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proteins, and many are in clinical development for cancer therapy. In addition, various combinations targeting more than one protein involved in modulating the immune response against cancers or with other anticancer approaches (targeted agents, chemotherapy, radia tion therapy) that may lead to enhanced antitumor activity are also being explored. An important aspect of these approaches is balancing sufficient release of the negative control of the immune response to allow immune-mediated attack on the tumors while not allowing too much of an immune response against normal tissues and thus induc ing severe autoimmune effects (e.g., against lung, liver, skin, thyroid, pituitary gland, gastrointestinal tract, or other organs). As is true for other immunotherapeutic approaches against cancer, major efforts are ongoing to better understand the mechanism of immune toxicity from these approaches and, therefore, ways of controlling this while not abrogating the antitumor effects. Improved knowledge of the biology of the interactions between the immune system and cancers continues to be rapid with the promise for additional significant improvements in use of immunotherapy to treat cancer. Given the success of vaccines against multiple viruses, many efforts have been made over decades to develop anticancer vaccines that would induce a sufficient immune response to lead to killing of cancer cells or even potentially prevention. This has been largely unsuccessful for the treatment of established cancers, although three vaccines are approved for use in cancer care: bacillus Calmette-Guérin (BCG) for intravesical treatment of superficial bladder cancer, sipuleucel-T for prostate can cer, and talimogene laherparepvec for direct injection into melanoma. Except for BCG, and then only for superficial bladder cancer, these have had relatively limited effectiveness. Perhaps more promising are vaccines combined with other forms of immunotherapy. Benefit may be enhanced by using a vaccine in combination with immune checkpoint inhibition therapy to delay recurrence of resected high-risk melanoma and provides hope that this approach may be effective in the future. However, further studies are needed to confirm this. IMPACT OF UNDERSTANDING CANCER BIOLOGY ON PREVENTION AND EARLY DETECTION The biggest impacts on decreasing cancer mortality come from pre vention followed by early detection. In addition to the critical role that new knowledge about cancer biology has in developing improved treatment approaches, it is also critical in enhancing preventative and early detection approaches. Examples in prevention include using knowledge about the roles of certain viruses in the development of some cancers to create vaccines for viruses (e.g., hepatitis B virus and human papillomavirus) to decrease the risk of developing cancer from these infections and using knowledge about how certain carcinogens cause cancer to work on controlling or eliminating carcinogenic agents (e.g., cigarette smoking and

asbestos). The development of sensitive methods for detecting circulating tumor DNA holds promise for earlier detection of cancer, although this has not yet been firmly established. Imaging agents for specific tissues (such as the use of proteins highly expressed on specific cancer tissues including prostate-specific mem brane antigen PET imaging to detect prostate cancer or HER2 to detect a subset of breast, gastric, and other cancers) or potentially against mutant proteins found in cancers (e.g., KRAS or p53 mutations) hold promise for earlier and more specific detection of cancer. As more is learned about cancer biology, this knowledge will also continue to be applied in preventative and early detection strategies. SUMMARY Just as human biology is complex, cancer biology is complex. Although each of the biological aspects of cancers and examples of targeting them has been addressed individually, clearly there is complicated cross-talk between these that occurs in all cancers that needs to be better understood to optimally treat different cancers. The explosion of information on tumor cell biology, metastasis, and tumor-host interactions (including angiogenesis, other tumor-stromal interactions, and immune evasion by tumors) has ushered in a new era of rational targeted therapy for cancers as well as the potential for individualized

therapy. Furthermore, it has become clear that specific molecular fac tors detected in individual tumors (gene mutations, gene expression profiles, miRNA expression, overexpression of specific proteins) can be used to tailor therapy and maximize antitumor effects.

Potentially of even greater impact on decreasing deaths from can cer, better understanding of the biology of early cancer development should ultimately lead to better approaches for prevention. And tech nologic development to improve sensitivity and specificity in detect ing cancer-specific molecules (e.g., mutated genes) provide hope that approaches for earlier detection of cancer can be developed. ■ ■FURTHER READING Agudo J et al: Targeting cancer cell dormancy. Nat Rev Cancer 24:97, 2024. Bhullar KS et al: Kinase-targeted cancer therapies: Progress, chal lenges and future directions. Mol Cancer 17:48, 2018. de Visser KE, Joyce JA: The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell 41:374, 2023. Finley LWS: What is cancer metabolism? Cell 186:1670, 2023. Fujii M et al: Decoding the basis of histological variation in human cancer. Nat Rev Cancer 24:141, 2024. Gacche RN: Changing landscape of anti-angiogenic therapy: Novel approaches and clinical perspectives. Biochim Biophys Acta Rev Cancer 1878:189020, 2023. Gerstberger S et al: Metastasis. Cell 186:1564, 2023. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov CHAPTER 78 12:31, 2022. Matthews HK et al: Cell cycle control in cancer. Nat Rev Mol Cell Principles of Cancer Treatment Biol 23:74, 2022. Pottier C et al: Tyrosine kinase inhibitors in cancer: Breakthrough and challenges of targeted therapy. Cancers (Basel) 12:731, 2020. Prager BC et al: Cancer stem cells: The architects of the tumor ecosystem. Cell Stem Cell 24:41, 2019. Reiter JG et al: An analysis of genetic heterogeneity in untreated cancers. Nat Rev Cancer 19:639, 2019. Romesser PB, Lowe SW: The potent and paradoxical biology of cellular senescence in cancer. Annu Rev Cancer Biol 7:207, 2023. Sharma P, et al: Immune checkpoint therapy: Current perspectives and future directions. Cell 186:1652, 2023. Tomuleasa C et al: Therapeutic advances of targeting receptor tyro sine kinases in cancer. Sig Transduct Target Ther 9:201, 2024. Yang K et al: Antigen presentation in cancer: Mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol 20:604, 2023. Yuan J, Ofengeim D: A guide to cell death pathways. Nat Rev Mol Cell Biol 25:379, 2024. Edward A. Sausville, Dan L. Longo

Treatment CANCER PRESENTATION Localized or systemic cancer is frequent in the differential diagnosis of a variety of common complaints. Affording patients the greatest opportunity for cure or meaningful prolongation of life is greatly aided by diagnosis of cancer early in its natural history. The spectrum of possible cancer-related interventions to make cure possible is shown in Table 78-1. ■ ■DETECTION OF A CANCER The term cancer, as used here, is synonymous with the term tumor, whose original derivation from Latin simply meant “swelling,” not

TABLE 78-1 Spectrum of Cancer-Related Interventions Asymptomatic patient screening (breast, cervix, colon, some lung) Consideration of cancer in a differential diagnosis Physical examination, imaging, or endoscopy to define a possible tumor Phlebotomy for molecular studies and circulating tumor cell characterization Diagnosis of cancer by biopsy or removal: Routine histology Specialized histology: immunohistochemistry Molecular studies Cytogenetic studies Staging the cancer: Where has it spread? Imaging (computed tomography, magnetic resonance imaging, positron emission tomography) Treatment Localized (surgical removal with or without local radiation therapy and/or topical therapy; may be curative) Local plus systemic, multimodality: cure advanced disease, reverse organ compromise Systemic, adjuvant (cure micrometastases; all evident disease has been locally treated) Systemic, neoadjuvant (before local therapy to improve local and systemic results) Systemic, palliative (improve symptoms, quality of life, progression-free PART 4 Oncology and Hematology survival) Supportive care During treatment: related to tumor effects on patient During treatment: to counteract side effects of treatment After treatment: to ameliorate the adverse effects of treatment Palliative and end of life When useful treatments are not feasible or desired otherwise specified. Swelling reflects increased interstitial fluid pres sure and increased cellular and stromal mass, compared to normal tissue. Leukemia, a cancer of the blood-forming tissues, presents in a disseminated form frequently without tumor masses. Tumors can also present by organ dysfunction, such as dyspnea on exertion from anemia caused by leukemia replacing normal marrow, cough from lung cancers, jaundice from tumors blocking bile ducts, or neurologic signs from gliomas. Hemorrhage frequently results from involvement of hollow viscera, but also may reflect altered platelet number or blood coagulation. Tumors may also present with a “paraneoplastic syn drome” owing to the effects of substances the tumor secretes. Although the fraction of patients with cancer as the basis for a presenting sign or symptom may be low, the implications of missing an early-stage tumor call for considering cancer as a basis for persistent signs or symptoms. Evidence of a tumor’s existence can come from careful physical examination, e.g., enlarged lymph nodes in lymphomas or palpable mass in a breast or soft tissue site. A mass may also be detected or con firmed by an imaging modality (e.g., x-ray, magnetic resonance imag ing [MRI], or ultrasound). Endoscopy may directly visualize a tumor. ■ ■ESTABLISHING A CANCER DIAGNOSIS Once a potential tumor is defined, establishing the diagnosis is the next step. This requires a biopsy procedure in most circumstances and pathologic confirmation that cancer is present; very rarely, where biopsy would be definitely injurious and imaging modalities are unequivocal, such as with a likely brainstem glioma, treatment might be reasonably considered based on clinical and imaging evidence with out biopsy. In addition to light microscopy, biopsied tissue also allows definition of genetic abnormalities and protein expression patterns to recommend best treatment (Table 78-2). The extent of specialized testing needs to be tailored to an individual patient’s case. Global DNA sequencing of genes expressed in tumors has not been shown to convey conclusive advantage in terms of sur vival. But the aggregate “mutational burden” present in tumors and the intactness of DNA repair genes (e.g., breast cancer susceptibility 1

TABLE 78-2 Diagnostic Biopsy: Standard-of-Care Molecular and Special Studies to Be Considered All solid tumors Tumor mutational burden Microsatellite instability DNA repair pathway intactness Homologous recombination DNA repair pathway intactness Breast cancer: primary and suspected metastatic Breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations Hormone receptor expression: estrogen, progesterone HER2/neu oncoprotein PI3KA mutation status Lung cancer: primary and suspected metastatic If nonsquamous non-small-cell: Epidermal growth factor receptor (EGFR) mutation ALK, ROS1, NRTK, NRG1 gene fusion BRAF V600E mutation Programmed cell death ligand 1 (PD-L1) expression Colon cancer: suspected metastatic KRAS mutation BRAF V600E mutation Gastrointestinal stromal tumor KIT mutation Melanoma BRAF mutation c-kit expression and KIT mutation if present Pancreatic cancer BRCA1/2 mutation Prostate cancer BRCA1/2 mutation Thyroid cancer RET gene alterations (mutations, translocations, amplification) Gliomas 1p/19q co-deletion Alkylguanine alkyltransferase promoter methylation Isocitrate dehydrogenase 1 and 2 mutation Leukemia (peripheral blood mononuclear cells and/or bone marrow) Cytogenetics Flow cytometry Treatment-defining chromosomal translocations/mutations Bcr-Abl fusion protein t(15;17) Inversion 16 t(8;21) FMS-associated tyrosine kinase (FLT3) mutation Nucleophosmin gene mutational status Isocitrate dehydrogenase 1 and 2 mutation Lymphoma Immunohistochemistry for CD20, CD30, and B- and T-cell markers Treatment-defining chromosomal translocations: t(14;18) t(8;14) Translocations involving ALK gene and 2 [BRCA1/2], microsatellite instability, homologous recombination pathway–associated genes) may suggest valuable treatment courses in tumors without curative potential. Optimally, an excisional biopsy occurs, in which the entire tumor mass is removed with a margin of normal tissue surrounding it. If an excisional biopsy cannot be performed, incisional biopsy is the proce dure of second choice: a wedge of tissue is removed, trying to include the majority of the cross-sectional diameter to minimize sampling error. Biopsy techniques that involve cutting into tumor risk facilitating

the spread of the tumor. Consideration with a surgeon of whether the biopsy approach is a potential prelude to a curative surgery may inform the approach taken. Core-needle biopsy usually obtains considerably less tissue but can provide information to plan a treatment. Fine-needle aspiration generally yields a suspension of cells from a mass. If positive for cancer, it may allow inception of systemic treatment, or it can pro vide a basis for planning a more extensive surgical procedure. A “negative” fine-needle aspiration cannot be taken as definitive evidence that a tumor is absent. In some instances, features of diagnostic imaging are sufficient to make a reliable diagnosis without obtaining tissue, usually with presence of a tumor-associated circulating diagnostic marker, e.g., α fetoprotein in hepatocellular carcinoma or prostate-specific antigen (PSA) in prostate cancer with apparent typical metastatic disease. ■ ■CANCER STAGING Defining the extent of disease determines whether localized treat ments, “combined-modality” approaches, or systemic treatments should initially be considered. Radiographic and other imaging tests can be helpful in defining the clinical stage; pathologic staging docu ments the histologic presence of tumor in tissue biopsies. Lymph node sampling in breast cancer, melanoma, lung, head and neck, colon, and other intra-abdominal cancers may provide crucial information. Staging systems define a “T” component related to the size of the tumor or its invasion into local structures, an “N” component related to the number and nature of lymph node groups with tumor involve ment, and an “M” component, based on the presence of local or distant metastatic sites. The various TNM components are then aggregated to stages, usually stage I to III or IV, depending on the anatomic site. The numerical stages reflect similar long-term survival outcomes of the respective TNM grouping stage after treatment tailored to the stage. In general, stage I tumors are T1 (reflecting

small size), N0 or N1 (reflect ing no or minimal node spread), and M0 (no metastases). Such earlystage tumors are usually amenable to curative approaches with local treatments. On the other hand, stage IV tumors have metastasized to distant sites or locally invaded viscera in a nonresectable way. They are treated with palliative intent, except for those diseases with exceptional sensitivity to systemic treatments such as chemotherapy or immuno therapy. Also, the TNM staging system is not useful in diseases such as leukemia, where bone marrow infiltration is never localized, or central nervous system (CNS) tumors, where tumor histology and the extent of feasible resection are more important in driving prognosis. CANCER TREATMENT The goal of cancer treatment is first to eradicate the cancer. If this is not possible, the goal shifts to palliation: amelioration of symptoms and preservation of quality of life while striving to extend life. When cure of cancer is possible, cancer treatments may be undertaken despite the certainty of severe toxicities, but these may produce toxicity with no benefit. Conversely, when the clinical goal is palliation, careful atten tion to minimizing the toxicity of treatments becomes a significant goal. The two main types of cancer treatment are local and systemic. Local treatments include surgery, radiation therapy (including photody namic therapy), and ablative approaches, including radiofrequency and thermal or cryosurgical approaches. Systemic treatments include che motherapy (including hormonal therapy and molecular targeted ther apy) and biologic therapy (including immunotherapy). The modalities are often used in combination. Oncology, the study of tumors including treatment approaches, is a multidisciplinary effort with surgical, radia tion, and internal medicine–related areas of oncologic expertise. Normal organs and cancers share the property of having a popula tion of cells actively progressing through the cell cycle, with their divi sion providing a basis for organ or tumor growth, and a population of cells not in cycle; these include stem cells, whose properties are being elucidated. Cancer stem cells serve as a basis for tumor initiating or repopulating cells. Tumors follow a Gompertzian growth curve (Fig. 78-1), with the growth fraction of a neoplasm high with small tumor burdens but declining until, at the usual time of diagnosis (tumor burden of 1–5 × 109) the growth fraction is only 1–4% for many

Growth fraction

Growth rate Percent of maximum

Lethal Tumor size Clinically detectable

Tumor burden logs of cells

Time, days FIGURE 78-1 Gompertzian tumor growth. The growth fraction of a tumor declines exponentially over time (top), peaking before it is clinically detectable (middle). Tumor size increases slowly, goes through an exponential phase, and slows again as the tumor has limitation of nutrients or host regulatory influences occur. The maximum growth rate occurs at 1/e, the point at which the tumor is about 37% of its maximum size (marked with an X). Tumor becomes detectable at a burden of about 109 (1 cm3) cells and kills the patient at a tumor cell burden of about 1012 (1 kg). CHAPTER 78 solid tumors. Thus the most rapid growth rate occurs before the tumor is detectable. An alternative explanation for such growth properties may also emerge from the ability of tumors at metastatic sites to recruit circulating tumor cells from the primary tumor or other metastases. Key features of tumor growth are the ability to stimulate new sup porting stroma through angiogenesis and ingrowth of fibroblasts and immune cells (Chap. 77). Principles of Cancer

Treatment LOCALIZED CANCER TREATMENTS ■ ■SURGERY Surgery is the most effective means of treating cancer. At least 40% of cancer patients are cured by surgery. Unfortunately, many patients with solid tumors have disease not practically removable. “Palliative” surger ies, however, may afford local control of tumor, preserve organ func tion, and achieve debulking that permits more effective subsequent therapy, while allowing more detailed staging. Cancer surgery aiming for cure is usually planned to excise the tumor completely with an adequate margin of normal tissue (the margin varies with the tumor and the anatomy). Such a resection is defined as an R0 resection. R1 and R2 resections, in contrast, are imprecisely defined pathologically as having microscopic or macroscopic, respectively, tumor at resection margins. Such outcomes may be the basis for reoperation to obtain optimal mar gins if feasible and of likely clinical utility. Extending the procedure to resect draining lymph nodes obtains prognostic information and may, in some anatomic locations, improve survival. Laparoscopic approaches are being used for primary abdominal and pelvic tumors, although with certain tumors (e.g., uterine and cervix), controversy exists as to the desirability of laparoscopic tumor removal. Lymph node spread may be assessed using the sentinel node approach, in which the first draining lymph node is defined by injecting a dye or radioisotope into the tumor site at operation and then resecting the first node to turn blue or collect isotope. Sentinel node assess ment appears to provide information without the risks (lymphedema, lymphangiosarcoma) associated with resection of all regional nodes. Advances in adjuvant chemotherapy (given systemically after removal of all local disease without evidence of metastatic disease) and radia tion therapy following surgery have permitted a decrease in the extent of primary surgery. Thus, “lumpectomy” with radiation therapy is as effective as modified radical mastectomy for breast cancer, and limbsparing surgery followed or preceded by adjuvant radiation therapy and chemotherapy has replaced amputation for most childhood

rhabdomyosarcomas and osteosarcomas. More limited surgery spares organ function, as in larynx and bladder cancer. In some settings (e.g., bulky testicular cancer or stage III breast cancer), surgery is not the first treatment modality used. After diagnostic biopsy, chemotherapy and/or radiation therapy is delivered, followed by a surgical procedure to remove residual masses; this is called neoadjuvant therapy. Coordi nation among the surgical oncologist, radiation oncologist, and medi cal oncologist is crucial.

Surgery may be curative in a subset of patients with metastatic disease. Patients with limited lung metastases from osteosarcoma may be cured by resection of the lung lesions. In patients with colon cancer who have fewer than five liver metastases restricted to one lobe and no extrahepatic metastases, hepatic lobectomy may produce longterm disease-free survival in 25% of selected patients. In the setting of hormonally responsive tumors, oophorectomy may eliminate estrogen production, and orchiectomy may reduce androgen production, hor mones that drive many breast and all prostate cancers, respectively. In selecting a surgeon or center for primary cancer treatment, consid eration must be given to the volume of cancer surgeries undertaken by the site. Studies in a variety of cancers have shown that increased annual procedure volume appears to correlate with outcome. Surgery is used in a number of ways for palliative or supportive care of the cancer patient. These include insertion and care of central venous catheters, control of pleural and pericardial effusions and ascites, caval interruption for recurrent pulmonary emboli, stabilization of cancerweakened weight-bearing bones, and control of hemorrhage, among others. Surgical bypass of gastrointestinal, urinary tract, or biliary tree obstruction or spinal cord decompression can alleviate symptoms and may prolong survival. Splenectomy may relieve symptoms and reverse

hypersplenism. Intrathecal or intrahepatic therapy relies on surgical placement of appropriate infusion portals. Surgery may correct other treatment-related toxicities such as adhesions or strictures. Plastic and reconstructive surgery can correct the effects of disfiguring primary treatment. Surgery is also a tool valuable in the prevention of cancers in high-risk populations. Prophylactic mastectomy, colectomy, oopho rectomy, and thyroidectomy are mainstays of cancer prevention in inherited cancer susceptibility syndromes. PART 4 Oncology and Hematology ■ ■RADIATION Radiation Biology and Medicine Therapeutic radiation is gen erally ionizing, causing breaks in DNA and generation of free radicals from cell water that damage cancer cell membranes, proteins, and organelles. Ionizing radiation + $H_2O \rightarrow H_2O^+ + e^-$

$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^\bullet$ $OH^\bullet \rightarrow$ cell damage Radiation damage is augmented by oxygen; hypoxic cells are more resistant. X-ray and gamma-ray photons are the forms of ionizing radiation most commonly used to treat cancer. Particulate ionizing radiation using protons has also become available. Radiation dose is quantitated based on the amount of energy absorbed by the tumor, not on radiation generated by the machine. The International System (SI) unit for radiation dose is the Gray (Gy): 1 Gy refers to 1 J/kg of tissue; 1 Gy equals 100 centigrays (cGy) of absorbed dose. A historically used unit appearing in the oncology literature, the rad (radiation absorbed dose), is defined as 100 ergs of energy absorbed per gram of tissue and is equivalent to 1 cGy. Radiation dose is measured by placing detectors at the body surface or in radiated phantoms that resemble human form and substance. The features that make a particular cell more or less sensitive to radiation involve DNA repair proteins that, in their physiologic role, protect against environ mentally related DNA damage. Localized Radiation Therapy Radiation effect is influenced by three determinants: total absorbed dose, number of fractions, and time of treatment. A typical course of radiation therapy should be described as 4500 cGy delivered to a particular target (e.g., mediastinum) over

5 weeks in 180-cGy fractions. Most curative radiation treatment programs are delivered once a day, 5 days a week, in 150- to 200-cGy fractions. Nondividing cells are more resistant than dividing cells; delivering radiation in repeated fractions is done to expose a larger number of tumor cells that have entered the division cycle. The energy of the radiation determines its ability to penetrate tissue. Low-energy x-rays (150–400 kV) scatter when they strike the body, resulting in more damage to adjacent normal tissues and less radiation deliv ered to the tumor. Megavoltage radiation (>1 MeV) has very low lateral scatter; this produces a skin-sparing effect, more homogeneous distribution of the radiation energy, and greater deposit of the energy in the tumor, or target volume. The transit volume includes the tissues through which the beam passes to the target volume. Computational approaches and delivery of many beams to converge on a target volume are the basis for “gamma knife” and related approaches to deliver high doses to tumor, sparing normal tissue. Therapeutic radiation is delivered in three ways: (1) teletherapy, with focused beams of radiation generated at a distance and aimed at the tumor within the patient; (2) brachytherapy, with encapsulated sources of radiation implanted directly into or adjacent to tumor tissues; and (3) systemic therapy, with radionuclides administered, for example, intravenously but perhaps targeted by some means to a tumor site. For example, systemically administered isotopes of iodide have an impor tant role in the treatment of thyroid neoplasms, owing to the selective upregulation of the iodide transporter in the tumor cell compartment. Likewise, isotopes of samarium and radium have been found useful in the palliation of bony metastases of prostate cancer owing to their selective deposition at the tumor-bone matrix interface. Teletherapy with x-

ray or gamma-ray photons is the most commonly used form of radiation therapy and also delivers particulate forms of radiation such as proton beams. The difference between photons and protons relates to volume with greatest delivery of energy: protons have a narrow range of energy deposition. Electron beams are a particulate form of radiation that, in contrast to photons and protons, have a very low tissue penetrance and are used to treat cutaneous tumors. Certain drugs used in cancer treatment may also act as radiation sensitizers. For example, compounds that incorporate into DNA (e.g., halogenated pyrimidines, cisplatin) augment radiation effects at local sites and are important adjuncts to radiation of certain tumors (e.g., squamous head and neck, uterine cervix, and rectal cancers). Toxicity of Radiation Therapy Although radiation therapy is most often administered to a local region, systemic effects, including fatigue, anorexia, nausea, and vomiting, may develop that are related in part to the volume of tissue irradiated, dose fractionation, radiation fields, and individual susceptibility. Radiation-injured tissues release cytokines that act systemically to produce these effects. Bone is among the most radio-resistant organs, with radiation effects being manifested mainly in children through premature fusion of the epiphyseal growth plate. By contrast, the male testis, female ovary, and bone marrow are the most sensitive organs. Any bone marrow in a radiation field will be eradicated by therapeutic irradiation. Organs with less need for cell renewal, such as heart, skeletal muscle, and nerves, are more resistant to immediate radiation effects. In radiation-resistant organs, the vas cular endothelium is the most sensitive component. Acute toxicities include mucositis, skin erythema (ulceration in severe cases), and bone marrow toxicity. Often these can be alleviated by periodic interruption of treatment. Chronic toxicities are more serious. Radiation of the head and neck region produces thyroid failure; cataracts and retinal damage can lead to blindness; salivary glands stop making saliva, which leads to dental caries and poor dentition. Mediastinal irradiation increases myocardial vascular disease. Other late vascular effects include chronic constric tive pericarditis, lung fibrosis, viscus stricture, spinal cord transection, and radiation cystitis or enteritis. A serious late toxicity is the development of hematologic tumors or second solid tumors in or adjacent to the radiation fields. Such tumors can develop in any organ or tissue and occur at a rate of ~1% per year beginning in the second decade after treatment.

■ ■OTHER LOCALIZED CANCER TREATMENTS Endoscopy allows placement of stents to unblock viscera, palliating, for example, gastrointestinal or biliary obstructions. Radiofrequency ablation (RFA) refers to microwave nonionizing radiation to induce thermal injury within a volume of tissue. RFA can be useful in the con trol of metastatic lesions, particularly in liver, that may threaten biliary drainage. Cryosurgery uses extreme cold to sterilize lesions in certain sites, such as prostate and kidney, at a very early stage, eliminating the need for modalities with more side effects such as surgery. Some chemicals (porphyrins, phthalocyanines) are preferentially taken up by cancer cells. When intense light, delivered by a laser, is shone on cells containing these compounds, free radicals are gener ated and the cells die. Such phototherapy is used to treat skin cancer; ovarian cancer; and cancers of the lung, colon, rectum, and esophagus. Palliation of recurrent locally advanced disease can sometimes be dra matic and last many months. Infusion of chemotherapeutic or biologic agents or radiationbearing delivery devices such as isotope-coated glass spheres into local sites through catheters have been used to treat disease limited to that site; in selected cases, prolonged control of truly localized disease has been possible. SYSTEMIC CANCER TREATMENTS The concept that systemically administered chemicals might have a useful effect on cancers was historically derived from three sets of observations. Paul Ehrlich in the nineteenth century observed that different dyes reacted with different cell and tissue components.

He hypothesized the existence of “magic bullets” that might bind to tumors, owing to the affinity of the agent for the tumor. Observation of the toxic effects of certain mustard gas derivatives on the bone mar row during World War I suggested that smaller doses of these agents might be used to treat tumors of marrow-derived cells. Finally, the fact that tumors from hormone-responsive tissues, e.g., breast tumors, could shrink after oophorectomy led to the idea that endogenous or exogenous substances might modulate tumor growth by altering its regulatory biology. Chemicals achieving each of these goals are cur rently used as cancer chemotherapy agents. Anecdotal reports of tumor regression following intratumoral injection of bacterial extracts raised the possibility of immune system– mediated tumor regression. Serotherapy of infectious disease in the preantibiotic era encouraged analogous efforts to develop vaccine- and antibody-based treatments for cancer. Administration of autologous immune cells obtained by pheresis procedures from a patient or puri fied from a patient’s removed tumor, activated by cytokines ex vivo, achieved durable disease control in a small fraction of patients with certain tumors, particularly renal cell cancers or melanoma. These observations provided the rationale for more modern efforts to treat tumors using cell-mediated immunity. Systemic cancer treatments are of three broad types. Cytotoxic chemotherapy agents are “small molecules” (generally with molecular mass <1500 Da) that cause major regression of experimental tumors growing in animals. These agents mainly target DNA structure or segregation of chromosomes in mitosis. Cancer molecular target therapies refer to small molecules designed and developed to interact with a defined macromolecule important in maintaining the malig nant state. As described in Chap. 77, successful tumors have activated biochemical pathways that lead to uncontrolled proliferation through the action of hormone receptor proteins, oncogene products, loss of cell cycle inhibitors, or loss of cell death regulation, and have acquired the capacity to replicate chromosomes indefinitely, invade, metasta size, and evade the immune system. Cancer biologic therapies are most frequently macromolecules, cells, or cell extracts that have a particular target (e.g., anti–growth factor receptor, cytokine, or immunomodula tory antibodies) or may have the capacity to induce a host immune response to kill tumor cells. Most recent additions to cancer biologic therapies include genetically modified cells that directly attack tumor cells and tumor-infecting viruses that can kill tumor cells but also elicit host antitumor immune responses.

■ ■SYSTEMIC CANCER THERAPY OVERVIEW

General Principles The therapeutic index of any drug is the degree of separation between toxic and therapeutic doses. Really useful drugs have large therapeutic indices, and this usually occurs when the drug target is expressed in the disease-causing compartment as opposed to the normal compartment. Cytotoxic chemotherapeutic agents have the unfortunate property that their main targets, DNA and microtubules, are present in both normal and tumor tissues. Therefore, they have relatively narrow therapeutic indices. Targeted agents can also cause effects on their target in normal tissues, or “off-target” effects on unre lated targets in organs experiencing damage. Biologic therapies may elicit misdirected immune responses on normal organ function. A key activity in oncology drug development is striving to administer a dose that can convey benefit with a minimal or tolerable side effect profile. Figure 78-2 illustrates steps in cancer drug development. Follow ing demonstration of antitumor activity in animal models, potentially useful anticancer agents are further evaluated to define an optimal schedule of administration and suitable drug formulation. Safety test ing in two animal species on an analogous schedule of administration defines the starting dose for a phase 1 trial in humans, usually but not always in patients with

cancer who have exhausted “standard” (already approved) treatments. The initial dose is usually one-sixth to one-tenth of the dose just causing easily reversible toxicity in the more sensitive animal species. If the agent is not intrinsically toxic, doses of drug achieving fractions of the useful plasma concentrations from model systems are studied. Escalating doses of drug are then given during the human phase 1 trial until reversible toxicity is observed or the desired drug concentration is achieved. Dose-limiting toxicity (DLT) defines a dose that conveys greater toxicity than would be acceptable in routine practice, allowing definition of a lower maximum-tolerated dose (MTD). The occurrence of toxicity is, if possible, correlated with plasma drug concentrations. The MTD or a dose just lower than the MTD is usually the dose suitable for phase 2 trials, where a fixed dose and schedule is administered to a relatively homogeneous set of patients with a particular tumor type. If no toxicity has emerged in phase 1 tri als, administration of the optimal biologic dose to achieve effective drug concentrations is undertaken. A partial response historically was defined as a decrease of at least 50% in a tumor’s bidimensional area obtained by imaging; more recent response criteria (e.g., Response Evaluation Criteria in Solid Tumors [RECIST]) may use a 30% decrease in aggregate unidimensional areas of target lesions. Response criteria for immunologically directed agents may allow a substantial transient increase in tumor volume as long as a patient’s clinical status is stable, as these agents may evoke inflammatory responses in tumors with subsequent shrinkage or stabilization of lesions. A complete response connotes disappearance of all tumor; progression of disease signifies an increase in size of existing lesions by >25% from baseline or best response or development of new lesions; stable disease fits into none of the above categories. CHAPTER 78 Principles of Cancer Treatment In a phase 3 trial, evidence of improved overall survival or improve ment in the time to progression of disease on the part of the new drug is sought in comparison to an appropriate control population. Data from the entire process are the basis for application to a regulatory agency to approve the new agent for commercial marketing. Cancer drug clinical trials conventionally use a toxicity grading scale where grade 1 toxicities do not require treatment, grade 2 toxici ties may require symptomatic treatment but are not life-threatening, grade 3 toxicities are potentially life-threatening if untreated, grade 4 toxicities are actually life-threatening, and grade 5 toxicities result in the patient’s death. Active efforts to quantitate effects of anticancer agents on quality of life also frequently occur in early development of oncology drugs. Development of targeted agents may proceed differently. While phase 1–3 trials are still conducted, focus on a particular tumor type even in phase 1 may be enabled by molecular analysis to define target expression in a patient’s tumor necessary for or relevant to the drug’s action. Ideally, pharmacodynamic studies would also assess whether the drug’s target has been affected. The failure of a targeted therapy can

Preclinical Model (e.g., mouse or rat) Phase II Untreated Growth delay Tumor size Rx Cytostatic Cytotoxic Time Unique patient number Phase II Unique patient number PART 4 Oncology and Hematology Time Time on Rx FIGURE 78-2 Steps in cancer drug discovery and development. Preclinical activity (top left) in animal models of cancers may be used as evidence to support the entry of the drug candidate into phase 1 trials in humans to define a correct dose and observe any clinical antitumor effect. The drug may then be advanced to phase 2 trials directed against specific cancer types, with rigorous quantitation of antitumor effects. Waterfall plots are a standard representation of how patients’ tumor sizes change in relation to treatment, with predefined cutoffs defining progression of disease (20% increase in size) or partial response (30% decrease in size) serving as benchmarks of potential valuable effect (top right). Swimmer plots (bottom left) allow the delineation of patients with especially long (or short) times on treatment even without

response, another basis in the former case for potential perceived clinical benefit of the treatment. Kaplan-Meier plots (bottom right) of survival indices in phase 3 comparative trials may allow definition of superiority, inferiority, or no difference of treatment effect compared to standard or no treatment. be either because the drug missed the target or it hit the target but the target was not central to the tumor's growth and survival. Within the past decade, agents have been approved for clinical use not in relation to an originating organ site of disease but across all organ types pos sessing certain molecular or biologic features. Useful cancer drug treatment strategies using conventional chemo therapy agents, targeted agents, hormonal treatments, or biologicals all have one of two valuable outcomes. They can induce cancer cell death, resulting in tumor shrinkage with corresponding clinical ben efit evidenced by improvement in patient survival, or increase in time until the disease progresses. Another potential outcome is induction of cancer cell differentiation or dormancy with loss of tumor cell replica tive potential and reacquisition of phenotypic properties resembling normal cells. Interaction of a chemotherapeutic drug with its target induces a "cascade" of further signaling steps. These signals ultimately lead to cell death by triggering proteases, nucleases, and endogenous regulators of the cell death pathway (Fig. 78-3) or differentiation by alteration of cancer genome function. Targeted agents differ from chemotherapy agents in that they do not indiscriminately cause macromolecular lesions but regulate the action of specific driver molecules regulating processes considered "hallmarks" of cancer, including unregulated proliferation, physiologic cell death, gene expression, angiogenesis, and escape from immune mechanisms retarding tumor development. Strategies in Systemic Cancer Management The past 35 years have witnessed a marked evolution in the systemic treatment of cancer not amenable to cure by locally applied treatments. Nonspecific cyto toxic agents of limited efficacy for most patients but highly active and curative in a minority disease types have been joined by targeted and biologic therapies. Table 78-3, A lists those tumors considered curable

% change tumor % alive (overall survival) or % relapse free

Phase III Treatment A Treatment B or no Rx by conventionally available chemotherapeutic agents even when dis seminated or metastatic. If a tumor is truly localized to a single site, consideration of surgery or primary radiation therapy should be given as well. Chemotherapy may be used as part of multimodality approaches to offer primary treatment to a clinically localized tumor (Table 78-3, B), interdigitated with radiation and surgery. Chemother apy can be administered as an adjuvant, i.e., in addition to surgery or radiation (Table 78-3, C), even after all clinically apparent disease has been removed. This use of chemotherapy has curative potential in, for example, lung, breast, and colorectal neoplasms, as it eliminates micro metastatic clinically unapparent tumor. Neoadjuvant chemotherapy refers to administration of chemotherapy before any surgery or radia tion to a local tumor in an effort to enhance the effect of subsequent local treatment. Chemotherapy is routinely used in doses that produce reversible acute side effects, primarily consisting of transient myelosuppression with or without gastrointestinal toxicity (usually nausea). "High-dose" chemotherapy regimens can produce markedly increased therapeutic effect, although at the cost of potentially life-threatening complica tions that require intensive support, usually in the form of hemato poietic stem cell support from the patient (autologous) or from donors matched for histocompatibility loci (allogeneic), or pharmacologic "res cue" strategies to block the effect of the high-dose chemotherapy on normal tissues. High-dose regimens have curative potential in defined clinical settings (Table 78-3, D). If cure is not possible, chemotherapy may be undertaken with the goal of palliating the tumor's effect on the host (Table 78-3, E). In this usage, value is perceived by

the demonstration of improved symptom relief, progression-free survival, or overall survival. The best data to support these different therapeutic approaches result from clinical research protocols. In the case of a new drug, these trials might be the

Tumor cell growth pathways Tumor cell death pathways Receptor-linked tyrosine kinase inhibitor GDP RAS P P + GTP RAS P13K RAF/MEK inhibitors P RAF Metabolism modulators AKT + MTOR Non receptor linked tyrosine kinase inhibitor MEK Multi kinase inhibitors Cell division Protein synthesis MAP Nuclear export inhibitors DNA digestion Nutrients, O2 Gene products CDK inhibitor Nucleus Autophagy Chromatin epigenetic modulators HR HR RNA Hormone anatgonists Immune cells Transcription factor inhibitors Blood vessels in tumor stroma FIGURE 78-3 Tumor growth and death pathways affected by targeted and cytotoxic agents. After a growth factor binds to its receptor (left side of figure), in the most commonly activated cell proliferation pathway, increased tyrosine kinase activity occurs, either by autophosphorylation of receptor-linked kinases or through recruitment of non-receptor-linked tyrosine kinases, which may also be active constitutively, without requiring a growth factor. This leads to docking of “adaptor” proteins to the phosphorylated tyrosines. One important pathway activated occurs after exchange of GDP for GTP in the RAS family of proto-oncogene products. GTP-RAS activates

the RAF kinase, leading to a phosphorylation cascade of MEK and MAP kinases. Mutated KRAS inhibitors have been defined, as well as RAF isoform and MEK inhibitors. The RAF/MEK/MAP kinase pathway ultimately alters gene function to activate cell cycle progression through cyclin-dependent kinases (CDKs). Another route to gene activation utilizes hormone receptors (HRs) interacting with tissue-specific growth regulators such as steroid hormones to alter gene function leading to cell cycle activation. Transcription factors acting at the level of RNA polymerase function at ensembles of gene promoters have proved difficult to target directly, but direct and indirect modulators of transcription factor activity have been defined. Receptor and non-receptor linked tyrosine phosphorylation can lead to activation of phosphatidylinositol3-kinase (PI3K) to produce the phosphorylated lipid phosphatidylinositol-3-phosphate, which activates the AKT kinase to act downstream on the mammalian target of rapamycin kinase (mTOR), directly increasing translation of key mRNAs for gene products regulating cell growth and stimulating cell metabolism by, for example, increasing glucose transporter function. Cytotoxic agents cause cell death (right side of figure) through apoptosis and/or induction of autophagy. Apoptosis is also stimulated by interruption of growth factor (GF) cytokine death signals (e.g., tumor necrosis factor receptor [TNF-R]), which activate “upstream” cysteine aspartyl proteases (caspases) to directly digest cytoplasmic and nuclear proteins, resulting in activation of “downstream” caspases; these activate nucleases to cause DNA fragmentation, a hallmark of apoptosis. Chemotherapy agents that create lesions in DNA or alter mitotic spindle function activate gene function to alter mitochondrial integrity. The antiapoptotic protein BCL2 attenuates mitochondrial toxicity, whereas proapoptotic gene products such as BAX, PUMA, etc., antagonize the action of BCL2. Damaged mitochondria release cytochrome C and apoptosis-activating factor (APAF), which activate caspase 9 to cause DNA fragmentation. In addition, membrane damage with activation of sphingomyelinases results in the production of ceramides that can cause direct damage to mitochondria. Protein translation is followed by a folding process in the Golgi apparatus. Misfolded proteins are processed through the proteasome for protease digestion and recycling of amino acids. Disruption of this process can contribute to autophagy, where the cell starves for critical nutrients, or itself induce apoptosis through a distinct pathway activated by misfolded protein accumulation. Antiangiogenic agents

and immune therapies work in the tumor stroma (lower left) on supporting elements including blood vessels and host inflammatory cells. basis for U.S. Food and Drug Administration (FDA) approval for com mercial use of the agent. Patients treated with palliative intent should be aware of their diag nosis and the limitations of the proposed treatments, have access to supportive care, and have suitable “performance status,” according to assessment algorithms such as the one developed by Karnofsky (see

Death signal receptor Apoptosis modulators Membrane damage TNF-R SMase BC12 Ceramide Mitochondrial damage Caspase 8 p53 + + Effector caspases Proapoptotic Gene Expression BAX PUMA NOXA PIGs, etc. + DNA damage or Cytochrome C Caspase 3 APAF Cell targets Caspase 9 Nuclease activation CHAPTER 78 + + Disordered chromosome structure or Cell targets Principles of Cancer Treatment Misfolded proteins Folded proteins Golgi Protein production Proteasome Proteosome inhibitors Peptides Amino acids Table 73-4) or by the Eastern Cooperative Oncology Group (ECOG) (see Table 73-5). ECOG performance status (PS) 0 patients are without symptoms; PS1 patients are ambulatory but restricted in strenuous physical activity; PS2 patients are ambulatory and active 50% or more of the time but unable to work; PS3 patients are capable of limited self-care but are active <50% of the time; and PS4 patients are totally

TABLE 78-3 Clinical Impact on Cancers with Cytotoxic Chemotherapy A. Advanced Cancers with Possible D. Cancers Possibly Cured with Cure Acute lymphoid and acute myeloid leukemia (pediatric/adult) Hodgkin’s disease (pediatric/adult) Lymphomas—certain types (pediatric/ adult) Germ cell neoplasms Embryonal carcinoma Teratocarcinoma Seminoma or dysgerminoma Choriocarcinoma Gestational trophoblastic neoplasia Pediatric neoplasms Wilms’ tumor Embryonal rhabdomyosarcoma Ewing’s sarcoma Peripheral neuroepithelioma Neuroblastoma Small-cell lung carcinoma Ovarian carcinoma B. Advanced Cancers Possibly Cured by High-Dose Chemotherapy with Stem Cell Support Relapsed leukemias, lymphoid and myeloid Relapsed lymphomas, Hodgkin’s and non-Hodgkin’s Chronic myeloid leukemia Multiple myeloma E. Cancers Responsive with Useful Palliation, But Not Cured, by Chemotherapy Bladder carcinoma Chronic myeloid leukemia Hairy cell leukemia Chronic lymphocytic leukemia Lymphoma—certain types Multiple myeloma Gastric carcinoma Cervix carcinoma Endometrial carcinoma Soft tissue sarcoma Head and neck cancer Adrenocortical carcinoma Islet cell neoplasms Breast carcinoma Colorectal carcinoma Glioma Lung cancer Small-cell Non-small-cell F. Tumors Poorly Responsive PART 4 Oncology and Hematology Chemotherapy, Radiation, ± Surgery Squamous carcinoma (head and neck) Squamous carcinoma (anus) Bladder carcinoma Breast carcinoma Carcinoma of the uterine cervix Esophageal carcinoma Non-small-cell lung carcinoma (stage III) Small-cell lung carcinoma C. Cancers Possibly Cured with in Advanced Stages to Chemotherapy Pancreatic carcinoma Biliary tract neoplasms Thyroid carcinoma Carcinoma of the vulva Prostate carcinoma Melanoma Hepatocellular carcinoma Salivary gland cancer Chemotherapy as Adjuvant to Surgery Breast carcinoma Colorectal carcinomaa Osteogenic sarcoma Soft tissue sarcoma aRectum also receives radiation therapy. confined to bed or chair and incapable of self-care. Only PS0, PS1, and PS2 patients are generally considered suitable for palliative (noncura tive) treatment. If there is curative potential, even poor-PS patients may be treated (especially if their symptoms are directly related to a cancer that may respond to treatment), but their prognosis is usually inferior to that of good-PS patients treated with similar regimens. Assessment of physiologic reserve through use of the geriatric assessment tool can be helpful, but no measure of comorbidities or physiologic reserve is considered standard. The turn of the millennium marked the arrival of new strategies for

cancer treatment. Prominent among these are cancer biologic therapy, which harnesses the use of immune system–derived reagents or strategies, and cancer targeted therapies, which are directed at specific molecular targets differentially expressed in malignant as opposed to normal tissues. ■ ■CANCER BIOLOGIC THERAPY Figure 78-4 presents the landscape of cancer biologic therapy agents and actions. The goal of biologic therapy is to manipulate the hosttumor interaction in favor of the host, potentially at an optimum biologic dose that might be different than MTD. As a class, biologic

therapies may be distinguished from cytotoxic and molecularly tar geted agents in that biologic therapies require activity (e.g., antigen expression or internalization) on the part of the tumor cell or on the part of the host (e.g., T-cell engagement or cytokine elaboration) to allow therapeutic effect. Antibody-Mediated Therapeutic Approaches Figure 78-4 illustrates current antibody-based strategies in cancer treatment. The ability to grow very large quantities of high-affinity monoclonal anti bodies directed at specific tumor antigens produced by animals allows the grafting of animal-derived antigen-combining sequences into human immunoglobulin genes (chimerized or humanized products) or derived de novo from mice bearing human immunoglobulin gene loci. Four general strategies have emerged using antibodies. Anti-tumor cell antibodies target tumor cells directly to inhibit intracellular functions or attract immune or stromal cells. Bispecific tumor engaging (BiTe) anti bodies directly bind to a tumor cell and to a host immune cell. Immu noregulatory antibodies target antigens expressed on host immune cells to boost the host's immune response to the tumor. Finally, antibody conjugates link the antibody to drugs, toxins, or radioisotopes to target these "warheads" for delivery to the tumor. Stroma-directed antibodies are currently available against tumor-supporting vasculature. ANTI-TUMOR CELL ANTIBODIES (FIG. 78-4) Humanized antibodies against the CD20 molecule expressed on B-cell lymphomas (rituximab and ofatumumab) are exemplary of antibodies that affect both signal ing events driving lymphomagenesis as well as activating immune responses against B-cell neoplasms. They are used as single agents and in combination with chemotherapy and radiation in the treatment of B-cell neoplasms. Obinutuzumab is an antibody with altered glycosyl ation that enhances its ability to activate killer cells; it is also directed against CD20 and is of value in chronic lymphocytic leukemia. Unintended side effects of any antibody include infusion-related hypersensitivity reactions, which can be managed with glucocorticoid and/or antihistamine prophylaxis, and prolonged infusion strategies. Anti-B-cell-directed antibodies can have the unintended effect of exacerbating immunosuppression with the emergence of increased opportunistic infections. Reactivation of latent infections may also occur; an assessment of a patient's hepatitis B and C status is conven tionally done before treatment. Concomitant use of antivirals directed against hepatitis may be indicated. Patients with HIV and lymphoma need antivirals optimized to minimize interaction with anti-lymphoma treatments; consultation with infectious disease specialists is war ranted. Anti-tumor cell antibodies also include approaches to activate complement and are exemplified by alemtuzumab directed against CD52; it is active in chronic lymphoid leukemia and T-cell malignan cies. Tumor lysis syndrome prophylaxis may be warranted. Epidermal growth factor receptor (EGFR)-directed antibodies (e.g., cetuximab and panitumumab) have activity in colorectal cancer refrac tory to chemotherapy, particularly when used to augment the activity of an additional chemotherapy program, and in the primary treatment of head and neck cancers treated with radiation therapy. Direct effects on the tumor may mediate an antiproliferative effect as well as stimu late the participation of host mechanisms involving immune cell or complement-mediated response to tumor cell–bound antibody. AntiEGFR antibodies can cause an acneiform rash requiring

topical antibi otic and glucocorticoid cream treatment; photosensitivity also occurs. The HER2/neu receptor overexpressed on epithelial cancers, espe cially breast and certain gastrointestinal cancers, was initially targeted by trastuzumab, with activity in potentiating the action of chemo therapy in breast cancer as well as evidence of single-agent activity. Trastuzumab appears to interrupt intracellular signals derived from HER2/neu and to stimulate anti-tumor cell immune mechanisms. The anti-HER2 antibody pertuzumab, specifically targeting the domain of HER2/neu responsible for dimerization with other HER2 family members, is more specifically directed against HER2 signaling func tion and augments the action of trastuzumab. Both trastuzumab and pertuzumab can damage cardiac function, particularly in patients with prior exposure to anthracyclines, and left ventricular function should be checked before treatment and monitored during treatment.

Anti-tumor cell antibody CCRX-4: Mogamulizumab CD19: Tafasitamab CD20: Obinutuzumab, Ofatumummab, Rituximab CD38: Daratumumab, Isatuximab CD52: Alemtuzumab EGFR: Cetuximab, Panitumumab
EGFR (exon20insert)/MET: Amivantamab GD2 Ganglioide: Dinutuximab HER2: Pertuzumab, Trastuzumab SLAMF7: Elotuzumab T Effector mechanisms Cells Complement T-Ag T cell Bispecific tumorT cell antibody T-Ag CD3-CD19: Blinatumomab CD3-CD20: Glofitamab, Epcoritamab, Mosunetuzumab CD3-BCMA: Teclistumab CD3-gp100Tcr: Tebentafusp Antigens Antigen presenting cell s AgMHC TcR – CTLA4 PD-L1 – Immune-regulating antibody – Cytotoxic T cell Tumor stroma T-regulatory cells Stroma + CTLA4: Ipilimumab, Tremelimumab LAG-3: Relatimab PD-1: Cemiplimab, Dostarlimab, Nivolumab, Pembrolizumab, Retifanlimab PD-L1: Atezolizumab, Avelumab, Durvalumab Blood vessel in tumor stroma Antistroma antibody VEGF: Bevacizumab VEGFR2: Ramucirumab FIGURE 78-4 Immunologic treatments for cancer. Anti–tumor cell antibodies targeting the indicated antigens (T-Ag) expressed on tumor cells or antibody-derived constructs (upper left) can either directly interfere with tumor cell function by, e.g., inhibiting growth-promoting pathways, or recruit host immune effector cells actively (especially through bispecific tumor-engaging [BiTe] strategies; middle left), Fc receptors, or cytotoxic mechanisms such as complement. Endogenous T cells can be activated by immunomodulatory cell targeting antibodies (lower left). Specifically, tumor cell–derived antigens are taken up by antigen-presenting cells (APCs), also in the stroma. Antigens are processed by the APCs to peptides presented by the major histocompatibility complex (MHC) to T-cell antigen receptors (TcRs), thus providing a positive (+) activation signal for the cytotoxic tumor cells to kill tumor cells bearing that antigen. Negative (–) signals inhibiting cytotoxic T-cell action include the CTLA4 receptor (on

T cells), interacting with the B7 family of negative regulatory signals from APCs, and the PD receptor (on T cells), interacting with the PD ligand-1 (PD-L1) (–) signal coming from tumor cells expressing the PD-L1. Strategies that inhibit CTLA4 and PD-1 function are a means of stimulating cytotoxic T-cell activity to kill tumor cells. Lymphocyte activating gene 3 (LAG3) has recently been shown to promote PD axis immunosuppression, and inhibition of that target has shown clinical value. Tumor stroma-directed antibodies cause anti–vascular endothelial cell growth factor (VEGF)–mediated antiangiogenic and tumor interstitial pressure-modulating strategies. Proceeding clockwise in the figure from the upper right, antibody-drug conjugates have recently been designed to deliver cytotoxic drugs, indicated by “T” (upper right). Relatively nonspecific immunomodulators include vaccines instilled directly into the tumor stroma, agents such as the “imids” that alter tumor and stromal cell cytokine production, and cytokines such as interferon or interleukin 2 (IL-2),

which can affect tumor-infiltrating lymphocyte function or have direct antitumor effects. Vaccines targeting tumor cell antigens or live attenuated oncolytic viruses injected into tumors can cause tumor cell lysis with induction of a prominent host antitumor immune response to virus antigens and target antigens (T-Ags) (middle right). In the right lower portion of the figure, strategies to deliver activated immune cells include harvest of autologous T cells that are then infected with a lentivirus or other construct that targets antigens (T-Ags) expressed on tumor cells (chimeric antigen receptor [CAR] T cells), with the targeted antigen indicated. The BiTe antibody blinatumomab was constructed to have an antiCD19 antigen-combining site directed at a cancer cell as one valency with an anti-CD3 binding site as the other. This antibody can bring T cells (with their anti-CD3 activity) close to neoplastic B cells bearing the CD19 determinant. Blinatumomab is active in B-cell neoplasms such as acute lymphocytic leukemia. Unique toxicities include cytokine release syndrome (fever, hypotension, tachycardia) and neurologic deterioration manifest initially by deterioration in handwriting accu racy, which can proceed to more florid cortical dysfunction, suggesting a need for dose pausing and/or glucocorticoid use.

Antibody-drug conjugate See Table 78-6 for: Antibody linked DNA disruptors Antibody linked microtubule agents Antibody linked topo I inhibitors T-Ag Nontargeted/indirect immunomodulator Host cells Tumor cell Bacille Calmette-Guerin (BCG) Glucocorticoids (high-dose) Imids: Lenalidomide, Pomalidomide, Thalidomide CHAPTER 78 T-Ag T-Ag V-ag V-ag Oncolytic or immunomodulating virus to V or T antigens V-ag V-ag Principles of Cancer Treatment V-ag V-ag CART Virus Talimogene laherparepvec Nadofaragene firadenovec CAR-T cellular therapy CD19: Axicabtagene ciloleucel, Brexucabtagene autoleucel, Tisagenlecleucel CD38: Ciltacabtagene autoleucel STROMA-DIRECTED ANTIBODIES (FIG. 78-4) The anti–vascular endo thelial growth factor (VEGF) antibody bevacizumab shows evidence of value in renal cancers, where activation of VEGF signaling occurs as part of disabled hypoxia-induced signaling in the tumor cells. When combined with chemotherapeutic agents, it may increase responses in colorectal and nonsquamous lung cancers. The mechanism for this effect may relate to improved delivery and tumor uptake of the cyto toxic, or even immunoregulatory, antibodies used to treat hepatocel lular cancer, owing to decreased tumor interstitial pressure. VEGF was originally isolated as a “tumor permeability factor” causing leakiness

of tumor blood vessels. When used in gliomas, it may, by decreasing vascular permeability, allow replacement of steroids to decrease intra cranial pressure. Bevacizumab has a number of side effects including hypertension, thrombosis, proteinuria, hemorrhage, and gastrointesti nal perforations with or without prior surgeries; these adverse events also occur with small-molecule drugs modulating VEGF receptor (VEGFR) function.

IMMUNOREGULATORY ANTIBODIES (FIG. 78-4) Purely immunoregu latory antibodies stimulate immune responses to mediate tumordirected cytotoxicity. An understanding of the tumor-host interface has revealed that cytotoxic tumor-directed T cells are frequently inhibited by ligands upregulated in the tumor cells. The programmed death ligand 1 (PD-L1; also known as B7-homolog 1) was initially recognized as inducing T-cell death through a receptor present on T cells, termed the programmed death (PD) receptor, which physiologically regulates the intensity of the immune response to any antigen. The PD family of ligands and receptors also regulates macrophage function, present in tumor stroma. These actions raised the hypothesis that antibodies directed against the PD signaling axis (both anti-PD-L1 and anti-PD) might be useful in cancer treatment by

allowing reactivation of the immune response against tumors. Ipilimumab, an antibody directed against the anti-CTLA4 (cytotoxic T lymphocyte antigen 4), which is expressed on T cells (not tumor cells), responds to signals from antigen-presenting cells (Fig. 78-4) and also downregulates the intensity of the T-cell proliferative response to antigens derived from tumor cells. Indeed, manipulation of the CTLA4 axis was the first demonstration that purely immunoregulatory anti body strategies directed at T-cell physiology could be safe and effec tive in the treatment of cancer. Ipilimumab, alone or in combination with PD-1-directed antibodies, is approved for treatment of metastatic melanoma and lung cancers. PART 4 Oncology and Hematology Nivolumab, directed against the PD-1 receptor, and atezolizumab (anti-PD-L1) are exemplary of anti-PD-1-directed immunoregula tory antibodies, with clinical benefits in many cancers (Table 78-4). Pembrolizumab is approved for first-line treatment of metastatic non-small-cell lung cancer tumors that express the PD-L1 ligand. This development was a milestone in cancer therapeutics, replacing chemotherapy in this patient subset. Lymphocyte activation gene 3 (LAG3) binds to major histocompatibility complex (MHC) on antigen-presenting cells to augment the effect of the PD-1 and CTLA4 pathways. Relatlimab is a first-in-class inhibitor of LAG3 action and augments the effect of nivolumab in melanoma. Importantly, the clinical observation that tumors most amenable to treatment with immunoregulatory antibodies were in sites (lung, skin, genitourinary) exposed to environmental carcinogens or occurred in patients with known mutations in DNA repair pathways stimulated specific research as to whether the “mutational burden” of tumors could predict value from anti-PD strategies. Results to date in general support this hypothesis and led to the first regulatory approvals for immunomodulating antibodies in a “tissue agnostic” fashion. Specifi cally, detection of deficiencies in a tumor DNA mismatch repair system or with evidence of increased tumor mutation burden is a specific indication for use of certain immunoregulatory agents, irrespective of the disease site of origin. The increased efficacy in the setting of higher tumor mutational burden is thought to be due to the presence of more proteins in the tumor structurally altered by mutation that can be rec ognized as foreign by the immune system. Prominent autoimmune hepatic, cardiac, endocrine, cutaneous, neurologic, and gastrointestinal adverse events can occur with the use of ipilimumab as well as the PD-1-directed antibodies. Emergency use of glucocorticoids may be required to attenuate severe toxicities. Although theoretically such glucocorticoid use can attenuate the antitumor effect, response rates do not appear to be compromised by their use to abrogate serious organ toxicity attributable to use of immunomodulatory antibodies. Importantly for the general internist, immunologic toxicities can occur late after exposure to the modulators of PD and CTLA4 action, even while the patient may have sustained control of tumor growth.

TABLE 78-4 Clinical Impact of Host T Lymphocyte–Modified Cellsa or Host T Lymphocyte–Directed Immunoregulatory Antibodiesc A. Advanced Cancers with Positive Effect (at least 25% of treated patients have stable disease or progression-free survival of ≥27 weeks or better) or Frequent or Unexpected Prolonged Responders (efficacy may be limited to CD expression–dependent or PD-1 ligand–expressing subtypes) Acute lymphoid leukemiab Adrenocortical carcinomac Breast cancer, hormone receptor negative, HER2 negative (with chemotherapy)c Colorectal cancer (microsatellite instability-high [MSI-H] or mismatch repair deficient, usually with fluoropyrimidine, oxaliplatin, or irinotecan)c Cervix, squamous carcinomac Cutaneous, squamous carcinomac Diffuse large B-cell non-Hodgkin’s lymphoma, not otherwise specifieda Diffuse large B-cell non-Hodgkin’s lymphoma, primary mediastinal subtypeb Endometrial carcinoma (with lenvatinib, if microsatellite instability-stable

[MSI-S] or mismatch repair wild-type)c Esophageal squamous carcinomac Gastric/gastroesophageal adenocarcinomac Head and neck squamous carcinomac Hepatocellular cancer (after sorafenib)c Hodgkin's diseasec Mantle cell lymphomaa Melanomac Merkel cell carcinomac Mesotheliomac MSI-H or mismatch repair–deficient solid tumors without satisfactory alternativec Mycosis fungoidesc Multiple myelomaa Non-small-cell lung carcinomac Paraganglioma/pheochromocytomac Renal cell carcinomac Sarcoma, alveolar soft partc Small-cell lung carcinomac Solid tumors with high tumor mutational burden (TMB) (≥10 mutations/ megabase) that have progressed following prior therapy without satisfactory alternative treatmentc Urothelial carcinomac (including bladder, ureter) B. Advanced Cancers with Insufficient Data to Support Host-Derived

T Lymphocyte or Immunoregulatory Antibody Treatmentd Acute myeloid leukemia Anus, squamous carcinoma Breast cancer, hormone receptor positive Breast cancer, hormone receptor negative, HER2 positive Biliary tract cancers (if MSI-S or mismatch repair wild-type) Chronic lymphocytic leukemia Chronic myeloid leukemia Gastrointestinal neuroendocrine/islet cell carcinoma Glioma, all grades including glioblastoma Germ cell neoplasms Ovarian cancer Osteogenic sarcoma Pancreas adenocarcinoma Pediatric tumors (Wilms', rhabdomyosarcoma, Ewing's, neuroblastoma, osteosarcoma) Prostate adenocarcinoma Salivary gland carcinoma Soft tissue sarcoma (except alveolar soft part) T-cell non-Hodgkin's lymphoma (except mycosis fungoides) Vulva, squamous carcinoma aChimeric antigen receptor (CAR)-modified autologous T cells in relapsed or refractory cases. bBoth CAR-modified autologous T cells or an immunoregulatory antibody. cT-cell-directed immunoregulatory antibody strategies including anti-PD-1 and/or anti-PD-L1 antibodies or bispecific tumor engaging (BiTe) antibodies against a particular tumor cell antigen. dUnless MSI-high, mismatch repair deficient, or TMB ≥10 mutations/megabase.

Nontargeted Immunomodulators (Fig. 78-4) Bacille Calmette-Guérin, a killed mycobacterial product, invokes a useful immune response when instilled locally into the bladder in the setting of preinvasive bladder cancers. The "imids" thalidomide, lenalidomide, and pomalidomide alter cytokine elaboration in the tumor microen vironment and have antiangiogenic actions. They are a cornerstone in the management of multiple myeloma. Thromboses (warranting consideration of prophylactic anticoagulation), gastrointestinal and neuropathic adverse events, and prominent teratogenicity can occur as a consequence of their use. "High-dose" glucocorticoids stimulate apoptosis in normal and neoplastic lymphoid cells and are a mainstay in the treatment of lymphoid leukemias, lymphomas, and plasma cell neoplasms. Cytokines Only interferon α (IFN-α) and interleukin 2 (IL-2) are considered for current treatment indications. IFN is not curative for any tumor but can induce partial responses in follicular lymphoma, hairy cell leukemia, chronic myeloid leukemia, melanoma, and Kaposi's sarcoma. It produces fever, fatigue, a flulike syndrome, malaise, myelosuppression, and depression and can induce clinically significant autoimmune disease. IL-2 exerts its antitumor effects indirectly through augmentation of immune function. Its biologic activity is to promote the growth and activity of T cells and natural killer (NK) cells. High doses of IL-2 can produce tumor regression in certain patients with metastatic mela noma and renal cell cancer. About 2–5% of patients may experience complete remissions that are durable. Patients may require blood pres sure support and intensive care to manage the toxicity. However, once the agent is stopped, most of the toxicities reverse completely within 3–6 days. Use of "high-dose" IL-2 regimens has been superseded by immunoregulatory antibodies. Efforts to develop new IL-2-based strat egies with less toxicity and improved efficacy are continuing. T Cell–Mediated Therapies Three types of currently used cancer treatments take advantage of the ability of T cells to kill tumor cells.

1. Transfer of allogeneic T cells. This occurs in three major settings: in allogeneic bone marrow transplantation; as purified lymphocyte transfusions following bone marrow recovery after allogeneic bone marrow transplantation; and as pure lymphocyte transfusions fol lowing immunosuppressive (nonmyeloablative) therapy (also called reduced-intensity or minitransplants). In each of these settings, the effector cells are donor T cells that recognize the tumor as being foreign, probably through minor histocompatibility differences. The main risk of such therapy is the development of graft-versushost disease because of the minimal difference between the cancer and the normal host cells. This approach has been useful in certain hematologic cancers refractory to chemotherapeutic strategies.
2. Transfer of autologous T cells. In this approach, the patient's own T cells are removed from the tumor-bearing host, manipulated in several ways in vitro, and given back to the patient. Tumor antigen– specific T cells can be developed after retroviral transduction of the desired T-cell antigen receptor and expanded to large numbers over many weeks ex vivo before administration. These chimeric antigen receptor (CAR) T cells (Fig. 78-4) have evidence of sustained value in patients with refractory hematopoietic neoplasms such as diffuse large B-cell lymphoma, multiple myeloma, and mantle cell lym phoma. Prominent adverse effects include cytokine release syndrome (fever, tachycardia, hypotension) and neurologic manifestations. Clinical investigations are seeking to develop solid-tumor antigendirected CAR strategies, as well as to utilize different immune cell populations such as NK cells to cause useful antitumor activity in ways that may allow "off-the-shelf" products not requiring manipu lation and purification of patients' autologous cells.
3. Tumor vaccines aimed at boosting T-cell immunity. Two types of vaccine approaches are currently approved. Purified autologous antigen-presenting cells can be pulsed with tumor, its membranes, or particular tumor antigens and delivered as a vaccine. Vaccine adjuvants such as granulocyte-macrophage colony-stimulating factor (GM-CSF) may be co-administered. One such vaccine, sipuleucel-T,

is approved for use in patients with asymptomatic or minimally symptomatic metastatic hormone-independent prostate cancer. In this approach, the patient undergoes leukapheresis, wherein mono nuclear cells (that include antigen-presenting cells) are removed from the patient's blood. The cells are pulsed in a laboratory with an antigenic fusion protein comprising a protein frequently expressed by prostate cancer cells, prostate acid phosphatase, fused to GMCSF, and matured to increase their capacity to present the antigen to immune effector cells. The cells are then returned to the patient in a well-tolerated treatment. Although no objective tumor response was documented in clinical trials, median survival was increased by about 4 months.

Another important vaccine strategy is directed at infectious agents whose action ultimately is tied to the development of human cancer. Hepatitis B vaccine in an epidemiologic sense prevents hepatocellular carcinoma, and a tetravalent human papillomavirus vaccine prevents infection by virus types currently accounting for 70% of cervical cancer. Unfortunately, these vaccines are ineffective at treating patients who have developed a virus-induced cancer.

Oncolytic or Immunomodulating Viruses (Fig. 78-4) Labo ratory studies in animals have utilized viruses to destroy tumors because tumor cells lack endogenous host mechanisms, e.g., IFN elaboration or recognition strategies of viral nucleic acids, that limit virus spread. Viral infection of

tumors also can stimulate a prominent host response to viral and tumor cell antigens, leading to immune effects against local tumor cells. Talimogene laherparepvec is a clinically approved attenuated herpes virus that acts to stimulate immune responses when instilled locally into melanoma deposits. Systemic effects are minimal in this application. This general strategy is being considered particularly in tumors not amenable to useful effects of currently approved immu noregulatory antibodies or in conjunction with immunoregulatory anti bodies. Nadofaragene firadenovec is an adenovirus construct instilled into the bladder; it is nonreplicating but can infect urothelial cells to deliver a gene resulting in consistently produced IFN-α2b, which has a local antitumor effect. It is useful in the treatment of superficial bladder cancers. It is not established whether infection of tumor cells, normal urothelial cells, or both contribute to the antitumor effect. CHAPTER 78 Principles of Cancer Treatment ■ ■CANCER CYTOTOXIC THERAPY Table 78-5 lists commonly used cytotoxic cancer chemotherapy agents and pertinent clinical aspects of their use, with particular reference to adverse effects that might be encountered by the generalist in the care of patients. The drugs were initially discovered through screening of chemicals and natural product extracts for evidence of antitumor activity in animals or were designed with knowledge of biochemi cal pathways affecting nucleic acid synthesis. They may be usefully grouped into two general categories: those affecting DNA and those affecting microtubules. As illustrated in Fig. 78-3, disruption of DNA or microtubule integ rity is a major trigger of cellular apoptosis pathways. An additional factor in drug effect stems from recent observations that tumor cells have increased tolerance of specific types of DNA damage owing to defects in DNA repair pathways. This state is thought to facilitate the survival of the neoplastic clone as it experiences DNA mutations dur ing the course of carcinogenesis. DNA-directed cytotoxic agents can create lesions in DNA that are poorly tolerated by cells with neoplasmpromoting DNA repair pathway mutations. This results in a “synthetic lethal” interaction of the drug with cells bearing the DNA repair path way mutation. Examples of a potential “synthetic lethal effect” will be pointed out in relation to clinical applications below. DNA-Interactive Agents DNA replication occurs during the syn thesis or S-phase of the cell cycle, with chromosome segregation of the replicated DNA in the M, or mitosis, phase. The G1 and G2 “gap phases” precede S and M, respectively. Chemotherapeutic agents have been divided into “phase-nonspecific” agents, which can act in any phase of the cell cycle, and “phase-specific” agents, which require the cell to be at a particular cell cycle phase to cause greatest effect.

TABLE 78-5 Commonly Used Cytotoxic Chemotherapy Agents DRUG ADVERSE EVENTS NOTES Direct DNA-Interacting Agentsa Alkylator or platinating drug Bendamustine Vehicle allergy, My, Der, ↑LFTs TLS, Ves, IR, DA-R, DA-H Carboplatin My, N, V, R Dose according to CrCl: to AUC of 5–7 mg/mL per min [AUC = dose/(CrCl + 25)] Chlorambucil Common alkylator Cisplatin N, V, Neu, My, R, Ototoxic, ↓K+, ↓Mg2+, ↓Ca2+ Osmotic diuresis, N, V prophylaxis, DA-R Cyclophosphamide Common alkylator, cystitis, cardiac (high dose) Liver required to activate, DA-R, DA-H, hydration ± mesna protects bladder Dacarbazine (DTIC) Common alkylator, Ves DA-R Ifosfamide My, common alkylator, bladder, CNS DA-R, must use concomitant mesna Lomustine (CCNU) Common alkylator but My, has delayed nadir, ↑LFTs Plm ± fibrosis: PFTs prior to treatment and repeat frequently; cease if fibrosis occurs Lurbinectedin My, ↑LFTs, N, V CYP3A4 Melphalan Common alkylator but My, has delayed nadir DA-R Oxaliplatin N, V, My, Neu Reversible laryngopharyngeal spasm risk Procarbazine Common alkylator, CNS Disulfiram-like effect with alcohol, MAOI, like HBP after tyramine-rich foods Temozolomide Common alkylator but My, has delayed nadir Pneumocystis prophylaxis Antitumor antibiotics and topoisomerase poisons Bleomycin Plm (↑FIO2 worsen), Der,

Raynaud’s, IR* Monitor DLCO before/during treatment, DA-R PART 4 Oncology and Hematology Dactinomycin My, N, V, mucositis, Ves, alopecia Radiation recall Doxorubicin, daunorubicin, epirubicin, idarubicin TOPOII; My, mucositis, alopecia, ↓LVEF acute/chronic, Ves Co-administration with heparin aggregate, secondary leukemia, DA-H, radiation recall Doxorubicin, liposomal TOPOII; My, ↓LVEF, IR*, PPED DA-H, radiation recall Etoposide TOPOII; My, alopecia, IR with rapid IV, N, V, mucositis DA-H, DA-R Irinotecan TOPOI; My, D: “early onset” with cramping, flushing, vomiting: treat with atropine; “late onset” after several doses: use loperamide 4 mg with first stool then 2 mg q2h until 12 h without stool up to 16 mg/24 h; My dependent on UGT1A1 phenotype, R, ILD Irinotecan, liposomal TOPOI; My, D (administer loperamide for D of any severity), IR*, ILD Mitoxantrone TOPOII; Ves, blue urine, nails, and sclerae Interacts with heparin; DA-H, alopecia, N, V, radiation recall Topotecan TOPOI; My, mucositis, N, V, alopecia DA-R, rare ILD Indirectly DNA-Interacting Agents Pyrimidine analogues Capecitabine My, D, PPED, cardiac adverse events, R, Der Oral prodrug of 5-FU Cytarabine (cytosine arabinoside [ara-C]) My, mucositis, CNS (high dose), conjunctivitis (high dose; use steroid eyedrops until 72 h after last dose), noncardiogenic pulmonary edema 5-Fluorouracil (5-FU) My, D, mucositis, CNS, Der, cardiac adverse events, PPED Toxicity enhanced by leucovorin by increasing “ternary complex” with thymidylate synthase; metabolism in tissue; dihydropyrimidine dehydrogenase deficiency increases toxicity; enhances warfarin effect Gemcitabine My, N, V, ↑LFT, fever/”flu syndrome” Rare ARDS; rare HUS, rare PRES, radiosensitization with long infusion Trifluridine/tipiracil My, mucositis, N, V, unusual PPED Trifluridine directly inhibits thymidylate synthase and is incorporated into DNA; tipiracil inhibits thymidine phosphorylase, which degrades trifluridine Purine analogues Fludarabine phosphate My, mucositis, CNS, Der Converted to F-ara ATP in cells by deoxycytidine kinase; DA-R 6-Mercaptopurine (6-MP), 6-thioguanine (6-TG) Mv, N, ↑LFT 6-MP metabolized by xanthine oxidase, decrease dose with allopurinol; 6-MP and 6-TG increased toxicity with thiopurine methyltransferase deficiency Antifolates Methotrexate My, ↑LFT with fibrosis with chronic use, Plm, R, mucositis Toxicity lessened by leucovorin, bypassing block of dihydrofolate reductase, excreted in urine; DA-R or hold; NSAIDs increase renal toxicity; sequestered in third space fluids Pemetrexed My Supplement folate/B12, omit for CrCl <45 mL/min Miscellaneous Antimetabolite-Like Agents Asparaginase Thrombosis by decrease of antithrombin IIII, but ↓fibrinogen can cause hemorrhage; ↑glucose; ↓albumin, hypersensitivity; CNS; pancreatitis; ↑LFTs Hydroxyurea My, N, mucositis, rare ↓CrCl DA-R, augments antimetabolite effect

Prodrug requires metabolism to active drug SN-38, which is cleared by UGT1A1 with degree of My dependent on patient UGT1A1 genotype, DA-H Consider guide dosing by UGT1A1 genotype testing, CYP3A4;

NO recommended dose for T Bili >ULN Metabolized in tissues by deamination but renal excretion prominent at doses

> “ 500 mg; therefore, DA-R in “high-dose” regimens Decrease protein synthesis; indirect inhibition of DNA synthesis by decreased histone synthesis; blocks methotrexate action (Continued)

(Continued) TABLE 78-5 Commonly Used Cytotoxic Chemotherapy Agents DRUG ADVERSE EVENTS NOTES Antimitotic agents Docetaxel IR*, VLS, My, ↑LFTs, Der, Neu, stomatitis, alopecia, N, V, D Premedicate with steroids, H1 and H2 blockers; DA-H; monitor for second primary malignancies; alcohol in vehicle Eribulin My, Neu, ↑QT DA-H, DA-R Ixabepilone My, Neu, IR*, N, V, D, alopecia Premedicate with steroids, H1 and H2 blockers; CYP3A4, DA-H Nab-paclitaxel My, Neu, Ves DA-H, CYP3A4, CYP2C8 Paclitaxel IR*, My, alopecia, N, V, D, mucositis, Neu, Ves Premedicate with steroids, H1 and H2 blockers; DA-H, CYP3A4, CYP2C8, alcohol in vehicle Vinblastine My, Ves, Neu, HBP, Raynaud's, Ves, ↑LFTs, ileus/ constipation (use prophylactic stool softeners) Vincristine Ves, Neu, SIADH, ileus/constipation (use prophylactic stool softeners) Vinorelbine My, Ves, allergic bronchospasm (immediate), dyspnea/ cough (subacute) Note: Data abstracted in part from publicly available U.S. Food and Drug Administration label. All agents in this class have the potential for prominent embryofetal toxicity; use without contraception by female patients of childbearing potential is not recommended. Effective contraception for female partners who are of childbearing potential of patients undergoing treatment should also be considered; use during lactation is also not recommended; all DNA interacting agents have theoretical risk of late secondary neoplasms, particularly where noted. Indications and events of prominent general medical importance include the following: ARDS, acute respiratory distress syndrome; AUC, area under concentration-time curve; Common alkylator toxicities: N, V, My, alopecia, mucositis, ↓fertility, cumulative lung toxicity; CNS, central nervous system (can include altered sensorium, cortical and cerebellar signs, dysarthria, altered seizure threshold); Cor, corneal keratopathy, consider pretreatment ophthalmologic exam with prophylactic lubricating eyedrops ± ocular steroids; CrCl, creatinine clearance; CYP___, interaction with drugs metabolized by the indicated cytochrome(s) P450; DA-H, dose adjust for hepatic dysfunction; DA-R, dose adjust for renal dysfunction; Der, dermatologic toxicity; HBP, high blood pressure; HUS, hemolytic-uremic syndrome; ILD, interstitial lung disease; IR, infusion reaction; IR*, infusion reaction prophylaxis specifically recommended; LFT, liver function tests; ↓LVEF, left ventricular ejection fraction, monitor echocardiogram; My, anemia, decrease in white blood cells, platelets, with risk of neutropenic fever, hemorrhage, therefore dose reduce or hold dose for decreased neutrophil or platelet counts unless marrow infiltrated by drug-responsive tumor; N, nausea; Neu, peripheral neuropathy; Plm, pulmonary; PPED, palmar-plantar erythrodysesthesia (i.e., hand-foot syndrome); PRES, posterior reversible leukoencephalopathy syndrome; PT, prothrombin time; PTT, partial thromboplastin time; ↑QT, pre- and intratreatment electrocardiogram monitoring, normalize K+, Mg2+, ionized Ca2+; R, renal injury possible; SIADH, syndrome of inappropriate antidiuretic hormone; TLS, risk of tumor lysis syndrome if brisk response; TOPO___, agent targets the indicated topoisomerase; UGT___, metabolism by UDP-glucuronosyltransferase of the indicated genotype; Ves, extravasation injury possible; V, vomiting; VLS, vascular leak syndrome; VOD, veno-occlusive liver disease. Alkylating agents (Table 78-5) as a class are cell cycle phase–nonspecific agents. They break down, either spontaneously or after normal organ or tumor cell metabolism, to reactive intermediates that covalently modify bases in DNA. This leads to cross-linkage of DNA strands or the appearance of breaks in DNA as a result of repair efforts. Damaged DNA cannot complete normal cell division; in addition, it activates apoptosis. Alkylating agents share common toxicities: myelosuppres sion, alopecia, gonadal dysfunction, mucositis, and pulmonary fibrosis. They also share the capacity to cause "second" neoplasms, particularly leukemia, years after use, particularly when used in low doses for pro tracted periods. Cyclophosphamide is inactive unless metabolized by the liver to 4-hydroxy-cyclophosphamide, which decomposes into an alkylating species, as well as to chloroacetaldehyde and acrolein. The latter causes chemical cystitis; therefore, excellent hydration must be maintained

while using cyclophosphamide. If severe, the cystitis may be attenu ated or prevented altogether (if expected from the dose of cyclophos phamide to be used) by mesna (2-mercaptoethanesulfonate). Liver disease impairs cyclophosphamide activation. Sporadic interstitial pneumonitis leading to pulmonary fibrosis can accompany the use of cyclophosphamide, and high doses used in conditioning regimens for bone marrow transplant can cause cardiac dysfunction. Ifosfamide is a cyclophosphamide analogue also activated in the liver, but more slowly, and it requires co-administration of mesna to prevent bladder injury. CNS effects, including somnolence, confusion, and psychosis, can fol low ifosfamide use; the incidence appears related to low body surface area or decreased creatinine clearance. Several alkylating agents are less commonly used. Bendamustine has activity in chronic lymphocytic leukemia and certain lymphomas. It is used in transplant preparation regimens. Melphalan shows variable oral bioavailability and undergoes extensive binding to albumin and α1-acidic glycoprotein. Mucositis appears more prominently; however, it has prominent activity in multiple myeloma. Nitrosoureas break down to carbamylating species that not only cause a distinct pattern of DNA base pair–directed reactivity but also can covalently modify proteins. Lomustine is used to treat brain tumors but causes delayed myelotoxicity and can cause lung injury. Procarbazine is metabolized

DA-H, unusual; Plm, CYP3A4 DA-H, CYP3A4; less My than with vinblastine; unusual Plm DA-H; less neurotoxic than other vincas CHAPTER 78 Principles of Cancer Treatment in the liver and possibly in tumor cells to yield a variety of free radical and alkylating species. In addition to myelosuppression, it causes hyp notic and other CNS effects, including vivid nightmares. It can cause a disulfiram-like syndrome on ingestion of ethanol. Both procarbazine and lomustine are used in the treatment of brain tumors. Dacarbazine (DTIC) is activated in the liver to yield the highly reactive methyl diazo nium cation. It causes only modest myelosuppression 21–25 days after a dose but causes prominent nausea on day 1. It is an important com ponent of treatment regimens for Hodgkin’s lymphoma and sarcomas. Temozolomide is structurally related to DTIC but is activated by non enzymatic hydrolysis in tumors and is bioavailable orally. Brain tumors with alkylguanine alkyl transferase deficiency are selectively susceptible to temozolomide, which alkylates the O6 position of guanine. Cisplatin was discovered fortuitously by observing that bacteria present in electrolysis solutions with platinum electrodes could not divide. Only the cis diamine configuration is active as an antitumor agent. In tumor cells, a chloride is lost from each position. The result ing positively charged species is an efficient DNA interactor, forming Pt-based cross-links. Therefore “platinating agents” are considered with alkylating agents as forming related lesions in DNA. Cisplatin is administered with abundant hydration, including forced diuresis with mannitol to prevent kidney damage; even with the use of hydra tion, gradual decrease in kidney function is common, along with noteworthy anemia. Hypomagnesemia frequently attends cisplatin use and can lead to hypocalcemia and tetany. Other common toxicities include neurotoxicity with stocking-and-glove sensorimotor neuropa thy. Hearing loss occurs in 50% of patients treated with conventional doses. Cisplatin is intensely emetogenic, requiring prophylactic anti emetics. Myelosuppression is less evident than with other alkylating agents. Chronic vascular toxicity (Raynaud’s phenomenon, coronary artery disease) is a more unusual toxicity. Carboplatin displays less nephro-, oto-, and neurotoxicity. However, myelosuppression is more frequent, and because the drug is exclusively cleared through the kid ney, adjustment of dose for creatinine clearance must be accomplished through use of various dosing nomograms. Oxaliplatin is a platinum analogue with noteworthy activity in colon cancers refractory to other treatments. It is prominently neurotoxic.

Lurbinectedin binds to DNA through the “DNA minor groove” with covalent interaction with the N2 position of certain guanines. Transient altered liver function can occur, as well as cytopenias. Lurbi nectedin has activity in small-cell lung cancer. The first example of this agent class, trabectedin, requires a prolonged infusion schedule but is active in certain sarcomas, in part due to its modulation of transcrip tion factor function.

Antitumor Antibiotics and Topoisomerase Poisons Anti tumor antibiotics are substances produced by bacteria that provide a chemical defense against hostile microorganisms. They bind to DNA directly and can frequently undergo electron transfer reactions to gen erate free radicals in close proximity to DNA, leading to DNA damage in the form of single-strand breaks or cross-links. Topoisomerase poi sons include natural products or semisynthetic derivatives that modify enzymes that allow DNA to unwind during replication or transcription. These include topoisomerase I, which creates single-strand breaks that then rejoin following the passage of the other DNA strand through the break. Topoisomerase II creates double-strand breaks through which another segment of DNA duplex passes before rejoining. Owing to the role of topoisomerase I in the replication fork, topoisomerase I poisons cause lethality if the topoisomerase I–induced lesions occur in S-phase. Doxorubicin intercalates into DNA, thereby altering DNA structure, replication, and topoisomerase II function. It can also undergo reduc tion of its quinone ring system, with reoxidation to form reactive oxy gen radicals. It causes predictable myelosuppression, alopecia, nausea, and mucositis. In addition, it can cause acute cardiotoxicity in the form of atrial and ventricular dysrhythmias, but these are rarely of clinical significance. In contrast, cumulative doses >550 mg/m2 are associated with a 10% incidence of chronic cardiomyopathy. The incidence of cardiomyopathy appears to be related to peak serum concentration, with low-dose, frequent treatment or continuous infusions better toler ated than intermittent higher-dose exposures. Cardiotoxicity has been related to iron-catalyzed oxidation and reduction of doxorubicin in the heart. Dexrazoxane is an intracellular chelating agent that can act as a cardio-protectant. Doxorubicin’s cardiotoxicity is increased when given together with trastuzumab, the anti-HER2/neu antibody. Radia tion recall or interaction with concomitantly administered radiation to cause local site complications is frequent. The drug is a powerful vesicant, with necrosis of tissue apparent 4–7 days after an extravasa tion; therefore, it should be administered into a rapidly flowing intra venous line. Dexrazoxane also can mitigate doxorubicin extravasation. Doxorubicin is metabolized by the liver, so doses must be reduced by 50–75% in the presence of liver dysfunction. Daunorubicin is closely related to doxorubicin and is preferable to doxorubicin owing to less mucositis and colonic damage with frequent high doses used in the curative treatment of leukemia. Idarubicin is also used in leukemia treatment and may have somewhat less cardiotoxicity. Encapsulation of daunorubicin into a liposomal formulation has attenuated cardiac toxicity with antitumor activity in Kaposi’s sarcoma, other sarcomas, multiple myeloma, and ovarian cancer. PART 4 Oncology and Hematology Mitoxantrone is a synthetic topoisomerase II–directed agent with a mechanism similar to the anthracyclines, with less but not absent cardiotoxicity, comparing the ratio of cardiotoxic to effective doses; it is still associated with a 10% incidence of cardiotoxicity at cumulative doses of >150 mg/m2. Etoposide binds directly to topoisomerase II and DNA in a reversible ternary complex. It stabilizes the covalent inter mediate in the enzyme’s action where the enzyme is covalently linked to DNA. Prominent clinical effects include myelosuppression, nausea, and transient hypotension related to the speed of administration of the agent. Etoposide is a mild vesicant but is relatively free from other large-organ toxicities. Camptothecins target topoisomerase I. Topotecan is a camptoth ecin derivative approved for use in gynecologic tumors and small-cell lung cancer. Toxicity is limited to

myelosuppression and mucositis. Irinotecan is a camptothecin with evidence of activity in colorectal carcinoma. Irinotecan is a prodrug, metabolized in the liver to SN-38, its active metabolite. Levels of SN-38 are particularly high in the set ting of Gilbert's disease, characterized by defective uridine diphosphate

glucuronosyl transferase (UGT) 1A1 and indirect hyperbilirubinemia, a condition that affects ~10% of the white population in the United States. In addition, irinotecan's myelosuppression is clearly influenced by the patient's genotype for UGT1As. Irinotecan causes a delayed (48–72 h) secretory diarrhea related to the toxicity of SN-38. The diar rhea can be treated effectively with loperamide or octreotide; immedi ate diarrhea when it occurs is responsive to atropine. Bleomycin remains an important component of curative regimens for Hodgkin's lymphoma and germ cell neoplasms. It forms complexes with Fe^{2+} while also bound to DNA. Oxidation of Fe^{2+} gives rise to superoxide and hydroxyl radicals, causing DNA damage. The drug causes little, if any, myelosuppression. Bleomycin is cleared rapidly, but augmented skin and pulmonary toxicity in the presence of renal failure necessitates dose reduction in renal failure. Bleomycin is not a vesicant and can be administered intravenously, intramuscularly, or subcutane ously. Common side effects include fever and chills, facial flush, and Raynaud's phenomenon. The most feared complication of bleomycin treatment is pulmonary fibrosis, which increases in incidence at >300 cumulative units administered and is minimally responsive to treat ment (e.g., glucocorticoids). The earliest indicator of an adverse effect is usually a decline in the carbon monoxide diffusing capacity (DLCO) or coughing, although cessation of drug immediately upon docu mentation of a decrease in DLCO may not prevent further decline in pulmonary function. Bleomycin is inactivated by a bleomycin hydro lase, which is poorly expressed in skin and lung. Because bleomycindependent electron transport is dependent on O_2, bleomycin toxicity may become apparent after exposure to transient very high fraction of inspired oxygen (FIO_2) even late after treatment. Thus, during surgi cal procedures, patients with prior exposure to bleomycin should be maintained on the lowest FIO_2 consistent with maintaining adequate tissue oxygenation. Dactinomycin interacts directly with DNA to inhibit RNA tran scription. It is important in the curative treatment of pediatric neoplasms, some of which also occur in young adults. Prominent myelosuppression, mucositis, alopecia, radiation recall, and nausea require management. Antimetabolites A broad definition of antimetabolites would include compounds that interfere with purine or pyrimidine synthesis. Some antimetabolites also cause DNA damage indirectly, through misincorporation into DNA. They tend to convey greatest toxicity to cells in S-phase, and the degree of toxicity increases with duration of exposure. Common toxic manifestations include stomatitis, diarrhea, and myelosuppression. Methotrexate inhibits dihydrofolate reductase, which regenerates reduced folates from the oxidized folates produced when thymi dine monophosphate is formed from deoxyuridine monophosphate. Without reduced folates, cells die a "thymine-less" death. N5-Tet rahydrofolate or N5-formyltetrahydrofolate (leucovorin) can bypass this block and rescue cells from methotrexate, which is retained in cells by polyglutamylation. Methotrexate is transported into cells by a membrane carrier, and high concentrations of drug can bypass this carrier and allow diffusion of drug directly into cells. These properties have suggested the design of "high-dose" methotrexate regimens with leucovorin rescue of normal marrow and mucosa as part of curative approaches to osteosarcoma in the adjuvant setting and hematopoi etic neoplasms of children and adults. Methotrexate is cleared by the kidney via both glomerular filtration and tubular secretion, and toxic ity is augmented by renal dysfunction and drugs such as salicylates, probenecid, and nonsteroidal anti-inflammatory agents that undergo tubular secretion. With normal renal function,

15 mg/m2 leucovorin will rescue 10−8–10−6 M methotrexate in 3–4 doses. However, with decreased creatinine clearance, doses of 50–100 mg/m2 are continued until methotrexate levels are <5 × 10−8 M. In addition to bone mar row suppression and mucosal irritation, methotrexate can cause renal failure itself at high doses owing to crystallization in renal tubules; therefore, high-dose regimens require alkalinization of urine with increased flow by hydration. Methotrexate can be sequestered in thirdspace collections and diffuse back into the general circulation, causing

prolonged myelosuppression. Less frequent adverse effects include reversible increases in transaminases and hypersensitivity-like pul monary syndrome. Chronic low-dose methotrexate can cause hepatic fibrosis. When administered to the intrathecal space, methotrexate can cause chemical arachnoiditis and CNS dysfunction. Pemetrexed is a folate-directed antimetabolite that inhibits the activity of several enzymes, including thymidylate synthetase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltrans ferase. To avoid toxicity to normal tissues, pemetrexed is given with low-dose folate and vitamin B12 supplementation. Pemetrexed has notable activity against certain lung cancers and, in combination with cisplatin, also against mesotheliomas. 5-Fluorouracil (5-FU) represents an early example of “rational” drug design in that tumor cells incorporate radiolabeled uracil more efficiently into DNA than normal cells. 5-FU is metabolized in cells to 5′FdUMP, which inhibits TS. In addition, misincorporation can lead to single-strand breaks, and RNA can aberrantly incorporate FUMP. 5-FU is metabolized by dihydropyrimidine dehydrogenase, and defi ciency of this enzyme can lead to excessive toxicity from 5-FU. Oral bioavailability varies unreliably, but prodrugs such as capecitabine have been developed that allow at least equivalent activity to parenteral 5-FU-based approaches. Intravenous administration of 5-FU leads to bone marrow suppression after short infusions but to stomatitis after prolonged infusions. Leucovorin augments the activity of 5-FU by pro moting formation of the ternary covalent complex of 5-FU, the reduced folate, and TS. Less frequent toxicities include CNS dysfunction, with prominent cerebellar signs, and endothelial toxicity manifested by thrombosis, including pulmonary embolus and myocardial infarc tion. Trifluridine is a fluorinated pyrimidine that as the triphosphate is directly incorporated into DNA, evoking DNA damage, and as the monophosphate can inhibit TS. It is administered as a fixed-dose combination with tipiracil, an inhibitor of trifluridine degradation by thymidine phosphorylase. Cytosine arabinoside (ara-C) is incorporated into DNA after for mation of ara-CTP, resulting in S-phase–related toxicity. Continuous infusion schedules allow maximal efficiency, with uptake maximal at 5–7 μM. Ara-C can be administered intrathecally. Adverse effects include nausea, diarrhea, stomatitis, chemical conjunctivitis, and cerebellar ataxia. Gemcitabine is a cytosine derivative that is similar to ara-C in that it is incorporated into DNA after anabolism to the triphosphate, rendering DNA susceptible to breakage and repair syn thesis, which differs from that in ara-C in that gemcitabine-induced lesions are very inefficiently removed. In contrast to ara-C, gem citabine appears to have useful activity in a variety of solid tumors, with limited nonmyelosuppressive toxicities. 6-Thioguanine and 6-mercaptopurine (6-MP) are used in the treat ment of acute lymphoid leukemia. Although administered orally, they display variable bioavailability. 6-MP is metabolized by xanthine oxi dase and therefore requires dose reduction when used with allopurinol. 6-MP is also metabolized by thiopurine methyltransferase; genetic deficiency of thiopurine methyltransferase results in excessive toxicity. Fludarabine phosphate is a prodrug of F-adenine arabinoside (F-ara-A). F-ara-A is incorporated into DNA and can cause delayed cytotoxicity even in cells with low growth fraction, including chronic lymphocytic leukemia and follicular B-cell lymphoma. CNS and peripheral nerve dysfunction and T-cell depletion leading to opportu nistic infections can occur in addition to myelosuppression. Agents that indirectly affect

purine and pyrimidine metabolism with anti-metabolite-like effects include hydroxyurea, which reversibly inhibits ribonucleotide reductase, resulting in S-phase block. It is orally bioavailable and useful for the acute management of myeloprolifera tive states. Asparaginase is a bacterial enzyme that causes breakdown of extracellular asparagine required for protein synthesis in certain leukemic cells. This effectively stops tumor cell DNA synthesis, as DNA synthesis requires concurrent protein synthesis. Because aspara ginase is a foreign protein, hypersensitivity reactions are common, as are effects on organs such as pancreas and liver that normally support continuing protein synthesis of secreted products. This may result in decreased insulin secretion with hyperglycemia, with or without

hyperamylasemia and clotting function abnormalities. Close moni toring of clotting functions should accompany use of asparaginase. Paradoxically, owing to depletion of rapidly turning over anticoagulant factors, thromboses particularly affecting the CNS may also be seen with asparaginase.

Mitotic Spindle Inhibitors Microtubules form the mitotic spin dle, and in interphase cells, they are responsible for the cellular “scaf folding” along which various motile and secretory processes occur. Microtubules are composed of repeating heterodimers of α and β iso forms of the protein tubulin. Vincristine binds to the tubulin heterodi mer with the result that microtubules are disaggregated. This results in the block of growing cells in M-phase, where a structurally disordered mitotic spindle apparatus is a powerful proapoptotic signal (Fig. 78-3). Vincristine is metabolized by the liver, and dose adjustment in the pres ence of hepatic dysfunction is required. It is a powerful vesicant, and infiltration can be treated by local heat and infiltration of hyaluroni dase. At clinically used intravenous doses, neurotoxicity in the form of glove-and-stocking neuropathy is frequent. Acute neuropathic effects include jaw pain, paralytic ileus, urinary retention, and the syndrome of inappropriate antidiuretic hormone secretion. Myelosuppression is not seen at conventional doses. Vinblastine is similar to vincristine, except that it tends to be more myelotoxic, with more frequent throm bocytopenia and also mucositis and stomatitis. Vinorelbine is a vinca alkaloid that appears to have differences in resistance patterns in com parison to vincristine and vinblastine; it may be administered orally. CHAPTER 78 The taxanes include paclitaxel and docetaxel. These agents differ from the vinca alkaloids in that the taxanes stabilize microtubules against depolymerization. The “stabilized” microtubules function abnormally and are not able to undergo the normal dynamic changes of microtubule structure and function necessary for cell cycle comple tion. Taxanes are among the most broadly active antineoplastic agents for use in solid tumors, with evidence of activity in ovarian, breast, prostate, and non-small cell lung cancers, and Kaposi’s sarcoma. They are administered intravenously, and their vehicles cause hypersensi tivity reactions. Premedication with dexamethasone (8–16 mg orally or intravenously 12 and 6 h before treatment) and diphenhydramine (50 mg) and cimetidine (300 mg), both 30 min before treatment, decreases but does not eliminate the risk of hypersensitivity reactions to the paclitaxel vehicle. A protein-bound formulation of paclitaxel (called nab-paclitaxel) has at least equivalent antineoplastic activity and decreased risk of hypersensitivity reactions. Paclitaxel may also cause myelosuppression, neurotoxicity in the form of glove-and-stocking numbness, and paresthesia. Docetaxel causes comparable degrees of myelosuppression and neuropathy. Docetaxel uses a different vehicle that can cause fluid retention in addition to hypersensitivity reactions; dexamethasone premedication with or without antihistamines is also generally used. Cabazitaxel is a taxane with somewhat better activity in prostate cancers than earlier generations of taxanes, perhaps due to superior delivery to

sites of disease. Principles of Cancer Treatment Epothilones represent a class of microtubule-stabilizing agents optimized for activity in taxane-resistant tumors. Ixabepilone has clear evidence of activity in breast cancers resistant to taxanes and anthra cyclines such as doxorubicin. Side effects include myelosuppression and peripheral sensory neuropathy. Eribulin is a microtubule-directed agent with activity in patients who have had progression of disease on taxanes. It alters dynamics of microtubule remodeling in cells. ■ ■ANTIBODY-DRUG CONJUGATES In an effort to improve therapeutic index and enhance antitumor effect, antibody-drug conjugates (ADCs; Fig. 78-4) have recently entered clin ical practice. In this approach, humanized monoclonal antibodies are covalently linked to cytotoxic agents by “linkers.” When bound to tar get antigens on tumor cells, the nature of the linker determines whether the cytotoxic agent is released only after the ADC is internalized by degradation in a lysosomal compartment, or release of the cytotoxin might occur extracellularly by proteases or physical properties of the tumor microenvironment, in the latter case allowing “bystander” cell killing. Of importance is selection of antibodies with sufficient tumor

TABLE 78-6 Antibody-Drug Conjugates TOXIC MECHANISM TARGET ANTIGEN DISEASE ACTIVITY NOTES DNA Structure Gemtuzumab ozogamicin CD33 Acute myeloid leukemia, CD33+ IR*, My, ↑LFTs ± VOD Inotuzumab ozogamicin CD22 Pre-B acute lymphoid leukemia IR*, My, ↑LFTs ± VOD, ↑QT Loncastuximab tesirine-lpyl CD19 Diffuse large B-cell lymphoma VLS, My, Der Microtubule Structure Ado-trastuzumab emtansine HER2 Breast cancer, HER2+ IR, ↑LFTs, ↓LVEF, My, Plm, Neu Belantamab mafadotin-blm CD38 Myeloma IR, My, Cor Brentuximab vedotin CD30 Hodgkin’s disease; anaplastic large-cell lymphoma; mycosis fungoides, CD30+ Enfortumab vedotin Nectin-4 Urothelial cancer ↑Glucose ± DKA, Neu, Cor, Ves, Der Mirvetuximab soravtansine-gynx Folate receptor α (FRα+) Ovary, peritoneal, fallopian tube cancer, FRα+ Cor, Neu, My Polatuzumab vedotin CD79b High-grade B-cell lymphoma Neu, IR*, My, PML, TLS, ↑LFTs Tisotumab vedotin-tftv Tissue factor Uterine cervix cancer Neu, ↑PT, ↑PTT, Cor, bleeding, Plm Topoisomerase I Fam-trastuzumab deruxtecan-nxki HER2 HER2 1+/weak BC, HER2 activating mutation+ NSCLC, HER2+ gastric Sacituzumab govitecan-bziy Trop2 Triple-negative BC, HR+/HER2– BC, urothelial cancer PART 4 Oncology and Hematology Note: Data abstracted in part from publicly available U.S. Food and Drug Administration label. All agents in this class have the potential for prominent embryofetal toxicity; use without contraception by female patients of childbearing potential is not recommended. Effective contraception for female partners who are of childbearing potential of patients undergoing treatment should also be considered; use during lactation is also not recommended; all DNA interacting agents have theoretical risk of late secondary neoplasms, particularly where noted. Indications and events of prominent general medical importance include the following: BC, breast cancer; Cor, corneal keratopathy, consider pretreatment ophthalmologic exam with prophylactic lubricating eyedrops ± ocular steroids; CYP___, interaction with drugs metabolized by the indicated cytochrome(s) P450; DA-H, dose adjust for hepatic dysfunction; DA-R, dose adjust for renal dysfunction; Der, dermatologic toxicity; DKA, diabetic ketoacidosis; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILD, interstitial lung disease; IR, infusion reaction; IR*, infusion reaction prophylaxis specifically recommended; LFT, liver function tests; ↓LVEF, left ventricular ejection fraction, monitor echocardiogram; My, anemia, decrease in white blood cells, platelets, with risk of neutropenic fever, hemorrhage, therefore dose reduce or hold dose for decreased neutrophil or platelet counts unless marrow infiltrated by drug-responsive tumor; N, nausea; Neu, peripheral neuropathy; Plm, pulmonary; PML, progressive multifocal leukoencephalopathy risk; PT, prothrombin time; PTT, partial thromboplastin time; ↑QT, pre- and intratreatment

electrocardiogram monitoring, normalize K+, Mg2+, ionized Ca2+; R, renal injury possible; TLS, risk of tumor lysis syndrome if brisk response; UGT___, metabolism by UDP-glucuronosyltransferase of the indicated genotype; V, vomiting; Ves, extravasation injury possible; VLS, vascular leak syndrome; VOD, veno-occlusive liver disease. cell selectivity to avoid damage to normal tissue. In addition, the linker strategy should have low spontaneous release of the cytotoxic agent prior to reaching the tumor environment. Table 78-6 lists currently approved ADCs and features of importance relevant to their use for the general internist. Three major groups of ADCs are currently available, based on the nature of the cytotoxic payload. ADCs targeting DNA structure include those based on calicheamicin, a DNA-interacting antitumor antibiotic too toxic for clinical use but, when used as an ADC, can be useful in the treatment of CD33+ acute myeloid leukemia (gemtuzumab ozogamicin) and CD22+ acute lymphocytic leukemia (inotuzumab ozogamicin). Patients must be monitored for hypersensitivity reactions and for hepatotoxicity due to veno-occlusive disease of hepatic veins, resulting from release of the calicheamicin or its metabolites in the liver. Likewise, the minor groove binder and DNA alkylator pyrrolo benzodiazepine dimer is the basis for CD19-directed loncastuximab tesirine-lpyl, whose use in refractory diffuse large B-cell lymphoma can be complicated by vascular leak syndrome, cytopenias, and cutaneous reactions. ADCs targeting microtubules (in all cases with the potential for cytopenias and neuropathic adverse events) are of two types. Maytan sine derivatives include ado-trastuzumab emtansine, which is an ADC employing the HER2/neu-directed trastuzumab and a highly toxic microtubule-targeted emtansine, which by itself is too toxic for human use; the ADC shows valuable activity in patients with breast cancer who have developed resistance to trastuzumab alone (still watch for cardiac and pulmonary side effects). Mirvetuximab soravtansine-gynx targets folate receptor α in refractory ovarian cancers (monitor for corneal side effects). The second microtubule-directed class of ADCs is derived from the microtubule poison monomethylauristatin E as cytotoxic agent. Brentuximab vedotin is an anti-CD30 ADC with activ ity in neoplasms such as Hodgkin’s lymphoma where the tumor cells frequently express CD30. Polatuzumab vedotin analogously targets

Neu, IR, My, Plm, R, TLS, CYP3A4, ↑LFTs, DA-H, DA-R N/V prophylaxis, ILD prompt evaluate cough, dyspnea, My, ↓LVEF IR*, N/V prophylaxis, diarrhea consider loperamide, My esp UGT1A1*28, consider G-CSF CD79a in B-cell lymphomas. Enfortumab vedotin uses an antibody to NECTIN4 to target the vedotin “warhead” to urothelial neoplasms expressing that target. Belantamab mafodotin targets BCMA (B-cell maturation) expressed myeloma but using a distinct microtubule toxin derived from auristatin F. Belantamab mafodotin can cause ocular keratopathy, which requires prospective monitoring. Topoisomerase I–directed ADCs, including fam-trastuzumab derux tecan-nxki and sacituzumab govitecan-bziy, are ADCs that allow specific targeting of camptothecin and SN-38, respectively to HER2positive neoplasms (monitoring for interstitial pneumonitis and cardiac dysfunction) and, in the latter case, triple-negative breast cancers, which abundantly express the antibody target Trop2, a cell surface glycoprotein first discovered in trophoblast cells (but diarrhea should be vigorously addressed with loperamide, similar to what might be encountered with irinotecan). Both agents can cause cytopenias, nausea, and vomiting. ■ ■CANCER MOLECULAR TARGETED THERAPY Agents in this class share the characteristic that they are directed at specific cancer cell molecular targets important in the proliferation of tumors. While these agents can ultimately lead to tumor cell death, this occurs by altered regulation of a specific biochemical pathway affecting tumor cell susceptibility to apoptosis or growth arrest (Fig. 78-3). Since many approved agents of this type are directed at specific mutations present at diagnosis or that arise during the course of a patient’s clinical course, their use must be guided by refined

diagnostic strategies. Initial molecular testing of a diagnostic biopsy, with repeated biopsies as war ranted, should be considered. Alternatively liquid biopsies to examine plasma DNA shed from tumors or present in circulating tumor cells have entered into routine clinical use to assist in making decisions about best strategies to consider. Hormone Receptor–Directed Therapy Steroid hormone receptor–related molecules were arguably the first “molecular target”

classes of anticancer drugs. When bound to their ligands, these recep tors can alter gene transcription in hormone-responsive tissues. While in some cases, such as breast cancer, demonstration of the target hor mone receptor is necessary for their use, in other cases such prostate cancer (androgen receptor) and lymphoid neoplasms (glucocorticoid receptor), the relevant receptor is always present in the tumor. Glucocorticoids are generally given in “pulsed” high doses in leu kemias and lymphomas, where they induce cell death in tumor cells. Cushing’s syndrome and inadvertent adrenal suppression on with drawal from high-dose glucocorticoids can be significant complica tions, along with infections common in immunosuppressed patients, in particular Pneumocystis pneumonia, which classically appears a few days after completing a course of high-dose glucocorticoids. Tamoxifen is a partial estrogen receptor (ER) antagonist; it antago nizes growth in wild-type (ER; also designated ESR1 to specify estro gen receptor α) breast tumors, mirroring its effect on breast tissue, but owing to agonistic activities in vascular and uterine tissue, side effects include increased risk of thromboembolic phenomena and a small increased incidence of endometrial carcinoma, which appears after chronic use (usually >5 years). Progestational agents—including medroxyprogesterone acetate, androgens including fluoxymesterone (Halotestin), and paradoxically, estrogens—have approximately the same degree of activity in primary hormonal treatment of breast can cers that have elevated expression of ER protein. Estrogen itself is not used often due to prominent cardiovascular and uterotropic activity. Aromatase refers to a family of enzymes that catalyze the forma tion of estrogen in various tissues, including ovary, peripheral adipose tissue, and some tumor cells. Aromatase inhibitors are of two types: irreversible steroid analogues such as exemestane and the reversible inhibitors such as anastrozole and letrozole. Anastrozole is superior to tamoxifen in the adjuvant treatment of breast cancer in postmeno pausal patients with ER-positive tumors. Letrozole treatment affords benefit following tamoxifen treatment. Adverse effects of aromatase inhibitors may include an increased risk of osteoporosis, fatigue, and altered serum lipids. ESR1 mutations of various types are detected at increased frequency after resistance to aromatase inhibitors occurs. Fulvestrant is the prototype of a selective ER degrader. As a result of its binding, the ER is degraded and ER-dependent proliferation may diminish. Metastatic prostate cancer is treated primarily by androgen depriva tion. Orchiectomy causes responses in 80% of patients. If not accepted by the patient, testicular androgen suppression can also be induced by luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide and goserelin. These agents cause tonic stimulation of the LHRH receptor, with loss of normal pulsatile activation resulting in net decreased output of luteinizing hormone (LH) by the anterior pituitary. Therefore, as primary hormonal manipulation in prostate cancer, one can choose orchiectomy or an LHRH agonist, but not both. This path way can also be blocked by relugolix, an oral gonadotropin-releasing hormone antagonist. The addition of androgen receptor blockers, including flutamide or bicalutamide, is of uncertain additional benefit in extending overall response duration, although pretreatment with these agents before LHRH agonists is important to avoid a surge in testosterone after initial LH release. Enzalutamide also binds to the androgen receptor and antagonizes androgen action in a mechanistically distinct way. Somewhat analogous to inhibitors of aromatase, agents have been derived that inhibit

testosterone and other androgen synthesis in the testis, adrenal gland, and prostate tissue. Abiraterone inhibits 17 α-hydroxylase/C17,20 lyase (CYP17A1) and has been shown to be active in prostate cancer patients experiencing disease progression despite androgen blockade. Tumors that respond to a primary hormonal manipulation may fre quently respond to second and third hormonal manipulations. Thus, breast tumors that had previously responded to tamoxifen have, on relapse, notable response rates to withdrawal of tamoxifen itself or to subsequent addition of an aromatase inhibitor or progestin. Likewise, initial treatment of prostate cancers with leuprolide plus flutamide may be followed after disease progression by response to withdrawal of

flutamide. These responses may result from the removal of antagonists from mutant steroid hormone receptors that have come to depend on the presence of the antagonist as a growth-promoting influence. Non-Receptor-Linked Tyrosine Kinase Antagonists Table 78-7 lists currently approved non–hormone receptor pathway-directed molecularly targeted chemotherapy agents, with features of their use of import to the generalist, particularly in recognizing potential druginduced morbidities and interactions with other classes of drugs. The basis for discovery of drugs of this type was the prior knowledge of oncogene-directed pathways driving tumor growth (Fig. 78-3). In most cases, non-receptor tyrosine kinases ultimately activate signal ing through the RAF/MEK/MAP kinase cascade, in common with the receptor-linked tyrosine kinases. Diagnostic demonstration of an active non-receptor tyrosine kinase may guide selection of an agent. A repeated preclinical and clinical observation in a variety of tumor types is that mutational activation of the tyrosine kinase target induces a state of “oncogene addiction” on the part of the tumor. This then is the basis for a “synthetic lethal” effect of the kinase inhibitor with respect to tumor viability.

In hematologic tumors, the prototypic agent of this type is imatinib, which targets the ATP binding site of the p210bcr-abl protein tyrosine kinase that is formed as the result of the chromosome 9;22 translo cation producing the Philadelphia chromosome in chronic myeloid leukemia (CML). Subsequent studies have shown value of imatinib in gastrointestinal stromal tumor (GIST) and certain myeloprolifera tive disorders, driven by certain mutants of cKIT and platelet-derived growth factor receptor (PDGFR). Imatinib has lesser activity in the blast phase of CML, where the cells may have acquired additional muta tions in p210bcr-abl itself or other genetic lesions. Imatinib’s side effects are relatively limited in most patients and include hepatic dysfunction, diarrhea, and fluid retention. Rarely, patients receiving imatinib have decreased cardiac function, which may persist after discontinuation of the drug. The quality of response to imatinib enters into the decision about when to refer patients with CML for consideration of stem cell transplant approaches. Nilotinib is a tyrosine protein kinase inhibitor with activity against p210bcr-abl but with increased potency and perhaps better tolerance by certain patients. Dasatinib, another inhibitor of the p210bcr-abl oncoproteins, also has activity against certain mutant variants of p210bcr-abl that are refractory to imatinib and arise during therapy or are present de novo. Dasatinib also has inhibitory action against kinases belonging to the src tyrosine protein kinase family; this activity may contribute to its effects. The T315I mutant of p210bcr-abl is resistant to imatinib, nilotinib, bosutinib, and dasatinib; ponatinib has activity in patients with this T315Ip210bcr-abl, but ponatinib has noteworthy associated thromboembolic toxicity. Use of this class of targeted agents is thus critically guided not only by the presence of the p210bcr-abl tyro sine kinase, but also by the presence of specific mutations in the ATP binding site. Asciminib is a first-in-class non-ATP site p210bcr-abl inhibi tor that also has activity in BRC/ABL T315I mutant CML. CHAPTER 78 Principles

of Cancer Treatment Janus kinases (JAK) 1 and 2 are mutated in certain myeloprolifera tive states; cytopenias and infrequent arrhythmias infrequently com plicate the use of ruxolitinib, the prototypic JAK inhibitor. Bruton's tyrosine kinase (BTK) is an intrinsic component of B-cell antigen receptor signaling activated in many types of proliferating B cells and B-cell neoplasms. Irreversible inhibitors of BTK, including ibrutinib, acalabrutinib, and zanubrutinib, have noteworthy activity in certain lymphomas. Cytopenias and cardiac arrhythmias can occur, along with propensity to infection (indeed, the BTK was discovered as deficient in congenital hypogammaglobulinemia, presenting with repeated infec tions in childhood). Initial use of the BTK inhibitors requires consid eration of prophylaxis against tumor lysis syndrome in case of a robust lympholytic effect of the agent. If and when resistance to irreversible BTK inhibitors develops (often associated with a C481S mutation), the noncovalent inhibitor pirtobrutinib may have activity. Receptor-Linked Tyrosine Kinase Antagonists Mutated EGFR drives a significant fraction of non-small-cell lung cancers (NSCLCs). Erlotinib and gefitinib are the prototypic EGFR antagonists that, in early clinical trials, showed evidence of responses in a small

TABLE 78-7 Molecularly Targeted Agents DRUG TARGET/INDICATION ADVERSE EVENTS NOTES Non-Receptor Tyrosine Kinase Antagonists Acalabrutinib BTK/certain B-cell malignancies My, atrial fibrillation/flutter, infection CYP3A4; avoid PPIs and stagger doses with H2 blockers; irreversible BTK inhibitor Asciminib BCR/ABL/CML chronic phase after 2 TKIs or with BCR/ABL T315I My, ↑lipase, ↑amylase, HBP, hypersensitivity, cardiac events Bosutinib BCR/ABL wild-type, some mutants/CML My, ↑LFT, cardiac, R, fluid retention CYP3A4, PPI (use short-acting antacids or H2 blocker staggered with dose) Dasatinib BCR/ABL/Ph+ CML, Ph+ ALL My, pulmonary hypertension, fluid retention, ↓LVEF, ↑LFT, Der Ibrutinib As with acalabrutinib My, stomatitis, HBP, arrhythmia, TLS CY3A4, second primary malignancy Imatinib ABL, BCR/ABL wild-type, cKIT PDGFR/ CML, some ALL, certain GISTs, eosinophil, mast cell, myelodysplastic syndromes My, edema, fluid retention, ↓LVEF, ↑LFT rare liver failure, GI perforation, Der, TLS, ↓CrCl Nilotinib BCR/ABL wild-type/CML CHF, ↑LFT, ↑QT, fluid retention, ↑lipase, TLS CYP3A4, CYP2C8, CYP2C9, CYP2D6, CYP2B6; no food 2 h before, 1 h after dose; monitor electrolytes, TFTs Pirtobrutinib As with acalabrutinib My, arrhythmia, infection, hemorrhage DA-R, CYP3A4; CYP2C8, 2C19, Pgp, BCRP substrates; reversible BTK inhibitor, second primary malignancy Ponatinib T315I mutant BCR/ABL CML Clotting, ↑LFT, TLS, ↓LVEF, pancreatitis, Neu, arrhythmia PART 4 Oncology and Hematology Ruxolitinib JAK1,2/myeloproliferative disorders My, dizziness, headache DA-R, DA-H, CYP3A4 or with fluconazole >200 mg doses except with GVHD Zanubrutinib As with acalabrutinib My, hemorrhage, cardiac arrhythmias CYP3A4 Receptor-Linked Tyrosine Kinase Antagonists Afatinib Nonresistant ATP site mutated EGFR/ NSCLC D, Der, Cor, ILD; ↑LFT DA-R, DA-Pgp inhibitors, no food 2 h before, 1 h after dose Alectinib ALK rearranged/NSCLC ↑LFT, ILD, R, bradycardia, ↑CPK Administer with food; can have muscle pain, tenderness, weakness Avapritinib PDGFR mutants/GIST, mastocytosis N, edema, CNS, sleep, mood change, hallucinations Capmatinib MET + exon 14 skip/NSCLC ILD, ↑LFT, photosensitivity, pancreatitis, hypersensitivity Ceritinib ALK rearranged/NSCLC GI, ↑LFT, ↑glucose, ↑QT, bradycardia, pancreatitis Crizotinib ALK rearranged/NSCLC; inflammatory myofibroblastic tumor, anaplastic largecell lymphoma ILD, ↑LFT, ↑QT, bradycardia, ↓vision CY3A4 Dacomitinib EGFR exon 19 deletion or exon 21 L858R/ NSCLC D, Der: hold and/or dose reduce; ILD (permanently discontinue) Erdafitinib FGFR2/3 altered/urothelial cancer after Pt regimen Der, D, stomatitis, retina (ophthalmologic exam before/during) Erlotinib As with afatinib; also wild-type EGFR/ NSCLC 2nd line or pancreatic 1st line with gemcitabine Der, D, R, ILD, ↑LFT, rare microangiopathic anemia Fruquintinib Target VEGFR1,2,3/CRC HBP, hemorrhage, arterial thromboses, infection, GI

perforation, ↑LFT, proteinuria, ↓wound healing, allergic bronchospasm Futibatinib FGFR2 gene fusions/ cholangiocarcinoma Retina (ophthalmologic exam before/during) CYP3A4, Pgp substrates; ↑PO4 due to effect on FGFR2/3/ Klotho, tissue and vascular calcification Gefitinib As with afatinib Der, D, ILD, ocular keratitis, GI perforation CYP3A4; avoid with PPIs; monitor warfarin effect Gilteritinib FLT3 mutated/AML ↑LFT, ↑QT, myalgia/arthralgia, N, V, GI, Der, edema, dyspnea Infigratinib FGFR2 variants/cholangiocarcinoma Retina (ophthalmologic exam before/during) CYP3A4, avoid gastric acid reduction or stagger with H2 blockers or locally acting agents, ↑PO4 due to effect on FGFR2/3/Klotho, soft tissue including myocardial mineralization Lapatinib HER2/HER2+ breast cancer ↓LVEF, ↑LFT, N, V, D, PPED CYP3A4, CYP2C8, Pgp substrate; interaction, ILD, ↑QT Larotrectinib NTRK gene fusion without a resistance mutation/any solid tumor CNS with potential cognitive impairment; ↑LFT CYP3A4 Lorlatinib ALK rearranged/NSCLC Hyperlipidemia, AV block, CNS including seizures, mental status changes Neratinib As with lapatinib N, V, D, abdominal pain, ↑LFT CYP3A4, aggressive D prophylaxis with loperamide; avoid PPIs and stagger H2 blocker doses

CYP3A4, CYP2C9, Pgp; not an ATP site inhibitor but inhibit by allosteric mechanism binding to myristoyl pocket in BCR/ABL CYP3A4, avoid PPIs and stagger doses with H2 blockers; caution with agents with ↑QT DA-H, DA-R, CYP3A4, CYP2D6; hemorrhage at tumor site in GIST, cardiogenic shock with high eosinophil levels; monitor TFTs with thyroid replacement CYP3A4, PRES possible CYP3A4, monitor for intracranial hemorrhage CYP3A4, CYP2C9; if ILD, permanently discontinue CYP2D6; avoid PPIs, use local antacids or give 6 h before or 10 h after H2 blockers CYP2C9, CYP3A4, also organic cation transporter 2 and Pgp substrates, give 6 h before/after Pgp substrates; ↑PO4 due to effect on FGFR2/3/Klotho CYP3A4, give 1 h before/2 h after meals, avoid PPIs, stagger with H2 blockers; alter warfarin effect CYP3A4; unusual, PPED, PRES Monitor for PRES, pancreatitis, ↑Cr, eye disorders CYP3A4 with severe ↑LFT with CYP3A interactors; monitor for ILD and discontinue if occur (Continued)

TABLE 78-7 Molecularly Targeted Agents (Continued) DRUG TARGET/INDICATION ADVERSE EVENTS NOTES Osimertinib EGFR exon 19 altered or exon 21L858R or T790M mutations/NSCLC ILD, ↑QT, ↓LVEF, Cor CYP3A4 Pemigatinib FGFR2 fusion or other rearrangement/ cholangiocarcinoma FGFR1 rearranged myeloid/lymphoid neoplasms N, D, stomatitis, ↑PO4 due to effect on FGFR2/3/Klotho Pralsetinib RET mutant or fusion/NSCLC, thyroid carcinomas ILD, HBP, hemorrhage, ↑LFT, TLS, ↓wound healing Quizartinib FLT3 mutated/AML ↑QT with risk of cardiac arrest CYP3A4 Repotrectinib Target ROS1 rearranged/NSCLC CNS, ILD, ↑LFT, myalgia, ↑CPK CYP3A4, Pgp, OCs; also target TRKA,B,C Selpercatinib RET mutant or fusion/NSCLC, thyroid carcinomas ↑LFT, ↑QT, HBP, bleeding, ↓wound healing; hold 1 week prior and 2 weeks after surgery Tepotinib MET with exon 14 skipping mutations/ NSCLC ILD, ↑LFT CYP3A4, Pgp; DA-H Tucatinib As with lapatinib ↑LFT, D CYP3A4, CYP2C8 KRAS-G12C/RAF/MEK Antagonists Adagrasib KRAS G12C mutation/NSCLC N, V, D, ↑LFT, ↑QT, ILD CYP3A4, CYP2C9, CYP2D6, agents that ↑QT Binimetinib Targets MEK/BRAF V600E or V600K mutated melanoma combined with encorafenib ↓LVEF, venous thrombosis; ocular, ILD, ↑LFT, rhabdomyolysis Cobimetinib Targets MEK/BRAF V600E or V600K melanoma combined with vemurafenib; alone in BRAF V600E or V600K histiocytic neoplasms Hemorrhage, retinal ↓LVEF, Der, photosensitivity, rhabdomyolysis, ↑LFT Dabrafenib Targets BRAF in BRAF V600E or V600K mutated tumors (not CRC) with trametinib Hemorrhage, uveitis ↓LVEF, Der, ↑glucose, hemolysis if G6PD deficient, pyrexia Encorafenib Targets BRAF in BRAF V600E or V600K mutated tumors combined with binimetinib (melanoma) or CRC with cetuximab Hemorrhage, uveitis, ↑QT

CYP3A4, organic anion transporter 1B1, BCRP interactions, new malignancies, cutaneous and noncutaneous Sotorasib KRAS G12C mutation/NSCLC ↑LFT, ILD, N, V, D Avoid with PPIs and H2 receptor antagonists; if necessary, administer 4 h before or 10 h after a local antacid, avoid CYP3A4, Pgp substrates Trametinib Targets MEK/BRAF V600E or V600K mutated tumors (not colorectal) combined with dabrafenib Hemorrhage, venous thromboembolism, ↓LVEF, ILD, pyrexia, Der, ↑glucose Vemurafenib Targets BRAF in BRAF V600E or V600K mutated melanoma and ErdheimChester disease Der including Stevens-Johnson, anaphylaxis and allergic hypersensitivity, ↑QT, ↑LFT, photosensitivity, radiation recall Multikinase Antagonists Axitinib VEGFR, PDGFR, KIT/RCC HBP, hemorrhage, thrombotic events; D, other GI including GI perforation, PPED, hypothyroidism, PRES, proteinuria, ↑LFT Brigatinib ALK, EGFR/NSCLC ILD, bradycardia, HBP, visual disturbances, ↑glucose, ↑CPK Cabozantinib VEGFR2, MET, AXL, RET/RCC, HCC, certain thyroid carcinoma HBP, hemorrhage, thrombotic events, D, other GI including fistula, perforation, wound healing, PRES, PPED, proteinuria, ONJ Capivasertib Target PIK3CA/AKT1/PTEN- axis; BC-HR(+) with mutation in pathway Hypersensitivity reactions, Der, ↑glucose, pneumonitis, ILD, D Entrectinib NRTK gene fusion/any solid tumor; ROS1 gene alteration/NSCLC ILD, ↑LFT, photosensitivity, ↓LVEF, CNS effect, skeletal fractures; hyperuricemia, ↑QT, Fedratinib JAK2, FLT3, RET/myeloproliferative diseases My, N, V, D, ↑LFT pancreatitis, encephalopathy: check thiamine levels prior, replete if deficient Lenvatinib VEGFR1/2/3, FGFR1/2/3/4, PDGFRα, KIT, RET/thyroid, RC, HCC, endometrial cancer HBP, ↓LVEF, bleeding, arterial/venous clots, RF, ONJ, proteinuria, ↑LFT, GI including D, fistula/perforation, ↓wound healing, ↑QT, ↓Ca2+, PRES, ↓TFT Midostaurin FLT3 mutated/AML newly diagnosed, mast cell neoplasms ILD; N, D CYP3A4; many other protein kinase targets in addition to FLT3

CYP3A4, retinal detachment: ophthalmologic exam with ocular tomography before and every 2–3 months during treatment CYP3A4, Pgp Avoid with antacids, but take if not avoidable with food if PPI or stagger with other antacid, CYP3A, CYP2C8 DA-H CHAPTER 78 CYP3A4, new malignancies, cutaneous and noncutaneous Principles of Cancer Treatment CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2B6, new malignancies, cutaneous and noncutaneous Colitis with GI perforation, ocular including retinal vein occlusion, new malignancies, cutaneous and noncutaneous Dupuytren’s contracture and plantar fascial fibromatosis has occurred; usually combined with cobimetinib in melanoma; CYP3A4, CYP1A2, CYP2D6, new primary cutaneous and noncutaneous neoplasms DA-H, CYP3A4/5 CYP3A4, decreased hormonal contraceptive effectiveness CYP3A4 CYP3A4, CYP2C9, BCRP substrates CYP3A4, ophthalmologic exam if vision change CYP3A4, CYP2C19 DA-H, DA-R (Continued)

TABLE 78-7 Molecularly Targeted Agents (Continued) DRUG TARGET/INDICATION ADVERSE EVENTS NOTES Pazopanib VEGFR 1/2/3, KIT, PDGFR, and FGFR/ RCC soft tissue sarcoma (not GIST or adipocytic) D, HBP; arterial and venous thrombosis ±

embolism, ↑QT, hemorrhage, ↑LFT potentially severe/fatal; GI perforation or fistula; proteinuria, ↓TFT, ↓LVEF, PRES, ILD, thrombotic microangiopathy Regorafenib VEGFR1/2/3, KIT, RET, PDGFR-α/β, FGFR1/2, TIE2, DDR2, Trk2A, Eph2A, RAF1, BRAF, BRAF V600E, SAPK2, PTK5, and ABL/CRC, GIST ↑LFT potentially severe/fatal; hemorrhage, thromboses, PPED, Der, HBP, ↓LVEF, ↑QT, GI perforation Sorafenib VEGFR2, VEGFR3, PDGFRβ, Flt3, KIT, RAF1, BRAF/RCC, HCC, differentiated thyroid carcinoma D, ↑LFT potentially severe/fatal; hemorrhage, PPED, Der, HBP, ↓LVEF, ↑QT, GI perforation Sunitinib VEGFRs; PDGFR, RET, KIT; other protein kinases/RCC, pancreatic

neuroendocrine, GIST HBP, ↑LFT potentially severe/fatal; hemorrhage, GI perforation, CHF, altered TFTs, ONJ, ↓wound healing, proteinuria, R Vandetanib VEGFR, RET, EGFR/medullary thyroid cancer D, Der, HBP, ↑QT, thromboses, ↓LVEF, fistulas, ILD, ONJ, proteinuria, PRES Cyclin-Dependent Kinase (CDK) Inhibitors Abemaciclib CDK4/6/HR+ BC D, My, ↑LFT, venous thromboembolism, ILD CYP3A4, avoid concomitant use of ketoconazole Palbociclib CDK4/6/HR+ BC D, My, stomatitis, ILD, D CYP3A4 Ribociclib CDK4/6/HR+ BC Der, ILD, ↑QT, ↑LFT, My CYP3A4, agents known to ↑QT PART 4 Oncology and Hematology Protein Homeostasis Modulators Bortezomib Proteasome inhibitor/multiple myeloma, mantle cell lymphoma Neu, N, V, D, C, ↓BP, My, ILD, ↑LFT worsening cardiac disease Carfilzomib Proteasome inhibitor/multiple myeloma ↓LVEF, myocardial ischemia, R, TLS, pulmonary including ARDS, ILD, HBP, IR*, thrombosis, hemorrhage, PRES, thrombocytopenia, thrombotic microangiopathy, ↑LFT potentially severe Ixazomib Proteasome inhibitor/multiple myeloma relapsed, not as maintenance Thrombocytopenia, N, V, D, C, Neu, edema, Der, thrombotic microangiopathy, ↑LFT Nuclear Export Inhibitor Selinexor Targets exportin 1/multiple myeloma, certain DLBCLs My, N, V, D, anorexia, ↓Na+, CNS, cataract development or progression Chromatin-Modifying Epigenetic Modulators DNA Hypomethylating Agents Azacytidine Target DNA methyltransferase/ myelodysplastic syndromes, AML My, ↑LFT, TL, CNS Monitor if renal impairment, more N, V, D if SC administration Decitabine As with azacytidine My Combined with cedazuridine (a cytidine deaminase inhibitor) in an oral regimen Histone Deacetylase Inhibitors Belinostat Peripheral T-cell lymphoma, relapsed or refractory My, ↑LFT, TLS, N, V Panobinostat Multiple myeloma, relapsed or refractory My, hemorrhage, ↑LFT, ↓Na+, ↓K+, ↓PO4, ↑Cr CYP3A4, CYP2D6, avoid agents that ↑QT Romidepsin CTCL after one systemic therapy My, ↑QT CYP3A4, alter warfarin effect, may ↓ effectiveness of oral contraceptives Vorinostat CTCL after two systemic therapies My, N, V, D, venous thrombosis, ↑glucose Monitor with mild or moderate liver disease Histone Methyltransferase Inhibitors Tazemetostat Target EZH2 mutant or nonmutant/ epithelioid sarcoma, certain follicular lymphomas N, V, C, abdominal pain CYP3A4, increased risk of secondary malignancies (MDS, AML, lymphomas) Transcription Factor Modulation Arsenic trioxide Target PML-RARα and redox homeostasis/t(15;17) acute promyelocytic leukemia ↑QT, hypersensitivity APL differentiation syndrome: with pulmonary dysfunction/infiltrate, pleural/pericardial effusion, fever, treat with dexamethasone ± hydroxyurea Belzutifan Target HIF2α/von Hippel-Lindau (VHL) disease–associated RCC, CNS hemangioblastomas, GI neuroendocrine tumors, non-VHL RCC after PD-1, VEGFR inhibitor Anemia, hypoxia, N, ↑Cr, ↑glucose CYP2C19, UGTB17 Glasdegib Targets smoothened receptor in hedgehog pathway/AML ↑QT CYP3A4, transmission to potentially pregnant partner through semen or to blood product recipient

CYP3A4, CYP22D6, CYP2C8 interaction; use with simvastatin increases the risk of ALT elevations and should be undertaken with caution; avoid with PPIs or H2 blocker, stagger with other antacid doses CYP3A4, impaired TSH suppression in thyroid cancer As with regorafenib CYP3A4, rare ↑QT, rare TLS in RCC and GIST with high tumor burden CYP3A4 Rare TLS, PRES Administer after a hemodialysis procedure DA-R, DA-H, CYP3A4 Advise against driving or dangerous equipment operation if CNS altered (Continued)

TABLE 78-7 Molecularly Targeted Agents (Continued) DRUG TARGET/INDICATION ADVERSE EVENTS NOTES Nirogacestat Targets γ-secretase to inhibit Notch signaling/desmoid tumor D (can be severe), ovarian dysfunction, ↑LFTs, PO4 and K+ abnormalities Sonidegib Targets smoothened receptor in hedgehog pathway/basal cell carcinoma locally advanced or metastatic Musculoskeletal adverse events with ↑CPK, potential R, N, V, D Tretinoin Target PML-RARα/t(15;17) acute

promyelocytic leukemia Der including cheilitis, skin dryness; ↑ intracranial pressure; ↑lipids, ↑LFT, usually resolve Vismodegib As with sonidegib Musculoskeletal adverse events, N, V, D, C Transmission to potentially pregnant partner through semen or to blood product recipient Apoptosis Modulation Venetoclax Targets BCL2/CLL, SLL; AML + azacytidine, decitabine, or low-dose cytarabine My, D, TLS CYP3A4, stagger with Pgp substrates, no live attenuated vaccines prior to, during, or after venetoclax treatment Metabolism Modulation: mTOR Inhibitors/PI Kinase/IDH Inhibitors Alpelisib PIK3CA mutated/HR+HER2– BC Der, hypersensitivity, ↑glucose, ILD, D CYP3A, CYP2C9, BCRP substrates Copanlisib PI3Kα,δ/FL My, HBP, noninfectious pneumonitis, ↑glucose, Der Duvelisib PI3Kδ,γ/CLL, SLL, FL My, infection, D, colitis, Der, pneumonitis, ↑LFTs Enasidenib IDH2 mutated/AML N, V, D, ↑LFTs AML differentiation syndrome with pulmonary dysfunction/infiltrate, pleural/pericardial effusion, fever treat with dexamethasone ± hydroxyurea Everolimus mTOR/RCC, tuberous sclerosis– associated neoplasms, HR+ BC, neuroendocrine, pancreatic, lung, GI NOT functional carcinoid My, noninfectious pneumonitis, infections, hypersensitivity reactions, R, impaired wound healing, ↑glucose, ↑lipids, stomatitis Ivosidenib IDH1 mutated/AML, cholangiocarcinoma, MDS ↑QT, Guillain-Barré syndrome CYP3A4, QT-prolonging agents; AML differentiation syndrome requiring corticosteroid treatment Idelalisib PI3Kδ/non-first-line CLL, SLL, FL Fatal or serious ↑LFTs, D, colitis with GI perforation, pneumonitis, infection, Der, hypersensitivity Olutasidenib IDH1/AML ↑LFTs CYP3A4, differentiation syndrome requiring corticosteroid ± hydroxyurea treatment Sirolimus protein bound particles mTOR/perivascular epithelioid cell tumor (PEComa) My, stomatitis, infection, ↓K+, IR, ↑glucose, ILD, hemorrhage, male infertility Temsirolimus mTOR/RCC Hypersensitivity, ↑LFTs, infection, ILD, stomatitis, thrombocytopenia, N, ↑glucose, ↑lipids, ↓wound healing, GI perforation, R ± proteinuria Poly-ADP Ribose Polymerase (PARP) Inhibitors Niraparib Ovarian, fallopian tube, or primary peritoneal cancer with good response to Pt My, N, V, D, HBP, PRES MDS Olaparib Ovarian: as with niraparib also with various BRCA or HRR mutations; BC mutant BRCA, HER2–; pancreatic mutant BRCA with good response to Pt; prostate with BRCA or HRR mutations My, N, stomatitis, DVT ± PE, rare ILD MDS, CY3A4 Rucaparib As with niraparib; prostate BRCA mutated after hormone and after taxane My, stomatitis, N, V, D, ↑LFTs MDS Talazoparib BC BRCA mutated HER2–; prostate cancer, castrate-resistant HRR mutation(+), with enzalutamide My, N, V, D, ↑LFTs MDS Miscellaneous 177Lu-dotatate Target somatostatin receptor (SSR)/ gastroenterohepatic neuroendocrine tumors (SSR)+ My, R, ↑LFTs, IR, Neuroendocrine hormonal crisis including flushing, diarrhea, hypotension, bronchoconstriction; secondary MDS, risks from radiation exposure 177Lu-vipivotide tetraxetan Target prostate-specific membrane antigen (PSMA)/refractory prostate cancer My, R Temporary or permanent infertility, risks from radiation exposure

CYP3A4; avoid PPIs and stagger doses with H2 blockers; nonmelanoma skin cancers; Der: monitor before and during treatment As with glasdegib As with arsenic trioxide; also headache, visual changes may indicate ↑intracranial pressure; check for papilledema CYP3A4 CHAPTER 78 CYP3A4 Principles of Cancer Treatment CYP3A4, Pgp substrates, angioedema with concomitant ACE inhibitors, consider alcohol-free mouthwash when starting treatment; risk of reduced efficacy of vaccination CYP3A4, not with bendamustine or rituximab CYP3A4, avoid live vaccines DA-H, CYP3A4 (Continued)

TABLE 78-7 Molecularly Targeted Agents (Continued) DRUG TARGET/INDICATION ADVERSE EVENTS NOTES Tagraxofusp-erzs Targets CD123 (IL-3 receptor)/blastic IR*, ↑LFTs, VLS Delivers a fragment of diphtheria toxin plasmacytoid dendritic cell neoplasm Ziv-aflibercept Targets VEGF by solubilized

VEGFR/CRC with chemotherapy after an oxaliplatin regimen ↓Wound healing with fistula, GI perforation, hemorrhage, HBP, DVT, arterial thromboembolism, proteinuria, PRES Note: Data abstracted in part from publicly available U.S. Food and Drug Administration label. All agents in this class have the potential for prominent embryofetal toxicity; use without contraception by female patients of childbearing potential is not recommended. Effective contraception for female partners who are of childbearing potential of patients undergoing treatment should also be considered; use during lactation is also not recommended. Gene products are in capital letters; genes are italicized in capitals. Indications and events of prominent general medical importance include the following: ACE, angiotensin-converting enzyme; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ARDS, acute respiratory distress syndrome; AV, atrioventricular; BC, breast cancer; BCRP, breast cancer resistance protein; BP, blood pressure; BRCA, breast cancer gene; BTK, Bruton's tyrosine kinase; C, constipation; CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CNS, can include altered sensorium, cortical and cerebellar signs, dysarthria, altered seizure threshold; Cor, corneal keratopathy, consider pretreatment ophthalmologic exam with prophylactic lubricating eyedrops ± ocular steroids; CRC, colorectal cancer; CrCl, creatinine clearance; CTCL, cutaneous T-cell lymphoma; CYP___, interaction with drugs metabolized by the indicated cytochrome(s) P450; D, diarrhea; DA-H, dose adjust for hepatic dysfunction; DA-R, dose adjust for renal dysfunction; Der, dermatologic toxicity; DLBCL, diffuse large B-cell lymphoma; DVT, deep vein thrombosis; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FL, follicular lymphoma; GIST, gastrointestinal stromal tumor; GVHD, graft-versus-host disease; H2, histamine receptor antagonist; HBP, high blood pressure; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; HR, hormone receptor; HUS, hemolytic-uremic syndrome; IDH, isocitrate dehydrogenase; ILD, interstitial lung disease; IR, infusion reaction; IR*, infusion reaction prophylaxis specifically recommended; LFT, liver function tests; LVEF, left ventricular ejection fraction monitor echocardiogram; MDS, myelodysplastic syndrome; MET, hepatocyte growth factor; My, anemia, decrease in white blood cells, platelets, with risk of neutropenic fever, hemorrhage, therefore dose reduce or hold dose for decreased neutrophil or platelet counts unless marrow infiltrated by drug-responsive tumor; N, nausea; Neu, peripheral neuropathy; NSCLC, non-smallcell lung cancer; OC, oral contraceptive; ONJ, osteonecrosis of the jaw; PDGFR, platelet-derived growth factor receptor; PE, pulmonary embolism; Pgp, P-glycoprotein drug resistance protein; Ph, Philadelphia chromosome; Plm, pulmonary; PML, progressive multifocal leukoencephalopathy risk; PPED, palmar-plantar erythrodysesthesia (i.e., hand-foot syndrome); PPI, proton pump inhibitor; PRES, posterior reversible leukoencephalopathy syndrome; Pt, platinating agent; PT, prothrombin time; PTT, partial thromboplastin time; ↑QT, increase of QT interval needs pre- and intratreatment electrocardiogram monitoring and normalizing K+, Mg2+, ionized Ca2+; R, renal injury possible; RCC, renal cell carcinoma; ROS1, receptor tyrosine kinase 1; SLL, small lymphocytic lymphoma; TFT, thyroid function test; TKI, tyrosine kinase inhibitor; TLS, risk of tumor lysis syndrome if brisk response; TOPO___, agent targets the indicated topoisomerase; TSH, thyroid-stimulating hormone; UGT___, drug metabolism by UDPglucuronosyltransferase of the indicated genotype; V, vomiting; VEGFR, vascular endothelial growth factor receptor; Ves, extravasation injury possible; VLS, vascular leak syndrome; VOD, veno-occlusive liver disease. PART 4 Oncology and Hematology fraction of patients with NSCLC. Subsequent studies by clinical oncol ogists in an effort to understand the basis of these excellent responses found that the probability of response to the agents was markedly increased in patients with an activating EGFR mutation, and current practice

now routinely profiles patients with NSCLC for the presence of sensitizing mutations of EGFR. Side effects were generally accept able, consisting mostly of acneiform rash (treated with glucocorticoid creams and clindamycin gel) and diarrhea. Patients with activating mutations who initially responded to gefitinib or erlotinib but who then had progression of the disease then acquired additional mutations in the enzyme, analogous to the mutational variants responsible for imatinib resistance in CML. Subsequent generations of EGFR antago nists have activity against more uncommon mutants (osimertinib) or a biochemically irreversible mechanism (dacomitinib). Mutated anaplastic lymphoma kinase (ALK) and activated RET oncogene likewise drive distinct fractions of NSCLCs. Alectinib, ceri tinib, crizotinib, and lorlatinib target ALK, but have prominent adverse cardiac, metabolic, and, in the case of lorlatinib, pulmonary events. Selpercatinib targets RET in NSCLCs (and thyroid cancers) but also with the chance of cardiac and liver toxicity. Repotrectinib is active in ROS1 mutant NSCLC. HER2-driven breast cancers may be usefully treated with lapatinib; diarrhea and cardiac dysfunction can occur. Neratinib or tucatinib may also be useful in HER2-positive breast cancers after trastuzumab has ceased to be of value; diarrhea and liver toxicity also require monitor ing and management. Alteration of fibroblast growth factor (FGF) signaling can contrib ute to the growth of urothelial carcinomas and cholangiocarcinomas. Erdafitinib and pemigatinib, respectively, may be of utility with care ful attention to ocular toxicity and hyperphosphatemia; the latter is an “on-target” toxicity of disrupting FGF receptor signaling in the kidney. Likewise, gilteritinib is active against the FMS-like tyrosine kinase-3 (FLT3) mutated in a fraction of poor-prognosis (treated by conventional chemotherapy) acute myeloid leukemias (AMLs). Car diac, hepatic, gastrointestinal, and neurologic adverse events can occur, along with “differentiation” of the AML cells with cytokine elaboration and pulmonary side effects, requiring management with steroids and potentially hydroxyurea. The neurotropic tyrosine kinase receptor (NRTK) undergoes trans location with fusion to a variety of different partner genes to produce

Administer over 1 h, not as push or bolus a family of chimeric proteins in a small fraction of a variety of solid tumors. Larotrectinib and entrectinib may be quite useful in manag ing these tumors; indeed, these agents are exemplary of “histology agnostic” agents, where the utility of the drug is not tied to a particular histologic diagnosis, but to the possession of a specific NRTK gene alteration. Neurotoxicity, a long half-life of the agents, and hepatotoxic adverse events are of concern. Neuroregulin 1 (produced by the NRG1 gene) undergoes gene fusions to produce activators of HER family heterodimer signaling, including HER3 and HER4; afatinib covalently binds to all HER family members and has activity in patients with NRG1 gene fusions. RAF/MEK Pathway Antagonists The RAS proto-oncogene family members (including HRAS, KRAS, and NRAS) act as “switches” to bind GTP in response to activation of receptor tyrosine kinases; RAS-GTP activates the RAF proto-oncogene–derived serine-threonine kinase. RAS mutations of various types result in persistent activation of RAS isoforms, resulting in hyperactivation of RAF and “downstream” kinases, including MEK and MAPK. Sotorasib is a first-in-class inhibi tor of KRAS G12C signaling that in early clinical reports has evidence of effecting stable disease in patients with a variety of neoplasm his tologies bearing that mutation, with fewer actual responses. Adagrasib also targets KRAS-G12C with a distinct pharmaceutical profile. Neither sotorasib nor adagrasib has activity against wild-type or other RAS mutants, but their discovery marked a milestone, encouraging continu ing efforts to produce RAS-directed therapeutics. The BRAF V600E mutation drives a substantial fraction of mela nomas and certain NSCLCs and has been detected in certain thyroid tumors, colorectal tumors, hairy cell leukemias, and unusual gliomas. BRAF inhibitors such as dabrafenib, vemurafenib, and encorafenib have activity as single agents in many such tumors but

are usually most active when co-administered as “doublets” with the MEK inhibitors trametinib, cobimetinib, and binimetinib, respectively, to promote “shutdown” of RAF/MEK signaling at more than pathway member. Cutaneous adverse events including generally indolent cutaneous second neoplasms, and thromboembolic, cardiac, and ocular toxicity can occur. Multikinase Inhibitors Agents in this class also target specific macromolecules promoting the viability of tumor cells. They are “small-molecule” ATP site-directed antagonists that inhibit more than

one protein kinase and may have value in the treatment of several solid tumors. Drugs of this type with prominent activity against the VEGFR tyrosine kinase have activity in renal cell carcinoma. Sorafenib is a VEGFR antagonist also with activity against the RAF serine-threonine protein kinase, and regorafenib is a closely related drug with value in relapsed advanced colon cancer. Pazopanib also prominently targets VEGFR and has activity in renal carcinoma and soft tissue sarcomas. Sunitinib has anti-VEGFR, anti-PDGFR, and anti-KIT activity. It causes prominent responses and stabilization of disease in renal cell cancers and GISTs. Side effects for agents with anti-VEGFR activity, similar to those of the anti-VEGF antibody bevacizumab, prominently include hypertension, proteinuria, and, more rarely, bleeding and clot ting disorders, perforation of scarred gastrointestinal lesions, and pos terior leukoencephalopathy, probably reflecting CNS vascular damage. Also encountered are fatigue, diarrhea, and hand-foot syndrome, with erythema and desquamation of the distal extremities, in some cases requiring dose modification, particularly with sorafenib. Other agents in this class include agents such as brigatinib (clinical activity in ALK-dependent NSCLC, but also with anti-EGFR action), entrectinib (clinical activity in NTRK fusion protein diseases, but also in ROS-mutated NSCLC), and fedratinib (clinical activity in myelo proliferative neoplasms, but with RET activity in addition to JAK2 and FLT3 antagonism). Agents with anti-RET activity are useful in certain differentiated thyroid cancers and RET-fusion NSCLC. Cyclin-Dependent Kinase Inhibitors Cyclin-dependent kinases (CDKs) are activated as the result of oncogene pathway activ ity, and CDK4 and CDK6 phosphorylate the retinoblastoma (RB) tumor-suppressor gene to allow entry into S-phase. Palbociclib, abe maciclib, and ribociclib, selective inhibitors of CDK4 and CDK6, have noteworthy activity in advanced breast cancers also expressing the ER, usually in conjunction with continued efforts to suppress ER signaling, and frequently in conjunction with mammalian target of rapamycin (mTOR) inhibitors. Further clinical investigations in other RB intact tumors may broaden their role. Protein Homeostasis Modulators The proteasome is a mac romolecular complex that degrades misfolded proteins tagged for removal by ubiquitin ligases. Proteasome inhibitors were originally designed as potential anti-inflammatory agents owing to proteasome activity to produce inflammatory cytokines but had unexpected anti proliferative activity in a variety of cell types. Proteasome inhibitors have clinical utility in myeloma and lymphoma, where unbalanced synthesis of immunoglobulin components can accumulate after pro teasome inhibitor treatment and induce apoptosis or starve cells for amino acids, inducing autophagy. Boronic acid proteasome inhibi tors, including bortezomib and ixazomib, cause thrombocytopenia, gastrointestinal dysfunction, and neuropathy. Carfilzomib is a distinct chemotype with attenuated neuropathy but increased incidence of infusion reactions and cytokine release, with attendant risk of cardio pulmonary adverse events. Exportin 1 is a nuclear membrane transport protein that is responsi ble for normal exit and entry of a variety of nuclear proteins. Selinexor is an inhibitor of exportin action, resulting in abnormal nuclear accu mulation of, for example, tumor-suppressor gene products or needed export of other products, such as oncogene products. Useful clinical activity has been seen in myeloma and diffuse large B-cell lymphomas including those arising from previously treated indolent lymphomas. Cytopenias, gastrointestinal

distress, and hyponatremia are features of its clinical use. Chromatin-Modifying Agents Gene function is altered not only by mutation of DNA structure but also by “epigenetic” mechanisms that alter the capacity of DNA to be transcribed or interact with regu latory proteins in the nucleus including transcription factors. Initial epigenetic approaches to modulate gene expression extended from the observation that 5′azacytidine and decitabine are misincorporated into DNA and then scavenge DNA methyl transferase to disable DNA methylation of cytosine near gene promoter regions and thus alter their transcription. This “hypomethylation” causes differentiation of AML

cells with notably less host toxicity than higher concentrations of these agents or indeed cytosine arabinoside, which does not have prominent hypomethylation activity.

Histone deacetylase inhibitors alter the histone protein “packing” density of chromatin and induce global changes in expression of cell cycle regulatory proteins. Vorinostat, belinostat, and romidepsin are useful in cutaneous and peripheral T-cell lymphomas; panobinostat has activity in multiple myeloma. The agents are generally well toler ated but with the potential for cytopenias. The histone methyltrans ferase inhibitor tazemetostat is a first-in-class inhibitor of histone methyltransferase with unique activity in epithelioid sarcoma owing to its modulation of transcriptional mechanisms unique to that tumor and, recently, in certain follicular lymphomas. Transcription Factor Modulation Distinct from hormone receptor agonists and antagonists, which as previously described mod ulate transcription factor activity by affecting the binding of endog enously produced ligands, such as androgens and estrogens, tretinoin (all-trans-retinoic acid) binds to the fusion protein PML-RARα pro duced as a result of the t(15,17) chromosomal translocation that under lies the pathogenesis of most cases of acute promyelocytic leukemia (APL). PML-RARα functions as transcriptional co-repressor of normal granulocyte maturation; inhibiting the repressor leads to clinical value in the curative treatment of APL. Adverse events include typical symp toms of hypervitaminosis A, including skin dryness, cheilitis, increased intracranial pressure, and the development of a “leukemia differentia tion syndrome” marked by fever and lung and other organ infiltration by newly differentiated leukocytes, which usually responds to gluco corticoids and hydroxyurea but can be life-threatening. Significantly, the coagulopathy of APL is attenuated. Arsenic trioxide nonspecifically affects PML-RARα and other targets by a redox mechanism, contrib uting to APL treatment with tretinoin regimens, but with a narrow therapeutic index particularly related to increase of the QT interval, which must be monitored during treatment, while also being carefully attentive to K+, Mg2+, ionized Ca2+, and other drugs that can alter QT. CHAPTER 78 Principles of Cancer Treatment Belzutifan is a novel agent that antagonizes directly the action of hypoxia-inducible factor 2 (HIF2) α, activated in von Hippel-Lindau (VHL) disease–related neoplasms and many sporadic clear cell renal carcinomas through loss of the VHL ubiquitin ligase tumor-suppressor gene. It is safe, but anemia and hypoxemia may occur. The sonic hedgehog factor pathway is regulated by the WNT ligands acting on smoothened receptors, named in reference to Drosophila mutants in which the pathway was originally revealed. In humans, the pathway acts during embryonic and fetal life and in certain neoplasms, and mediates effects on transcription through Gli proteins. Hedgehog pathway inhibitors sonidegib and vismodegib are useful in nonsurgi cally treatable cutaneous basal cell carcinomas, and glasdegib is active in certain AMLs where the pathway is active (see Table 78-7). The notch pathway was likewise first noted in Drosophila and acts in metazoans to signal cell position and motion. Notch receptors respond to their ligands by undergoing endocytosis and processing by a γ-secretase, followed by translocation to the nucleus, and function as specific gene transcription factors. The notch pathway

has long been known to be active in hematopoietic tumors, but observation has shown confirmed activity in desmoid tumors, inflammatory mesenchymal tumors with poor evidence of control by conventional cytotoxic agents, by nirogace stat, the first γ-secretase inhibitor to enter clinical practice. Cancer Cell Metabolism Modulators Oncogenic transforma tion causes a “rewiring” of cellular metabolism away from oxidative phosphorylation to glycolysis (historically defined as the “Warburg effect” of aerobic glycolysis in animal and human tumors) with atten dant tolerance of hypoxia and production of metabolites important for sustaining cell proliferation. Recent clinical studies have defined clinical value from inhibitors of the cell lipid membrane localized phos phoinositide-3 (PI3) kinase, mTOR, and extra-mitochondrial isocitrate dehydrogenase isoforms 1 and 2. mTOR is a kinase whose inhibition was originally discovered as the basis for activity by the immunosuppressant rapamycin, isolated from a soil bacterium (originally obtained from Rapa Nui), which had

evidence of antitumor activity in animals as well as decreased T-cell proliferation. Sirolimus as a protein-bound formulation is used for certain soft tissue tumors. Temsirolimus and everolimus are mTOR inhibitors with activity in renal cancers. They produce stomatitis and fatigue; some hyperlipidemia (10%) and myelosuppression (10%); and rare lung toxicity and immunosuppression in regimens used clinically. Everolimus is also useful in patients with hormone receptor–positive breast cancers displaying resistance to hormonal inhibition and in certain neuroendocrine and brain tumors, the latter arising in patients with sporadic or inherited mutations in the pathway activating mTOR. PI3 kinase is activated by numerous oncogenic tyrosine kinases to ultimately cause a cascade of metabolic alterations including increased glucose uptake and activation of mTOR isoforms, which selectively increase translation efficiency of key regulators of cell cycle progression and protein synthetic capacity.

Isoform-specific PI3 kinase inhibitors are of increasing importance in breast cancers with mutated PI3Kα (alpelisib; hyperglycemia and cutaneous eruptions can occur) or owing to selective use of PI3Kδ by lymphoid tissues in lymphomas (idelalisib, copanlisib, and duvelisib). Isocitrate dehydrogenase (IDH) inhibitors (ivosidenib specific for IDH1 and enasidenib specific for IDH2) have activity in tumors with IDH mutants (AML, cholangiocarcinomas) that generate the “onco metabolite” 2-hydroxyglutarate, which alters DNA and histone meth yltransferase activity. The drugs thus function indirectly as epigenetic chromatin modulating agents through effects on cellular metabolism. Vorasidenib, an IDH1/2 inhibitor with very favorable distribution across the blood-brain barrier, is in very advanced stages of develop ment for certain brain tumors with IDH mutations. DNA Repair Pathway Modulators DNA repair systems act physiologically to lessen the impact of environmental genomic damag ing agents and influence the susceptibility to certain chemotherapy agents. DNA repair enzyme mutations underlie inherited cancer sus ceptibility syndromes such as mutated BRCA tumor-suppressor gene– associated breast and ovarian cancers, among others. PART 4 Oncology and Hematology Laboratory investigations revealed that poly-ADP ribose poly merase (PARP) acts as a synthetic lethal gene with mutations in the homologous recombination repair pathway, including the BRCA gene. PARP responds to detection of DNA lesions by creating chains of poly-ADP, which serve as scaffolds for the localization of DNA repair proteins still active even with mutated BRCA isoforms. However, with out PARP activity, the scaffolds cannot form, and the DNA damage becomes lethal. This observation immediately suggested the potential utility of PARP inhibitors (e.g., olaparib) as treatments potentially useful for BRCA-induced tumors. Recently, PARP inhibitor utility has been extended to tumors that do not

harbor BRCA mutations but have given evidence of responding to platinum drugs, as a way of extending the useful effect of the chemotherapy treatment. This finding under scores the likelihood that sensitivity to DNA-directed cytotoxic drugs on the part of a tumor is at least in part related to the drugs' ability to take advantage of a sensitizing effect of a tumor's endogenous DNA repair capacity. Miscellaneous Targeted Therapies High-affinity binding to receptors on tumor cells can target toxic agents besides drugs to tumor cells, exemplified by the IL-3–diphtheria toxin fusion protein tagraxofusp-erzs, targeting the IL-3 receptor (CD123) and useful in blastic plasmacytoid dendritic cell neoplasms (Table 78-7). Capillary leak syndrome induced due to adventitious "off-target" delivery of the toxin component requires careful monitoring of fluid balance to avoid pulmonary dysfunction in particular. The somatostatin receptor conjugated to a chelate of 177-lutetium can deliver targeted radiation to gastroenterohepatic endocrine neoplasms expressing that receptor. Acutely, release of vasoactive and locally acting hormonal components from dying tumor cells and myelosuppression can occur. Renal dam age and the risk of second hematopoietic tumors can complicate con tinuing use of the agent. Likewise, 177-lutetium can be delivered via conjugation to a ligand of prostate-specific membrane antigen (PSMA) in the treatment of hormone-resistant prostate cancer. Ziv-aflibercept is not an antibody, but a solubilized VEGF receptor VEGF binding

domain, and therefore may have a distinct mechanism of action from bevacizumab but with similar side effects. RESISTANCE TO CANCER TREATMENTS Resistance mechanisms to the conventional cytotoxic agents were initially characterized in the late twentieth century as defects in drug uptake, metabolism, or export by tumor cells. The multidrug resistance (MDR) gene, encoding P-glycoprotein (Pgp), is prototypic of trans port proteins that efficiently excrete many drugs from tumor cells; no clinically useful modulator of this process has yet emerged. Drug-

metabolizing enzymes such as cytidine deaminase are upregulated in resistant tumor cells, and this is the basis for so-called "high-dose cytarabine" regimens in the treatment of leukemia. Another resistance mechanism defined during this era involved increased expression of a drug's target, exemplified by amplification of the dihydrofolate reduc tase gene, in patients who had lost responsiveness to methotrexate, or mutation of topoisomerase II in tumors that relapsed after topoisom erase II modulator treatment. A second class of resistance mechanisms involves loss of the cellular apoptotic mechanism activated after the engagement of a drug's target by the drug. This occurs in a way that is heavily influenced by the biol ogy of the particular tumor type. For example, decreased alkylguanine alkyltransferase expression defines a subset of glioblastoma patients with the prospect of enhanced benefit from treatment with temozolo mide but has no value in predicting benefit from temozolomide in epithelial neoplasms. Likewise, ovarian cancers resistant to platinating agents have decreased expression of the proapoptotic gene BAX. A related class of resistance mechanisms emerged from sequencing of the targets of agents directed at oncogenic kinases, revealing mutated targets, as described previously (e.g., p210bcr-ablT315I). This reflects the phenomenon of tumor heterogeneity with distinct populations of sub clones that arise in a tumor during the process of carcinogenesis. These subclones share to variable degrees mutations that may promote the growth of some subclones but that are absent or are no longer relevant to the growth of other subclones. This general mechanism of resis tance is emerging as a basis for limited value of clinical responses to sotorasib, where sequencing of tumor DNA after clinical resistance has documented "treatment-emergent" mutations in KRAS itself as well as alterations in other proto-oncogenes and their targets. Really useful targeted therapies address a

“driver mutation” present in all subclones. Finally, other mechanisms of resistance to targeted agents include the upregulation of alternate means of activating the pathway targeted by the agent. Thus, melanomas initially responsive to BRAF V600E antagonists such as vemurafenib may reactivate RAF signaling by employing variant isoforms that can bypass the drug. Likewise, inhibi tion of HER2/neu signaling in breast cancer cells can lead to the emer gence of variants with distinct ways of activating downstream effectors such as PI3 kinase. Mechanisms of resistance to immune checkpoint inhibitors such as nivolumab and ipilimumab have not been well defined, but initial characterization of tumors resistant to these agents demonstrates alterations in antigen presentation pathways, concordant with the basis for checkpoint inhibitor action. SUPPORTIVE CARE DURING CANCER TREATMENT ■ ■MYELOSUPPRESSION Most cytotoxic chemotherapeutic agents affect bone marrow function. Polymorphonuclear leukocytes (PMNs; t1/2 = 6–8 h), platelets (t1/2 = 5–7 days), and red blood cells (RBCs; t1/2 = 120 days) have most, less, and least susceptibility, respectively, to usually administered cytotoxic agents. Maximal neutropenia occurs 6–14 days after conventional doses of anthracyclines, antifolates, and antimetabolites. Alkylating agents differ from each other in the timing of cytopenias. Nitrosoureas, DTIC, temozolomide, and procarbazine can display delayed marrow toxicity, first appearing 6 weeks after dosing. Complications of myelosuppression relate to the missing cells’ func tion. Febrile neutropenia refers to the clinical presentation of fever

TABLE 78-8 Indications for the Clinical Use of G-CSF or GM-CSF Preventive Uses With the first cycle of chemotherapy (so-called primary CSF administration) Not needed on a routine basis Use if the probability of febrile neutropenia is ≥20% Use if patient has preexisting neutropenia or active infection Age >65 years treated for lymphoma with curative intent or other tumors treated by similar regimens Poor performance status Extensive prior chemotherapy Dose-dense regimens in a clinical trial or with strong evidence of benefit With subsequent cycles if febrile neutropenia has previously occurred (so-called secondary CSF administration) Not needed after short-duration neutropenia without fever Use if patient had febrile neutropenia in previous cycle Use if prolonged neutropenia (even without fever) delays therapy Therapeutic Uses Afebrile neutropenic patients No evidence of benefit Febrile neutropenic patients No evidence of benefit May feel compelled to use in the face of clinical deterioration from sepsis, pneumonia, or fungal infection, but benefit unclear In bone marrow or peripheral blood stem cell transplantation Use to mobilize stem cells from marrow Use to hasten myeloid recovery In acute myeloid leukemia G-CSF of minor or no benefit GM-CSF of no benefit and may be harmful In myelodysplastic syndromes Not routinely beneficial Use intermittently in subset with neutropenia and recurrent infection What Dose and Schedule Should Be Used? G-CSF: 5 mg/kg per day subcutaneously GM-CSF: 250 mg/m2 per day subcutaneously Pegfilgrastim: one dose of 6 mg 24 h after chemotherapy When Should Therapy Begin and End? When indicated, start 24–72 h after chemotherapy Continue until absolute neutrophil count is 10,000/μL Do not use concurrently with chemotherapy or radiation therapy Abbreviations: CSF, colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor. Source: From the American Society of Clinical Oncology: J Clin Oncol 24:3187, 2006. and <1500 granulocytes/μL. Management of febrile neutropenia is considered in Chap. 79. Colony-stimulating factors (CSFs) are used to augment bone marrow production of PMNs. The American Society of Clinical Oncology has developed practice guidelines for the use of granulocyte CSF (G-CSF) and GM-CSF (Table 78-8). Dangerous degrees of thrombocytopenia do not frequently compli cate the management of patients with solid tumors receiving cytotoxic chemotherapy (with the possible exception of certain carboplatincontaining

regimens), but they are frequent in patients with hemato logic neoplasms. Severe bleeding related to thrombocytopenia occurs with increased frequency at platelet counts <20,000/μL in patients with acute leukemia and <10,000/μL in patients with solid tumors and is prevalent at counts <5000/μL. The precise “trigger” point at which to transfuse patients has been defined as a platelet count of 10,000/μL or less in patients without medical comorbidities that may increase the risk of bleeding. This issue is important not only because of the costs of frequent transfusion but

also because unnecessary platelet transfusions expose the patient to the risks of allosensitization and loss of value from subsequent transfu sion, as well as the infectious and hypersensitivity risks inherent in any transfusion. Careful review of medication lists to prevent exposure to nonsteroidal anti-inflammatory agents and maintenance of clotting factor levels adequate to support near-normal prothrombin and partial thromboplastin time tests are important in minimizing the risk of bleeding in the thrombocytopenic patient.

Anemia associated with chemotherapy can be managed by transfu sion of packed RBCs. Transfusion is not undertaken until the hemo globin falls to <80 g/L (8 g/dL), compromise of end-organ function occurs, or an underlying condition (e.g., coronary artery disease) calls for maintenance of hemoglobin >90 g/L (9 g/dL). Randomized trials in certain tumors have raised the possibility that erythropoietin (EPO) use may promote tumor cell survival. ■ ■NAUSEA AND VOMITING The most common side effect of chemotherapy administration is nausea, with or without vomiting. Nausea may be acute (within 24 h of chemotherapy), delayed (>24 h), or anticipatory of the receipt of chemotherapy. Highly emetogenic drugs (risk of emesis >90%) include DTIC, cyclophosphamide at >1500 mg/m2, and cisplatin; moderately emetogenic drugs (30–90% risk) include carboplatin, cytosine arabi noside (>1 g/m2), ifosfamide, conventional-dose cyclophosphamide, and anthracyclines; low-risk (10–30%) agents include 5-FU, taxanes, etoposide, and bortezomib, with minimal risk (<10%) afforded by treatment with antibodies, bleomycin, busulfan, fludarabine, and vinca alkaloids. CHAPTER 78 Principles of Cancer Treatment Serotonin antagonists (5-HT3) and neurokinin 1 (NK1) receptor antagonists are useful in “high-risk” chemotherapy regimens. The combination acts at both peripheral gastrointestinal and CNS sites that control nausea and vomiting. For example, the 5-HT3 blocker dolasetron, 100 mg intravenously or orally; dexamethasone, 12 mg; and the NK1 antagonist aprepitant, 125 mg orally, are combined on the day of administration of severely emetogenic regimens, with repeti tion of dexamethasone (8 mg) and aprepitant (80 mg) on days 2 and 3 for delayed nausea. Alternate 5-HT3 antagonists include ondansetron, given as 0.15 mg/kg intravenously for three doses just before and at 4 and 8 h after chemotherapy; palonosetron at 0.25 mg over 30 s,

30 min before chemotherapy; and granisetron, given as a single dose of 0.01 mg/kg just before chemotherapy. Emesis from moderately emetic chemotherapy regimens may be prevented with a 5-HT3 antagonist and dexamethasone alone for patients not receiving doxorubicin and cyclophosphamide combinations; the latter combination requires the 5-HT3/dexamethasone/aprepitant on day 1, but aprepitant alone on days 2 and 3. Emesis from low-emetic-risk regimens may be prevented with 8 mg of dexamethasone alone or with non-5-HT3, non-NK1 antagonist approaches including the following. Antidopaminergic phenothiazines act directly at the chemoreceptor trigger zone (CTZ) in the brainstem medulla and include prochlor perazine (Compazine), 10 mg intramuscularly or intravenously, 10–25 mg orally, or 25 mg per rectum every 4–6 h for up to four doses; and thiethylperazine, 10 mg by potentially all of the above

routes every 6 h. Haloperidol is a butyrophenone dopamine antagonist given at 1 mg intramuscularly or orally every 8 h. Metoclopramide acts on peripheral dopamine receptors to augment gastric emptying and is used in high doses for highly emetogenic regimens (1–2 mg/kg

intravenously 30 min before chemotherapy and every 2 h for up to three additional doses as needed); intravenous doses of 10–20 mg every 4–6 h as needed or 50 mg orally 4 h before and 8 and 12 h after chemotherapy are used for moderately emetogenic regimens. 5-9-Tet rahydrocannabinol (Marinol) is a rather weak antiemetic compared to other available agents, but it may be useful for persisting nausea and is used orally at 10 mg every 3–4 h as needed. Olanzapine, an “atypical antipsychotic” acting at multiple neurotransmitter receptors, may be of value, most clearly in cases refractory to the measures described above. Some practice guidelines have endorsed its earlier use in adults receiv ing highly emetogenic chemotherapy regimens in combination with an NK1 antagonist plus a 5-HT3 antagonist plus dexamethasone.

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