CHAPTER 1

Overview of Cancer Therapy

Lisa Holle
Jane Pruemer
Hyejin Kim

LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Identify differences between normal cells and malignant cells.
2. Classify cancer drugs based on their mechanism of action.
3. Describe toxicities that are common to a given class of cancer drugs.
4. Identify the different definitions used to evaluate the response of the tumor to therapy.

INTRODUCTION

What Is Cancer?

Cancer is a group of diseases, not one single entity. An understanding of the characteristics of cancer is important to understanding the principles and practices of cancer management. This chapter will outline the basic characteristics of cancer, its potential causes, the basic pharmacology and pharmacotherapy of medications used in the treatment of cancer, and the terms used to determine response to anticancer therapy. This chapter is meant to be an introduction to cancer therapy rather than a comprehensive review. For a more thorough review of cancer therapy, please see the *References* and the *Suggested Reading* list.

Normal cells grow, divide, and die in an orderly, predictable fashion. Cancer cells are different than normal cells in that they continue to grow, divide, and form new, abnormal cells. Although there are many different types of cancer, they have several characteristics in common. Both normal and cancer cells progress through 4 distinct phases of cell division known as the cell cycle: G_1 phase (growth), S phase (synthesis), G_2 phase (2nd growth phase), and M phase (mitosis). Following cell division, the cell will enter a resting phase (G_0 phase). Cancer cells, however, exhibit excessive growth, possess an extended life span, and have metastatic potential. They have the means to invade tissues surrounding them and to spread throughout the body, destroying distant tissues and organs. If allowed to continue to grow, the cancer will ultimately cause death.

One of the first steps in cancer cell development is DNA damage. Damaged DNA is inheritable and accounts for 5%–10% of all cancers.[1,2] More often, mutations in the DNA may occur by exposure to environmental factors or random cellular events. Substances that may act as carcinogens or initiators of cancer include chemical, physical, and biologic agents.[3] Exposure to chemicals (eg, aniline dye, benzene) may occur through occupational and environmental contact, as well as lifestyle habits. Physical agents that act as carcinogens include ultraviolet light and ionizing radiation. These types of radiation induce mutations by forming free radicals that damage DNA and other cellular components. Viruses are biologic agents that may be associated with certain cancers.[4] The Epstein-Barr virus is believed to be an important factor in the initiation of Burkitt's lymphoma. Likewise, infection with the human papillomavirus is known to be a major cause of head and neck cancer and cervical cancer (**Table 1-1**).[4–13]

Recently, because of advances in genomic information, there is significant progress in the understanding of genetic changes that lead to the development of cancer. Two major classes of genes have been identified in the course of cancer development: oncogenes and tumor suppressor genes. Oncogenes develop from normal genes (proto-oncogenes) and can have effects in all phases of cancer development. Changes of proto-oncogenes can occur through point mutation, chromosomal rearrangement, or gene amplification by exposure to carcinogenic agents (**Table 1-2**).[14–17] The result is dysregulation of normal cell growth and proliferation.

In contrast, tumor suppressor genes regulate and inhibit inappropriate cellular growth and proliferation. The p53 gene is an example of a tumor suppressor gene. Mutation of p53 is one of the most common genetic changes associated with cancer, and it is estimated to occur in half of all malignancies.[18] Inactivation of p53 is linked to a variety of malignancies including astrocytomas, breast, colon, lung, cervix, and bone cancers.

Table 1-1 Potential Causes of Cancer[4–13]

Risk Factor	Associated Cancer
Environmental	
Radiation	Leukemia, breast, thyroid
UV radiation	Melanoma, skin
Radon	Lung
Viruses	Leukemia, lymphoma, anal, nasopharyngeal, cervical, oropharyngeal, liver
Lifestyle	
Alcohol	Esophageal, larynx, liver, gastric, oropharynx
Tobacco	Bladder, esophageal, lung, larynx, lip, mouth, pharynx
Dietary	
Low fiber, high fat	Colorectal, breast, endometrial, gallbladder
Reproductive history	
Late first pregnancy, 0 or low parity	Breast, ovarian
Medications	
Alkylating agents	Leukemia, bladder
Azathioprine	Lymphoma
Chloramphenicol	Leukemia
Diethylstilbestrol	Vaginal in daughters of users
Estrogens	Breast, endometrial
Tamoxifen	Endometrial
Occupational exposure	
Aniline dye	Bladder
Asbestos	Lung, mesothelioma
Benzene	Leukemia
Cadmium	Lung
Chromium	Lung
Nickel	Lung, nasal sinus
Vinyl chloride	Leukemia, liver

The current theory for the development of cancer supports the concept that carcinogenesis is a multistep process. The first step is *initiation*, which requires a cell to be exposed to carcinogenic substances (Table 1-1) that produce genetic damage (Table 1-2). If not repaired, the damage results in irreversible cellular mutations and selective growth advantage, allowing the mutated cells the potential to develop into a clonal population of cancer cells. The second step, *promotion*, occurs as the environment is altered to favor the growth of the mutated cell population over normal cells. The promotion phase may be a reversible process. The third step is the *transformation* phase, when the mutated cells become cancerous.

Table 1-2 Types of Genetic Mutations[14–17]

Mutation	Description	Example
Point mutations	Change in 1 base pair in the genetic material may lead to a single amino acid substitution in a critical portion of the protein.	K-Ras gene in non–small cell lung cancer
Deletions	Removal of 1 or more base pairs may result in loss of expression of a protein.	13q in multiple myeloma
Insertions	Addition of 1 or more base pairs may result in altered expression of a protein.	Epidermal growth factor receptor (EGFR) exon 20 in lung adenocarcinoma
Translocations	All or part of a gene recombines with other genes, which may result in altered expression of a protein.	Philadelphia chromosome (also known as bcr-abl or translocation [9;22]) in chronic myeloid leukemia
Amplifications	Increase in the amount of DNA from a specific region of a chromosome, which may result in altered expression of a protein.	Overexpression of HER-2 in breast cancer

Progression is the final stage of neoplastic growth, which involves further genetic changes, increased cell proliferation, tumor invasion into local tissues, and metastases to distant sites.[19]

Modalities of Cancer Treatment

The following 3 major modalities exist for the treatment of cancer: surgery, radiation, and drug therapy. This chapter will focus on the use of pharmacotherapy to treat cancer. Drug therapy may have systemic effects (eg, intravenous cisplatin) or local effects (eg, carmustine wafers) and can treat the primary cancer as well as metastatic sites. Chemotherapy is a group of drugs that interfere with DNA (genes) of fast-growing cells. Biologic therapies are made from a living organism or its products and include cytokines, antibodies, vaccines, and growth factors. Targeted therapies are drugs that are designed to target specific tumor antigens or molecules critical to the survival and growth of cancer cells.

Cancer Therapy Medications

While surgery and radiation specifically target the tumor, cancer therapy medications affect the whole body through various mechanisms of action. New cancer therapy drugs have greater efficacy and less toxicity than first-generation cancer therapy drugs developed 50 years ago. Additionally, due to greater knowledge of cancer therapy delivery, including optimal dose and frequency of dosing, they are more efficacious and less toxic in the treatment of cancer.[20]

Cancer therapy medications can be given as the primary treatment for some cancers, such as lymphoma and leukemia. It can also be given as adjuvant therapy, after the cancer has been surgically removed, to improve survival and delay or prevent disease recurrence. Neoadjuvant therapy is given before surgery to shrink tumors to permit less extensive surgery. Maintenance therapy is the continued use of cancer medications to help lower the risk of recurrence after the first cancer therapy treatment or to prevent the spread of disease in patients with advanced cancer. When cancer is not curable, cancer therapy may be administered palliatively to reduce symptoms caused by tumors.

CLASSES OF CHEMOTHERAPY AGENTS

Chemotherapy agents (also referred to as antineoplastics) are commonly classified by their mechanism of action or by their source of origin.[19] Traditional antineoplastics target rapidly dividing cells and have activity in 1 or more sites of the cell cycle. Those drugs with major activity at 1 site of the cell cycle are known as cell-cycle specific drugs, whereas those with activity at multiple sites are known as cell-cycle nonspecific drugs. However, not all cytotoxicity is a result of disruption of the cell cycle. Intracellular activity may also result in cytotoxicity, such as direct lymphocyte toxicity or inhibition of signal transduction pathways involved in proliferation, survival, and metastases of cancer cells. The following sections describe the various classes of antineoplastics used in the treatment of cancer. The clinical uses, mechanism of action, side effects, and practical patient management for these agents are reviewed. For more thorough information about each of these drugs, please see the *Suggested Reading* list at the end of this chapter.

Microtubule-Targeting Drugs

Mitotic inhibitors disrupt mitosis, a phase of cell division in which a cell duplicates and separates the chromosomes in its cell nucleus. These agents are considered to

be cell-cycle specific (mostly in the M phase of the cell cycle) chemotherapy drugs and include the vinca alkaloids, taxanes, epothilones, eribulin, and estramustine.

Vinca Alkaloids

The vinca alkaloids include vinblastine, vincristine, and vinorelbine, which are used to treat some solid tumors, as well as lymphomas and leukemias. Vinca alkaloids are derived from the periwinkle plant and bind to tubulin, the structural protein that polymerizes to form the microtubules that make up the mitotic spindle. The vinca alkaloids inhibit the assembly of microtubules; thus, they inhibit microtubule polymerization. The microtubules are also important in nerve conduction and neurotransmission, and loss of this function results in some of the toxicities seen with these agents. Although structurally similar with the same mechanism of action, the vinca alkaloids possess different activities and toxicity profiles. Vinblastine and vinorelbine are more often associated with dose-limiting myelosuppression, whereas vincristine causes less bone marrow suppression but more neurotoxicity.[19] In regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) used to treat lymphomas, the maximum single dose limit for vincristine is generally 2 mg because of the high risk of neurotoxicity.[21] The neurotoxicity is a neuropathy that affects sensation and motor function with paresthesias of the fingers and toes as the most common clinical manifestations. Hoarseness, facial palsies, or jaw pain occur due to damage of cranial nerves and constipation or colicky abdominal pain occur due to autonomic neuropathy. These side effects are often reversible, however, in some cases, the neuropathy may persist. Therapy should be discontinued when the effects are disabling. Recently, a liposomal formulation of vincristine was approved for use in Philadelphia chromosome-negative (t [9;22] chromosomal translocation) acute lymphoblastic leukemia patients. The formulation was developed to allow higher doses of the drug to be administered with fewer side effects. The liposomal vincristine dose is 2.25 mg/m^2, nearly double the usual dose of vincristine; however, the toxicity profile is comparable to standard vincristine.[22]

Taxanes

The taxanes are plant alkaloids and include paclitaxel, docetaxel, and cabazitaxel. Paclitaxel was isolated from the bark of the North American Pacific yew tree, *Taxus brevifolia*, in the early 1970s.[19] Docetaxel is a semisynthetic

compound produced from 10-deacetylbaccatin-III, which is found in the needles of the European yew tree, *Taxus baccata*. Cabazitaxel is a semisynthetic taxane from a diastereoisomer of 10-deacetylbaccatin-III, derived from the needles of various *Taxus* species. These agents possess antimitotic activity by binding to tubulin and promoting its assembly into microtubules while simultaneously inhibiting disassembly. In contrast to vinca alkaloids, these agents promote microtubule polymerization. This leads to the stabilization of microtubules and results in the inhibition of mitotic and interphase cellular functions. Taxanes also have other actions that can cause cancer cell death, such as antiangiogenesis. Cross-resistance between the taxanes is incomplete.[23] Myelosuppression is a dose-limiting toxicity of the taxanes.[24] Fluid retention is more common with docetaxel, whereas paclitaxel has increased neurotoxicity and hypersensitivity reactions.[25] The diluent (eg, Cremophor EL [polyoxyethylated castor oil] with paclitaxel) and the emulsifier (eg, polysorbate 80 with docetaxel and cabazitaxel) used to formulate these drugs are associated with hypersensitivity reactions; thus, patients require premedications to prevent this side effect. See **Table 1-3** for premedication recommendations and precautions associated with the taxanes.[26–33]

Recently, a nanoparticle albumin-bound paclitaxel product, which is not associated with hypersensitivity reactions, became available for the treatment of breast cancer. No premedications are thus needed for this product. It is important to note that the dosing for nanoparticle albumin-bound paclitaxel is different than paclitaxel. Other side effects are similar between the different taxanes, including myelosuppression, neuropathy, and myalgias.

Epothilones

The epothilones work in the mitotic phase of the cell cycle by promoting microtubule polymerization.[19] The only currently available epothilone derivative in the United States is ixabepilone, approved as monotherapy to treat metastatic or locally advanced breast cancer following failure with anthracyclines, taxanes, and capecitabine. It can also be used in combination with capecitabine following failure of an anthracycline and a taxane. Mitotic inhibitors are known for their potential to cause peripheral nerve injury, which can be a dose-limiting side effect for this class of chemotherapy agents. The other toxicities associated with ixabepilone are similar to those of the taxanes, with the exception of fluid retention, which does not occur with ixabepilone.

Table 1-3 Anticancer Agents Requiring Special Premedications/ Precautions[26–33]

Agent (Brand Name)	Premedications	Precautions
Alemtuzumab (Campath)	Diphenhydramine 50 mg and acetaminophen 500-1000 mg PO 30 minutes prior to first infusion and each dose escalation	Monitor and premedicate for infusion-related reactions. Prophylaxis against *Pneumocystis jiroveci* pneumonia and herpes simplex virus recommended upon initiation of treatment and continuing 2 months after or until CD4+ count is ≥ 200 cells/microliter, whichever occurs later.
Bevacizumab (Avastin)		Monitor for infusion-related reactions (uncommon); no premedications required. Do not administer to patients with recent hemoptysis, GI perforation, serious bleeding, or nephrotic syndrome. Monitor blood pressure every 2–3 weeks during treatment; treat with appropriate antihypertensive therapy as necessary. Check urine for protein; hold for proteinuria > 2 grams/24 hours. Do not initiate bevacizumab for at least 28 days after surgery and until the surgical wound is fully healed.
Bleomycin (Blenoxane)		Hypersensitivity reactions can occur with any dose of bleomycin, regardless of test dosing; more common in lymphoma patients. Test dosing and premedication vs close clinical monitoring is controversial. Pulmonary fibrosis can occur; risk higher in elderly patients, lifetime cumulative dose > 400 units, smoking, patients receiving concurrent oxygen therapy, and possibly with concurrent granulocyte colony-stimulating factor use.

Agent (Brand Name)	Premedications	Precautions
Busulfan (Busulfex, Myleran)	Prevent seizures with high doses (transplant regimens) by using phenytoin or high dose clonazepam or lorazepam, during and for at least 48 hours following completion of therapy	
Cabazitaxel (Jevtana)	Premedicate with an antihistamine (eg, diphenhydramine 25 mg IV), a corticosteroid (dexamethasone 8 mg IV), and an H_2 antagonist (eg, ranitidine 50 mg IV) 30 minutes prior to administration	Avoid in patients with sensitivity to polysorbate 80. Severe hypersensitivity reactions require discontinuation.
Carboplatin (Paraplatin)		Hypersensitivity reactions can occur with any cycle, but most common after 6-8 cycles. Discontinuation or desensitization is recommended for future doses after a hypersensitivity reaction occurs.
Cetuximab (Erbitux)	Diphenhydramine 50 mg IV 30-60 minutes prior to first dose	Premedication prior to subsequent treatments based on clinical judgment and presence/severity of prior infusion reactions. Observe patient for 1 hour after infusion. Interrupt infusion if infusion-related reaction occurs, and rechallenge with 50% reduction in infusion rate if reaction was not severe.
Cisplatin (Platinol)	Prehydrate with 1-2 liters of fluid over 1 to 12 hours prior to administration; maximum rate of 500 mL/hour	Consider mannitol (50-gram to 100-gram dose) or furosemide for diuresis if patient cannot tolerate fluid load
Cytarabine (Cytosar)	For doses > 1.5 g/m^2: initiate corticosteroid ophthalmic drops (eg, prednisolone 1%, 1 drop to each eye every 8 hours during treatment and until 24-72 hours after therapy)	For doses > 1.5 g/m^2, monitor for neurotoxicity with neurology checks (have patient sign name) before each dose, or every 8 hours.

(*continues*)

Table 1-3 Anticancer Agents Requiring Special Premedications/ Precautions[26–33] (*continued*)

Agent (Brand Name)	Premedications	Precautions
Docetaxel (Taxotere)	Dexamethasone 8 mg PO BID × 3 days, starting the day prior to treatment. Weekly docetaxel: Dexamethasone 8 mg PO every 12 hours × 3 doses (24 mg/week) beginning the evening before docetaxel dosing. **Note**: Dose may be omitted in patients who have developed tolerance to the drug Hormone-refractory metastatic prostate cancer: given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours, and 1 hour before docetaxel	Avoid in patients with severe hypersensitivity to polysorbate 80. Severe hypersensitivity reactions require discontinuation.
Ibritumomab tiuxetan (Zevalin)	Diphenhydramine 50 mg PO and acetaminophen 650 mg PO 30 minutes prior to treatment	
Interferon-alfa (Roferon-A, Intron A)	Acetaminophen 650 mg PO 30 minutes prior to treatment, repeat q 4 h prn for flu-like symptoms, including fever and chills	Roferon-A no longer manufactured. Intron A still available
Interleukin-2 (Aldesleukin)	Acetaminophen 650 mg PO prior to each dose q 4 h plus nonsteroidal anti-inflammatory drug (NSAID) (indomethacin 25 mg PO prior to each dose q 6 h or naproxen 500 mg PO BID during therapy). High dose, bolus (> 600,000 units/kg): H_2 receptor antagonist (cimetidine, famotidine, or ranitidine)	**Note**: Do *not* use corticosteroids with high-dose IL-2.

Agent (Brand Name)	Premedications	Precautions
Irinotecan (Camptosar)	**Acute diarrhea** (1st 24 hours after administration): 0.25 mg to 1 mg atropine as needed. **Delayed diarrhea**: (> 24 hours): 4 mg loperamide load, then 2 mg q 2 h or alternatively, 4 mg q 4 h around the clock until diarrhea free for 12 hours. **Note**: Will exceed package insert recommended dose of 16 mg/day.	
Ixabepilone (Ixempra)	Oral H_1 (diphenhydramine) and H_2 (cimetidine, famotidine, or ranitidine) antagonists 1 hour prior to infusion. If history of hypersensitivity, premedication with corticosteroid is recommended	Contains 39.8% dehydrated alcohol Formulated with Cremophor EL (polyoxyethylated castor oil; (hypersensitivity possible)
Methotrexate (Trexall)	High dose (> 100 mg/m^2) requires: • Administration of leucovorin at 24 hours, or no later than 42 hours, after methotrexate administration and continue until methotrexate level is less than 0.05 µmol • Hydrate with IV fluids containing sodium bicarbonate to maintain urine pH above 7 to enhance solubility of methotrexate in urine and precipitation in kidneys	Avoid all NSAIDS prior to and during therapy. Consider interactions with drugs known to alter plasma protein binding or renal elimination of methotrexate (eg, salicylates, sulfisoxazole, NSAIDs, penicillin, probenecid). Avoid high-dose vitamin C supplementation including excessive consumption of juice containing vitamin C (eg, orange juice).
Ofatumumab (Arzerra)	Acetaminophen (1000 mg), oral or IV antihistamine (eg, cetirizine 10 mg orally or equivalent), and corticosteroid 30–120 min prior to administration. Full-dose corticosteroid recommended	Monitor and premedicate for infusion-related reactions. Interrupt infusion and institute treatment if reaction occurs; may require subsequent rate modification. Avoid live vaccine administration during treatment.

(*continues*)

Table 1-3 Anticancer Agents Requiring Special Premedications/ Precautions[26–33] (*continued*)

Agent (Brand Name)	Premedications	Precautions
Ofatumumab (Arzerra) (*continued*)	for doses 1, 2, and 9; in absence of grade 3 infusion-related reaction, gradually reduce corticosteroid dose for doses 3 through 8; administer full or half-dose corticosteroid with doses 10 through 12 if grade 3 infusion-related reaction did not occur with dose 9	
Oxaliplatin (Eloxatin)		Hypersensitivity reactions can occur with any cycle, but most commonly after 6-8 cycles. Discontinuation or desensitization is recommended for future doses after a hypersensitivity reaction occurs.
Paclitaxel (Taxol)	Dexamethasone 20 mg PO at 12 hours and 6 hours prior to therapy, or 10 mg to 20 mg, once, IV at 30 minutes prior to paclitaxel infusion with diphenhydramine 50 mg IV/PO and H_2-receptor antagonist (famotidine or ranitidine). **Note**: Weekly paclitaxel, 8-10 mg IV dexamethasone with diphenhydramine and H_2 receptor antagonist as above prior to paclitaxel; dexamethasone can be decreased to 4 mg with subsequent cycles if tolerated	Avoid in patients with severe hypersensitivity to Cremophor EL (polyoxyethylated castor oil). Severe hypersensitivity reactions require discontinuation. **Note**: Cimetidine usually not given due to potential drug–drug interactions.
Panitumumab (Vectibix)	While there are no premedications recommended, monitor for infusion-related reactions	

Agent (Brand Name)	Premedications	Precautions
Pemetrexed (Alimta)	Dexamethasone 4 mg PO BID day before, day of, and day after treatment. Folic acid 350-1000 mcg PO daily starting 5-7 days prior to treatment, continued throughout treatment and for 21 days after last treatment. Vitamin B_{12} 1000 mcg IM, once, 7 days prior to treatment and every 3 cycles (or every 9 weeks) thereafter	
Pralatrexate (Folotyn)	Folic acid 1 to 1.25 mg orally once daily beginning 10 days before the first dose of pralatrexate; continue during the full course of therapy and for 30 days after the last dose. Vitamin B_{12} 1 mg IM within 10 weeks prior to the first dose and every 8-10 weeks thereafter (may be given the same day as treatment with pralatrexate) Diphenhydramine 50 mg PO and acetaminophen 650 mg PO 30 minutes prior to treatment	
Rituximab (Rituxan)		Interrupt infusion if infusion-related reaction occurs, and rechallenge with 50% reduction in infusion rate unless reaction is severe. Screen patients at high risk of hepatitis B virus (HBV) infection before initiation of rituximab and closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following rituximab therapy.
Temsirolimus (Torisel)	Diphenhydramine 25 mg to 50 mg IV 30 minutes before the start of each dose	Significant drug–drug interactions. Use caution with inhibitors and inducers of CYP3A4.

(*continues*)

Table 1-3 Anticancer Agents Requiring Special Premedications/ Precautions[26–33] (*continued*)

Agent (Brand Name)	Premedications	Precautions
Tositumomab (Bexxar)	Diphenhydramine 50 mg PO and acetaminophen 650 mg PO 30 minutes prior to or during treatment	Thyroid-protective premedication: Initiate thyroid-protective drugs 24 hours prior to the dosimetric dose and continue daily dosing for a minimum of 14 days following the therapeutic dose. The following regimens are recommended: • Saturated solution of potassium iodide (SSKI) 4 drops orally 3 times daily or • Lugol's solution 20 drops orally 3 times daily or • Potassium iodide tablets 130 mg orally once daily Do not administer tositumomab dose unless the patient has received at least 3 doses of SSKI, 3 doses of Lugol's solution, or 1 dose of 130-mg potassium iodide tablet.
Trastuzumab (Herceptin)	Diphenhydramine 50 mg PO and acetaminophen 650 mg PO 30 minutes prior to treatment	Infusion-related symptoms most commonly occur during infusion or within 24 hours.

Eribulin

Eribulin is the newest mitotic inhibitor that is a synthetic analog of halichondrin B, a compound found in a marine sponge.[34] It was approved by the Food and Drug Administration (FDA) in 2010 for the treatment of metastatic breast cancer in patients who have previously received at least 2 chemotherapeutic regimens that should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.[26] Eribulin inhibits microtubule growth by depolymerization without affecting the shortening phase and sequesters tubulin into nonproductive aggregates.[34] This leads to disruption of mitotic spindles, arrest of the cell cycle at the G_2/M phase, and subsequent apoptotic cell death. The most common side effects associated with eribulin are neutropenia, anemia, fatigue, peripheral neuropathy, and constipation.[34]

Estramustine

A combination of an alkylating agent (*nor*-nitrogen mustard) that is linked by a carbamate bridge with estradiol, estramustine is a unique drug.[19] It was developed with the intent that the estrogenic portion of the molecule would facilitate the uptake of the alkylating agent into hormone-sensitive prostate cancer cells. However, the compound was found to be devoid of alkylating activity due to unanticipated stability of the carbamate bridge and lack of alkylating activity of the intact molecule. Furthermore, the intact estramustine molecule did not show any significant binding to estrogen receptors. Although the drug did not exert the expected hormonal or alkylating effects for which it was developed, estramustine exerts cytotoxic effects by microtubule depolymerization and inhibits mitosis.[35] Common side effects include gynecomastia, edema, and elevated hepatic enzymes.[26]

Alkylating Agents

Alkylating agents are active against blood-related cancers, such as non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic leukemias, and multiple myeloma, and are also effective in breast, ovarian, lung, and some gastrointestinal cancers.[19] Alkylating agents work by damaging the DNA of cancer cells to prevent them from dividing. Their specific mechanism of action is covalent bonding of highly reactive alkyl groups or substituted alkyl groups with nucleophilic groups of proteins and nucleic acids. These covalent interactions result in cross-linking between 2 DNA strands or between 2 bases in the same strand of DNA. Reactions between DNA and RNA and between the alkylators and proteins may also occur, but the main damage that results in cell death is inhibition of DNA replication. These agents are considered non–cell-cycle specific chemotherapy drugs.

Nitrogen Mustard and Its Derivatives

Classical alkylators include the original nitrogen mustard drug, mechlorethamine; cyclophosphamide; ifosfamide; bendamustine; and thiotepa. Mechlorethamine is a common component of one of the regimens used to treat Hodgkin's lymphoma and is highly emetogenic, with nausea and vomiting occurring in over 90% of patients within the first 3 hours of administration.[36] Cyclophosphamide and ifosfamide are nitrogen mustard derivatives and are not active as parent compounds. They must be activated by metabolism via the cytochrome

P450 enzyme CYP3A4.[19] Acrolein, a metabolite of both of these agents, has little antitumor effect but is responsible for the hemorrhagic cystitis adverse effect associated with these drugs. Mesna is a chemoprotectant agent, which is given prior to, during, and after ifosfamide and sometimes cyclophosphamide in order to prevent hemorrhagic cystitis.[37] Bendamustine has a benzimidazole ring that makes it only partially cross-resistant with the other alkylating agents.[38] Thiotepa and busulfan are polyfunctional alkylating agents, which are mostly used in hematopoietic stem cell transplantation conditioning regimens. All of the nitrogen mustard agents cause myelosuppression as one of their primary side effects.

Nitrosoureas

A unique feature of the nitrosoureas is their lipophilicity and ability to cross the blood–brain barrier.[19] These agents play a very important role in the management of primary brain cancers. Carmustine (BCNU) and lomustine (CCNU) are metabolized to reactive alkylating compounds and isocyanate moieties that exert cytotoxic effects. In addition to being available as an intravenous medication, carmustine is also available in a biodegradable wafer for direct implantation into the surgical cavity after resection of brain tumors.[19] The most common side effects of carmustine and lomustine are nausea and vomiting, nephrotoxicity, and myelosuppression. Streptozocin is another nitrosourea that possesses a glucose moiety rather than the chlorethyl side chain that most nitrosoureas have. The glucose moiety is responsible for streptozocin's specificity for pancreatic islet cells and reduced myelotoxicity.[36]

Nonclassical Alkylating Agents

Although they do not have the structures of classical alkylating agents, dacarbazine, procarbazine, and temozolomide are capable of binding covalently to DNA, causing cellular damage. Both dacarbazine and temozolomide are metabolized to the same intermediary, MTIC (5–[3–methyltriazen–1–yl] imidazole–4–carboxamide).[39] Dacarbazine requires the liver for activation; temozolomide does not. Dacarbazine has poor absorption and is available only in an intravenous form. Temozolomide is nearly 100% bioavailable when taken on an empty stomach and is an orally available medication. Dacarbazine penetrates the central nervous system poorly, but temozolomide readily crosses the blood–brain barrier, achieving therapeutically active concentrations in the central nervous system.

Heavy Metal Compounds

Cisplatin, carboplatin, and oxaliplatin are platinum derivatives with cytotoxicity due to platinum binding to DNA and the formation of intrastrand cross-links between neighboring guanines.[19] These are non–cell-cycle specific agents. Cisplatin is a platinum-chloride complex, carboplatin is a structural analog of cisplatin with the chloride groups replaced by a carboxycyclobutane ring, and oxaliplatin is a platinum compound complexed with an oxalate ligand and diaminocyclohexane. Cross-resistance between cisplatin and carboplatin is common, whereas oxaliplatin's spectrum of activity is different from the other platinums and includes significant activity against colorectal cancer.[19,40] The side effects profile for the platinums vary significantly for individual agents. Cisplatin causes significant nephrotoxicity, ototoxicity, peripheral neuropathy, emesis, and anemia.[19] Supportive care measures, including hyperhydration and antiemetic therapy, are vital to the effective use of cisplatin. Carboplatin has less nephrotoxic, neurotoxic, ototoxic, and emetogenic potential than cisplatin, but causes more myelosuppression.[19] Carboplatin is most often dosed via pharmacokinetic parameters using the Calvert formula [Dose in mg = AUC × (CrCl + 25)].[41] For more information on pharmacokinetic dosing and the factors involved in calculating the creatinine clearance see the chapter titled, *Dosing Calculations*, elsewhere in this text. Oxaliplatin is only rarely associated with clinically significant nephrotoxicity and does not appear to cause ototoxicity.[42] It has less emetogenic potential than cisplatin, but it can cause unusual peripheral neuropathies, including cold-induced neuropathies and pharyngolaryngeal dysesthesias.[42] All platinum agents have the potential to cause hypersensitivity reactions.[19]

Antimetabolites

Antimetabolites are in a class of drugs that interfere with DNA and RNA production. They are often analogs of the nucleotides that make up DNA and RNA.[19] In general, the antimetabolites are effective in a specific cycle of cell growth (S phase). The most common adverse effects associated with the antimetabolites are those seen on the rapidly dividing cells of the body, such as the bone marrow, gastrointestinal tract, hair follicles, and reproductive system. The subclasses of antimetabolites include the pyrimidines, cytidine analogs, purine antimetabolites, and folate antagonists.

Pyrimidines

Fluorinated analogs of the pyrimidine uracil include fluorouracil and its oral prodrug, capecitabine. The metabolites of these drugs (fluorodeoxyuridine monophosphate [FdUMP], fluorodeoxyuridine triphosphate [FdUTP], and fluorouridine triphosphate [FUTP]) are incorporated into RNA and DNA and inhibit the enzyme thymidylate synthase (TS) to interfere with cancer cell growth.[19,43] The administration of leucovorin forms a stable ternary complex between fluorouracil, TS, and leucovorin that enhances inhibition of TS and blocks the synthesis of thymidylate. The mechanism of cytotoxicity is influenced by the method of administration; continuous infusion of fluorouracil is associated with thymidylate synthase inhibition, whereas the incorporation into RNA and DNA is associated with the bolus administration of fluorouracil. Pyrimidines are effective in colorectal, breast, gastric, and head and neck cancers. The most common side effects of pyrimidines include myelosuppression, stomatitis, diarrhea, and hand-foot syndrome. Myelosuppression is more common with the bolus administration of fluorouracil, whereas diarrhea and hand-foot syndrome are more common with capecitabine and the continuous infusion of fluorouracil.

Cytidine Analogs

Cytidine analogs include cytarabine, gemcitabine, azacitidine, decitabine, and nelarabine. Cytarabine is an analog of cytosine and is phosphorylated within tumor cells to inhibit DNA polymerase, ultimately preventing DNA elongation.[19,43] Cytarabine is effective in leukemias and lymphomas and may be administered as a low-dose continuous infusion, high-dose intermittent infusion, or intrathecally. A liposomal formulation is also available for intrathecal use. The toxicity of cytarabine is dose dependent but includes myelosuppression and, at high doses, cerebellar toxicity and ophthalmic irritation. Gemcitabine is a deoxycytidine analog, similar in structure to cytarabine. It also inhibits DNA polymerase as well as ribonucleotide reductase, resulting in prevention of DNA elongation. It is used in pancreatic, breast, lung, and ovarian cancers, non–small cell lung cancer, and in some lymphomas. Myelosuppression, flu-like symptoms within the first 24 hours after administration, and rash are the most common side effects associated with gemcitabine. Azacitidine and decitabine are directly incorporated into DNA, inhibiting DNA methyltransferase and causing hypomethylation of DNA, which ultimately causes cellular differentiation and apoptosis. These drugs are used to treat myelodysplastic syndrome and acute myeloid leukemia. Myelosuppression is the most common side effect. Additionally, renal dysfunction and injection-site

reactions can occur with azacitidine, and decitabine is associated with constipation, edema, headache, and nausea. Nelarabine, a treatment for T-cell acute lymphoblastic leukemia, is a prodrug that accumulates in leukemic blasts to prevent DNA synthesis and cell death.[26,43] Myelosuppression and fatigue are the most common side effects associated with nelarabine.

Purine Antimetabolites

Purine antimetabolites are represented by mercaptopurine, thioguanine, fludarabine, cladribine, clofarabine, and pentostatin. Mercaptopurine and thioguanine are oral purine analogs that are converted to ribonucleotide to inhibit purine synthesis.[19,26,43] These drugs are metabolized by thiopurine S-methyltransferase (TPMT). Genetic polymorphisms of TMPT may result in reduced activity and decreased tolerance. In addition to myelosuppression that occurs with all purine antimetabolites, rash, mild nausea, and cholestasis often occur with mercaptopurine and thioguanine. Fludarabine, a purine adenine analog, interferes with DNA polymerase to cause chain termination and inhibits transcription by RNA incorporation. It is used in the treatment of chronic lymphocytic leukemia, some lymphomas, and refractory acute myelogenous leukemia. Significant myelosuppression and immunosuppression can occur, resulting in an increased risk of opportunistic infections. Prophylactic antibiotics and antivirals are recommended until CD4 counts normalize. Cladribine, once phosphorylated into an active form, is incorporated into DNA, resulting in DNA synthesis inhibition and chain termination. It is used to treat hairy cell leukemia, chronic lymphocytic leukemia, and some forms of lymphoma. In addition to myelosuppression and immunosuppression, fever is common. Clofarabine is a deoxyadenosine analog that is active in myeloid leukemia and myelodysplastic syndrome. Side effects include myelosuppression, liver dysfunction (severe but transient), skin rashes, and hand-foot syndrome. Pentostatin is an inhibitor of adenosine deaminase, which ultimately blocks DNA synthesis through RNA ribonucleotide reductase inhibition. Pentostatin is used in hairy cell leukemia. Side effects for pentostatin include myelosuppression, immunosuppression, rash, conjunctivitis, and myalgias.

Antifolates

The antifolates include methotrexate, pemetrexed, and pralatrexate. Methotrexate, a folic acid analog, inhibits dihydrofolate reductase in both malignant and nonmalignant cells, ultimately reducing purine and thymidylic acid synthesis, which are needed for DNA formation and cell division.[19,43] When methotrexate is

administered in high doses, leucovorin, a reduced folate, is administered 24 hours after methotrexate to bypass the dihydrofolate reductase block in normal cells. Similarly to the other antimetabolites, myelosuppression, nausea/vomiting, and stomatitis can occur with methotrexate. Renal tubular necrosis can occur with high-dose methotrexate; thus, vigorous hydration with sodium bicarbonate to maintain an alkaline pH is recommended to increase the solubility of methotrexate and prevent precipitation in the renal tubules. Methotrexate is used in lymphoma, acute lymphocytic leukemia, and gastric, esophageal, bladder, and breast cancers. It can also be administered via the intrathecal route. Pemetrexed is an antifolate that inhibits the following 3 enzymes involved in thymidine and purine synthesis: dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase. This drug is used in mesothelioma and non–small cell lung cancer. Common side effects include myelosuppression, rash, diarrhea, and nausea/vomiting. Patients should receive both folic acid and cyanocobalamin (vitamin B_{12}) to reduce bone marrow suppression and diarrhea. To prevent rash, a corticosteroid, such as dexamethasone, should be administered the day before, the day of, and the day after pemetrexed administration. Pralatrexate inhibits DNA, RNA, and protein synthesis by selectively entering cells expressing reduced folate carrier and competing for the dihydrofolate reductase-binding site to inhibit dihydrofolate reductase. It is used in T-cell lymphomas. Side effects include myelosuppression, mucositis, fatigue, and edema. As with pemetrexed, folic acid and cyanocobalamin should be administered to patients receiving pralatrexate (see Table 1-3 for specific premedication dosing information).

Topoisomerase Inhibitors

The enzymes responsible for maintaining DNA structure during replication and transcription are the topoisomerases I and II.[19] These enzymes relieve the torsional strain during the unwinding of DNA by producing strand breaks. Topoisomerase I produces single-strand breaks; topoisomerase II causes double-strand breaks. There are 3 major groups of antineoplastic agents that affect topoisomerase enzymes. They include camptothecin, podophyllotoxin, and the anthracene derivatives.

Camptothecin Derivatives

Topoisomerase inhibitors, such as irinotecan and topotecan, interfere with enzymes that are important for accurate DNA replication and arrest cells in the S phase.[19] Both of these agents inhibit topoisomerase I. Irinotecan must undergo metabolism to SN–38 by uridine diphosphate glucosyltransferase (UGT), an

enzyme, which may be variably inherited with a mutation. Inheritance of this genetic mutation may result in an increased risk of diarrhea and neutropenia associated with irinotecan use. These agents are used to treat colorectal, lung, ovarian, gastrointestinal, and other cancers.

Podophyllotoxin Derivatives

Etoposide and teniposide are semisynthetic podophyllotoxins that arrest cells in the S or early G_2 phase and are considered cell-cycle, phase specific.[19] In addition to binding to tubulin and interfering with microtubule formation, they also damage cells by causing strand breakage by inhibiting topoisomerase II. Etoposide is used for a variety of both hematologic and solid tumors; whereas, teniposide is primarily used for hematologic malignancies. Etoposide is available as solution for intravenous injection, oral formulation, and as etoposide phosphate (the prodrug formulation of etoposide) for intravenous injection; teniposide is available as an intravenous injection. The intravenous formulation of etoposide is formulated in polyethylene glycol (PEG) and polysorbate 80. Teniposide is solubilized in polyoxyethylated castor oil (Cremophor EL). These formulations contribute to hypersensitivity reactions and hypotension associated with rapid infusions. These effects may be minimized by slowly infusing the drug over 30 minutes to 1 hour and if necessary, premedicating with diphenhydramine and hydrocortisone. Other toxicities associated with these agents include myelosuppression and peripheral neuropathies.

Anthracene Derivatives

The anthracyclines of the anthracene group include doxorubicin, daunorubicin, idarubicin, and epirubicin.[19] Mitoxantrone is an anthracenedione. Anthracyclines are classified as antitumor antibiotics that interfere with enzymes involved in DNA replication. They are intercalating agents that insert between base pairs of DNA resulting in structural changes that interfere with DNA and RNA synthesis. They are also topoisomerase II inhibitors causing double-strand DNA breaks. The anthracyclines also undergo electron reduction to form oxygen free-radicals that are responsible for anthracycline's cardiotoxicity and extravasation ulceration profile. Because they can damage the heart, anthracyclines have a lifetime dose limit.[44] Refer to **Clinical Pearl 1-1** for calculating total anthracycline cumulative dose when multiple, different anthracycline drugs have been administered. Mitoxantrone is also an intercalating topoisomerase II inhibitor but it has less potential to form oxygen free radicals, thus, less cardiotoxicity. Anthracyclines treat a variety of tumors and work in all phases of the cell cycle.

CLINICAL PEARL 1-1

A 5% risk of cardiotoxicity occurs with anthracyclines when the maximum cumulative dose is reached. The following table shows the cumulative dose at which a 5% cardiotoxicity risk occurs and the conversion factor between anthracyclines. This allows the clinician to calculate a total anthracycline cumulative dose if a patient has received multiple, different anthracyclines.[44]

Anthracycline	Conversion Factor	% Cardiotoxicity at Cumulative Dose
Doxorubicin	1	5% at 450 mg/m^2
Daunorubicin	0.5	5% at 900 mg/m^2
Epirubicin	0.5	5% at 935 mg/m^2
Idarubicin	2	5% at 225 mg/m^2
Mitoxantrone	2.2	5% at 200 mg/m^2

Examples:

A patient received a total of 120 mg/m^2 of daunorubicin. What is the equivalent in doxorubicin dosing?

Take 120 mg/m^2 × 0.5 = 60 mg/m^2 of doxorubicin.

A patient received a total of 36 mg/m^2 of idarubicin. What is the equivalent doxorubicin dose?

Take 36 mg/m^2 × 2 = 72 mg/m^2 of doxorubicin.

Note: It is common in clinical practice to calculate the risk of cardiotoxicity in terms of the total cumulative doxorubicin dose.

Miscellaneous Agents

Arsenic trioxide is an organic element that acts as a differentiating agent in the treatment of acute promyelocytic leukemia (APL). It induces the maturation of cancer cells into normal cells. It also can cause programmed cell death or apoptosis.[19] The most common toxicities of this agent include the APL differentiation syndrome, which is characterized by fever, dyspnea, weight gain, pulmonary infiltrates, and pleural or pericardial effusions, with or without leukocytosis.[45]

Asparaginase is an enzyme derived from *Escherichia coli* or *Erwinia chrysanthemi.* L-asparagine is a nonessential amino acid that can be made by most mammalian cells, except for some lymphoid malignancies.[19] Asparaginase causes degradation of any available asparagine in these tumor cells, resulting in inhibition of protein synthesis and ultimate cell death. The primary side effects seen with asparaginase include glucose intolerance and bleeding disorders, due to a decreased production of insulin and clotting factors. Hypersensitivity may also occur with asparaginase; however, pegaspargase is a pegylated formulation of asparaginase that allows for less frequent administration and less hypersensitivity than the native formulation.[46] In 2012, production of *E coli* derived asparaginase was discontinued.

Bleomycin, an antitumor antibiotic, is derived from a fungal species and is a mixture of several proteins. It is cell-cycle specific (G_2 phase).[19] Bleomycin causes DNA strand breakage via free radical formation. It is inactivated by an enzyme called aminohydrolase, which is in low concentrations in the skin and lungs, thus accounting for the pulmonary toxicity of the drug. Baseline pulmonary tests and monitoring for pulmonary toxicity is a must during bleomycin treatment. Other side effects include fever, nausea, and vomiting. Bleomycin is used in the treatment of testicular cancer and Hodgkin's lymphoma. The agent is dosed in either units or milligrams, and 1 unit = 1 mg.

Histone deacetylase (HDAC) inhibitors cause an accumulation of acetylated histones and induce cell cycle arrest or apoptosis of transformed cancer cells.[19,26] Two HDAC inhibitors, romidepsin and vorinostat, are currently marketed**.** Both of these drugs are used in the treatment of T-cell lymphoma. Romidepsin is an intravenous agent, whereas vorinostat is an oral agent. The most common side effects of these drugs include fatigue, myelosuppression, and gastrointestinal disturbances, such as nausea and diarrhea. Vorinostat is also associated with an increase in serum glucose, creatinine, and urine protein.[47] A high risk of infection and electrocardiogram changes have been seen with romidepsin.[26]

Hydroxyurea inhibits ribonucleotide reductase, causing the production of short strands of DNA.[19] Its primary role in the management of cancer lies in its ability to rapidly reduce white blood cell counts in patients with acute or chronic leukemias. It has a greater role today in the management of patients with sickle cell disease by increasing the production of hemoglobin F. The most common side effect is myelosuppression.

Retinoids (vitamin A and its metabolites) regulate the expression of genes that control cell growth and differentiation by binding to retinoid receptors.[19,43] Tretinoin (all-trans retinoic acid) is a naturally occurring derivative of vitamin A, which is not cytotoxic but promotes the maturation of promyelocytic cells with

the t(15;17) cytogenetic marker. It is used in the treatment of APL. Headache, fatigue, weakness, and fever are the most common side effects. Retinoic acid syndrome is a life-threatening syndrome characterized by fever, respiratory distress, and hypotension, which can occur at any time during therapy. Prompt recognition and treatment with corticosteroids is required. Bexarotene is a synthetic retinoid that activates retinoid X receptors, affecting cellular differentiation and proliferation. It is used in cutaneous T-cell lymphoma in patients who are refractory to other therapy. Common side effects include hypercholesterolemia, pancreatitis, hypothyroidism, leukopenia, and triglyceride elevations.

TARGETED THERAPY

Researchers have learned more about specific molecular changes responsible for cancer growth, resulting in a new class of drugs called targeted therapies.[19] These targeted agents are designed to interfere with biochemical processes and signaling pathways that control cancerous cell growth, ultimately resulting in suppression of cell cycle progression, proliferation, and survival.

Targeted therapies include monoclonal antibodies that target cell surface glycoproteins, growth factor receptors, and ligands; agents that inhibit epidermal growth factors or vascular endothelial growth factors; agents that inhibit enzymes responsible for degrading proteins that control cell cycles; agents that inhibit the activity of intracellular signaling pathways involved in cancer cell growth and proliferation; immunomodulating agents that have anticancer activity; and cytokines that have antitumor and immune stimulation activity.

Monoclonal Antibodies

Monoclonal antibodies (MoABs) were among the first targeted agents. The original MoABs were made entirely from mouse cells; today, the MoABs are chimeric, humanized, or fully human where they differ in the amount of foreign component.[19] MoABs are classified into those that target cell-surface antigens and those that target growth factor receptors or ligands. MoABs may also be conjugated to a toxin, chemotherapy agent (eg, ado-trastuzumab, brentuximab vedotin), or radioactive particle (eg, ibritumomab tiuxetan, tositumomab). **Table 1-4** describes the nomenclature of MoAB names, which can provide insight into the target/disease class and the source of the MoAB.[48] The suffix *-mab* is used for all MoABs and is always preceded by identification of the animal source of the product and the target or general disease state the MoAB is treating.

Table 1-4 Nomenclature of Monoclonal Antibodies[48]

Monoclonal antibody name = prefix + **target/disease class infix** + *source infix* + stem (mab)[a]

Prefix (Identifies the Distinctive Product)	**Target/Disease Infix**	**Source Infix**	**Example**
ibri	-**t(u)(**m) tumor	-o- mouse	ibri**tu***mo*mab tiuxetan
beva	-**c(i)(**m) Cardiovascular	-zu- humanized	beva**ci***zu*mab
ipi	-**l(i)**(m) Immunomodulating	-u- fully human	ipi**li***mu*mab
deno	-**s(o)** Bone	-u- fully human	deno**s***u*mab
ofa	-**t(u)**(m) tumor	-u- fully human	ofa**tu***mu*mab
tras	-**t(u)**(m) tumor	-zu- humanized	tras**tu***zu*mab
ri	-**t(u)**(m) tumor	-xi- chimeric	ri**tu***xi*mab

Hypersensitivity and infusion-related reactions may occur with MoABs administration along with development of human antimouse antibodies (HAMA); risks are generally greatest with murine MoAB, least with humanized MoAB, and are not expected with fully human MoAB.[19] These symptoms can be mild with fever, chills, nausea, and rash, to severe with manifestations of life-threatening anaphylaxis with cardiopulmonary collapse. Chest or back pain may also occur with MoAB administration. The reactions are generally more severe with initial infusion and should subside with subsequent treatments. Patients must be closely monitored while receiving MoAB and premedication with antihistamines and acetaminophen is recommended for most MoABs. Starting with slower infusion rates with incremental increases as the patient tolerates also minimizes infusion-related reactions.[19] Table 1-3 lists drugs, including MoABs, that require premedications to prevent infusion-related reactions.

Alemtuzumab, brentuximab vedotin, ibritumomab tiuxetan, ofatumumab, rituximab, and tositumomab are used for the treatment of hematologic malignancies; ado-trastuzumab emtansine, bevacizumab, cetuximab, ipilimumab, panitumumab, and trastuzumab are used in the treatment of solid tumors.

Angiogenesis Inhibitors

Angiogenesis is the development of new blood vessels, and when this process is unregulated in cancer, it can lead to tumor growth, invasion, and metastasis. Angiogenesis inhibitors prevent the formation of new blood vessels in the tumor, thus decreasing the delivery of nutrients and oxygen, resulting in growth delay of the tumor. Most antiangiogenic drugs target vascular endothelial growth factors (VEGFs), the VEGF receptors, platelet-derived growth factor receptors (PDGFRs), or the production of endothelial cells that are involved in the formation of blood vessels. Bevacizumab was the first successful MoAB to inhibit angiogenesis. Antiangiogenic drugs that are not MoABs include the immunomodulators thalidomide, lenalidomide, and pomalidomide; the tyrosine kinase inhibitors axitinib, cabozantinib, pazopanib, sorafenib, sunitinib, and vandetanib; and the recombinant fusion-protein ziv-aflibercept.

Immunomodulators

Thalidomide, lenalidomide, and pomalidomide are immunomodulators thought to act primarily as antiangiogenic agents in the treatment of malignancies.[19,26] They may, however, have additional mechanisms of action. They are primarily used in the treatment of multiple myeloma. The most common side effects of these agents are peripheral neuropathies, somnolence, constipation, rash, dizziness, and orthostatic hypotension. Lenalidomide and pomalidomide cause less somnolence and peripheral neuropathies than thalidomide, but are associated with myelosuppression. All of these immunomodulators are associated with thrombotic issues, especially when given in combination with steroids for the treatment of multiple of myeloma, and prophylactic thrombotic therapy should be considered. Because of the teratogenic potential of these drugs, all pharmacies and prescribers must be enrolled in the respective risk evaluation and mitigation strategy programs, THALOMID REMS (risk evaluation and mitigation strategy) (formerly known as the System for Thalidomide Education and Prescribing Safety [S.T.E.P.S.] program) for thalidomide, the REVLIMID REMS (formerly known as the RevAssist program) for lenalidomide, and the POMALYST REMS for pomalidomide. For more information on the REMS program, see the chapter titled, *Drug Safety and Risk Management,* elsewhere in this text.

Tyrosine Kinase Inhibitors

Tyrosine kinases are mediators of the signaling cascade that is important in cell proliferation, differentiation, migration, metabolism, and apoptosis.

These enzymes are tightly regulated in normal cells, but mutations, overexpression, and stimulation can result in malignant cell transformation.[49] Tyrosine kinase inhibitors (TKIs) block enzymes with a variety of functions, including angiogenesis and inhibition of cancer cell growth.

Erlotinib is an oral agent that is a selective epidermal growth factor receptor– (EGFR-) tyrosine kinase inhibitor that blocks signal transduction pathways involved in proliferation, survival, and metastases of cancer cells.[19] Rash and diarrhea are the most common side effects. Clinical studies suggest that the development of a rash is predictive of its antitumor effect and response to therapy. There are drug interactions with CYP3A4 inducers and inhibitors. Erlotinib is indicated for non–small cell lung cancer and pancreatic cancer.

Sunitinib and sorafenib inhibit multiple tyrosine kinases, including VEGFR-2 and PDGFR, which are involved in angiogenesis; c-KIT, which is involved with gastrointestinal tumors; and FLT3, which is involved in leukemia.[19] Diarrhea, rash, fatigue, and hypertension occur with both agents. Sunitinib can cause congestive heart failure, and sorafenib has been reported to cause hand-foot syndrome. These agents have activity against renal cell cancers, gastrointestinal stromal tumors, and are being evaluated for other cancers. Similar to erlotinib, drug interactions occur with CYP3A4 inducers and inhibitors.[49,50]

Lapatinib inhibits EGFR and HER-2 (also known as human epidermal growth factor receptor 2, ErbB-2).[19] It is effective in combination with capecitabine in breast cancer patients overexpressing HER-2 who have previously received trastuzumab and chemotherapy. Diarrhea, rash, hepatotoxicity, and QT interval prolongation are most common side effects. Significant CYP450-mediated drug interactions exist.

Imatinib, often considered the first designer targeted agent, is an inhibitor of the tyrosine kinase activity of the BCR-ABL fusion gene of patients with chronic myelogenous leukemia (CML).[19] Prevention of tyrosine-kinase phosphorylation of the fusion gene inhibits downstream activation of cellular proliferation. Bosutinib, dasatinib, and nilotinib are second-generation TKIs that also bind to the BCR-ABL tyrosine kinase domain.[19,51] The advantage of these agents is that they have activity in CML patients with BCR-ABL fusion gene mutations that confer resistance to imatinib. Patients with the T315I gene mutation are resistant to all of the 3 TKI inhibitors. Ponatinib is also a TKI but was designed to be effective in patients with T315I mutation.[26] Adverse effects of imatinib include rash, fluid retention, myelosuppression, nausea, muscle cramps, elevation of liver enzymes, and headaches. Dasatinib and nilotinib have toxicities similar to that of imatinib, although dasatinib also has been reported to cause hypocalcemia and more significant pleural effusions. Bosutinib is associated with diarrhea,

nausea, and thrombocytopenia, and ponatinib is associated with rashes, dry skin, abdominal pain, headache, and constipation.[51] All of these agents have extensive drug–drug interactions with substrates, inducers, and inhibitors of CYP3A4 and other CYP450 enzymes.

Other newly approved tyrosine kinase inhibitors target a variety of tyrosine kinases and are used in several different types of malignancies (**Clinical Pearl 1-2**). Afatinib is a tyrosine kinase inhibitor of EGFR, HER2, and HER4. It is FDA approved for the first-line treatment of patients with metastatic non–small cell lung cancer whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations detected by an FDA-approved test.[51] Common side effects include diarrhea, rash, acneiform, stomatitis, paronychia, dry skin, decreased appetite, and pruritis. Axitinib is an inhibitor of VEGFR–1, –2, and –3, approved for the treatment of advanced renal cell carcinoma. Common side effects include diarrhea, hypertension, fatigue, decreased appetite, and hand-foot syndrome. Cabozantinib is a pan-tyrosine kinase inhibitor. It is used in medullary thyroid cancer. Common side effects include diarrhea, stomatitis, hand-foot syndrome, and decreased weight. Crizotinib is an ALK and ROs1 inhibitor that is approved for ALK-positive non–small cell lung cancer. Common side effects include vision disorders, nausea, diarrhea, constipation, and edema. Dabrafenib selectively inhibits mutated forms of BRAF kinases that result from mutations in the BRAF gene, including BRAFV600E, which is found in 70% of melanomas. It is approved for patients with unresectable or metastatic melanoma with the BRAFV600E mutation. Side effects include hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and hand-foot syndrome. Regorafenib is a multikinase inhibitor, which targets angiogenic, stromal, and oncogenic tyrosine kinase receptors. It is approved for metastatic colorectal cancer and is associated with fatigue, decreased appetite, hand-foot syndrome, and diarrhea. Trametinib is mitogen-activated protein kinase (MEK) inhibitor, which specifically binds and inhibits MEK 1 and 2, resulting in inhibition of cell signaling and cellular proliferation of various cancers. It is specifically indicated in patients with unresectable or metastatic melanoma with BRAFV600E or BRAFV600K mutations as detected by an FDA approved test. Common side effects include rash, diarrhea, and lymphedema. Vemurafenib also selectively inhibits the BRAFV600E gene and is indicated for metastatic melanoma with BRAFV600E mutation. Side effects include arthralgia, rash, alopecia, fatigue, and photosensitivity reactions. Vandetanib blocks VEGF and EGF. It is indicated for medullary thyroid cancer. Side effects include diarrhea, rash, acne, nausea, and hypertension. Most of these drugs are metabolized by CYP450 enzymes; therefore, drug interactions should be reviewed before administration.

CLINICAL PEARL 1-2

FDA Approved Drugs on the CenterWatch website (http://www.centerwatch.com/drug-information/fda-approvals/) is a good source to keep updated with newly approved oncology drugs. For more in-depth information for verifying/prescribing the regimens and reported side effects, primary literature should be reviewed.

Miscellaneous Targeted Agents

Bortezomib is a proteasome inhibitor with significant activity in the treatment of multiple myeloma and mantle cell lymphoma.[19] Carfilzomib is a second-generation proteasome inhibitor.[51] The proteasome is an enzyme complex that breaks down proteins that regulate the cell cycle. Inhibition of the proteasome ultimately results in inactivation of NFκB, which prevents the transcription of genes that promote cancer growth.[19] The most common side effects of bortezomib and carfilzomib include fatigue, malaise, weakness, nausea, and diarrhea. Serious side effects that have been reported include myelosuppression and peripheral neuropathies (bortezomib greater than carfilzomib).

Temsirolimus and everolimus are known as mTOR (mammalian target of rapamycin) inhibitors. An mTOR is a part of the signaling pathway important in the growth and replication of various cell pathways.[19] Temsirolimus and everolimus are indicated for the treatment of renal cell cancer; everolimus is also indicated in advanced breast cancer and primary neuroendocrine tumors.[26] Adverse reactions include rash, fatigue, mucositis, nausea, hyperglycemia, hyperlipidemia, myelosuppression, and abnormal liver function tests. Drug interactions with CYP3A4 inducers or inhibitors can occur with both of these agents.

Vismodegib is a hedgehog signaling pathway inhibitor.[51] The hedgehog pathway promotes cellular development and cell division. It is indicated for metastatic basal cell carcinoma, in which this pathway is overactivated. Side effects include muscle spasms, alopecia, dysgeusia, weight loss, and nausea.

Ziv-aflibercept is a recombinant fusion protein designed to bind to VEGF and placental growth factor, with angiogenic properties.[51] This drug is indicated for colorectal cancer when combined with 5-flouroruacil, leucovorin, and irinotecan. Common side effects include myelosuppression, diarrhea, proteinuria, and stomatitis.

Interferon and Interleukin-2

Interferon-alfa and interleukin-2 are immunologic agents that have demonstrated anticancer effects. Interferon-alfa has cell growth inhibiting and apoptosis inducing characteristics, and exerts direct cytotoxic effects via caspase activation.[52] Adverse effects include flu-like symptoms, fever, extreme fatigue, psychiatric symptoms (depression, anxiety), sleep disturbances, and dose-related myelosuppression.[26] Interleukin-2 enhances lymphocyte mitogenesis and induces lymphocyte killing of cancer cells. Interleukin-2 may cause capillary leak syndrome, as well as associated hypotension, pulmonary edema, total body edema, cardiac arrhythmias, and renal abnormalities.[26]

HORMONAL AGENTS

Hormonal agents are typically used in the treatment of breast, uterine, and prostate cancers. These agents do not work directly on cancer cells. Rather, they inhibit the hormonal activation of cancer cell growth, either by competing for hormone receptors or by limiting the endogenous production of hormones.

Antiestrogens

Antiestrogens bind to estrogen receptors, inhibiting receptor-mediated gene transcription. This in turns prevents the effect of estrogen.[53] Selective estrogen receptor modulators (SERMs), such as tamoxifen, toremifene, and raloxifene, act as estrogen antagonists in breast tissue, but mimic estrogen in other tissues, such as uterine (eg, tamoxifen and toremifene), bone (eg, tamoxifen and raloxifene), and lipid tissue (eg, tamoxifen, toremifene, and raloxifene). Tamoxifen and toremifene can be used for treatment of breast cancer and risk reduction of breast cancer in high-risk patients. For cancer therapy, raloxifene is only indicated for risk reduction of invasive breast cancer in postmenopausal women at high risk of developing invasive breast cancer with or without osteoporosis. Adverse effects of SERMs include hot flashes, vaginal dryness, and thrombosis. Due to the estrogen-like effects on the uterus with tamoxifen and toremifene, endometrial hyperplasia is another potential adverse effect of these agents. Unlike SERMs, fulvestrant is a pure antiestrogen that down-regulates estrogen receptors and only has antagonist effects.

Aromatase Inhibitors

Aromatase inhibitors block estrogen production by inhibiting the enzyme aromatase, which is involved in the synthesis of estrogens from androstenedione.[53]

These agents are used mainly in postmenopausal women because the main source of estrogen in these women is from peripheral conversion of androstenedione into estrone and estradiol by aromatases. Anastrozole and letrozole are nonsteroidal agents that reversibly inactivate aromatase, while exemestane is a steroidal agent that permanently inactivates the enzyme. Common adverse effects of this class include bone loss/osteoporosis, hot flashes, arthralgias/myalgias, mild fatigue, and nausea.

Luteinizing Hormone Releasing Hormone Analogs and Antagonists

Chemical or surgical estrogen/androgen ablation is the common hormonal therapy in premenopausal women with breast cancer and men with prostate cancer, respectively.[19] Chemical castration is accomplished with the administration of luteinizing hormone releasing hormone (LHRH) analogs (leuprolide, goserelin, triptorelin). These drugs work by down-regulating LHRH receptors in the pituitary gland, subsequently leading to castrate levels of estrogens or testosterone. However, the initial administration of LHRH analogs can cause a flare response that stimulates cancer growth in the first few weeks due to the temporary rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.[19,54] Other side effects include hot flashes and bone loss, as well as amenorrhea in women and decreased libido (more commonly reported in men). Degarelix is an LHRH antagonist that reversibly binds to LHRH receptors in the pituitary gland, decreasing testosterone to castrate levels. It causes a rapid decrease in testosterone levels without a flare response. Liver enzyme increases and bone loss are common side effects.

Antiandrogens

Bicalutamide, flutamide, and nilutamide are nonsteroidal antiandrogens that competitively inhibit dihydrotestosterone and testosterone at their binding sites. These agents can be used as monotherapy or in addition to LHRH agonists in prostate cancer patients.[19] The combination of antiandrogens with LHRH analogs often reduce the flare symptoms associated with the administration of LHRH agonists. Adverse effects of the antiandrogens agents include hot flashes, gynecomastia, diarrhea, and liver function abnormalities. Enzalutamide, a second-generation antiandrogen, has a higher affinity for the androgen receptor and no agonist effects.[51] It is used in metastatic castration-resistant prostate cancer patients who have previously received docetaxel. Enzalutamide is associated

with fatigue, diarrhea, flushing, and musculoskeletal pain. Abiraterone acetate is a prodrug that is hydrolyzed to abiraterone, a steroidal progesterone derivative that selectively and irreversibly inhibits CYP17A1 enzyme that is involved with testosterone production.[55-57] It is used in combination with prednisone for metastatic castration-resistant prostate cancer. Common side effects include joint swelling/discomfort, hypokalemia, edema, hot flushes, and diarrhea.

RESPONSE TO TREATMENT

Various terms are used to describe a patient's response to cancer therapies. Clinicians often describe these responses as a cure, complete response, partial response, stable disease, or progressive disease. **Table 1-5** includes some common definitions related to treatment response for solid tumors.[58,59] These response definition guidelines for solid tumors were developed to provide a more uniform reporting of tumor responses. The RECIST (response evaluation criteria in solid tumors) criteria were first developed in 2000 and then revised in 2009.

The response criteria for hematological tumors are different because they are not defined by measurable masses. Leukemias, lymphomas, and multiple myeloma responses are defined by the elimination of abnormal cells, return of tumor markers to normal levels, or improved function of affected organs (eg, normal peripheral blood counts). Additionally, measuring the cytogenetic response is often performed in patients with known cytogenetic abnormalities and is often correlated with disease relapse. The National Comprehensive Cancer Network Guidelines for Treatment of Cancer include response criteria and the corresponding supporting references in each of their cancer site guidelines.[60]

In addition, various survival end points are used to describe treatment responses. Overall survival, disease-free survival, progression-free survival, and clinical benefit response (Table 1-5) are all used to describe cancer treatment responses. The challenge to the clinical researcher is to correlate the patient's quality of life to these various responses.

Performance Status

One of the most likely factors to help predict response to chemotherapy is a patient-specific factor referred to as performance status. The presence or absence of other disease states affects the overall functional status of a patient, which has a great impact on patient response to cancer treatment. The overall functional status of

a patient may be described using performances scales such as the Karnofsky score or the Eastern Cooperative Oncology Group (ECOG) scale (**Table 1-6**).[61–63] For many cancers, the patient's performance status at the time of diagnosis is the most important predictor of response.

Table 1-5 Common Definitions of Responses to Cancer Treatments[58,59]

Term	Definition
Cure	The patient is entirely free of disease and has the same life expectancy as a cancer-free individual.
Stable disease (SD)[a]	Solid tumor mass that is neither decreasing nor increasing in extent or severity.
Complete response (CR)[a]	Complete disappearance of all solid tumor masses without evidence of new disease for a least 1 month after treatment.
Partial response (PR)[a]	A 30% or greater decrease in the solid tumor size and no evidence of any new disease for at least 1 month.
Overall response (OR)[a]	CR + PR
Clinical benefit response	Subjective improvement in the symptoms caused by cancer without a defined response.
Progression free survival (PFS)	The length of time during and after treatment in which a patient is living with disease that does not get worse.
Overall survival (OS)	The percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease.
Time to progression (TTP)	A measure of time after a disease is diagnosed (or treated) until it starts to get worse.

[a] Generally for solid tumors based on the RECIST criteria. For hematologic malignancies, see National Comprehensive Cancer Network guidelines for specific response criteria definitions.

Table 1-6 Performance Status Scales[61–63]

ECOG		Karnofsky		
Grade	**Description**	**Status**	**Score**	**Description**
			100%	Normal activity; no complaints; no evidence of disease.
0	Fully active, able to carry on all predisease performance without restriction.	Able to carry on normal activity and work; no special care needed.	90%	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).		80%	Normal activity with effort; some signs or symptoms of disease.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70%	Cares for self; unable to carry on normal activity or do active work.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.		60%	Requires occasional assistance, but is able to care for most personal needs.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.		50%	Requires considerable assistance and frequent medical care.
5	Dead		40%	Disabled; requires special care and assistance.
		Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30%	Severely disabled; hospital admission is indicated; death not imminent.
			20%	Very sick; hospital admission necessary; active supportive treatment necessary.
			10%	Moribund; fatal processes progressing rapidly.
			0%	Dead

SUMMARY

Carcinogenesis is a multistep process that includes initiation, promotion, transformation, and progression. Cancer therapy medications are the cornerstone of systemic treatment and include chemotherapy, hormonal therapy, biologic therapy, and targeted therapies. Typically, common toxicities are associated with a class of therapies that are often classified based on the mechanism of action. A thorough understanding of the mechanism of action and toxicity of cancer therapies as well as assessing the response to therapy is important for safe preparation and administration of the first and subsequent cycles of cancer therapy. Additional chapters in this text provide more details.

REFERENCES

1. American Cancer Society. Heredity and cancer. http://www.cancer.org/Cancer/CancerCauses/GeneticsandCancer/heredity-and-cancer. Revised March 28, 2013. Accessed June 13, 2013.
2. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta, GA: American Cancer Society; 2013.
3. US Department of Health and Human Services. Public Health Service, National Toxicology Program. *Report on Carcinogens.* 12th ed; 2011. http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf. Accessed June 13, 2013.
4. Liao JB. Viruses and human cancer. *Yale J Biol Med.* 2006; 79:115–122.
5. Initiative for Vaccine Research. Viral cancers. World Health Organization website. http://www.who.int/vaccine_research/diseases/viral_cancers/en/index1.html. Accessed June 13, 2013.
6. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007; 370:890–907.
7. D'souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Prev Med*. 2011; 53(suppl 1):S5-S11.
8. American Cancer Society. Known and probable human carcinogens. http://www.cancer.org/cancer/cancercauses/othercarcinogens/generalinformationaboutcarcinogens/known-and-probable-human-carcinogens. Revised May 10, 2013. Accessed June 13, 2013.
9. Chabner BA, Chabner Thomson E. Cellular and molecular basis of cancer. The Merck Manual for Health Care Professionals website. http://www.merckmanuals.com/professional/hematology_and_oncology/overview_of_cancer/cellular_and_molecular_basis_of_cancer.html. Revised February 2013. Accessed June 13, 2013.
10. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst.* 2011; 103:1827–1839.
11. National Cancer Institute. Endometrial cancer prevention (PDQ). http://www.cancer.gov/cancertopics/pdq/prevention/endometrial/HealthProfessional/page3#Section_159. Revised February 15, 2013. Accessed June 13, 2013.

12. Ruddon RW. *Cancer Biology.* 4th ed. New York, NY: Oxford University Press; 2007:78–94.
13. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst*. 1997;89:1132–1138.
14. Oxnard GR, Lo PC, Nishinio M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J. Thorac Oncol.* 2013;8(2):179–184.
15. Munshi NC, Avet-Loiseau H. Genomics in multiple myeloma. *Clin Cancer Res.* 2011;17:1234–1242.
16. National Cancer Institution at the National Institutes of Health. Understanding cancer series. http://www.cancer.gov/cancertopics/understandingcancer/cancergenomics/AllPages. Accessed June 13, 2013.
17. Riley GJ, Marks J, Pao W. KRAS mutations in non–small cell lung cancer. *Proc Am Thor Soc.* 2009;6:201–205.
18. Weinberg RA. How cancer arises. *Sci Am.* 1996;275:62–71.
19. Medina PJ, Shord SS. Cancer treatment and chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2011:2191–2228.
20. Yap TA, Sandhu SK, Workman P, de Bono JS. Envisioning the future of early anticancer drug development. *Nat Rev Cancer*. 2010;10:514–523.
21. Griggs J, Mangu P, Anderson H, et al. Appropriate chemotherapy dosing for obese patients with cancer: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2012;30(13):1553–1561.
22. Liesveld J, Asselin B. It's all in the liposomes: vincristine gets a new package. *J Clin Oncol.* 2013;31:657–659.
23. Gligorov J, Lotz JP. Preclinical pharmacology of the taxanes: implications of the differences. *The Oncologist.* 2004;9(suppl 2):3–8.
24. Rowinsky E. Microtubule-targeting natural products. In: Kufe DW, Bast RC, Hait WN, et al, eds. *Cancer Medicine.* 7th ed. Hamilton, Ont, Canada: BC Decker; 2006:699–721.
25. Verweij J, Clavel M, Chevalier B. Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. *Ann Oncol*. 1994;5:495–505.
26. Lexi-Comp Online. Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc. http://online.lexi.com/. Accessed June 13, 2013.
27. DRUGDEX System [Internet database]. Greenwood Village, CO: Thomson Healthcare. Accessed June 13, 2013.
28. National Comprehensive Cancer Network templates. Available at: http://www.nccn.org/ordertemplates/default.asp. Accessed June 13, 2013.
29. Eberly AL, Anderson GD, Bubalo JS, Mccune JS. Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy.* 2008;28(12):1502–1510.
30. Richards D, Coleman J, Reynolds J, Coleman J. *Oxford Handbook of Practical Drug Therapy*. New York, NY: Oxford University Press; 2011:576.
31. Lam MS. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother*. 2005;39(11):1897–1902.
32. Santoso JT, Lucci JA III, Coleman RL, Schafer I, Hannigan EV. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol.* 2003;52:13–18.

33. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist.* 2007;12:601–609.
34. Preston JN, Trivedi MV. Eribulin: a novel cytotoxic chemotherapy agent. *Ann Pharmacother*. 2012;46:802–811.
35. Dahllof B, Billstrom A, Cabral F, Hartley-Asp B. Estramustine depolymerizes microtubules by binding to tubulin. *Cancer Res.* 1993;53:4573–4581.
36. Dorr RT, Von Hoff DD. *Cancer Chemotherapy Handbook*. 2nd ed. Norwalk, CT: Appleton & Lange; 1994.
37. Hensley ML, Hagerty KL, Kewalramani T, Slack JA. American Society of Clinical Oncology clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol.* 2009;27:127–145.
38. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol.* 2009;27:1492–1501.
39. Tsang LLH, Farmer PB, Gescher A, et al. Characterization of urinary metabolites of temozolomide in humans and mice and evaluation of their cytotoxicity. *Cancer Chemother Pharmacol.* 1990;26:429–436.
40. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol*. 1996;52:1855–1865.
41. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7:1748–1756.
42. Grothey A, Goldberg RM. A review of oxaliplatin and its clinical use in colorectal cancer. *Expert Opin Pharmacother.* 2004;5:2159–2170.
43. Brundage D. Cancer chemotherapy and treatment. In: Chisolm-Burns MA, Schwinghammer TL, Wells BG, et al, eds. *Pharmacotherapy: Principles & Practice.* 2nd ed. New York, NY: McGraw-Hill; 2010:1445–1474.
44. Keefe DL. Anthracycline-induced cardiomyopathy. *Semin Oncol.* 2001;28:2–7.
45. Emadi A, Gore SD. Arsenic trioxide–an old drug rediscovered. *Blood Rev.* 2010; 24:191–199.
46. Holle LM. Pegaspargase: an alternative? *Ann Pharmacother.* 1995;29:1042–1044.
47. Kavanaugh SA, White LA, Kolesar JM. Vorinostat: a novel therapy for the treatment of cutaneous T-cell lymphoma. *Am J Health-Syst Pharm.* 2010;67:793–797.
48. American Medical Association. Monoclonal antibodies. http://www.ama-assn.org//ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies_page. Accessed June 13, 2013.
49. Paul M, Mukhopadhyay AK. Tyrosine kinase–role and significance in cancer. *Int J Med Sci.* 2004;1:101–115.
50. Wood LS. Managing the side effects of sorafenib and sunitinib. *Comm Oncol.* 2006;3:558–562.
51. FDA Approved Drugs.http://www.centerwatch.com/drug-information/fda-approvals/. Accessed June 13, 2013.
52. Thyrell L, Hjortsberg L, Arulampalam V, et al. Mechanisms of Interferon-alpha induced apoptosis in malignant cells. *Oncogene*. 2002;21:1251–1262.
53. Michaud LB, Barnett CM, Esteva FJ. Breast cancer. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2011:2229–2270.

54. Weckermann D, Harzmann R. Hormone therapy in prostate cancer: LHRH antagonists versus LHRH analogues. *Eur Urol*. 2004;46:279–283.
55. Ryan CJ, Cheng ML. Abiraterone acetate for the treatment of prostate cancer. *Expert Opin Pharmacother.* 2013;14:91–96.
56. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368:138–148.
57. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364:1995–2005.
58. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2009;92:205–216.
59. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
60. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. http://www.nccn.org/clinical.asp. Accessed June 13, 2013.
61. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press. 1949;199–205.
62. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–655.
63. Schag CC, Heinrich RL, Ganz PA. Karnosky performance status revised: reliability, validity and guidelines. *J Clin Oncol*. 1994;2:187–193.

SUGGESTED READING

- Perry MC, Doll DC, Freter CE. *Chemotherapy Source Book*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
- Skeel RT, Khleif SN. *Handbook of Cancer Chemotherapy*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
- Package inserts for individual drugs.