at certain sites, including lung, gastrointestinal tract, and head and neck cancers, is associated with an even greater risk of suicide. Risk of suicide appears to be highest immediately after diagnosis and decreases thereafter but remains increased for years as compared to suicide rates in the general population. Suicide rates are higher among patients with advanced disease at diagnosis but not among patients with multiple primary tumors. Other risk factors for suicide include male sex, white race, and being unmarried, similar risk factors for suicide in the general population. In addition, adult survivors of childhood cancers are at increased risk for suicidal ideation related to cancer diagnosis as well as posttreatment mental and physical health problems, even many years after completion of therapy.

Management

Treatment modalities include pharmacotherapy (Table 37.4) and psychotherapy. Electroconvulsive therapy (ECT) is highly effective in the treatment of major depressive disorder resistant to pharmaco- and psychotherapy. Selection of an antidepressant in major depression should be based on a number of considerations such as active medical problems, the potential for drug interactions, prior treatment

Table 37.3 Risk Factors for Suicide

Historical Considerations	Clinical Descriptors
Prior suicide attempts	Elderly men
Family history of suicide	Recent loss and poor social support
Prior psychiatric illness	Current depression, anxiety, substance abuse
History of substance abuse	Advanced cancer, pain, poor prognosis
Impulsive behavior	Delirium, psychosis, illogical thoughts

Table 37.4 Commonly Used Antidepressants in Patients with Cancer

Generic Names* (Brand Names)	Dose Range (mg)	Class and Common Adverse Effects
SSRIs		**Class effects:** GI symptoms, weight changes, sleep disruption, sexual dysfunction, agitation, anxiety
Fluoxetine (Prozac, Sarafem)[a,b,c]	5–80	Long T1/2, weekly dosing available
Sertraline (Zoloft)[a,c]	12.5–200	GI symptoms common
Paroxetine (Paxil CR)[b,c]	10–60	Anticholinergic effects, withdrawal syndrome
Citalopram (Celexa)[c]	10–40	Doses above 40 mg/d are not recommended due to the increased risk for QT prolongation. Patients over the age of 60 or those with hepatic or renal dysfunction should not exceed doses of 20 mg/d.
Escitalopram (Lexapro)[a]	5–20	Structurally similar to citalopram
Fluvoxamine (Luvox CR)[a]	25–300	Commonly used for obsessive-compulsive disorder. Many drug interactions. Contraindicated with pimozide, thioridazine, mesoridazine, CYP1A2, 2B6, 2C19, and 3A4 inhibitors
Novel antidepressants		
Venlafaxine (Effexor XR)[b]	18.75–300	GI symptoms, sexual dysfunction, anticholinergic effects, hypertension at dose >225 mg/d, reduces hot flashes
Mirtazapine (Remeron, (SolTab))[d]	7.5–45	Sedation, dry mouth, increased appetite and weight gain, constipation, dizziness common. Low incidence of sexual dysfunction
Bupropion (Wellbutrin (XL/SR), Forfivo XL, Zyban)[b]	37.5–450	Zyban approved for smoking cessation. GI symptoms, tremor, increased risk for seizures at high dose or with CNS lesions. May treat sexual side effects of other antidepressants
Trazodone	25–400	Sedation, orthostatic hypotension, priapism, some weight gain
Duloxetine (Cymbalta)	20–60	GI symptoms, headache, dizziness; also indicated for generalized anxiety disorder, diabetic neuropathy, and fibromyalgia
CNS stimulants		**Class effects:** Insomnia, agitation, GI symptoms, headache, tics. Can affect blood pressure and heart rate
Methylphenidate[a] Concerta, Metadate (CD/ER), Methylin, Quillivant XR, Ritalin (LA/SR)[b]	2.5–72	
Dextroamphetamine (Dexedrine)[a,b]	2.5–60	Has been associated with serious cardiovascular events
Tricyclic antidepressants		**Class effects:** Dry mouth, sedation, GI symptoms, headache, ECG changes, orthostatic hypotension, anticholinergic effects
Amitriptyline (Elavil)[a]	25–150	
Desipramine (Norpramin)	25–150	
Nortriptyline (Pamelor)[a,c]	25–150	Tremor
Doxepin (Sinequan)[a,c]	10–300	Potent antihistamine, used for itching

CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor.
*Drugs with sedating effects are listed in italics.
[a]FDA approval for use in children/adolescents.
[b]Sustained-release and extended-release formulations available.
[c]Liquid formulation available.
[d]Orally disintegrating tablets or wafers available.

Table 37.5 Antidepressant Inhibitors: CYP2D6

Strong	Fluoxetine, paroxetine, bupropion
Moderate	Duloxetine, sertraline, fluvoxamine
Mild	Citalopram, escitalopram
Minimal	Venlafaxine, mirtazapine,[a] desvenlafaxine[a]

[a]Based on limited data.
Adapted from: Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. *J Clin Psychiatry*. 2009;70(12):1688-1697.

response, and an optimal match between the patient's target symptoms and the side-effect profile of the antidepressant (e.g., using a sedating agent for the patient with anxiety and insomnia).

Potential interactions with cancer therapeutics should also be considered. For example, several antidepressants are inhibitors of cytochrome P-450 2D6. This inhibition reduces the metabolism of tamoxifen to its active metabolite, endoxifen. Venlafaxine (Effexor) has the least inhibitory effect at 2D6 and thus is preferred in breast cancer patients taking tamoxifen (Table 37.5).

An antidepressant frequently used in patients with cancer is mirtazapine (Remeron) as it is sedating, causes weight gain, has few significant drug interactions, and is a 5HT-3 receptor antagonist (i.e., has antiemetic properties). Mirtazapine may also be used as an augmentation agent for depression treatment in conjunction with SSRIs. Elderly patients or patients with medical comorbidities (especially hepatic impairment) generally require smaller dose of antidepressants.

Anxiety Disorders

Many medical conditions seen in the oncology setting, such as heart failure, respiratory compromise, seizure disorders, pheochromocytoma, and chemotherapy-induced ovarian failure, may cause anxiety. Additional conditions that may cause both anxiety and depression are listed in Table 37.1. Similarly, anxiety is an adverse effect of numerous medications such as high-dose corticosteroids. In particular, dopamine-blocking antiemetics may cause akathisia, an adverse effect characterized by subjective restlessness and increased motor activity, which is commonly misdiagnosed as anxiety. Initiation of treatment with an antidepressant may also induce a transient anxiety state. It is important to inform patients of this potential side effect in order to improve adherence.

Management

In addition to behavioral therapy and psychotherapy, BZDs are the medications that are most frequently used for the short-term treatment of anxiety (Table 37.6). For anxiety that persists beyond a few weeks, treatment with an antidepressant (see Table 37.4) is indicated. BZDs are often started concurrently with an antidepressant as a "bridge therapy" as there is a typical delay in therapeutic effect for antidepressants of up to several weeks. If the patient has already been taking an SSRI, it is important not

Table 37.6 Preferred BZDs in the Oncology Setting

	Lorazepam (Ativan)	Clonazepam (Klonopin)
Dose equivalency	1 mg	0.25 mg
Dose range	0.25–2 mg PO, sublingual, IM or IV routes, every 1–6 h based on clinical need (maximum daily dose, 8 mg)	0.25–1 mg PO route, every 8–12 h
Advantages	Fast onset of action	Less frequent dosing than with Lorazepam
	Multiple routes of administration (oral, IV, IM)	Longer half-life orally
	Liquid available	disintegrating wafer available

BZD, benzodiazepines; IM, intramuscularly; IV, intravenously; PO, orally.

Table 37.7 Commonly Used Neuroleptics in the Oncology Setting

	Initial Dose (mg)	Administrative Routes and Schedules	Maximum Daily Dose (mg)
haloperidol[a,b] (Haldol)	0.25–1 PO, or IV	Every 2–12 h SC, IM,	20
Chlorpromazine[a] (Thorazine)	12.5–50 PO, IM or IV	Every 4–12 h	300
Risperidone[a,b,c,d] (Risperdal [M-Tab])	0.25–2 PO	Every 12 h	6
Olanzapine[a,c] (Zyprexa [Zydis])	2.5–10 PO	Every 12–24 h	20
Quetiapine[a] (Seroquel)	25–50 PO	Every 12–24 h	800

EPS, extrapyramidal symptoms; IM, intramuscularly; IV, intravenously; PO, orally; SC, subcutaneously.
[a]FDA approval for a use in children/adolescents.
[b]Liquid formulation available.
[c]Orally disintegrating tablets or wafers available.
[d]Sustained release and extended release formulations available.

to discontinue it (with the exception of fluoxetine because of its long half-life) abruptly to avoid a withdrawal syndrome that may include gastrointestinal distress, flu-like symptoms, insomnia, agitation, and irritability. Low-dose second-generation antipsychotics are often useful for severe and persistent anxiety or for conditions such as anxiety secondary to steroids and delirium (Table 37.7).

The following issues associated with BZD use require attention:

- BZDs are the treatment of choice for delirium caused by alcohol or sedative–hypnotic withdrawal but predictably worsen other types of delirium.
- In patients with hepatic failure, lorazepam, temazepam, or oxazepam are the preferred BZDs as they do not require oxidation for metabolism.
- BZDs may result in "disinhibition," especially in delirium, substance abuse, "organic" disorders, and preexisting personality disorders. Disinhibition is more common in children and elderly patients.
- The abrupt discontinuation of BZDs with short half-lives (e.g., alprazolam [Xanax]) can cause rebound anxiety and precipitate a withdrawal syndrome.
- Long-term use of BZDs may lead to cognitive problems, tolerance, and dependence. Time-limited use is recommended.

Delirium

Delirium is an acute confusional state characterized by fluctuating cognitive impairment, perceptual disturbances, mood changes, delusions, and sleep–wake cycle disruption. Patients can have a hyperactive (agitated), hypoactive (quiet), or mixed (alternating hyper/hypoactive) delirium. Virtually any psychiatric symptom can be a manifestation of delirium. Anxiety and/or labile mood are common presentations often misdiagnosed as "depression." Patients who are elderly, on multiple medications, or who have underlying brain pathology are more prone to delirium. Surgical patients who undergo prolonged, extremely invasive, or multiple surgeries with repeated anesthesia are also at higher risk for delirium. Delirium in terminally ill patients is very common and often underdiagnosed. Several cancer-related therapies can induce delirium including methotrexate, ifosfamide, cytosine arabinoside, interferon-α, and interleukin-2. Total brain radiation may also cause cognitive changes and delirium.

Management

The first step in the management of delirium is making sure the patient is safe by attending to environmental cues including reorienting the patient and providing a personal nursing assistant (sitter) to prevent falls. Identifying and treating precipitating factors (including medical conditions such as

infection) and discontinuing nonessential medications that may be deliriogenic (such as BZDs, anticholinergics, or opioids) will be important to the treatment of the delirium. Haloperidol (Haldol) continues to be the prototypical first-generation antipsychotic agent most frequently used in delirium because of its ease of administration (oral, IM, or IV) and many clinical trials proving its efficacy. Common adverse effects of the first-generation antipsychotics include sedation and hypotension. Newer second-generation antipsychotics such as olanzapine (Zyprexa) and risperidone (Risperdal) may also be used in the treatment of delirium and are associated with sedation, weight gain, and metabolic syndrome. Recent concerns have been raised about an increased risk of sudden death associated with antipsychotic use in elderly patients. These data suggest a small increase in the relative risk of death which must be weighed against the substantial mortality risks of untreated delirium.

ADDITIONAL CONSIDERATIONS FOR PSYCHOPHARMACOLOGIC MANAGEMENT IN PEDIATRIC ONCOLOGY

Cancer is the fourth leading cause of death among 10- to 24-year-olds and the leading cause of nonacute death among youth. Life-threatening illness in a child or an adolescent is traumatic and can be associated with anxiety and depression. Although many patients cope well with and adapt to the trauma, symptoms of depression such as fatigue, cognitive impairment, decreased social interaction and exploration, and anorexia may be part of a cytokine or immunologic response to cancer and its treatments. Psychotropic medications can improve quality of life for children with cancer. These medications do not replace comprehensive, multimodal, multidisciplinary care but are adjuncts to decrease discomfort and improve functioning of medically ill children.

Assessment and Diagnosis in Pediatric Oncology

A thorough psychiatric assessment is needed to make a correct diagnosis and to institute treatment. Typically, this assessment is based on multiple brief examinations of the child and information gathered from additional sources including family, staff, and teachers. A patient's biologic vulnerability to depression and anxiety may be inferred from (a) a family history of a mood or anxiety disorder, or other psychiatric disorder, and (b) previous psychiatric symptoms or psychiatric treatment.

Common complaints in medically ill children include

- Anxiety
- Pain
- Difficulty in sleeping
- Fatigue
- Feeling "bored"

Adult psychiatric syndromes of adjustment disorder, major depression, anxiety, and delirium apply to children as well, but anxiety, rather than depression, is the most frequent diagnosis. Important determining factors for pharmacologic intervention are severity and duration of psychiatric symptoms.

Psychopharmacologic Treatment of Pediatric Patients

In 1994, manufacturers and federally funded researchers were mandated to study medications such as antidepressants in children. Although there have been no randomized, controlled antidepressant trials in depressed medically ill children, and the dose of psychiatric medications for children with cancer has not been systematically studied, antidepressants have been useful for treating anxiety and depression. Body weight, Tanner staging, clinical status, and potential for medications to interact are considered in deciding doses. See Tables 37.4 and 37.7 for psychotropics with U.S. Food and Drug Administration (FDA) approval for use in children and adolescents.

BZDs, such as lorazepam and clonazepam, used in low doses in conjunction with nonpharmacologic distraction techniques, may be appropriate for procedures that induce considerable anxiety in children. Clonazepam is longer acting and may be helpful with more pervasive and prolonged anxiety symptoms. BZDs can cause sedation, confusion, and behavioral disinhibition. Their use should be carefully

monitored, especially in those patients with CNS dysfunction. BZD withdrawal precipitated by abrupt discontinuation occurs most frequently on transferring the patient from intensive care settings.

Antihistamines have been used to sedate anxious children. Diphenhydramine, hydroxyzine, and promethazine may be helpful for occasional insomnia. However, antihistamines are not helpful for persistent anxiety and their anticholinergic properties can precipitate or worsen delirium. Intravenous diphenhydramine may be misused because it can induce euphoria when given by IV push. Very high doses of IV diphenhydramine can also provoke seizures.

Fluoxetine is the only FDA-approved SSRI for depression in children older than 6 years. Fluoxetine and sertraline are approved for obsessive-compulsive disorder in children older than 6 years while fluvoxamine is approved for those who are 8 years and older. Fluoxetine, with its active metabolite norfluoxetine, and fluvoxamine are potent inhibitors of cytochrome P-450 (CYP) 3A3 and 3A4. They are contraindicated with macrolide antibiotics, azole antifungal agents, and several other medications. Escitalopram is approved for depression in those 12 years and older, while citalopram is not approved for use in those under 18. Amitriptyline is approved for depression in children who are 12 years or older. TCAs are useful for treating insomnia, weight loss, anxiety, and some pain syndromes.

Some antidepressants may contribute to suicidal thinking in children and young adults through age 24 years as noted in FDA black box warnings. This possibility warrants careful monitoring of suicidality in all children treated with antidepressants. Use of non-FDA-approved psychopharmacologic agents in children with cancer may be considered for extreme or prolonged distress and poor functioning but must be monitored closely.

Children and adolescents who cannot tolerate antidepressants may benefit from stimulants for depression and apathy. Psychostimulants are generally well tolerated and have a rapid onset of action. Children with delirium, hallucinations, severe agitation, or aggression may be safely treated with low-dose first-generation antipsychotics such as haloperidol or second-generation antipsychotics such as risperidone and olanzapine.

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 dealing with cancer survival. Routine psychological screening of children with cancer and survivors can detect ongoing distress. Psychopharmacologic consultation may also help children with postradiation or postchemotherapy conditions related to attention, mood, and anxiety disorders.

SPECIALIST REFERRAL

Many psychiatric symptoms can be readily addressed by the primary oncologist or oncology service through counseling and pharmacotherapy. Sometimes it is helpful to involve a psychiatric specialist to assist with psychopharmacology and other supportive interventions. There are a growing number of practitioners working within oncology centers who focus on issues associated with cancer diagnosis, treatment, and survivorship. The subspecialty of psychosocial oncology (or psycho-oncology) has existed in some centers since the 1970s. There is a great deal of variability of access to psychosocial specialists at cancer centers and in the community. Some centers have dedicated services, while others utilize practitioners from palliative, general psychiatric, or psychosomatic medicine services. It may be beneficial for oncologists to establish relationships with local community mental health providers in settings where a dedicated service is not available.

Determining the appropriateness of a referral to assist with psychopharmacology can be difficult for some oncology providers. The National Comprehensive Cancer Network (NCCN) has established guidelines for management and referral for psychosocial issues in The Clinical Practice Guidelines in Oncology. There is a section on Distress Management (current version 2.2013) that includes referral and treatment algorithms for psychiatric, social, pastoral, and substance-related issues. A simple screening tool called the "Distress Thermometer" exists to help determine the need for referral to supportive services including referral to psychiatric care. The NCCN guidelines are available online at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive. Additionally, a report from the Institute of Medicine establishes the standard of care for addressing psychosocial issues in the oncology setting (http://www.iom.edu/Reports/2007/Cancer-Care-for-the-Whole-Patient-Meeting-Psychosocial-Health-Needs.aspx).

SUMMARY

Psychiatric syndromes are frequently misdiagnosed and poorly treated in patients with cancer. Before initiating psychopharmacologic therapy, underlying medical disorders and adverse effects of medication must be addressed and potential drug interactions anticipated. Psychiatric symptoms should then be treated promptly and aggressively. Consultation from a psychiatrist is indicated in the following circumstances when the patient (a) has a complex psychiatric history and is taking multiple psychotropic medications; (b) exhibits depressive symptoms associated with extreme guilt, anxiety, and/or suicidal thoughts; (c) is confused, hallucinating, agitated, or violent; and/or (d) is nonadherent with care or rejects treatment and seeks physician-assisted suicide.

REVIEW QUESTIONS

1. A 67-year-old male is receiving interferon-α for metastatic melanoma. He develops pneumonia and is admitted to the inpatient oncology service. He begins treatment with IV antibiotics and shows improvement over 2 days of admission. Unfortunately, he becomes confused on the third day of admission with agitation, difficulty sleeping, and fluctuating level of consciousness. He is afebrile and hemodynamically stable. What should be done next?
   - **A.** Start a low dose of lorazepam as needed for sleep and agitation.
   - **B.** Schedule low-dose haloperidol just prior to bedtime.
   - **C.** Change the patient's antibiotic regimen.
   - **D.** Review the patient's medication list and systematically look for medical causes of the confusion.
2. A 60-year-old woman has been doing well with treatment with tamoxifen for estrogen receptor-positive breast cancer. She has had several unfortunate events happened including losing her mother and her best friend in the same month. She begins to feel excessively guilty, wakes early in the morning, loses weight, and stops her normal hobbies and exercise routine due to lack of energy. She presents for follow-up and asks for help. What is the best pharmacologic intervention for this patient?
   - **A.** Start the patient on venlafaxine.
   - **B.** Give the patient a 2-week supply of clonazepam for sleep and excessive guilt.
   - **C.** Reduce her tamoxifen dose.
   - **D.** Start a combination of zolpidem for sleep and paroxetine for sleep.
3. A 72-year-old male with advanced pancreatic cancer has been struggling with his diagnosis and treatment. He has had severe abdominal pain which has been difficult to control and has essentially stopped eating over the past few weeks. He feels burdensome to his wife and daughter and becomes more detached from those around him. His family is concerned because he has made several statements that he does not feel he deserves to live anymore and his cancer is a "punishment for his life sins." What would be most important in assessing the patient's risk for self-harm?
   - **A.** His current functional status
   - **B.** Any past history of self-harm
   - **C.** His current medications
   - **D.** His financial status
4. A 7-year-old girl is diagnosed with acute lymphoblastic leukemia. She is admitted to the children's hospital for induction therapy. The child is noted to be shy on admission and has progressive anxiety over the first few days of treatment. She does not sleep through the night and stays in her bed through the day. Her nurse suspects she may have an anxiety problem. What would be most important in assessing the girl's symptomology?
   - **A.** Administration of a standardized childhood anxiety screening tool
   - **B.** A psychiatry consult to screen for anxiety, abuse, and depression
   - **C.** Administration of a low dose of an antihistamine as needed
   - **D.** A review of the girl's development and recent social history with her parents

Suggested Readings

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38

Management of Emesis

David R. Kohler

RADIATION- AND CHEMOTHERAPY-ASSOCIATED EMETIC SYMPTOMS

Radiation- and chemotherapy-associated emetic symptoms are labeled as "acute" or "delayed" by their temporal relationship with the start of emetogenic treatments (Fig. 38.1). Although the terms are useful for describing clinical events and approaches to symptom management, the assignment of symptom onset and duration to fixed periods predated identification of the principal neural mechanisms that elicit acute- and delayed-phase symptoms, and remain an oversimplification of physiologic events that occur when emetogenic treatments are repeated within the span of a single day or on 2 or more consecutive days.

Acute-Phase Symptoms

Emetic symptoms that occur within 24 hours after treatment are identified as acute-phase symptoms (Table 38.1). Acute-phase symptoms 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-phase symptoms occurs within 2 to 6 hours after treatment.
- Onset is generally within 1 to 3 hours after commencing chemotherapy. Notable exceptions include
  - Mechlorethamine (nitrogen mustard), which generally induces rapid symptom onset ($\leq$1 hour).
  - Cyclophosphamide, after intravenous administration, and carboplatin have long latency periods before acute-phase onset, and symptoms may persist or intermittently recur for $\geq$12 hours after treatment.

Delayed-Phase Symptoms

Delayed-phase symptoms are defined as those that occur >24 hours after treatment (Table 38.1) and are 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 some cases, drugs with moderate emetic risk may cause delayed-phase symptoms (Table 38.2). Symptoms may occur 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 control during the acute phase. Although emesis

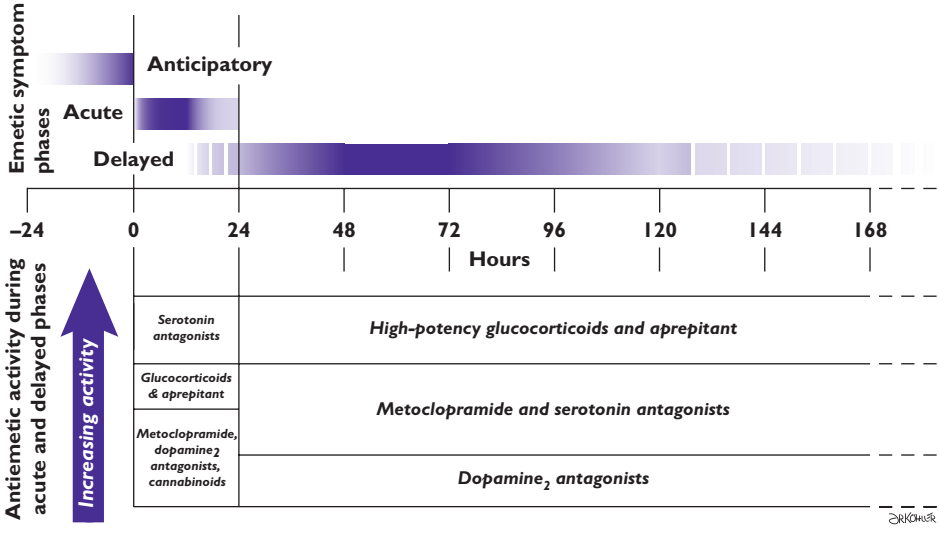

FIGURE 38.1 Comparison of emetic symptom phases and antiemetic activity. Top: Temporal relation between the start of emetogenic treatment (hour 0) and emetic symptom phases. For each phase, shaded bars indicate generally when nausea and emesis occur before and after emetogenic treatment; greater intensity of shading approximates the incidence of symptoms. Bottom: The most highly active antiemetic categories ranked by relative effectiveness against acute-phase (0 to 24 hours) and delayed-phase (>24 hours) emetic symptoms.

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 emetic symptoms occur before repeated exposure to an emetogenic treatment as an aversive conditioned response as a consequence of poor emetic control during prior therapy. Although anxiolytic amnestic drugs are helpful in preventing and delaying anticipatory symptoms, complete control throughout all antineoplastic treatments is the best preventive strategy against developing symptoms. Behavioral therapies such as relaxation techniques and systematic desensitization are recommended if symptoms occur. After symptoms develop, medical intervention during subsequent emetogenic treatment is limited to preventing the reinforcement of conditioned stimuli, which may exacerbate anticipatory symptoms.

EMETOGENIC (EMETIC) POTENTIAL

Emetic potential or risk and symptom patterns vary among medications used in antineoplastic chemotherapy and radiation therapy techniques.

Chemotherapy

Intrinsic emetogenicity (Table 38.3) is an antineoplastic drug's propensity for causing emetic symptoms. Drug dose or dosage is often the second most significant factor affecting emetogenic potential and the duration for which symptoms persist.

Table 38.1 Onset and Duration of Emesis with Selected Chemotherapy Agents

Drug	Onset of Emesis (h)	Duration of Emesis (h)
Aldesleukin	0–6	—
Altretamine	3–6	—
Asparaginase	1–3	—
Bleomycin	3–6	—
Carboplatin	6–8	>24
Carmustine	2–6	4–24
Chlorambucil	48–72	—
Cisplatin	1–6	24–48+
Cyclophosphamide	6–18	6–24+
Cytarabine	6–12	3–5
Dacarbazine	1–5	1–24
Dactinomycin	2–6	12–24
Daunorubicin	2–6	24
Doxorubicin	4–6	6–24+
Etoposide	3–8	6–12
Fluorouracil	3–6	3–4
Hydroxyurea	6–12	—
Ifosfamide	1–6	6–12
Irinotecan	2–6	6–12
Lomustine	2–6	4–12
Mechlorethamine	0.5–2	1–24
Melphalan	6–12	—
Mercaptopurine	4–8	—
Methotrexate	4–12	3–12
Mitomycin	1–6	3–12
Mitotane	Long latency	Persistent
Paclitaxel	3–8	3–8
Pentostatin	Long latency	Persistent (>24)
Plicamycin	4–6	12–24
Procarbazine	24–27	Variable
Streptozocin	1–4	12–24
Teniposide	3–8	6–12
Thioguanine	4–8	—
Thiotepa	6–12	Variable
Vinblastine	4–8	—
Vincristine	4–8	—
Vinorelbine	4–8	—

Adapted from: Borison HL, McCarthy LE. Neuropharmacology of chemotherapy-induced emesis. *Drugs.* 1983;25(Suppl 1):8-17 and Aapro M. Methodological issues in antiemetic studies. *Invest New Drugs.* 1993;11(4):243-253.

Table 38.2 Antineoplastic Drugs Implicated in Delayed Emesis

Drug	Dosages (mg/m²)	Combinations that Exacerbate Developing Symptoms
Carboplatin	≥300	± Other cytotoxic agents
Cisplatin	≥50	
Cyclophosphamide	≥600	+ Anthracycline combinations ± Other cytotoxic agents
Doxorubicin	≥50	

Table 38.3 Emetic Risk for Single Agents as a Function of Drug, Dosage, and Route of Administration

Drugs and Drug Combinations	Acute-Phase Emetic Potential (Incidence[a]) High (>90%), Moderate (30–90%), Low (10–30%), Minimal (≤10%)			
	MASCC/ESMO	ASCO	NCCN	Product Labeling
Aldesleukin			Moderate[b] (>12–15 million international units/m^2); low[b] (≤12 million international units/m^2)	
Alemtuzumab	Moderate[c]	Moderate[d]	Minimal[b]	
Altretamine (orally)	High[e]		Moderate–high[b]	
Amifostine			Moderate[b] (>300 mg/m^2); low[b] (≤300 mg/m^2)	
Arsenic trioxide			Moderate[b]	
Asparaginase			Minimal[b]	
Axitinib (orally)			Minimal–low[b]	
Azacitidine	Moderate[c]	Moderate[d]	Moderate[b]	
Bendamustine	Moderate[c]	Moderate[d]	Moderate[b]	
Bevacizumab	Minimal[c]	Minimal[d]	Minimal[b]	
Bexarotene (orally)			Minimal–low[b]	
Bleomycin	Minimal[c]	Minimal[d]	Minimal[b]	
Bortezomib	Low[c]	Low[d]	Minimal[b]	
Bosutinib (orally)			Minimal–low[b]	
Brentuximab vedotin			Low[b]	
Busulfan	Minimal[c]	Minimal[d]	Moderate[b]	
Busulfan (orally)			Moderate–high[b] (≥4 mg/d); minimal–low[b] (<4 mg/d)	
Cabazitaxel		Low[d]	Low[b]	
Capecitabine (orally)	Low[e]		Minimal–low[b]	
Carboplatin	Moderate[c]	Moderate[d]	Moderate[f]	
Carfilzomib			Low[b]	
Carmustine	High[c]	High[d]	High (>250 mg/m^2)[b]; moderate[g] (≤250 mg/m^2)	
Catumaxomab	Low[c]			Moderate
Cetuximab	Low[c]	Minimal[d]	Minimal[b]	
Chlorambucil (orally)	Minimal[e]		Minimal–low[b]	
Cisplatin	High[c]	High[d]	High[b]	
Cladribine	Minimal[c]	Minimal[d]	Minimal[b]	
Clofarabine	Moderate[c]	Moderate[d]	Moderate[b]	
Crizotinib			Moderate–high[b]	
Cyclophosphamide	High (≥1,500 mg/m^2)[c]; moderate (<1,500 mg/m^2)[c]	High[d] (≥1,500 mg/m^2); moderate[d] (<1,500 mg/m^2)	High (>1,500 mg/m^2)[b]; moderate[b] (≤1,500 mg/m^2)	
Cyclophosphamide (orally)	Moderate[e]		Moderate–high[b] (≥100 mg/m^2 per d); minimal–low[b] (<100 mg/m^2 per d)	

(*Continued*)

Table 38.3 Emetic Risk for Single Agents as a Function of Drug, Dosage, and Route of Administration (Continued)

	Acute-Phase Emetic Potential (Incidence[a]) High (>90%), Moderate (30–90%), Low (10–30%), Minimal (≤10%)			
Drugs and Drug Combinations	**MASCC/ESMO**	**ASCO**	**NCCN**	**Product Labeling**
Cyclophosphamide + Anthracycline (including daunorubicin, doxorubicin, epirubicin, idarubicin; an "AC" regimen)	Moderate[c] ("…with a particularly great risk of nausea and vomiting")[c]	High[d]	High[b] (only doxorubicin and epirubicin are included in the definition of an "AC" regimen)	
Cytarabine	Moderate (>1,000 mg/m²)[c]; low (≤1,000 mg/m²)[c]	Moderate[d] (>1,000 mg/m²); low[d] (≤1,000 mg/m²)	Moderate[b] (>200 mg/m²); low[b] (100–200 mg/m²); minimal[b] (<100 mg/m²)	
Dacarbazine	High[c]	High[d]	High[b]	
Dactinomycin		High[d]	Moderate[g]	
Dasatinib			Minimal–low[b]	
Daunorubicin	Moderate[c]	Moderate[d]	Moderate[f]	
Daunorubicin, liposomal				Low
Decitabine			Minimal[b]	
Denileukin diftitox			Minimal[b]	
Dexrazoxane			Minimal[b]	
Docetaxel	Low[c]	Low[d]	Low[b]	
Doxorubicin	Moderate[c]	Moderate[d]	High (>60 mg/m²)[b]; moderate[f] (≤60 mg/m²)	
Doxorubicin, liposomal	Low[c]	Low[d]	Low[b]	
Epirubicin	Moderate[c]	Moderate[d]	High (>90 mg/m²)[b]; moderate[f] (≤90 mg/m²)	
Eribulin mesylate			Low[b]	
Erlotinib	Minimal[e]		Minimal–low[b]	
Estramustine			Moderate–high[b]	
Etoposide	Low[c]	Low[d]	Low[b]	
Etoposide (orally)	Low[e]		Moderate–high[b]	
Everolimus (orally)	Low[e]		Minimal–low[b]	
Fludarabine	Minimal[c]	Minimal[d]	Minimal[b]	
Fludarabine (orally)[g]	Low[e]		Minimal–low[b]	
Floxuridine			Low[b]	
Fluorouracil	Low[c]	Low[d]	Low[b]	
Gefitinib (orally)[h]	Minimal[e]		Minimal–low[b]	
Gemcitabine	Low[c]	Low[d]	Low[b]	
Hydroxyurea (orally)	Minimal[e]		Minimal–low[b]	
Idarubicin	Moderate[c]	Moderate[d]	Moderate[b]	
Ifosfamide	Moderate[c]	Moderate[d]	High (≥2,000 mg/m²)[b]; moderate[f] (<2,000 mg/m²)	
Imatinib (orally)	Moderate[e]		Minimal–low[b]	

Interferon-α			Moderate[b] (≥10 million international units/m^2); low[b] (>5 to <10 million international units/m^2); minimal[b] (≤5 million international units/m^2)	
Ipilimumab			Minimal[b]	
Ixabepilone	Low[c]	Low[d]	Low[b]	
Lapatinib	Low[e]		Minimal–low[b]	
Lenalidomide	Low[e]		Minimal–low[b]	
Lomustine			Moderate–high[b] (single day)	
Mechlorethamine	High[c]	High[d]	High[b]	
Melphalan			Moderate[b] (>50 mg/m^2)	
Melphalan (orally)	Minimal[e]		Minimal–low[b]	
Mercaptopurine			Minimal–low[b]	
Methotrexate	Low[c]	Low[d]	Moderate[f] (≥250 mg/m^2); low[b] (>50 to <250 mg/m^2); minimal[b] (≤50 mg/m^2)	
Methotrexate (orally)	Minimal[e]		Minimal–low[b]	
Mitomycin	Low[c]	Low[d]	Low[b]	
Mitotane			Moderate–high[b]	
Mitoxantrone	Low[c]	Low[d]	Low[b]	
Nelarabine			Minimal[b]	
Nilotinib (orally)			Minimal–low[b]	
Ofatumumab			Minimal[b]	
Omacetaxine mepesuccinate				Low
Oxaliplatin	Moderate[c]	Moderate[d]	Moderate[b]	
Paclitaxel	Low[c]	Low[d]	Low[b]	
Paclitaxel protein (albumin-)-bound particles			Low[b]	
Panitumumab	Low[c]	Low[d]	Minimal[b]	
Pazopanib (orally)			Minimal–low[b]	
Pegaspargase			Minimal[b]	
Peginterferon			Minimal[b]	
Pemetrexed	Low[c]	Low[d]	Low[b]	
Pentostatin			Low[b]	
Pertuzumab			Minimal[b]	
Plicamycin[i]				Low–moderate[i]
Pralatrexate		Minimal[d]	Low[b]	
Procarbazine (orally)	High[e]		Moderate–high[b]	
Regorafenib (orally)			Minimal–low[b]	
Rituximab		Minimal[d]	Minimal[b]	
Romidepsin			Low[b]	
Ruxolitinib (orally)			Minimal–low[b]	
Sorafenib (orally)	Minimal[e]		Minimal–low[b]	

(*Continued*)

Table 38.3 Emetic Risk for Single Agents as a Function of Drug, Dosage, and Route of Administration (Continued)

	Acute-Phase Emetic Potential (Incidence[a]) High (>90%), Moderate (30–90%), Low (10–30%), Minimal (≤10%)			
Drugs and Drug Combinations	**MASCC/ESMO**	**ASCO**	**NCCN**	**Product Labeling**
Streptozocin	High[c]	High[d]	High[b]	
Sunitinib (orally)	Low[e]		Minimal–low[b]	
Tegafur uracil[i] (orally)	Low[e]			
Temozolomide (injection)	Low[c]		Moderate[b]	
Temozolomide (orally)	Moderate[e]		Moderate–high[b] (>75 mg/m^2 per d); minimal–low[b] (≤75 mg/m^2 per d)	
Temsirolimus	Low[c]	Low[d]	Minimal[b]	
Teniposide				Low–moderate
Thalidomide (orally)	Low[e]		Minimal–low[b]	
Thioguanine (orally)	Minimal[e]		Minimal–low[b]	
Thiotepa			Low[b]	
Topotecan	Low[c]	Low[d]	Low[b]	
Topotecan (orally)			Minimal–low[b]	
Trastuzumab	Low[c]	Low[d]	Minimal[b]	
Tretinoin (orally)			Minimal–low[b]	
Valrubicin			Minimal[b]	
Vandetanib (orally)			Minimal–low[b]	
Vemurafenib (orally)			Minimal–low[b]	
Vinblastine	Minimal[c]	Minimal[d]	Minimal[b]	
Vincristine	Minimal[c]	Minimal[d]	Minimal[b]	
Vincristine, liposomal			Minimal[b]	
Vinorelbine	Minimal[c]	Minimal[d]	Minimal[b]	
Vinorelbine (orally)[g]	Moderate[e]			
Vismodegib (orally)			Moderate–high[b]	
Vorinostat (orally)			Minimal–low[b]	
Ziv-Aflibercept				Minimal

[a]Assignment to emetic risk categorizes (high, moderate, low, minimal) follows guidelines published by oncology professional organizations. Emetic potential for drugs not yet categorized by one of the listed organizations are estimated from product labeling for the drug given as a single agent at a dosage, schedule, and route of administration approved by the U.S. Food and Drug Administration (FDA), or, in the case of drugs marketed outside the United States, from product-specific Summaries of Product Characteristics.

[b]National Comprehensive Cancer Network (NCCN) Guidelines™, Antiemesis, Version 1.2013 (National Comprehensive Cancer Network, Inc.; release dated December 6, 2012).

[c]MASCC/ESMO (Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology) Antiemetic Guideline 2011. URL: http://www.mascc.org/antiemetic-guidelines [Last accessed December 21, 2012] and Roila F, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol.* 2010;21(Suppl 5):v232-v243.

[d]American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update (Basch E, et al. *J Clin Oncol.* 2011;29:4189-4198).

[e]MASCC/ESMO Antiemetic Guidelines 2011, Single ORAL agents.

[f]The agent may be highly emetogenic in some patients. NCCN Guidelines™, Antiemesis, Version 1.2013.

[g]The indicated drug has not received FDA approval for oral administration, i.e., product formulations for oral administration are not commercially available in the United States.

[h]In the United States, gefi tinib is only available to patients already enrolled on the Iressa Access Program (restricted distribution program) administered by AstraZeneca Pharmaceuticals, LP.

[i]The product is not currently commercially available in the United States.

[j]The agent may be less emetogenic when given by continuous (protracted) administration.

The number of emetogenic drugs used in combination, administration schedule, treatment duration, and route of administration are also mitigating factors. Emetic potential may be lessened or eliminated by protracted drug delivery over hours or days, and increased by rapid drug administration, repeated emetogenic treatments, and brief intervals between repeated doses (Table 38.3). When emetogenic treatment is given on more than 1 day, physiologic processes associated with acute- and delayed-phase symptoms may overlap and both should be considered in designing effective antiemetic prophylaxis. The potential and duration for delayed symptoms depend upon the sequence in which emetogenic drugs are administered and the emetogenic risk each drug presents.

Radiation

The emetic potential of ionizing radiation correlates directly with the amount given per dose or fraction, the total dose administered, and the rate of administration. Large treatment volumes (>400 cm^2); fields including the upper abdomen, upper hemithorax, and whole body; and a history of poor emetic control with chemotherapy are risk factors for severe emesis. Emetic potential increases when radiation and chemotherapy are administered concomitantly ("radiochemotherapy").

PATIENT RISK FACTORS

Patients at greatest risk for emetic symptoms include

- 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, NSAIDS), may predispose to and exacerbate emetic symptoms during treatment and complicate good emetic control.

PRIMARY ANTIEMETIC PROPHYLAXIS

Primary prophylaxis is indicated for all patients whose antineoplastic treatment presents at least a low risk of producing emetic symptoms, that is, when >10% of persons receiving similar chemotherapy or radiation therapy without antiemetic prophylaxis are predicted to experience emetic symptoms (Table 38.3).

- Planning effective antiemetic primary prophylaxis
  - Evaluate the emetic potential for each drug included in treatment, which includes the severity, onset, and duration of symptoms associated with individual drugs (Table 38.1), and how drug dose or dosage, schedule, and route of administration may affect those factors.
  - Patients who receive combination chemotherapy should receive antiemetic prophylaxis based on the most emetogenic component of treatment.
    - Include primary prophylaxis against acute-phase symptoms for all treatments with low, moderate, or high emetic potential, and delayed-phase prophylaxis for treatments with moderate or high emetic potential.
    - For patients who receive antineoplastic 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.

- Patients who receive moderately or highly emetogenic treatment for more than 1 day should receive antiemetic prophylaxis appropriate for the drug with greatest emetogenic potential on each day of treatment.
- If antineoplastic treatment is associated with delayed emetic symptoms, continue antiemetic prophylaxis:
  - For at least 3 days after highly emetogenic treatment is completed.
  - For at least 2 days after moderately emetogenic treatment is completed.
- Treatment-appropriate antiemetic prophylaxis should precede each emetogenic treatment and proceed on a fixed schedule. Patients should not be expected to recognize symptom prodromes and to rely on unscheduled (i.e., *as needed*) antiemetics.
- Antiemetics should be given at the lowest effective doses.
- Patients' responses to antiemetic prophylaxis and treatment should be monitored and documented with standardized validated tools.
  - Healthcare providers historically underestimate the incidence and severity of emetic symptoms, 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.
  - The MASCC has developed and makes available online 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 to 120 hours) after emetogenic treatment.
    - The MASCC Antiemesis Tool (MAT), a guide for using the tool, and an outcomes score sheet are available in 12 languages in digital formats for downloading, and in an application for handheld devices.
    - Information about gaining approval for using the MAT is available online at www.mascc.org

Figure 38.2 integrates evidence-based guidelines for treatment-appropriate antiemetic prophylaxis recommended by the National Comprehensive Cancer Network, the Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology, the American Society of Clinical Oncology, and the consensus of experts in oncology. Recommendations are based on assessment of emetic risk and generally apply to adult patients, but may not be appropriate in all clinical situations. 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.

Clinicians may expect to encounter a minority of patients who do not respond to treatment-appropriate antiemetic prophylaxis recommended by oncology specialty organizations' guidelines. Suboptimal antiemetic prophylaxis places patients at risk for breakthrough and refractory emetic symptoms and debilitating morbidity, which may adversely affect their 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 pharmacologic prophylaxis, including

- The emetogenic risk associated with treatment.
  - The appropriateness of initial antiemetic prophylaxis for the emetogenic challenge presented by treatment
    - Selection of drugs, doses/dosages, and 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).

- Whether concomitantly administered medications may potentially compromise the effectiveness of the antiemetics utilized by including additional emetogenic medications or through pharmacokinetic interactions.

Empiric secondary prophylaxis and treatment for patients who demonstrate suboptimal antiemetic control should follow a rational approach. Pharmacologic 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 addressed by medications already in use. Unfortunately, drugs used empirically often are less safe at effective or clinically useful doses and schedules (e.g., dopaminergic and cannabinoid receptor antagonists) than agents recommended for primary prophylaxis. Whether used adjunctively or as replacement for initial prophylaxis, second-line alternatives may increase treatment costs and the risks of overtreatment and adverse effects.

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, more than 50% of patients who receive moderately or highly emetogenic therapy still may experience delayed or breakthrough nausea or emesis in spite of good control achieved acutely. 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 from the outset of treatment have access to antiemetic medications for treating breakthrough symptoms, whether through orders for treatment during a visit or admission to a healthcare facility or, for outpatients, a supply of antiemetic medication and clear instructions about how to use it in supplementing or modifying their initial antiemetic regimen. 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 even in patients who achieve overall good or better emetic control.

Suboptimal Control

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.

Emetic Potential	Acute Phase[a, b, c]	Delayed Phase[a, b, c, d]
HIGH Risk PARENTERALLY administered chemotherapy	**• ORAL ROUTE AVAILABLE**	**• ORAL ROUTE AVAILABLE**
	Dolasetron 100 mg PO x1 dose; **or** **Granisetron** 2 mg PO x1 dose, or 1 mg PO q.12 h x2 doses; **or** **Ondansetron** 16–24 mg PO x1 dose	**Dexamethasone** • If given with aprepitant or fosaprepitant, give: 8 mg/day PO on days 2, 3, and 4[e, f] • If not given with aprepitant or fosaprepitant, give: 8 mg PO q.12 h on days 2, 3, and 4[e, f]
	+ Dexamethasone 12 mg PO x1 dose[e, g, h]	**+ Aprepitant** • If aprepitant 125 mg PO or fosaprepitant 115 mg IV was given on day 1, give: 80 mg/day PO on days 2 and 3
	+ Aprepitant 125 mg PO x1 dose	**± Lorazepam** 0.5–2 mg PO or SL q.4–6 h
	± Lorazepam 0.5–2 mg PO or SL q.4–6 h	
	• ORAL ROUTE NOT AVAILABLE	**• ORAL ROUTE NOT AVAILABLE**
	Granisetron 0.01 mg/kg IV x1 dose, or 3.1 mg/24 h via transdermal patch*; **or** **Ondansetron** 0.15 mg/kg IV x1 dose (maximum single dose, 16 mg)[j]; **or** **Palonosetron** 0.25 mg IV x1 dose (preferred)[k]	**Dexamethasone** • If given with aprepitant or fosaprepitant, give: 8 mg/day IV on days 2, 3, and 4[e, i, f] • If not given with aprepitant or fosaprepitant, give: 8 mg IV q.12 h on days 2, 3, and 4[e, i, f]
	+ Dexamethasone 12 mg IV x1 dose[e, g, h, i]	**Aprepitant** • If fosaprepitant 150 mg was given on day 1, no additional aprepitant is given.
	+ Fosaprepitant 150 mg IV x1 dose, or 115 mg IV (with oral doses on subsequent days)	**± Lorazepam** 0.5–2 mg IV q.4–6 h
	± Lorazepam 0.5–2 mg IV q.4–6 h	
MODERATE Risk PARENTERALLY administered chemotherapy	**• ORAL ROUTE AVAILABLE**	**• ORAL ROUTE AVAILABLE**
	Dolasetron 100 mg PO x1 dose; **or** **Granisetron** 2 mg PO x1 dose, or 1 mg PO q.12 h x2 doses; **or** **Ondansetron** 16–24 mg PO x1 dose	**Dexamethasone** 8 mg/day PO days 2 and 3[e, g] **± Aprepitant**[l] • If fosaprepitant 150 mg was given on day 1, no additional aprepitant is given. • If aprepitant 125 mg PO or fosaprepitant 115 mg IV was given on day 1, give: 80 mg/day PO on days 2 and 3 **or**
	+ Dexamethasone 8–12 mg PO x1 dose[e, g, h]	**Dolasetron** 100 mg/day PO days 2 and 3; **or** **Granisetron** 1–2 mg/day PO or 1 mg PO q.12 h days 2 and 3; **or** **Ondansetron** 8 mg q.12 h *or* 16 mg/day PO days 2 and 3
	± Aprepitant[l] 125 mg PO x1 dose	**± Lorazepam** 0.5–2 mg PO or SL q.4–6 h
	± Lorazepam 0.5–2 mg PO or SL q.4–6 h	
	• ORAL ROUTE NOT AVAILABLE	**• ORAL ROUTE NOT AVAILABLE**
	Granisetron 0.01 mg/kg IV x1 dose, or 3.1 mg/24 h via transdermal patch*; **or** **Ondansetron** 8–16 mg IV x1 dose, or 0.15 mg/kg IV x1 dose (maximum single dose, 16 mg)[j]; **or** **Palonosetron** 0.25 mg IV x1 dose (preferred[k])	**Dexamethasone** 8 mg/day IV days 2 and 3[e, i]; **or** **Granisetron** 0.01 mg/kg per day IV days 2 and 3, or continue 3.1 mg/24 h via transdermal patch[m]; **or** **Ondansetron** 8 mg/day IV days 2 and 3, or 0.15 mg/kg per day IV days 2 and 3 (maximum single dose, 16 mg)[j]
	+ Dexamethasone 8–12 mg IV x1 dose[e, h, i]	**± Lorazepam** 0.5–2 mg IV q.4–6 h
	± Fosaprepitant[l] 150 mg IV x1 dose, or 115 mg IV (with oral doses on subsequent days)	
	± Lorazepam 0.5–2 mg IV q.4–6 h	

Emetic Potential	Acute Phase[a, b, c]		Delayed Phase
LOW Risk **PARENTERALLY administered chemotherapy**	• ***ORAL ROUTE AVAILABLE*** **Dexamethasone** 8–12 mg PO once; **or** **Dolasetron** 100 mg PO x1 dose; **or** **Granisetron** 2 mg PO x1 dose, or 1 mg PO q.12 h x2 doses; **or** **Ondansetron** 16–24 mg PO x1 dose	**or** **Prochlorperazine** 10 mg PO every 4–6 h[n]; **or** **Metoclopramide** 10 – 40 mg PO every 4–6 h[n] **+** **Diphenhydramine** 25 – 50 mg PO every 4–6 h **± Lorazepam** 0.5 – 2 mg PO or SL every 4–6 h	***Primary prophylaxis is not indicated***
	• ***ORAL ROUTE NOT AVAILABLE*** **Dexamethasone** 8 – 12 mg IV once[k]; **or** **Granisetron** 0.01 mg/kg IV x1 dose, **or** **Ondansetron** 0.15 mg/kg IV x1 dose (maximum single dose, 16 mg)[j]	**or** **Prochlorperazine** 10 mg IV every 4 – 6 h[n, o]; **or** **Metoclopramide** 1–2 mg/kg IV every 4–6 h[n] **+** **Diphenhydramine** 25–50 mg IV every 4–6 h **± Lorazepam** 0.5–2 mg IV or SL every 4–6 h	
MINIMAL Risk **PARENTERALLY administered chemotherapy**	***Routine primary antiemetic prophylaxis is not indicated*** • If emetic symptoms occur, follow the guidelines for breakthrough symptoms, and continue antiemetic treatment for at least the duration of emetogenic treatment. • Consider using antiemetic prophylaxis appropriate for low emetic risk during subsequent emetogenic treatments.[c]		***Primary prophylaxis is not indicated***

Prophylaxis during Second and Subsequent Emetogenic Treatments

Control achieved during previous cycle	*Intervention*
No emetic symptoms →	No change in initial antiemetic regimen.
Nausea without emesis Emetic symptoms controlled by rescue ("breakthrough") medications →	Include in prophylaxis for repeated emetogenic treatment medications that were effective in treating breakthrough symptoms during the previous cycle. • Antiemetic prophylaxis should be given around the clock at scheduled intervals.
Uncontrolled emetic symptoms →	Acute management • Implement fluid and electrolyte support. • Escalate antiemetic doses or shorten administration intervals with agents currently in use, or add agents from other pharmacological classes. • Add nonpharmacological interventions. Management during repeated treatments • Escalate antiemetic primary prophylaxis to the next greater emetic potential level

FIGURE 38.2 (*continued*)

Emetic Potential	Initial Prophylaxis[b, c]	Breakthrough Symptoms
HIGH to MODERATE Risk **ORALLY administered chemotherapy**	Start antiemetics before emetogenic treatment; continue daily with scheduled doses (not "as needed"): **Dolasetron** 100 mg PO daily; **or** **Granisetron** 2 mg PO daily, or 1 mg PO q.12 h; **or** **Ondansetron** 16–24 mg PO daily [a] **± Lorazepam** 0.5–2 mg PO or SL q.4–6 h	Add one or more antiemetics for breakthrough symptoms.[p]
LOW to MINIMAL Risk **ORALLY administered chemotherapy**	Start antiemetics if/as needed. If antiemetics are needed, give a dose before subsequent emetogenic treatment and continue daily: **Metoclopramide** 10–40 mg PO x1 dose, and then, q.4–6 h PRN, **or** **Prochlorperazine** 10 mg PO x1 dose, and then, q.4–6 h PRN, **or** **Haloperidol** 1–2 mg PO x1 dose, and then, q.4–6 h PRN [a, n] **± Lorazepam** 0.5–2 mg PO or SL q.4–6 h	Add one or more antiemetics for breakthrough symptoms.[p]

Prophylaxis for Radiation Therapy

Emetic Potential	*Primary Prophylaxis*[a, b, c]	*Treatment for Breakthrough Symptoms*[b]
High Risk Total body irradiation (TBI) or total nodal irradiation (TNI)	A $5HT_3$ receptor antagonist before each RT fraction[q]; e.g.: **Dolasetron** 100 mg PO daily; **or** **Granisetron**[r] 2 mg PO daily *or* 1 mg PO q.12 h or 0.01 mg/kg IV q.12 h; **or** **Ondansetron**[r] 8 mg PO *or* 0.15 mg/kg IV (maximum single dose, 16 mg) q.8 – 12 h; **or** **Palonosetron** 0.25 mg IV every second day of RT + **Dexamethasone** 4 mg PO or IV before the first 5 RT fractions[e] • Continue for at least 24 h after RT is completed	Add agents from other pharmacological classes (see guidance for "Treatment for Breakthrough Symptoms with Emetogenic Treatment")
Moderate Risk Fields that include the abdomen, hemibody, upper body, or mantle	A $5HT_3$ receptor antagonist as above • An optimal duration for prophylaxis after RT has not been identified ± **Dexamethasone** 4 mg PO or IV before the first 5 RT fractions[e]	
Low Risk Fields limited to the lower thorax, pelvis, head and neck, carnium and spine, or cranium (e.g., radiosurgery)	Any of the 5-HT_3 receptor antagonists used as described above	5-HT_3 receptor antagonist as prophylaxis or rescue • Continue use before each remaining RT fraction
Minimal Risk Fields limited to the breast or extremities	Any of the 5-HT_3 receptor antagonists used as described above	A $5HT_3$ receptor antagonist **or** D_2 receptor antagonist Metoclopramide[n] 20 mg PO, or Prochlorperazine 10 mg PO or IV • Continue use before each remaining RT fraction
RT + Chemotherapy	Give antiemetic prophylaxis appropriate for the chemotherapy in use	

Prophylaxis and Treatment for Anticipatory Symptoms

Prevention

Complete protection against emetic symptoms preempts or delays developing anticipatory symptoms

Behavior modifiation and relaxation techniques for prevention and treatment

Systematic desensitization, distraction, biofeedback, relaxation, guided imagery, hypnosis

Acupuncture or acupressure for prevention and treatment

Adjunctive pharmacotherapy[c]

lorazepam 0.5–2 mg PO or sublingually
• The night before and morning of single-day treatment, repeated every 6 – 12 h on days of emetogenic treatment; **or**

alprazolam 0.5–2 mg PO
• The night before and morning of single-day treatment, repeated four times daily on days of emetogenic treatment

FIGURE 38.2 (*continued*)

Treatment for Breakthrough Symptoms with Emetogenic Treatment[a, b, c, o]

- Add to the current regimen a drug that is pharmacologically different from drugs already in use:

Glucocorticoids[d]

Dexamethasone	12 mg PO daily, or 12 mg IV daily[i]; **or**
Methylprednisolone	125 mg IV daily

Serotonin Receptor Antagonists[a]

Dolasetron	100 mg PO daily; **or**
Granisetron	0.01 mg/kg IV daily, or 2 mg PO daily, *or* 1 mg PO every 12 h; **or**
Ondansetron	8 mg IV daily, *or* 0.15 mg/kg IV daily (maximum single dose, 16 mg)[j], or 8 mg PO daily; **or**
Palonosetron	0.25 mg IV x1 dose, or 0.25 mg IV every 2nd day for emetogenic treatment on multiple consecutive days

Cannabinoids

Dronabinol	5–10 mg PO every 3–6 h; or
Nabilone	1–2 mg PO twice daily

Benzodiazepines

Lorazepam	0.5–2 mg PO, SL, IV, or IM, every 4–12 h; **or**
Alprazolam	0.5–2 mg PO or SL, every 6–12 h; **or**
Midazolam	0.04 mg/kg slow IV over 3–5 minutes

Dopamine Receptor Antagonists[h]

Metoclopramide[n]	20–40 mg IV every 6 h, or 0.5–2 mg/kg IV every 6 h, or 20–40 mg PO every 6 h; **or**
Haloperidol[n]	0.5–2 mg IV every 4–6 h, or 1–5 mg PO every 4–6 h; **or**
Prochlorperazine[n]	10–30 mg IV every 6 h, or 25 mg PR every 4–6 h, or 10 mg PO every 4–6 h; **or**
Thiethylperazine[n]	10–20 mg IV every 6 h, or 10–20 mg PO every 4–6 h; **or**
Perphenazine[n]	2–4 mg IV every 8 h, or 2–4 mg PO every 8 h; **or**
Promethazine	12.5–25 mg IV every 4–6 h, or 12.5–25 mg PO every 8 h; **or**

Antimuscarinic and Histamine Receptor Antagonists

Scopolamine transdermal	1.5 mg/patch topically, (delivers 1 mg) every 72 h; **or**
Meclizine	12.5–50 mg PO every 12 h (maximum 100 mg/24 h); **or**
Dimenhydrinate	50–100 mg PO every 4–6 h (maximum 400 mg/24 h); **or**
Cyclizine	50 mg PO every 4–6 h (maximum 200 mg/24 h)

Mechanism of Action Not Categorized

Olanzapine	2.5–5 mg PO twice daily, or 10 mg PO daily before starting emetogenic chemotherapy

FIGURE 38.2 Algorithms for antiemetic prophylaxis and treatment for parenterally and orally administered emetogenic drugs. 5-HT_3, serotonin (5-HT_3 subtype); ASCO, American Society of Clinical Oncology; D_2, dopamine (D_2 subtype); IM, intramuscular; IV, intravenous; MASCC/ESMO, Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network®; PO, oral; PR, rectal; RT, radiation therapy; SL, sublingual. [a]Medications are not listed in order of preference except where indicated. Pharmacologically similar alternatives are circumscribed by a broken line. [b]Oral prophylaxis should begin 1 hour before commencing cytotoxic treatment. IV prophylaxis may be given minutes before emetogenic treatment. [c]Antiemetic prophylaxis should be repeated each day emetogenic treatment is administered. [d]Delayed-phase prophylaxis may begin 12 to 24 hours after the start of emetogenic treatment. [e]Consider administering a histamine (H_2 subtype) receptor antagonist (other than cimetidine) *or* a proton pump inhibitor concurrently with dexamethasone to prevent GI irritation. [f]The recommended schedule for dexamethasone is twice daily if used without aprepitant and once daily if used with aprepitant. [g]Increase dexamethasone dose to 20 mg if it is given without aprepitant or fosaprepitant. [h]Dexamethasone 12 mg is the only dexamethasone dose tested in combination with aprepitant in large randomized trials. [i]When administered IV, dexamethasone should be given as a short infusion over 10 to 15 minutes to prevent uncomfortable sensations of warmth. [j]Product labeling for ondansetron approved by the FDA recommends single intravenously administered doses should not exceed 16 mg. [k]MASCC/ESMO guidelines recommend combination antiemetic prophylaxis with dexamethasone and palonosetron for all chemotherapy with moderate emetic risk, including chemotherapy regimens containing an anthracycline and cyclophosphamide (an "AC" regimen) when an NK_1 receptor antagonist cannot be used in combination with dexamethasone and a 5-HT_3 receptor antagonist. NCCN Guidelines® recommend palonosetron as the preferred 5-HT_3 receptor antagonist antiemetic in combination with dexamethasone for antiemetic prophylaxis for patients who receive intravenous chemotherapy with high or moderate emetogenic risk. [l]NCCN Guidelines recommend adding aprepitant in primary antiemetic prophylaxis for selected antineoplastics when those medications are given at dosages associated with moderate emetogenic risk, including carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate. [m]Granisetron Transdermal System (Sancuso®; ProStraken Inc., Bedminster, NJ), an adhesive-backed patch, contains 34.3 mg granisetron and delivers an average daily dose of 3.1 mg. [n]Generally, regimens containing D_2 receptor antagonists and metoclopramide doses ≥20 mg should include primary prophylaxis with anticholinergic agents against acute dystonic extrapyramidal reactions, for example, diphenhydramine 25 to 50 mg PO or IV every 6 hours. Benztropine and trihexyphenidyl are alternatives. Parenteral administration is preferred for prompt treatment of extrapyramidal symptoms, as well as interrupting or discontinuing the drug which provoked the adverse reaction. [o]When administered IV, phenothiazines should be given over 30 minutes to prevent hypotension. [p]Medications identified for breakthrough symptoms should be added to a patient's primary antiemetic prophylaxis regimen without replacing drugs used in primary prophylaxis unless drugs used to treat breakthrough symptoms duplicate mechanistically those used in primary prophylaxis or a patient has experienced unacceptable adverse effects attributable to a component of primary prophylaxis. [q]Continue for at least 24 hours after completion of radiation treatment. [r]ASCO guideline update (2011) identifies granisetron and ondansetron as the 5-HT_3 receptor antagonists preferred in prophylaxis against radiation-induced emetic symptoms.

- Consider replacing an antiemetic medication that requires ingestion and absorption from the GI tract or percutaneous absorption with the same or a different drug administered by an alternative administration route (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.
  - Rectal suppositories are a practical alternative for patients who cannot ingest medications, but the rate and extent of absorption varies among drugs and patients.
    - Clinicians should query and ascertain patients' willingness to comply with rectal administration.
  - Sustained- and extended-release formulations (oral and transdermal 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 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 and Treatment

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:

- 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 proved of value in controlling breakthrough symptoms or another drug that acts through the same pharmacologic mechanism.
- For regimens that included a 5-HT_3 antagonist, consider switching to a different 5-HT_3 antagonist.
  - There is evidence, albeit meager, that suggests all patients may not achieve the same measure of antiemetic control with all 5-HT_3 antagonists.
- Consider adding an anxiolytic drug to the patient's regimen.
- Consider adding aprepitant 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.

NONPHARMACOLOGIC INTERVENTIONS

- Guidance for patients that may preserve nutritional status and alleviate emetic symptoms includes:
  - Eat small frequent meals low in fat content, especially for patients with anorexia or early satiety.
  - Choose healthful foods.
    - Avoid foods and beverages known or found to produce nausea.
    - Advise patients to avoid favorite foods particularly at times when symptoms may be expected to prevent developing conditioned aversions to those foods.
  - Eat foods served at room temperature.
  - 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.
      - Odors, appearance, taste, and texture ("mouth feel").
      - Greasy and fried foods and brewing coffee may provoke symptoms.
    - Use 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.

ANTIEMETIC DRUGS

Serotonin (5-HT_3 Subtype) Receptor Antagonists

Acute Phase

- 5-HT_3 antagonists are safer and more effective against acute-phase symptoms than other medications with clinically useful antiemetic activity.
- All 5-HT_3 antagonists provide equal benefit at maximally effective dosages. Administering more than a maximally effective dose does not substantially improve emetic control.
- Single-dose prophylaxis is preferred for acute-phase symptoms. Additional doses of dolasetron, granisetron, or ondansetron within the first 24 hours after emetogenic treatment have not been shown to improve emetic control.
- Dolasetron, granisetron, ondansetron, and palonosetron have excellent oral bioavailability and provide equivalent antiemetic protection after either oral or parenteral administration.

Delayed Phase

- Metoclopramide and prochlorperazine are less expensive, and as effective as dolasetron, granisetron, and ondansetron at controlling emetic symptoms.
- Palonosetron has the longest half-life among commercially available 5-HT_3 antagonists, and is the only drug in the class that has received FDA approval for use in delayed-phase prophylaxis of emetic symptoms associated with moderately emetogenic chemotherapy.
  - A single 0.25 mg dose of palonosetron is recommended before starting chemotherapy, but other doses and schedules have proven safe (see below).

Potential Side Effects

- Side effects common to all 5-HT_3 antagonists include
  - Headache
  - Constipation
  - Diarrhea
  - Transiently increased hepatic transaminase concentrations
  - Transient ECG changes, decreased cardiac rate, and cardiovascular adverse effects (see drug-specific comments below)

Dolasetron

- The oral tablet formulation is approved for use in antiemetic prophylaxis in initial and repeat courses of moderately emetogenic chemotherapy in patients aged ≥2 years.
- The frequency and magnitude of adverse effects associated with dolasetron use are related to serum concentrations of hydrodolasetron, its active metabolite.
- On December 17, 2010, the U.S. Food and Drug Administration (FDA) announced the removal of the indication for dolasetron mesylate injection for preventing nausea and vomiting associated with initial and repeated courses of emetogenic chemotherapy, and the addition to product labeling of a contraindication against this use in pediatric and adult patients. The FDA Communication explained dolasetron mesylate causes a dose-dependent prolongation in cardiac QT, PR, and QRS intervals, which can increase the risk of developing torsade de pointes, which may be fatal [FDA Drug Safety Communication: Abnormal heart rhythms associated with use of Anzemet (dolasetron mesylate). URL: http://www.fda.gov/Drugs/DrugSafety/ucm237081.htm. Last accessed December 6, 2012.].

- Risk factors for serious abnormal arrhythmias include:
  - Underlying structural heart disease and preexisting conduction system abnormalities, for example, patients with congenital long-QT syndrome, with complete heart block, or at risk for complete heart block
  - Elderly individuals
  - Sick sinus syndrome, atrial fibrillation with slow ventricular response, myocardial ischemia, persons receiving drugs known to prolong the PR interval (e.g., verapamil) and QRS interval (e.g., flecainide and quinidine)
  - Hypokalemia or hypomagnesemia
    - Serum potassium and magnesium concentrations should be evaluated, and, if abnormal, corrected before initiating treatment with dolasetron.
    - Potassium and magnesium concentrations should be monitored after dolasetron administration as clinically indicated.
    - Patients at risk for developing hypokalemia or hypomagnesemia while receiving dolasetron should be monitored with ECG.
- The FDA also recommended ECG monitoring in patients with congestive heart failure, bradycardia, underlying heart disease, and in the elderly and patients with renal impairment who receive dolasetron.
- Dolasetron mesylate tablets may still be used in antiemetic prophylaxis for emetogenic chemotherapy, because the risk of developing aberrant cardiac conduction with the oral formulation is considered less than what has been observed with dolasetron injection.
- Dolasetron mesylate injection also retained FDA approval for the prevention and treatment of postoperative nausea and vomiting, because dosages for that indication (0.35 mg/kg per dose) are less than those used in antiemetic prophylaxis for chemotherapy (1.8 mg/kg per dose), and therefore, are less likely to adversely affect cardiac electrophysiology.

Granisetron

- Used in antiemetic prophylaxis in initial and repeat courses of emetogenic cancer therapies.
  - Granisetron injection has received FDA approval for use in patients aged ≥2 years.
    - Injectable products may contain benzyl alcohol, which has been associated with serious adverse reactions including death in neonates.
  - Oral formulations (tablets and solution) have not received FDA approval for use in pediatric patients.
- Granisetron transdermal patch (Sancuso®; ProStrakan, Inc., Bedminster, NJ), an adhesive backed patch, 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 duration.
    - Safety and effectiveness in patients aged <18 years have not been established.
  - A patch is applied to clean, dry, intact skin on the outer upper arm 24 to 48 hours before administration of emetogenic chemotherapy and remains in place ≥24 hours after chemotherapy is completed.
  - The duration of application should not exceed 7 days.
  - During clinical development, patients who received granisetron 3.1 mg per day transdermally experienced a slightly greater incidence of constipation than patients who received 2 mg per day granisetron orally (5.4% vs. 3%, respectively) and a lesser incidence of headache than patients who received 2 mg per day granisetron orally (0.7% vs. 3%, respectively).
  - Continuous administration of transdermal granisetron may increase the potential for 5-HT_3 receptor antagonists to mask progressive ileus and gastric distention attributable to malignancy or another pathology.
  - Granisetron may degrade with exposure to natural or artificial sunlight, and an in vitro study has 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 covered for 10 days after a patch is removed.
- ECG abnormalities are rare at FDA-approved dosages and schedules.

Ondansetron

- Used in antiemetic prophylaxis in initial and repeat courses of emetogenic cancer therapies:
  - Ondansetron injection has received FDA approval for use in patients ≥6 months of age.
  - Oral formulations (tablets, orally disintegrating tablets, and solution) have received FDA approval for use in patients aged ≥4 years receiving emetogenic chemotherapy.
- The risk of adverse effects at dosages and schedules currently approved by the FDA is low.
  - The risk of ECG abnormalities associated with use has been shown to vary directly with the dose administered.
- On June 29, 2012, the FDA announced preliminary results from a clinical study conducted by GlaxoSmithKline showed that ondansetron prolongs the cardiac QT interval in a dose-dependent manner, which could predispose patients to develop an abnormal and potentially fatal ventricular tachyarrhythmia known as torsades de pointes (FDA Drug Safety Communication: New information regarding QT prolongation with ondansetron [Zofran] URL: http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm. Last accessed December 6, 2012).
  - Risk factors for developing QT prolongation with ondansetron include:
    - Underlying heart conditions, such as congenital long QT syndrome, congestive heart failure, or bradyarrhythmias
    - Hypokalemia and hypomagnesemia
    - Concomitant use of medications that also are associated with QT prolongation
  - A comparison between single intravenous 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 milliseconds, respectively.
  - Consequently, product labeling was amended to state ondansetron 0.15 mg/kg administered intravenously over 15 minutes every 4 hours for three doses may continue to be used in adults and children with chemotherapy-induced nausea and vomiting, but no single intravenous dose should exceed 16 mg.
    - Ondansetron product labeling includes warnings against using the drug in patients with congenital long QT syndrome and recommends ECG monitoring in patients with uncorrected electrolyte abnormalities such as hypokalemia or hypomagnesemia, congestive heart failure, bradyarrhythmias, and in patients concomitantly using other medications that can prolong the QT interval.
    - 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.
  - Recommendations for a single, orally-administered, 24-mg ondansetron dose in prophylaxis against chemotherapy induced nausea and vomiting were not affected.

Palonosetron

- FDA approved for use in patients aged ≥18 years in 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 is the 5-HT_3 receptor antagonist for antiemetic prophylaxis recommended preferentially by:
  - American Society of Clinical Oncology guidelines for patients who receive intravenous chemotherapy with moderate emetic risk
  - National Comprehensive Cancer Network® guidelines for patients who receive intravenous chemotherapy with high or moderate emetogenic risk
  - Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology guidelines for patients treated with chemotherapy regimens containing an anthracycline and

cyclophosphamide (an "AC" regimen) when an NK_1 receptor antagonist cannot be used in combination with dexamethasone and a 5-HT_3 receptor antagonist, and for all chemotherapy with moderate emetic risk in combination with dexamethasone

- There is a low risk of adverse effects at dosages and schedules currently approved by the FDA.
- The risk of ECG abnormalities including QTc prolongation has been shown less than that associated with dolasetron and ondansetron.
  - FDA-approved product labeling indicates single doses of palonosetron 0.25, 0.75, or 2.25 mg in 221 healthy adult men and women in a double-blind, randomized, parallel, placebo, and positive (moxifloxacin) controlled trial demonstrated no significant effect on any ECG interval including QTc interval duration.
- Product labeling for palonosetron injection indicates a single dose before starting chemotherapy, but safety has been demonstrated with other doses and schedules:
  - 10 mcg/kg single dose (healthy subjects).
  - 0.75 mg single dose before chemotherapy.
  - 0.25 mg per dose every second day for three doses with dexamethasone before chemotherapy.
  - 0.25 mg per day for 3 consecutive days (healthy subjects).
  - 0.25 mg per day for 1, or 2 or 3 consecutive days (prior to high-dose chemotherapy).
    - No differences were observed in control of vomiting over a 7-day evaluation period among patients who received 1, 2, or 3 doses.
    - Only about 8% of patients who received one dose and about 20% of patients who received two or three doses were without emesis and did not receive rescue medications.
  - Palonosetron 0.25 mg IV followed at least 72 hours after the initial dose by a second 0.25-mg dose for breakthrough symptoms was effective in 67% of patients who experienced nausea or vomiting.
- Oral palonosetron in August 2008 received FDA approval for prevention of acute-phase symptoms associated with initial and repeated courses of moderately emetogenic chemotherapy; however, an oral formulation has not yet become commercially available in the United States.

Pharmacogenomics

- Pharmacogenomic evaluation may help to identify patients at risk for suboptimal and adverse responses to 5-HT_3 receptor antagonists, which are substrates for catabolism by cytochrome P450 (CYP) enzymes (Table 38.4).
- CYP2D6 is polymorphically expressed among human populations.
  - Persons with more than two functionally competent (wild-type) *CYP2D6* alleles may have increased metabolic capacity (characterized as ultra-rapid metabolizers), which has been associated with

Table 38.4 Catabolism of 5-HT3 Receptor Antagonists by Cytochrome P450 Enzymes

5-HT_3 Receptor Antagonists	CYP Catalysts for Metabolism	Metabolites (Activity vs. Parent Drug)
Hydrodolasetron (primary, highly active dolasetron metabolite)	For hydrodolasetron, primarily CYP2D6, also CYP3A subfamily and flavin monooxygenase	Oxidation (inactive)
Granisetron	CYP3A subfamily	Oxidation, then conjugation (inactive)
Ondansetron	Primarily CYP3A4. Also, CYP2D6 and CYP1A2	Hydroxylation, then conjugation (inactive)
Palonosetron	Primarily CYP2D6, also CYP3A4 and CYP1A2	*N*-oxide-palonosetron (<1% activity), 6-*S*-hydroxypalonosetron (<1% activity)

diminished emetic control in patients who received 5-HT_3 receptor antagonists 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 receptor antagonists for which CYP2D6 metabolism predominates.

- Patients who express genetic polymorphism for the 5-HT_3 receptor or ABCB1 (MDR1, P-glycoprotein) transporter may experience suboptimal antiemetic responses with 5-HT_3 receptor antagonists.

Glucocorticoids

- High-potency glucocorticoids such as dexamethasone and methylprednisolone are effective as single agents against mild to moderate acute-phase symptoms.
- Dexamethasone and methylprednisolone are active against both acute- and delayed-phase symptoms.
  - At clinically useful doses, dexamethasone and methylprednisolone are equally effective after either intravenous or oral administration.
  - Both dexamethasone and methylprednisolone enhance the antiemetic effectiveness of 5-HT_3 and NK_1 receptor antagonists when used concomitantly.
- Prophylaxis and treatment are empirically based; safety and efficacy comparisons are lacking.
- In antiemetic prophylaxis for emetogenic treatment given on a single day, single doses of dexamethasone and methylprednisolone are as effective as multiple-dose schedules.
  - Optimal dosages and schedules have not been determined, but there is no evidence that single doses of dexamethasone >20 mg improves antiemetic response.
- Potential for adverse effects after a single dose 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 receptor antagonists or proton pump inhibitors) is recommended 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 problem when high-potency glucocorticoids are used for brief periods.
- Glycemic control may be a problem in patients with incipient or frank diabetes.

Neurokinin (NK_1 Subtype) Receptor Antagonists

- Currently, aprepitant and fosaprepitant dimeglumine, a pro-drug for aprepitant, are the only NK_1 receptor subtype antagonist antiemetics that have received FDA approval for use in patients aged ≥18 years. Approval was based on studies with emetogenic chemotherapy given on a single day.
- Aprepitant is recommended for use in combination with a glucocorticoid; a 5-HT_3 receptor antagonist is added for acute-phase emetic symptoms.
- Utilization in prophylaxis for emetogenic chemotherapy given on a single day (day 1; Table 38.5).

Table 38.5 Dosing of NK1 Receptor Subtype Antagonist Antiemetics[a]

	Day 1	Days 2 and 3[b]
Oral only	Aprepitant 125 mg orally, 1 hour before starting chemotherapy	Aprepitant 80 mg/d orally in the morning for 2 d[b]
IV and Oral	Fosaprepitant 115 mg intravenously, 30 min before starting chemotherapy	
IV only	Fosaprepitant 150 mg intravenously, 30 min before starting chemotherapy	No additional doses

[a]Use with multiple-day chemotherapy regimens or for >5 consecutive days has not been adequately studied.
[b]Aprepitant has been safely given for up to 5 days: an initial dose of 125 mg orally (day 1), followed by doses of 80 mg orally given daily for 4 consecutive days (days 2–5). Evidence in support of safety and effectiveness for longer durations of use (up to 12 days) is limited.

- Potential drug interactions:
  - Aprepitant is a substrate and moderate inhibitor of the CYP enzyme CYP3A4, and a moderate inducer of CYP3A4 and CYP2C9. Inhibition may occur after a single dose; induction occurs after repeated doses.
    - 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 either dexamethasone or methylprednisolone is used in combination with aprepitant for antiemetic prophylaxis, decrease orally administered glucocorticoid doses by 50% and intravenous doses by 25%.
    - 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 receptor antagonist and high-potency glucocorticoids include:
  - Abdominal pain
  - Epigastric discomfort
  - Hiccups
  - Anorexia
  - Dizziness
  - Asthenia
  - Fatigue

Dopamine (D_2 Subtype) Receptor Antagonists

- Optimal doses and schedules have not been established.
- Overall, antiemetic activity varies directly with D_2 receptor antagonism.
- Adverse effects correlate with dose and frequency of administration, and include:
  - Sedation
  - Extrapyramidal reactions (dystonias, akathisia, dyskinesia)
  - Anticholinergic effects
  - ECG changes (haloperidol, droperidol)
  - Hypotension with rapid intravenous administration (phenothiazines)
- Anecdotal evidence supports the use of D_2 receptor antagonists with 5-HT_3 antagonists $\pm$ steroids for acute-phase symptoms, and with steroids, metoclopramide, or lorazepam for delayed-phase symptoms.

Metoclopramide

- Metoclopramide has affinity for several neurotransmitter receptors associated with antiemetic activity, but is often categorized among D_2 receptor antagonists, and, at high doses, becomes a competitive antagonist at vagal and central 5-HT_3 receptors.
- Activity against delayed-phase symptoms is equivalent to that of ondansetron.
- GI prokinetic effects may benefit patients with intercurrent GI motility disorders or gastroesophageal reflux disease.
- Long-term use has been associated with developing tardive dyskinesia which may be irreversible.

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, during, and after completing emetogenic treatments.
  - Benzodiazepines are clinically useful for mitigating akathisias associated with D_2 receptor antagonists.

- Available products:
  - Lorazepam, midazolam, and diazepam are available in oral and injectable formulations.
  - Alprazolam is available in solid formulations for oral administration.
    - 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 cannabinoids are agonists at endocannabinoid (CB_1 subtype) receptors.
  - Dronabinol is an oral formulation of Δ^9-tetrahydrocannabinol (Δ^9-THC) with antiemetic activity similar to low doses of prochlorperazine.
  - Nabilone is a synthetic CB_1 receptor agonist formulated for oral administration.
  - Cannabinoids are controlled substances (schedule II) in the United States.
- Antiemetic benefit may be achieved without producing psychotropic effects. Cannabinoid use is empiric since optimal doses and administration schedules have not been determined.
- The incidence of adverse effects associated with dronabinol and nabilone is greater than with phenothiazines at doses and schedules that produce comparable antiemetic effects.
- Adverse effects 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:
  - 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) Receptor Antagonists

- Utility in preventing and treating emetic symptoms is not defined.
- Anticholinergics may be most effective in prophylaxis; less effective after emetic symptoms develop.
- Anticholinergics are useful in prophylaxis and treatment for patients whose emetic symptoms are referable to movement.
- Individual agents have in different proportions 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:
  - 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

Other Neurotransmitter Antagonists

- Olanzapine, an atypical neuroleptic or antipsychotic, is a potent antagonist at multiple neurotransmitter receptors, including muscarinic, serotonergic, dopaminergic, and histaminergic receptors.
  - Adverse effects include:
    - Somnolence and insomnia
    - Nervousness, agitation

- Headache
- Dizziness and orthostatic hypotension
- Weight gain, new-onset diabetes, hyperlipidemia, and increased serum alanine aminotransferase with prolonged use
- CAUTION: Product labeling for olanzapine includes a boxed warning about its use in elderly patients. In clinical trials, elderly patients (≥65 years) with dementia-related psychosis experienced an increased incidence of death and adverse cerebrovascular events including stroke.
- Olanzapine is a substrate for oxidation to an inactive metabolite catalyzed by CYP1A2 and direct glucuronidation catalyzed by uridine diphosphate glucuronosyltransferase (UGT) enzymes, UGT1A4 and UGT2B10.
  - Olanzapine's pharmacokinetic behavior is susceptible to drugs and substances that induce and inhibit CYP1A2 (e.g., carbamazepine, fluvoxamine, tobacco).

STRATEGIES FOR COMBINING ANTIEMETICS

Antiemetics in combination can be more effective than single agents by targeting two or more operative neural pathways.

- Numerous studies have demonstrated that control of acute-phase emetic symptoms improves significantly with the combination of 5-HT_3 receptor antagonists and high-potency glucocorticoids. Acute-phase symptom control is further augmented when aprepitant is used in combination with a 5-HT_3 receptor antagonist and a glucocorticoid.
- Delayed-phase symptom control is improved by the combination of high-potency glucocorticoids and aprepitant. However, aprepitant may compromise the safety of concomitantly administered medications due to its effects on CYP metabolizing enzymes.
  - In cases where prophylaxis against delayed-phase symptoms is indicated but concurrent medications make the use of aprepitant problematic, glucocorticoids alone or in combination with either metoclopramide or a 5-HT_3 or D_2 receptor antagonist may improve control of symptoms.

REVIEW QUESTIONS

1. A 57-year-old woman with breast cancer returns to the outpatient clinic to receive her first cycle of adjuvant chemotherapy with docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 50 mg/m^2. All three drugs are administered intravenously on the first day of a 3-week cycle. Which of the following regimens is most consistent with antiemetic primary prophylaxis recommended by MASCC/ESMO, ASCO, and NCCN guidelines?

A. A single dose of dolasetron 100 mg PO + dexamethasone 20 mg PO + fosaprepitant 150 mg IV prior to chemotherapy.

B. Any serotonin (5-HT_3) receptor antagonist + dexamethasone 20 mg PO prior to chemotherapy + a 3-day regimen of aprepitant (125 mg PO day 1 before chemotherapy, then 80 mg per day PO days 2 and 3).

C. Palonosetron 0.25 mg IV + fosaprepitant 115 mg IV + dexamethasone 12 mg IV on day 1, followed by dexamethasone 8 mg per day PO on days 2 and 3.

D. Granisetron 2 mg PO + dexamethasone 12 mg PO + fosaprepitant 150 mg IV prior to chemotherapy, followed by dexamethasone 8 mg per day PO for 3 days on days 2 to 4.

E. Ondansetron 24 mg IV + fosaprepitant 150 mg IV prior to chemotherapy.

2. At presentation in clinic, the same patient's height and weight are measured. Her height is 170.2 cm (67″); current weight is 110 kg (243 lb). A pretreatment analysis of serum chemistries revealed the following (results outside of normal ranges identified by up and down arrows):

Na	↓ 130 mmol/L	Albumin	↓ 2.2 mg/dL
K	3.2 mmol/L	Ca	↓ 1.95 mmol/L
Cl	↓ 93 mmol/L	Mg	↓ 0.58 mmol/L
Total CO_2	27 mmol/L	P	3.4 mg/dL
BUN	11 mg/dL	Alkaline phosphatase	92 U/L
Creatinine	↓ 0.52 mg/dL	ALT	22 U/L
Glucose	↑ 226 mg/dL	AST	↑ 43 U/L
		Total bilirubin	0.4 mg/dL
		Total protein	6.6 g/dL

Her medical history includes

- Type 2 diabetes managed with extended-release metformin 2,000 mg daily
- Hypertension controlled with losartan 100 mg + hydrochlorothiazide 12.5 mg per day
- A 2-year history of depression for which she takes controlled-release paroxetine 50 mg daily

What factors should the patient's healthcare providers take into consideration in selecting antiemetic agents?

A. Dexamethasone should be excluded from her antiemetic regimen to prevent exacerbating hyperglycemia.
B. A potential for pharmacokinetic drug interactions between particular 5-HT_3 receptor antagonists (dolasetron, palonosetron) and paroxetine.
C. Recommendations for empiric antiemetic doses (not based on body weight) should be doubled to compensate for obesity.
D. A potential for adverse pharmacodynamic drug interactions between particular 5-HT_3 receptor antagonists (dolasetron, ondansetron) and paroxetine.
E. Choices B and D.

3. In addition to the emetogenicity of antineoplastic treatment, what patient-specific factors place the patient at increased risk for suboptimal emetic control?

A. Comorbid pathologies associated with diabetes
B. Female sex
C. Depressive disorder
D. History of motion sickness
E. Difficulty with emesis during pregnancy
F. Chronic constipation

4. A 20-year-old male with a recent diagnosis of nonseminomatous germ cell tumor presents for his first course of BEP chemotherapy (bleomycin 30 units per dose IV for three doses on days 1, 8, and 15 + etoposide 100 mg/m^2 per day IV on days 1 to 5 + cisplatin 20 mg/m^2 per day IV on days 1 to 5). What antiemetic regimen would you choose for primary prophylaxis?

A. Aprepitant 125 mg PO on day 1 before chemotherapy, then 80 mg per day PO on days 2 to 5 with granisetron 2 mg per day PO + dexamethasone 20 mg per day PO both given before chemotherapy for 5 days on days 1 to 5.
B. Any 5-HT_3 receptor antagonist daily before chemotherapy for 5 days + fosaprepitant 150 mg per dose IV for 3 doses on days 1, 3, and 5, prior to chemotherapy.
C. Dexamethasone 12 mg per day IV for 5 days on days 1 to 5 prior to chemotherapy, then 8 mg per day PO for 3 days on days 6 to 8 + palonosetron 0.25 mg per dose IV for 3 doses on days 1, 3, and 5, before chemotherapy.

(*continued*)

D. Granisetron 34.3 mg transdermal patch applied 24 hours before starting chemotherapy and left in place for 7 days (1 day after completing emetogenic chemotherapy) + dexamethasone 12 mg per day PO for 5 days on days 1 to 5 prior to chemotherapy, then 8 mg per day PO for 3 days on days 6 to 8 + aprepitant 125 mg PO on day 1 before chemotherapy, then 80 mg per day PO on days 2 to 5.

E. Any 5-HT_3 receptor antagonist daily before chemotherapy for 5 days + aprepitant 125 mg PO on day 1, then 80 mg per day PO on days 2 and 3 before chemotherapy + dexamethasone 8 mg PO daily for 8 days.

5. A 41-year-old patient with ovarian cancer presents to the outpatient clinic for a second cycle of carboplatin (dosed to achieve a standardized systemic exposure consistent with an estimated area under the plasma concentration vs. time curve [AUC]) AUC = 4 mg/mL·min and docetaxel 75 mg/m^2, both drugs are administered intravenously, sequentially, on the first day of a 21-day cycle. The patient's previous (first) treatment cycle was complicated by facial flushing, nausea, and shortness of breath during docetaxel administration. Docetaxel administration was transiently interrupted until symptoms abated, and then resumed at a slower administration rate without recurrent symptoms. Although the patient achieved complete protection from vomiting during the first 24 hours after treatment, she reported experiencing three vomiting episodes during the 2 days after she received chemotherapy and nausea that persisted throughout the week after treatment in spite of having received outpatient prescriptions appropriate for prophylaxis against delayed symptoms for a moderately emetogenic risk treatment regimen. However, you learn when she returns to clinic for a second cycle of chemotherapy, she had not had her antiemetic prescriptions filled and did not continue antiemetic prophylaxis as planned during the 3 days that followed her last treatment. The patient's medical history is significant for a history of severe and persistent nausea and vomiting during the first and second trimesters of pregnancy and episodes of motion sickness as a function of where she is seated when traveling by automobile and when she participated in boating excursions during family vacations. Would you modify the patient's antiemetic regimen to prevent or manage persistent symptoms after chemotherapy, and, if so, in what way?

A. Do nothing to modify the previous strategy for antiemetic prophylaxis, but discuss with the patient how compliance with plans for antiemetic prophylaxis while she is an outpatient is an essential part of treatment for her neoplastic disease by preventing debilitating and serious complications associated with uncontrolled emetic symptoms, and doing so improves the likelihood she will be able to complete treatment without compromising her ability to tolerate chemotherapy with respect to doses and scheduling.

B. Consider escalating the aggressiveness of antiemetic prophylaxis to a regimen appropriate for highly emetogenic treatment.

C. Consider adding an anxiolytic before starting chemotherapy and as needed during treatment to prevent the patient from developing anticipatory symptoms.

D. Use the antiemetic regimen previously employed, but add an anticholinergic agent to mitigate symptoms related to motion sickness.

E. Add a dopaminergic (D_2) receptor antagonist during antineoplastic treatment and for 3 days afterward to "saturate" neuroreceptors unaffected by previously used antiemetics.

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39

Medical Nutrition Therapy

Marnie G. Dobbin

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.
- Malnourished patients incur higher costs for their care, 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.

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 proinflammatory cytokines (TNF, IL-1, IL-6, and IFN) can lead to hypermetabolism and to anorexia due to changes in gherlin, seratonin, and leptin production. Tumor production of proteolysis-inducing factor and lipid-mobilizing factor contribute to loss of muscle and fat mass. Inefficient energy metabolism and insulin resistance lead to further depletion of lean body mass.
- Patients with cancer cachexia may not be able to sustain their weight despite adequate nutritional intake.
- 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 Healthcare Accreditation standards state that inpatients are to be screened for nutritional risk within 1 day of admission. Validated screening tools such as the Subjective Global Assessment (SGA) form, developed by Jeejeebhoy et al. (1987) and adapted for use with oncology patients by Dr. Faith Ottery (www.ons.org/webcasts/downloads/pg-sga.pdf), may be especially helpful in the outpatient setting. Patients can complete the form in a few minutes during their medical appointments. The form covers questions about weight change, dietary intake, gastrointestinal symptoms, and functional capacity.
- Members of the healthcare team then gather additional data about metabolic demand (presence of fever, use of corticosteroids, etc.) and complete a nutrition-related physical assessment. The patient-generated tool (PG-SGA) not only aids in identifying the need for nutritional counseling and/or pharmacologic intervention, but also conveys to the patient that nutrition is a primary concern of the medical team.

NUTRITIONAL ASSESSMENT

- Registered dietitians (RD) use anthropometric data, biochemical indices, nutritional physical assessment, and dietary and medical histories to assess the nutritional status of patients and to determine appropriate intervention.
- Rate of weight change is the most useful parameter for identifying patients at nutritional risk. An unintentional weight loss of >5% per month, >2% per week, >7.4% in 3 months, or >10% in 6 months is associated with severe risk of malnutrition. Comparison of current weight to usual weight is more useful than comparing current weight to an ideal or desirable weight. Loss of more than 15% of usual weight may indicate a risk of protein–energy malnutrition.

BODY COMPOSITION

- Obtaining baseline measurements of body composition and comparing these measurements over time can be helpful for monitoring nutritional status. Measures of muscle mass include the use of skin calipers to measure mid-arm circumference (MAC) and mid-arm muscle circumference (MAMC). Triceps skinfold measurements can be used to estimate fat stores.
- Bioelectric impedance (BIA) is an inexpensive, noninvasive method for measuring body fat and fat-free mass, based on the principle that lean tissue has greater conduction and lower impedance than fatty tissue.
- Body mass index (BMI) correlates well with body fat, morbidity, and mortality (Table 39.1). However, BMI could incorrectly categorize highly muscled patients or those with edema or ascites as having excess fat stores. A BMI correlation of <18.5 is associated with protein–energy malnutrition.

PROTEIN

- If energy intake is inadequate, catabolism of protein will occur, especially as tumors preferentially metabolize protein. Limiting cancer patients' 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, and their protein requirements are 50% above those of healthy individuals.

Table 39.1 Body Mass Index (BMI)

	Weight (kg)									
Height (cm)	45	50	55	60	65	70	75	80	85	95
150	20	22.2	24.4	26.7	28.9	31.1	33	35.6	37.8	42.2
155	18.7	20.8	22.9	25.0	26	29.1	31.2	33.3	35.4	39.5
160	17.6	19.5	21.5	23.4	25.4	27.3	29.3	31.3	33.2	37.1
165	16.5	18.4	20.2	22.0	23.9	25.7	27.5	29.4	31.2	34.9
170	15.6	17.3	19.0	20.8	22.5	24.2	26.0	27.7	29.4	32.9
175	14.7	16.3	18.0	19.6	21.2	22.9	23.8	26.1	27.8	31.0
180	13.9	15.4	16.3	18.5	20.1	21.6	23.2	24.7	26.2	29.3
185	12.8	14.6	16.1	17.5	19.0	20.5	21.9	23.4	24.8	27.8
190	12.5	13.9	15.2	16.6	18.0	19.4	20.8	22.2	23.6	26.3
BMI										
≥40	Obesity grade III									
35–39.9	Obesity grade II									
30–14.9	Obesity grade I									
25–29.9	Overweight									
18.5–25	Normal weight									
17–18.4	Protein–energy malnutrition grade I									
16–16.9	Protein–energy malnutrition grade II									
<16	Protein–energy malnutrition grade III									
% Usual weight[a]										
85–95%	Mild malnutrition									
75–84%	Moderate malnutrition									
0–74%	Severe malnutrition									

[a]Rate of weight loss associated with severe risk of malnutrition: >5% per month, >2% per week, >7.4% in 3 mo, or >10% in 6 mo.

- 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. Inflammatory processes can lead to loss of lean body mass, and low levels of transport proteins are correlated with poor clinical outcome, but the relationship with nutritional status is indirect. Dietary history and nitrogen balance measurements are more reliable measures of protein adequacy.

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 (RQ). This can be done with a portable metabolic cart operated by a respiratory therapist, or by a handheld device recently approved by the FDA.
- There are a variety of recommended calculations for estimating energy, fluid, and protein requirements (Table 39.2). 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 cancer patients. Overfeeding can increase infection and induce respiratory distress, hyperglycemia, and fatty liver.
- The initial calorie goal for critically ill patients should be to meet their estimated resting energy expenditure (Table 39.3).

Table 39.2 Estimates of Energy Requirements

Patient/Condition	Kilocalories[a]
Acutely ill; obese (BMI 30–50)	21/kg
Cancer	25–30/kg
Hypermetabolism; malabsorption	35/kg
Stem cell transplant	30–35/kg

[a]Fever increases energy needs by ~14%/°F.

Table 39.3 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).

NUTRITIONAL INTERVENTION

- Nutritional counseling by an RD is associated with improvement in 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.
- Nutritional intervention by an RD may include education on individualized nutritional goals for energy, protein, and micronutrients, modification of foods and feeding schedules, fortification of foods with modular nutritional products, supplementation with meal-replacement products, or recommendations for appropriate nutritional support (Tables 39.4 and 39.5).
- Self-imposed diets and the use of dietary supplements should be evaluated by an RD for possible risks to the patient and for their potential to confound protocol results.
- A national registry of RDs is available from the Academy of Nutrition and Dietetics (eatright.org).

MICRONUTRIENT CONSIDERATIONS

- Although two-thirds of American adults are overweight or obese (BMI >25), the majority do not meet their requirements for magnesium, vitamin B_6, zinc, and calcium. Optimal dietary intake of vitamins A, C, and E is rare, and patients often take excessive amounts of supplementary antioxidants. Use of dietary supplements should be evaluated as part of a nutritional assessment.
- When treatment involves oxidation (such as radiation therapy), pharmacologic doses of antioxidants might interfere with the treatment objective and may protect the tumor. A diet including foods that are good sources of antioxidants, along with a multivitamin providing 100% to 200% of recommended levels for most nutrients, has not been shown to be harmful and is recommended for patients on limited diets who are undergoing cancer treatment.
- Patients with low levels of ionized calcium, elevated AlkP, and a history of corticosteroid use and risk for osteoporosis should have their vitamin D levels assessed by measuring levels of cholecalciferol [25(OH)D]. Calcitrol, the 1,25 dihydroxy form of vitamin D, is not a reliable indicator of vitamin D status due to its short half-life and dysregulation in the presence of deficiency. The best available current data indicate that a serum 25(OH)D level of >32 ng/mL (80 mmol/L) is a supportable goal.
- Repleting vitamin D stores is associated with improved insulin sensitivity, enhanced immunity, improved musculoskeletal function (reduced falls and fractures), and a beneficial effect on bone mineral density. Low levels of cholecalciferol are commonly found in the elderly, dark-skinned individuals, the obese, and those with malabsorption syndromes and osteoporosis.

Table 39.4 Common 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 to 75 g of carbohydrate per meal; most women need 45 to 60 g per meal. If a snack is taken, 15 to 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 g/100 g of cheese) and yogurt is naturally low in lactose due to microorganisms consuming the lactose as milk is converted into yogurt. Probiotics may be helpful
Early satiety	Calorically dense foods/nutrition products (e.g., 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 MCT–oil fortified foods/products. A diet with <30% of kcal from fat or <40 g of fat/d may be unrealistic 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	Semielemental palatable products, trials of pancreatic enzymes, bile acid sequestrants, and medium-chain triglycerides (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/d 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 butters, 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

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 is indicated (Table 39.6).

Table 39.5 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:	
Predialysis GFR 26–55 mL/min	0.8
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

GFR, glomerular filtration rate.

Table 39.6 Indications for Entereal or Parenteral Nutrition

Enteral nutrition (EN)
- Functional GI tract but the patient is unable to meet nutritional needs orally

Parenteral nutrition (PN)
- The malnourished patient cannot meet nutritional needs with enteral nutrition
- The patient has failed the EN trial with appropriate tube placement
- Enteral nutrition is contraindicated due to underlying disease or treatment
  - Paralytic ileus
  - Mesenteric ischemia
  - Bowel obstruction
  - GI fistula unless enteral access may be placed distal to the fistula or volume of output < 200 mL/d

Discontinue PN when oral or enteral nutrition provides $>60\%$ of nutritional needs.

Enteral Nutrition

- Reviews of nutritional support practices indicate that parenteral nutrition (PN) is often instituted even when safer, more physiologic enteral nutritional (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.

Parenteral Nutrition

- PN (Table 39.7) 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.

Table 39.7 Sample Parenteral Nutrition Recommendations

	Infants/Children (3–30 kg)	Adolescents (≥30 kg)	Adults
Water	1,500–1,800 mL/m²/d 1,500 mL/kg for first 20 kg and 25 mL/kg for remaining weight	1,500 mL/m²/d	1,500 mL/m²/d 35 mL/kg or 1 mL/kcal
Energy	70–110 cal/kg/d	40–60 cal/kg/d	20–35 cal/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)
Max dextrose oxidation rate	12–15 mg/kg/min	5–13 mg/kg/min	4–5 mg/kg/min
Max 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	—
Max	2–3 g/kg/d	1.5–2 g/kg/d	2 g/kg/d
IVFE	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% IVFE		
Initial	1 g/kg/d	1 g/kg/d	At goal; usually ≥250 mL 20% IVFE for ~30% of total kcal
Advance	1 g/kg/d	1 g/kg/d	—
Minerals			
Max	2–3 g/kg/d	2 g/kg/d	2 g/kg/d (60% of total kcal)
Sodium	2–4 mEq/kg/d	2–3 mEq/kg/d	1–2 mEq/kg 60–150 mEq/d max 155 mEq/L
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 mcg/kg/d (40 mcg/max)	2 mcg/kg/d (40 mcg/max)	40 mcg
Trace metals and multivitamins	Daily	Daily	Daily

IVFE, intravenous fat emulsion.

- 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, or vomiting are especially vulnerable. Initially, no more than 50% of estimated needs (~15 kcal/kg/day and no more than 150 g dextrose/day) are recommended. Because thiamin is an important coenzyme for carbohydrate metabolism, the addition of 10 to 100 mg of thiamin is warranted.

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 <300 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 >300 mg/dL (but <600 mg/dL); however, stopping lipid altogether can worsen liver dysfunction. Slowing the rate of infusion of intravenous fat emulsion (IVFE) to between 6 and 12 hours may help with TG clearance. Five hundred milliliters per week of 20% IVFE can prevent essential fatty acid deficiency in adults.

Parenteral Nutrition–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 aminotranferase concentrations. Parenteral nutrition–associated liver disease (PNALD) is usually a complication of overfeeding; it has become less common in the last 10 years, since calories provided via PN have become more appropriate.

Parenteral Nutrition–Associated Cholestasis

- Parenteral nutrition–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.
- IVFE exceeding 1 g/kg/day is associated with chronic PNAC and severe PNALD (5 mL of 20% IVFE = 1 g fat). Cyclic PN (generally 8 to 12 hours) has shown better results in terms of improved liver enzymes and conjugated bilirubin concentrations compared to continuous PN infusions. Fat emulsions containing a combination of medium-chain and long-chain TGs (not yet available in the United States) may reduce liver complications as well.

REVIEW QUESTIONS

1. A patient presents with cachexia and more than 7% weight loss in the past month. He reports that his food intake has been constant even while his weight continues to decrease. He has no gastrointestinal symptoms or fever. The most likely reason for his weight loss is
   - **A.** The patient has an inaccurate perception of his recent intake.
   - **B.** Energy expenditure and nitrogen losses are increased in those with cancer.
   - **C.** Lipolysis has occurred as a result of a preferential use of fat for energy which spares lean body mass.
   - **D.** There is increased turnover of free fatty acids, glucose, and protein.
2. A moderately malnourished patient with stomach cancer is admitted for a gastrectomy to be followed by chemotherapy (leucovorin + 5FU + oxaliplatin). Resting energy expenditure is 1,800 kcal. The patient has been drinking oral nutrition products formulated for postgastrectomy patients, but 1 week after surgery the patient is still unable to tolerate more than 300 kcal a day by mouth. Which is the most appropriate nutrition intervention?
   - **A.** PN should be initiated
   - **B.** A trial of EN via jejunostomy
   - **C.** Track intake; encourage continued use of postgastrectomy oral nutrition product
   - **D.** B and C
3. A woman with end-stage breast cancer and bony metastases has begun treatment for hypercalcemia of malignancy. Her usual diet includes foods high in calcium. Which of the following is NOT indicated?
   - **A.** A low calcium diet to limit exogenous sources of calcium
   - **B.** Discontinuation of drugs that contain vitamin D, calcium, or vitamin A
   - **C.** Rehydration to correct calciuresis-related dehydration
   - **D.** Diuresis to manage or prevent fluid overload
4. What are the most likely reasons for a patient's serum albumin and prealbumin levels to decrease from near normal levels at the time of admission to below reference range 1 week after admission?
   - **A.** Inadequate protein intake
   - **B.** An acute-phase protein response as seen during a fever
   - **C.** Intravascular dilution
   - **D.** Both B and C

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40

Pain and Palliative Care

Eric G. Bush and Anne Berger

DEFINITIONS

- Palliative care is based on a holistic model of symptom management. It concerns improving the quality of life (including end-of-life care) for patients and their families facing life-threatening illnesses by preventing, identifying, and relieving suffering associated with physical, psychosocial, and spiritual problems. For cancer patients, pain is the most common reason for palliative care consultation.
- 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 over time, it is classified as chronic pain.
- Pain is usually, but not always, associated with tissue damage. It is always subjective and may be influenced by emotional, psychological, social, and spiritual factors, as well as financial concerns and fear of death.
- Neuropathic (stimulus-independent) pain is characterized by dysesthesia, allodynia, or hyperalgesia. It may be secondary to direct tumor involvement or may be treatment related after surgery, radiation, or chemotherapy. Agents associated with chemotherapy-related neuropathic pain include vincristine, cisplatin, procarbazine, and thalidomide (or thalidomide analogs). Neuropathic pain may be treated effectively with antidepressants or anticonvulsants.

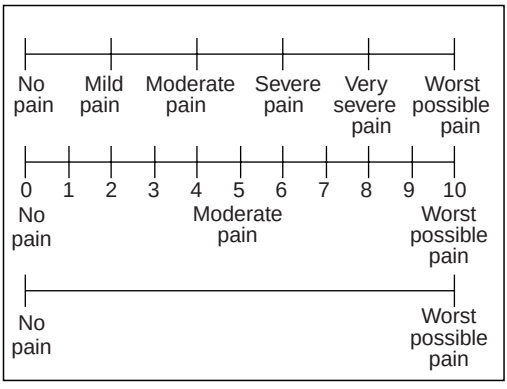
EPIDEMIOLOGY

- Most cancer patients experience some degree of pain, especially in the advanced and 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 (WHO), and effective treatments are available for 70% to 90% of cases.
- Nevertheless, an estimated 40% of cancer patients remain undertreated for reasons related to the health care provider, the patient and family, or cultural mores. The most frequent cause of under treatment is misconceptions about the use of opioids.

ASSESSMENT

- Proper pain assessment can help to establish a good doctor/patient relationship, guide the therapeutic regimen, improve pain management, maximize patient comfort and function, and increase patient 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, physicians can utilize nonverbal pain scales (PAIN-AD, Wong-Baker Faces, CNVI).
- For rapid assessment of acute pain, select a simple measurement of pain intensity (Fig. 40.1) and record the measurement for treatment evaluation.

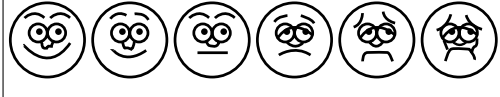
Visual Analog Scale



Word Descriptor Scale

0 = No pain
1 = Mild pain
2 = Distressing pain
3 = Severe pain
4 = Horrible pain
5 = Excruciating pain

Graphic Scale



Verbal Scale

"On a scale of 0 to 10, with 0 meaning no pain and 10 meaning the worst pain you can imagine, how much pain are you having now?"

Functional Pain Scale

0 = No pain
1 = Tolerable and pain does not prevent any activities
2 = Tolerable and pain prevents some activities
3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading
4 = Intolerable and pain prevents use of telephone, TV viewing, or reading
5 = Intolerable and pain prevents verbal communication

FIGURE 40.1 Common tools for assessment of pain intensity. (Adapted from the American Geriatrics Society [AGS] Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. *J Am Geriat Soc.* 1998;46:635-651; Gloth FM III, Scheve AA, Stober CV, et al. The functional pain scale (FPS): reliability, validity, and responsiveness in a senior population. *J Am Med Direct Assoc.* 2001;3:110-114; and Gloth FM III. Assessment. *Handbook of Pain Relief in Older Adults: An Evidence-Based Approach*. Totowa, NJ: Humana Press; 2003:17.)

- Patients should be reassessed frequently by inquiring how much their pain has been relieved after each treatment. A consistent disparity between patient's self-report of pain and their ability to function necessitates further assessment to ascertain the reason for the disparity.
- Underlying anxiety and depression can increase patient suffering. Inadequate assessment of these factors may result in under- or overtreatment with analgesics.

TREATMENT

- Severe pain should be considered a medical emergency; timely and aggressive management should be provided until the pain becomes tolerable. Aggressive pain management, with the goal of attaining maximal functional ability, is especially important with cancer patients.
- Sedatives and anxiolytics alone should not be used to manage pain as they can mask the behavioral response to pain without providing analgesia.
- NSAIDs or acetaminophen should be used to manage mild to moderate pain, unless contraindicated.
- Opiates are the foundation of management for severe pain.
- For cancer-related anxiety and depression, treatment approaches include tricyclic antidepressants, SNRIs, SSRIs, spiritual, and psychosocial intervention.

OPIATES

- Opiate 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 opiate.
- Tolerance and physical dependence are expected with long-term opiate treatment and should not be confused with psychologic dependence (addiction).
- Equianalgesic doses of oral opiates (Table 40.1) should be prescribed when necessary.
- Begin administration of opiates at lowest effective dose and titrate as necessary. No maximal therapeutic dose for analgesia has been established.
- Immediate-release opiates (mu receptor agonists) are short-acting and may be appropriate for acute incidental pain, or to initiate and titrate opiate therapy. Long-acting opiates are used around the clock for baseline pain and to maintain analgesia.
- Methadone can be an excellent agent for management of pain, but utilization or consideration should prompt referral to a pain specialist.
- Titration of opiates: 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 up to 100% and reassess at peak effect.
- Early side effects often improve or resolve with repeated doses. With the exception of constipation, tolerance often develops rapidly to most of the common opiate-related adverse effects.
- Common adverse effects of opiates include constipation, sedation, nausea/vomiting, pruritus, sweating, dry mouth, and weakness.
- Uncommon adverse effects of opiates include dyspnea, urinary retention, confusion, hallucinations, nightmares, myoclonus, dizziness, dysphoria, and hypersensitivity/anaphylaxis.

Long-Term Opiate Use

- Physicians have an ethical and regulatory duty to inform the patient of the risks and benefits of long-term opiate use, particularly when initiating treatment in patients at high risk for misuse of opiates (utilize random urine drug tests, referrals to pain management physicians and pain contracts in high-risk patients).

Table 40.1 Opiate Doses Equianalgesic to Morphine 10 mg Intramuscular[a] for Treatment of Chronic Pain in Cancer Patients

Drug	mg PO	mg IM	Half-Life (h)	Duration (h)	Considerations
Morphine	20–30[b]	10	2–3	2–4	Standard for comparison
Morphine CR	20–30	10	2–3	8–12	Various formulations are not bioequivalent
Morphine SR	20–30	10	2–3	24	
Oxycodone	20		2–3	3–4	
Oxycodone CR	20		2–3	8–12	
Hydromorphone	7.5	1.5	2–3	2–4	Potency may be greater, i.e., IV hydromorphone: IV morphine = 3:1 rather than 6.7:1 during prolonged use
Methadone	20	10	12–190	4–12	Although a 1:1 ratio with morphine was used in a single-dose study, there is a change with repeated administration. Dose reduction of 75%–90% needed when switching to methadone
Oxymorphone	10	1	2–3	2–4	Available in oral, rectal, and injectable forms
Levorphanol	4	2	12–15	4–6	
Fentanyl			7–12		Can be administered as continuous IV or SC. infusion; based on clinical experience, 10 mcg IV = 1 mg IV morphine
Fentanyl TS			16–24	48–72	Based on clinical experience, 100 mcg/h is roughly equianalgesic to morphine 200 mg PO per day

CR, controlled release; IM, intramuscular; IV, intravenous; PO, oral; SR, sustained release; subQ, subcutaneous; TS, transdermal system.

[a]Studies to determine equianalgesic doses of opiates have used IM morphine. In clinical practice, IM and IV routes are considered equivalent and the IV route is most common.

[b]Although the PO:IM morphine ratio was 6:1 in a single-dose study, other observations indicate a ratio of 2–3:1 with repeated administration.

Adapted from Derby S, Chin J, Portenoy RK. Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. *CNS Drugs*. 1999;9:99-109.

- Certain factors, such as personal or family history of substance abuse, risk of diversion of opiates, or lack of compliance, dictate a multidisciplinary approach, including the involvement of a pain specialist.
- Long-term use of opiates should always be supported by maximal use of coanalgesics and adjuvants, psychological therapy, and appropriate follow-up.

Risks of Long-Term Opiate Use

- Addiction: Extremely rare in cancer patients
- Physical dependence: Manifested by withdrawal syndrome at cessation or dose reduction
- Tolerance: Diminution of one or more of the opiate's effects over time
- Pseudoaddiction: Iatrogenic syndrome that develops in response to inadequate pain management

Termination of Opiate Therapy

- When opiates are no longer required for pain management, appropriate tapering is essential to reduce the risk of withdrawal syndromes. The recommended regimen involves reducing dosage by 10% to 20% daily, or more slowly if symptoms such as anxiety, tachycardia, sweating, or other autonomic symptoms arise.
- Symptoms may be relieved by clonidine 0.1 to 0.2 mg per day PO or low-dose transdermal patch every third day.

ADJUVANT ANALGESICS

- An adjuvant analgesic is any drug with a primary indication other than pain, but with proven analgesic effect in specific circumstances.
- Indications include poor response to opiate, opiate toxicity, or pain that is more responsive to adjuvant (i.e., neuropathic, bone, visceral, or myofascial pain).
- Adjuvants should be tried one at a time until analgesia is achieved or side effects become intolerable. If only partial analgesia is reached at maximal dose of one adjuvant, consider adding a second adjuvant.
- Potential benefits of adjuvant analgesia include targeting of multiple pain pathways, complementary pharmacodynamic activity, potentially synergistic analgesic effects, and reduced adverse events with comparable efficacy.

NONPHARMACOLOGIC THERAPY

- Psychologic and behavioral interventions may enhance the benefits of pain medications or help to reduce their use.
- Integration of these modalities into treatment should be culturally sensitive and tailored to patients' individual needs.
- Modalities include, among others, acupuncture, relaxation/biofeedback, recreation/art/music therapy, reiki/healing touch, transcutaneous electrical nerve stimulation (TENS), myofascial trigger release, and behavioral counseling.

REVIEW QUESTIONS

1. A 58-year-old male with a history of metastatic renal cell carcinoma is admitted to the oncology service for worsening pain. His pain previously had been well controlled with twice daily use of hydrocodone 5 mg/acetaminophen 500 mg tablets. His primary focal pain complaint includes left hip pain confirmed by radiography to be osseous metastatic disease. The patient rates his pain as 8/10 on a visual analog scale (VAS) and assessment confirms a clearly uncomfortable gentleman of stated age. Which of the following would be an appropriate initial parenteral analgesic to better control his pain?
   A. Propoxyphene
   B. Meperidine
   C. Hydromorphone
   D. Oxycodone
   E. Ibuprofen
2. The patient in question 1 now has improved pain control after choosing an appropriate analgesic. The patient is utilizing a total of 100 mg of oral morphine equivalents and has improved pain and functionality with a pain rating of 3/10 on a VAS. Which of the following would be an appropriate long-acting opiate to initiate at this time?
   A. Methadone tablets 30 mg PO TID
   B. Oxycodone extended release tablets 80 mg PO TID
   C. Morphine sulfate extended release tablets 100 mg PO TID
   D. Oxycodone immediate release tablets 30 mg PO q4h
   E. Fentanyl transdermal patch 25 mcg topically q72h
3. The patient in questions 1 and 2 continues to have good pain relief (VAS 3/10) after receiving appropriate long and short-acting opiate analgesics. He continues to utilize short-acting analgesics twice daily. In total this utilization equivocates to 30 mg of oral morphine equivalents. He is now ready for discharge home, which of the following would be an appropriate regimen for breakthrough pain that the patient could receive at home?
   A. Hydromorphone 8 mg tablets BID prn pain
   B. Morphine sulfate immediate release 30 mg tablets BID prn pain
   C. Oxycodone immediate release tablets 30 mg BID prn pain
   D. Hydromorphone 4 mg tablets BID prn pain
   E. Fentanyl transdermal patch 25 mcg topically q72h

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Central Venous Access Device

Uzer Khan and Hannah W. Hazard

Once the diagnosis of cancer has been made, the oncology patient will go through rigorous staging that results in the development of a plan of care for the newly diagnosed. Typically, blood tests are drawn to help facilitate the staging and treatment of the patient's disease. Additionally, tests are done to document the patient's clinical well-being and monitor the progress of their treatment. Added to this is the potential for a rigorous venous sampling schedule and the use of contrast agents during radiologic imaging studies done for staging purposes. Most of these studies can be instituted without establishment of a long-term venous access device. However, it is prudent to assess the need for central venous access early in treatment. Chemotherapy administration for the cancer patient may be delivered on 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 and results in platelet aggregation and subsequent thrombosis. Implanted venous access devices are either tunneled through the periphery or bypass the periphery altogether and are directly implanted in the central venous system. In both circumstances, trauma to the peripheral veins is reduced. The instillation of potentially damaging substances is more tolerable in the central veins, which have a much larger volume of blood flow and thicker vein walls. Once the decision has been made that a patient will benefit from a CVAD, various issues are brought into consideration. Factors to consider include specific patient characteristics and preferences, the patient's history and associated comorbidities, and the specific infusion needs. The various options for venous access can then be considered in a cooperative fashion.

The initial interaction with the patient should be used to evaluate the level of care they will be capable of providing for whichever vascular device is ultimately selected. Moreover, lifestyle and habits 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 low 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. Occupational and recreational activities should be assessed and device selection and positioning modified accordingly.

A history of previous venous device placement must be assessed as this could modify the preferred site of device insertion. Moreover, any surgical interventions or currently placed devices such as AICDs 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 (i.e., straight wires instead of J-curved wires). Patient allergies need to be documented as well and the device and surgical equipment

modified accordingly. 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. Moreover, evidence of dilated superficial veins may herald an undisclosed central venous stenosis that may complicate catheter placement.

The ultimate type of infusion needed will 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 in situations where they are only accessed intermittently.[2] 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.

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 ability to provide self-care of the device, the patient's preference (which may be influenced by vanity, an appropriate consideration in the decision-making process), and the cost of the catheter. Additional factors to take into consideration are the potential for daily maintenance needs such as flushes and dressing changes that may not be covered by insurance. A bone marrow transplant patient, for example, 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 has been associated with very few contraindications. Patients with uncontrolled coagulopathy are at risk for developing hematomas at sites of dissection and around catheter insertion sites. These patients' coagulopathy should first be corrected before CVADs requiring more dissection are placed, such as subcutaneous ports. A bloodstream infection, as demonstrated by positive blood cultures, is also a contraindication for chronic CVADs due to the high chance that these catheters will become colonized and require subsequent removal. The CVAD may be placed once the infection has been adequately treated and negative blood cultures are documented.

Certain CVADs that require the positioning of a subcutaneous device over the chest may not be appropriate options in situations of trauma, burns, or certain types of tumor. 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.

INFUSION DEVICES

Venous access devices can be categorized into five groups based on the mechanism of insertion and catheter dwell. These categories include peripheral angiocatheters, peripherally inserted central catheters (PICCs), percutaneous, nontunneled central catheters, tunneled central catheters, and implanted ports. Each category is then further defined by device-specific characteristics such as flow rates, lumen size, catheter tip location, and dwell time. In utilizing this process, it is easier to identify which catheter meets the specific needs of the patient (Table 41.1).

Peripheral Angiocatheter

The simplest access utilized in patients is the standard peripheral intravenous angiocatheter (PIV). The angiocatheters are relatively easy to insert and remove. Specialized training or certification is not

Table 41.1 Summary of Types of Venous Access Catheters

Type of Catheter	Indications	Limitations
Peripheral angiocatheters and midline catheters	Hydration, PPN, short-term access	Frequent infiltration/phlebitis; easily dislodged; short dwell time (up to 72° PIV, 2–4 wk midline); cannot be used for solutions with extreme pH or osmolarity; not for home-going patients
Peripherally inserted central catheters	Hydration, antibiotic, blood infusion/withdrawal, chemotherapy, medication administration; dwell up to 1 year or more	Requires weekly dressing change and flushing, must keep dry at all times, limited flow rates, visible, easily dislodged, higher occlusion rate, avoid placement if potential dialysis in future
Nontunneled catheters a) Central lines b) Temporary rigid dialysis catheters	a) Acute-care medication, large-bore access, hydration, all IV medication, CVP measurements b) Hemodialysis, stem cell collection and transplant requiring only double-lumen access, plasmapheresis treatment	Short dwell time: 7–14 d central lines, 1–4 wk rigid catheters; higher risk of infection than tunneled catheter; increased risk of dislodgement; uncomfortable on clavicle; highly visible
Tunneled 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 transplant access 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
Implanted ports a) Chest ports b) Arm ports	Intermittent IV access, chemotherapy, hydration, antibiotics, lab draws	Requires needle stick to access, difficult to access in obese patients

CVP, central venous pressure; IV, intravenous; PIV, peripheral intravenous catheter; PPN, peripheral parenteral nutrition.

required for standard insertions and most practitioners are qualified to place a PIV. These catheters come in a variety of gauges and lengths to accommodate patients with small vasculature 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. Therapeutic agents with extremes of pH (normal pH = 7.35 to 7.45) or osmolarity (normal 280 to 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.[3] One exception is parenteral nutrition in which dextrose contents are under 10% and the osmolarities >500 mOsm/L (INS). In this case, it is considered safe to administer this therapy peripherally. Limitations of PIV catheters include short dwell time (1 to 3 days), high thrombophlebitis rates, thrombosis

and shear of the vessel, infiltration into the surrounding tissue, cellulitis, and pain with infusions. As a result of these limitations, PIVs are reserved primarily for hospital/clinic use and management by health-care professionals.

Midline Catheters

One subclass of peripheral angiocatheters is the midline catheter. Midline catheters are PICCs. They are usually inserted into the antecubital fossa or into the brachial veins with the guidance of a handheld ultrasound device. The catheter is then advanced 8″ to 10″, just proximal to the axillary line. 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 1 to 2 weeks with careful monitoring for complications.[3] 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. This benefit yields less costly insertion fees and simplification of insertion-related malpositioning. Phlebitis and thrombosis are also less likely to occur when compared to central venous lines. Midlines are particularly beneficial in patients who would otherwise require serial placements and replacements of short PIVs and do not need the long-term access or central venous dwell of a PICC line. Midline catheters can also be used in the setting of a relative contraindication to PICC access such as in patients with end-stage renal disease where the central veins should be accessed as minimally as possible.

Midline catheters do have limitations. First, their tips do not reside centrally so infusates are limited to those that are safe for PIVs. 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.

Peripherally Inserted Central Catheter

The peripherally inserted central venous catheter (CVC) was first described in 1975 by Hoshal in a case series in which he described using a 61 cm silicone catheter that was threaded to the superior vena cava (SVC) through the basilic or cephalic veins. The series demonstrated successful application of the concept in the implementation of total parenteral nutrition with 30 of 36 catheters lasting the entire duration of treatment (up to 56 days).

A PICC is a long, flexible catheter that is inserted into a peripheral vein and advanced into the central circulation. It is typically placed in a vein of the upper arm, although it can also be introduced in the internal or external jugular veins, the long or short saphenous veins, the temporal vein, or the posterior auricular veins. The saphenous vein, temporal vein, and posterior auricular veins are usually reserved for pediatric patients. Once the vein is cannulated, the catheter is digitally advanced until its distal tip resides in the SVC or the IVC. There is minimal risk to chest organs as compared to catheters placed directly in the central venous system. 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. The external component is secured to skin, preferably with a removable locking device or sutures.

PICCs come in single, double, or triple lumens in a variety of sizes. The catheters have a small outer diameter allowing for initial insertion into smaller vessels prior to advancement centrally and are radiopaque for visualization of catheter tip placement on chest radiograph. These devices can be modified in length, specific to each patient. Some PICCs are approved for use with power injectors that can rapidly administer a radiologic contrast bolus. Insertion can be done during inpatient hospitalization, outpatient settings, and in the home by certified nurses.

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 lab draws. Power-injectable PICCs may be utilized in patients where frequent contrasted imaging studies are likely.

The relatively small lumen and long length result in decreased flow rates, especially with infusions of viscous solutions such as blood products or intravenous nutrition therapy and often cannot be used for gravity-driven infusions when pumps are unavailable such as in home settings. Due to their small caliber, these lines are not considered adequate intravenous access for resuscitation in the setting of hemodynamic compromise. 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. The patient's modesty may be compromised due to visibility of the external component. There are activity limitations including no straining maneuvers such as heavy lifting or straining that could alter the intrathoracic pressure that could lead to catheter malposition. Malpositioning 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 during catheter dwell is forbidden secondary to infection risks. Patients may not be candidates for PICCs if they have had surgical alteration of anatomy, lymphedema, ipsilateral radiation to the chest or arm, or loss of skin integrity at the anticipated insertion site, or anticipate future dialysis access needs.

However minimal, PICC-related complications should be recognized. These include infection, phlebitis, vein thrombosis, catheter occlusion, catheter breakage/leaking, and inadvertent removal prior to completion of therapy (Table 41.2). Oncology patients are at increased risk for venous thrombus

Table 41.2 Tabulation of Complications of Various Venous Access Approaches

Complication	PICC (%)	Nontunneled Central Catheters (%)	Tunneled Central Catheters (%)	Implanted Catheters (%)
Examples of access	PICC	Central line, rigid temporary catheter	Traditional, dialysis, hybrid	Peripheral port(s), chest port(s)
Arterial puncture				2.4
Malposition	5–10	5–10	5–10	0.5 5–10
Pneumothorax	0.2–6.0	0.2–6.0	0.2–6.0	0.3 0.2–6.0
Venous thrombosis asymptomatic, symptomatic, cancer patient	3.4 AS = 30–74 (L) S = 3.4–3.9 (L)		AS = 23–39 (L) S = 4.7–10 (L)	0.8% (general venous thrombosis) AS = 2–30 (L) S = 0–9 chest (L) S = 2–30 arm (L)
Bacteremia	0.4–20	20–22	10–20	
Pocket infection				0.5
Cardiac tamponade	0.25–1.4	0.25–1.4	0.25–1.4	0.25–1.4
Phlebitis	6.6			
Additional complications Hemothorax Tunnel infection Air embolism				
Comments	Tabulation from cancer patients			Tabulation from cancer patients
References	3, 7, 9–12	3, 6, 9–12, 15	6, 9–12, 15	6, 9–12, 15

PICCs, peripherally inserted central catheters.

formation secondary to their malignancy, treatment regimen, and the trauma of catheter insertion.[8] Improper final tip positioning and subclavian access as opposed internal jugular access may also contribute to thrombosis.[9,10] In cancer patients, PICCs have been shown to have less incidence of deep venous thrombosis than tunneled catheters used for the same purpose.

Percutaneous Central Venous Catheters

Aubaniac was the first to describe cannulation of a central vein (the subclavian) for venous access.[11] 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 CVCs or temporary rigid hemodialysis/apheresis catheters. The CVC is utilized in the hospital setting for acute central venous access with a dwell time of up to 14 days. CVCs are typically used for rapid infusion, multiple infusates needed simultaneously, or hemodynamic monitoring (central venous pressure measurement). Thus, CVCs are for use in acute care settings, thus reserving them for hospitalized patients only.

Frequent assessment of the catheter for integrity, dislodgment, and site evaluation is required. Flushing of each catheter lumen is performed frequently for patency. Complications related to these devices include infection, bleeding, inadvertent arterial access, air embolism, pneumothorax, hemothorax, cardiac perforation and 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. During catheter dwell, 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.

The rigid, nontunneled, central catheters are typically used for acute hemodialysis, hemodialysis access after removal of an infected tunneled dialysis catheter, stem cell collection for autologous transplant or healthy donor collection, or therapeutic apheresis. These catheters can be placed by certified nurse practitioners, physician assistants, or physicians in a surgical suite, or in interventional radiology. Image guidance is essential. Catheter exchange at the same venous site can indefinitely maintain 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. This practice should be reserved for the patient with truly limited central venous access.

The catheter exit site must be kept dry with an intact occlusive dressing changed biweekly to minimize infection risks. The lumens are given a high-dose heparin lock to maintain patency. Accidental dislodgment of the rigid catheter can occur even though sutures are placed. Due to the large caliber of these devices, unrecognized dislodgement can lead to life-threatening hemorrhage. Usage of these catheters and dressing changes are typically reserved for certified dialysis technicians to provide optimal consistent management. Dressing changes and flushing for patients undergoing stem cell collection are managed by nursing services.

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 access site. The tip of the catheter should terminate in the SVC/right atrial junction or IVC/right atrial junction. A retention cuff, which causes inflammation and ingrowth into the cuff, is integrated on the catheter. The cuff is positioned approximately 1 to 2 cm within the skin insertion point. The cuff serves as a barrier to bacterial migration along the tract into the central circulation. After tunneling, the catheter is threaded into the central circulation via the jugular veins, subclavian vein, femoral vein, or lumbar vein access (only in vein-compromised patients).

Tunneled catheters can be further divided into three types: traditional tunneled catheters, dialysis catheters, and hybrid tunneled catheters. The traditional tunneled catheters are best known as the Hickman or Broviac catheter. These are intended for patients requiring long-term central venous access use

such as total parenteral nutrition, chemotherapy, chronic medication administration, and blood infusion or sampling. The second are the dialysis catheters. These are typically used for hemodialysis but more recently they have been utilized for stem cell collection and posttransplant venous access. The final catheter type, the hybrid tunneled catheter, is most often used for stem cell collection, transplant access, or photophoresis treatments in graft-versus-host disease in transplant patients. All three of these catheters are available in single, double, or triple lumens, with a variety of lumen sizes and catheter lengths. These catheters are known for lower infection rate 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. Tunneled catheters with high-dose heparin lock solution require removal of the lock prior to catheter use to prevent inadvertent systemic heparinization. Catheters containing valve devices may only require saline flushes, thus simplifying this regime.

Complications of tunneled catheters include those associated with the insertion procedure (i.e., bleeding, air embolus, pneumothorax, hemothorax, and cardiac dysrhythmia) as well as long-term issues (i.e., infection, migration, thrombosis, and catheter shear). Most medical centers will stock catheter repair kits that allow for the salvage of cracked or leaking catheter. Extrusion of the cuff from the subcutaneous position is an indication for replacement or removal of the tunneled catheter.

Implanted Ports

Implanted ports are CVCs attached to a reservoir with a self-sealing septum. The reservoir is surgically implanted into a pocket in the subcutaneous tissue and the attached catheter is tunneled subcutaneously before advancement into the central venous circulation.

The implanted port is ideal for patients undergoing intermittent or cyclic therapy when daily access is not required. Ports are suited to chemotherapy administration or venous access for lab draws in vein-compromised patients requiring chronic venous access. It should be noted that the need for a port in a cancer patient should be anticipated such that healing and recovery after the procedure has been completed prior to the neutropenia and weakness of chemotherapy sets in. Newer models of implanted ports allow power injections of contrast material for radiologic imaging. Medical device companies also promote ports with differing flow patterns or characteristics within the reservoir chamber (i.e., "the port") that claim to improve infusion, blood draws, and lower thrombosis rates. 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 privacy 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 number of punctures into the septum and 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 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 an alternative until such a time when a port may be better tolerated.

The locations of the subcutaneous port most commonly used include a location on the anterior chest wall, the arm, or thigh placement 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 needle stick as the port is being accessed, but the discomfort may be minimized by applying topical anesthetics, to the skin over the port prior to the needle stick. While the port is accessed, it requires daily flushing. It must be flushed after each use as well. When the port is not actively being used, monthly flushes are required to maintain patency. Complications associated with ports are rare and are divided into early and late events. Early complications in oncology patients include hematomas, malposition, and iatrogenic pneumothoraxes. Late complications are dominated by catheter thrombosis and infection; however, catheter facture and embolization can also occur.

Power Injection Catheters

Catheters, such as PICCs and infusaports, have been studied in the past for safety in power injection with mixed results in efficacy. This is dependent 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 as outlined by the manufacturers have limited the use of most catheters for power injection, until recently. Optimal contrast imaging requires uniform contrast delivery, which is best achieved by power injection at 2 mL per second. In fact, these limitations have led to current trends in catheter manufacturing in which some catheters can tolerate 300 PSI (Bard Access). Candidates for power injection catheters include those anticipated to have recurring contrast medium injection studies. Herts et al. studied a variety of CVCs including standard CVC, tunneled catheters, and implanted ports and found that power injections are possible without harm to the patients or the catheters.[15] Their findings suggest usage of central lines as a possible alternative to peripheral angiocatheters. Institutional policies are needed to address this as there may be additional training required of the staff prior to utilizing such devices to minimize complications. Special equipment may be required for accessing power injection ports so as to prevent rupture or extravasation. In addition, the more rigid catheter required for power injection may lead to increased complications such as phlebitis or thrombosis.

Valve Technology

Ongoing clinical presentation of heparin allergies, specifically heparin-induced thrombocytopenia, has led to marketing of catheters with valve technology. The valve remains closed unless acted upon by negative (aspiration) or positive (infusion) pressure. It is this technology that opposes central venous pressure and prevents the reflux of blood into the catheter tip during the cardiac cycle or changes in intrathoracic pressure that naturally occurs in everyday life such as with straining of vomiting. 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 as well as decreased infection rate. Lamont et al. found the PASV (Boston Scientific Corporation, Natick, MA) valved implanted port had a lower incidence of difficulty in obtaining a blood return than the Groshong (Bard Access System, Salt Lake City, UT), which resulted in less nursing time troubleshooting malfunctioning or poorly functioning catheters. Valve technology has been incorporated into some catheters at the distal tip or in the proximal end piece. This technology is also available as an "add-on" device for catheters. A saline-only flush is recommended; however, heparin flushes are not a contraindication.

REVIEW QUESTIONS

1. A 54-year-old male has been admitted to the hospital for neutropenic fever after his most recent dose of chemotherapy. He is currently getting neoadjuvant therapy for advance rectal cancer via a double-lumen PICC. You are called to the bedside by the nurse for mental status changes, hypotension, and tachycardia. The nurse also reports a large volume bloody bowel movement. The next most appropriate step is
   - **A.** Move the patient to the appropriate level of acuity, send labs for coagulation studies and an H/H, establish two large-bore peripheral IVs, and type and screen.
   - **B.** Move the patient to the appropriate level of acuity, send labs for coagulation studies and an H/H, establish two large-bore peripheral IVs, and type and cross for 4U PRBCs.
   - **C.** Move the patient to the appropriate level of acuity, send labs for coagulation studies and an H/H, and type and cross for 4U PRBCs.
   - **D.** Move the patient to the appropriate level of acuity, and send labs for coagulation studies and an H/H bolus 1 L of crystalloid.
   - **E.** Bolus 1 L crystalloid, send labs, and call GI.

2. Which component of the vein, when injured with repeated venopuncture, is responsible for generating platelet aggregation and eventual thrombosis?
- **A.** The valve
- **B.** The adventitia
- **C.** The tunica media
- **D.** The tunica intima
- **E.** The lamina

3. A 34-year-old woman has recently been diagnosed with stage III (T3, N1) invasive ductal cancer. Her tumor is Her-2/neu positive and she will be having a year of Herceptin in addition to her systemic chemotherapy. The most appropriate venous access is
- **A.** Peripheral IV
- **B.** Midline catheter
- **C.** Nontunneled catheter
- **D.** Infusaport
- **E.** Tunneled catheter such as a Hickman

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SECTION Twelve

Common Office Procedures and Other Topics

42

Procedures in Medical Oncology

Kerry Ryan, George L. Carter, and Suzanne G. Demko

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

Written informed consent, or a legally sufficient substitute, must be obtained before every procedure described here and filed in the patient's medical record.

ANESTHESIA

All procedures are typically performed under local anesthesia. For certain patients and procedures, premedication with a narcotic (fentanyl) and a benzodiazepine (midazolam) should be considered. 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.

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 particular circumstances may transfuse for platelets <20,000.
- Skin infection at the proposed site of biopsy.
- Biopsy at previously radiated site may cause fibrosis; consider an alternative site.
- Avoid sternal aspirate in patients with thoracic aortic aneurysm or lytic bone disease of ribs or sternum.
- Heparin, low-molecular heparin, or warfarin should be discontinued before procedure and may be resumed after hemostasis is achieved.

Anatomy

- Sternal aspiration
  - 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 (Fig. 42.1)
  - Patient is prone or in lateral decubitus position.
- Anterior iliac crest aspiration and biopsy (for patients with history of radiation to pelvis or extremely obese patients)
  - Patient is supine.

Procedure

- Sternal aspiration
  - Identify landmarks, clean the area, and position a fenestrated drape using sterile technique.
  - In the area to be aspirated, infiltrate the skin, subcutaneous tissues, and periosteum with 1% lidocaine for anesthesia. Using the infiltration needle, "sound" the surface of the bone to approximate the distance from skin to periosteum.

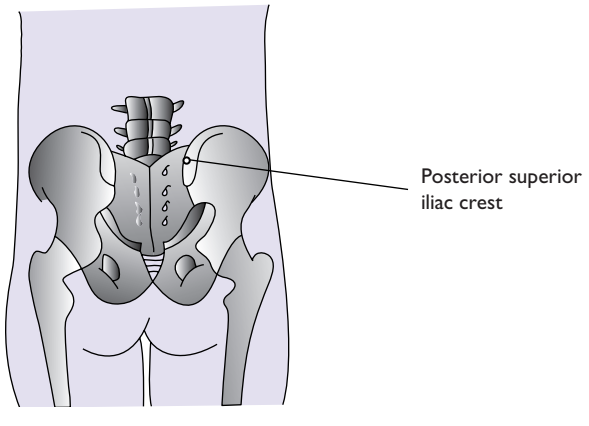

FIGURE 42.1 Biopsy site in the posterior superior iliac spine. The needle should be directed toward the anterior superior iliac spine.

- Use a 16-gauge sternal aspiration needle with guard to prevent penetration of the posterior table of the sternum. Adjust needle guard based on the approximate distance from skin to periosteum.
- Make a 2 mm superficial skin incision with a surgical blade in the midsternum, medial at the second intercostal space.
- Introduce the aspiration needle with guard, using gentle, corkscrew-type pressure to advance the needle until fixed in bone. Remove obturator, attach a 10 to 12 mL syringe, and aspirate. The pain of this procedure cannot be prevented but lasts only a few seconds.
- Obtain 1 mL of aspirate. An amount >1 mL will be diluted by peripheral blood.
- Spicules of bone marrow will be present unless significant fibrosis is present or the marrow is packed with leukemia or other malignancy.
- If no specimen is obtained, replace the obturator and carefully advance the needle 2 to 3 mm to repeat aspiration.
- Prepare smears for evaluation.

■ Posterior superior iliac spine aspiration and biopsy

- The technique described here is for the Jamshidi bone marrow needle. Other available needles, such as the HS Trapsystem Set, Goldenberg Snarecoil, and T-Lok bone marrow biopsy system, are variations of the Jamshidi with their own specific instructions. Also available is the On Control Bone Marrow Biopsy System that utilizes a battery-powered drill to insert the needle into the iliac bone.
- 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.
- 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 a case, a touch preparation of the biopsy often provides sufficient cellular material for diagnostic evaluation.
- 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 needlestick 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 no 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 the planned site of LP.
- Heparin, low-molecular heparin, or warfarin should be discontinued before procedure and may be resumed after hemostasis is achieved.

Anatomy

- Avoid interspaces above L3 (Fig. 42.2), as the conus medullaris rarely ends below L3 (L1–L2 in adults, L2–L3 in children).
- The L4 spinous process or L4–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.

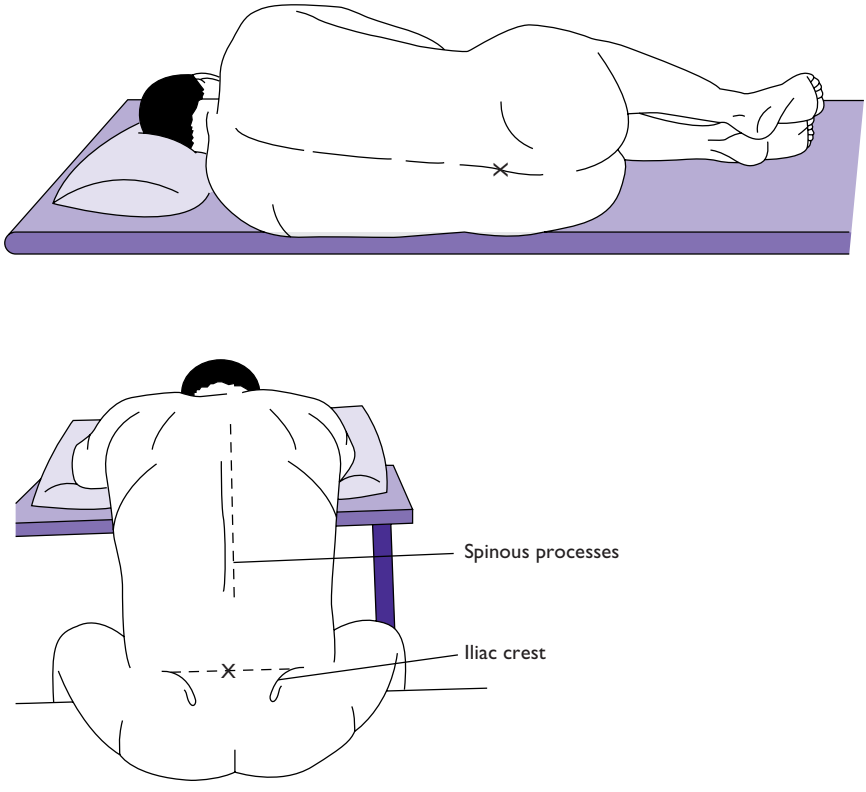

FIGURE 42.2 Anatomy of the lumbar spine. Ideal needle insertion is between L3 and L4 interspace, which can be found where the line joining the superior iliac crests intersects the spinous process of L4. Positioning of the patient for lumbar puncture: in lateral decubitus or sitting position. (From Zuber TJ, Mayeaux EF. *Atlas of Primary Care Procedures*. Philadelphia, PA: Lippincott Williams & Wilkins; 1994:13.)

Procedure

- Describe the procedure to the patient, with assurances that you will explain what you are about to do before you do it.
- Patient should be in a lateral decubitus or sitting position. 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 (Fig. 42.2).
- Identify anatomic landmarks and the interspace to be used for the procedure.
- Using sterile technique, prepare the area and one interspace above or below it with povidone–iodine solution. Drape the patient, establishing a sterile field.
- Using 1% lidocaine/bicarb mixture, anesthetize the skin and deeper tissues, carefully avoiding epidural or spinal anesthesia.
- 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.
- When the presence of CSF is confirmed, attach a manometer to measure opening pressure. Collect 8 to 15 mL of CSF. If special studies are required, 40 mL of CSF may be safely removed. Four sample tubes should be sent as follows: tube 1, cultures; tube 2, chemistries (especially glucose and protein); tube 3, cell count and differential; tube 4, cytopathology or other special studies (flow cytometry, cytogenetics, etc.).
- Replace the stylet, withdraw the needle, observe the site for CSF leak or hemorrhage, and bandage appropriately.
- Ease the patient into a recumbent position and maintain for 60 minutes.

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 (peaks 20–40), and patients with a history of headache prior to LP. Patients should be encouraged to remain recumbent if possible, drink plenty of fluids, and take over-the-counter analgesics. For severe, persistent spinal headache (up to 1 week is possible), stronger medication, caffeine, or an analgesic 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.

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

- Place the patient in a comfortable supine position at the edge of a bed or table.
- Identify the area of the abdomen to be accessed (Fig. 42.3).
- Prepare the area with povidone–iodine solution and establish a sterile field by draping the patient.
- Anesthetize the area with a 1% lidocaine/bicarb mixture.
- 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 (Fig. 42.4).
- 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.
- 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.
- 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.
- 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.

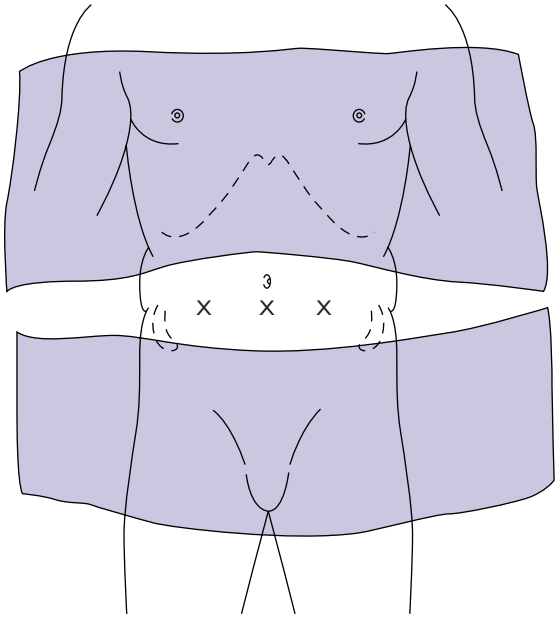

FIGURE 42.3 Sites for diagnostic paracentesis. (From Zuber TJ, Mayeaux EF. *Atlas of Primary Care Procedures.* Philadelphia, PA: Lippincott Williams & Wilkins; 1994:46.)

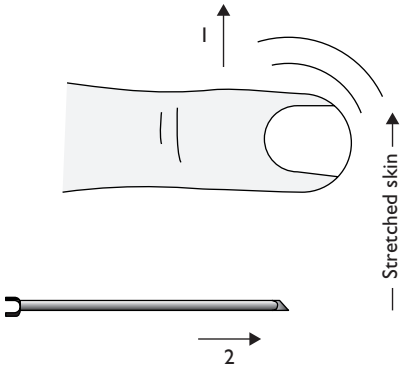

FIGURE 42.4 Z-track technique for inserting needle into peritoneal cavity. (From Zuber TJ, Mayeaux EF. *Atlas of Primary Care Procedures*. Philadelphia, PA: Lippincott Williams & Wilkins; 1994:47.)

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.
- Bullous emphysema (increased risk of pneumothorax).
- Cardiovascular disease.
- Patients on mechanical ventilation with PEEP 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

If chest radiographs suggest loculation of fluid, decubitus films and possibly computed tomography or ultrasound may be required before thoracentesis is attempted.

Anatomy

- Carefully ascertain the location of the diaphragm to avoid accidental injury to abdominal organs and viscera.
- 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.
- Perform thoracentesis through the seventh or eighth intercostal space, along the posterior axillary line. With guidance from fluoroscopy, sonography, or computed tomography, 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.

- 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

- 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-guage needle advance toward the rib and then "walk" over the superior edge of the rib (Fig. 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.
- 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 by vacutainer. Withdrawing more than 1,000 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.
- 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; pneumothoraces involving >50% lung collapse do.

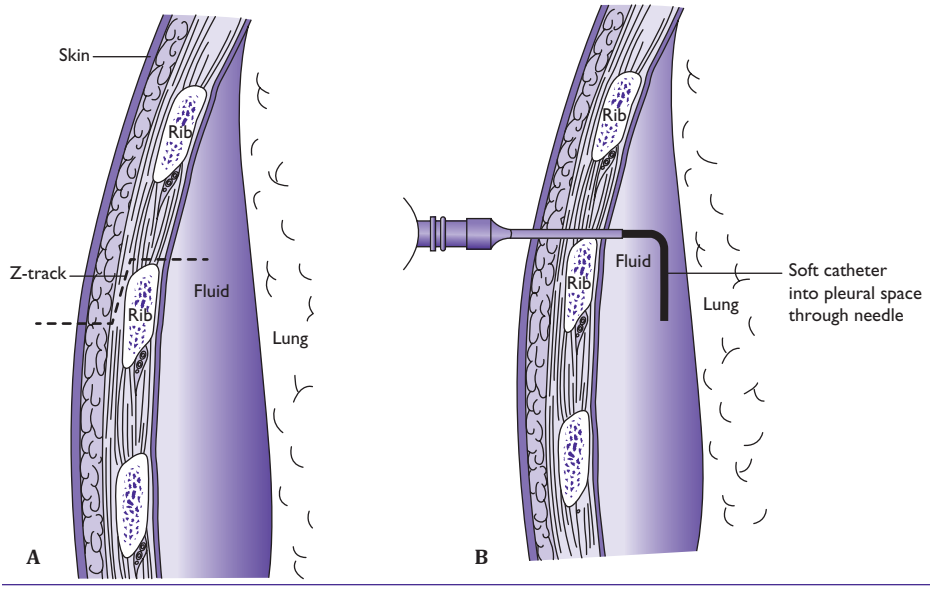

FIGURE 42.5 Thoracentesis. (A) Z-track technique for anesthetizing to prevent injury to neurovascular bundle. (B) Advancement of soft plastic catheter through the needle into pleural space. (From Zuber TJ, Mayeaux EF. *Atlas of Primary Care Procedures*. Philadelphia, PA: Lippincott Williams & Wilkins; 1994:26-27.)

Complications

- Pneumothorax
- Air embolism (rare)
- Infection
- Pain at the puncture site
- Bleeding
- Splenic or liver puncture

REVIEW QUESTIONS

1. A 34-year-old male presents to your oncology office with a newly diagnosed stage Burkitt cell lymphoma. He is complaining of headaches and his wife states he has unstable gait and fallen a number of times at home. What should your next step be?
   A. Perform an emergent LP to rule out leptomeningeal disease.
   B. Prescribe the patient pain medication for his headache.
   C. Perform a MRI or CT of his brain before proceeding to a LP.
2. A 56-year-old male with stage IV diffuse large B-cell lymphoma presents for his staging workup following six cycles of R-CHOP. You are planning on doing a bone marrow on him today to complete his restaging. Two months ago he has had a deep venous thrombosis and is now on enoxaparin 100 mg/kg subcutaneously twice daily. He took his morning dose, 2 hours ago. Do you proceed with the bone marrow today?
   A. Yes
   B. No
3. A 64-year-old female presents with metastatic ovarian cancer and is short of breath. She is found to have a large right-sided pleural effusion and you decide to perform a thoracentesis. What intercostal spaces should you perform a thoracentesis through?
   A. Ninth or tenth intercostal space
   B. Seventh or eighth intercostal space
   C. Sixth or seventh intercostal space
   D. Fifth or fourth intercostal space

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43

Diagnosis-Driven Individualization of Cancer Care

Philippe C. Bishop, Chris Bowden, Garret Hampton, and Lukas Amler

Personalized medicine has become a reality for many cancer patients. This is due in part to significant advances in our understanding of cancer, including fundamental mechanistic insights into the genesis and evolution of a malignancy and multiple large-scale studies that have described the spectrum of genetic abnormalities in common cancers (e.g., The Cancer Genome Atlas, or TCGA). Coupled with the routine use of tissue sampling in the clinic, the ability to efficiently analyze these tissues at a molecular level, and the increasing availability of targeted therapies, these advances have provided physicians with the tools to select the proper therapy (or therapies) at the right time in the course of disease management for patients with cancer (e.g., lung, breast, and colon cancers).

This chapter is intended to give a brief overview of personalized oncology care driven by diagnostics. We discuss novel approaches, selected technologies, and their application in the clinic, as well as mechanisms of resistance and their implications for the approach to personalized care. Lastly, we provide an outlook on the future in the field, including the universal adoption of multiplex diagnostics into routine clinical practice.

PATIENT JOURNEY

The clinical journey of an individual diagnosed with cancer is illustrated in Figure 43.1. At the ontset, a screening test, symptom, finding on physical exam, or abnormality on laboratory or imaging study will lead to the identification of a tumor. In most instances, a biopsy or surgical excision of the primary tumor or site of metastasis will establish a pathologic diagnosis.

Historically, clinical management decisions and prognostic estimates were primarily based on the results of histopathologic analyses of tumor tissue and various clinical factors (e.g., weight loss, performance status, age). Tumor behavior and response to treatment are, however, inadequately explained by tissue of origin, histology, and clinical factors alone. Patient outcomes can be significantly improved when the molecular profile (i.e., overexpressed proteins, activated signaling pathways, and genetic alterations) of the tumor and of the associated tissue microenvironment are integrated into treatment decisions. In combination with other diagnostic and demographic data, along with quality-of-life considerations, these profiles can be used to guide individualized therapeutic options to potentially improve the response to therapy and patient outcomes. Where curative or palliative options fail, the diagnostic cycle begins again with characterization of the tumor and its microenvironment, since treatment may have led to resistance and failure of the therapeutic strategy. This information may guide subsequent

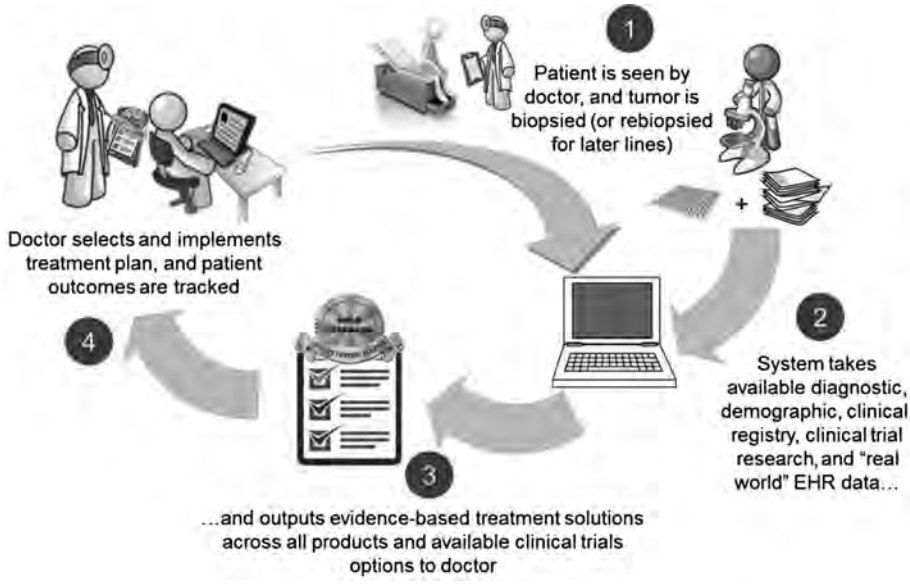

FIGURE 43.1 Patient journey.

therapeutic interventions, potentially enabling the selection of targeted agent combinations to overcome acquired resistance and manage disease. Throughout these iterations, the information generated is not only key to guiding therapy, but may also further increase our understanding of the dynamic nature of cancer biology and inform future opportunities for research and drug development.

MOLECULAR DIAGNOSTICS

The more comprehensive understanding of the genetic makeup of tumors achieved in the past decade has resulted in molecular diagnoses being offered to patients with metastatic breast, colon, lung, central nervous system malignancies, melanoma, and leukemia/lymphoma. Diagnostic techniques commonly employed include immunohistochemistry (IHC), which can detect aberrant expression, localization, and phosphorylation levels of proteins; in situ hybridization (ISH), which reports on the localization and expression of messenger RNA (mRNA); fluorescence ISH (FISH), which can determine chromosomal abnormalities and gene copy number alterations; and polymerase chain reaction (PCR)-based methods, which can detect somatic mutations deletions or Fusions in key oncogenes in addition to quantifying mRNA expression. Formalin-fixed and paraffin-embedded (FFPE) tissues from surgical or biopsied specimens are often used for testing in the clinic. Other clinical specimens, such as fresh frozen tissues derived from biopsies, are also used to some extent, typically in the context of early drug development, to assess drug activity and mechanism of action, as well as to understand mechanisms of resistance upon progression. Table 43.1 provides examples of the types of molecular analyses that are used to inform the selection of therapeutic agents for patients.

In most of these examples, a single diagnostic test is used to identify specific "driver mutations" (genetic aberrations causally implicated in oncogenesis or tumor survival) for which targeted therapies exist. Validated, diagnostic assays that are approved by regulatory authorities to specifically guide treating physicians regarding which therapeutic option to choose are called "companion diagnostics." Examples are diagnostic tests that detect the aberrant expression of specific therapeutic targets (e.g., human epidermal growth factor receptor 2 [HER2] in breast cancer) or factors predicting resistance to targeted

Table 43.1 Examples of Molecular Targets, Associated Diagnostic Modalities, and Drugs Indicated for These Patients

Malignancy	Target	Diagnostic Technology	Agent(s)
BC	*HER2*	IHC or FISH/ISH	Trastuzumab, pertuzumab, and trastuzumab emtansine
CML	*BCR-ABL*	Cytogenetics, FISH, Quantitative RT-PCR	Imatinib, dasatinib, nilotinib, and bosutinib
CRC	EGFR—*KRAS* resistance marker	*KRAS*—DNA PCR	Cetuximab and panitumumab
Melanoma	*BRAF*	DNA PCR	Vemurafenib
NHL	CD20 antigen	IHC	Rituximab and ofatumumab
NSCLC	*ALK*	FISH	Crizotinib
	EGFR	PCR sequencing	Erlotinib and gefitinib
	KRAS	PCR sequencing	Selumetinib[a]
	MET	IHC	Onartuzumab[a]

BC, breast cancer; CML, chronic myelogenous leukemia; CRC, colorectal cancer; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; RT-PCR, real-time quantitative polymerase chain reaction.
[a]Experimental agents currently in clinical trials.

agents (e.g., the presence of *v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog [KRAS]* in colorectal tumors that confer resistance to epidermal growth factor receptor [EGFR]-targeting antibodies). Although these represent significant advances, obtaining information on a single genetic variable from tumor samples at a single point in time may not be informative, as it does not take into consideration additional tumor, microenvironment, or host factors that may also affect treatment outcomes. Finally, the inevitable emergence of resistance to targeted therapies for the majority of patients with metastatic disease supports the need for the assessment of multiple molecular features using a variety of platforms serially over the course of the patient treatment journey.

Several techniques now allow for the simultaneous analysis of multiple genes in tumor tissue. Single nucleotide polymorphisms (SNPs) affecting metabolic enzymes in the genomes of individual patients have identified subsets of patients at increased risk of drug toxicity, resulting in now-routine screening and possible dose adjustments for those treated with thiopurines or irinotecan. SNPs arising from somatic mutations in tumor cells can now be analyzed in a high-throughput fashion using oligonucleotide probes bound to a solid support. Array-comparative genomic hybridization, examines DNA copy number changes and provides information on gene amplifications and deletions found in tumors. DNA microarrays are widely used in predictive and prognostic examinations of cancer genomes. These employ microscopic arrays of oligonucleotides or cDNA attached to solid supports ("gene chips") to which fluorescently labeled DNA transcribed from sample RNA is hybridized, providing the data used to generate "gene signatures." Although not yet practical for patient-level purposes, global genomic characterization of tumors using, in part, whole-genome DNA sequencing has been used to elucidate core signaling pathways in pancreatic cancer and glioblastoma multiforme (GBM), in the former case identifying a set of 12 core pathways and processes genetically altered in most tumors and in the latter case revealing a link between *O6-methylguanine DNA-methyltransferase* (*MGMT*) promoter methylation and a hypermutator phenotype in treated GBMs. Real-time quantitative PCR (RT-PCR) assays, although limited to the examinations of several hundred "candidate" genes rather than an entire genome, are increasingly used for tumor classification, in addition to predictive and prognostic purposes. Finally, direct analysis of proteins ("proteomics") eliminates the potential discordance between mRNA and protein expression levels. Although more technically challenging to address in a high-throughput fashion than genomic methods, profiling of a limited number of proteins of interest in serum or tissue is now possible using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF).

RESISTANCE

Recent insights into the nature of innate and acquired resistance in cancer provides further support for the implementation of a multiplex diagnostics approach. As a comparison, these resistance mechanisms are similar to those found in infectious diseases, where they also represent a major challenge to therapy.

As highlighted in Table 43.2, there are multiple ways in which cancers become resistant to targeted therapy. In chronic myelogenous leukemia (CML), for example, mutations in the target of the drug imatinib, the tyrosine kinase BCR-ABL, represent the most common way in which resistance to imatinib is acquired. Most of the current evidence suggests that these mutations are preexistent in the primary cancer in a small number of cells and subsequently selected following treatment. Current strategies for managing these patients make use of agents specifically developed to be effective against the mutated forms of the target protein. Other mechanisms of resistance include gene amplification (e.g., androgen receptors in hormone-refractory prostate cancer), drug inactivation due to host metabolic factors (e.g., cytochrome P450 2D6 [CYP2D6] metabolism of tamoxifen in breast cancer), and, importantly, "oncogene bypass," in which the drug target remains unchanged and sensitive to inhibition, but alternative signaling pathways are used in tumor cells to bypass the primary driver mutation. This is made possible by the fact that the human kinome, or set of protein kinases, contains more than 500 members, and cancer cells typically express multiple receptor tyrosine kinases (RTKs), which converge on common downstream effectors. An example of the oncogene bypass mechanism, which may represent a broad category of resistance, was recently reported. The authors demonstrated that rather than a mutation in the binding pocket of a kinase itself, resistance (e.g., to *BRAF* inhibition) may be overcome through the expression of a RTK ligand (e.g., hepatocyte growth factor [HGF]) that activates other RTKs (e.g., MET) that have similar downstream effects. Selection pressure elicited by therapy is postulated to result in expansion of tumor cells overexpressing this receptor. Notably, for resistance emerging through this mechanism, the ligand need not derive directly from tumor cells but may instead be produced in the stroma. This may explain the apparent correlation between high HGF levels and resistance to vemurafenib, which targets $BRAF^{V600E}$ in patients with metastatic melanoma. The resulting hypothesis that dual inhibition of *BRAF*/*MEK* and either *HGF*, *MET*, or insulin-like growth factor-1 receptor/phosphatidylinositol-3-kinase (IGF-1R/PI3K) may circumvent innate and acquired resistance has been borne out in cellular assays but not yet in the clinic.

In addition, host factors may also play a role in resistance to targeted cancer therapies. For example, germline alterations in the pro-apoptotic protein BCL-2 like 11 (BIM) may serve as a biomarker to identify individuals less likely to benefit from tyrosine kinase inhibitor (TKI) therapy in CML and non–small cell lung cancer (NSCLC). As suggested by cellular assays, the addition of BH3 mimetic agents to TKI therapy might restore sensitivity in this subgroup; however, clinical validation of the safety and efficacy of such a combination regimen is needed. On the other hand, such a multitargeted approach, using highly active therapies, has proven successful in the treatment of infectious diseases, such as HIV, and could similarly forestall the emergence of resistance in oncology and prolong the survival of cancer

Table 43.2 Common Mechanisms of Resistance

Mechanism	Possible Example
Drug target mutation	Imatinib resistance in chronic myelogenous leukemia
Drug target mutation	Erlotinib resistance in non–small cell lung cancer
Targeted pathway bypass or reactivation	BRAF inhibitor resistance in V600-positive melanoma
Drug inactivation/failure to activate prodrug	Failure to produce active tamoxifen metabolite in breast cancer patients with genetic CYP2D6 variants
Persistence of cancer stem cells	Imatinib resistance in chronic myelogenous leukemia
Signaling pathway feedback	Resistance to mTOR inhibitors
Epithelial mesenchymal transition	Erlotinib resistance in non–small cell lung cancer

CYP2D6, cytochrome P450 2D6.

patients. Clearly, with many mechanisms at play, multiplex diagnostic information will be a prerequisite for such approaches, whether measured on the same or different platforms.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Currently, molecular targeted therapies with clinically relevant companion diagnostic assays that enable proper patient selection are a reality for a significant fraction of patients with cancer. The increasing availability of commercial companion diagnostic and prognostic gene signature assays have contributed to their rapid adoption in community clinical practice. Thus, diagnostic platforms are increasingly guiding treatment decisions today.

While the overall progress toward personalized medicine is exciting and rapidly evolving, many challenges remain. The first is that tumor tissue will remain limiting; for example, assessment of two to three companion diagnostic tests in a lung cancer sample with current requirements of several tissue sections each would deplete available tissue. Second, as cancers become increasingly fragmented into actionable disease subsets, the requirement for multiplex diagnostics will increase.

Multiplex analyses and comprehensive profiling of tumors is becoming routine at many academic institutions, but they are not yet a standard part of practice. Advances in our understanding of various cancers and the identification of driver mutations for these cancers illustrate the need for multiplex analyses. For example, there are a number of known driver mutations in NSCLC (Fig. 43.2), and an analysis of FFPE tumor samples from patients with NSCLC by FISH, IHC, and Sanger sequencing found that 54% of patients had targetable driver mutations. However, only 22% of advanced NSCLC patients received targeted therapy, illustrating the need for comprehensive genomic characterization of tumors to aid in identifying patients that would benefit from targeted therapies, as well as potential targets for drug development.

In addition, performing such a comprehensive analysis to obtain information on all relevant molecular characteristics of the tumor based on a single biopsy at the time of diagnosis or recurrence would make personalized treatment selection for patients much more efficient than the current practice of ordering individual tests for each molecular aberration. In turn, patients and physicians could then select the appropriate targeted therapies, such as erlotinib and gefitinib for mutations in EGFR, a major target implicated in lung cancer with downstream effects on both the *AKT*/*PI3K* pathway and the *MAPK* pathway, regulating cell growth proliferation, and death. Furthermore, as the underlying molecular mechanisms for specific cancers are further elucidated, in part, through these analyses, additional therapies become available, such as crizotinib for patients with lung cancer shown to be constitutively activated by the *echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase* (*EML4-ALK*) fusion oncogene, which in turn drives activation of the *RAS*/*RAF*/*MEK*/*MAPK* pathway.

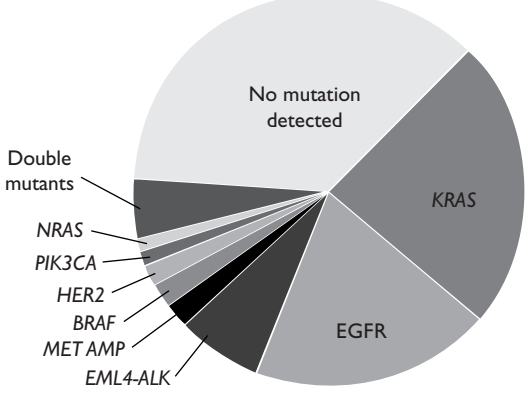

FIGURE 43.2 Potential driver mutations.

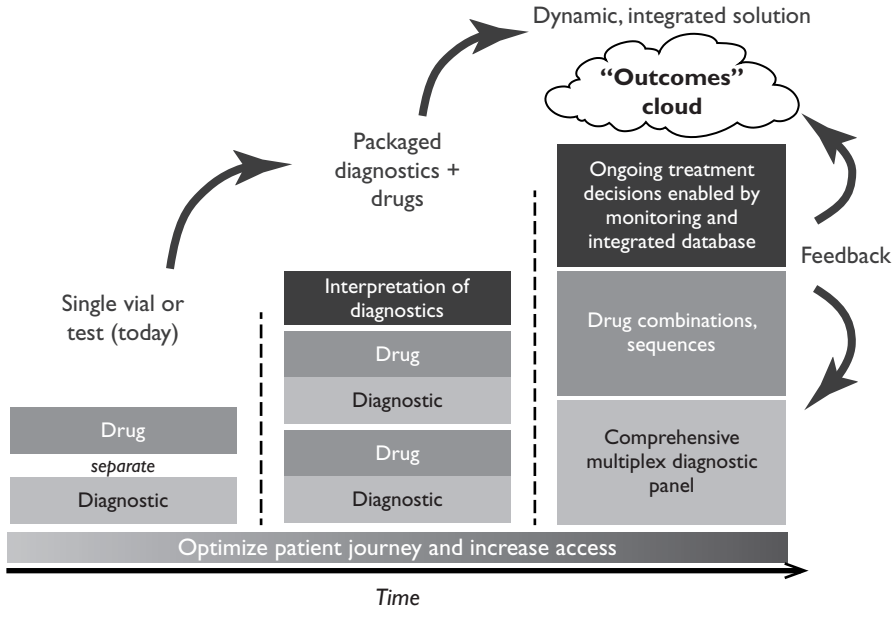

FIGURE 43.3 The future: combined diagnostics, drugs, and data into a disease solution. Diagnostic and treatment decision strategies are rapidly evolving from separate drugs and diagnostics to integrated diagnostics that are comprehensive, with clinical and continuous diagnostic information playing an important role in treatment decisions.

Moving forward, multiplex diagnostics will likely take the form of both nucleic acid platforms (e.g., next-generation sequencing of RNA and DNA), as well as IHC-based techniques. Another possibility is that, in some cases, less invasive methods might be employed, such as blood-based assessments that utilize circulating tumor cells, circulating protein, or tumor DNA, that may have utility in the prognosis, prediction, and, ultimately, even the monitoring of resistance to therapy.

Taken together, advances in the understanding of cancer biology on a molecular level, coupled with the increasing adoption of more comprehensive multiplex diagnostics and the availability of novel targeted agents, have the potential to transform the treatment of and extend the lives of patients with cancer (Fig. 43.3).

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Basic Principles of Radiation Oncology

Deborah Citrin

As one of the three widely accepted modalities in the management of cancer, radiotherapy (RT) maintains perhaps the most "alternative" form; it is neither chemical nor invasive. Indeed, because of the general lack of understanding of the physics and biology underlying the principle and practice of RT, many clinicians and patients remain perplexed by its ability to cure disease and the constant evolution in its delivery to maintain the therapeutic window, ultimately designed to preserve quality of life and functionality while eradicating disease.

RADIATION BIOLOGY AND PHYSICS

Although radiobiology and physics are clearly separable in theory, and many textbooks have been written to focus on one or the other, a practical understanding of one subject cannot be easily delineated from the other.

Prior to discussing the biology and antineoplastic activity of RT, it is important to understand the basic physical properties of contemporary RT, in terms of both its activity and its production by a modern linear accelerator. The most common form of RT used today is a photon, or packet of x-rays. Discovered by Wilhelm Röntgen in 1895, photons were found to blacken photographic film; as these "new kinds of ray" were unable to be measured at the time, they were called "x-rays." Shortly following their discovery, Wilhelm Freund treated a mole with the x-rays, giving birth in 1897 to the field of therapeutic radiology or radiation oncology. The following year, in 1898, Antoine Bequerel discovered radioactivity and the Curie family isolated radium. Indeed, because of the transportability and ease of administration, radioactive elements such as radium remained the preferred route of RT until only recently. Subsequent experiments demonstrated that the energy released by the radioactive decay of an element, so-called γ-ray, was identical to that artificially produced by a gas tube, an x-ray. Today, most modern RT consists of photons produced by linear accelerators, though there are many effective and curative applications from radioactive decay, generally termed brachytherapy.

Mechanism of Action

RT, in any of its forms, represents ionizing radiation because the energy passed from RT to the tissues is sufficient to cause an outer orbital electron to be released, thus ionizing or charging the tissue's atom. Specifically, x-rays and γ-rays are forms of electromagnetic radiation, while the less commonly used forms of RT (protons, neutrons, mesons, carbon ions) are generally termed particulate radiation

because they have mass. Despite the fact that RT "excites" or ionizes tissue particles, and thus can be measured by calories, it does not increase the temperature of the recipient or induce a thermal effect. So-called radiation burns are not thermal; the erythema of the skin is a reflection of the denudement of the superficial layers of the skin, caused by the increased cellular turnover induced by RT, leaving behind the better-vascularized deeper dermal tissues to show through as red.

When RT is delivered it is either directly or indirectly ionizing. Particulate, charged, or heavy ions deliver their energy to the tissue by direct effect; that is, these particles have enough kinetic energy to directly alter the genetic material with which they make contact. On the other hand, electromagnetic RT (γ- and x-rays) affect cells by indirectly ionizing them. These rays give up their energy to the absorbed tissues, thus causing the formation of fast-moving charged particles. Typically, the energy of an x-ray or γ-ray is passed to many circulating electrons (often called free radicals), which then go on to interact with various host tissues, including the genetic material of cancer cells. It is this interaction with the DNA of cancer cells that underlies the biology of RT.

Linear Accelerator

Modern RT is manufactured by a complex machine called a linear accelerator. The basic premise of this technology is that electrons are accelerated to a frequency of 3,000 megacycles per second and then are shot at a tungsten steel target. The negatively charged electrons are then repelled by the orbiting electrons of the steel target and, as they are deflected away and change direction, they lose some energy. In the observation of Newton's laws regarding conservation of energy, the energy lost by the deflection of the electron interaction is gathered into a form, called an x-ray. The gathered x-rays (photons) are then shot out of the head of the linear accelerator into the patient. There are many beam-modifying devices (wedges, compensators, and blocks, among others) that can be placed between the accelerator and patient to conform the radiation to accomplish its goal of sparing normal tissues while targeting tumors.

Treatment Planning

In order to determine the methods and specifics by which the beam should be modified to accomplish its goals, the radiation oncologist works closely with several specialists. In fact, because of the complexity and ever-changing landscape of the field of radiation oncology, the days when the single clinician could consult a patient, set them up for treatment, calculate the physical parameters of the RT, and actually deliver the treatment are extinct. Many clinicians have been trained to operate all elements of the department, but this remains inefficient and the increasing volume of patients for whom radiation therapy is a necessary modality has relegated the clinician to consultation of the patient, delineation of the treatment target, prescription of the RT, and oversight of the various affiliated healthcare professionals responsible for the myriad of treatment responsibilities.

In today's modern department, a simulator technologist sets the patient on a fluoroscopy unit or CT simulator to determine the site to be treated. The medical dosimetrist then takes the clinician's prescription and assists in determining the most appropriate beam arrangement to accomplish the goals of therapy. The medical physicist, whose main responsibility is to ensure the machines are properly referenced and operating without any problems on a daily basis, calculates the dose delivered by the machine to coincide with the prescription without error. The radiation technologists then actually deliver the radiation therapy, closely following all set-up data provided to them by the physician, dosimetrist, and simulator technologist. The radiation technologist may also be responsible for performing ultrasounds, x-rays, or CT scans of the patient prior to each treatment fraction to ensure that the location receiving treatment is without error. The radiation oncology nursing team then evaluates the patient every few days of treatment to ensure there are no concerning side effects that require attention and they, along with the physician, initiate the appropriate clinical response. Furthermore, with the increasing realization that RT is often improved by sensitizing tumors with targeted agents and cytotoxic and cytostatic chemotherapeutics, the nurse and physician need to be more aware of potential interactions, toxicities, and tumor-response parameters than previously encountered when RT alone was delivered. Because of the evolving combined- or multimodality approach to many cancers, it is important to mention the pure biologic characteristics of tumors and normal tissues, to

appreciate how and why RT alone has become less commonly used in the definitive and curative treatment of cancer.

FUNDAMENTALS OF RADIOBIOLOGIC PRINCIPLES

There are four fundamental radiobiologic principles that are considered by a radiation oncologist when determining the course of RT to be delivered: cellular repair, repopulation, redistribution, and reoxygenation.

Cellular Repair

The ability of a cell to repair potentially lethal damage induced by RT remains one of the basic differences between malignant and normal tissues. Normal cells maintain an enhanced ability to repair RT damage, while malignant cells generally do not have that capacity. However, at a certain threshold dose of RT even normal, nonmalignant tissues lose the capacity to recover and therefore attention to dose is critically important to avoid permanent damage to uninvolved tissues. Estimates and guidelines have been published to guide clinicians on total doses, daily doses, and volumes of tissue irradiated, beyond which normal tissue toxicities will be encountered.

Cellular Repopulation

Cellular repopulation is a phenomenon often observed following the initiation of RT. The often-recited theory to explain this event is that as a percentage of cells are destroyed by RT, the remaining living cells have access to greater relative blood supply and nutrients, among other probable growth-related cytokines, resulting in greater growth of the remaining fraction of cells. Indeed, this is observed clinically in head and neck cancers, cervical cancers, and lung cancers prompting the standard that definitive RT be completed as soon as possible and without avoidable treatment breaks.

Cellular Redistribution

Cellular redistribution refers to the portion of the cell cycle within which a cell resides at a specific time. Tumors divide at varying rates and portions of the cell cycle are inherently more sensitive to antineoplastic agents. Notably, RT most effectively eradicates cells in the G2-M junction, while cells in the S1 portion of the cell cycle are relatively unresponsive. The benefits and purpose of exploiting cellular redistribution underlie the concept of fractionated RT. By dividing the RT dose daily over many weeks, there is a greater chance that RT delivery will coincide with cells in the responsive portion of the cell cycle, resulting in greater cell kill. As a corollary, cellular cytostatic agents thought to cause cellular arrest in a certain portion of the cell cycle (i.e., tamoxifen) have been theorized to potentially reduce the benefits of RT, though recent studies have demonstrated the absence of a clinical decrement.

Cellular Reoxygenation

Cellular reoxygenation remains one of the most critical elements of RT effect. The indirect ionization occurs when electromagnetic radiation (x-rays) enter target tissues and excite electrons, typically from cellular water, to free radical status. These free radicals then directly alter the tumor's DNA, inflicting a potentially lethal injury. If the damaged DNA interacts with oxygen, the damage is no longer reversible and is said to be "fixed." In vitro and clinical data clearly demonstrate that relative tissue hypoxia reduces the killing effect of RT. In many tumor sites, including cervix and head and neck, low oxygen levels or relatively low hemoglobin levels significantly reduce the benefits of RT. Further evidence that electron free radicals are the "smart bombs" formed by RT is the clinical loss of local control when antioxidants (namely, megadoses of vitamin C and E) are ingested concurrent with RT.

Clinical Radiation Oncology

Radiation is used to treat a variety of malignancies with curative intent. Radiation can be used alone, or in combination with surgery and/or chemotherapy. Often, the use of radiation in combination

with chemotherapy or surgery can be used for a strategy of reducing morbidity of therapy or improving functional outcomes. For example, the use of limited surgery and radiation to the breast has been used as an alternative to mastectomy. Similarly, the use of chemotherapy combined with radiation has been found to be a successful method to preserve the larynx in patients with advanced laryngeal tumors.

RT may also be used to palliate symptoms of advanced cancer. Malignant spinal cord compression, superior vena cava syndrome due to tumor, and airway compromise are all oncologic emergencies that may be treated with RT. Radiation may also be used to palliate symptoms of bone pain, to treat brain metastases, and to treat other symptoms caused by mass effect from tumors.

With the exception of fatigue, the side effects of radiation are dependent on the area of the body being treated. For example, alopecia and skin irritation and redness may occur in the area being treated. Patients receiving radiation to the chest may experience cough, dysphagia, and odynophagia during treatment, while patients treated to the pelvis may experience loose bowel movements or urinary frequency. Most side effects of radiation resolve within a few weeks to months after treatment is completed. Less frequently, patients may experience long-term side effects after treatment. Included in the rare late toxicities is a risk of a cancer caused by radiation in the site treated.

RADIOSENSITIZATION

Sensitization refers to the increased clinical response of a tumor to a combination of any agent delivered concurrently with RT. Almost every cytotoxic systemic agent has the ability to sensitize tumors to RT. Many targeted and biologic drugs also have this ability, especially if they inhibit DNA repair or pathways associated with survival after radiation (such as EGFR) are inhibited. Most potent in their ability to sensitize are the anthracyclines and platinum agents, though the newer taxanes and gemcitabine have clearly demonstrated an ability to increase both tumor and normal tissue response to RT. The mechanism behind chemotherapy-induced cellular sensitization to RT appears to be a result of the incorporation of halogenated pyrimidines into the tumor's DNA. The new analog weakens and damages the DNA, rendering it incapable of repairing RT-induced injury. Experiments have shown that only several generations of substitutions can inflict this type of DNA injury; thus the most effective sensitization occurs when the systemic agent is delivered concurrently with RT, or for several cycles prior to the RT. Because of the increased normal tissue effect of concurrent therapies, they are considered only when a significant survival benefit has been proven in randomized trials. Combined modality therapy is currently the accepted standard for patients with a range of malignancies, such as cervical cancer, advanced head and neck cancer, glioblastoma, and gastrointestinal malignancies. For other cancers, such as breast cancer, RT is typically given without concurrent chemotherapy.

INTENSITY-MODULATED RADIOTHERAPY

Intensity-modulated radiotherapy (IMRT) refers to any technology wherein dose is modified to differentially treat target tumor and uninvolved normal tissues. Several different techniques are currently in use to accomplish IMRT, including customized brass-based tissue compensators and multileaf collimation, the latter of which is used in a dose delivery system that is either dynamic or static. The dynamic system arcs around the patient, delivering different beamlets from each beam's-eye view of the tumor, accomplishing this dose delivery from an almost limitless number of angles. The static systems aim and shoot x-rays from each angle and then the machine stops and rotates before targeting the tumor from a new angle; this dose delivery is usually accomplished from four to eight different angles. IMRT allows the delivery of radiation in a more conformal nature than was provided by other techniques used previously, thereby sparing normal tissues from higher doses.

STEREOTACTIC THERAPIES

New techniques have been developed to increase the conformality of treatment with the goals of minimizing the amount of tissue receiving high doses of irradiation and allowing delivery of larger fractional doses. An example is stereotactic radiation which is usually accomplished by immobilizing the patient with specialized equipment that provides a high degree of accuracy and precision. This allows treatments to be delivered to a smaller area since less margin for patient movement is given. Often, these treatments are given in one to five large fractions instead of the typical daily fractionation used for conventional treatments. These treatments can be used for tumors in many locations, including the brain and are also commonly used for patients with oligometastatic disease.

PARTIAL-BREAST IRRADIATION

Partial-breast irradiation (PBI) refers to any technique used to irradiate a portion of the breast. The most commonly used technique includes intracavitary methods (Mammosite, Contura, Savi), wherein a balloon with one to eight catheters jointly housed are postoperatively placed within the surgical tumor bed. High-dose–rate brachytherapy is then delivered remotely and directly to the tumor bed, typically twice daily for 1 week. A prospective phase 3 Intergroup trial comparing PBI to standard whole-breast RT is currently accruing patients to determine whether PBI is equal. Other forms of PBI include three-dimensional conformal RT (using external beam RT directed at the tumor bed with a noncoplanar beam arrangement of generally three to four beams), intraoperative electron beam teletherapy (mostly used in Europe where the exposed tumor bed is irradiated with a single high-dose beam), and low- or high-dose rate interstitial brachytherapy (where intraoperative catheters are placed within and surrounding the tumor bed cavity). Interstitial brachytherapy has the longest experience of PBI, though the operating room time, potential need for an inpatient admission, and risk of developing a pneumothorax has made this technique less favorable for patient and clinician.

PROTONS

The most commonly used form of electromagnetic radiation in the field of radiation oncology is photons, or x-rays. These particles are uncharged and their energy slowly dissipates when they enter the body. Depending upon the location of the tumor and the angle or beam perspective, other uninvolved structures receive radiation and this leads to side effects. Most photon beams require between 1 and 1.5 cm of normal tissue to traverse before enough dose has built up to achieve maximum dose effect, and the dose then regresses over a 2 to 5 cm length of tissue beyond the target tumor.

Protons are charged particles with very different physical characteristics than x-rays or photons. Protons enter the body at a very low energy level and can rapidly escalate to maximum energy over a few millimeters, deep within the body. This effect, called a Bragg peak, allows the length over which maximum dose is delivered to be minimized and thus less normal tissue receives a high dose. Protons have been shown to be effective when tumors are closely situated adjacent to critical structures, where any considerable radiation dose could be devastating, such as the spinal cord, brain, retina, or developing tissues in a child.

Because of the extraordinary expense associated with the creation of protons, their use has been limited to very few malignancies and few centers have maintained any degree of expertise with their use. Because of increasing pressure to maximize economic advantages, however, more centers have recently begun to develop their own proton beam facilities and the use of this special particle beam has started to evolve, with the more common prostate and lung cancers now being treated. Much data have been generated comparing the normal tissue dosing and side effects of protons, but direct randomized comparisons with other types of RT delivery in regard to side effects and outcomes are not available.

REVIEW QUESTIONS

A 43-year-old woman is diagnosed with breast cancer. She was found to have disease amenable to breast conservation, in which she will receive lumpectomy and radiation. It is felt that she will require chemotherapy based on the tumor characteristics.

1. Which type of radiation is NOT appropriate for delivering treatment as part of breast-conserving therapy for breast cancer patients?
   - **A.** Brachytherapy
   - **B.** Whole-breast RT
   - **C.** Radionuclide therapy
   - **D.** PBI
2. The patient undergoes RT to the breast. She can expect which of the following side effects?
   - **A.** Nausea
   - **B.** Skin redness on the breast
   - **C.** Alopecia
   - **D.** Urinary frequency
3. Dividing radiation treatment into several doses or fractions is used for which reason?
   - **A.** To decrease oxygen delivery to tumors
   - **B.** To increase the likelihood of damaging tumor cells in a sensitive phase of the cell cycle
   - **C.** To increase the number of DNA single-strand breaks in tumor cells
   - **D.** To decrease the vasculature of tumors
4. The lethality of radiation to tumors occurs primarily through interactions with which cellular components?
   - **A.** Carbohydrates
   - **B.** Exosomes
   - **C.** Lipid bilayer
   - **D.** DNA
5. IMRT is used to treat the patient with breast cancer. Which of the following is a benefit of using IMRT compared to other external beam radiation approaches?
   - **A.** More damage to DNA
   - **B.** More conformal treatment
   - **C.** Higher dose given to the tumor
   - **D.** Shorter overall treatment time

Suggested Readings

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Clinical Genetics

Julie Nangia, Annie Su, and Sarah Zentack

Clinical genetics is the specialty that involves the diagnosis and management of hereditary disorders. As an oncologist, recognition of these syndromes is critical in order to provide proper care related to cancer therapy decisions, to increase screening that could detect cancer at early stages (which are more often cured), to identify unaffected family members, and to offer chemoprevention or risk-reducing prophylactic surgeries if indicated. Features of hereditary cancer include the following in an individual patient: multiple primary tumors in the same or different organs, bilateral primary tumors in paired organs, multifocal cancer within a single organ, younger-than-usual age at diagnosis, tumors with rare histology, tumors occurring in the sex not usually affected (i.e., breast cancer in men), and a constellation of tumors associated with a known genetic syndrome.

If a hereditary cancer syndrome is suspected (Table 45.1), a focused exam specific to the syndrome should be done (i.e., dermatologic and head circumference for Cowden syndrome) and genetic counseling with an expanded pedigree detailing the types of cancer, bilaterality, age at diagnosis, and medical record documentation as needed (i.e., pathology reports of primary cancers or carcinogen exposure) should be offered to the patient. 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. Options exist for family planning including prenatal diagnosis and assisted reproduction. Patients should be made aware of the Genetic Information Nondiscrimination Act of 2008 (GINA), which prohibits the use of genetic information in health insurance and employment but unfortunately does not apply to life insurance coverage.

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 mutations in the *BRCA1/2* genes, tumor suppressor genes that play a role in DNA repair. These mutations account for 65% of hereditary breast cancer and have an autosomal dominant pattern of inheritance. The incidence is 1 in 700 for the general population and 1 in 40 in the Ashkenazi Jewish population.

Mutations in these genes are associated with a very high risk of both breast cancer (up to 87%) and ovarian cancer (up to 44%). The *BRCA1* gene is associated with triple-negative breast cancer histology

Table 45.1 Hereditary Cancer Syndromes

Syndrome	Gene	Associated Cancers/Tumors
Birt Hogg Dube	*FLCN*	RCC
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	Breast, ovarian, prostate, pancreatic, melanoma
Cowden syndrome	*PTEN*, *SDH*	Breast, endometrial, thyroid, kidney, melanoma, and colorectal
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
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric cancer, lobular breast cancer
Hereditary leiomyomatosis	*FH*	Type 2 papillary RCC
Hereditary melanoma	*p16*	Melanoma, pancreas
Li–Fraumeni syndrome	*p53*	Breast, sarcoma, leukemia, brain tumors, adrenocorticoid, lung bronchoalveolar
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Colon, endometrial, ovarian, gastric, small bowel, biliary, pancreatic, upper urinary tract, skin, brain
MEN1	*MEN1*	Parathyroid, pituitary, pancreatic, or extrapancreatic
MEN2A	*RET*	Medullary thyroid, pheochromocytoma, parathyroid
MEN2B	*RET*	Medullary thyroid, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas
MUTYH-associated polyposis	*MUTYH*	Similar to FAP above
NBCCS	*PTCH*	Basal cell, medulloblastoma
Peutz–Jeghers syndrome	*STK11*	Colon/rectum, breast, stomach, small bowel, pancreas, lung, cervix, ovaries, testicles
Von Hippel–Lindau disease	*VHL*	Clear cell RCC, pheochromocytomas, neuroendocrine

and both genes are associated with ovarian cancer of epithelial origin, often serous histology. Other cancers such as pancreatic cancer, prostate cancer, and melanoma can also be seen, particularly in patients with *BRCA2* gene mutations. *BRCA1/2* testing is recommended in individuals:

- From a family with a known deleterious *BRCA1/2* mutation
- With a personal history of breast cancer and one of the following:
  - Diagnosed below the age of 45
  - Diagnosed below the age of 50 with 1 or more close blood relative with breast cancer younger than 50 and/or 1 or more blood relative with epithelial ovarian cancer at any age
  - Two breast primaries when the first breast cancer diagnosis occurred at less than 50 years of age
  - Diagnosed below the age of 60 with triple-negative breast cancer
  - Diagnosed below the age of 50 with limited family history
  - Diagnosed at any age with 2 or more close blood relatives (first-, second-, or third-degree relatives) with breast and/or epithelial ovarian cancer at any age
  - Diagnosed at any age with two or more close blood relatives with pancreatic cancer at any age
  - Close male blood relative with breast cancer
  - Individuals of ethnicity associated with higher mutation frequency (i.e., Ashkenazi Jewish)
- With a personal history of epithelial ovarian cancer
- With a personal history of male breast cancer
- With a personal history of pancreatic cancer at any age with two or more close blood relatives with breast and/or ovarian and/or pancreatic cancer at any age

Testing of unaffected individuals should only be considered when no affected family member is available and family history reveals a first- or second-degree relative meeting the above criteria. In this circumstance, the significant limitations of interpreting results should be discussed since a negative test result in an unaffected individual can be uninformative. Testing consists of full sequencing of the *BRCA1/2* genes as well as BART testing (*BRCA* analysis rearrangement test), which identifies large genomic rearrangements not picked up by routine sequencing.

If a *BRCA* mutation is found, the following recommendations should be implemented for women: breast self-examination training and education starting at age 18, clinical breast examination every 6 to 12 months starting at age 25, and annual mammography and MRI screening starting at age 25 or individualized based on earliest age of onset in the family. The addition of breast MRI to mammography increased the rate of breast cancer detection from 45% to 95% in one study, and most cancers were detected at stage 0 or 1. Prophylactic mastectomy can reduce the risk of breast cancer by 90% to 100%, and in those who decline surgery, chemoprevention with tamoxifen or raloxifene has been shown to reduce the risk of breast cancer by at least 50% and is a reasonable alternative along with close monitoring. Given the elevated risk for ovarian cancer and the lack of effective screening, risk-reducing salphingo-oopherectomy (RRSO) is recommended between the ages of 35 to 40, or upon completion of childbearing. Until then, a CA125 level and a transvaginal ultrasound should be considered every 6 months starting at age 30 or 5 to 10 years prior to the earliest age of diagnosis of ovarian cancer in the family.

For men, the risk of breast cancer is 2% to 8% and is usually seen after age 50. Breast self-examinations should start at the age of 35 and baseline mammography can be considered at the age of 40 and continued only if gynecomastia or parenchymal/glandular breast density is present. Chemoprevention and prophylactic mastectomies are not offered to men because the incidence of breast cancer is not nearly as high as in women. Male carriers also have a higher risk for both prostate and pancreatic cancer than the general population. Prostate cancer screening should start at age 40 with a baseline digital rectal examination (DRE) and PSA level and repeated per the NCCN guidelines which can be reviewed separately.

For both men and women, annual skin examinations are recommended given the increased risk of melanoma, and the general population screening guidelines for colon cancer prevention should be followed. For pancreatic cancer prevention, alcohol and tobacco use should be avoided. Screening can be offered to individuals with a strong family history with either EUS or MRI every 1 to 3 years and an annual CA 19-9 level. Studies looking at pancreatic cancer screening are limited and the utility of screening is not completely known.

Cowden Syndrome

Cowden syndrome is an autosomal dominant syndrome with an incidence of 1 in 200,000. It is caused by a loss of function in the tumor suppressor *PTEN* gene and is associated with multiple hamartomas in a variety of tissues, characteristic dermatologic manifestations, and an increased risk of breast, endometrial, thyroid, kidney, melanoma, and colorectal cancers. The lifetime risk of breast cancer is 25% to 50%, although it may be as high as 85%. Thyroid cancer develops in two-third of carriers and can occur in childhood. Pathology is usually follicular, rarely papillary, and never medullary. Renal cell carcinoma (RCC) can be seen in 13% to 34% of carriers. The prevalence of colon polyps is 66% to 93% and they are usually hamartomatous or inflammatory polyps with a lifetime risk of 16% for colon cancer. Neurologic manifestations include dysplastic gangliocytoma of the cerebellar cortex, macrocephaly, and mental retardation/developmental delay/autism. Women commonly have benign abnormalities such as breast hamartomas, uterine fibroids, and ovarian cysts. Men often have lipomatosis of the testes seen as hyperechoic lesions on testicular ultrasound. Both men and women frequently have benign thyroid lesions, such as adenomas and multinodular goiter. Benign esophageal acanthosis can also be seen.

The diagnostic criteria are divided into pathognomic criteria, major criteria, and minor criteria. The pathognomic criteria include mucocutaneous lesions such as facial trichilemmomas (skin tags), acral keratoses (thickened area of skin that may be red, yellow, or brown), or pappilomatous oral lesions (small wart-like growths). The major criteria include breast cancer, thyroid cancer, macrocephaly, endometrial cancer, and dysplastic gangliocytoma of the cerebellar cortex. The minor criteria include benign structural thyroid disease, mental retardation, hamartomatous gastrointestinal (GI) tract polyps, benign cystic breast disease, lipomas or fibromas, and genitourinary tract tumors. Both the NCCN and the International Consortium Cowden Consortium have criteria for testing high-risk individuals and guidelines for the care of carriers. In the absence of family history, Cowden syndrome is diagnosed if any of the following are present: six or more facial papules including at least three trichilemmomas, facial papules and oral pappilomatous, oral pappilomatous and acral keratoses, or six of more acral keratoses on the hands and feet. One major and three minor or four minor criteria are also considered diagnostic. If there is a family history of Cowden syndrome, then one pathognomonic, one major, or two minor criteria are diagnostic. Only 20% to 34% of individuals who meet these criteria have germline *PTEN* mutations. *PTEN* testing includes sequencing of the entire coding region and deletion/duplication analysis. Mutations have also been reported in the *PTEN* promoter region and in other genes including succinate dehydrogenase (SDH) subunits B and D.

The management guidelines for women with Cowden syndrome include breast self-examination training and education starting at age 18, clinical breast examination every 6 to 12 months starting at age 25, and annual mammography and MRI screening starting at age 25 or individualized based on earliest age of onset in family. There are no specific guidelines for endometrial cancer screening and carriers should be educated and followed closely, with a prompt response to symptoms. Risk-reducing mastectomies and hysterectomy can be considered. Men and women should have an annual physical examination starting at age 18 or 5 years prior to the youngest age of diagnosis of cancer in their family with emphasis on the breast and thyroid examination. Baseline thyroid ultrasound should be done at age 18 and annually after that. Screening colonoscopies starting at age 35, annual dermatologic examinations, and education about the signs and symptoms of cancer can be considered.

Li–Fraumeni Syndrome

Li–Fraumeni syndrome (LFS) is a hereditary syndrome associated with a wide range of cancers that appear at an unusually young age. It has an autosomal dominant pattern of inheritance and is associated with mutations in the *p53* tumor suppressor gene, which plays a major role in DNA repair. The absence of this gene allows for the survival and proliferation of cells with damaged DNA. The lifetime risk of cancer is nearly 100%, with 90% of individuals diagnosed with cancer by age 60. 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 sarcoma before the age of 45, a first-degree relative with cancer before the age of 45, and a first- or second-degree relative with cancer before the age of 45 or sarcoma at any age. Chompret criteria include one of the following:

- A proband who has a tumor belonging to the LFS spectrum (sarcoma, premenopausal breast cancer, brain tumor, adrenocorticoid tumor, leukemia, or lung bronchoalveloar cancer) before age 46 *and* at least one first- or second-degree relative with a tumor in the LFS spectrum before age 56 or with multiple 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 age 46.
- A proband who is diagnosed with adrenocortical tumor or choroid plexus tumor regardless of age irrespective of family history.

Testing of individuals who meet either of these criteria or women with breast cancer before age 35 who have tested negative for the *BRCA1/2* mutations is recommended.

The management guidelines for women with LFS include breast self-examination training and education starting at age 18, clinical breast examination every 6 to 12 months starting at age 25, and annual mammography and MRI screening starting at age 25 or individualized based on earliest age of onset in family. All carriers should have an annual physical examination including skin and neurologic examinations. Radiation therapy should be avoided if possible (i.e., mastectomy instead of lumpectomy for breast cancer) due to the increased risk of radiation-induced malignancies. Colonoscopy screening should start no later than age 25. Other options for screening should be discussed with the patient such as whole-body MRI, abdominal ultrasound, and brain MRI. Targeted surveillance should be based on family history.

HEREDITARY GI SYNDROMES

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder characterized by germline mutations in DNA mismatch repair (MMR) genes. The absence of these genes results in a significantly increased risk of cancer formation of up to 80%, with the most common carcinomas located in the colon, rectum, and uterus.

Lynch syndrome accounts for 2% to 3% of all colon cancers with a lifetime risk of up to 70%. Compared to those with sporadic colon cancer, HNPCC patients are usually younger in age (45 vs. 65 years old) and have more poorly differentiated, mucinous tumors found in the right colon. Despite these more aggressive histologic features, affected patients have better 5-year survival rates compared to those with common sporadic colorectal cancer, likely due to the lower risk of metastases. Though uncommon, a small subset (10%) of HNPCC patients will have synchronous (two primary tumors) or metachronous (second tumor developing at least 6 months after the first) cancers.

Endometrial carcinoma is the most common extracolonic tumor in Lynch syndrome, accounting for about 2% of all uterine cancer and with a reported incidence as high as 70% in female carriers. Similar to colon cancer in Lynch syndrome, women are typically younger in age at diagnosis (50 vs. 60 years old). Other sites at increased risk of cancer development include the ovaries, stomach, small bowel, pancreas, hepatobiliary system, upper urinary tract (renal pelvis and ureter), skin, and brain. The chances of developing cancer in these various organs vary depending on which gene is mutated, but the incidence can be as high as 20%.

Defects in the MMR system, which identifies base-pair mismatches and repairs them, is 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 is not a MMR gene, inactivates *MSH2* and also causes Lynch syndrome. In Lynch syndrome, a germline mutation results in a defective allele and is passed from parent to offspring. When the second copy is inactivated through one of several mechanisms (acquired somatic mutation, loss of heterozygosity, promoter hypermethylation), a defective MMR system ensues, resulting in a failure to repair DNA mismatches and an increased rate of mutations (genomic instability). DNA mismatches tend to occur in areas of repeated nucleotide sequences called microsatellites. An accumulation of mutations in these regions leads to expansion or contraction of the microsatellites, termed microsatellite instability. This addition or deletion of nucleotides leads to a change in the DNA reading frame during RNA synthesis, eventually resulting in the substitution of

different amino acids into the end protein product or early termination of protein synthesis. Carcinogenesis occurs when a cancer-related gene or protein (i.e., one that regulates cell growth or apoptosis) is affected by these frameshift mutations.

Germline mutations in one of the four MMR genes or *EPCAM* can lead to the development of Lynch syndrome, although the clinical picture varies depending on which gene is affected. The most common mutations involve *MLH1* and *MSH2*. Both genes result in a markedly increased risk of colorectal carcinoma (up to 70%); however in some studies, the risk of extracolonic cancers including endometrial carcinoma is higher in families with *MSH2* mutations. Patients with *MSH6* mutations have a lower risk and a later age of onset of colorectal cancer as well as a higher risk of endometrial cancer compared to those with *MLH1* and *MSH2* mutations. Families with *PMS2* mutations have an even more attenuated phenotype with a lower overall cancer risk. Biallelic inheritance of mutations in one of these MMR genes causes constitutional mismatch repair-deficiency syndrome (CMMRD) and is associated with the development of Lynch syndrome-associated cancers, as well as childhood cancers, hematologic malignancies, brain tumors, early-onset colorectal cancers, and neurofibromatosis features such as café-au-lait spots.

Patients suspected to have Lynch syndrome can be screened through the detection of either microsatellite instability by polymerase chain reaction (PCR) or the absence of the MMR protein product by immunohistochemistry (IHC). PCR detects microsatellite instability by identifying expansion or contraction of the microsatellite regions. If 30% or more of the markers show instability, then the tumor is considered to have high levels of microsatellite instability (i.e., MSI-H or microsatellite unstable), suggesting a defect in a DNA MMR gene. Patients with low levels of microsatellite instability (i.e., MSI-L or microsatellite stable) are unlikely to carry this genetic defect. IHC uses antibodies to detect MMR proteins. These antibodies specifically recognize the C-terminal end of the MMR protein. The loss of this epitope due to mutations in the MMR gene causing either a truncated or lost protein product results in a negative test. Unlike PCR, IHC has the advantage of identifying the missing protein product, and by proxy, which gene is affected. Confirmation of Lynch syndrome requires germline testing for the MMR gene mutation as guided by the results of IHC.

Microsatellite instability is sensitive but not specific for Lynch syndrome. MSI-H can be found in up to 15% of sporadic colorectal cancers, most commonly due to the loss of *MLH1* via epigenetic silencing from hypermethylation of the *MLH1* promoter region. Acquired loss of *MLH1* can be differentiated from germline mutations of *MLH1* as seen in Lynch syndrome through the presence of *BRAF* mutations. For unknown reasons, *BRAF* mutations are almost universally present in sporadic colorectal cancers but rarely seen in Lynch syndrome. In patients who have microsatellite unstable colorectal tumors with loss of *MLH1* on IHC, testing for *BRAF* mutations or *MLH1* methylation should be done to rule out sporadic cases. If these tests are negative, then patients should be offered germline testing. The loss of other MMR genes in colorectal cancer, primarily *MSH2* and *MSH6*, is more specific for Lynch syndrome and these patients should proceed directly to MMR gene testing and genetic counseling.

Identifying patients who are at high risk for having Lynch syndrome remains a challenging task. The Amsterdam criteria and the Bethesda guidelines were created to help identify families at risk; however, the Amsterdam criteria lack sensitivity and both lack specificity. As many as 50% of families who meet the Amsterdam criteria, and 80% of patients meeting the Bethesda guidelines, do not have Lynch syndrome. Nonetheless, families meeting these criteria should be offered genetic counseling, and testing should be done on the youngest living member with colorectal cancer.

Amsterdam criteria—3–2–1 rule (three affected members, two generations, one under age 50)

- Three or more relatives with an HNPCC-associated cancer, one of whom is a first-degree relative of the other two and in whom FAP has been excluded
- Two affected generations
- One or more HNPCC-associated cancer diagnosed before the age of 50

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, 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
- A patient with colorectal cancer who has two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Colorectal cancer surveillance with colonoscopies should begin at the age of 20 to 25. Screening for endometrial cancer with endometrial biopsy and ovarian cancer with transvaginal ultrasound and a CA125 level should begin at the age of 30 to 35 years, or 10 years prior to the earliest age of cancer diagnosis in the family, whichever comes first. Controversy exists surrounding the screening of other extracolonic cancers and no firm recommendations have been established except for annual skin surveillance. Primary prophylactic colectomy is generally not recommended. Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be considered in high-risk patients who are 35 years or older or have finished childbearing.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the presence of numerous colorectal adenomatous polyps (typically more than 100), caused by germline mutations in the tumor suppressor adenomatous polyposis coli (*APC*) gene located on chromosome 5. FAP has a number of associated extracolonic carcinomas, but unlike colorectal cancer which has near complete penetrance, the penetrance for extracolonic tumors is variable.

FAP accounts for less than 1% of all colorectal cancer diagnosed in the United States. Seventy-five percent of FAP cases are due to inherited germline mutations of the *APC* gene, whereas 25% of patients acquire new or de novo mutations and have no family history of FAP. Inactivating mutations of both copies of the *APC* gene is required for the development of adenomas and, subsequently, carcinoma. In normal circumstances, APC is involved in the phosphorylation of β-catenin resulting in its degradation by proteolysis. In the absence of APC, β-catenin accumulates within the cell and activates several genes involved in cell growth and division.

Two variants of FAP have been described—classic FAP and attenuated FAP (AFAP). Patients with classic FAP typically have more than 100 adenomatous polyps, often 1,000s, with a nearly 100% risk of developing colorectal carcinoma if left untreated. On the other hand, AFAP patients have fewer adenomas (between 10 and 100) and present at a later age (44 vs. 16 years of age) than those with the classic phenotype. A lower yet still significant risk of colorectal cancer development is seen (up to 80%) with a later age of cancer diagnosis (56 vs. 40 years of age) and a predilection for the right colon (up to 75%).

Although FAP is more infamously known for its risk of colorectal cancer, patients also have an elevated risk of developing extracolonic polyps as well. These polyps can be found in the gastric fundus (i.e., body of the stomach), gastric antrum, duodenum, periampullary region, gallbladder, bile duct, and the small bowel. Risk of cancer progression depends on the location of the polyps, with the highest risk seen in the duodenum and periampullary region.

Extraintestinal manifestations, both malignant and benign, are also seen in families with FAP. Malignant extraintestinal tumors are rare (1% to 3% lifetime risk) and include follicular or papillary thyroid 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 refers to the association of familial colon cancer with CNS tumors, primarily medulloblastomas in FAP and gliomas in Lynch syndrome. No single gene mutation is characteristic of Turcot syndrome. Gardner syndrome refers to families with FAP who also have osteomas and soft tissue tumors. The *APC* gene is the same culprit in both Gardner syndrome and FAP.

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 as well as all first-degree relatives of affected patients. Commercial genetic testing detects most mutations in the *APC* gene. A negative test in the setting of high clinical suspicion does not rule out the diagnosis as there are other genes that can cause polyposis and all at-risk patients should undergo surveillance regardless of the

results. Testing for *MUTYH*-associated polyposis which is a recessive syndrome caused by mutation in the *MUTYH* gene should also be considered in those who test negative for a mutation in the *APC* gene.

Surveillance of the colon involves either flexible sigmoidoscopy or full colonoscopy depending on the FAP subtype. Patients with classic FAP typically have rectosigmoid involvement; therefore, flexible sigmoidoscopy alone should be sufficient. AFAP patients, on the other hand, more commonly develop tumors in the right colon and should proceed directly to full colonoscopies. Screening should start no earlier than age 10 in families with classic FAP and age 20 to 25 with attenuated phenotypes given the later age of initial polyp presentation and cancer diagnosis. Patients found to have profuse polyposis, multiple large (>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. Screening for extracolonic cancers remains controversial. No consensus guidelines have been firmly established and data has yet to show a clear benefit for routine surveillance.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer is an autosomal dominant disorder caused by germline mutations in the *CDH1* gene that codes for E-cadherin, a cell-adhesion protein that allows cells to interact with each other and is critical for cell development, differentiation, and architecture. Individuals who harbor these germline mutations have a greater than 80% lifetime risk of developing diffuse gastric cancer by age 80 with a median age of onset of 38. These gastric cancers form beneath an intact mucosal surface, causing gastric wall thickening rather than the formation of a discrete mass. Because they are only visible late in the disease process, early detection is extremely challenging. Therefore, screening of high-risk individuals should begin at the age of 16 to 18, and in those who are found to be carriers, prophylactic gastrectomy is recommended after the age of 20.

Like diffuse gastric cancer, the absence of E-cadherin expression is also the key underlying defect in lobular breast carcinoma. Female carriers therefore have a 60% lifetime risk of developing lobular breast carcinoma by age 80. Optimal breast cancer screening has not been clearly established.

The International Gastric Cancer Linkage Consortium (IGCLC) clinical criteria are as follows:

- Two cases of gastric cancer in first-degree relatives, with one confirmed diffuse gastric cancer case diagnosed before the age of 50
- Three confirmed diffuse gastric cancer cases in first- or second-degree relatives, independent of age
- Diffuse gastric cancer before the age of 40 years without a family history
- Families with both diffuse gastric cancer and lobular breast cancer, with one diagnosed before the age of 50 years

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is a rare, autosomal dominant disorder characterized by multiple GI hamartomatous polyps, mucocutaneous pigmentation, and an increased risk of malignancies. Diagnosis is made clinically but the detection of *STK11* gene mutations can help solidify the diagnosis. A negative genetic test however does not exclude the diagnosis since up to 20% of patients with a clinical diagnosis of PJS do not have identifiable mutations. Diagnosis requires any one of the following:

- Two or more histologically confirmed PJ polyps
- PJ polyps and a family history of PJS
- Characteristic mucocutaneous pigmentation and a family history of PJS
- PJ polyps in an individual with characteristic mucocutaneous pigmentation

Skin lesions seen in PJS resemble freckles. They are small (1 to 5 mm in size), flat, blue-gray to brown spots, and are commonly found around the mouth and nose, in the buccal mucosa, hands and feet, perianal areas and genitals. Malignant transformation is rare. GI polyps frequently occur in the small intestine, colon/rectum, and stomach. They can be found as early as the first decade of life but cause problems later, between the ages of 10 and 30. About half of PJS patients present with obstruction from intussusception, abdominal pain, and bleeding, while the other half are asymptomatic and diagnosed

based on family history. 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 an increased risk is also seen in the breast, stomach, small bowel, pancreas, lung, cervix, ovaries, and testicles.

OTHER GENETIC SYNDROMES

Von Hippel–Lindau Disease

Von Hippel–Lindau disease is an autosomal dominant disorder involving germline mutations of the *VHL* gene found on chromosome 3. A variety of benign and malignant conditions are associated with VHL disease, including hemangioblastomas of the CNS (cerebellum and spine) and retina, clear cell RCCs, pheochromocytomas, pancreatic cysts and neuroendocrine tumors, endolymphatic sac tumors of the middle ear, and epididymal and broad ligament cysts. Unlike sporadic cases, VHL-associated tumors tend to occur in younger patients (mean age of initial presentation of 26 years) and are more often multifocal and bilateral in nature. Diagnosis of VHL disease is based on the detection of germline mutations in the *VHL* gene in patients with one or more VHL-associated tumors.

Multiple Endocrine Neoplasia 1 and 2

Multiple endocrine neoplasia (MEN) syndromes are rare with an incidence of 1 in 30,000. MEN1 occurs when tumors are found in two of the three main endocrine glands (parathyroid, pituitary, and pacreatico-duodenum). Nearly 100% of individuals with MEN1 will have primary hyperparathyroidism by age 50, 10% to 20% will have pituitary tumors (prolactinoma, growth hormone-secreting, corticotrophin-secreting, or nonhormone secreting), and 60% to 70% will have pancreatic or extrapancreatic tumors (gastrinoma, insulinoma, vasoactive-intestinal polypeptide-secreting, glucagonoma, pancreatic polypeptide-secreting, or nonhormone secreting).

MEN2 is subdivided into three distinct subtypes: MEN2A, MEN2B, and familial medullary thyroid cancer. The genetic defect in these disorders involves the *RET* proto-oncogene on chromosome 10. MEN2A is characterized by >90% of individuals having medullary thyroid cancer, 40% to 50% with pheochromocytoma, 10% to 20% with parathyroid hyperplasia, and cutaneous lichen amyloidosis. MEN2B is characterized by medullary thyroid cancer, pheochromocytomas, and other features such as mucosal neuromas, intestinal ganglioneuromas, and marfanois habitus. There is also a variant of MEN2A characterized by familial medullary thyroid cancer. DNA testing for the *MEN1* and *RET* genes is available commercially.

Hereditary Pheochromocytoma/Paraganglioma Syndrome

Pheochromocytomas and paragangliomas are a component of an inherited syndrome in 10% to 50% of cases. Tumors are commonly seen in the head and neck region but can be seen in the thorax, abdomen/pelvis, or urinary bladder. They are often associated with mutations in the SDH subunits (D, B, and C have all been described). Individuals diagnosed with a pheochromocytoma or paraganglioma should be evaluated for a hereditary syndrome.

Dermatologic Syndromes

Approximately 10% of melanomas are hereditary and can be linked to several genes, most commonly the *p16* gene. Genetic testing should be considered in individuals with melanoma who have a family history of melanoma and/or pancreatic cancer, multiple primary melanomas, and young age at diagnosis.

Nevoid basal cell carcinoma syndrome (NBCCS) also known as Gorlin syndrome is a rare multisystem disorder due to mutations in the *PTCH* gene with an incidence of 1 in 57,000 to 164,000 and autosomal dominant pattern of inheritance. Affected individuals have multiple developmental abnormalities, early onset of multiple nevoid basal cell carcinomas (BCC), and a variety of other cysts and tumors including medulloblastomas by age 35. Radiation should be avoided in these individuals as it can induce the formation of several aggressive BCCs.

Renal Syndromes

There are several hereditary RCC syndromes. Hereditary leiomyomatosis has an autosomal dominant pattern of inheritance and is caused by mutations in the fumarate hydratase (*FH*) gene; it is associated with both cutaneous and uterine leiomyomatosis and papillary type 2 RCC. Birt Hogg Dube syndrome has an autosomal dominant pattern of inheritance and is caused by mutations in the folliculin gene (*FLCN*); it is associated with the development of RCC, pulmonary cysts often causing pneumothorax, and skin lesions such as fibrofolliculomas. Familial papillary renal cancer has an autosomal dominant pattern of inheritance caused by mutations in the *MET* gene and is associated with the development of type 1 papillary RCC which are often multifocal or bilateral.

Fanconi Anemia

Fanconi anemia (FA) is an autosomal recessive disorder with an incidence of 1 in 350,000 characterized by congenital abnormalities (café-au-lait spots, short stature, abnormality of thumbs, microcephaly or hydrocephaly, hypogonadism and developmental delay), progressive bone marrow failure, and an increased incidence of malignancies. Patients are usually diagnosed in childhood, but it is important to recognize the syndrome in adults who present with solid malignancies since this would affect therapy decisions (i.e., avoiding radiation and chemotherapy if possible).

REVIEW QUESTIONS

1. A 28-year-old woman is diagnosed with a small triple-negative breast cancer. There is no family history of breast cancer. Her father was an only child and is healthy. What genetic testing do you recommend initially?
   - **A.** None—there is not family history of cancer
   - **B.** *BRCA1/2* sequencing including BART
   - **C.** *p53* testing
   - **D.** *PTEN* testing
   - **E.** *STK11* testing
2. Which of the following is NOT in the Chompert tumor spectrum for LFS?
   - **A.** Breast cancer
   - **B.** Sarcoma
   - **C.** Leukemia
   - **D.** Colon cancer
   - **E.** Brain tumors
3. Which of the following cancers is NOT seen with Cowden syndrome?
   - **A.** Breast
   - **B.** Lung cancer
   - **C.** Endometrial
   - **D.** Thyroid
   - **E.** Kidney
4. A 45-year-old male comes to you for a second opinion. He was diagnosed with colon cancer a month ago after presenting with fatigue, dyspnea on exertion, and right upper quadrant abdominal pain. Colonoscopy revealed a large nonobstructing tumor at the hepatic flexure and biopsy showed a poorly differentiated, mucinous-producing colon adenocarcinoma. Staging studies showed local extension into the liver capsule but no intrahepatic lesions or widespread metastatic disease was seen. His family history is significant for a mother diagnosed with uterine carcinoma at the age of 47, a maternal aunt with ovarian cancer diagnosed in her 50s, and her daughter who was recently found to have a brain tumor. His maternal grandfather died when the patient was

(*continued*)

very young from what he thinks was either stomach or pancreatic cancer. What gene mutation does this patient likely harbor?

A. Germline mutation of the *APC* gene on chromosome 5
B. Somatic mutation of the *CDH1* gene and subsequent loss of E-cadherin
C. Germline mutation of *MSH2*
D. Germline *STK11* gene mutation

5. A surgeon refers a 30-year-old patient to you for preoperative clearance. The patient was found to have a hemangioblastoma of the cervical spine causing progressively worsening radiculopathy and weakness of her right arm. She has hypertension for which she takes amlodipine and family history is significant for kidney cancer and a "slow-growing" tumor in the pancreas on her father's side. Before the patient undergoes surgery to resect the hemangioblastoma, what condition must be ruled out first?

A. Metastatic breast cancer with leptomeningeal spread
B. Pheochromocytoma
C. Malignant melanoma
D. Pancreatic adenocarcinoma with liver metastases

Suggested Readings

1. GeneReview. http://www.ncbi.nlm.nih.gov/books/NBK1116/
2. National Center for Biotechnology Information. *Gene Tests*. http://www.ncbi.nlm.nih.gov/sites/GeneTests
3. NCCN Clinical Practice Guidelines in Oncology. *Colorectal Cancer Screening*. Version 2.2012. http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
4. NCCN Clinical Practice Guidelines in Oncology. *Genetic/Familial High-Risk Assessment: Breast and Ovarian*. Version 1.2012. http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
5. NCCN Clinical Practice Guidelines in Oncology. *Prostate Cancer Early Detection*. Version 2.2012. http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
6. Patel SD, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep*. 2012;14:428-438.
7. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Counsel*. 2009;18:13-27.
8. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. *Mayo Clin Proc*. 2010;85(12):1111-1120.

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Anticancer Agents

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Please note that all information has been obtained from current product labeling as of January 31, 2013. 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. Emetogenic potential is based on the incidence of acute emesis in product labeling and/or based on classification by national chemotherapy-induced nausea and vomiting (CINV) guidelines—minimal, <10%; low, 10% to 30%; moderate, 30% to 90%; and high, >90% (see Chapter 38).

ABIRATERONE (ZYTIGA)

Mechanism of Action

- Androgen biosynthesis inhibitor of 17 α-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

- In combination with prednisone for the treatment of metastatic castration-resistant prostate cancer.

FDA-Approved Dosage

- 1,000 mg (four 250 mg tablets) PO once daily in combination with prednisone 5 mg administered PO twice daily. 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

- Hepatic (moderate, Child–Pugh class B): yes
- Hepatic (severe, Child–Pugh class C): avoid use
- Renal: no

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 LFTs
- PULM: cough, dyspnea, nasopharnygitis, and upper respiratory tract infection
- Other: contusion, 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 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, 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.
- Abiraterone is an inhibitor of CYP2D6. Avoid coadministration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (e.g., 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.
- Abiraterone is not indicated for use in women. Pregnancy category X: abiraterone can cause fetal harm when administered to a pregnant woman.

ALDESLEUKIN (PROLEUKIN)

Mechanism of Action

- Cellular immunity activation

FDA-Approved Indications

- Metastatic renal cell carcinoma (RCC)
- Metastatic melanoma

FDA-Approved Dosage

- 600,000 international units/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 pruritis
- GI: diarrhea, N/V (moderate), 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.
- 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.

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, 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 $\leq$ 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 (i.e., 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 per week should not be administered because these doses are associated with a higher incidence of pancytopenia.

- Premedicate patients with an antihistamine (e.g., 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, refer to www.campath.com or contact the Campath Distribution Program (1-877-422-6728).
- 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 (PCP) (e.g., trimethoprim/sulfamethoxazole) and herpesvirus infections (e.g., famciclovir or equivalent) should be utilized.
- Do not administer as an intravenous push or bolus.
- Careful monitoring of blood pressure 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.

ALTRETAMINE (HEXALEN)

Mechanism of Action

- Unknown, but like an alkylating agent in structure

FDA-Approved Indications

- Ovarian cancer: second-line, palliative treatment of persistent or recurrent ovarian cancer

FDA-Approved Dosage

- 65 mg/m^2 orally four times daily; total daily dose: 260 mg/m^2 for 14 or 21 consecutive days every 28 days

Dose Modification Criteria

- Myelosuppression: yes
- Nonhematologic toxicity (GI intolerance and progressive neurotoxicity): yes

Adverse Reactions

- GI: N/V (moderate)
- HEMAT: myelosuppression (WBC, RBC, and platelets)
- NEURO: peripheral sensory neuropathy, mood disorders, ataxia, and dizziness

Comments

- Monitor for neurologic toxicity

ANASTRAZOLE (ARIMIDEX)

Mechanism of Action

- Selective, nonsteroidal aromatase inhibitor

FDA-Approved Indications

- Breast cancer
  - Adjuvant treatment: postmenopausal women with hormone receptor-positive early breast cancer
  - First-line therapy: postmenopausal women with hormone receptor-positive or hormone receptor 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 (low) and diarrhea
- HEPAT: elevated liver function tests (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 anastrazole

ARSENIC TRIOXIDE (TRISENOX)

Mechanism of Action

- The mechanism is not completely defined.
- Induces apoptosis in NB4 human promyelocytic leukemia cells in vitro and causes damage or degradation of the fusion protein PML/RAR-α.

FDA-Approved Indications

- Acute promyelocytic leukemia (APL): 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

- APL induction: 0.15 mg/kg IV over 1 to 2 hours daily until bone marrow remission. Total induction dose should not exceed 60 doses.
- APL consolidation: 0.15 mg/kg IV over 1 to 2 hours daily × 25 doses over a period up to 5 weeks. Consolidation treatment should begin 3 to 6 weeks after completion of induction therapy.

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 (moderate), diarrhea, abdominal pain, anorexia, and constipation
- HEMAT: leukocytosis and myelosuppression
- HEPAT: elevated LFTs
- NEURO: headache, dizziness, and paresthesias
- 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 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.

ASPARAGINASE (ELSPAR, ERWINAZE)

Mechanism of Action

- Asparaginase depletes asparagine, an amino acid required by some leukemic cells

FDA-Approved Indications

- Elspar (asparaginase derived from *Escherichia coli*): acute lymphoblastic leukemia (ALL) induction therapy (component of multiagent chemotherapeutic regimen)

- Erwinaze (asparaginase derived from *Erwinia chrysanthemi*): ALL induction therapy for patients who have developed hypersensitivity to *E. coli*–derived asparaginase

FDA-Approved Dosage

- Consult current literature for doses.
- Elspar: ALL induction therapy—6,000 international units/m^2 IM or IV three times a week.
- Erwinaze: ALL induction therapy—25,000 international units/m^2 intramuscularly 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
- 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.
- Hypersensitivity and anaphylactic reactions can occur.
- Consult package insert regarding test doses and desensitization schedules.
- Intramuscular administration has a lower incidence of hypersensitivity reactions compared to intravenous administration.
- Intravenous infusions should be over at least 30 minutes.

AXITINIB (INLYTA)

Mechanism of Action

- Inhibits receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3

FDA-Approved Indications

- Advanced RCC after failure of one prior systemic therapy

FDA-Approved Dosage

- 5 mg orally twice should be administered daily. Swallow whole with a glass of water. Administer axitinib doses approximately 12 hours apart with or without food.

Dose Modification Criteria

- Hepatic (mild, Child–Pugh class A): no
- Hepatic (moderate, Child–Pugh class B): yes
- Hepatic (severe, Child–Pugh class C): not studied
- Renal (mild, moderate, and severe): no
- End-stage renal disease (CrCl $<$15 mL/minute): use caution
- Tolerability/toxicity: yes

Adverse Reactions

- Cr: creatinine increased
- CV: hypertension
- DERM: dry skin, palmar-plantar erythrodysesthesia, and rash
- ELECTRO: decreased bicarbonate, hyperkalemia, hypernatremia, hypocalcemia, hyponatremia, and hypophosphatemia
- ENDO: hyperglycemia, hypoglycemia, and hypothyroidism
- GI: abdominal pain, anorexia, constipation, diarrhea, dysgeusia, N/V (minimal to low), and stomatitis
- GU: proteinuria
- HEMAT: anemia, leukopenia, lymphopenia, and thrombocytopenia
- HEPAT: hypoalbuminemia, hyperbilirubinemia, increased alkaline phosphatase, and increased LFTs
- NEURO: headache
- PULM: cough and dyspnea
- Other: asthenia, arterial and venous thromboembolic events, dysphonia, fatigue, hemorrhage, pain in extremity, and weight decreased

Comments

- Blood pressure should be well controlled prior to starting axitinib, and should be monitored regularly during treatment.
- 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 gastrointestinal bleeding and should not be used in these patients.
- Gastrointestinal 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.
- Concomitant use of strong CYP3A4/5 inhibitors should be avoided. If coadministration is necessary, decrease the axitinib dose by half.
- Pregnancy category D: Axitinib may cause fetal harm when administered to a pregnant woman.

AZACITIDINE (VIDAZA)

Mechanism of Action

- Antimetabolite is 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

- 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 myelomonocytic leukemia.

FDA-Approved Dosage

- 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.

Dose Modification Criteria

- Renal: no data (use with caution)
- Hepatic: no data (use with caution)
- Myelosuppression: yes
- Nonhematologic toxicity (renal tubular acidosis, renal 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 (moderate), diarrhea, constipation, anorexia, abdominal pain, and hepatotoxicity
- GU: increased Cr and 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, and peripheral edema

Comments

- Teratogenic (pregnancy category D): 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 intravenous azacitidine in combination with other chemotherapeutic agents for non-MDS conditions.

BCG LIVE (INTRAVESICAL) [THERACYS, TICE BCG]

Mechanism of Action

- Local inflammatory and immune response

FDA-Approved Indications

- Treatment and prophylaxis of carcinoma in situ of the urinary bladder and for the prophylaxis of primary or recurrent-stage Ta and/or T1 papillary tumors following transurethral resection (TUR)

FDA-Approved Dosage

- TheraCys: Vial contains 81 mg (dry weight) or $10.5 \pm 8.7 \times 10^8$ colony-forming units with accompanying 3 mL diluent vial.

- One reconstituted vial (81 mg/3 mL), diluted in 50 mL sterile, 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 (induction therapy) followed by one treatment at 3, 6, 12, 18, and 24 months after initial treatment (maintenance therapy)

- 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
- Other: malaise, fever, and chills; infectious complications (uncommon)

Comments

- TheraCys and TICE BCG are not bioequivalent products and may not be used interchangeably.
- 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.

BENDAMUSTINE HYDROCHLORIDE (TREANDA)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- 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 30 minutes on days 1 and 2 of a 28-day cycle, up to six cycles
- NHL: 120 mg/m^2 IV over 60 minutes on days 1 and 2 of a 21-day cycle, up to eight cycles

Dose Modification Criteria

- Myelosuppression: yes
- Nonhematologic toxicity: yes
- Renal: No data; use with caution in patients with mild-to-moderate renal impairment, avoid in patients with CrCL <40 mL per minute.
- Hepatic: No data; use with caution in patients with mild hepatic impairment, avoid in patients with moderate to severe hepatic impairment.

Adverse Reactions

- DERM: rash, pruritis, toxic skin reactions, and bullous exanthema
- GI: N/V (moderate), diarrhea, and mucositis

- HEMAT: myelosuppression
- INFUS: fever, chills, pruritis, 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 (e.g., 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 allopurinol during the first 1 to 2 weeks of therapy in patients at high risk.
- Severe skin reactions have been reported necessitating drug therapy to be withheld or discontinued.
- Bendamustine hydrochloride is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. Some metabolism via cytochrome P450 1A2 (CYP1A2) occurs forming active metabolites; thus, potential drug interactions with CYP1A2 inhibitors or inducers should be considered.
- Pregnancy category D: Bendamustine may cause fetal harm when administered to a pregnant woman.

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: First- or second-line treatment of patients with metastatic carcinoma of the colon or rectum; in combination with intravenous 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 RCC: In combination with interferon-α.

FDA-Approved Dosage

- Metastatic colorectal cancer: Administered as an intravenous infusion (5 mg/kg or 10 mg/kg) every 2 weeks when used in combination with intravenous fluorouracil-based chemotherapy.
  - 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 intravenous infusion every 3 weeks in combination with carboplatin and paclitaxel.
- Glioblastoma: 10 mg/kg intravenous infusion every 2 weeks.
- Metastatic RCC: 10 mg/kg intravenous infusion every 2 weeks in combination with interferon-α.

- Do not administer as an intravenous 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
- GI: N/V (minimal), diarrhea, abdominal pain, gastrointestinal perforation, and wound dehiscence
- GU: proteinuria and nephrotic syndrome
- INFUS: fever, chills, wheezing, and stridor
- NEURO: headache
- PULM: dyspnea and wheezing stridor
- Other: epistaxis and other mild-to-moderate hemorrhagic events; serious hemorrhagic events; wound healing complications; deep vein thrombosis or other thromboembolic events; asthenia

Comments

- Bevacizumab can result in the development of gastrointestinal perforation 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. The risk of CNS bleeding in patients with CNS metastases receiving bevacizumab has not been evaluated.
- Blood pressure monitoring should be conducted every 2 to 3 weeks during therapy and more frequently in patients who develop hypertension.
- Monitor urinalysis serially for proteinuria; patients with a 2+ or greater urine dipstick reading should undergo further assessment (e.g., a 24-hour urine collection).
- Pregnancy category C: 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 (RXRs).
- 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

FDA-Approved Dosage

- 300 mg/m^2 orally daily with a meal

Dose Modification Criteria

- Renal: no (caution due to possible protein binding alterations)
- Hepatic: use with caution
- Toxicity: yes

Adverse Reactions

- CV: peripheral edema
- DERM: dry skin, photosensitivity, rash, and pruritus
- ENDO: hypothyroidism and hypoglycemia (diabetic patients)
- GI: nausea, pancreatitis, and abdominal pain
- HEMAT: leukopenia and anemia
- HEPAT: elevated LFTs
- NEURO: headache
- Ocular: cataracts
- Other: lipid abnormalities (elevated triglycerides, elevated total and LDL cholesterol, and decreased HDL cholesterol), asthenia, and infection

Comments

- Monitor fasting blood lipid tests prior to initiation of bexarotene and weekly until the lipid response is established (usually occurs within 2 to 4 weeks) and then at 8-week intervals thereafter.
- Monitor LFTs prior to initiation of 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.
- Bexarotene is a teratogen (category X) 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, diarrhea, and constipation
- GU: impotence

Comments

- Monitor LFTs prior to treatment, at regular intervals for the first 4 months, and periodically thereafter.

BLEOMYCIN (BLENOXANE)

Mechanism of Action

- Unknown, but may inhibit DNA and RNA synthesis

FDA-Approved Indications

- Squamous cell cancers, NHL, testicular cancer, Hodgkin disease, malignant pleural effusions

FDA-Approved Dosage

- The product labeling recommends a test dose (2 units or less) for the first two doses in lymphoma patients.
- From 0.25 to 0.50 units/kg (10 to 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 (>70 years old), underlying emphysema, prior thoracic radiotherapy, high cumulative doses (e.g., >450 units), and high single doses (>30 units).
- Patients who have received bleomycin may be at increased risk of respiratory failure during the post-operative recovery period after surgery. Use the minimal tolerated concentration of inspired oxygen and modest fluid replacement to prevent pulmonary edema.

BORTEZOMIB (VELCADE)

Mechanism of Action

- Bortezomib is a reversible inhibitor of the 26S proteosome, a large protein complex that degrades ubiquinated 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: first-line therapy in combination with melphalan and prednisone and in relapsed disease as a single agent
- Mantle cell lymphoma: second-line therapy in mantle cell lymphoma patients who have received at least one prior therapy

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 intravenous 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 cycle are rest periods.)
- Multiple myeloma (relapsed disease) and mantle cell lymphoma: 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 to 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 to 35). At least 72 hours should elapse between consecutive doses of bortezomib.

Dose Modification Criteria

- Renal: no data (use caution)
- Hepatic: yes (moderate or severe hepatic impairment)
- Myelosuppression: yes
- Nonhematologic toxicity (e.g., neuropathy and neuropathic pain): yes

Adverse Reactions

- CV: hypotension (including orthostatic hypotension and syncope) and edema
- DERM: rash
- GI: N/V (low), diarrhea, anorexia, and constipation
- HEMAT: myelosuppression (thrombocytopenia > anemia > neutropenia)
- NEURO: peripheral neuropathy, neuropathic pain, dizziness, and headache
- Ocular: diplopia and blurred vision
- PULM: dyspnea
- Other: asthenia, fatigue, fever, insomnia, and arthralgia

Comments

- The reconstitution volume/concentration is different for the intravenous 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 intravenous route. Starting bortezomib subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy.

BOSUTINIB (BOSULIF)

Mechanism of Action

- Tyrosine kinase inhibitor (TKI) that inhibits the Bcr–Abl kinase that promotes chronic myelogenous leukemia (CML); also an inhibitor of Src-family kinases including Src, Lyn, and Hck.

FDA-Approved Indications

- Chronic, accelerated, or blast-phase Philadelphia chromosome-positive (Ph+) CML with resistance or intolerance to prior therapy.

FDA-Approved Dosage

- 500 mg orally once daily with food

Dose Modification Criteria

- Hepatic (mild, moderate, and severe): yes
- Renal (CrCL 25 to 90 mL per minute): no
- Renal (CrCL <25 mL per minute): not studied
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: pruritus and rash
- GI: abdominal pain, anorexia, diarrhea, and N/V (low)
- HEMAT: anemia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- NEURO: dizziness and headache
- PULM: cough, nasopharnygitis, and respiratory tract infection
- Other: arthralgia, asthenia, back pain, fatigue, fluid retention, and pyrexia

Comments

- Avoid the concomitant use of strong or moderate CYP3A and/or P-glycoprotein (P-gp) inhibitors and inducers.
- Bosutinib may increase the plasma concentrations of drugs that are P-gp substrates, such as digoxin.
- Proton pump inhibitors (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.
- Pregnancy category D: Bosutinib may cause fetal harm when administered to a pregnant woman.

BRENTUXIMAB VEDOTIN (ADCETRIS)

Mechanism of Action

- Antibody–drug conjugate (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, 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

- Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multiagent chemotherapy regimens in patients who are not ASCT candidates.
- Systemic anaplastic large cell lymphoma after failure of at least one prior multiagent chemotherapy regimen.

FDA-Approved Dosage

- 1.8 mg/kg as an intravenous infusion over 30 minutes every 3 weeks.
- Do not administer as an intravenous push or bolus.
- 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.

Dose Modification Criteria

- Hepatic: unknown
- Renal: unknown
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Effects

- DERM: alopecia, night sweats, pruritus, and rash
- GI: abdominal pain, constipation, diarrhea, N/V (low), and oropharyngeal pain
- HEMAT: anemia, neutropenia, lymphadenopathy, and thrombocytopenia
- INFUS: anaphylaxis, breathing problems, chills, fever, and rash
- NEURO: dizziness, headache, and motor and sensory peripheral neuropathy
- PULM: cough, dyspnea, and upper respiratory tract infection
- 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 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.
- Pregnancy category D: Brentuximab vedotin 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; 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. Adjusted IBW (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/day): low, intravenous: moderate
- HEMAT: severe myelosuppression
- HEPAT: veno-occlusive disease
- NEURO: seizures
- PULM: pulmonary fibrosis

Comments

- Therapeutic drug monitoring to determine area under the curve (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.

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

- 25 mg/m^2 as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment

Dose Modification Criteria

- Hepatic: avoid use
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

- Renal (CrCL 30 to 120 mL per minute): no
- Renal (CrCL <30 mL per minute): use caution
- End-stage renal disease: use caution

Adverse Effects

- DERM: alopecia
- GI: abdominal pain, anorexia, constipation, diarrhea, dysgeusia, dyspepsia, and N/V (low)
- HEMAT: anemia, leukopenia, neutropenia, and thrombocytopenia
- INFUS: hypersensitivity reactions
- NEURO: peripheral neuropathy
- PULM: cough and dyspnea
- Other: arthralgia, asthenia, back pain, fatigue, and pyrexia

Comments

- Cabazitaxel should not be used in patients with neutrophil counts of ≤1,500/mm^3
- Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >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. 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 (≥65 years of age) 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 compared to younger patients.
- Since cabazitaxel is extensively metabolized in the liver, it should not be given to patients with hepatic impairment (total bilirubin ≥ upper limit of normal [ULN], or AST and/or ALT≥ 1.5XULN).
- 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 PVC 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.
- Diarrhea and electrolyte abnormalities may be severe, and require intensive measures.
- 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.
- Pregnancy category D: Cabazitaxel may cause fetal harm when administered to a pregnant woman.

CABOZANTINIB (COMETRIQ)

Mechanism of Action

- Inhibits tyrosine activity of RET; MET; VEGFR-1, -2, and -3; KIT; TRKB; FLT-3; AXL; and TIE-2

FDA-Approved Indications

- Progressive, metastatic medullary thyroid cancer

FDA-Approved Dosage

- 140 mg orally once daily.
- Do not eat for at least 2 hours before and at least 1 hour after taking cabozantinib.

Dose Modification Criteria

- Hepatic (moderate, severe): use not recommended
- Renal (mild, moderate): no
- Renal (severe): unknown
- Hematologic: yes
- Nonhematologic toxicity: yes

Adverse Effects

- CV: hypertension
- DERM: palmar-plantar erythrodysesthesia and wound complications
- ELECTRO: hypocalcemia and hypophosphatemia
- GI: abdominal pain, constipation, decreased appetite, diarrhea, nausea, 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

- Gastrointestinal perforations and fistula formation have been reported. Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage have 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 28 days prior to scheduled surgery.
- Monitor blood pressure 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 28 days 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.
- For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily dose of cabozantinib by 40 mg.
- For patients who require treatment with a strong CYP3A4 inducer, increase the daily cabozantinib dose by 40 mg as tolerated. The daily dose of cabozantinib should not exceed 180 mg. Do not ingest foods or nutritional supplements (e.g., St. John's Wort) known to induce CYP450 activity.
- Pregnancy category D: 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.

CAPECITABINE (XELODA)

Mechanism of Action

- Antimetabolite that is enzymatically converted to fluorouracil in tumors

FDA-Approved Indications

- Colorectal cancer
  - 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 (after paclitaxel) if anthracycline is not indicated.

FDA-Approved Dosage

- Give 1,250 mg/m^2 orally twice daily (total daily dose: 2,500 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 to 80 mL per minute): no
- Renal (moderate impairment; CrCl 30 to 50 mL per minute): yes
- Hepatic (mild-to-moderate impairment due to liver metastases): no
- 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 (low), diarrhea, mucositis, abdominal pain, anorexia, and hyperbilirubinemia
- HEMAT: myelosuppression
- 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-derivative anticoagulation therapy. Anticoagulant response (INR and prothrombin time [PT]) should be monitored frequently to adjust anticoagulant dose accordingly.

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 body surface area (BSA)-based dosing.
- Calvert formula for carboplatin dosing:
  Total dose in milligrams = (target AUC) × [glomerular filtration rate (GFR) + 25].

- The target AUC of 4 to 6 mg/mL/minute 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 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)
- ELECTRO: Mg, Na, Ca, and K alterations
- GU: Inc. 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 (e.g., Calvert equation) dosing. The current IDMS method to measure serum creatinine appears to underestimate serum creatinine values compared to older methods when the serum creatinine values are relatively low (e.g., 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 proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome

FDA-Approved Indications

- Multiple myeloma in patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy

FDA-Approved Dosage

- Recommended cycle 1 dose is 20 mg/m^2/day. If tolerated, increase cycle 2 dose and subsequent cycle doses to 27 mg/m^2/day.
- Carfilzomib is administered intravenously over 2 to10 minutes, on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17 to 28). Each 28-day period is considered one treatment cycle.

Dose Modification Criteria

- Hepatic (for baseline impairment): not studied
- Renal (for baseline impairment): no

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- Cr: acute renal failure and increased serum creatinine
- CV: cardiac toxicity, CHF, and pulmonary arterial hypertension
- GI: diarrhea and nausea (low)
- 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, and upper respiratory tract infection
- Other: back pain, edema, fatigue, pyrexia, 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. Prior to each dose in cycle 1, give 250 to 500 mL of IV normal saline or other appropriate IV fluid. Give an additional 250 mL to 500 mL of IV fluids as needed following carfilzomib administration. Continue IV hydration as needed in subsequent cycles.
- Premedicate with dexamethasone 4 mg orally or intravenously prior to all cycle 1 doses, during the first cycle of dose escalation, and if infusion reaction symptoms develop or reappear. Infusion reactions can develop up to 24 hours after administration of carfilzomib.
- Monitor platelet counts frequently 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 heart failure and ischemia.
- Monitor for pulmonary hypertension. Monitor for and manage dyspnea immediately.
- Cases of hepatic failure have been reported. Monitor liver enzymes and bilirubin frequently during treatment.
- Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.
- Pregnancy category D: Carfilzomib can cause fetal harm when 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: retinal hemorrhages
- PULM: pulmonary fibrosis (acute and delayed)

Comments

- Risk of pulmonary toxicity increases with cumulative total doses >1,400 mg/m^2 and in patients with a history of lung disease, radiation therapy, or concomitant bleomycin.

CETUXIMAB (ERBITUX)

Mechanism of Action

- Recombinant chimeric monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor (EGFR) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) 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 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 5-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: 400 mg/m^2 intravenous infusion over 120 minutes administered 1 week prior to the first course of radiation therapy or on the day of initiation of platinum-based therapy with 5-FU followed by subsequent weekly doses of 250 mg/m^2 intravenous infusion over 60 minutes for the duration of radiation therapy (6 to 7 weeks) or until disease progression or unacceptable toxicity when administered in combination with platinum-based therapy with 5-FU. Complete cetuximab administration 1 hour prior to radiation therapy or platinum-based therapy with 5-FU.
- Squamous cell carcinoma of the head and neck (monotherapy): The recommended initial dose is 400 mg/m^2 intravenous infusion over 120 minutes followed by subsequent weekly doses of 250 mg/m^2 intravenous infusion over 60 minutes until disease progression or unacceptable toxicity.

- Metastatic colorectal carcinoma (monotherapy or in combination with irinotecan or FOLFIRI [irinotecan, 5-FU, leucovorin]): 400 mg/m^2 intravenous infusion over 120 minutes as an initial loading dose (first infusion) followed by a weekly maintenance dose of 250 mg/m^2 IV infusion over 60 minutes. Therapy is continued until disease progression or unacceptable toxicity. Complete cetuximab administration 1 hour prior to FOLFIRI.
- Premedication with an H_1 antagonist (e.g., 50 mg of diphenhydramine intravenously 30 to 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, nail toxicity
- ELECTRO: Mg, Ca, and K alterations
- GI: nausea, 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.
- Pregnancy category C: 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 intravenous push or bolus.

CHLORAMBUCIL (LEUKERAN)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Palliation of CLL, Hodgkin lymphoma, 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/day dose is used except for Hodgkin lymphoma, in which 0.2 mg/kg/day 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/day.

Dose Modification Criteria

- Myelosuppression: yes

Adverse Reactions

- DERM: rash and rare reports of progressive skin hypersensitivity reactions
- GI: N/V (minimal)
- 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 radiotherapy.

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: yes
- Myelosuppression: yes

Adverse Reactions

- ELECTRO: Mg, Na, Ca, and K alterations
- GI: N/V ($\geq$50 mg/m^2: high, $<$50 mg/m^2: moderate
- GU: increased Cr and BUN (cumulative)
- HEMAT: myelosuppression and anemia
- HEPAT: increased LFTs (especially AST and bilirubin)
- NEURO: neuropathy, paresthesia, and ototoxicity
- Ocular: 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 (e.g., 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

FDA-Approved Dosage

- 0.09 mg/kg intravenously by continuous infusion over 24 hours daily $\times$ 7 days (a single course of therapy)
- Inadequate data on dosing of patients with renal or hepatic insufficiency

Dose Modification Criteria

- Renal: no data
- Hepatic: no data

Adverse Reactions

- DERM: rash
- GI: N/V (minimal)
- HEMAT: myelosuppression and lymphopenia
- NEURO: fatigue, headache, and peripheral neuropathy
- Other: fever

Comments

- Immunosuppression (lymphopenia) persists for up to 1 year after cladribine therapy.

CLOFARABINE (CLOLAR)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Acute lymphoblastic leukemia (ALL): pediatric patients (age 1 to 21 years) with relapsed or refractory ALL after at least two prior regimens

FDA-Approved Dosage

- 52 mg/m^2 by intravenous 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
- 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 (e.g., 100 mg/m^2 hydrocortisone on days 1 through 3) may be of benefit in preventing SIRS or capillary leak.
- Hepatobiliary toxicities were frequently observed in clinical trials.
- Dose adjustment is required in patients with renal impairment. Clofarabine may also cause nephrotoxicity; avoid concomitant nephrotoxic agents during therapy.
- Pregnancy category D: Clofarabine may cause fetal harm when administered to a pregnant woman.

CRIZOTINIB (XALKORI)

Mechanism of Action

- Inhibitor of receptor tyrosine kinases including anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (HGFR, c-Met), and recepteur d'origine nantais (RON).

FDA-Approved Indications

- Locally advanced or 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

- Hepatic: not studied, use caution
- Renal (mild, moderate): no
- Renal (severe, end-stage renal disease): not studied
- Hematologic toxicity: yes (except lymphopenia, unless associated with clinical events)
- Nonhematologic toxicity/tolerability: yes

Adverse Reactions

- CV: QT interval prolongation
- GI: abdominal pain, anorexia, constipation, diarrhea, dysgeusia, esophageal disorder, N/V (moderate), and stomatitis
- HEMAT: lymphopenia
- HEPAT: increased LFTs
- NEURO: dizziness, headache, and neuropathy
- Ocular: vision disorder
- PULM: cough, dyspnea, 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.
- Advise patients to keep crizotinib in the original container. Do not crush, dissolve, or open capsules.
- The aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH may decrease the solubility of crizotinib and subsequently reduce its bioavailability.
- 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 QTc prolongation, and in those who have recurrent grade 3 QTc prolongation.
- 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.
- Pregnancy category D: 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 (intravenous): many dosing regimens reported; consult current literature
- Oral: 1 to 5 mg/kg/day (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 ($\geq$1,500 mg/m^2: high, $<$1,500 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 intravenous 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), ALL, blast-phase 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 $\times$ 7 days *OR* 100 mg/m^2 IV every 12 hours $\times$ 7 days. Consult current literature for alternative dosing regimens (e.g., high-dose regimens such as $\geq$1 gm/m^2/dose).
- Intrathecally: (use preservative-free diluents) 30 mg/m^2 intrathecally every 4 days until cerebrospinal fluid (CSF) 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).
- Neurotoxicity: Yes.

Adverse Reactions

- DERM: rash, 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: 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.

CYTARABINE LIPOSOME INJECTION (DEPOCYT)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Intrathecal treatment of lymphomatous meningitis

FDA-Approved Dosage

- Given only by intrathecal route either via an intraventricular reservoir or directly into the lumbar sac over a period of 1 to 5 minutes.
- Patients should be started on dexamethasone, 4 mg PO or IV twice daily × 5 days beginning on the day of the cytarabine liposome injection.
- Induction: 50 mg intrathecally every 14 days × two doses (weeks 1 and 3).
- Consolidation: 50 mg intrathecally every 14 days × three doses (weeks 5, 7, and 9) followed by an additional dose at week 13.
- Maintenance: 50 mg intrathecally every 28 days × four doses (weeks 17, 21, 25, and 29).

Dose Modification Criteria

- Neurotoxicity: yes

Adverse Reactions

- NEURO: Chemical arachnoiditis, headache, asthenia, confusion, and somnolence

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 disease (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 disease: 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

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
  - 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

DASATINIB (SPRYCEL)

Mechanism of Action

- Tyrosine Kinase Inhibitor (BCR–ABL, SRC family, c-KIT, EPHA-2, and PDGFRβ)

FDA-Approved Indications

- CML
  - Initial therapy in newly diagnosed adults with Ph+ CML in chronic phase.
  - Chronic, accelerated, or myeloid or lymphoid blast-phase CML with resistance or intolerance to prior therapy including imatinib.
- ALL: adults with Ph+ ALL with resistance or intolerance to prior therapy

FDA-Approved Dosage

- 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

Dose Modification Criteria

- Myelosuppression: yes
- Nonhematologic toxicity: yes; renal: no data
- Hepatic: no (use with caution)

Adverse Reactions

- CV: CHF, QT prolongation, left ventricular dysfunction, and myocardial infarction
- DERM: skin rash
- GI: N/V (minimal) and diarrhea
- HEMAT: myelosuppression and hemorrhage
- NEURO: headache
- PULM: pleural effusion, pulmonary edema, pericardial effusion, dyspnea, and pulmonary arterial hypertension
- Other: fluid retention (e.g., edema), fatigue, and musculoskeletal pain

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 cytochrome P450 3A4 isoenzyme. Screen for drug interactions with CYP 3A4 inhibitors or inducers.
- Use with caution in patients who have or may develop QT prolongation. Correct hypokalemia or hypomagnesemia prior to starting therapy.
- 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.
- Pregnancy category D: 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 ANLL or ALL, children and adults

FDA-Approved Dosage

- ANLL: in combination with cytarabine
  - Age <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 <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 to 550 mg/m^2 in adults or >300 mg/m^2 in children), arrhythmias
- DERM: nail hyperpigmentation, rash, alopecia, 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 (e.g., 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 CITRATE LIPOSOME INJECTION (DAUNOXOME)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- Advanced HIV-associated Kaposi sarcoma (first-line therapy)

FDA-Approved Dosage

- 40 mg/m^2 IV over 60 minutes × one dose every 2 weeks

Dose Modification Criteria

- Hepatic: yes
- Renal: yes
- Myelosuppression: yes

Adverse Reactions

- CV: CHF and arrhythmias
- DERM: nail, alopecia, hyperpigmentation, and rash
- GI: N/V (low), mucositis, and diarrhea
- HEMAT: myelosuppression
- INFUS: back pain, flushing, and chest tightness (infusion-related reactions usually subside with interruption of the infusion, and generally do not recur if the infusion is then resumed at a slower rate)
- Other: red-tinged urine, fever, chills, and fatigue

Comments

- Do not confuse with nonliposomal forms of daunorubicin.
- Liposomal formulations of the same drug may not be equivalent.
- Evaluate cardiac function by history and physical examination of each cycle and determine left ventricular ejection fraction (LVEF) function at total cumulative doses of daunorubicin citrate liposome injection of 320 mg/m^2 and every 160 mg/m^2 thereafter in anthracycline-naive patients. In patients with preexisting cardiac disease, a history of radiotherapy encompassing the heart, or those who previously received anthracyclines (doxorubicin >300 mg/m^2 or equivalent) should have cardiac function (LVEF) monitored before daunorubicin citrate liposome injection therapy and every 160 mg/m^2 thereafter.

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

- 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 intravenous infusion over 3 hours repeated every 8 hours for 3 days. Cycles may be repeated every 6 weeks.
- 20 mg/m^2 by intravenous infusion over 1 hour once daily for 5 days. Repeat cycle every 4 weeks.

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, arthralgis, and limb or back pain

Comments

- Pregnancy category D: 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.

DEGARELIX (FIRMAGON)

Mechanism of Action

- Gonadotropin-releasing hormone (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

- Hepatic (mild, moderate): None, but testosterone concentrations should be monitored monthly until medical castration is achieved since hepatic impairment can lower degarelix exposure.
- Hepatic (severe): Use with caution.

- Renal (CrCL 50 to 80 mL per minute): None.
- Renal (CrCL <50 mL per minute): 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 γ-glutamyltransferase (GGT)
- Other: back pain, chills, fatigue, and increased weight

Comments

- Long-term androgen deprivation therapy prolongs the QT interval. The benefits of androgen deprivation therapy should be weighed against the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or CHF and in patients taking class IA (e.g., quinidine, procainamide) or class III (e.g., 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.
- Degarelix is not indicated for use in women. Pregnancy category X: degarelix can cause fetal harm when administered to a pregnant woman.

DENILEUKIN DIFTITOX (ONTAK)

Mechanism of Action

- Fusion protein composed of diphtheria toxin fragments linked to interleukin-2 (IL-2) sequences; interacts with IL-2 cell surface receptors and inhibits cellular protein synthesis.

FDA-Approved Indications

- Treatment of persistent or recurrent cutaneous T-cell lymphoma (CTCL) in patients whose malignant cells express the CD25 component of the IL-2 receptor

FDA-Approved Dosage

- Cells should be tested for CD25 before administration.
- 9 or 18 μg/kg IV over at least 15 minutes daily × 5 days; repeat cycles every 21 days. Infusion should be stopped or infusion rate should be reduced for severe infusion-related reactions.

Adverse Reactions

- CV: vascular leak syndrome (hypotension and edema hypoalbuminemia), hypotension, and thrombotic events
- DERM: rash and pruritis

- GI: N/V (low), anorexia, and diarrhea
- HEMAT: anemia
- HEPAT: increased LFTs
- INFUS: acute hypersensitivity-type reactions consisting of one or more of the following—hypotension, back pain, dyspnea, vasodilation, rash, chest pain or tightness, tachycardia, dysphagia, syncope, allergic reactions, or anaphylaxis
- NEURO: dizziness
- Ocular: loss of visual acuity and color vision
- PULM: dyspnea and cough
- Other: flulike syndrome consisting of one or more of the following—fever and/or chills, asthenia, digestive symptoms, myalgias, and arthralgias (appears several hours to days after dose infusion)

Comments

- Consider premedication with antipyretics and antihistamines; have emergency medications and resuscitative equipment readily available during administration.
- Monitor weight, blood pressure, and serum albumin for vascular leak syndrome. Patients with preexisting low serum albumin levels may be predisposed to the syndrome.
- Monitor patients carefully for infection.
- Monitor visual acuity and color vision.

DOCETAXEL (TAXOTERE)

Mechanism of Action

- Microtubule assembly stabilization

FDA-Approved Indications

- 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: androgen-independent (hormone refractory) metastatic-prostate cancer (in combination with prednisone)
- Gastric cancer: advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction (in combination with cisplatin and fluorouracil), 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 fluorouracil)

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.
- NSCLC
  - First-line therapy (combined with cisplatin): 75 mg/m^2 IV over 1 hour $\times$ one dose every 3 weeks (administered immediately prior to cisplatin)
  - Second-line therapy (single agent): 75 mg/m^2 IV over 1 hour $\times$ 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 fluorouracil).
- Head and neck cancer
  - Induction chemotherapy followed by radiotherapy (TAX323): 75 mg/m^2 IV over 1 hour on day 1 only (in a combination regimen with cisplatin and fluorouracil), repeat cycle every 3 weeks for four cycles.
  - Induction chemotherapy followed by chemoradiotherapy (TAX324): 75 mg/m^2 IV over 1 hour on day 1 only (in a combination regimen with cisplatin and fluorouracil), 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 pruritis, nail changes (pigmentation, onycholysis, and pain), and alopecia
- GI: N/V (low), diarrhea, and mucositis
- 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, and asthenia

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.
- Lower dose, weekly dosage regimens are commonly utilized. Consult current literature for dose guidelines.
- Use non-DEHP plasticized solution containers and administration sets.

DOXORUBICIN (ADRIAMYCIN AND OTHERS)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- ALL, acute myeloblastic leukemia, Wilms tumor, neuroblastoma, soft tissue and bone sarcoma, breast, ovarian, thyroid, bronchiogenic, 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 3 weeks
- In combination with other agents: 40 to 60 mg/m^2 IV × one dose, repeated every 3 to 4 weeks

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

- Vesicant

DOXORUBICIN HCL LIPOSOME INJECTION (DOXIL)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- AIDS-related Kaposi sarcoma (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 per minute 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
- Palmar-plantar erythrodysesthesia: yes
- Myelosuppression: yes
- 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, pruritis, 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 (e.g., cumulative doses ≥400 to 550 mg/m^2 depending on risk factors).

ENZALUTAMIDE (XTANDI)

Mechanism of Action

- Inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA.

FDA-Approved Indications

- Patients with metastatic castration-resistant prostate cancer who have previously received docetaxel

FDA-Approved Dosage

- 160 mg orally once daily with or without food

Dose Modification Criteria

- Hepatic (Child–Pugh class A or B): no
- Hepatic (Child–Pugh class C): unknown
- Renal (CrCL 30 to 89 mL per minute): no
- Renal (<30 mL per minute, 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 (e.g., 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 moderate and strong CYP3A4 inducers or CYP2C8 inducers as they can alter the plasma exposure of enzalutamide.
- 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.
- Enzalutamide is not indicated for use in women. Pregnancy category X: enzalutamide can cause fetal harm when administered to a pregnant woman.

EPIRUBICIN (ELLENCE)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- 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 $\times$ 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 fluorouracil)
- FEC 100: 100 mg/m^2 IV $\times$ one dose on day 1 only, repeated every 21 days for six cycles (combined with cyclophosphamide and fluorouracil)

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, radiation recall, and tissue damage/necrosis with extravasation
- GI: N/V (moderate) and mucositis
- HEMAT: myelosuppression
- Other: facial flushing, and secondary malignancies

Comments

- Vesicant

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

- 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.

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

- Hepatic (Child–Pugh class A or B): yes
- Hepatic (Child–Pugh class C): not studied
- Renal (mild): none
- Renal (CrCL 30 to 50 mL per minute): yes
- Renal (CrCL <30 mL per minute): not studied
- Hematologic toxicity: yes
- Nonhematologic toxicity: yes

Adverse Effects

- DERM: alopecia
- CV: QT prolongation
- GI: anorexia, constipation, diarrhea, 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 class 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.
- Pregnancy category D: 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

- Tyrosine Kinase Inhibitor (EGFR type 1 [EGFR/HER1])

FDA-Approved Indications

- NSCLC
  - Maintenance therapy in patients with locally advanced or metastatic disease whose disease has not progressed after four cycles of platinum-based first-line chemotherapy
  - Locally advanced or metastatic disease after failure of 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: yes, use with caution
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: rash, pruritis, dry skin, bullous, and exfoliative skin disorders
- GI: N/V (minimal), diarrhea, anorexia, and gastrointestinal perforation
- GU: renal insufficiency, acute renal failure, and hepatorenal syndrome
- HEPAT: elevated LFTs, hepatic failure, and hepatorenal syndrome
- Ocular: conjunctivitis, keratoconjunctivitis sicca, corneal perforation, or ulceration
- PULM: 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 (e.g., 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.
- Erlotinib is metabolized through cytochrome P450 3A4 and 1A2 isoenzymes. Screen for drug interactions with CYP 3A4 and 1A2 inhibitors or inducers. Other interactions include cigarette smoking (reduced erlotinib exposure), coumarin-derived anticoagulants (increased INR and bleeding events), and agents which reduced gastric pH (PPIs, H_2 antagonists, and antacids).
- Pregnancy category D: 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

- 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 nausea
- 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 to100 mg/m^2 IV over 30 to 60 minutes daily × 5 days (days 1 to 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 intravenous dose rounded to the nearest 50 mg.

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: alopecia, rash, urticaria, and pruritis

- GI: N/V (low), mucositis, and anorexia
- HEMAT: myelosuppression
- INFUS: hypotension (infusion rate–related), anaphylactic-like reactions (characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension)
- Other: secondary malignancies

ETOPOSIDE PHOSPHATE (ETOPHOS)

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 to 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 intravenous 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 to 30 minutes have been utilized).

Dose Modification Criteria

- Renal: yes

Adverse Reactions

- DERM: alopecia, rash, urticaria, and pruritis
- 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 intravenous administration. Enhanced water solubility also allows for lower dilution volumes and more rapid intravenous 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 (mTORC1) and thus inhibition of mTOR kinase activity.

FDA-Approved Indications

- Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- Progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced, or metastatic.
- Advanced RCC after failure of treatment with sunitinib or sorafenib.
- Renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.
- Pediatric and adult patients with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

FDA-Approved Dosage

- Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC: 10 mg orally once daily with or with out food.
- SEGA with TSC: 4.5 mg/m^2 orally once daily.

Dose Modification Criteria

- Hepatic (Child–Pugh class A, B, or C): yes
- Renal: no
- 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, mucositis, nausea (minimal to low), and stomatitis
- GU: proteinuria
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- NEURO: headache
- PULM: cough, pneumonitis, and respiratory tract infection
- Other: asthenia, fatigue, fever, 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 and TSC in conjunction with therapeutic drug monitoring. Maintain trough concentrations of 5 to15 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.
- Pregnancy category D: 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 5 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: depression, insomnia, and anxiety
- Other: tumor site pain, asthenia, fatigue, increased sweating, and fever

FLOXURIDINE

Mechanism of Action

- Antimetabolite (catabolized to fluorouracil)

FDA-Approved Indications

- Palliative management of gastrointestinal 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/day by continuous arterial infusion. The higher dose ranges (0.4 to 0.6 mg/kg/day) 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

- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: myocardial ischemia
- DERM: alopecia, dermatitis, and rash
- GI: N/V, stomatitis, diarrhea, enteritis, gastrointestinal 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 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 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.

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, gastrointestinal ulceration, and bleeding
- HEMAT: myelosuppression
- NEURO: acute cerebellar syndrome, nystagmus, headache, visual changes, and photophobia
- Other: anaphylaxis and generalized allergic reactions

Comments

- Fluorouracil may be given as continuous intravenous infusion or by rapid intravenous administration (intravenous bolus or push). The method of administration will change the toxicity profile of fluorouracil (e.g., greater potential for GI toxicities such as mucositis and diarrhea with continuous intravenous infusions and more hematologic toxicity with bolus administration).

FLUTAMIDE (EULEXIN)

Mechanism of Action

- Antiandrogen

FDA-Approved Indications

- 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, 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 international normalized ratio (INR) closely

FULVESTRANT (FASLODEX)

Mechanism of Action

- Estrogen receptor antagonist

FDA-Approved Indications

- Breast cancer: second-line treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy

FDA-Approved Dosage

- 500 mg intramuscular 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; severe impairment: not tested

Adverse Reactions

- CV: peripheral edema
- ENDO: hot flashes
- GI: N/V, constipation, diarrhea, abdominal pain, and anorexia
- NEURO: headache
- Other: pain, pharyngitis, injection site reactions, and asthenia

GEFITINIB (IRESSA)

Mechanism of Action

- Tyrosine Kinase Inhibitor (primarily EGFR)

FDA-Approved Indications

- NSCLC: monotherapy for the treatment of patients with locally advanced or metastatic NSCLC, after failure of both platinum-based and docetaxel chemotherapies, who are benefiting or who have benefited from gefitinib

FDA-Approved Dosage

- 250 mg orally daily

Dose Modification Criteria

- Renal: not evaluated in severe impairment, use with caution
- Hepatic: no

Adverse Reactions

- DERM: rash, acne, dry skin, and pruritus
- GI: N/V (minimal), diarrhea, anorexia, and elevated LFTs
- Ocular: 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

- Access to gefitinib is restricted (via the Iressa Access Program) based on the lack of survival benefit in a placebo-controlled trial in advanced recurrent NSCLC and the availability of other drugs that do prolong life.
- 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.
- Gefitinib is extensively hepatically metabolized, predominantly by cytochrome (CYP) 3A4. Be aware of potential drug interactions with either potent inhibitors or inducers of CYP 3A4. A dose increase of gefitinib to 500 mg per day may be considered when given concomitantly with a potent CYP 3A4 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 fluorouracil.
- 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): 1,000 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 1,000 mg/m^2 IV over 30 minutes once weekly for 3 consecutive weeks out of every 4 weeks.
- NSCLC (combination therapy with cisplatin)
  - 4-week schedule: 1,000 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of each 28-day cycle. Cisplatin (100 mg/m^2 IV $\times$ one dose) should be administered after gemcitabine only on day 1, *OR*
  - 3-week schedule: 1,250 mg/m^2 IV over 30 minutes on days 1 and 8 of each 21-day cycle. Cisplatin (100 mg/m^2 IV $\times$ one dose) should be administered after gemcitabine only on day 1
- Metastatic breast cancer (combination therapy with paclitaxel): 1,250 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 $\times$ one dose (day 1 only) before gemcitabine administration.

- Ovarian cancer: 1,000 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

- Clearance in women and elderly is reduced.
- Intravenous 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.

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 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 peri-menopausal 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 radiotherapy 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 radiotherapy.
- Breast cancer: 3.6 mg subcutaneous depot every 4 weeks.

Dose Modification Criteria

- Renal: no
- Hepatic: no

Adverse Reactions

- CV: transient changes in blood pressure (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 bone mineral density, 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, renal impairment
- Other: tumor flare in the first few weeks of therapy, loss of bone mineral density, osteoporosis, bone fracture, 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

- Melanoma; recurrent, metastatic, or inoperable ovarian cancer; resistant CML; and primary squamous cell carcinomas of the head and neck (excluding the lip) in combination with radiation therapy. Hydroxyurea is also indicated in adult patients with sickle cell anemia with recurrent moderate-to-severe painful crises.

FDA-Approved Dosage

- Dose based on actual or IBW, whichever is less
- Solid tumors
  - Intermittent therapy: 80 mg/kg orally as a single dose every third day
  - Continuous therapy: 20 to 30 mg/kg orally daily
  - In combination with irradiation for head and neck cancer: 80 mg/kg orally as a single dose every third day, beginning 7 days before initiation of irradiation and continued indefinitely thereafter, based on adverse effects and response
- Resistant CML: 20 to 30 mg/kg orally daily
- 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, and hyperpigmentation
- GI: N/V (minimal), diarrhea, anorexia, mucositis, and constipation
- HEMAT: myelosuppression (leukopenia, anemia > thrombocytopenia)
- NEURO: drowsiness (large doses)

Comments

- Capsule contents may be emptied into glass of water and taken immediately (some inert particles may float on surface).
- Patients should be counseled about proper handling precautions if they open the capsules.

IDARUBICIN (IDAMYCIN)

Mechanism of Action

- Intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- In combination with other agents for adult acute myeloid leukemia (AML; FAB M1 to M7)

FDA-Approved Dosage

- AML induction in combination with cytarabine: 12 mg/m^2 slow intravenous injection (over 10 to 15 minutes) daily for 3 days

Dose Modification Criteria

- Renal: use with caution
- Hepatic: yes
- 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.

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. Give MESNA 20% (wt/wt; 240 mg/m^2 per dose for a 1.2 g/m^2 ifosfamide dose) at time of ifosfamide, and then 4 and 8 hours after ifosfamide.

Dose Modification Criteria

- Renal: unknown
- Hepatic: unknown
- Myelosuppression: yes
- 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; administer MESNA concurrently; monitor for microscopic hematuria
- 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.

IMATINIB MESYLATE (GLEEVEC)

Mechanism of Action

- Inhibitor of multiple tyrosine kinases including the Bcr–Abl tyrosine kinase, which is created by the Ph abnormality in CML. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events.

FDA-Approved Indications

- CML:
  - First-line therapy for newly diagnosed adult and pediatric patients with 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
- 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 platelet-derived growth factor receptor (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-PDGFR α-fusion kinase and patients who are FIP1L1–PDGFR α-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 per day as clinically indicated (see package insert for criteria).
  - Adult patients, accelerated phase: 600 mg orally daily. Doses may be escalated to 800 mg per day (400 mg orally twice daily) as clinically indicated (see package insert for criteria).
  - Pediatric patients: 340 mg/m^2 orally daily (NTE 600 mg per day).
- ALL
  - Adult patients: 600 mg orally daily
  - Pediatric patients: 340 mg/m^2 orally daily (NTE 600 mg per day)
- 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 per day is recommended, consider increasing dose from 100 to 400 mg per day 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–PDGFR α-fusion kinase start with 100 mg per day, may consider increasing dose from 100 to 400 mg per day in the absence of adverse drug reactions and insufficient response to therapy.

- DFSP: 800 mg per day (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 mg 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, 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 cytochrome p450 (CYP) 3A4 enzyme is the major enzyme responsible for the metabolism of imatinib. Be aware of potential drug interactions with either potent inhibitors or inducers of CYP 3A4. 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 age >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 (e.g., every 2 to 3 months).
- Pregnancy category D: Imatinib 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 3 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, and pruritus, crusting, erosion/ulceration, erythema, flaking/scaling, swelling, and vesculation/postulation
- NEURO: headache
- Ocular: 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.

INTERFERON α-2B (INTRON A)

Mechanism of Action

- Cell proliferation suppression, macrophage phagocytic activity enhancement, lymphocyte cytotoxicity enhancement

FDA-Approved Indications

- Oncology indications (adults, ≥18 years of age): hairy cell leukemia, malignant melanoma (adjuvant therapy to surgical treatment), AIDS-related Kaposi sarcoma, follicular lymphoma (clinically aggressive disease in conjunction with anthracycline-containing combination chemotherapy)
- Other indications: condyloma acuminata, chronic hepatitis C, chronic hepatitis B

FDA-Approved Dosage

- Hairy cell leukemia: 2 million international units/m^2 IM or SC three times a week for up to 6 months.
- Malignant melanoma—Induction: 20 million international units/m^2 IV for 5 consecutive days per week for 4 weeks. Maintenance: 10 million international units/m^2 SC three times per week for 48 weeks.
- Kaposi sarcoma: 30 million international units/m^2 SC or IM three times a week until disease progression or maximal response has been achieved after 16 weeks of treatment.
- Follicular lymphoma (in combination with an anthracycline-containing chemotherapy regimen): 5 million international units SC three times a week for up to 18 months.

Dose Modification Criteria

- Serious adverse events: yes

Adverse Reactions

- DERM: skin rash and alopecia
- ENDO: thyroid abnormalities
- GI: diarrhea, N/V, anorexia, taste alteration, and abdominal pain
- HEMAT: myelosuppression
- HEPAT: increased LFTs
- NEURO: dizziness, depression, suicidal ideation, and paresthesias
- PULM: dyspnea, pulmonary infiltrates, pneumonitis, and pneumonia
- Other: flulike symptoms (fever, chills, headache, fatigue, malaise, and myalgia), hypersensitivity reactions, ophthalmologic disorders, and autoimmune disorders

Comments

- Patients with a preexisting psychiatric condition, especially depression, should not be treated.
- Use with caution in patients with pulmonary disease, diabetes mellitus, coagulopathies, cardiac disorders, autoimmune diseases, or ophthalmologic disorders.
- Recommended laboratory monitoring includes CBCs, blood chemistries, LFTs, and thyroid-stimulating hormone (TSH) prior to beginning treatment and then periodically thereafter.
- Other recommended baseline studies include a chest x-ray and an ophthalmologic exam.

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

- Unresectable or metastatic melanoma

FDA-Approved Dosage

- 3 mg/kg administered IV over 90 minutes every 3 weeks for a total of four doses

Dose Modification Criteria

- Hepatic (mild): none
- Hepatic (moderate, severe): not studied
- Renal impairment: none
- Immune-mediated toxicity: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: dermatitis, rash, and pruritus
- ENDO: adrenal insufficiency, hypogonadism, hypophysitis, hypopituitarism, hyperthyroidism, and hypothyroidism
- GI: enterocolitis and diarrhea
- HEPAT: elevated LFTs, hyperbilirubinemia, and immune-mediated hepatitis
- NEURO: motor or sensory neuropathy
- Other: fatigue

Comments

- Ipilimumab can cause severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these reactions manifest during treatment; however, a minority can occur weeks to months after discontinuation of therapy.
- Permanently discontinue ipilimumab for severe immune-mediated adverse reactions and administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions.
- Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including LFTs and thyroid function tests at baseline and before each dose.
- Do not shake ipilimumab. Administer the diluted solution through a nonpyrogenic, low-protein-binding in-line filter.
- Pregnancy category C: 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 fluorouracil and leucovorin
  - Second-line therapy (single agent) after fluorouracil-based therapy

FDA-Approved Dosage

- First-line combination-agent dosing: See product labeling for fluorouracil/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

- 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, and anorexia, flatulence
- HEMAT: myelosuppression

- HEPAT: increased bilirubin and LFTs
- NEURO: insomnia and dizziness
- PULM: dyspnea, coughing, and rhinitis
- Other: asthenia and fevers

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.

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 (e.g., 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 (e.g., diphenhydramine) and an H_2 antagonist (ranitidine).

- Ixabepilone is metabolized through CYP 3A4 isoenzyme. Screen for drug interactions with CYP 3A4 inhibitors or inducers. A dose modification is suggested if concomitantly used with a potent CYP 3A4 inhibitor.
- Pregnancy category D: Ixabepilone may cause fetal harm when administered to a pregnant woman.

LAPATINIB (TYKERB)

Mechanism of Action

- Tyrosine Kinase Inhibitor of EGFR Type 1 (EGFR/HER1) and human epidermal receptor type 2 (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 hormone receptor-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: 1,250 mg orally once daily on days 1 to 21 continuously in combination with capecitabine (dosed on days 1 to 14) in a repeating 21-day cycle.
  - Hormone receptor-positive, HER2-positive metastatic breast cancer: 1,500 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 (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.

- Lapatinib is metabolized through CYP 3A4 isoenzyme. Screen for drug interactions with CYP 3A4 inhibitors or inducers. Dose modifications may be necessary if concomitant use is unavoidable with potent inhibitors or inducers.
- Pregnancy category D: Lapatinib 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

- MDS: treatment of patients with transfusion dependent anemia due to low- or intermediate-1 risk MDSs associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
- Multiple myeloma: second-line therapy of multiple myeloma patients in combination with dexamethasone who have received at least one prior therapy

FDA-Approved Dosage

- MDS: 10 mg orally daily with water
- Multiple myeloma: 25 mg orally daily on days 1 to 21 of a 28-day treatment cycle in combination with dexamethasone. Dexamethasone is dosed at 40 mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles of therapy. Thereafter, dexamethasone is dosed at 40 mg orally daily on days 1 to 4 every 28 days.

Dose Modification Criteria

- Renal: yes
- Hepatic: no data
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: edema
- DERM: rash, pruritis, and dry skin
- ELECTRO: hypokalemia
- GI: diarrhea, constipation, N/V (minimal to low), abdominal pain, and anorexia
- HEMAT: myelosuppression
- NEURO: dizziness, headache, insomnia, and tremor
- PULM: dyspnea, cough, and nasopharyngitis
- Other: thromboembolic events, fatigue, fever, arthralgia, back or limb pain, and muscle cramps

Comments

- Revlimid 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.
- Pregnancy category X. 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 patient consent, 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.

LETROZOLE (FEMARA)

Mechanism of Action

- Selective, nonsteroidal aromatase inhibitor

FDA-Approved Indications

- Breast cancer
  - For adjuvant treatment of postmenopausal women with hormone receptor-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 treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer
  - Second-line treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy

FDA-Approved Dosage

- 2.5 mg orally daily

Dose Modification Criteria

- Renal (CrCl ≥10 mL per minute): no
- Hepatic (mild-to-moderate impairment): no
- Hepatic (severe impairment): yes

Adverse Reactions

- GI: nausea (minimal), constipation, and diarrhea
- NEURO: headache
- Other: hot flashes, fatigue, musculoskeletal pain, arthralgia, and peripheral edema

LEUPROLIDE ACETATE (LUPRON, LUPRON DEPOT, LUPRON DEPOT-3 MONTH, LUPRON DEPOT-4 MONTH, VIADUR)

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

- Palliative treatment of advanced prostate cancer
- Other indications: endometriosis, uterine leiomyomata (fibroids), central precocious puberty

FDA-Approved Dosage

- Prostate cancer: Lupron—1 mg SC daily; Lupron depot—7.5 mg IM monthly; Lupron depot -3 month—22.5 mg IM every 3 months; Lupron depot-4 month—30 mg IM every 4 months; Viadur implant—one implant (contains 72 mg of leuprolide acetate) every 12 months

Adverse Reactions

- CV: transient changes in blood pressure (hypo- or hypertension)
- 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 bone mineral density, osteoporosis, bone fracture, and asthenia

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.
- Because of different release characteristics, a fractional dose of the 3-month or 4-month lupron depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

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 (>60 mg/m^2–high, ≤ 60 mg/m^2–moderate) 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 1,100 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.

MECHLORETHAMINE (MUSTARGEN)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Systemic (intravenous) palliative treatment of bronchogenic carcinoma, CLL, 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

- Intravenous 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 per day. Dosage should be based on ideal dry body weight.
- MOPP regimen (Hodgkin disease): Mechlorethamine 6 mg/m^2 IV × 1 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 azospermia

Comments

- Vesicant

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 1,000 mg intramuscular 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 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: 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 intramuscular 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 per day)
- Endometrial cancer: 10 mg PO QID to 80 mg PO QID (four times daily; total daily dose: 40 to 320 mg per day)

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 per day (consult current literature).

MELPHALAN (ALKERAN); MELPHALAN INJECTION

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Multiple myeloma: palliative treatment (oral tablets and injection)
- Ovarian cancer: palliative treatment of nonresectable epithelial carcinoma of the ovary (oral tablets)

FDA-Approved Dosage

- Multiple myeloma.
  - Oral administration: 6 mg orally daily $\times$ 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.

- Intravenous 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.

■ 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; high dose intravenous: moderate); diarrhea, mucositis, and anorexia
■ HEPAT: increased LFTs
■ PULM: pulmonary toxicity (pulmonary fibrosis, 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 intravenous 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.

MERCAPTOPURINE (PURINETHOL)

Mechanism of Action

■ Antimetabolite

FDA-Approved Indications

■ 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, alopecia;
■ GI: anorexia, N/V (minimal), mucositis
■ HEMAT: myelosuppression
■ HEPAT: hepatotoxicity
■ Other: tumor lysis syndrome

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 (TMPT). TMPT genotyping or phenotyping can identify patients who are homozygous deficient or who have low or intermediate TMPT activity and who would need dose reduction to avoid mercaptopurine toxicity.

METHOTREXATE

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- Neoplastic disease indications: gestational tumors (choriocarcinoma, chorioadenoma destruens, hydatidiform mole), 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 NHL, and nonmetastatic osteosarcoma (high-dose therapy followed by leucovorin rescue)
- Other indications: psoriasis (severe, recalcitrant, disabling); rheumatoid arthritis (severe)

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, 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 ($\leq$50 mg/m^2: minimal, >50 to <250 mg/m^2: low, $\geq$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 intravenous 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 (e.g., 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.
- Nonsteroidal anti-inflammatory drugs 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 intravenous regimens.

MITOMYCIN

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)

FDA-Approved Dosage

- Single-agent therapy: 20 mg/m^2 IV $\times$ 1 dose repeated every 6 to 8 weeks.
- Refer to current literature for alternative dosing regimens and combination regimens.

Dose Modification Criteria

- Renal: yes
- Myelosuppression: yes

Adverse Reactions

- CV: CHF (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

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. Doses are usually increased incrementally to 9 to 10 g per day or until maximum tolerated dose is achieved. Maximum tolerated dose range varies from 2 to 16 g per day but has usually been 9 to 10 g per day. Total daily doses should be administered in three to four divided doses.

Adverse Reactions

- DERM: transient skin rashes
- GI: anorexia, N/V, and diarrhea
- NEURO: vertigo, depression, lethargy, somnolence, and dizziness
- Other: adrenal insufficiency

Comments

- Institute adrenal insufficiency precautions.
- 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.

MITOXANTRONE (NOVANTRONE)

Mechanism of Action

- Interacts with DNA; intercalating agent; topoisomerase II inhibition

FDA-Approved Indications

- ANLL (myelogenous, promyelocytic, monocytic, erythroid acute leukemia) in adults (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 $\times$ 3 days (days 1, 2, and 3) in combination with cytarabine; consolidation, 12 mg/m^2 IV daily $\times$ 2 days (days 1 and 2) in combination with cytarabine
- Prostate cancer: 12 to 14 mg/m^2 IV $\times$ 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 to moderate), 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.

NELARABINE (ARRANON)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- T-cell ALL and T-cell lymphoblastic lymphoma: in patients whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens

FDA-Approved Dosage

- Adult: 1,500 mg/m^2 intravenous 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 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 (e.g., intravenous hydration, urinary alkalization, and allopurinol) should be initiated prior to nelarabine therapy for patients considered to be at risk.
- Pregnancy category D: Nelarabine may cause fetal harm when administered to a pregnant woman.

NILOTINIB (TASIGNA)

Mechanism of Action

- Tyrosine Kinase Inhibitor (Bcr–Abl, PDGFR, and c-KIT)

FDA-Approved Indications

- CML
  - Initial therapy in newly diagnosed adults with Ph+ CML in chronic phase
  - Chronic-phase and accelerated-phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib

FDA-Approved Dosage

- CML—Newly diagnosed Ph+ CML-chronic phase: 300 mg orally twice daily; resistant or intolerant Ph(+) CML-chronic phase or accelerative phase: 400 mg orally twice daily. 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, pruritis
- ELECTRO: hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia
- GI: N/V (minimal), constipation, and diarrhea
- HEMAT: myelosuppression
- HEPAT: elevated LFTs
- NEURO: headache
- PULM: cough and dyspnea
- Other: fatigue, elevated lipase, fever, asthenia, peripheral edema, arthralgia/mylagia, 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 (e.g., 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 on patients treated with nilotinib.
- Nilotinib is metabolized through the CYP 3A4 isoenzyme. Screen for potential drug interactions with CYP 3A4 inhibitors or inducers. Dose modification may be necessary if concomitant use with a potent CYP 3A4 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.
- Pregnancy category D: 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, anorexia, and constipation
- HEPAT: increased LFTs (monitor LFTs periodically because of rare associations with cholestatic jaundice, hepatic necrosis, and encephalopathy)
- NEURO: dizziness
- Ocular: 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.

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

- CLL refractory to fludarabine and alemtuzumab.

FDA-Approved Dosage

- CLL—twelve doses administered as follows:
  - 300 mg initial dose by intravenous infusion (dose 1), followed 1 week later by
  - 2,000 mg by intravenous infusion weekly for seven doses (doses 2 to 8), followed 4 weeks later by
  - 2,000 mg by intravenous infusion every 4 weeks for four doses (doses 9 to 12)
- Do not administer as an intravenous push or bolus.

Dose Modification Criteria

- Infusion reactions: modify rate
- Hepatic: unknown
- Renal (33 to 287 mL per minute): no

Adverse Reactions

- DERM: rash
- GI: diarrhea and nausea (minimal)
- HEMAT: anemia and neutropenia
- 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 and fatigue

Comments

- Serious infusion reactions can occur. Premedicate prior to each dose with oral acetaminophen, oral or intravenous antihistamine, and intravenous corticosteroid. Do not reduce the corticosteroid dose for doses 1, 2, and 9. For doses 3 through 8 and 10 through 12, follow corticosteroid dose modifications as outlined in the package insert. Infusion reactions occur more frequently with the first two infusions.
- Progressive multifocal leukoencephalopathy (PML) can occur. Monitor for neurologic signs or symptoms.
- Screen patients at high risk of hepatitis B virus (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.
- Pregnancy category C: There are no adequate or well-controlled studies of ofatumumab in pregnant women.

OMACETAXINE MEPESUCCINATE (SYNRIBO)

Mechanism of Action

- Inhibits protein synthesis and is independent of direct Bcr–Abl binding.

FDA-Approved Indications

- 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 subcutaneous injection twice daily for 14 consecutive days of a 28-day cycle.
- CML maintenance dose: 1.25 mg/m^2 administered by subcutaneous injection twice daily for 7 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

- Hepatic: unknown
- Renal: unknown
- Hematologic toxicity: 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, 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, gastrointestinal 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.
- Pregnancy category D: Omacetaxine mepesuccinate may cause fetal harm when administered to a pregnant woman. Omacetaxine mepesuccinate may impair male fertility.

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 fluorouracil and leucovorin.
  - Treatment of advanced colorectal cancer in combination with infusional fluorouracil and leucovorin.

FDA-Approved Dosage

- Combined therapy with infusional fluorouracil and leucovorin (FOLFOX regimen)
- **Day 1**: Oxaliplatif 85 mg/m^2 IV over 120 minutes × 1 dose given concurrently with leucovorin 200 mg/m^2 IV over 120 minutes × 1 dose *followed by* fluorouracil 400 mg/m^2 intravenous bolus over 2 to 4 minutes × 1 dose *followed by* fluorouracil 600 mg/m^2 intravenous continuous infusion over 22 hours.
- **Day 2**: Leucovorin 200 mg/m^2 IV over 120 minutes × 1 dose *followed by* fluorouracil 400 mg/m^2 intravenous bolus over 2 to 4 minutes × 1 dose *followed by* fluorouracil 600 mg/m^2 intravenous 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: yes (severe renal impairment)
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CNS: peripheral sensory neuropathies (see comments below) and headache
- CV: edema and thromboembolic events
- 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
- Other: fatigue, fever, back pain, pain, 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.
- 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 to 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, 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).
- 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 H_2 antagonists (e.g., cimetidine or ranitidine) 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 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 over 3 hours every 3 weeks. Consult current literature for alternative regimens.
- Adjuvant therapy of node-positive breast cancer: 175 mg/m^2 IV 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 over 3 hours every 3 weeks or 100 mg/m^2 IV 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.

PACLITAXEL PROTEIN-BOUND (ABRAXANE)

Mechanism of Action

- Microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization.

FDA-Approved Indications

- Metastatic 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.
- Locally advanced or metastatic NSCLC as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

FDA-Approved Dosage

- Metastatic breast cancer: 260 mg/m^2 IV 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 AUC 6 mg·min/mL is given intravenously on day 1 of each 21-day cycle immediately after protein-bound paclitaxel administration.

Dose Modification Criteria

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Hepatic (mild): no
- Hepatic (moderate, severe): yes
- Renal: not studied

Adverse Effects

- Cr: increased serum creatinine
- CV: abnormal ECG
- DERM: alopecia
- GI: diarrhea and nausea (low)
- 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: blurred vision, keratitis, and ocular/visual disturbances
- Other: arthralgia, asthenia, edema, fatigue, myalgia, and nail changes

Comments

- Contraindicated if neutrophil count is $<$1,500 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.
- Pregnancy category D: 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.

PANITUMUMAB (VECTIBIX)

Mechanism of Action

- Monoclonal antibody to the human EGFR.

FDA-Approved Indications

- Colorectal cancer: Indicated as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

FDA-Approved Dosage

- 6 mg/kg intravenous infusion over 60 minutes every 14 days. Doses higher than 1,000 mg should be administered over 90 minutes.

Dose Modification Criteria

- Renal: no (not studied in patients with severe impairment)
- Hepatic: no (not studied in patients with severe impairment)

- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- DERM: dermatitis acneiform, pruritis, 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, and bronchospasm, hypotension
- Ocular: conjunctivitis, ocular hyperemia, and increased lacrimation
- PULM: pulmonary fibrosis (rare)
- Other: fatigue

Comments

- KRAS mutation predicts for a lack of response to anti-EGFR agents like panitumumab. Panitumumab is not indicated for the treatment of patients with KRAS mutation-positive metastatic colorectal cancer or for whom KRAS 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. If toxicity does not improve to ≤grade 2 within 1 month, permanently discontinue panitumumab. If dermatologic toxicity does improve to ≤grade 2 after withholding no more than two doses, treatment may be resumed at 50% of the original dose. See product labeling for further information on dose adjustments.

PAZOPANIB (VOTRIENT)

Mechanism of Action

- Multityrosine kinase inhibitor of VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, PDGFR-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (Kit), IL-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).

FDA-Approved Indications

- Advanced RCC.
- Advanced soft tissue sarcoma (STS) 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

- Hepatic (mild): no
- Hepatic (moderate): yes

- Hepatic (severe): not recommended
- Renal (mild and moderate): no
- Renal (severe): no
- Peritoneal dialysis or hemodialysis: not studied

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, dysgeusia, and N/V (minimal to low)
- GU: proteinuria
- HEMAT: leucopenia, lymphocytopenia, neutropenia, and thrombocytopenia
- HEPAT: increased bilirubin and increased LFTs
- PULM: dyspnea
- Other: decreased appetite, decreased weight, hemorrhage, infection, musculoskeletal pain, thrombosis, tumor pain, and increased lipase

Comments

- Severe and fetal 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.
- 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 electrocardiograms and electrolytes should be considered.
- CHF and decreased LVEF have occurred. Monitor blood pressure 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 gastrointestinal 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 gastrointestinal perforation or fistula.
- Permanently discontinue pazopanib if signs or symptoms of RPLS occur.
- Blood pressure should be well controlled prior to initiating pazopanib. Monitor blood pressure 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 $\geq$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.
- Pregnancy category D: Pazopanib may cause fetal harm when administered to a pregnant woman.

PEGASPARAGASE (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

- ALL
  - First-line therapy as a component of a multiagent chemotherapeutic regimen.
  - ALL and hypersensitivity to native forms of L-asparaginase.

FDA-Approved Dosage

- ALL: 2,500 international units/m^2 IM or IV 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
- 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, and history of serious allergic reactions to pegasparagase

PEGINTERFERON α-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 mcg/kg SC weekly for eight doses followed by,
- 3 mcg/kg SC weekly for up to 5 years.

Dose Modification Criteria

- Hematologic toxicity: yes

- Nonhematologic toxicity: yes
- Performance status, tolerability: yes
- Hepatic: not studied
- Renal: not studied

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, dysgeusia, and N/V (minimal)
- HEPAT: hyperbilirubinemia, increased alkaline phosphatase, and increased LFTs
- NEURO: aggressive behavior, bipolar disorders, depression, encephalopathy, hallucinations, headache, increased risk of relapse in recovering drug addicts, mania, psychoses, and suicidal and homicidal ideation
- Ocular: 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 1,000 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.
- Pregnancy category C: 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 NSCLC
  - 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 locally advanced or metastatic nonsquamous NSCLC after prior chemotherapy

FDA-Approved Dosage

- Malignant pleural mesothelioma: 500 mg/m^2 IV over 10 minutes on day 1 of each 21-day cycle.
- NSCLC: 500 mg/m^2 IV over 10 minutes on day 1 of each 21-day cycle.
- When pemetrexed is combined with cisplatin for malignant pleural mesothelioma or in first-line therapy for NSCLC, the recommended dose of cisplatin (in combination with pemetrexed) is 75 mg/m^2 IV over 2 hours beginning approximately 30 minutes after the end of pemetrexed.
- See comments below regarding premedication regimen for pemetrexed.

Dose Modification Criteria

- Renal (CrCl >45 mL per minute): no, renal (CrCl <45 mL per minute): 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 (most common daily dose: 400 μg) 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 intramuscular dose of vitamin B_{12} (1,000 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).
- Pregnancy category D: 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.

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
- Myelosuppression: yes

Adverse Reactions

- DERM: rash;
- GI: N/V (moderate)
- 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 intravenous hydration (500 to 1,000 mL) before and after each pentostatin dose to reduce the risk of nephrotoxicity.

PERTUZUMAB (PERJETA)

Mechanism of Action

- Recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4.

FDA-Approved Indications

- HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

FDA-Approved Dosage

- Initial dose is 840 mg administered as a 60-minute intravenous infusion,
- Followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion.

Dose Modification Criteria

- Nonhematologic toxicity: yes
- Hepatic: unknown
- Renal (mild, moderate): no
- Renal (severe $<$30 mL per minute): unknown

Adverse Reactions

- CV: Left ventricular dysfunction
- DERM: alopecia, mucosal inflammation, paronychia, and rash
- GI: diarrhea and nausea (mild)
- HEMAT: anemia, leucopenia, 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.
- When administered with pertuzumab, the recommended initial dose of docetaxel is 75 mg/m^2, which can be escalated to 100 mg/m^2 every 3 weeks if the initial dose is well tolerated.
- 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 (i.e., a drop in LVEF to <40% or LVEF of 40% to 45% with a 10% or greater absolute decrease below pretreatment values); discontinue if the LVEF has not improved or has declined further.
- 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.
- Pregnancy category D: pertuzumab may cause fetal harm when administered to a pregnant woman. Studies in animals have resulted in oligohydramnios, delayed renal development, and death.

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 (GBM) 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 results in a dose of 61.6 mg).

Adverse Reactions

- GI: N/V (low)
- NEURO: meningitis, abscess, and brain edema
- Other: abnormal healing, pain, and fever

Comments

- Wafers can be broken in half. Proper handling and disposal precautions should be observed.

PONATINIB (ICLUSIG)

Mechanism of Action

- Tyrosine Kinase Inhibitor 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-phase, accelerated-phase, or blast-phase CML that is resistant or intolerant to prior TKI therapy or Ph+ acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy

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

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Hepatic (mild): no
- Hepatic (moderate to severe): avoid use
- Renal: not studied

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(low), and pancreatitis
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs
- NEURO: headache, peripheral neuropathy, and stroke
- 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 blood pressure 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.

- 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 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.
- Pregnancy category D: 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 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 radiotherapy 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 intravenous 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, 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 intravenous push over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles

Dose Modification Criteria

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Hepatic: not evaluated
- Renal (moderate, severe): use with caution, and monitor for toxicity due to increased exposure
- End-stage renal disease and/or dialysis: avoid

Adverse Effects

- Cr: increased serum creatinine
- CV: tachycardia
- DERM: bullous exfoliative skin reactions including toxic epidermal necrolysis and Stevens–Johnson, 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 1.0 to1.25 mg orally on a daily basis.
- Pralatrexate should not be diluted. It is a clear, yellow solution.
- Coadministration with probenecid or other drugs that may affect relevant transporter systems (e.g., NSAIDs) require close monitoring for signs of systemic toxicity.
- Pregnancy category D: Pralatrexate can cause fetal harm when administered to a pregnant woman. Women should be advised against breastfeeding while being treated with pralatrexate.

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), 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 (MAO) inhibitor; avoid tyramine-rich foods, sympathomimetic drugs, antidepressant agents (e.g., tricyclic or SSRIs). 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 moderate or severe impairment)
- Myelosuppression: no
- Nonhematologic toxicity: no

Adverse Reactions

- CV: peripheral edema
- GI: N/V (minimal)
- 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 (e.g., 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.

REGORAFENIB (STIVARGA)

Mechanism of Action

- Kinase inhibitor of multiple membrane-bound and intracellular kinases

FDA-Approved Indications

- Metastatic colorectal cancer in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy

FDA-Approved Dosage

- 160 mg orally once daily with a low-fat breakfast for the first 21 days of each 28-day cycle

Dose Modification Criteria

- Nonhematologic toxicity: yes
- Hepatic (Child–Pugh class A or B): no
- Hepatic (Child–Pugh class C): not studied
- Renal (CrCL 60 to 89 mL per minute): no
- Renal (CrCL 30 to 59 mL per minute): unknown
- Renal (severe, or end-stage renal disease): not studied

Adverse Effects

- CV: cardiac ischemia, cardiac infarction, and hypertension
- DERM: Hand–foot skin reaction
- ELECTRO: hypocalcemia, hypokalemia, hyponatremia, and hypophosphatemia
- GI: decreased appetite, diarrhea, mucositis, and N/V (minimal to 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, 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.
- 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 blood pressure 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.
- Gastrointestinal 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 uridine diphosphate glucuronsyltransferases (UGT) 1A9 and 1A1, which may increase the exposure of UGT1A1 substrates (e.g., irinotecan).
- Pregnancy category D: regorafenib may cause fetal harm when administered to a pregnant woman. Results from animal studies indicate that regorafenib can impair male and female infertility.

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

- 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.
- CLL: In combination with fludarabine and cyclophosphamide (FC) in previously untreated and previously treated CD20-positive CLL.
- Other: Rheumatoid arthritis, granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA).

FDA-Approved Dosage

- Premedication with acetaminophen and an antihistamine (e.g., 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 IV 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 $\times$ 1 dose the day prior to initiation of FC chemotherapy, followed by 500 mg/m^2 IV on day 1 of cycles 2 to 6 (every 28 days).
- Rate titration: For the first infusion start at 50 mg per hour, and then may increase by 50 mg per hour every 30 minutes up to a maximum of 400 mg per hour. 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 per hour, and then may increase by 100 mg per hour every 30 minutes up to a maximum of 400 mg per hour.
  - 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, pruritis, 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, 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.

- Rituximab is commonly combined with cytotoxic chemotherapy agents in various subtypes of B-cell NHL. Consult current literature for dosing regimens.

ROMIDEPSIN (ISTODAX)

Mechanism of Action

- Histone deacetylase inhibitor

FDA-Approved Indications

- CTCL in patients who have received at least one prior systemic therapy
- PTCL in patients who have received at least one prior therapy

FDA-Approved Dosage

- 14 mg/m^2 administered intravenously 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

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Hepatic (mild): no
- Hepatic (moderate, severe): not studied, use with caution
- Renal: no
- End-stage renal disease: not studied, use with caution

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, dysgeusia, diarrhea, N/V (low), and stomatitis
- HEMAT: anemia, lymphopenia, neutropenia, and thrombocytopenia
- HEPAT: elevated LFTs and hypoalbuminemia
- 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.
- 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 medicine 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.
- Pregnancy category D: Based on its mechanism of action and findings in animals, romidepsin 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

- Intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis

FDA-Approved Dosage

- Starting dose: 20 mg orally twice daily for patients with a platelet count greater than 200×10^9/L
- Starting dose: 15 mg orally twice daily for patients with a platelet count between 100×10^9/L and 200×10^9/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

Dose Modification Criteria

- Hematologic toxicity: yes
- Hepatic impairment: use and dose modification depend on platelet count
- Renal (mild): no
- Renal (moderate, severe, end-stage renal disease): use and dose modification depend on platelet count

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 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 nasogastric (NG) tube using an appropriate syringe. Flush NG tube with 75 mL of water.
- Active serious infections should have resolved before starting therapy.
- Pregnancy category C: There are no adequate and well-controlled studies of ruxolitinib in pregnant women.

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

- INFU: back pain, chills, fatigue, fever, hypertension, nausea, joint ache, respiratory events (dyspnea, hypoxia, bronchospasm), N/V, and tachycardia

Comments

- 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, natural killer 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 intravenous 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.

SORAFENINIB (NEXAVAR)

Mechanism of Action

- Tyrosine Kinase Inhibitor (Raf kinases, VEGFR-2, -3, FLT-3, KIT, PDGFR-β)

FDA-Approved Indications

- Advanced RCC
- Unresectable hepatocellular carcinoma

FDA-Approved Dosage

- 400 mg orally twice daily without food (1 hour before or 2 hours after eating)

Dose Modification Criteria

- Renal: no (not studied in patients who are on dialysis)
- Hepatic: no (not studied in patients with severe hepatic impairment)
- Myelosuppression: no
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension, cardiac ischemia/infarction (see comments), QT prolongation
- DERM: palmar-plantar erythrodysesthesia, rash, alopecia, pruritis, dry skin, erythema, severe bullous, and exfoliative skin reactions
- ELECTRO: hypophosphatemia
- GI: N/V (minimal), diarrhea, anorexia, abdominal pain, and gastrointestinal 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 of modification for severe toxicity (see product labeling).
- Monitor blood pressure 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 a hepatocellular cancer trial, the incidence of cardiac ischemia/infarction was higher in the sorafenib-treated patients (2.7%) compared to the placebo group (1.3%).
- 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 (e.g., 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.
- Pregnancy category D: May cause fetal harm when administered to a pregnant woman.

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 $\times$ 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 1,500 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, 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

- Tyrosine Kinase Inhibitor (VEGFR-1, -2, -3, FLT-3, KIT, PDGFR-α, β, CSF-1R, RET)

FDA-Approved Indications

- GIST: after disease progression on or intolerance to imatinib mesylate
- Advanced RCC
- Advanced pancreatic neuroendocrine tumors (pNET)—progressive, well-differentiated pNET in patients with unresectable locally advanced or metastatic disease

FDA-Approved Dosage

- GIST and RCC: 50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off. Sunitinib may be taken with or without food.
- pNET: 37.5 mg orally once daily continuously without a scheduled off-treatment period.

Dose Modification Criteria

- Renal: no (not studied in patients with renal impairment)
- Hepatic: no (not studied in patients with severe hepatic impairment)
- 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
- GI: N/V (low), diarrhea, mucositis/stomatitis, dyspepsia, abdominal pain, constipation, altered taste, and anorexia
- 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 blood pressure and treat as needed.
- 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 electrocardiograms 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.
- Pregnancy category D: may cause fetal harm when administered to a pregnant woman.

TAMOXIFEN (NOLVADEX)

Mechanism of Action

- Nonsteroidal antiestrogen

FDA-Approved Indications

- Breast cancer treatment
  - Treatment of metastatic breast cancer
  - Adjuvant treatment of node-positive and node-negative breast cancer following breast surgery and breast irradiation
  - Reduction in breast cancer incidence
    - Ductal carcinoma in situ (DCIS): to reduce the risk of invasive breast cancer following breast surgery and radiation
    - High-risk women, at least 35 years of age with a 5-year predicted risk of breast cancer $\geq$1.67% as calculated by the Gail model (see package insert).

FDA-Approved Dosage

- Breast cancer treatment: 20 mg orally daily or 10 to 20 mg PO twice daily (20 to 40 mg per day). Adjuvant therapy should be continued $\times$ 5 years. Doses $>$20 mg per day should be given in divided doses (morning and evening).
- Breast cancer incidence reduction (DCIS and in high risk women): 20 mg orally daily $\times$ 5 years.

Adverse Reactions

- CV: thromboembolism, stroke, PE
- DERM: skin rash
- ENDO: hot flashes
- GI: N/V (minimal) and anorexia
- GU: menstrual irregularities, pruritis vulvae, vaginal discharge, or bleeding
- HEMAT: bone marrow depression
- Ocular: vision disturbances and cataracts
- PULM: dyspnea, chest pain and hemoptysis
- Other: dizziness, headaches, tumor or bone pain, pelvic pain, and uterine malignancies

Comments

- 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. Healthcare professionals can access a breast cancer risk assessment tool on the NCI 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.

TEMOZOLOMIDE (TEMODAR)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Glioblastoma Multiforme (GBM): Newly diagnosed patients used concomitantly with radiotherapy 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 GBM: 75 mg/m^2 orally or IV daily × 42 days concomitant with focal radiotherapy followed by maintenance temozolamide for six cycles. The temozolamide dose should be continued throughout the 42-day concomitant period up to 49 days to achieve acceptable hematologic and nonhematologic parameters (see package insert). *Pneumocystis jiroveci* prophylaxis is required during the concomitant administration of temozolamide and radiotherapy and should be continued in patients who develop lymphocytopenia.
- Maintenance phase
  - Cycle 1: 150 mg/m^2 orally or IV daily × 5 followed by 23 days without treatment starting 4 weeks after the temozolamide + RT phase.
  - Cycles 2 to 6: Dose is 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 per day 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 × 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 intravenous formulations has only been established when the intravenous 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 (moderate—reduced by taking on an empty stomach), constipation, anorexia
- NEURO: headache
- Other: asthenia, fatigue, and alopecia. 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 temozoloamide 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 to 40 days) and 28 days for neutrophils (range 1 to 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 temozoloamide should not be started until the ANC and platelet count exceed these levels. See the package insert for dose modification guidelines.

TEMSIROLIMUS (TORISEL)

Mechanism of Action

- Inhibitor of mammalian target of rapamycin (mTOR)

FDA-Approved Indications

- Advanced Renal Cell Carcinoma

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, pruritis, nail disorder, and dry skin
- ENDO: hyperglycemia/glucose intolerance
- ELECTRO: hypophosphatemia and hypokalemia
- GI: N/V (low); 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.
- Pregnancy category D: May cause fetal harm when administered to a pregnant woman.

TENIPOSIDE (VUMON)

Mechanism of Action

- Topoisomerase II inhibitor

FDA-Approved Indications

- Refractory childhood ALL: induction therapy as a second-line treatment (in combination with other agents)

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 (low), and mucositis
- HEMAT: myelosuppression
- Other: anaphylaxis and hypersensitivity

Comments

- 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.

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.

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 to 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.

- Pregnancy category X. 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 patient consent, 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. 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.

THIOGUANINE (TABLOID)

Mechanism of Action

- Antimetabolite

FDA-Approved Indications

- ANLL: remission induction, 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)
- 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 thiopurine S-methyltransferase (TMPT). TMPT genotyping or phenotyping can identify patients who are homozygous deficient or who have low or intermediate TMPT 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.

THIOTEPA (THIOPLEX)

Mechanism of Action

- Alkylating agent

FDA-Approved Indications

- Superficial papillary carcinoma of the bladder, controlling intracavitary effusions secondary to diffuse or localized neoplasms of the serosal cavities, breast cancer, ovarian cancer, Hodgkin disease, and lymphosarcoma

FDA-Approved Dosage

- Intravenous administration: 0.3 to 0.4 mg/kg IV × one dose repeated at 1- to 4-week intervals. Consult current literature for alternative dosing regimens.
- Intravesical administration: Patients with papillary carcinoma of the bladder 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.

Adverse Reactions

- CNS: dizziness, headache, blurred vision, and conjunctivitis
- DERM: alopecia and pain at the injection site
- GI: anorexia, N/V (low), and mucositis at high doses
- GU: amenorrhea, reduced spermatogenesis, dysuria, and chemical or hemorrhagic cystitis (intravesical)
- HEMAT: myelosuppression
- Other: fever, hypersensitivity reactions, fatigue, weakness, and anaphylaxis

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)
- 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 intravenous infusion on day 1 only; repeated every 21 days (21-day cycle)

Dose Modification Criteria

- Renal (mild impairment, CrCl 40 to 60 mL per minute): no
- Renal (moderate impairment, CrCl 20 to 39 mL per minute): yes
- Renal (severe impairment, <20 mL per minute): 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 ≥1,500 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 (e.g., cyclosporine, elacridar, ketoconazole, ritonavir, saquinavir) can cause significant increases in topotecan exposure.
- Pregnancy category D: May cause fetal harm if administered to a pregnant woman.

TOREMIFENE (FARNESTON)

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

Adverse Reactions

- CV: thromboembolism, stroke, PE, and QT prolongation
- DERM: skin discoloration and dermatitis
- ELECTRO: hypercalcemia
- ENDO: hot flashes
- GI: N/V (minimal), constipation, and elevated LFTs
- GU: vaginal discharge and vaginal bleeding
- NEURO: dizziness and depression
- Ocular: 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 QTc 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 CYP enzyme 3A4 (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 (e.g., wafarin and phenytoin).

TRASTUZUMAB (HERCEPTIN)

Mechanism of Action

- Humanized monoclonal antibody directed at the human epidermal growth factor receptor 2 protein (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 5-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 intravenous infusion over 90 minutes followed by subsequent once weekly doses of 2 mg/kg by intravenous 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 intravenous 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 intravenous infusion over 90 minutes followed by subsequent doses of 6 mg/kg as an intravenous 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 intravenous infusion over 90 minutes followed by subsequent once weekly doses of 2 mg/kg by intravenous infusion over 30 minutes until disease progression.
- Metastatic gastric cancer: Initial dose of 8 mg/kg as an intravenous infusion over 90 minutes followed by subsequent doses of 6 mg/kg as an intravenous 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, nausea, vomiting, 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

- 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 intravenous 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.
- Trastuzumab can cause fetal harm when administered to a pregnant woman (pregnancy category D).

TRETINOIN (VESANOID)

Mechanism of Action

- Induces maturation, cytodifferentiation, and decreased proliferation of Acute Promyelocytic Leukemia 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 complete remission is documented. Therapy should be discontinued 30 days after complete remission is obtained or after 90 days of treatment, whichever comes first.

Adverse Reactions

- CV: hypertension, arrhythmias, and flushing
- DERM: dry skin/mucous membranes, rash, pruritis, alopecia, and mucositis
- GI: N/V, 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: visual changes
- Other: dyspnea, fever, shivering, retinoic acid–APL syndrome (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 $>5 \times 10^9$/L) or with rapidly evolving leukocytosis.
- Consult current literature for APL treatment regimens.

TRIPTORELIN (TRELSTAR)

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

- Palliative treatment of advanced prostate cancer

FDA-Approved Dosage

- Trelstar 3.75 mg intramuscular injection every 4 weeks
- Trelstar11.25 mg intramuscular injection every 12 weeks
- Trelstar 22.5 mg intramuscular injection every 24 weeks

Adverse Reactions

- CV: hypertension and peripheral edema
- ENDO: hot flashes, gynecomastia, breast pain, 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 bone mineral density, osteoporosis, bone fracture, and asthenia

Comments

- Use with caution in patients at risk of developing ureteral obstruction or spinal cord compression.

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, rearranged during transfection (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

- 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

Dose Modification Criteria

- Nonhematologic toxicities: yes
- Hepatic (mild): no
- Hepatic (moderate, severe): use is not recommended
- Renal (mild): no
- Renal (CrCL <30 to 49 mL per minute): yes

Adverse Reactions

- CV: heart failure, hypertension, and QT prolongation
- DERM: acne, dermatitis acneiform, dry skin, pruritis, 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 to 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.
- 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.
- Pregnancy category D: 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

- Unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

FDA-Approved Dosage

- 960 mg orally twice daily.

Dose Modification Criteria

- Nonhematologic toxicity: yes
- Hepatic (mild to moderate): no
- Hepatic (severe): exercise caution
- Renal (mild to moderate): no
- Renal (severe): exercise caution

Adverse Reactions

- CV: QT prolongation
- DERM: alopecia, cutaneous squamous cell carcinoma, dry skin, erythema, hyperkeratosis, hypersensitivity reaction (generalized rash, erythema, bullous exfoliative skin reactions [e.g., Stevens–Johnson, toxic epidermal necrolysis]), new primary malignant melanoma, photosensitivity, pruritus, rash, and skin papilloma
- GI: decreased appetite, constipation, diarrhea, and N/V (minimal to low)
- HEPAT: increased alkaline phosphatase, increased bilirubin, and increased LFTs
- NEURO: headache
- Ocular: 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.
- 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.
- Pregnancy category D: Vemurafenib 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 disease, NHL, mycosis fungoides, Kaposi sarcoma, histiocytic lymphoma, 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 step wise format up to a maximum dose of 18.5 mg/m^2 to maintain WBC >3,000 $cells/mm^3$ (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 intravenous route. Fatalities have been reported when other vinca alkaloids have been given intrathecally.
- Label syringe: Administer only intravenously; fatal if given intrathecally. Label outerwrap (if used): "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

VINCRISTINE (ONCOVIN AND OTHERS)

Mechanism of Action

- Inhibits microtubule formation

FDA-Approved Indications

- Acute leukemia.
- Vincristine has shown to be useful in combination with other agents for Hodgkin disease, NHL, 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: ophthalmoplegia and extraocular muscle paresis
- PULM: pharyngitis
- Other: jaw pain

Comments

- Vesicant.

- Administer only by the intravenous route. Fatalities have been reported when vinca alkaloids have been given intrathecally.
- Label syringe: Administer only intravenously; fatal if given intrathecally. Label outerwrap (if used): "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."
- A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine.

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

- Ph– ALL in second or greater relapse or whose disease has progressed following two or more antileukemia therapies.

FDA-Approved Dosage

- 2.25 mg/m^2 IV over 1 hour once every 7 days
- For intravenous use only; fatal if given by other routes

Dose Modification Criteria

- Hematologic toxicity: yes
- Nonhematologic toxicity: yes
- Hepatic (mild, moderate): no
- Hepatic (severe): not studied
- Renal: not studied

Adverse Effects

- CV: hypotension
- GI: bowel obstruction, constipation, diarrhea, ileus, and nausea (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 to 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.
- Pregnancy category D: Vincristine sulfate liposome may cause fetal harm when administered to a pregnant woman.

VINORELBINE (NAVELBINE)

Mechanism of Action

- Inhibits microtubule formation

FDA-Approved Indications

- NSCLC: First-line treatment as a single agent (stage IV) or in combination with cisplatin (stage III or IV) for ambulatory patients with unresectable, advanced 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, *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 $\times$ one dose on day 1 and 29, then every 6 weeks
- Flush line with 75 to 125 mL of fluid (e.g., 0.9% sodium chloride) after administration of vinorelbine.

Dose Modification Criteria

- Renal: no
- Hepatic: yes
- Neurotoxicity: yes
- Myelosuppression: 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 intravenous route. Fatalities have been reported when other vinca alkaloids have been given intrathecally.

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

Dose Modification Criteria

- Hepatic: unknown
- Renal: unknown

Adverse Reactions

- DERM: alopecia
- ELECTRO: azotemia, hypokalemia, and hyponatremia
- GI: anorexia, constipation, diarrhea, N/V (low), and taste disorders (ageusia, dysgeusia)
- Other: amenorrhea, decreased appetite, fatigue, muscle spasms, and arthralgias

Comments

- Pregnancy category D: 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.
- Systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased in the presence of drugs that inhibit P-gp (e.g., clarithromycin, erythromycin, and azithromycin).
- PPIs, H_2-receptor antagonists, and antacids may reduce vismodegib's bioavailability.

VORINOSTAT (ZOLINZA)

Mechanism of Action

- Histone deacetylase 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

Dose Modification Criteria

- Renal: no
- Hepatic: yes (use with caution in mild-to-moderate impairment, contraindicated with severe impairment)
- Myelosuppression: yes
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: QTc prolongation
- DERM: alopecia
- ENDO: hyperglycemia
- GI: N/V (low), diarrhea, anorexia, weight loss, constipation, and taste disorders (dysgeusia, dry mouth)
- GU: increased Cr and proteinuria
- HEMAT: myelosuppression (thrombocytopenia, anemia)
- Other: constitutional symptoms (fatigue, 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.
- QTc 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 gastrointestinal bleeding have been reported with concomitant use of vorinostat and other HDAC inhibitors (e.g., valproic acid).
- Pregnancy category D: 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 5-fluorouracil, leucovorin, and irinotecan-(FOLFIRI).

FDA-Approved Dosage

- 4 mg/kg IV over 1 hour every 2 weeks

Dose Modification Criteria

- Renal: no
- Hepatic: no (mild-to-moderate impairment), not evaluated in severe impairment
- Nonhematologic toxicity: yes

Adverse Reactions

- CV: hypertension and arterial thromboembolic events
- GI: diarrhea, stomatitis, weight loss, decreased appetite, abdominal pain, gastrointestinal fistula, perforation, or hemorrhage
- GU: increased serum creatinine and proteinuria
- HEMAT: myelosuppression (leukopenia, neutropenia, and thrombocytopenia)
- HEPAT: increased LFTs
- NEURO: headache, 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 blood pressure 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 per 24 hours. 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.
- Pregnancy category C: 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 Readings

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.

Part I Performance Status Scales/Scores: Performance Status Criteria

ECOG (Zubrod)		Karnofsky		Lansky[a]	
Score	**Description**	**Score**	**Description**	**Score**	**Description**
0	Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints, no evidence of disease	100	Fully active, normal
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework/office work	90	Able to carry on normal activity; minor signs or symptoms of disease	90	Minor restrictions in physically strenuous activity
2	Ambulatory and capable of all self-care but unable to carry out any activities related to work. Up and about more than 50% of waking hours	80	Normal activity with effort; some signs or symptoms of disease	80	Active, but tires faster than in previous phase
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	70	Cares for self, unable to carry on normal activity or do active work	70	Both greater restriction of play activity and less time spent in such activity than in previous phase
4	Completely disabled. Cannot carry on any self-care; totally confined to bed or chair	60	Requires occasional assistance, but is able to care for most of his/her needs	60	Up and around, but minimally active in play; keeps busy with quieter activities than in previous phase
		50	Requires considerable assistance and frequent medical care	50	Gets dressed, but lies around much of the day; no active play; able to participate in quiet play and activities

(*Continued*)

Part I (Continued)

ECOG (Zubrod)		Karnofsky		Lansky[a]	
Score	**Description**	**Score**	**Description**	**Score**	**Description**
		40	Disabled, requires special care and assistance	40	Mostly in bed; participates in quiet activities
		30	Severely disabled, hospitalization indicated; death not imminent	30	In bed; needs assistance even for quiet play
		20	Very sick, hospitalization indicated; death not imminent	20	Often sleeping; play entirely limited to very passive activities
		10	Moribund, fatal processes progressing rapidly	10	No play; does not even get out of bed

ECOG, Eastern Cooperative Oncology Group.

Karnofsky and Lansky performance scores are intended to be multiples of 10.

[a]The conversion of the Lansky to ECOG scales is intended for National Cancer Institute reporting purposes only.

APPENDIX 2

Answers to Review Questions

CHAPTER 1

1. E. This patient likely has HPV-associated oropharynx cancer, which tends to occur at a slightly younger age than smoking- and alcohol-related cancers. He is expected to have a 30% to 50% better prognosis compared to patients with the same site and stage of cancer who have a history of smoking and alcohol abuse. Because of the stage of disease, considerations for cure include definitive chemoradiation, and surgery followed by adjuvant radiation (with concomitant chemotherapy if positive margins or extracapsular spread). He could also be entered into clinical trials evaluating less toxic therapies in this group of patients.

2. E. This is a young patient with little or no smoking history and an oral cancer. Consideration should be given to inheritable abnormalities in DNA repair, such as Fanconi anemia in this patient, especially given the history of leukemia in a sibling. She is at risk for second primaries, particularly in the oral cavity and should be monitored carefully for this. The limited stage of disease and the risk of more primaries in the oral cavity make surgery (in this case, wide local excision or partial glossectomy) the best choice of treatment. Because of the size of the primary tumor, she should have elective neck dissection, because the risk of microscopic nodal involvement is at least 30% even with negative physical examination and CT.

3. C. This is a patient who emigrated from a region where nasopharyngeal carcinoma is endemic. Supraclavicular lymph node-positive nasopharyngeal carcinoma qualifies as locally advanced disease (stage IVB in this case). Nasopharyngeal carcinoma does have a strong association with EBV, unlike other head and neck malignancies, some of which are associated with HPV infection. The recommended treatment for locally advanced nasopharyngeal carcinoma is concurrent cisplatin chemotherapy and radiation with adjuvant chemotherapy with cisplatin and 5-FU; 5-year overall survival near 50% to 60% is seen in modern series. Surgery is rarely indicated for nasopharyngeal carcinoma.

4. D. This is a relatively typical course for a patient receiving concurrent chemoradiation for an oropharyngeal squamous cell carcinoma. Oral candidiasis is not uncommon in this setting, and is treated with antifungal medications at the time it is discovered; prophylactic treatment is not generally indicated. Percutaneous feeding tube removal is not scheduled for a specific time frame, but is only done once a patient can demonstrate a sustained ability to take adequate nutrition orally. A thorough dental evaluation and any procedures, particularly extractions, should be done before initiating chemoradiation. Healing ability will be impaired after chemoradiation, and extractions pose a risk for the development of osteoradionecrosis. Cholinergic agonists can be considered for xerostomia that persists for 1 to 2 years after chemoradiation and is troublesome. For large (>6 cm, N_3) adenopathy, a planned neck dissection after definitive chemoradiation is standard at many institutions.

5. E. In locally advanced carcinoma of the larynx, cisplatin and concurrent radiation results in improved larynx preservation and similar survival compared to surgery followed by radiation and compared with chemotherapy followed by radiation or radiation alone. However, adding cetuximab to the combination of cisplatin and radiation has not

been shown to improve outcomes over those achieved with just concurrent cisplatin and radiation. Postoperative cisplatin and radiation do improve local control and progression-free survival in patients with nodal extracapsular extension and positive margins. The choice of treatment will depend on the patient's overall condition, the likelihood that voice can be preserved with nonoperative primary treatment, and the patient's preference. Radiation alone could be considered for a patient that cannot tolerate combined chemoradiation or surgery followed by combined chemoradiation, but this patient has a good performance status and medical condition, as well as family support.

CHAPTER 2

1. A. The patient with good performance status with newly diagnosed metastatic squamous cell lung cancer would benefit from systemic chemotherapy. Histology of NSCLC is important in treatment selection. Patients with squamous histology have shown showed improved survival with cisplatin/gemcitabine as initial chemotherapy treatment compared with pemetrexed/cisplatin (B is incorrect). Bevacizumab is not recommended in patients who are at increased risk of bleeding: squamous histology, tumor location close to major blood vessels, tumor necrosis, cavitation or pre-existing hemoptysis (C and D are incorrect).

2. E. Randomized trials of screening with chest radiography with or without sputum cytology have shown no reduction in lung-cancer mortality (C and D are incorrect). The National Lung Screening Trial (NLST), a randomized trial compared annual screening by low dose chest CT scanning with chest x-ray for three years found a reduction in lung cancer related mortality and all cause mortality in high-risk patients screened with low dose CT scan. However the high-risk population was defined by NLST as individuals between 55 and 74 years of age with at least 30 pack-year cigarette smoking, and former smokers who had quit within the previous 15 years. There is no data to support lung cancer screening in a person with the risk- profile described in the question (A and B are incorrect).

3. B. The patient has stage IIIB disease (T2N3). Stage IIIB lung cancers are not amenable to curative surgical resection unless they are highly selected (A and C are incorrect). For patients with stage IIIB disease with good performance status, combined modality therapy with chemotherapy and radiation is recommended. Concurrent chemotherapy and radiation is superior to sequential therapy (D is incorrect).

CHAPTER 3

1. A. Small cell carcinomas express TTF1 and epithelial markers (CK7 and keratin) most commonly. Neuroendocrine markers (chromogranin and synaptophysin) are often positive in this disease, but can be negative in 10% of small cell carcinoma cases.

2. B. 10% to 14% of patients with small cell carcinoma have brain metastases at diagnosis. Therefore some form of brain imaging (CT or MRI) is indicated. The role of PET/CT in SCLC is debatable. Mediastinoscopy is an invasive investigation used in the staging of locally advanced non–small cell lung cancer. A bone marrow examination is not routinely recommended in this disease.

3. C. This patient has limited stage disease, as he has disease that can be confined to one radiation field. Limited and extensive stages are part of the Veteran's Association Classification system. Stage I disease would not involve ipsilateral mediastinal lymph nodes, and stage IV disease would include distant metastases. The TNM staging system is not commonly used in SCLC, but should be encouraged.

This patient's comorbidities include a history of head trauma 20 years ago which has impaired his short-term memory. He is otherwise fit and independent, with a PS of 1.

4. C. Phase III data support the treatment of LS SCLC with combined chemoradiotherapy. Concurrent chemotherapy has been shown to be superior to sequential therapy. Chemotherapy alone (options A and B) would be more appropriate treatment options for extensive stage disease.

5. C. Prophylactic cranial irradiation has been shown to improve both morbidity and mortality in limited and ES SCLC that demonstrates a response to chemotherapy. However, there is a significant incidence of neurocognitive decline as a long-term toxicity of this treatment. Therefore, in this patient, a discussion would have to take place regarding the pros and cons of this prophylactic treatment in a patient with known neurocognitive impairment.

CHAPTER 4

1. B. Endoscopic ultrasound (EUS) provides the most staging information on a patient with apparently localized esophageal cancer. In the absence of distant metastatic disease, establishing T and N stages is the primary concern, as this will guide his treatment plan. While PET/CT has greater sensitivity for metastatic disease than CT alone, it does not have the same sensitivity for nodal staging.

2. D. SCC is more common in the upper esophagus than the lower, and is more strongly associated with alcohol intake and cigarette smoking. The prognosis for patients with SCC has not been shown to differ from those with adenocarcinoma, but it appears to be a more chemo- and radiosensitive disease. In addition to this, the operative approach for resection of tumors in the upper esophagus can result in more operative morbidity. In light of this, there is a rationale for treating with definitive chemoradiotherapy. Standard chemotherapy protocols in this treatment include cisplatin combined with fluorouracil, or oxaliplatin combined with fluorouracil. Although this approach has not been compared directly to a surgical approach, the outcomes from studies are similar, and the potential operative morbidity is avoided.

3. D. Patients diagnosed with metastatic esophageal adenocarcinoma have been shown to benefit from palliative chemotherapy from a number of studies, and the cisplatin/fluorouracil regimen is one of the most widely studied. Recent advances in understanding the molecular biology of cancer have led to targeted therapies being developed in a number of diseases. The HER2 oncogene is overexpressed in approximately 15% of esophagogastric cancers, and a recent study has shown that the addition of trastuzumab, a monoclonal antibody directed against the HER2 receptor, to cisplatin and fluorouracil chemotherapy results in improved tumor response and survival. VEGFR is implicated in tumor angiogenesis, and studies evaluating antiangiogenic agents such as bevacizumab are ongoing. The EGF receptor is also overexpressed in many esophagogastric cancers, but studies investigating the use of agents targeting this receptor have failed to show a benefit. ERCC1 levels appear to be associated with sensitivity to platinum chemotherapy in esophageal cancer, but their use in clinical practice is currently not recommended outside of a clinical trial.

CHAPTER 5

1. D. This patient has an early-stage primary gastric lymphoma localized to GI tract. Pathology is consistent with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue tumor (MALT lymphoma) which is typically associated with *Helicobacter pylori* infection. Primary gastric lymphoma accounts for 3% of gastric neoplasms and 10% of lymphomas. *H. pylori*-induced gastritis leads to the accumulation of CD4+ lymphocytes and mature B cells in the gastric lamina propria resulting in the activation of T cells with B-cell proliferation and lymphoid follicle formation which eventually evolve into a monoclonal lymphoma. The treatment of choice for *H. pylori*-positive early-stage disease (stagey/IIE) is eradication of *H. pylori*. This would provide 50% to 80% histologic complete response and long-term remission. However, patients with t(11:18) translocation are typically not responsive to *H. pylori* therapy and external beam radiation (RT) is recommended. Local RT (total dose of 25 to 30 Gy) results in high rates of overall and complete responses (100% and 98%, respectively) and 5-year disease-free and overall survival rates of 98% and 77%, respectively. Bone scans are not routinely recommended for MALT lymphoma. Surgery is reserved for patients with obstructive symptoms or bleeding and chemotherapy is reserved for higher grade gastric lymphomas.

2. B. The risk of gastric cancer increases 15 to 20 years after partial gastrectomy surgery with the relative risk of 1.5 to 3. The mechanism is thought to be due to gastric production of *N*-nitroso carcinogens in the gastric remnant. These compounds are generated from nitrate and nitrite by gastric bacteria, which have overgrown from postoperative hypochlorhydria. In addition, gastric reflux of bile with increased level of bile acids may play a role. The increasing risk of gastric stump cancer with duration of postoperative period suggests a dose–response relationship and supports this mechanism of carcinogenesis. There are no sufficient data to support routine endoscopic surveillance for patients with previous partial gastrectomy for peptic ulcer disease. However, the threshold should be low to endoscopically evaluate upper GI symptoms. If surveillance is considered, it should be initiated 15 to 20 years postgastrectomy.

Routine screening for gastric cancer is not recommended in the United States, where the overall gastric cancer burden is low. Periodic upper endoscopy can be offered to patients who are considered to be at increased risk; however, the benefits and risks are unclear.

3. C. The patient has metastatic gastric adenocarcinoma and the goal of treatment is palliation. He has a reasonable performance status with no major comorbidities. Therefore, the standard of care is to screen for HER2 expression status by immunohistochemistry (IHC) and gene amplification by florescence in situ hybridization (FISH) if IHC is equivocal. If HER2 is positive, chemotherapy with trastuzumab is recommended as a first-line treatment. Data from the randomized phase III ToGA study showed that the addition of the monoclonal antibody against HER2 (trastuzumab) to cisplatin/fluoropyrimidine provided significantly higher objective response rates (47% vs. 35%) and improved median overall survival compared to chemotherapy alone (13.8 vs. 11.1 months; p= 0.0046). Since EGD did not show active bleeding and the patient did not have uncontrolled pain from the tumor, RT is not indicated at this point. There is no role for concurrent or sequential chemoradiation for metastatic gastric cancer. Bevacizumab with chemotherapy in metastatic gastric cancer did not show a survival advantage in the phase III trial and should not be offered outside of a clinical trial, particularly given the patient's recent bleeding event.

4. D. The adjuvant treatment options for R0 resected gastric tumor are chemoradiation and potentially chemotherapy if D2 resection is achieved. At least 16 lymph nodes need to be examined for adequate sampling. D2 resection involves removal of extensive lymph nodes including perigastric, hepatic, left gastric, celiac, and splenic arteries; splenic hilar nodes; +/– splenectomy. D2 resection is not routinely performed in the United States and only performed in the experienced centers because of the significant postoperative morbidity and mortality. Subjecting the patient to a repeat surgical intervention is not justified given the negative margins and adequate node sampling. The INT-0116 trial demonstrated a survival benefit with adjuvant chemoradiation (5-FU/leucovorin before, during, and after radiation therapy) compared to surgery alone in patients who received less than a D2 resection. Oral fluropyrimidine (S-1) for 1 year adjuvant after D2 resection showed improvement in overall survival and relapse-free survival and is approved for adjuvant therapy in Japan. S-1 is not commercially available in the United States. Perioperative (pre- and postoperative) polychemotherapy using ECF (epirubicin, cisplatin, and infusional 5-FU) is an acceptable standard of care, but the patient did not receive preoperative chemotherapy. Therefore, chemoRT would be the best option to improve relapse-free and overall survival.

5. C. The patient has a resectable gastric cancer, likely T2N1-2M0 disease. A randomized phase III (MAGIC) trial showed that perioperative chemotherapy with ECF (epirubicin, cisplatin, 5FU) given for 3 months before and after surgery resulted in significantly improved 5-year progression-free survival (HR 0.66; 95% CI 0.53 to 0.81; $p < 0.001$) and overall survival (36% vs. 23%) compared to surgery alone. After perioperative polychemotherapy, the resected tumors were significantly smaller and less advanced with similar postoperative complications or deaths between two arms. Neoadjuvant concurrent chemoRT is more commonly used for esophageal, GEJ, and gastric cardia cancers than for potentially resectable noncardia gastric adenocarcinomas. There are no randomized trials addressing the benefit of preoperative chemoRT in noncardia gastric cancer. No survival benefit was observed with adjuvant radiation alone after surgery. Preoperative chemotherapy in combination with bevacizumab is still under investigation and should not be used outside the context of a clinical trial.

CHAPTER 6

1. B. This patient has been diagnosed with a stage I (T1a N0 M0) well-differentiated gallbladder adenocarcinoma, which was incidentally found postsurgical resection. Among patients with T1a lesions with negative tumor margins, survival rates approach 100% with simple cholecystectomy alone. These patients may be observed postcholecystectomy. Extended cholecystectomy is recommended for patients with T1b or greater lesions. If the malignancy was an incidental finding similar to the patient above, preoperative restaging should be considered first to rule out metastatic disease. Chemotherapy is recommended in patients with T1b or greater disease with an unresectable lesion. If chemotherapy were the preferred option, gemcitabine and cisplatin combination therapy would be the recommended route. Hospice discussion is not relevant in this patient population as survival rates approach 100% with cholecystectomy for T1a lesions.

2. C. The patient discussed above appears to have a stage III (T4 N1 MO) poorly differentiated extrahepatic cholangiocarcinoma. Surgical resection (R0) remains the only possibility for cure; however, due to tumor involvement of the blood vessels, the surgical team determined this patient's tumor to be unresectable. In patients with unresectable disease, combination chemotherapy with gemcitabine and cisplatin is the current standard of care for upfront therapy. A 2010 *New England Journal of Medicine* article demonstrated that gemcitabine and cisplatin in combination improved overall survival and progression-free survival compared to gemcitabine alone. Chemoradiation can be used as first-line treatment in patients with locally advanced disease; however, chemotherapy of choice would be a fluoropyrimidine instead of gemcitabine. Surveillance would not be an option for this patient due to the aggressive nature of this disease.

CHAPTER 7

1. D. This patient has advanced cirrhosis and a new liver lesion that is confirmed as HCC based on radiographic and biochemical criteria. According to the American Association for the Study of Liver Disease (AASLD) guidelines, no tissue confirmation of HCC is required when these criteria are met. In fact, percutaneous biopsy has been linked with the potential for cancer seeding along the biopsy track, which could limit the patient's eligibility for liver transplant. PET scanning is generally not helpful in the workup and management of localized HCC. Up to half of HCC lesions are not FDG-avid on PET scan, so the modality is not indicated, except in the workup of potential metastatic sites. Liver resection and liver transplant are both considered potentially curative treatment modalities for a patient with a solitary HCC, but in this case, the advanced underlying cirrhosis suggested by thrombocytopenia, portal hypertension, and decreased synthetic function (low albumin) means that resection is contraindicated. The patient would be at extremely high risk for perioperative mortality and would likely progress to fulminant liver failure shortly after a major hepatectomy. Liver transplant is the most appropriate treatment plan in this case, pending formal review by a multidisciplinary group and the timely availability of a donor organ.

2. B. This patient has metastatic HCC, so there is no indication for curative intent therapy. There is no role for debulking surgery in patients with HCC, as it will not impact survival. Liver transplant is not indicated here, as the tumor burden is clearly outside the Milano/Mazzaferro criteria, with the presence of extrahepatic disease (we do not have details on the extent of the liver masses, only that they are multifocal). Since no transplant is on offer, there is no indication for bridging therapy with TACE. He has BCLC stage C disease, for which TACE is not recommended as primary therapy, in this case due to the significant extrahepatic disease burden. The fact that the patient has retained a reasonable performance status of ECOG 1 indicates that he is still a candidate for some form of therapy—there are options to consider before hospice referral. Sorafenib is the only approved systemic agent for the first-line treatment of advanced HCC and is the appropriate choice in this case. Therapy is palliative in nature, but improved PFS has been shown in a number of randomized clinical trials comparing sorafenib with best supportive care. An alternative option here may be to consider enrolling on a first-line clinical trial, if one were available at this tertiary care center.

3. B. This woman has developed HCC arising from NAFLD (nonalcoholic fatty liver disease) and has BCLC stage B disease (intermediate stage). The extent of liver disease in this case means that surgical resection is not an option, but the typical recommendation would be for some form of liver-directed therapy. There are no obvious contraindications to TACE in this scenario. A number of meta-analyses have suggested PFS and OS benefit from intra-arterial therapy, and most centers would offer this patient TACE or TAE (bland embolization, with no chemotherapeutic component). While sorafenib is an approved agent for advanced HCC, not amenable to curative intent therapy, the PFS benefit is not as great as that seen with TACE/TAE in this clinical setting (BCLC stage B). Similarly, a chemotherapy-based clinical trial would not be appropriate to offer a patient who is a candidate for liver-directed therapy, as in this case.

4. C. This patient underwent appropriate up-front therapy for solitary HCC in a noncirrhotic liver. He was not a candidate for liver transplant, as his tumor was greater than 5 cm in maximal diameter, but he was an excellent candidate for surgical resection due to his preserved liver function. Despite this good surgical outcome, he still has a high risk of tumor recurrence, especially in light of the vascular invasion

seen on the pathology specimen. However, there is no evidence to suggest that adjuvant therapy, either radiation or systemic chemotherapy, will impact this risk of recurrence in patients with HCC. As such, the recommendation here is for interval surveillance with imaging and laboratory data (AFP). The most common site for recurrence remains the liver remnant, and other potential sites include lymph nodes, lung, adrenal gland, and bone. Treatment options at the time of recurrence will depend on the extent and location of that recurrence. Liver transplant workup is not appropriate in this case, as the original tumor was clearly outside the Milano/Mazzaferro criteria.

CHAPTER 8

1. C. This patient's presentation, symptoms, and complete blood count are consistent with iron deficiency anemia (IDA). Although she reports possible hemorrhoidal bleeding, a microcytic anemia in a nonmenstruating female should raise concern for occult blood loss from the gastrointestinal tract (large polyp, cancer, etc.). Given her history of bright red blood per rectum and evidence of IDA, colonoscopy is the next best test to order. FOBT or FIT tests are excellent screening tests for a colorectal malignancy, but should only be used in a screening, not in a diagnostic setting. A PET scan is not indicated at this time, even if a colorectal malignancy is confirmed, as a more appropriate imaging study in that setting would include a contrasted CT scan. In addition, primary colon cancers or large polyps can be difficult to identify with PET scan due to the normal biologic uptake of fluorodeoxyglucose by the surrounding bowel. Although mammograms are age-appropriate screening tests for breast cancer, they are not a priority currently for this scenario.

2. E. Hereditary nonpolyposis colon cancer (HNPCC or Lynch syndrome) is an autosomal dominant genetic condition which increases the risk of cancers of the GI tract including colon, pancreatic, gastric, hepatobiliary, and small bowel, as well as ovary, endometrium, and genitourinary tract. It is caused by a germline mutation occurring in the DNA mismatch–repair genes (e.g., *hMSH2*, *hMLH1*, *hPMS1*, and *hPMS2*), which can be assayed directly or indirectly reflected by MSI. The inheritance pattern follows the Amsterdam criteria including three or more relatives with an associated cancer, two or more successive generations affected, one or more relatives diagnosed before the age of 50 years, and one should be a first-degree relative of the other two. It commonly presents with poorly differentiated tumors or mucinous histology in the right side of the colon. The APC gene is involved in FAP, which presents with hundreds of colonic polyps. The *BRCA1* gene is most commonly involved in breast and ovarian carcinomas. The *STK11* tumor suppressor gene is mutated in Peutz–Jeghers Syndrome. The *CHD1* gene encodes for the E-cadherin protein with loss resulting in hereditary diffuse gastric and lobular breast cancers.

3. C. This patient has a completely resected stage IIIB (pT2N2aM0) sigmoid colon cancer. Adjuvant chemotherapy for 6 months is the standard of care treatment for stage III colon cancers to improve OS. There are multiple acceptable regimens available, all of which include a fluoropyrimidine (e.g., 5-FU or capecitabine) with or without oxaliplatin. There is no role for irinotecan or biologic agents in the adjuvant setting. Additional resection is not warranted given the specimen had negative margins, and at least 12 lymph nodes were removed indicating adequate sampling. Radiation therapy has a limited role and is not recommended routinely in colon cancer due to bowel mobility, risk of small bowel toxicity, and risk of damage to anastomotic sites.

4. B. Bevacizumab is a monoclonal antibody that inhibits VEGFA. It is approved in combination with fluoropyrimidine-based therapy as first-line treatment of metastatic colon cancer and has been shown to improve response rates and OS. Cetuximab and pmab are both monoclonal antibodies that target EGFR and are effective only in patients with metastatic CRC harboring wild-type K-*ras*. Cetuximab is approved for use in disease refractory to treatment with irinotecan and for first-line treatment in combination with FOLFIRI chemotherapy. Panitumumab is approved as a single agent to improve progression-free survival in heavily pretreated patients. Regorafenib is the first and currently only small molecule tyrosine multikinase inhibitor approved for heavily pretreated patients with advanced CRC. Rituximab is an anti-CD20 monoclonal antibody highly effective in B-cell neoplasms and autoimmune conditions. It does not have a role in colon cancer.

5. D. Her rectal cancer clinical stage is IIIB (cT2N2aM0). Based on randomized controlled trials, neoadjuvant chemotherapy concurrent with radiation (chemoRT), followed by surgical resection and

additional 4 months of postoperative systemic chemotherapy is considered the standard of care for patients with stage II and III rectal cancers. The German Rectal Cancer Group compared neoadjuvant chemoRT followed by adjuvant systemic chemotherapy to initial surgical resection followed by adjuvant chemoRT and systemic chemotherapy. Patients in the neoadjuvant group had significantly less local recurrence rates, better tolerance of the therapy, and no increased surgical complications. However, OS was not impacted. This sequence represents the standard of care for patients with stage II and III rectal cancers who are candidates for trimodality therapy. Transanal mucosal resections are not an appropriate surgical procedure for this patient who most likely will require a low anterior resection with total mesorectal excision.

CHAPTER 9

1. C. Adjuvant chemotherapy has been shown by the CONKO and ESPAC studies to result in a small survival benefit compared to control. While lymph node positivity does have prognostic relevance, it does not influence the decision about whether to administer adjuvant therapy, perhaps because the vast majority of node-negative patients will still experience disease recurrence.

2. D. While Folfirinox has become the new standard of care for this situation there may be other factors (e.g., comorbid conditions or contraindications such as biliary obstruction) which may preclude this intensive regimen. Single-agent gemcitabine is defensible based on the relative lack of randomized studies in support of combination treatment. Erlotinib is also an FDA-approved option for this indication.

3. D. Ca-199 is nonspecific and insensitive for the detection of early onset disease. Therefore it has no value as a screening test. Jaundice itself can result in Ca-199 elevations; therefore, if it is to be used to follow therapy (as an adjunct to, rather than in place of, imaging), the baseline measurement should be poststent placement. Ca-199 has been shown to have prognostic value in both the pre- and postoperative settings.

CHAPTER 10

1. B. The updated RTOG shows that concurrent 5-FU + MMC with RT was superior to neoadjuvant CDDP + 5-FU followed by concurrent CDDP + 5-FU with RT in terms of overall survival (78% vs. 70%) and DFS (57.8% vs. 67.8%). Thus, answer "A" cannot be correct. The ACT II trial demonstrated that MMC/5-FU + RT was equivalent to concurrent 5-FU + MMC with RT + maintenance chemotherapy. Maintenance therapy did not impact overall survival or DFS. Thus, answer "C" would not be correct. Finally, answer "D" is not correct as 5-FU/MMC + concurrent RT was superior to 5-FU + concurrent RT as demonstrated in RTOG 87-04 in terms of DFS, CFS, and local-regional control.

2. C. The National Cancer Database has provided 5-year survival of anal canal carcinoma patients by stage for both squamous and nonsquamous histologies. The database is based on cases diagnosed from 1998 to 1999 and included 3,598 cases.

For squamous cell histology, the 5-year survival is as follows: stage I = 71.4%, stage II = 63.5%, stage IIIA = 48.1%, stage IIIB = 43.2%, and stage IV = 20.9%. For nonsquamous histology, the 5-year survival is as follows: stage I = 59.1%, stage II = 52.9%, stage IIIA = 37.7%, stage IIIB = 24.4%, and stage IV = 7.4%. The prognosis shows a statistically worst survival stage for stage between squamous and nonsquamous cell histologies, except for stage IIIA.

3. C. Early reports indicated that some HIV-positive patients were receiving less than optimal therapy due to concerns for treatment toxicity. However, patients with a CD4 count of ≥200 can have excellent control of their disease with acceptable morbidity. Those with CD4 counts of <200, however, may require a modification in their treatment regimen such as omission of MMC or a reduction in the RT field and/or dose. UCSF analyzed 17 HIV-positive patients and documented CD4 counts. All nine patients with a CD4 count ≥200 had control of their disease. Four patients did require a treatment break of 2 weeks, but no hospitalizations occurred. Among the eight patients with CD4 counts <200, four experienced lowered blood counts, intractable diarrhea, or moist desquamation. Four of eight ultimately required colostomies for either treatment-related toxicity or for salvage for disease. Disease, though, was controlled in seven of eight patients. Thus, based on the UCSF experience with HIV-positive patients, one

should consider modifying the treatment regimen particularly if CD4 counts are less than 200. Thus, for this patient with a CD4 count >200, he should receive full dose chemotherapy with 5-FU and MMC and full dose radiation therapy.

4. C. After patients have completed definitive chemoradiation therapy, patients should be followed up clinically in 8 to 12 weeks after therapy. Cummings demonstrated that mean time for tumor regression was 3 months but regression of a tumor could occur up to 12 months. Thus, if there is persistent disease at 8 to 12 weeks, patients should be followed up closely (every month) to document regression. As long as there is documented regression on serial examinations, patients may continue to be monitored. However, at any point if there is progression, then biopsy followed by salvage APR should be considered. Thus, answer "C" is correct and "A" is incorrect and immediate APR should not be considered. Answer "B" also is incorrect as chemotherapy alone has not been shown of benefit in this situation. Finally, although option "D" could be considered, as salvage radiation has been attempted, typically salvage APR would be considered in the future if the patient later progresses on future serial examination.

5. B. Toxic deaths from CMT have ranged from 0% to 5%. In the UKCCCR study, 6/116 (2%) experienced toxic death, mostly due to septicemia. The EORTC trial reported on 1 toxic death out of 110 patients. In RTOG 8704 study, four patients (3%) experienced death in the MMC arm. More recently, there were no reported toxic deaths in both RTOG 98-11 and ACT II trials. The ACCORD 03 trial, a four-arm randomized trial, showed similar toxic deaths across all four arms (A = 1 [1%], B = 2 [2.6%], C = 3 [3%], D = 1 [1%]).

CHAPTER 11

1. E. Adjuvant imatinib for 3 years. The size and mitotic rate of this patient's tumor fall in the high risk of recurrence category warranting 3 years of adjuvant therapy with imatinib based on the phase III clinical trial reported by Joensuu et al. in 2012. There is no role for adjuvant therapy with either radiation therapy or cytotoxic chemotherapy in GIST.

2. A. Increase the dose of imatinib to 400 mg twice daily. Patients with exon 9 mutations have a higher likelihood of resistance to imatinib. The Meta-GIST trial showed improved progression-free survival with the 800 mg daily dose of imatinib for patients with exon 9 mutations. The current recommendation is to increase the dose of imatinib to 800 mg daily if patients are not responding to the standard initial dose of 400 mg daily.

3. E. Systemic therapy with a fluoropyrimidine and oxaliplatin. Chemotherapy for metastatic SBA improves survival over no treatment. The most promising survival data from multiple retrospective studies involves the combination of a fluoropyrimidine with oxaliplatin in the first-line treatment for patients with metastatic SBA. There is no clear role for radiation therapy to liver lesions located in bilateral liver lobes.

CHAPTER 12

1. E. The patient is an unaffected family member with a strong family history. Her family history includes breast cancer, ovarian cancer, and pancreatic cancer. She has a high risk of having a *BRCA2* mutation. The next step is to do genetic counseling and testing. Bilateral mastectomy and prophylactic salpingo-oophorectomy are not recommended for every patient with a mutation. It should be decided case by case. CT/PET scan is not studied for screening in high-risk patients and it should not be used. Breast MRI and pelvic ultrasound can be considered, if she has a mutation. The role of serum markers in mutation carriers is debated. CA-125 may be used in addition to the vaginal ultrasound in patients with a BRCA mutation.

2. C. This patient will meet the inclusion criteria for ACOSOG Z 0011. In that study, patients with sentinel lymph node-positive (one to two nodes) disease were randomized between complete axillary node dissections and no further axillary surgery; no further axillary surgery arm had similar PFS and OS compared to complete axillary node dissection. Lymph node positive, by itself, is not a criterion for receiving chemotherapy. She could be in the luminal type A breast cancer and may very well be treated with endocrine therapy only. The SWOG study showed that Oncotype can be done in patients with node-positive disease also.

3. B. She has a IIB cancer and in the conventional sense she should receive chemotherapy. But many luminal type A patients (ER/PR positive and Ki-67 less than 14 as per St. Galen criteria) can be treated with only endocrine therapy, and not chemotherapy. She does not meet the criteria for radiation therapy after mastectomy (tumor more than 5 cm, four or more lymph nodes or other poor prognostic features). Even patients older than 65 will benefit from chemotherapy, if that is indicated.

4. D. Ado-trastuzumab emtansine 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. Ado-trastuzumab emtansine 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 3 EMILIA trial that compared trastuzumab emtansine with capecitabine + lapatinib in advanced HER2-positive breast cancer showed a substantial improvement in progression-free survival (PFS) and OS with the conjugate. This patient does not meet the criteria for the CLEOPATRA study and pertuzumab is approved in first-line metastatic breast cancer.

5. C. About 10% of patients receiving everolimus can develop pneumonitis. In a majority of patients, after ruling out an infectious cause, the patient can be managed with corticosteroid, discontinuation of the therapy until it is resolved. In grade 1 to 3 pneumonitis, everolimus can be restarted after appropriate supportive therapy and once the symptoms have resolved to grade 1 with a dose reduction.

CHAPTER 13

1.A. Cytoreductive nephrectomy is most likely to benefit patients who are good surgical candidates as well as candidates for postnephrectomy systemic therapy, such as those with a good performance status, a relatively slow rate of disease progression, and those with relatively low metastatic burden (as demonstrated in a randomized phase 3 study where interferon was offered postnephrectomy). Patients described in B to D are less likely to benefit from this approach as they do not satisfy one or more of the above criteria.

2. D. Complete responses are seen in 7% to 9% of metastatic clear cell RCC patients receiving high-dose IL-2, with the majority of these remaining disease-free for long periods. The efficacy of IL-2 has not been adequately evaluated in patients with non–clear cell histologies and the use of this agent is largely restricted to clear cell RCC patients. There are no randomized phase 3 studies demonstrating survival benefit with IL-2.

3. B. This patient appears to have "standard" risk metachronous metastatic clear cell RCC. Sunitinib has been shown to prolong progression-free survival compared to IFN-α in a randomized phase 3 trial in patients with previously untreated metastatic clear cell RCC. Axitinib and everolimus have both shown clinical benefit in previously treated patients, while temsirolimus is associated with improved OS compared to IFN-α in "poor risk" patients. While high-dose IL-2 may be a reasonable option for this patient, there are no randomized studies demonstrating benefit for this agent over other available therapies.

4. D. There are no standard systemic therapy options of proven benefit at this time for most patients with advanced RCC patients with non–clear cell histologies. While foretinib, a MET inhibitor, as well as inhibitors of the VEGF and mTOR pathways have activity in small subsets of these patients, their utility in the majority of patients with non–clear cell RCC remains to be established.

5. C. A renal mass in a young man with skin findings suggestive of cutaneous leiomyomata, a family history of kidney cancer, and uterine fibroids should arouse suspicion for hereditary leiomyomatosis and renal cell cancer (HLRCC), a familial kidney cancer syndrome characterized by germ-line mutations in the gene encoding the Krebs cycle enzyme, FH.

CHAPTER 14

1. B. The indications of adjuvant radiation after RP include T3 disease (such as extracapsular extension or seminal vesicle involvement) or positive surgical margins. The finding of lymph node-positive disease during prostatectomy is not an indication for radiotherapy, although limited data support the use of ADT in such patients.

2. D. This patient has a rising PSA after a 12-month response to bicalutamide, an ARA. ARAs including flutamide, nilutamide, and bicalutamide all can have agonistic properties over time in 10% to 15% of patients who respond to such treatments. Therefore, in an asymptomatic patient, the best approach is to withdraw the bicalutamide and reevaluate the patient in 6 weeks (or 4 weeks if the patient was on flutamide or nilutamide). There is no indication for chemotherapy or abiraterone in a patient without confirmed metastatic disease. While imaging is not inappropriate in this patient, a bone scan with a CT scan would be more appropriate than an MRI alone. Nonetheless, given the lack of symptoms, this could be done after the evaluation for a withdrawal response. Unless there is concern that the patient does not have castrate levels of testosterone, switching from a GnRH agonist to a GnRH agonist will provide no benefit.

3. D. Clinical trials have demonstrated a survival benefit for sipuleucel-T in patients with metastatic, CRPC with minimal symptoms. There is no current indication for patients with castration-sensitive disease.

4. B. A phase 3 study in non-mCRPC patients with high risk of bone metastasis demonstrated that denosumab can delay bone metastasis in this population. It is important to note that this is not an FDA indication for this treatment; however, the study demonstrates the growing ability to target CaP in the bone microenvironment. Zoledronic acid has been shown to delay skeletal-related events in castration-resistant, metastatic disease. Calcium/vitamin D is indicated in all men with castration levels of testosterone to delay osteopenia. Cabozantinib has shown promising preliminary results in resolving bone metastasis and is currently in phase 3 trials in CaP.

5. C. Although new therapies have increased options for treating metastatic CaP, docetaxel with prednisone remains the most appropriate therapies for moderate or higher levels of symptoms related to metastatic, CRPC. There are no definitive data to support the use of docetaxel with radiation or surgery in newly diagnosed CaP.

CHAPTER 15

1. D. Radical cystectomy and pelvic lymphadenectomy are the "gold standard" therapeutic modalities for locoregional, muscle-invasive bladder cancer. In men, this includes removal of the prostate gland, seminal vesicles, and proximal urethra. In women, it includes removal of the urethra, uterus, fallopian tubes, anterior vaginal wall, and surrounding fascia. Almost one of four patients have unsuspected nodal metastases (24%) found with pelvic lymph node dissection, despite negative preoperative staging. This extensive surgery ensures a low rate of pelvic recurrence even in lymph node-positive patients and 25% of these lymph node-positive patients experienced long-term survival. A proper lymph node dissection is important. In addition, the number of lymph nodes examined in cystectomy specimens has been reported to impact patient outcome.

2. D. Bladder cancer is common around the world. Cigarette smoking is thought to account for more than half of all cases of TCCs of the bladder in the United States. There is a marked male predominance and it is predominantly a neoplasm that occurs in patients aged >50 years. In addition, numerous specific chemicals have been identified as bladder carcinogens in humans, some relating to specific occupational exposures to arylamines (found in cigarette smoke, permanent hair dyes, and other environmental sources). Treatment with cytostatic drugs, especially cyclophosphamide, is associated with increased risk of bladder cancer, as is treatment with radiotherapy. In developing countries, especially in the Middle East and parts of Africa (Nile River Valley), bladder cancer occurs most commonly secondary to schistosomiasis, which is frequently associated with the development of squamous cell carcinoma similar to that of other chronic inflammatory processes of the lower urinary tract. Arsenic has been indicated as a bladder carcinogen in Argentina, Chile, and Taiwan.

3. A. The presence of carcinoma in situ is an indication for intravesical BCG therapy. It is important to note that there is muscle present in the biopsy; this allows the correct assessment of the invasiveness of the tumor. Cystectomy would be indicated for recurrent or persistent disease only. Other indications for the use of intravesical BCG include treatment of the residual non–muscle-invasive papillary tumor, and prophylaxis against recurrence of superficial tumors and against progression after resection of a tumor.

4. D. The most common presenting symptom for patients with bladder cancer is hematuria. Patients may also have urinary symptoms such as frequency and discomfort. In the absence of a urinary tract infection, patients over 50 years of age should be evaluated with cystoscopy and urine cytology. A CT scan of the abdomen and pelvis should be done only if the lesions seen on cystoscopy appear high grade, or suggestive of muscle invasion. CT of the chest is premature in this patient with hematuria.

5. B. Neoadjuvant chemotherapy with cisplatin combination chemotherapy improves survival in patients with muscle-invasive bladder cancer and good renal function. However, a large proportion of patients are ineligible for cisplatin chemotherapy based on renal function or functional status. There are limited data as to the efficacy and survival benefit of non–cisplatin-based regimens in the neoadjuvant or adjuvant setting. Therefore, patients with muscle-invasive bladder cancer who are intolerant/ineligible for cisplatin-based chemotherapy should proceed to cystectomy.

CHAPTER 16

1. B. This is a nonseminoma germ cell tumor in the anterior mediastinum because of the elevated HCG and AFP. Patients with Klinefelter syndrome have an increased risk of developing mediastinal germ cell tumor. This is not the case with Down syndrome. Seminoma is unlikely because of the elevated AFP. Primary mediastinal B-cell lymphoma and thymoma are both unlikely because of the elevated tumor markers.

2. C. Elevated levels of HCG without AFP are suggestive of a seminoma. CD30 and cytokeratin are positive in embryonal carcinoma. NANOG and OCT4 may be expressed in seminoma, but the expression of SOX2 is indicative of a nonseminomatous (embryonal) component. C117 (c-*kit*) is expressed by seminoma but not by embryonal carcinoma or yolk sac tumor.

3. E. This is an intermediate-risk stage III seminoma. Surveillance is recommended for lymph node mass that is ≤3 cm after chemotherapy.

4. E. Bleomycin is not recommended for patients with signs of pulmonary compromise especially if the DLCO has declined by more than 40% from baseline. Hence, BEP is not acceptable. Four cycles of EP is not sufficient for this case of poor risk nonseminoma and carboplatin-based regimen are not as effective as ciplatin-containing regimen. VeIP is a salvage therapy for relapsed or refractory disease.

5. C. Based on the International Consensus Risk Classification, the 5-year OS for poor risk nonseminoma is 48%.

6. B. All patients should be counseled on sperm banking prior to therapy for testicular germ cell tumor.

7. C. Increased copy number of 12p is seen in nearly all cases of testicular germ cell tumor. It may be one or more copies of i(12p) or tandem duplication of 12p.

8. B. Residual mass with yolk sac element requires two additional cycles of chemotherapy. More than two cycles will likely be an overtreatment. Surveillance is not an adequate option.

CHAPTER 17

1. A. After initially achieving a clinical complete remission as a result of management of her advanced ovarian carcinoma with the minimum standard of care, this patient presents with a rising CA-125 (based on three successive rising CA-125 with the last value above 100) and no other evidence of disease. She is asymptomatic. This situation was studied in a large phase 3 trial in Europe. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomized trial; Rustin et al. (2010). There was no difference in survival (HR = 1.00) and thus no benefit from earlier initiation of therapy for only a rising CA-125. Furthermore, deterioration of quality of life began a median of 3 months earlier in the early treatment group. These data support not treating for only a rising CA-125. When this patient ultimately develops tissue evidence of recurrence, she should be classified as potentially platinum sensitive due to her treatment-free interval of >18 months, substantially greater than the 6 months required for definition, and treated with a carboplatin-based doublet. She should be evaluated for secondary surgical cytoreduction, which should be done if the surgeon feels that he/she can remove all gross disease. This is a controversial conclusion in the

United States, where many use the Rustin CA-125 criteria (at least doubled and over 100) as an indicator for therapy, even when evaluable disease is observed on examination and/or imaging.

2. D. RRSO has been shown to reduce risk of ovarian/tubal/peritoneal cancer to 5% and is recommended for all women who are at high risk and who have completed childbearing. Optimal time for surgery is upon completion of child-bearing and 10 years prior to the youngest age at cancer presentation in the family. Screening with transvaginal sonography, CA-125, or pelvic examination has not been shown to reduce ovarian carcinoma mortality or lead to early detection in the general population or the high-risk population. It is, however, recommended for women who have not completed childbearing or who do not wish RRSO. Oral contraceptives can reduce the risk of ovarian cancer by as much as 50% in the general population; they have not been conclusively shown to be safe and effective in the mutation-carrier population. Oral contraceptives also have a 1.6 RR for the risk of breast cancer.

3. B. This patient has stage IIIC optimally debulked ovarian carcinoma and should receive chemotherapy following surgery. According to the consensus of all cooperative groups worldwide dealing with ovarian carcinoma, the minimum treatment of choice is six cycles of paclitaxel plus carboplatin. The National Cancer Institute issued a clinical alert in January of 2006 declaring IP therapy to be the treatment of patients with small-volume residual disease (optimal cytoreduction), but the alert also noted that there was no clear benefit of any one IP regimen because of toxicity (GOG 172). More recently, the GOG 218 showed that the addition of bevacizumab to paclitaxel/carboplatin plus bevacizumab maintenance produces a superior progression-free survival with the data too early to determine whether there will be a survival difference, but this is not for optimally debulked ovarian cancer patients and bevacizumab is not FDA approved for any ovarian cancer indication in the United States.

CHAPTER 18

1. C. Hormonal therapy is preferred as first-line intervention for recurrent or metastatic endometrial cancer due to its lower toxicity profile and response rate similar to chemotherapy. Hormonal therapy produces responses in 15% to 30% of patients and is associated with survival twice as long as in nonresponders. On average, responses last for 1 year. TAM is reserved for second-line hormone therapy. Currently, NCCN guidelines recommend the use of bevacizumab only after progression on prior cytotoxic chemotherapy. External beam radiotherapy is used in the metastatic setting if it can be directed to a particular tumor site. In this case the patient has bilateral lung nodules so systemic therapy is preferred.

2. D. There is currently insufficient evidence to recommend routine surveillance with MRI, ultrasound or hysteroscopy for detection of endometrial cancer in patients on TAM. Women taking TAM should have a gynecologic evaluation according to the same guidelines for women not taking TAM. The presence of symptoms such as abnormal vaginal bleeding should trigger prompt investigation.

3. E. The patient's strong family history of colon cancer diagnosed in family members at a young age is strongly suggestive of HNPCC also known as Lynch syndrome. Lynch syndrome is caused by an autosomal dominant disorder characterized by a germline mutation in mismatch repair genes and is associated with tumors exhibiting microsatellite instability. Lynch syndrome is associated with increased risk of cancers of the colon, endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin. The ACS recommends that women with HNPCC undergo annual endometrial biopsy after age 35, since the lifetime risk of endometrial cancer in patients with HNPCC is 40% to 60%. Prophylactic hysterectomy and BSO is a risk-reducing option that should be considered by women who have completed childbearing, since the lifetime risk of ovarian cancer in patients with Lynch syndrome is 10% to 20%.

4. A. In stage III and IV metastatic papillary serous endometrial cancer referral for clinical trials is strongly recommended as there is no FDA-approved standard of care. A reasonable first-line treatment is chemotherapy, for example, with a triplet regimen such as cisplatin, doxorubicin, and paclitaxel, or carboplatin and paclitaxel doublet. Hormone therapy with medroxyprogesterone acetate is only recommended for endometrioid subtype and is not recommended for papillary serous and clear cell subtype. Vaginal brachytherapy alone is generally reserved for localized disease (stage I disease and stage II grade 1).

CHAPTER 19

1. B. Cervical cancer is caused by exposure to high-risk strains of HPV not HSV. Greater than 99% of cervical cancers harbor HPV DNA and HPV types 16 and 18 account for 70% of those cervical cancers. The rest of the epidemiologic information is correct. The higher incidence of cervical cancer among minorities in the United States is thought to be due to barriers in screening secondary to lack of insurance, low income, and immigration from low screening countries.

2. A. Major prognostic factors are stage, nodal involvement, tumor size, depth of cervical stroma invasion, LVSI, and to a lesser extent histologic type and grade. Spread is usually orderly starting from the cervix to the pelvic nodes, along lymphovascular planes to the iliac (pelvic) lymph nodes and finally to the para-aortic lymph nodes. Hematogenous spread is typically a late occurrence but most commonly involves lung, liver, and bone. Patients with microinvasive cervical cancer have minimal risk (1% or less) of metastatic disease and are adequately treated with a cervical conization or simple hysterectomy.

3. D. Because the global burden of cervical cancer is in low-resource countries where abilities to surgically stage may be limited, cervical cancer is clinically staged. Imaging may include CT or combined PET/CT and MRI when available, for treatment planning purposes only. Hydronephrosis seen on intravenous pyelogram represents stage IIIB disease. If hydronephrosis is noted on CT scan or CT-IVP, this is also acceptable to determine stage IIIB disease, because the same finding would likely be apparent on traditional IVP.

4. B. Although chemoradiation is superior to surgical therapy for advanced disease, both treatments have comparable survival for early-stage disease. Chemoradiation avoids a surgical procedure, while the benefits of radical hysterectomy include preservation of ovarian function, avoidance of acute and chronic radiation–induced changes to the genitourinary and gastrointestinal systems, and obtaining a surgical specimen for prognostic purposes. Cervical conization or simple hysterectomy would not be appropriate for this patient, since she has visible disease. If future fertility is desired, radical trachelectomy with pelvic lymph node dissection can be considered. Since this patient is near or at menopause, a fertility-sparing procedure would not be appropriate.

5. D. The patient has an isolated central pelvic recurrence after chemoradiotherapy. Since she has already likely received the maximum dose of pelvic radiation, additional radiation would not be appropriate. Any chemotherapeutic regimen would only be palliative; however, pelvic exenteration performed for a centrally recurrent disease provides a 5-year survival of approximately 50%.

CHAPTER 20

1. C. The patient has stage IVB disease. Pelvic exenteration is a radical surgery with significant morbidity and uncertain survival benefit. Chemoradiation may allow less extensive resection. There are no data for tamoxifen in the management of SCC of the vulva. Brachytherapy would be inadequate treatment for stage IVB disease.

2. B. There is no proven standard of care for relapsed stage IV SCC of the vulva. Since the patient appears to have a good performance status, referral for a clinical trial is appropriate. Repeat radiation to the pelvis would not be recommended given that the treatment was <2 years ago and is unlikely to give benefit.

3. E. In patients in whom invasive disease is not suspected or seen on biopsy, laser ablation is an appropriate therapy. Radical vulvectomy is reserved for invasive disease. Observation is not appropriate since invasive disease may develop.

CHAPTER 21

1. A. More than 85% of patients with Ewing sarcoma carry the characteristic EWS-FLI translocation. RMS is a small blue round cell tumor as well, which in the alveolar RMS subtype may carry the PAX7/

FKHR translocation. The recommended treatment for Ewing sarcoma is multimodality therapy including surgery, radiation, and multiagent chemotherapy.

2. E. Osteosarcoma occurs in children and adolescents and older adults. The treatment of choice is neoadjuvant chemotherapy followed by surgical resection. Oligometastatic disease is curable with surgical resection. There is no characteristic chromosomal translocation for osteosarcoma.

3. F. RMS is a tumor primarily of the soft tissues, but may also grow in bone. The standard treatment involves 8 to 12 cycles of chemotherapy with VAC in addition to radiation and surgical resection if feasible. RMS occurs in infants, where it carries a better prognosis and may present as a primary bladder rumor.

CHAPTER 22

1. A. The tumor is thin (less than 1 mm deep) without ulceration or mitosis, and hence has a very low risk of harboring occult metastasis in the regional lymph nodes (AJCC stage IA). Sentinel lymph node biopsy is not recommended in tumors 1 mm or lower unless the tumor has ulceration or mitosis. High-dose interferon is recommended in patients at high risk of recurrence in tumor that is deeply invading with ulceration or that with lymph node metastasis and ulcerated primary.

2. C. The independent factors of prognosis in patients with cutaneous melanoma are depth of invasion, age more than 65 years, ulceration, tumor stage, and mitosis more than 0/mm^2.

3. D. The patient has an isolated metastatic tumor to the lung. He has no other signs of tumor metastasis and a surgical treatment could render a durable complete remission in about 25% of instances. He will need to be closely followed clinically and with imaging studies.

4. D. This young patient is very sick and requires a treatment that will work relatively quickly. High-dose IL-2 is not an option since it does not work quickly and the patient is too sick to tolerate this agent. Single-agent dacarbazine has a low response rate of about 7% to 12% and is not likely to help in this patient, while infusion of ipilimumab is not the appropriate option at this time, since its onset of action is very slow. This patient's tumor is positive for BRAF mutation and prompt administration of vemurafenib is likely to prevent rapid progression of this tumor and result in clinical benefit.

5. C. Polyoma viral DNA is found integrated in more than 90% of Merkel cell tumors raising a possibility of association with a viral etiology in this tumor.

CHAPTER 23

1. B. Patients with t(8;21) or inv(16) have a favorable prognosis and benefit most from HDAC consolidation. These patients do not seem to benefit from autologous or allogeneic transplant in first remission.

2. D. This patient has a very high suspicion of APL considering she is young, female, and appears to have disseminated intravascular coagulopathy (DIC). This is an oncologic emergency and ATRA therapy should be started as soon as APL is suspected. APL is a very curable disease, but unfortunately 10% of patients die early in the treatment course, typically from DIC and bleeding complications. Hydration and allopurinol are part of the initial therapy of acute leukemias, but are not the most important aspect for this patient. A bone marrow examination will need to be performed, but ATRA therapy should be started regardless. If the patient is found to have APL, she should be treated with anthracycline-based chemotherapy.

3. B. Approximately 25% to 30% of patients with ALL will have t(9;22). These patients are considered a very poor prognostic group. The addition of imatinib to standard ALL treatment regimens has been shown to be well tolerated with profound improvements in remission rates and survival. Rituximab and ofatumumab would not benefit this patient considering his disease does not express CD20. There are very limited data on the use of Alemtuzumab in patients will ALL.

CHAPTER 24

1. D. Del 13q is the most common cytogenetic abnormality in CLL, occurring in 50% of cases as either alone or in combination with other genetic mutations. Patients who have del 13q as their only

abnormality have a more favorable prognosis. Their disease follows a more indolent course and their survival is similar to age-matched controls. The expression of CD38 and unmutated IgVH is associated with a poorer prognosis. They have a shorter overall survival and higher risk of relapse following treatment. Trisomy 12 is associated with an intermediate prognosis.

2. C. This patient most likely has AIHA, a known hematologic complication of CLL. Further evaluation may be notable for spherocytes on peripheral blood smear and a positive direct antiglobulin test, but neither is always present with AIHA. Other labs suggestive of hemolysis include an elevated indirect bilirubin, elevated LDH, and a low haptoglobin. Prednisone dosed at 1 mg/kg/day is the typical initial therapy for AIHA. Improvement in hemoglobin can be seen within a couple of weeks. Prednisone should be tapered off slowly once the hemoglobin and hemolysis labs normalize. This patient is hemodynamically stable with no history of cardiovascular disease, so a blood transfusion is not necessary at this time. Chemotherapy would only be indicated in this patient if corticosteroids were unsuccessful in controlling her AIHA. If corticosteroids were unsuccessful, fludarabine would not be the treatment of choice as it can potentiate AIHA. A bendamustine-based regimen would be more appropriate. Although rituximab can be used for AIHA, it is not typically used as a front-line option in part because of its cost relative to steroids.

3. B. Cyclophosphamide is an alkylating agent that has been demonstrated to cause myeloid neoplasias 3 to 8 years after exposure. These myeloid neoplasias, including MDS and AML, are typically associated with abnormalities of chromosomes 5 and 7. Fludarabine has been associated with a small risk of MDS and AML, but this is typically in patients who have received other chemotherapeutics as well. Rituximab has been associated with a delayed neutropenia a few months after exposure, but is not associated with secondary malignancies when administered by itself. CLL is associated with other malignancies such as colon and skin cancer. There are rare case reports of CLL transforming to AML in previously untreated patients, but no clear evidence of transformation to MDS.

CHAPTER 25

1. C. Based on the Baccarani score this would be termed a failure to TKI therapy. An optimal response would be at least a partial cytogenetic response, with the Ph clone being less than 35%. A suboptimal response would be minor cytogenetic response, with the Ph clone being between 36% and 65%. This would be termed a failure due to no cytogenetic response and evidence of a new mutation.

2. C. Cytogenetic clonal evolution portends for a poor prognosis as well as is more commonly found in AP and BP. This patient does not have any cytogenetic response, as well as clonal evolution; therefore he is a candidate for an allogeneic stem cell transplant if a donor is found. Due to his T315I mutation the optimal TKI for him would be ponatinib. There are no data for doubling the dasatinib dose. Changing to ponatinib alone would not address his clonal evolution. Cytotoxic chemotherapy is not necessary at this point as he is still in CP, but could be indicated if he was in BP.

CHAPTER 26

1. E. The myeloid neoplasms have overlapping clinical characteristics, because after all, many of the causative mutations can occur in the different categories of MPNs or MDS. Mr. Jones' demographic and constellation of symptoms, signs, and investigation observations thus far: shortness of breath, bruises, splenomegaly, macrocytic anemia, and thrombocytopenia are compatible with any of the above diagnoses. Other less likely differential diagnoses include portal hypertension from liver cirrhosis or portal vein thrombosis, since there were no suggestions of chronic liver disease risk factors, symptoms or signs in the history, and physical examination. Although he has had foreign travel to compel consideration of unusual protozoal illnesses such as malaria during the history and physical examination, this was sufficient to indicate that this diagnosis, or other protozoal illnesses, is highly unlikely. Determining the specific diagnosis, and Mr. Jones' risks for complications, will require further evaluation.

2. E. The reticulocyte count and lactate dehydrogenase are of course routine components in the evaluation of anemia, to better understand if the cause is from decreased production or increased destruction. Although the observations thus far do not place hemolytic anemia high on the differential diagnoses

list, these parameters are nonetheless highly valuable baseline measures in the evaluation and management of myeloid malignancies, since they can be followed over time to confirm that therapy is changing things in the right direction, with decreasing LDH and increasing functional marrow as represented by appropriate reticulocyte count levels for the degree of anemia. The JAK2 V617F mutation is part of the diagnostic criteria for the MPNs, because of its highly recurrent association with these conditions. Bone marrow aspirate for morphologic evaluation and karyotype analysis are invaluable in classifying an MPN and in evaluating risk, a very pertinent consideration in Mr. Jones who is a potential candidate for allogeneic stem cell transplant. Although the clinical picture suggests that chronic myeloid leukemia is a less likely MPN, the treatment implications of this diagnosis are profound, and there is a need to rule out this diagnosis. It can be legitimately argued, however, that the clinical picture of Mr. Jones does not compel urgent evaluation to rule out CML, and that instead of FISH analysis, Dr. Brown can wait for the results of standard metaphase karyotyping of the bone marrow.

3.A. The diagnostic evaluation suggests that the diagnosis is primary MF, although an MDS/MPN overlap neoplasm remains in the differential diagnosis. The clinical features and observations suggest that Mr. Jones is at least in an intermediate risk or even in a high-risk category (e.g., by the DIPSS plus risk classification system) of MF. Furthermore, he is relatively young. Thus, allogeneic stem cell transplant must be considered, and at a minimum, Mr. Jones and his sibling should be HLA typed. His predominant symptom complex relates to anemia, with a possibility also of platelet dysfunction in addition to the thrombocytopenia. Thus, pending evaluation for transplant, management of anemia is indicated, including transfusion if necessary, and consideration for androgens such as danazol. If Mr. Jones does not have a sibling match, and if unrelated donor transplant is not an option, then experimental therapies should be considered; these could include DNMT1-depleting drugs such as 5-azacytidine or decitabine. Although Mr. Jones has splenomegaly, this is asymptomatic, and a JAK2 inhibitor is not indicated. For the same reasons, HU is not indicated. Erythropoietin could be considered if erythropoietin levels are inappropriately low (e.g., <200 milliunits/mL). Although it is possible that they are, since levels were not checked, it seems unlikely given Mr. Jones' age and normal renal function tests. Iron supplements would only be indicated if Mr. Jones is iron deficient, again unlikely given the constellation of observations, the MCV, and Mr. Jones' sex. Of course, iron studies should be performed.

CHAPTER 27

1.C. This patient has a M-protein and has >10% plasma cells in the bone marrow in the absence of any end-organ damage. A useful acronym to remember is CRAB—HyperCalcemia, Renal failure, Anemia, and Bone lesions. MGUS patients also have no evidence of end-organ damage but have an M-spike <3 g/dL and <10% clonal plasma cells in the bone marrow. Negative congo red staining points against amyloid deposition. This patient does not have MM as she has no evidence of end-organ damage. The correct answer is SMM.

2.A. The patient is progressing on thalidomide and dexamethasone therapy with worsening anemia, renal failure, and increasing urine M-spike. This patient most likely has light chain cast nephropathy. Increasing the dose of thalidomide is unlikely to induce a response and will probably increase the propensity for adverse effects. Lenalidomide and melphalan should be avoided in patients with advanced renal failure and response is seen after few weeks of therapy. Bortezomib does not need dose adjustments and can induce rapid responses and is the preferred drug for myeloma patients with renal failure.

CHAPTER 28

1.A. Although the majority of BL cases harbor t(8;14), other MYC-activating translocations can also occur in this disease. The (11;14) translocation is present in virtually all cases of mantle cell lymphoma, but is associated with overexpression of cyclin D1. The (14;18) translocation is present in most cases of follicular lymphoma, but is associated with overexpression of bcl-2. The (2;5) translocation is associated with ALK-positive anaplastic large cell lymphoma, which has a better prognosis than its ALK-negative counterpart. Lastly, 11q deletions are associated with bulky lymphadenopathy and relatively poor prognosis in CLL/SLL, although the inclusion of cyclophosphamide into the therapeutic regimen may to some extent overcome this adverse prognostic significance.

2. B. The NF-κB pathway is constitutively activated in ABC-DLBCL, leading to upregulation of multiple antiapoptotic transcription factors. Targeting of NF-κB and its downstream regulators is currently a focus of intense research, and early studies are demonstrating promising results.

3. C. The patient has stage IV DLBCL with a high/intermediate IPI and requires immediate therapy with the current standard of care regimen, R-CHOP-21. R-CHOP-14 with growth factor support has not demonstrated any advantage over R-CHOP-21, and there is a trend toward increased toxicity with the former. R-hyper-CVAD is a dose-intensive regimen used in BL. Response assessment after completion of therapy using both metabolic (FDG-PET) and anatomic (CT) imaging is appropriate for DLBCL, as the achievement of PET-negative status without complete anatomic resolution of lymphadenopathy is now considered equivalent to anatomic complete response (CR). Imaging after two to four cycles of therapy is recommended to ensure chemoresponsive disease; however, evidence of good response on interim imaging should not be used to shorten the duration of therapy. Any patient with BM involvement at diagnosis must have documented clearance by repeat BM aspirate/biopsy prior to designation of CR.

4. E. There is a high suspicion for transformation of this patient's FL into an aggressive large cell lymphoma, given his rapidly progressive disease and the variably intense FDG uptake on PET. The approach to treating this patient may change considerably if transformation is identified, and consequently a biopsy of the most hypermetabolic and/or rapidly growing focus of disease (the site with the highest likelihood of transformation) is indicated prior to initiation of salvage therapy. Answers A, B, and C are all reasonable therapies for relapsed FL. BM biopsy is indicated for both staging and diagnostic purposes.

5. E. This patient's clinical presentation and histologic findings are classic for PMBL. Classic Hodgkin lymphoma is characterized by the presence of Reed–Sternberg cells, and the malignant lymphocyte immunophenotype is typically CD30+, CD15+, and CD45–. T-lymphoblastic lymphoma is the nodal manifestation of T-ALL, and immunophenotype is consistent with T-cell origin (CD19/20–, CD2+, CD7+). SLL is the nodal/aleukemic manifestation of CLL, does not typically present as an isolated mediastinal mass, and consists of small malignant lymphocytes with dim CD20 expression. Mantle cell lymphoma is a variably aggressive lymphoma with a striking male predominance that typically presents with both nodal and extranodal (BM, peripheral blood, GI tract) involvement and is confirmed by the presence of t(11;14).

CHAPTER 29

1. C. In young HL patients, measures to ensure fertility preservation before starting chemotherapy are of paramount importance. While infertility due to ABVD chemotherapy is uncommon, sperm banking (which is relatively inexpensive and readily available) in a male patient before starting treatment is important for two reasons: (1) To document normal sperm count and motility at baseline, since suboptimal sperm count and quality is not uncommon in HL patients even before initiating chemotherapy. (2) Sperm banking is often not feasible in patients, who have refractory disease after ABVD chemotherapy before starting salvage regimens associated with high probability of causing infertility. Bone marrow aspiration biopsy is not required in patients with stage IA or IIA disease, and bilateral bone marrow biopsies are not needed in HL. Infuse-A-port is often inserted before starting chemotherapy, but ABVD-like regimens can be safely administered using peripheral intravenous access only.

2. B. The patient in this question has favorable risk, early-stage (IIA) HL, according to the German Hodgkin Study Group (GHSG) criteria. The HD10 trial by GHSG showed that in patients with favorable early-stage HL, two cycles of ABVD followed by 20 Gy of involved field radiation was not inferior to more aggressive options. Option A is appropriate for patients with *unfavorable* nonbulky early-stage HL. R-CHOP (C) is not an option of HL (at least in the front-line setting). Subtotal radiation therapy is inferior of chemotherapy combined with involved field radiation therapy and is not recommended.

3. D. HL is a highly curable hematologic malignancy; however, delays in administering chemotherapy on time (A and B) or reducing dose intensity (E) can negatively impact the probability of long-term disease control and are not recommended. Administration of growth factors (e.g., filgrastim) with ABVD has been shown to be associated with increased pulmonary toxicity and is not routinely recommended

(B and C). ABVD can be safely administered to HL patients with growth factor support and regardless of ANC at the day of chemotherapy.

4. A. The patient in this question shows evidence of chemosensitive disease after second-line therapy with ICE regimen. High-dose therapy and autologous transplantation are curative for relapsed, chemosensitive patients with HL and remains the standard of care of this patient population (A). Patients with relapsed HL should be referred to a transplant center for transplant planning soon after a relapse is confirmed (ideally before starting salvage chemotherapy regimens). Chemotherapy alone (C) in this setting is inferior to chemotherapy followed by autologous transplantation. Similarly allogeneic transplantation (B) is generally not indicated in first relapse, outside the setting of a clinical trial. There is no role of brentuximab vedotin maintenance after chemotherapy (D).

CHAPTER 30

1. B. A patient with normal cytogenetics AML is treated upfront with induction and consolidation therapy followed by close observation in CR1. At the time of first relapse, apart from reinduction chemotherapy, every attempt must be made to HLA type the patient at the earliest and find a suitable donor for an allogeneic HCT in CR2. Since she does not have a sibling donor, a National Marrow Donor Program search must be initiated to locate a suitable donor. Time is vital as it takes 3 to 6 months to obtain an allograft from an URD. She has a 70% chance of finding a HLA-matched donor. Choice A is not a therapeutic option for this patient; autologous HCT is sometimes considered as consolidation therapy in CR1, ideally in a clinical trial setting; C and D are wrong as allogeneic HCT should be considered in first relapse or CR2 and deferring it will considerably worsen her prognosis.

2. D. Use of carmustine (BCNU) as part of high-dose therapy can cause delayed interstitial pneumonitis and present with typical findings as described in the question. The correct management includes obtaining a pulmonary function test including diffusion lung capacity of carbon monoxide and the use of steroids (D). BCNU can cause pulmonary fibrosis which may take years to manifest. The described symptoms, lack of productive cough, and negative chest x-ray point against bacterial pneumonia and hence choice A is not the best answer. The compliant use of trimethoprim–sulfamethoxazole effectively protects the patient against *Pneumocystis* pneumonia and hence switching to inhaled pentamidine (B) is not indicated.

3. C. Evaluation of the potential donor (sibling and unrelated) is an important part of pretransplant workup. Only serious or life-threatening illness that endangers the donor or history of malignancy within the past 5 years (except nonmelanoma skin cancers) are considered absolute contraindications (A). While there is a theoretical risk for AML with the use of growth factors, this has not been observed in healthy donors and family history does not pose an increased risk either (D). Subablative chemotherapy (e.g., Cy) prior to growth factor–mobilized progenitor cell collection is only considered for autotransplant. Growth factor–mobilized progenitor cell collection is very well tolerated barring minor bone pain, a rare risk of spontaneous splenic rupture, and no long-term effects (C).

4. A. The triad of findings (hyperbilirubinemia, right upper quadrant pain, and weight gain/ascites) in the first 3 weeks after myeloablative allogeneic HCT should strongly raise the suspicion of SOS. Pre-existing liver disease, conditioning regimens containing combination of Cy with Bu and higher dose TBI, and prior exposure to gemtuzumab ozogamicin are all risk factors for developing SOS. With the advent of intravenous Bu with levels followed closely and restricting the radiation dose to 12 to 13 Gy has dramatically decreased the incidence. Acute GVHD must be considered in the differential and sometimes liver biopsy is required. In this case choice B is wrong as the clinical features fit SOS. Hepatosplenic candidiasis, once common, is very effectively prevented with azole prophylaxis and thrombotic microangiopathy is unlikely with normal peripheral smear (C and D).

CHAPTER 31

1. E. The presentation of mediastinal and/or retroperitoneal nodes in men aged below 65 years places germ cell tumor high on the differential list. Therefore, CT chest, abdomen, and pelvis and tumor

markers β-hCG and AFP should be obtained for both men and women. For men over 40, a PSA should also be obtained. For women, workup for breast cancer should also be performed, with ER/PR and Her-2 immunohistochemistry, mammogram and breast ultrasound, and/or MRI breast. If all workups are negative, review the case with the pathologist for further workup to differentiate testicular, ovarian, or non–small cell lung cancer.

2. D. Patients with adenocarcinoma with mediastinal nodes as the only site of disease most likely have either germ cell tumor or non–small cell lung cancer primary. Patients aged below 50 years should be treated for poor-risk germ cell tumor. However, patients aged between 40 and 50 years could also be treated for non–small cell lung cancer. Patients aged 50 years and older should be treated for non–small cell lung cancer. Testicular ultrasound should be performed if β-hCG and/or AFP levels are elevated.

3. E. A primary site in the genital or anorectal areas, including the surrounding skin, is often identified in most patients with squamous cell carcinoma involving inguinal nodes. The prognosis for these patients is good. Curative therapy is available for some of these patients. If there is no primary site found, lymphadenectomy with or without adjuvant radiation therapy can result in long-term survival.

CHAPTER 32

1. B. Age <50 (answer A) is a good prognostic factor. Answer B is a poor prognostic factor. MGMT promoter methylation is an excellent prognostic factor, but lack of methylation indicates a tumor unlikely to respond to temozolomide, which conveys prognosis at or below the median OS in the 2006 Stupp trial of XRT with temozolomide. Gross total resection (answer C) is a good prognostic indicator in GBM. A Karnofsky performance status of 90 (answer D) is excellent and places this patient in the good prognostic group (KPS >70 presurgery).

2. D. While all answers are not unreasonable, the standard of care in this patient would be D. Clinical trials have demonstrated the superiority of resection followed by WBRT when compared with surgery alone or WBRT alone. Of course, an informed discussion with the patient about the potential risks and benefits of each procedure may also end up in the patient choosing hospice care, but an informed discussion would include conveying to the patient that her length and quality of life may be significantly improved by choosing answer D.

3. D. While radiotherapy (answer A) is capable of inhibiting growth of meningiomas, it is not considered a front-line option in a patient without symptoms, especially if the lesion is surgically resectable. WBRT (answer B) is not a reasonable choice for meningioma management in any setting. Surgical resection (answer C) is a good choice for management of meningioma and would be the ideal choice in a patient with symptomatic disease. However, because this patient has no symptoms, it is probably best to recommend observation (answer D) for him with regular follow-up examinations and MRIs at fixed intervals, which would depend on the pace of growth seen with serial MRI scans. While it would not be incorrect to choose surgery, observation offers less likelihood of morbidity. There is no need for surgery followed by radiotherapy (answer E) to the resection cavity in an asymptomatic patient without evidence of progression or atypical/malignant features.

CHAPTER 33

1. B. The purpose of this question is to understand the management of patients with previously untreated metastatic PTC. Unlike most malignancies, resection of the primary tumor and lymph nodes should be performed in all patients with metastatic disease. This is because these patients are still potentially curable with subsequent radioactive iodine treatment. Complete responses are seen in approximately 45% of patients. This is particularly the case for young patients with multiple pulmonary metastases. A preoperative diagnostic radioactive iodine scan would not be useful for two reasons: all of the iodine would concentrate in the thyroid, and the patient has had a recent CT scan with IV contrast. Iodinated contrast will interfere with the diagnostic scan by increasing the circulating iodine. For this reason (and because radioactive iodine is intended for remnant ablation and metastases, not primary tumors), treatment

with radioactive iodine is not an appropriate first step in this patient's management. Doxorubicin-based chemotherapy and clinical trials with kinase inhibitors are reserved for patients with radioactive iodine refractory disease.

2. C. The purpose of this question is to recognize the appropriate time to initiate therapy with a kinase inhibitor in advanced MTC. Vandetanib and cabozantinib are tyrosine kinase inhibitors that are approved for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease. Both were approved based on improvement in progression-free survival compared to placebo, but demonstrated no improvement in overall survival. Therefore, given the treatment-related risks, use in patients with indolent, asymptomatic, or slowly progressing disease is typically not recommended. Answer B is incorrect because we do not know the results of his imaging. Asymptomatic patients with elevated calcitonin and negative imaging should not receive vandetanib. If disease is present, there are several options to be considered depending on the disease burden and location. They include surgical resection if feasible, localized therapy such as radiofrequency ablation or chemoembolization, vandetanib, or cabozantinib therapy. Answers A and E are incorrect because MTC is derived from parafollicular or C cells. This cell type does not incorporate iodine or have TSH receptors. Therefore, TSH suppression and radioactive iodine are not effective therapies. Answer D is incorrect because while external beam radiation is sometimes used, it is not done empirically without imaging to assess for resectable disease. Further, MTC is not particularly radiosensitive. Answer C is the best answer. If his imaging is negative, his calcitonin should be repeated in 3 to 6 months. If it is stable, no further imaging is indicated. If it continues to rise, it rapidly increases, or he develops new symptoms, further imaging should be done.

3. D. The purpose of this question is to understand the role of mitotane for the treatment of ACC. Mitotane is an adrenocortolytic therapy with objective tumor responses seen in approximately one-third of patients with metastatic disease. Its primary benefit (achieved in approximately 75% of cases) is the reduction of symptoms related to the ectopic hormone production of these tumors. This patient has associated Cushing syndrome with weight gain, weakness, and hypertension, and is therefore particularly in need of an adrenocortolytic therapy. Both streptozocin and the combination of cisplatin, doxorubicin, and etoposide (EDP) are often used with mitotane. These two regimens, in combination with mitotane, were studied head to head in a clinical trial as first-line therapy for patients with locally advanced or metastatic disease that is not amenable to surgery. EDP with mitotane was superior to streptozocin and mitotane with regard to overall response rate and progression-free survival; however, there was no overall survival advantage.

4. B. The purpose of this question is to understand the clinical presentation and diagnosis of Zollinger–Ellison syndrome and gastrinoma. This patient's clinical symptoms are suggestive of Zollinger–Ellison syndrome, the condition associated with a gastrinoma that is characterized by refractory peptic ulcer disease, diarrhea, and gastric hyperacidity. Patients who are suspected of gastrinoma with an elevated gastrin level should undergo a secretin stimulation test as the next step in diagnosis. Secretin stimulates secretion of gastrin from gastrinomas, but not from normal G cells. As a result, gastrin levels will rise after secretin infusion in patients with gastrinomas. A positive secretin stimulation test is generally considered a rise in gastrin of ≥200 pg/mL. After the diagnosis of gastrinoma is made, it must be localized using imaging. EUS, octreotide scan (somatostatin receptor scintigraphy), CT, and MRI are all useful imaging modalities to localize gastrinomas. ^{131}I-MIBG is structurally similar to norepinephrine and is typically used to diagnose pheochromocytomas.

CHAPTER 33

1. A. Decrease in transfusion rates is the only benefit of ESAs consistently demonstrated in RCTs and meta-analyses. Consistent evidence does not exist for the rest of the attributes provided in the choices (especially at higher Hb levels). Strikingly, in the case of choice C, at least one meta-analysis of 53 pooled RCTs showed that the use of ESAs is significantly associated with shorter survival.

2. C. As per the current guidelines and FDA label, the ESAs are best recommended for cancer-induced anemia to decrease the need of blood transfusions when the Hb levels fall below 10 g/dL. Between 10 and 12 g/dL there is a lack of consistent evidence to say that ESAs would decrease transfusion requirement.

There is also an emerging body of evidence that shows that ESAs are associated with significantly increased mortality. For the patient in choice B, the symptomatic anemia may warrant a blood transfusion instead for quick relief. Although there still lack consensus data on the use of ESA based on the intent of chemotherapy regimen, FDA labeling restricts the use to those being treated with palliative intent.

3. A. Routine adjunctive use of CSF for FN is not recommended unless the patient has risk factors for infection-associated complication, including age >65, expected prolonged neutropenia (>10 days), profound neutropenia (<100/μL), sepsis syndrome, hospitalization, pneumonia, invasive fungal infection, or uncontrolled primary disease. In a clinical scenario described in choice B, the use of G-CSF may be justified as a secondary prophylaxis. Citron et al. showed that dose-dense regimen supported by G-CSF has superior clinical outcome. The ASCO guideline recommends administering CSF to patients who had dose-limiting neutropenic event that could otherwise impact planned dose of chemotherapy from a prior cycle of chemotherapy when no CSFs were given. In a clinical scenario described in choice C, the use of G-CSF may be justified as a treatment of FN with a high-risk feature of profound neutropenia (ANC <100/μL). Likewise, a patient in choice D has FN with at least two high-risk features—age above 65 and likely a postobstructive pneumonia. Thus, the use of G-CSF is justified. In choice E, the use of G-CSF may be justified as primary prophylaxis. TPF regimen is myelosuppressive and the goal of induction therapy is curative. The patient has one high-risk feature (age above 65).

4. B. Cochrane meta-analysis reported by Bohlius et al. concluded that CSFs, when used as a prophylaxis in patients with malignant lymphoma undergoing conventional chemotherapy, reduce the risk of neutropenia, FN, and infection. No evidence exists to suggest that either G-CSF or GM-CSF provide a significant advantage in terms of complete tumor response, freedom from treatment failure, or overall survival. Choice A is false because no data exist that compared pegfilgrastim and filgrastim in this disease setting. Citron et al. reported that dose-dense regimen supported by G-CSF had superior clinical outcome compared with conventional chemotherapy in node-positive breast cancer patients. Choice C is false. The meta-analysis by Clark et al. showed the use of CSF in chemotherapy-induced FN was associated with statistically significant reduction in the hospital stay, and shorter time to neutrophil recovery. Reduction in infection-related morality or overall mortality was not statistically significant. Choice D is wrong because ASCO 2006 update guidelines recommend the use of CSFs with first- and subsequent cycle chemotherapy to prevent FN when the risk is greater than 20%. Choice E is false. Gurion et al. reported that the addition of CSFs to chemotherapy yielded no difference in all-cause mortality at 30 days and at the end of follow-up or in overall survival. There was no difference in complete remission rates, relapse rates, and disease-free survival. CSFs did not decrease the occurrence of bacteremias, nor the occurrence of invasive fungal infections. CSFs marginally increased adverse events requiring discontinuation of CSFs as compared to the control arm.

CHAPTER 35

1. D. Fever during neutropenia is a medical emergency, and antibiotics should be started without delay. AML during transplant is not a "low-risk patient" who could be considered for oral antibiotics. The recommended first-line agents for fever during neutropenia include cefepime, piperacillin–tazobactam, imipenem, and meropenem. Vancomycin is not routinely indicated as part of the starting regimen, except under one of the following circumstances: hemodynamic instability, known MRSA carrier, clinically apparent catheter infection, pneumonia, and mucositis. Mucositis has been associated with bacteremia caused by *Streptococcus mitis* with severe sepsis and high mortality, and this is the reason this patient should receive vancomycin. Most authorities consider that imipenem and meropenem offer enough coverage against *S. mitis* to be used as single agents.

2. E. This question is about when to change antibiotics during fever and neutropenia. Persistent fever alone is not an indication to change the antibiotic regimen, but hemodynamic decompensation as seen in this patient mandates antimicrobial changes. Although antifungal coverage can be considered, the patient has been febrile only for 48 hours and she is hypotensive: both details make antibacterial agent changes more important, so option A cannot be the right choice. Antibiotic coverage for known VRE colonization is very reasonable for a patient who is known to be colonized with it and is not responding to standard antibiotic therapy. However, there is no indication that the catheter is infected with VRE.

The single culture bottle for coagulase-negative *Staphylococcus* is more suggestive of a contaminated culture or, at most, catheter colonization. Thus the suggestions regarding vancomycin and the catheter are distractors—the issue here is not catheter-associated bacteremia, but hemodynamic instability during neutropenia. There is no indication to remove the catheter. More importantly, the history of prior ESBL infection suggests the possibility of a gram-negative infection resistant to cefepime. This must be addressed with expanded gram-negative coverage. The best option is E, which addresses the known prior pathogens (ESBL and VRE) and the possibility of a *Candida* infection that could break through and cause hypotension.

3. D. This question is about persistent fever during neutropenia. In this case D is the best answer, although all the other options have some merits. Answer E is wrong: antibiotics should not be discontinued during fever and neutropenia to test for drug fever, as this strategy resulted in high frequency of septic shock in a randomized trial. Daptomycin could be stopped (current guidelines support discontinuing the gram-positive coverage if no clinical specimen has shown a microorganism that requires it), but this does not address the persistent fever, so option B is not adequate. Maintaining the same coverage after 5 days of persistent fever (option A) is not the standard of practice. In this case, it is appropriate to look for a fungal infection by obtaining CT of the chest and sinuses and expand the antifungal coverage. There has been one randomized trial comparing adding amphotericin in all cases of persistent fever with adding it only when there was ancillary evidence of fungal infection (serologic markers, abnormal CT, and others), and in fact this so-called preemptive addition of amphotericin was inferior to the standard empirical management.

4. C. There is no indication to obtain PPD, galactomannan, or hepatitis C serology before chemotherapy for lymphoma. However, hepatitis B reactivation has been very well documented following CHOP-R. Individuals with evidence of chronic virus B infection (carriers or people with chronic hepatitis) who are going to receive chemotherapy for lymphoma need to be treated prophylactically with lamivudine or entecavir. It is unknown for how long after completion of treatment the antiviral medicines should be continued, as reactivation of hepatitis B post-CHOP-R has happened several months out.

CHAPTER 36

1. A. SCC most often involves the thoracic spine, followed by lumbosacral and cervical spine.

2. D. A is not correct because immediate RT is only indicated for patients with symptomatic SVC syndrome presenting with stridor or mental status changes from cerebral edema. B is not correct because without histologic diagnosis, certain malignancies may not be responsive to glucocorticoids and chemotherapy. C is not correct because thrombolytic therapy and anticoagulation should only be considered for thrombosis causing SVC syndrome. D is the correct answer. Endovascular stenting can result in rapid resolution of symptoms. Accurate histologic diagnosis of the patient's malignancy can guide further therapy and care. RT may obscure the biopsy findings.

3. H. Zolendronic acid should only be used after adequate hydration. Densosumab is preferred in the setting of renal failure, and osteonecrosis of jaw is associated with this agent as well.

4. F.

CHAPTER 37

1. D. Delirium is an acute disturbance of consciousness with reduced ability to focus, sustain, or shift attention. Patients may demonstrate an array of symptoms including changes in cognition, memory deficits, disorientation, speech/language disturbances, delusions, and perceptual abnormalities. A medical workup is required as delirium, by definition, has an underlying medical or neurologic cause. Haloperidol would be a reasonable choice for management of agitation in a patient without contraindications such as QTc prolongation or other cardiovascular risk factors. BZDs such as lorazepam should generally be reserved for delirium related to alcohol or BZD withdrawal. The Academy of Psychosomatic Medicine has an online monograph on evidence-based management of delirium available at: http://www.apm.org/library/monographs/delirium/APM-EACLPP_DeliriumMonograph.pdf.

2. A. Differentiating between nonclinical mood changes and a clinical diagnosis of major depressive disorder (MDD) can be difficult for many cancer patients. The somatic symptoms of cancer and cancer treatment can mimic the diagnostic and statistical manual criteria for MDD. The patient in this case has many symptoms that point strongly to a diagnosis of MDD such as excessive guilt, early morning awakening, and anhedonia (a lack of interest in her normal hobbies and activities). An antidepressant would be a reasonable management choice for this individual. Tamoxifen is broken down to its active metabolite, endoxifen, by cytochrome P-450 2D6. Many antidepressants have an inhibitory effect on 2D6 substrates and therefore could potentially inhibit the conversion to endoxifen. Venlafaxine (Effexor) has minimal inhibitory effect at 2D6 and would be the best antidepressant choice in this patient. Paroxetine would be a poor choice as it is a potent inhibitor at 2D6. A medication to help sleep and/or anxiety may be a reasonable choice in this patient but would not address the core depressive symptoms. Clonazepam could be used to help address anxiety and sleep but does not address symptoms such as excessive guilt. Zolpidem is commonly used to help sleep but would not help the other symptoms this patient is experiencing.

3. B. The patient's age and gender are major contributors to risk factors for self-harm. The strongest predictor of self-harm is a prior history of self-harm. The other issues listed such as his financial status or his medications could potentially contribute to self-harm but are not as predictive as prior history. Recent data suggest a correlation to receiving a diagnosis of cancer and suicide, with highest risk of suicide in the first 4 weeks of cancer diagnosis. Highest rates of suicide in cancer patients are seen in esophageal, pancreatic, liver, and lung cancer.

4. D. Given this girl's admission for chemotherapy, it will be challenging to differentiate insomnia from anxiety from that of chemotherapy-related side effects and new environment (the hospital) versus preexisting anxiety without reviewing her developmental and social history. After full review of history with both patient directly and her parents, it will then be important to determine whether the patient might require an anxiolytic (BZD or antihistamine). The general rule with children is to use low doses of anxiolytics for short duration if required.

CHAPTER 38

1. D. Combination chemotherapy that includes doxorubicin (an anthracycline) and cyclophosphamide (an "AC" regimen) is categorized by current ASCO and NCCN guidelines as presenting high emetic risk. Docetaxel is also emetogenic, albeit categorized among drugs associated with low emetic risk. Guideline-driven recommendations advise prophylaxis appropriate for the most emetogenic component of treatment; therefore, antiemetic prophylaxis appropriate for treatment with high emetic risk is indicated, which includes combination of a 5- HT_3 receptor antagonist, dexamethasone, and aprepitant (or fosaprepitant). Option A limits glucocorticoid use to only the first day of treatment, which deviates from ASCO and NCCN recommendations for delayed-phase prophylaxis, but remains consistent with MASCC/ESMO recommendations; however, concurrent use of aprepitant (or fosaprepitant) with dexamethasone increases the steroid's bioavailability and, therefore, a 20 mg dose of dexamethasone in combination with fosaprepitant substantially exceeds the 12 mg dose recommended by MASCC/ESMO, ASCO, and NCCN guidelines. Option B complies with the components of acute-phase prophylaxis recommended by NCCN and ASCO guidelines. Again, however, a 20 mg of dexamethasone in combination with aprepitant on day 1 exceeds the 12 mg dose recommended by all three guidelines. Delayed-phase prophylaxis follows MASCC/ESMO recommendation, but is inconsistent with ASCO and NCCN recommendations by omitting dexamethasone on days after chemotherapy. Acute-phase prophylaxis described in option C closely resembles all three guidelines' recommendations for acute-phase prophylaxis, but the omission of aprepitant on days 2 and 3 after a 115 mg dose of fosaprepitant is inconsistent with FDA-approved labeling and all three guidelines' recommendations for use of an NK_1 receptor antagonist on those days. The addition of dexamethasone on days 2 and 3, while consistent with ASCO and NCCN guidelines, is a deviation from MASCC/ESMO guidance. Option D most closely complies with all three professional guidelines by including fosaprepitant on an administration schedule appropriate for the dose administered, a 5-HT_3 receptor antagonist only on day 1, and dexamethasone given at a dose appropriate for use with fosaprepitant (or aprepitant), on a schedule consistent with

ASCO guidelines, and a duration of use consistent with ASCO and NCCN guidelines. Option E eliminates entirely the glucocorticoid component of prophylaxis recommended by all three guidelines for the day of treatment and describes a dose of ondansetron that exceeds the FDA warnings against intravenously administered single doses >16 mg to prevent serious adverse effects on cardiac electrophysiology.

2. E. Dexamethasone and other steroids given systemically for antiemetic prophylaxis often destabilize blood glucose control in diabetic patients, more so in patients whose blood glucose is not well controlled before receiving steroid medications. Increased lability in blood glucose control does not, however, preclude high-potency glucocorticoid use in an antiemetic regimen, but requires more intensive blood glucose monitoring and adjusting and supplementing antidiabetic medications during steroid use and withdrawing antidiabetic drugs after steroids are discontinued until blood glucose again stabilizes to within goals for glycemic control. Therefore, the prohibition described in option A is unnecessary as long as healthcare providers and patients recognize the need for more intensive blood glucose monitoring and altering antidiabetic treatment to maintain glycemic control during steroid use. Option B is correct. Paroxetine is a substrate and potent inhibitor of the CYP CYP2D6 enzyme, the primary catalyst for phase 1 metabolism of palonosetron and hydrodolasetron, dolasetron's active metabolite. The rate at which substrates for CYP2D6 are metabolized is often described as "capacity limited" by virtue of two or more substrates in competition, or an amount of one or more substrates that overwhelm enzyme availability. Therefore, the half-life of one or more drugs competing for metabolism catalyzed by CYP2D6 may be substantially increased and, consequently, pharmacodynamic effects associated with pharmacologically active substrates may be exaggerated and persist for unpredictably lengthy periods due to protracted elimination. Ondansetron also is a substrate for CYP2D6, but like palonosetron, it is a substrate for phase 1 metabolism through alternative catalysts, including CYP3A4, a high-capacity enzyme. It is unsafe and, therefore, not possible to temporarily discontinue paroxetine during antineoplastic treatment as a means to avoid interaction with other CYP2D6 substrates. Rapid dose decreases and abrupt discontinuation of paroxetine have been associated with a withdrawal syndrome characterized by a variety of severe somatic, psychiatric, and neurologic adverse effects. With respect to option C, there is presently no evidence supporting dose or schedule modification of empirically dosed antiemetics based on extremes of body weight. Among high-potency glucocorticoids and 5-HT_3 and NK_1 receptor antagonists, the safest and most effective antiemetics in clinical use, recommendations for weight-based dosing appear in FDA-approved product labeling only for ondansetron and granisetron, and, with respect to intravenously administered ondansetron, labeling includes warnings against exceeding 16 mg for single doses. Option D is also correct. Paroxetine use has been associated with aberrations in cardiac electrophysiology including prolongation of ventricular repolarization and, in combination with other CYP2D6 substrate drugs with similar deleterious effects on cardiac conduction, has been implicated in causing torsades de pointes. Both dolasetron and ondansetron have been associated with cardiac QT interval prolongation, which is the basis for contraindications and warnings that appear in current labeling for both products. The potential for serious abnormal arrhythmias is increased by electrolyte abnormalities including hypokalemia and hypomagnesemia and by paroxetine's potential for altering the elimination of 5-HT_3 receptor antagonists by inhibiting CYP2D6. The patient's healthcare providers should prudently replace magnesium and confirm achieving serum magnesium concentrations within a range of normal values before giving ondansetron intravenously or dolasetron in antiemetic prophylaxis. Option E is the best response, because it acknowledges the validity of both B and D.

3. B. Option A is an attractive choice because gastroparesis and altered GI motility are complications associated with diabetes. Compromised GI motility is a risk factor for emetic symptoms independent of the emetogenicity of treatment, but the selection is based on inference rather than evidence provided by the case history. Option B, female sex, is a well-documented risk factor for poor emetic control. With respect to C, anxiety preceding antineoplastic treatments often accompanies developing and frank anticipatory emetic symptoms. Anecdotally, anxiety during antineoplastic treatments appears to exacerbate emetic symptoms, but other behavioral disorders including clinical depression, have not been associated with emetic outcomes. With respect to options D, E, and F, predilection for motion or travel sickness and severe and persistent emetic symptoms during pregnancy, respectively, are recognized risk factors for

poor emetic control during antineoplastic treatment, but the case history does not identify either condition. Likewise, constipation is included among pathologic factors associated with altered GI motility or obstruction that, when coincident with emetogenic treatment, predispose toward poor emetic control. In addition, constipation is a common side effect associated with paroxetine use, but again, the patient's case history reveals nothing suggesting compromised or altered GI motility. Additional dialog between the patient and her healthcare providers is warranted to establish whether she has experienced difficulty with bowel movements rather than assuming an additional risk factor exists.

4. D. Cisplatin alone or in combination with other emetogenic drugs is associated with high emetic risk. Therefore, in addition to providing antiemetic prophylaxis appropriate for the most component of combination chemotherapy with the greatest emetic risk, our strategy for prophylaxis from the second through the fifth day of treatment should include medications appropriate to provide protection against both acute- and delayed-phase symptoms. Antiemetic prophylaxis for multiple-day emetogenic treatments has been less well studied than prophylaxis for treatments given on a single day, and professional guidelines are less explicit about how some antiemetics should be used to optimally protect against emetic symptoms associated with multiple-day treatments (i.e., palonosetron and NK_1 receptor antagonists). Consequently, some extrapolation and assumptions are required from what is known about the effectiveness of prophylaxis for single-day treatments leavened with knowledge about the pharmacokinetic and pharmaceutical characteristics of available antiemetics and, if known, patient-specific pharmacogenomic characteristics that may affect drug metabolism. Clinicians also must ascertain whether (1) the emetogenic risk of treatment is the same or varies among treatment days and (2) the physiologic changes that underlie acute- and delayed-phase symptoms are operative concurrently, which may require antiemetic prophylaxis appropriate for one or both phases on each treatment day. When treatment includes drugs with high and moderate emetogenic risks on different days, also consider whether antiemetic prophylaxis against delayed-phase symptoms is indicated after emetogenic treatment is completed and the duration for which prophylaxis should continue. Although the present case scenario is realistic, it is simplified by a regimen without daily variation in emetic risk and a patient without concomitant medications or conditions that could complicate antiemetic selection and use. The regimen described in option A is well designed to give protection against both acute- and delayed-phase symptoms during the days on which antineoplastic treatment is given, but omits prophylaxis against delayed-phase symptoms likely to occur during the days following treatment. In addition, a 20 mg dose of dexamethasone is excessive when given with aprepitant. Option B deviates from ASCO, MASCC/ESMO, and NCCN guidelines by omitting the antiemetic benefit obtained by combining a high-potency glucocorticoid with either or both 5-HT_3 and NK_1 receptor antagonists. Repeated administration of fosaprepitant at a 150 mg dose on an intermittent schedule also is not supported by FDA-approved product labeling or the three professional guidelines. Option C meets the MASCC/ESMO guidelines' recommendations with respect to 5-HT_3 receptor antagonist and high-potency glucocorticoid on days of emetogenic treatment without an NK_1 receptor antagonist, and comes close to both ASCO and NCCN guidelines, but, in contrast with the last two guidelines, the regimen omits an NK_1 receptor antagonist on treatment days and dexamethasone use for 2 or three days after completing emetogenic therapy. Option D includes continuous transdermal administration of granisetron from a topically applied patch, a delivery system appropriate for multiple-day emetogenic treatment. A patch delivers granisetron 3.1 mg per day percutaneously during continuous application for up to 7 days. In addition, the regimen includes a high-potency glucocorticoid during emetogenic treatment and for 3 days afterward at doses, administration schedules, and for durations of use consistent with ASCO and NCCN guidelines' recommendations, and an NK_1 receptor antagonist as suggested by both ASCO and NCCN guidelines. Option E includes a 5-HT_3 receptor antagonist and dexamethasone on the days when emetogenic treatment is given consistent with all three professional guidelines' recommendations and for 3 days after chemotherapy is completed which follows ASCO's and NCCN's recommendations, but deviates with respect to dexamethasone doses given on days 1 to 5. The regimen also deviates from MASCC/ESMO recommendations by including a NK_1 receptor antagonist during multiday chemotherapy and from ASCO and NCCN guidelines' suggestions with respect to the duration of aprepitant use.

5. B. All three professional antiemetic guidelines label carboplatin as presenting moderate emetic risk, but current NCCN guidelines qualify that categorization by including carboplatin among antineoplastics that may be highly emetogenic in some patients. Although NCCN guidelines do not identify patient subgroups or characterize risk factors that may predispose toward high emetic risk from carboplatin, we should recognize in the present case factors that place her at increased risk for poor emetic control during and after chemotherapy, such as female sex, and from her history, motion sickness, and pregnancy complicated by severe persistent emetic symptoms. As a result of poor emetic control during her first treatment cycle, the patient has acquired an additional risk factor that predisposes for poor emetic control during subsequent emetogenic treatments and for developing a conditioned emetic response, that is, anticipatory symptoms. Arguably, initial prophylaxis did not receive a fair trial because the patient did not complete the antiemetic regimen planned for her first treatment cycle, but the aggregate factors are both historical and acquired that predispose toward poor emetic control and carboplatin's mutable emetogenic risk between moderate and high suggest pursuing a more aggressive approach to achieve the goal of antiemetic prophylaxis: complete emetic control with each cycle or course of treatment. Option A describes rechallenge with the antiemetic regimen previously attempted reinforced by reinstruction and encouragement to comply with the plan for self-administered medication and monitoring. A reasonable approach in a patient without risk factors for poor emetic control and receiving treatment for which emetic risk was more certain, but the mitigating risk factors noted above are arguments for antiemetic prophylaxis escalated from the previously planned regimen. Option B, escalating the aggressiveness of antiemetic prophylaxis, is suggested by the NCCN guidelines' characterization of carboplatin-containing regimens as highly emetogenic in some patients, and, from the same resource, a caveat within "Principles for Managing Breakthrough Emesis," specifically: "Based on the patient's experiences, the chemotherapy regimen may actually be more emetogenic than generally classified." Option C is an attractive adjunctive intervention, and may serve to quell what anxiety contributes toward developing and exacerbating emetic symptoms, but evidence for improvement on the effectiveness of antiemetic prophylaxis with a high-potency glucocorticoid combined with 5-HT_3 and NK_1 receptor antagonists is lacking. Options D and E are empiric approaches to "cover all the bases." Acknowledging neurotransmitters are the principle mediators in initiating and propagating emetic symptoms, anticholinergic and dopaminergic (D_2) receptor antagonists potentially may add preventative or therapeutic benefit. However, the more prudent course before attempting empiric replacement and supplementation would be to optimize emetic control with high-potency glucocorticoids, and 5-HT_3 and NK_1 receptor antagonists, which, by comparison with anticholinergic and antidopaminergic agents, are more effective and possess better therapeutic indices.

CHAPTER 39

1. D. The multifactorial causes of weight loss in patients with cancer include cellular and metabolic derangements that lead to depletion of fat and muscle stores. Historically, it was thought that patients with cancer had increased energy expenditure, but measured resting energy expenditure in those with cancer is widely variable and an association with extent of tumor and energy expenditure has not been found. Unlike simple starvation, where glucose turnover is slowed and lean body mass is preserved, there is a maladaptaion to starvation in cancer with increased glucose turnover, increase in wasteful metabolic cycles, increased protein turnover, increased muscle protein degradation, and depletion of adipose stores due to increased lipolysis.

2. D. As summarized in the ASPEN Guidelines, "Nutrition support therapy is appropriate in patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time (7 to 14 days)." EN is preferred for patients who are unable to maintain adequate nutritional intake by mouth as it maintains the functional integrity of the gastrointestinal tract. EN via jejunostomy feeding tubes can be successful in patients postgastrectomy. PN would only be appropriate if the patient failed an EN trial with appropriate tube placement. Tracking oral intake will allow the tube feeding volume to be adjusted according to oral intake, so that adequate nutrition can be provided, with eventual weaning off of EN.

3. A. Hypercalcemia of malignancy does not respond to a low calcium diet. NCI's PDQ cancer information summary on hypercalcemia indicates that "even though the gut has a role in normal calcium

homeostasis, absorption is usually diminished in individuals with hypercalcemia, making dietary calcium restriction unnecessary."

4. D. A patient with low albumin and prealbumin levels may or may not be malnourished. Albumin and prealbumin lack specificity and sensitivity as indicators of nutritional status. They can be reduced by nonnutritional factors such as hypervolemia and inflammation. Earlier reports associating these proteins with nutritional status did not account for the variable of inflammation. These serum hepatic transport proteins are considered negative acute-phase proteins because liver synthesis of these proteins decreases in response to chronic or acute inflammation. C-reactive protein, a positive acute-phase protein, can be measured to help clarify whether active inflammation is present. If C-reactive protein is elevated and albumin or prealbumin are reduced, then inflammation is likely. In order to diagnose a malnutrition syndrome, further information suggesting loss of body cell mass or compromised nutritional intake would be needed. In addition, the half-life of albumin is 18 to 21 days and so a 1-week period is too soon to detect changes in albumin synthesis alone.

CHAPTER 40

1. C. The patient currently is in a "pain crisis" warranting utilization of stronger analagesics. Based on DOME (daily oral morphine equivalents), 1 mg of intravenous hydormorphone is approximately four times as strong as the hydrocodone the patient had previously taken. Additionally, propoxyphene, oxycodone, and ibuprofen are not available parenterally. Meperidine has metabolites that can be epileptogenic.

2. E. When initiating a long-acting opiate after achieving control of acute pain, the long-acting opiate should be initiated at roughly 50% of the DOME. Among the choices offered, choice E the fentanyl transdermal patch provides 50 mg or roughly 50% of the required analgesia. All the other choices provide much stronger doses of opiates which could possibly result in adverse effects.

3. D. Among the choices listed, choice D is the only one that provides the 30 mg of DOME; all the other choices provide much stronger doses of opiates which could possibly result in adverse effects.

CHAPTER 41

1. B. In the setting of hypotension and the possibility of an acute GI bleed, standard PICC lines or any central venous access line other than a cordis is insufficient as a resuscitative line. In the scenario detailed above, the appropriate management of the patient is to move him to a critical care bed, send coagulation studies, establish large poor IVs (16G if possible), and type and cross the patient for 4U of packed red blood cells. Type and screen is insufficient in this setting. While blousing with a crystalloid is appropriate, it should be a temporizing intervention with plans for infusion of blood products to be initiated at the same time.

2. D. Damage to the tunica intima results in platelet aggregation and thrombosis of the vein. The end result is the loss of peripheral veins for access for not only venous infusions but also for venous sampling.

3. D. The use of peripheral IV in this setting is not ideal as the patient will be getting a year of therapy in addition to multiple doses of chemotherapy. This will lead to eventual loss of peripheral IV access. The midline catheter cannot stay in place for a year; a nontunneled catheter is too unstable in the long-term setting as it has a high likelihood of being inadvertently dislodging and the subsequent potential for hemorrhage. The tunneled catheter is a reasonable option for long-term chemotherapy, but her therapy will be every 2 to 3 weeks and so constant access to the vein is not necessary. Additionally, a tunneled catheter is much more visible, thereby potentially impeding the privacy of a young woman. The infusaport can be placed in a pocket on the chest wall in a location that can be hidden by garments and therefore from the general public.

CHAPTER 42

1. C. A contraindication to performing a LP is the presence of unequal pressures between the supratentorial and infratentorial compartments. This is usually deduced from the following characteristics on imaging of the brain: midline shift; loss of suprachiasmatic and basilar cisterns; posterior fossa mass;

loss of superior cerebellar cistern; or loss of the quadrigeminal plate cistern. When a patient presents with neurologic symptoms, imaging of the brain is necessary prior to performing LP.

2. B. No, anticoagulation should be held prior to a bone marrow biopsy. The patient should hold his Enoxaparin 24 hours prior to the bone marrow. If the patient was on coumadin, he should be transitioned over to a low-molecular heparin, and this should be held 24 hours prior to the bone marrow.

3. B. In the absence of fluoroscopic guidance, a thoracentesis should be performed through the seventh or eighth intercostal space.

CHAPTER 44

1. C. Multiple types of radiation can be used to treat breast cancer as part of breast conservation, but all are directed at the breast. Brachytherapy, whole-breast RT, and partial breast RT may all be used to treat breast cancer. Systemic radionucleide therapy is not appropriate as part of breast conserving therapy but may be used as palliative therapy in patients with metastatic disease and in the management of thyroid cancer.

2. B. Most of the effects of radiation occur in the treated area. One of the most common side effects of radiation is skin irritation and redness at the treated site. Patients may also experience fatigue. Alopecia would be unlikely unless the head was treated. Similarly, nausea is unlikely unless the head or abdomen is treated.

3. B. Dividing radiation into smaller doses takes advantage several aspects of tumor biology. First, this allows more tumor cells to be exposed to radiation in a sensitive phase of the cell cycle since different cells will be cycling at different times. In addition, many normal tissues can repair better than tumors, thus giving smaller doses at different times instead of one large dose takes advantage of this by letting normal tissue repair in between. Additionally, tumors tend to be better oxygenated after a dose of radiation, likely through killing of competing tumor cells, thus increasing oxygenation and sensitivity to radiation.

4. D. Damage to DNA is the primary mechanism of lethality after exposure to radiation. Although many organelles and cellular components may be damaged by radiation, these do not typically result in lethality.

5. B. IMRT is a method that allows a highly conformal treatment. Similar doses are given compared to other external beam RT approaches so the overall treatment time, total dose, and DNA damage are similar.

CHAPTER 45

1. B. Any woman with triple negative breast cancer under the age of 60 should have testing for *BRCA1/2* testing including BART. Choice A is not the correct answer because she needs genetic testing. C is not the correct answer because she should have *BRCA* testing first. If *BRCA* testing is negative, it is recommended for all women with breast cancer under the age of 30 have *p53* testing. D and E are not correct because she does not meet criteria for *PTEN* testing or Peutz–Jeghers syndrome.

2. D. The tumor spectrum for LFS includes sarcoma, premenopausal breast cancer, brain tumor, adrenalcorticoid tumor, leukemia, and lung bronchoalveloar cancer.

3. B. The rest of the tumors are seen commonly with Cowden syndrome.

4. C. This patient has the classic presentation of colon cancer in a family history consistent with Lynch syndrome. Colon cancer associated with Lynch syndrome is typically found in the right colon and, despite the aggressive histologic features, does not metastasize as often as sporadic cases. Lynch syndrome is caused by germline mutations of the MMR genes, of which *MLH1* and *MSH2* are the most common.

5. B. Von Hippel–Lindau disease is commonly associated with hemangioblastoma of the CNS, clear cell RCC, pancreatic neuroendocrine tumors, and pheochromocytomas. In this patient whose family history is highly suspicious for VHL disease, a concomitant diagnosis of pheochromocytoma must be ruled out prior to surgery to minimize perioperative complications and avoid the use of β-blockade.

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