CHAPTER 10

General Principles of Chemotherapy

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Since the introduction of chemotherapy for the treatment of childhood leukemia more than 70 years ago,[1] the prognosis of childhood cancer has improved dramatically (Fig. 10.1). The 5-year survival rate for this group of diseases, many of which were uniformly fatal in the prechemotherapy era, was 83% for all forms of childhood cancer diagnosed between 2002 and 2008.[2] This striking improvement is a direct result of the incorporation of anticancer drugs into treatment regimens that previously relied only on surgery or radiotherapy for the primary tumor. The multimodality approach, which integrates surgery and radiotherapy to control local disease with chemotherapy to eradicate systemic (metastatic) disease, is the standard approach to treating most childhood cancers.

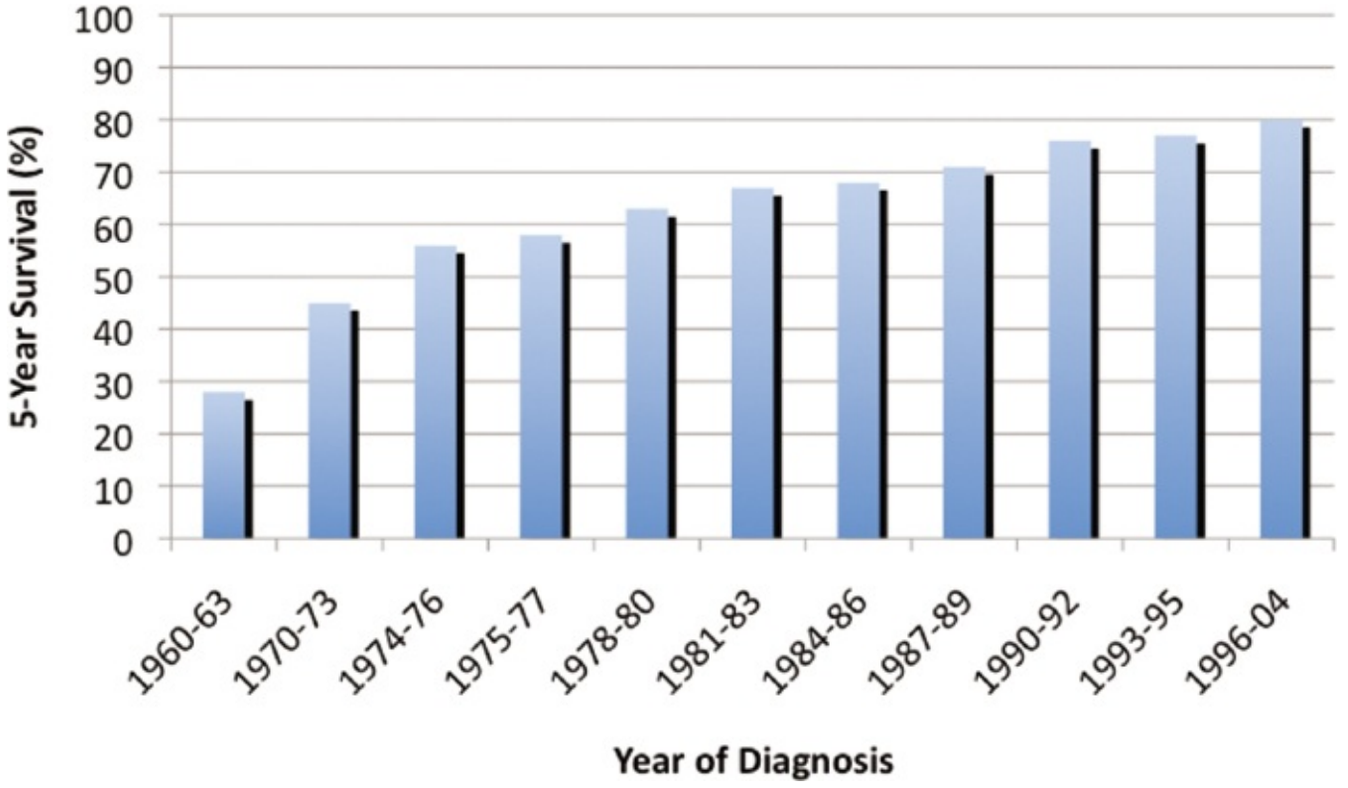

Figure 10.1 Five-year survival rate for all childhood cancers diagnosed between 1960 and 2004. (Data from Silverberg E, Boring CC, Squires TS. Cancer statistics, 1990. *CA Cancer J Clin* 1990;40:9–26; Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10–30; Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.)

PRINCIPLES OF CANCER CHEMOTHERAPY

The ultimate goal of multimodality treatment is to cure the patient of cancer. The traditional model for curing cancer is based on the successful model of curing bacterial infections. This strategy attempts to exploit differences between cancer and normal host cells and eradicate or kill all cancer cells in the body. This "killing paradigm"[3] has had a profound impact on our approach to anticancer drug discovery, drug development, and the design of treatment regimens that incorporate cytotoxic anticancer drugs. Understanding the genetic basis of cancer in children, the use of genomics for risk stratification, and the identification of oncogenic driver mutations and fusion oncoproteins has transitioned the approach of anticancer drug discovery away from cytotoxic agents and toward agents that target genomic vulnerabilities in cancer cells.

The predominant strategy for anticancer drug discovery has historically been high-throughput in vitro screening to evaluate the antiproliferative or cancer cell killing effects of candidate drugs in tumor cell lines. In the past, the precise mechanism of action of the candidate drugs was not critical to the selection process, and, for many agents, the mechanism of action was not defined until after the drugs were in widespread clinical use. This nonmechanistically based screening identified cytotoxic and nonselective drugs. As a result, most conventional anticancer drugs produce substantial acute toxicity and late effects. The more recent development of agents that target specific molecular vulnerabilities of cancer may increase the selectivity. These targeted agents may be less myelosuppressive and the toxicity profiles have shifted to gastrointestinal, dermatologic, and other nonhematologic toxicities.

Conventional frontline treatment regimens for most childhood cancers include multiple cytotoxic anticancer drugs administered at their maximum tolerated dose (MTD) intensity—regimens that typically produce substantial toxicity. Methods of rescuing or circumventing anticancer drug toxicity, such as the administration of hematopoietic growth factors and bone marrow or hematopoietic stem cell transplant (HSCT) to alleviate hematologic toxicity, have been incorporated into treatment regimens to allow for administration of higher doses of cytotoxic drugs.

The basic principles that guide our current use of cancer chemotherapy are based on the goal of curing patients by eradicating all cancer cells and on empiric observations made in early clinical trials involving children with drug-sensitive cancers. These principles include the use of multidrug combination regimens (i.e., combination chemotherapy), the administration of chemotherapy before the development of clinically evident metastatic disease (i.e., adjuvant chemotherapy), and the administration of drugs at the maximally tolerated dose rate (i.e., dose intensity).

Combination Chemotherapy

The importance of administering anticancer drugs in combination regimens was first appreciated in the treatment of acute lymphoblastic leukemia (ALL). Compared with single-agent therapy, the use of drug combinations significantly increased the percentage of patients

achieving complete remission and prolonged the duration of their remissions. At best, only 60% of patients treated with a single agent achieved a complete remission, but standard three- and four-drug combination induction regimens achieved long-term complete remission rates that exceeded 95%.

The primary rationale for combination chemotherapy is to overcome drug resistance to individual agents, the incidence of which can exceed 50% even in newly diagnosed cancers.[4] Combination chemotherapy also may prevent or delay the development of acquired resistance. Traditionally, combination chemotherapy regimens contain drugs with demonstrated single-agent activity against the type of tumor being treated, with a preference for agents that produced complete responses in advanced or recurrent disease; drugs that are non–cross-resistant to overlap against drug-resistant subpopulations of tumor cells; drugs with nonantagonistic (i.e., additive or synergistic) mechanisms of action; and drugs with nonoverlapping toxicity profiles, allowing each agent to be administered at its optimal dose and schedule. These concepts pertain to the addition of targeted therapy to current chemotherapy regimens. In addition, combinations of targeted agents must demonstrate the mechanism for additivity or synergy with conventional agents or other targeted agents.

Adjuvant Chemotherapy

Anticancer drugs are most effective when administered in the adjuvant setting to patients who are without overt evidence of residual disease after local therapy but who are at high risk for relapse at metastatic sites. Before the routine use of adjuvant chemotherapy, relapse at metastatic sites occurred in 60% to 95% of children with localized solid tumors after local therapy measures. The aim of adjuvant chemotherapy is to prevent metastatic recurrence by eliminating micrometastatic tumor deposits that are present at the time of diagnosis in the lungs, bone, bone marrow, lymph nodes, or other sites. Adjuvant chemotherapy is efficacious for most of the common pediatric cancers.

The mathematical modeling experiments of Goldie and Coldman, which assume that a curable tumor is one with no drug-resistant tumor cells and that the development of drug resistance is the result of a random genetic event, predict that the chance for cure is maximized if all available active drugs are given simultaneously in the adjuvant setting, when there is minimal residual disease and a low probability that drug-resistant cells are present.[5]

The selection of appropriate drugs and the optimal timing of drug therapy relative to definitive local therapy are important. Traditionally, drugs have been selected on the basis of their activity in advanced disease. Animal models and clinical experience have shown that regimens producing the most dramatic responses in metastatic or recurrent disease have the greatest likelihood of being curative in the adjuvant setting.[6]

Adjuvant chemotherapy should begin as soon as possible after definitive local therapy; delays to allow for recovery from local therapy may compromise the chance of cure. One strategy to avoid delays caused by potential adverse interactions between chemotherapy and surgery or irradiation is the administration of neoadjuvant chemotherapy, that is, administration of drug therapy before definitive local therapy. This approach may also

improve local control of the primary tumor by shrinking the primary and making it more amenable to surgical resection, in addition to providing earlier therapy for micrometastases.[7]

Dose Intensity

Most cytotoxic anticancer drugs have a steep dose–response curve, and a small increment in the dose can significantly enhance the therapeutic effect of a drug in preclinical studies. In animal tumor models, a 2-fold increase in the dose of cyclophosphamide can result in a 10-fold increase in tumor cell killing. The relative dose intensity is calculated by normalizing the dose rate ($mg/m^2/wk$) for each agent to the dose rate in an arbitrarily selected standard regimen and then averaging the relative dose intensities for all agents in the regimen to derive the relative dose intensity for the regimen.

For some childhood cancers, relapse rates are significantly lower in patients receiving more dose-intense chemotherapy. Children with ALL receiving standard doses of methotrexate (MTX) and mercaptopurine had a median survival of 15 months compared to 6 months for the group randomized to a half-dose maintenance regimen.[8] Oral mercaptopurine dose intensity during maintenance therapy is also predictive of event-free survival in ALL; however, prescribing higher doses could be counterproductive if greater hematologic toxicity resulted in treatment delays.[9] Retrospective analyses of osteosarcoma trials demonstrated a two- to threefold higher relapse rate in patients receiving less than 75% to 80% of their recommended dose of chemotherapy. The relationship between individual drug dose intensities and disease outcome in osteosarcoma and Ewing sarcoma suggests that doxorubicin dose intensity is an important determinant of response in osteosarcoma and disease-free survival of patients with Ewing sarcoma.[10] Similarly, a meta-analysis of clinical trials of children with neuroblastoma showed that dose intensity of a four-drug regimen correlated with response and survival.[11]

Prospective randomized trials to assess the importance of dose intensity in childhood cancers have also been performed with mixed results. The administered dose intensity of dactinomycin and doxorubicin in pulse-intensive regimens for Wilms tumor was significantly higher than it was for the standard treatment regimens, but there was no survival advantage in the enhanced dose intensity arm.[12] A 33% increase in dose intensity in a five-drug chemotherapy regimen for localized Ewing sarcoma achieved by shortening the dosing interval (interval compression) from 21 to 14 days resulted in a higher 5-year event-free survival (73% vs. 65%, $p = 0.045$) on the compressed regimen; however, there was similar overall survival in both arms (77% vs. 83%, $p = 0.056$).[13]

Maximizing dose intensity of cytotoxic agents requires patient and physician willingness to tolerate drug toxicities; more aggressive supportive care of patients experiencing these side effects; and selective rescue of the patient from toxicity, such as with HSCT or the administration of granulocyte growth factors (filgrastim, peg-filgrastim). Other methods to increase dose intensity include regional chemotherapy (e.g., intra-arterial, intrathecal delivery) to achieve high drug concentrations at local tumor sites while minimizing systemic drug exposure; and new treatment schedules, such as long-term continuous infusions, or new formulations such as nanoparticles that may allow more drug to be administered over a given

period. For cytotoxic chemotherapy, the schedule of administration and rationale for dose intensity is related to time to recover from acute toxicity. For targeted agents that are administered orally, dose intensity encompasses daily dose and scheduling, including the need for drug holidays or discontinuous schedules, such as 5 days/week with a 2-day break. In addition, understanding of pharmacokinetics, the kinetics of target engagement, and side effects are important factors in considering whether maximum dose intensity or continuous administration is optimal.

CLINICAL PHARMACOLOGY OF ANTICANCER DRUGS

Pediatric oncologists coordinate the administration of complex combination chemotherapy regimens to children in the setting of multimodal therapy. Cytotoxic anticancer drugs have the lowest therapeutic index of any class of drugs and predictably produce significant, even life-threatening toxicity at therapeutic doses.[14] Implementing dose reductions or delays in therapy to attenuate toxicities may compromise the therapeutic effect and place patients at an increased risk for disease recurrence, a uniformly fatal event with most childhood cancers. Carefully balancing the risk of therapy-related toxicities against the risk of tumor recurrence from inadequate treatment must be maintained. Crucial adjustments in the dose and schedule of chemotherapy needed to achieve this balance are often empirical, because therapeutic drug monitoring for most anticancer drugs is not available. To ensure optimal safety and efficacy, it is necessary to have an in-depth knowledge of the clinical pharmacology of these drugs, including their mechanisms of action, pharmacokinetics, pharmacogenetics, spectrum of toxicities, mechanisms of resistance, and potential for drug interactions.

Mechanism of Action

Recent advances in cancer cell genomics and cell biology have provided critical insights into the pathogenesis of many forms of childhood cancer and have led to a new focus on the development of targeted, more selective cancer treatments. Most current conventional anticancer drugs used in the frontline treatment of childhood cancers are cytotoxic drugs that nonselectively and irreversibly damage vital macromolecules (e.g., DNA or RNA; Fig. 10.2) or metabolic pathways that are also critical to normal cells. As a result, they cause many undesirable and potentially severe toxic effects. For example, alkylating agents are chemically reactive compounds that damage DNA by covalently bonding to and cross-linking nucleobases within the DNA; antimetabolites block the synthesis of nucleotide precursors or are directly incorporated into DNA as fraudulent bases; and topoisomerase inhibitors such as the anthracyclines, epipodophyllotoxins, and camptothecins interfere with DNA religation, resulting in protein-associated DNA strand breaks.

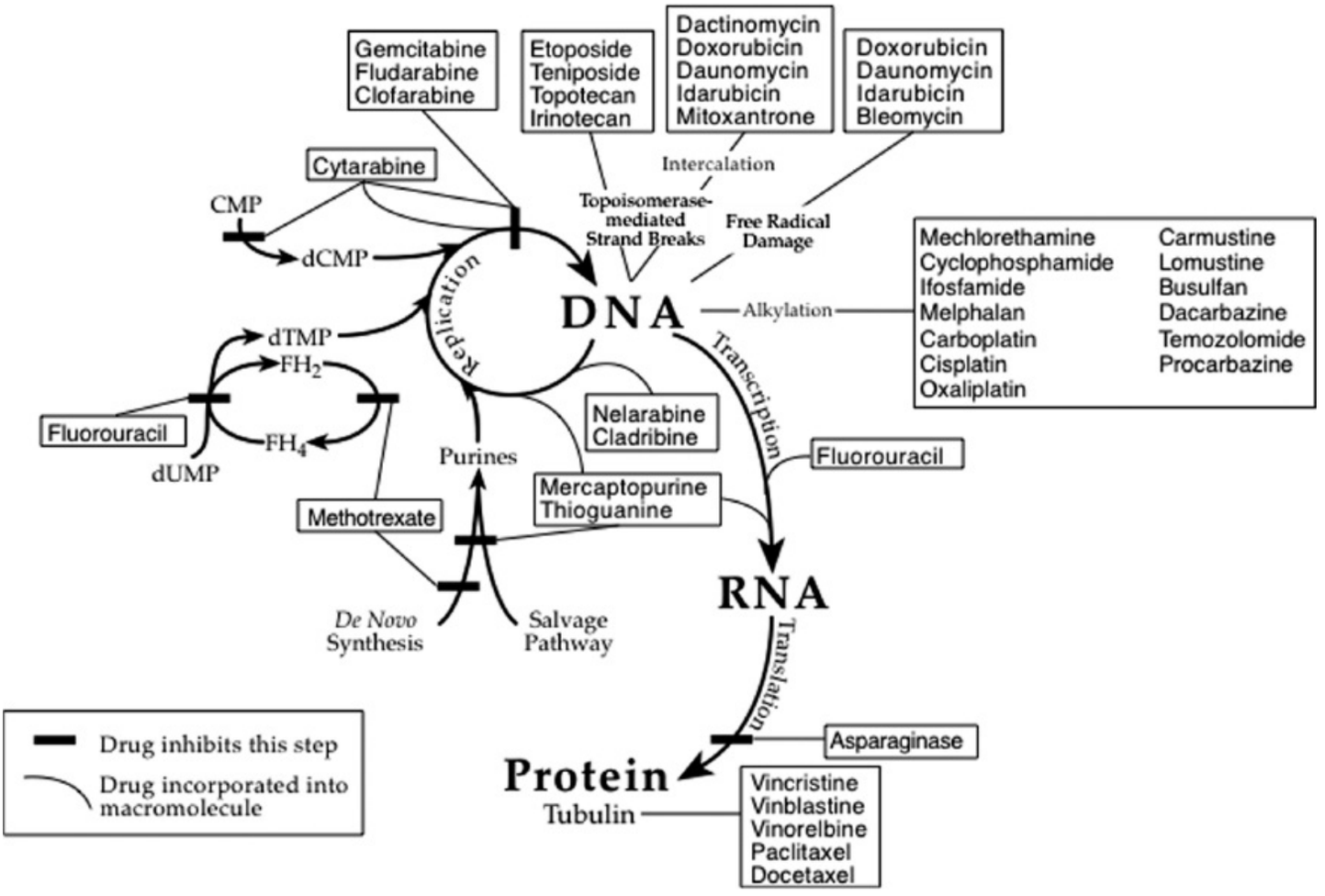

Figure 10.2 Site of action of the commonly used cytotoxic anticancer drugs.

Targeted anticancer drugs block the activation of cellular signal-transduction pathways by inhibiting the protein kinase activity of critical cell membrane receptors and downstream effector proteins.[15] Activation of these pathways occurs through sequential phosphorylation of pathway proteins usually on a tyrosine, serine, or threonine moiety. Activating mutations in receptors and effector proteins plays a critical role in the pathogenesis of many cancers. Targeted drugs that inhibit the protein kinase activity of these constitutively activated signaling proteins block the transduction of the aberrant signal and, thereby, control cellular proliferation. Cellular receptors and effectors that are targets for these agents include VEGFR, FGFR, KIT, RET, ALK, BRAF, MET, JAK, NTRK, mTOR, ABL, and MEK.[16]

An understanding of the mechanism of drug action is useful in predicting which cancers may respond to the drug depending on their biochemical, cytokinetic, and genomic profiles and which drug combinations may produce additive or synergistic antitumor effects. Combining agents that together enhance the inhibition of vital intracellular processes through sequential or concurrent blockade or that lead to complementary inhibition of specific metabolic pathways has been a traditional strategy for the design of combination regimens.[17] Devising approaches to combine molecularly targeted drugs with conventional cytotoxic chemotherapy is the next challenge. Tumor genetic profiling for selection of molecularly targeted drugs is an approach to personalize cancer therapy.

A drug's schedule of administration may also be influenced by its mechanism of action.

For example, the antimetabolites, which are inhibitory only during the S phase in the cell cycle, tend to be more cytotoxic if administered by prolonged infusion. This approach ensures that a greater number of tumor cells are exposed to the drug as they pass through the S phase.

Pharmacokinetics

The discipline of pharmacokinetics deals with quantitative aspects of drug disposition in the body, including absorption, distribution, metabolism, and excretion, referred to as ADME (Table 10.1). Pharmacokinetic studies have revealed substantial interpatient variability in drug disposition and systemic drug exposure with most anticancer drugs.[18] Administering a standard dose of etoposide, doxorubicin, or cyclophosphamide to a group of children results in a 2 to 10-fold range in systemic drug exposure, as measured by the area under the plasma drug concentration–time curve (AUC).[19] Substantial variability in systemic drug exposure is also observed with orally administered agents such as MTX and mercaptopurine.[20] Assuming that drug effect is more closely related to systemic drug exposure than is the dose, these differences in drug disposition could account for the variability in toxicities and responses observed with most combination chemotherapy regimens employing standardized doses of individual agents.[21] Variability in anticancer drug disposition in children may also result from age-related developmental changes in body composition and excretory organ function including variation in rate of metabolism and excretion of drug by the kidneys or liver, variation in the extent of drug-protein binding, drug interactions, and pharmacogenetics.

TABLE 10.1 Pharmacokinetic Terms

Term	Common Abbreviation	Units	Definition
Clearance	Cl	Vol/time (mL/min)	Used to quantify the rate of drug elimination; expressed in terms of volume of plasma cleared of drug per unit of time. Total clearance is the sum of renal, metabolic, spontaneous chemical degradation, and biliary (fecal) elimination. When the true bioavailability of a drug is not known, (e.g., drugs with only an oral formulation), the term “apparent” clearance is used and is abbreviated Cl/F.
Half-life	$t_{1/2}$	Time (h)	Time required to reduce the drug concentration by 50%. Plasma drug disappearance frequently has multiple phases with differing rates of disappearance (e.g., rapid distribution phase, terminal or elimination phase). Half-lives listed for drugs in this chapter are the post-distributive (terminal, elimination) half-lives, unless otherwise noted.

Area under the curve	AUC	Conc. × time (μM•h)	Quantitates total drug exposure; integral of drug conc. over time or the area under the plasma concentration–time curve; used in calculation of clearance and bioavailability
Volume of distribution	Vd; Vd_{ss}	Volume (L)	Relates plasma conc. to total amount of drug in the body (i.e., volume required to dissolve the total amount of drug to give the final conc. found in plasma); a property of the drug rather than a real volume or physiologic compartment
Bioavailability	F	Fraction (%)	Rate and extent of absorption of a drug, frequently synonymous with the fraction of a dose absorbed when administered by some route other than intravenous.
Biotransformation			Enzymatic metabolism of a drug; may result in the activation of a prodrug, conversion to other biologically active intermediates, or inactivation of a drug

Conc., concentration.

An important determinant of variability in anticancer drug pharmacokinetics is the rate of drug metabolism. Drug-metabolizing enzymes are divided into two groups depending on the type of reaction that they catalyze. Phase I reactions (e.g., oxidation, hydrolysis, reduction, demethylation) introduce or expose a functional group (e.g., hydroxyl group) on the drug. These reactions usually diminish the drug's pharmacologic activity, but some prodrugs, such as cyclophosphamide, are converted to active metabolites by these enzymes. Phase II conjugation reactions covalently link a highly polar conjugate (e.g., glucuronic acid, sulfate, glutathione, amino acids, acetate) to the functional group created by the phase I reaction. The conjugated drugs are highly polar, usually devoid of pharmacologic activity, and rapidly excreted.

The significant interpatient variation in systemic drug exposure with current dosing methods, the toxic nature of these agents, and the potential importance of dose intensity in cancer chemotherapy point to the need for more precise, individualized dosing methods for anticancer drugs,[22] such as the adaptive dosing techniques that have been successfully applied to individualize carboplatin dose. Examples of therapeutic drug monitoring include serial measurement of MTX concentrations to determine the duration of leucovorin rescue following high-dose methotrexate (HDMTX) therapy, and monitoring of busulfan to achieve a safe and effective drug exposure in HSCT conditioning regimens.[23] A prerequisite for these individualized dosing methods is the establishment of the relation between a drug's pharmacokinetics and pharmacodynamics (toxicity or therapeutic effect). Systemic drug exposure (AUC) of anticancer drugs is usually the best correlate of the drug's toxic or therapeutic effects. Parameters other than AUC, such as peak or trough concentration or average steady-state concentration, can also be evaluated for clinical correlations. In addition, population pharmacokinetic modeling can be employed to determine sources of variability in

drug exposure or simulate relationship between dose, schedule, and effect. Pharmacokinetic parameters are important for determining the optimal dose, schedule, and route of administration of the drug. For most patients with cancer, real-time pharmacokinetics and therapeutic drug monitoring do not play a significant role in clinical care. However, knowledge of the route of elimination of a drug is helpful in adjusting the dosage for patients with hepatic or renal dysfunction.

Physiologic differences between children and adults can affect drug disposition and must be considered in determining the appropriate dose and schedule for children. Developmental differences in drug absorption, plasma protein or tissue binding, functional maturation of excretory organs, and drug distribution (Table 10.2) can result in differences in systemic drug exposure for children compared with adults treated with the same dose. The most dramatic changes in excretory organ function and body composition occur during the first few days to months of life, but there are very limited data on the disposition of anticancer drugs in infants.[24]

TABLE 10.2 Physiologic Differences in Children That May Influence Drug Disposition

Organ or Compartment	Value at Birth[a]	Age Adult Values Are Reached[b]	Effect on Drug Disposition[c]
Kidney			
Size	↑		
Renal blood flow	↓	1 y	↓ Renal excretion
Glomerular filtration	↓	6 mo–1 y	↓ Renal excretion
Tubular function	↓	1 y	↓ Tubular secretion
Liver			
Size	↑		
Phase I drug-metabolizing enzymes[d]	↓	Variable (oxidative enzymes increase rapidly after birth) ↑ Activity in young children	↓ Metabolic clearance ↑ Metabolic clearance

Phase II drug-metabolizing enzymes[e]	↑ Sulfatation ↓ Other enzymes	Variable (6 mo for glucuronidation)	↓ Metabolic clearance
Biliary excretion	↓	6 mo	↓ Biliary excretion
Gastrointestinal			
Acid secretion	↓	3 mo	Altered drug absorption and stability
Motility	↓	6–8 mo ↑ Transit time in young children	Delayed absorption More rapid absorption
Body composition			
Blood volume	↑	Adolescence	
Extracellular fluid	↑	48 mo	↑ Distribution volume
Total body water	↑	4 mo	↑ Distribution volume
Fat	↓	Adolescence ↑ From 4–12 mo of age	↓ Distribution volume of lipophilic drugs ↑ Distribution volume of lipophilic drugs
Cerebrospinal fluid volume	↑	3 y	↑ Distribution volume of intrathecal drugs
Protein binding	↓	1 y	↑ Free-drug levels

[a]↓, decreased; ↑, increased (compared with adult values and relative to body surface area or weight).
[b]Relative to body surface area or weight.
[c]Refer to Table 10.5 to determine which drugs may be affected by alteration of renal, biliary, or metabolic function.
[d]Oxidation, hydrolysis, reduction, and demethylation.
[e]Conjugation, acetylation, and methylation.

Central Nervous System Pharmacology of Anticancer Drugs

The penetration of the anticancer drugs into the central nervous system (CNS) is relevant to

the treatment childhood cancers, because primary and metastatic tumors of the brain or meninges are common in children and because anticancer drugs are associated with acute and chronic neurotoxicity. The degree of drug penetration across the blood–brain barrier (BBB) is determined by the physicochemical properties of the drug, such as lipophilicity, molecular size, and degree of ionization, and the free (nonprotein bound) drug concentration in plasma.[25] Most anticancer drugs penetrate poorly into the cerebrospinal fluid (CSF), which is also used as a surrogate for BBB penetration (Table 10.4). Strategies employed to circumvent limited penetration into the CNS are listed in Table 10.3.

TABLE 10.3 Treatment Strategies to Circumvent the Blood–Brain Barrier

Strategy	Examples
High-dose systemic chemotherapy	High-dose methotrexate, cytarabine
Identifying drugs that penetrate the blood–brain barrier (cross into CSF)	Thiotepa, topotecan
Disruption of the blood–brain barrier	Osmotic disruption with mannitol
Regional drug administration	
Intrathecal injection	Methotrexate, cytarabine
Intra-arterial injection	Cisplatin
Interstitial therapy	Gliadel

TABLE 10.4 Pharmacologic Properties of the Commonly Used Anticancer Drugs

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Drug	Synonyms	Route[a]	Dose/m^2	Schedule[b]	Mechanism of Action	Toxicities[c]	Antitumor Spectrum	Mechanisms of Resistance[d]
				Alkylating Agents				
Mechlorethamine	Mustargen, HN_2, nitrogen mustard	IV	6 mg	Weekly × 2, q 28 d	Alkylation; cross-linking	M, N&V, A, phlebitis, vesicant, mucositis	Hodgkin disease	↓Transport, ↑ DNA repair, ↑ GT
Cyclophosphamide	Cytoxan, CTX	IV PO	250–1,800 mg 100–300 mg	Daily × 1–4 d, q 21–28 d Daily	(Prodrug) alkylation; cross-linking	M, N&V, A, cystitis, water retention; cardiac (HD)	Lymphomas, leukemias, sarcomas, neuroblastoma	↑ IC catabolism, ↑ DNA repair, ↑ GT
Ifosfamide	IFOS, IFEX	IV	1,600–2,400 mg	Daily × 5, q 21–28 d	(Prodrug) alkylation; cross-linking	M, N&V, A, cystitis, NT, renal; cardiac (HD)	Sarcomas, germ cell	↑ IC catabolism, ↑ DNA repair, ↑ GT
Melphalan	Alkeran, L-PAM	IV PO IV	10–35 mg 4–20 mg 140–220 mg	q 21–28 d Daily for 1–21 d Single dose (BMT)	Alkylation; cross-linking	M, N&V; mucositis and diarrhea (HD)	Rhabdomyosarcoma; sarcomas, neuroblastoma, and leukemias (HD)	↓Transport, ↑ DNA repair, ↑ GT
Lomustine	CeeNU, CCNU	PO	100–150 mg	Single dose, q 4–6 wk	Alkylation; cross-linking; carbamoylation	M, N&V, renal, and pulmonary	Brain tumors, lymphoma, Hodgkin disease	↓ Uptake, ↑ IC catabolism, ↑ DNA repair
Carmustine	BiCNU, BCNU	IV	200–250 mg	Single dose, q 4–6 wk	Alkylation; cross-linking; carbamoylation	M, N&V, renal, and pulmonary	Brain tumors, lymphoma, Hodgkin disease	↓ Uptake, ↑ IC catabolism, ↑ DNA repair
Busulfan	Myleran	PO PO	1.8 mg 37.5 mg	Daily q 6 h for 4 d (BMT)	Alkylation; cross-linking	M, A, pulmonary; N&V, mucositis, NT, hepatic (HD)	CML; leukemias (BMT)	↑ DNA repair, ↑ GT
Cisplatin	Platinol, CDDP	IV IV	50–200 mg 20–40 mg	Over 4–6 h, q 21–28 d Daily × 5, q 21–28 d	Platination; cross-linking	M (mild), N&V, A, renal, NT, ototoxicity, HSR	Testicular and other germ cell, brain tumors, osteosarcoma, neuroblastoma	↓ Uptake, ↑ DNA repair, ↑ GT
Carboplatin	CBDCA	IV	400–600 mg 100–175 mg	Single dose or daily × 2, q 28 d; weekly × 4, q 6 wk	Platination; cross-linking	M (Plt), N&V, A, hepatic (mild), HSR	Brain tumors, germ cell, neuroblastoma, sarcomas	↓ Uptake, ↑ DNA repair, ↑ GT
Oxaliplatin	Eloxatin	IV	85–130 mg	Single dose q 21 d	Platination; cross-linking	NT	Colorectal cancer	↓ Uptake, ↑ DNA repair
Dacarbazine	DTIC	IV	250 mg	Daily × 5, q 21–28 d	(Prodrug) methylation	M (mild), N&V, flulike syndrome, hepatic	Neuroblastoma, sarcomas, Hodgkin disease	↑ DNA repair
Temozolomide	TMZ	PO/IV	125–200 mg 90 mg	Daily × 5, q 28 d or daily × 42 d	(Prodrug) methylation	M, N&V	Brain tumors	↑ DNA repair

Procarbazine	Matulan, PCZ	PO	100 mg	Daily for 10–14 d	(Prodrug) methylation; free radical formation	M, N&V, NT, rash, mucositis	Hodgkin disease, brain tumors	↑ DNA repair
ThioTEPA	Tepadina	IV	5 mg/kg	Q12h × 2 doses	Alkylation	M, N&V, NT, rash	BMT	
Antimetabolites								
Methotrexate	MTX	PO, IM, SC IV	7.5–30 mg 10–33,000 mg	Weekly or biweekly Bolus or CI (6–42 h)	Interferes with folate metabolism	M (mild), mucositis, rash, hepatic; renal, NT (HD)	Leukemia, lymphoma, osteosarcoma	↓ Transport, ↑ target enzyme, ↓ polyglutamation
Mercaptopurine	Purinethol, 6-MP	PO	75–100 mg	Daily	(Prodrug) incorporated into DNA and RNA; blocks purine synthesis, interconversion	M, hepatic, mucositis	Leukemia (ALL, CML)	↓ Activation, ↑ IC catabolism
Thioguanine	6-TG	PO PO	75–100 mg 40–60 mg	Daily × 5–7 Daily	(Prodrug) incorporated into DNA and RNA; blocks purine synthesis, interconversion	M, N&V, mucositis, hepatic (SOS)	Leukemia (ALL, AML)	↓ Activation, ↑ IC catabolism
Fludarabine phosphate	F-ara-AMP	IV	25 mg	Daily × 5	(Prodrug) incorporated into DNA; inhibits DNA polymerase, ribonucleotiDereductase	M, opportunistic infections, neurotoxicity (high dose)	Leukemia (AML, CLL), indolent lymphomas	↓ Membrane transport, ↓ IC activation, ↑ IC catabolism
Clofarabine	Clolar	IV	52 mg	Daily × 5	(Prodrug) incorporated into DNA; inhibits DNA polymerase, ribonucleotide reductase	M, hepatic, hypokalemia, systemic inflammatory response syndrome	Leukemia	
Nelarabine	Arranon	IV	400–650 mg	Daily × 5	(Prodrug) incorporated into DNA	Somnolence, peripheral neuropathy, Guillan–Barre	T-cell leukemia	
Cytarabine	Ara-C, cytosine arabinoside, Cytosar	IV, SC IV	100–200 mg 3,000 mg	q 12 h or CI for 5–7 d q 12 h for 4–8 doses	(Prodrug) incorporated into DNA; inhibits DNA polymerase	M, N&V, mucositis, GI, flulike syndrome; NT, ocular, skin (HD)	Leukemia, lymphoma	↓ Activation, ↓ transport, ↑ dCTP, ↑ IC catabolism
Gemcitabine	Gemzar, dFdC	IV	1,000 mg	Weekly × 3	(Prodrug) incorporated into DNA; inhibits DNA polymerase, ribonucleotide reductase	M, N&V, hepatic, mucositis, flulike syndrome, edema, rash	Hodgkin; possibly sarcomas	
Fluorouracil	5-FU	IV IV	500 mg 800–1200 mg	Single or daily × 5 CI (24–120 h)	(Prodrug) inhibits thymidine synthesis; incorporated into RNA, DNA	M (bolus), mucositis, N&V, diarrhea, skin, NT, ocular, cardiac	Carcinomas, hepatic tumors	↑ IC catabolism, ↓ Activation, ↑ target enzyme, altered target enzyme

Topoisomerase Inhibitors								
Doxorubicin	Adriamycin, ADR	IV IV IV	45–75 mg 20–30 mg 45–90 mg	Single, q 21 d Weekly CI (24–96 h)	Intercalation; DNA strand breaks (Topo II); free radical formation	M, mucositis, N&V, A, diarrhea, vesicant, cardiac (acute, chronic)	Leukemia (ALL, ANL), lymphomas, most solid tumors	Multidrug resistance, ↓Topo II
Daunomycin	Daunorubicin, DNR	IV	30–45 mg	Daily × 3 or weekly	Intercalation; DNA strand breaks (Topo II); free radical formation	M, mucositis, N&V, diarrhea, A, vesicant, cardiac (acute, chronic)	Leukemia (ALL, ANL), lymphomas	Multidrug resistance, ↓Topo II
Idarubicin	IDA	IV PO	10–15 mg 30–40 mg	Daily or weekly × 3 Daily × 3	Intercalation; DNA strand breaks (Topo II); free radical formation	M, mucositis, N&V, diarrhea, A, vesicant, cardiac (acute, chronic)	Leukemia (ALL, ANL), lymphomas	Multidrug resistance, ↓Topo II
Mitoxantrone	Novantrone, MITO	IV	8–12 mg	Daily × 3–5 d	Intercalation; DNA strand breaks (Topo II)	M, mucositis, N&V, A, bluish color to urine, veins, sclera, nails	Leukemia (ALL, ANLL), lymphomas	Multidrug resistance, ↓Topo II
Dactinomycin	Cosmegen, ACT-D, actinomycin-D	IV IV	0.45 mg (15 mcg/kg) 1.35–1.8 mg (45–60 mcg/kg)	Daily × 5, q 3–6 wk Single dose q 3–6 wk	Intercalation; DNA strand breaks (Topo II)	M, N&V, A, mucositis, vesicant, hepatic (SOS)	Wilms, sarcomas	Multidrug resistance, ↓Topo II
Etoposide	VePesid, VP-16	IV PO	60–120 mg 50 mg	Daily × 3–5, q 3–6 wk Daily × 21 d q 4 wk	DNA strand breaks (Topo II)	M, A, N&V, mucositis, mild NT, hypotension, HSR, secondary leukemia; diarrhea (PO)	Leukemias (ALL, ANL), lymphomas, neuroblastoma, sarcomas, brain tumors	Multidrug resistance, ↓ or altered Topo II, ↑ DNA repair
Topotecan	Hycamptin	IV	1.4–4.5 mg	Daily × 5, q 3 wk	DNA strand breaks (Topo I)	M, diarrhea, mucositis, N&V, A, rash, hepatic	Neuroblastoma, rhabdomyosarcoma	↓ or altered Topo I, multidrug resistance
Irinotecan	CPT-11, Camptosar	IV	50 mg	Daily × 5, q 3 wk	(Prodrug) DNA strand breaks (Topo I)	M, diarrhea, N&V, A, hepatic, dehydration, ileus	Rhabdomyosarcoma	↓ or altered Topo I, multidrug resistance
Tubulin Inhibitors								
Vincristine	Oncovin, VCR	IV	1.0–1.5 mg (max, 2.0 mg)	Weekly × 3–6	Mitotic inhibitor; blocks microtubule polymerization	NT, A, SIADH, hypotension, vesicant	Leukemia (ALL), lymphomas, most solid tumors	Multidrug resistance, altered tubulin subunit
Vinblastine	Velban, VLB	IV	3.5–6.0 mg	Weekly × 3–6	Mitotic inhibitor; blocks microtubule polymerization	M, A, mucositis, mild NT, vesicant	Histiocytosis, Hodgkin, testicular	Multidrug resistance, altered tubulin subunit
Vinorelbine	Navelbine	IV	30 mg	Weekly	Mitotic inhibitor; blocks microtubule polymerization	M, mild NT, A, vesicant	Rhabdomyosarcoma, Hodgkin	Multidrug resistance, altered tubulin subunit

Paclitaxel	Taxol	IV	135–250 mg	CI for 3 or 24 h, q 3 wk	Mitotic inhibitor; blocks microtubule depolymerization	M, HSR, A, NT, mucositis, cardiac, EtOH poisoning	Germ cell tumors	Multidrug resistance, altered tubulin subunits, ↑ Raf kinase
Docetaxel	Taxotere	IV	100–125 mg	q 3 wk or Weekly × 4, q 6 wk	Mitotic inhibitor; blocks microtubule depolymerization	M, HSR, A, NT, rash, edema, mucositis	Sarcoma	Multidrug resistance, altered tubulin subunits
Miscellaneous								
Arsenic trioxide	Trisenox, As_2O_3	IV	0.15 mg/kg	Daily up to 60 doses	Apoptosis; degradation of PML/RAR-alpha	Hepatic, N&V, abnormalities, QTc prolongation	Acute promyelocytic leukemia	
Native asparaginase	Elspar, L-ASP	IV, IM	6,000–25,000 IU	3 times per wk	Asparagine depletion; ↓ Protein synthesis	HSR, coagulopathy, pancreatitis, hepatic, NT	Leukemia (ALL), lymphoma	↑ IC asparagine synthase
PEG-Asparaginase	Oncaspar, PEG-ASP	IV, IM	2,500 IU	Every 1–4 wk	Asparagine depletion; ↓ protein synthesis	HSR, coagulopathy, pancreatitis, hepatic, NT	Leukemia (ALL), lymphoma	↑ IC asparagine synthase
Bleomycin	Blenoxane, BLEO	IV, IM, SC	10–20 units	Weekly	Free radical–mediated DNA strand breaks	Lung, skin, fever, mucositis, alopecia, HSR, Raynaud, N&V	Lymphoma, testicular and other germ cell	↑ IC catabolism, ↑ DNA repair
Dexamethasone	Decadron, DEX	PO, IV, IM	6 mg	Daily	Receptor-mediated lympholysis	Protean (see text)	Leukemia, lymphomas, brain tumors	Loss or defect in glucocorticoid receptor
Prednisone	Deltasone, PRED	PO	40 mg	Daily	(Prodrug) receptor-mediated lympholysis	Protean (see text)	Leukemia, lymphomas	Loss or defect in glucocorticoid receptor
Prednisolone		PO, IV	40 mg	Daily	Receptor-mediated lympholysis	Protean (see text)	Leukemia, lymphomas	Loss or defect in glucocorticoid receptor
All-*trans*-retinoic acid	ATRA, Tretinoin, Vesanoid	PO	45 mg	Daily for induction Daily × 7 d q 28 d for maintenance	Differentiation agent	Retinoic acid syndrome, pseudotumor cerebri, cheilitis, conjunctivitis, dry skin, ↑ triglycerides	Acute promyelocytic leukemia	Mutations in *PML-RAR*a
13-*cis*-Retinoic acid	13*c*RA, Isotretinoin, Accutane	PO	160 mg	Daily × 14 q 28 d	Differentiation agent	Cheilitis, conjunctivitis, xerosis, pruritus, headache, bone and joint pain, ↑ triglycerides, ↑ Ca^{++}	Minimal residual disease neuroblastoma	
Trabectedin	Yondelis	IV	1.5 mg or 1.1 mg	24 h CI q 3 wk 3 h infusion q 3 wk	Reversible alkylation binding DNA minor groove	M, N&V, hepatic, rhabdomyolysis, fatigue	Soft-tissue sarcoma	
Small-Molecule Pathway Inhibitors								
Imatinib mesylate	Gleevec, STI-571	PO	340 mg	Daily	Inhibits BCR-ABL, VEGF, c-Kit kinases	N&V, fatigue, M, headache, GI	Ph+ CML	Mutations in bcr-abl, multidrug resistance
Dasatinib	Sprycel	PO	60–85 mg (adult: 100–140 mg flat)	Daily	Inhibits BCR-ABL, c-KIT, PDGFβ receptor, EPHA2, SRC family kinases	Fluid retention events, rash, nausea, bleeding, diarrhea	CML, Ph+ ALL	Mutations in bcr-abl
Ruxolitinib	Jakafi	PO	50 mg	Twice daily	Inhibits JAK/STAT pathway	M, ↑ creatinine phosphokinase	Myelofibrosis	
Crizotinib	Xalkori	PO	165–280 mg (adult: 250 mg flat)	Twice daily	Inhibits ALK	Hepatic, neutropenia, fatigue, pneumonitis	ALK or ROS1 positive non–small cell lung cancer	Mutation in ALK
Ceritinib	Zykadia	PO	500–550 mg	Daily	Inhibits ALK	Hepatic, pneumonitis, prolonged QTc, pancreatitis	ALK-positive non–small cell lung cancer	
Lortatinib	Lorbrena	PO	(adult: 100 mg flat)	Daily	Inhibits ALK	↑ triglycerides, ↑ cholesterol, hepatic, peripheral neuropathy, and mood disturbance	ALK-positive non–small cell lung cancer	
Larotrectinib	Vitraki, LOXO-101	PO	100 mg (max 100 mg flat dose)	Twice daily	Inhibits NTRK fusions	Fatigue, N&V, hepatic, dizziness, diarrhea	NTRK fusion–positive tumors	Mutation in NTRK
Vemurafenib	Zelboraf	PO	550 mg (adult: 960 mg flat dose)	Twice daily	Inhibits $BRAF^{V600E}$	Rash, arthralgia, skin papilloma, QTc prolongation, retinal vein occlusion	Melanoma $BRAF^{V600E}$	
Selumetinib	AZD6244	PO	25 mg (adult: 75 mg flat dose)	Twice daily	Inhibits MAP kinase pathway	↑ Lipase, ↑ amylase, acneiform rash, ↓ left ventricular function	Plexiform neurofibromas Neurofibromatosis-1	
Sirolimus	Rapamycin, Rapamune	PO	2 mg	Twice daily	Inhibits mTOR	Renal dysfunction, hypertension, pneumonitis, infection	Immunosuppressive therapy	

Temsirolimus	Torisel	IV	75 mg	Weekly q 3 w	Inhibits mTOR	Renal dysfunction, hypertension, pneumonitis, infection	Renal cell carcinoma	
Trametinib	Mekinist	PO	0.025–0.032 mg/kg (adult: 2 mg flat dose)	Daily	Inhibits MAP kinase pathway	Diarrhea, acneiform rash, ↓ left ventricular function, retinal vein occlusion	Melanoma	
Copanlisib	Aliqopa	IV	Adult: 60 mg (flat dose)	Weekly × 3, every 28 d	Inhibits PI3 kinase	Hyperglycemia, hypertension, noninfectious pneumonitis	Relapsed follicular lymphoma	
Axitinib	Inlyta	PO	2.4 mg (adult 5–7.5 mg flat dose)	Twice daily	Inhibits VEGF	Diarrhea, hypertension, fatigue, rash, N&V	Renal cell carcinoma	
Regorafenib	Stivarga	PO	72 mg (adult: 160 mg flat dose)	Daily × 21 d, every 28 d	Inhibits VEGF	Hepatic, fatigue thrombocytopenia	Colon cancer	
Sorafenib	Nexavar	PO	150–200 mg	Twice daily	Inhibits VEGFR-2, PDGFR-β, FLT-3, c-KIT, RAF	Rash, hypertension, diarrhea, N&V, bleeding	Renal cell carcinoma, hepatocellular carcinoma	
Pazopanib	Votrient	PO	160 mg (oral solution); 450 mg (tablet)	Daily	Inhibits VEGFR1, 2, 3; PDGFRα and β; c-KIT	Hypertension, N&V, fatigue, diarrhea, elevations in LFTs	Renal cell carcinoma, sarcoma	
Sunitinib	Sutent	PO	15 mg (adults: 50 mg flat dose)	Daily × 4 wk followed by 2 wk rest	Inhibits c-KIT, FLT-3, VEGFR2, PDGFRβ	Cardiac, hypertension, diarrhea, N&V, GI, mucositis, bleeding, rash	GIST, renal cell carcinoma	
Vandetanib	Caprelsa	PO	100 mg	Daily	Inhibits VEFR1, 2, 3; EGFR, RET	Hypertension, rash, diarrhea, prolongation of QTc	Medullar thyroid carcinoma	
Monoclonal Antibodies								
Rituximab	Rituxan	IV	375 mg	Weekly × 4 wk	Anti-CD20 (MoAb)	Infusion reaction, lymphopenia, Stevens–Johnson syndrome	B-cell malignancies, NHL, post-HSCT lymphoproliferative disorders	
Dinutuximab	Unitux, ch14.18	IV	17 mg	Daily 10 h infusion × 4 d, q 21–28 d	Anti-G_{D2} (MoAb)	Infusion reaction, HSR, pain, capillary leak syndrome, transverse myelitis	Neuroblastoma	
Bevacizumab	Avastin	IV	10–15 mg/kg	Every 2 wk	Anti-VEGF (MoAb)	Rash, proteinuria, hypertension, bleeding, impaired wound healing	Colon cancer, lung cancer, glioblastoma	
Gemtuzumab ozogamicin	Myelotarg, GO	IV	3–5 mg	2-h infusion	Anti-CD33 conjugate to N-acetyl-γ-calcheamicin (ADC)	Infusion reactions, M, hepatic, sinusoidal obstructive syndrome	AML	
Brentuximab vendotin	ADCEtris, SGN-30	IV	1.8 mg/kg	Every 3 wk	Anti-CD30 conjugated to monomethyl auristatin E (ADC)	M, N&V, fatigue, peripheral neuropathy, anorexia, fever	Hodgkin, anaplastic large cell lymphoma	
Inotuzumab ozogamicin	Bespona, IO	IV	0.8 mg followed by 0.5 mg	Weekly × 3 wk	Anti-CD22 conjugated to calcheamicin (ADC)	Infusion reactions, M, hepatic, sinusoidal obstructive syndrome	B-cell malignancies including ALL	
Blinatumomab	Blincyto	CI	5 mcg/m^2/d × 7 d followed by 15 mcg/m^2/d × 3 wk	Continuous × 4 wk followed by 2-wk break	CD-19, CD-3 (BiTE)	Cytokine release syndrome, fever, neurotoxicity, fatigue, M, edema	ALL	

[a]ADC, antibody-drug conjugate; BiTE, bispecific antibody; IM, intramuscular; IV, intravenous; MoAB, monoclonal antibody; PO, oral; SC, subcutaneous.

[b]CI, continuous infusion; d, day; h, hour; HSCT, hematopoietic stem cell transplant; wk, week.

[c]A, alopecia; GI, gastrointestinal toxicity; HD, high dose; HSR, hypersensitivity reaction; M, myelosuppression; NT, neurotoxicity; N&V, nausea and vomiting; SOS, sinusoidal obstructive syndrome.

[d]↑, increased; ↓, decreased; dCTP, deoxycytidine triphosphate; GT, glutathione-S-transferase; IC, intracellular.

High-Dose Systemic Therapy for Meningeal and Central Nervous System Tumors

Limited CNS penetration of some anticancer agents can be overcome by administering high doses systemically, an approach successfully applied with MTX and cytarabine. The advantages of systemic over intrathecal administration include sustained CSF drug concentrations with prolonged intravenous (IV) infusions and better drug penetration into the

deep perivascular spaces and brain parenchyma. However, MTX concentrations are not uniform throughout the subarachnoid space at steady state during a continuous IV infusion of MTX. The lumbar CSF concentrations are higher than are ventricular CSF concentrations.[26] The other disadvantage of this approach is the potential for severe systemic toxicity.[27]

Very high systemic MTX doses can be safely delivered with leucovorin rescue, and therapeutic CSF concentrations of MTX can be achieved.[28] The CSF penetration of cytarabine is more favorable than that of MTX but is dose dependent. In one study, the CSF:plasma ratio of cytarabine decreased from 33% to 18% with an increase in the dose from 4,000 to 18,000 mg/m^2 administered as a 72-hour infusion.[29] The standard high-dose (3,000 mg/m^2) regimen given every 12 hours results in persistent cytotoxic concentrations of cytarabine in the CSF, in part because the elimination half-life of cytarabine in CSF is eightfold longer than it is in plasma, because of the low levels of cytidine deaminase in the brain and CSF.[30] High-dose IV cytarabine appears to be effective in treating CNS leukemia and lymphoma but is associated with tremendous systemic toxicity.[31]

Other agents for which the systemic approach may be applicable include cyclophosphamide and thiotepa. Cyclophosphamide in high doses (80 mg/kg/d for 2 days) appears to be active against brain tumors.[32] The systemic approach may also be more appropriate for thiotepa. After IV administration, plasma and CSF drug concentrations are equivalent, and significant amounts of the active metabolite, TEPA, also penetrate into the CNS.

Intrathecal Chemotherapy

Poor penetration of systemically administered anticancer drugs into the CSF can be circumvented by direct injection of the agents into the CSF. Intrathecally injected chemotherapy (e.g., MTX, cytarabine) is highly effective as primary or preventive therapy for meningeal leukemia and lymphoma. As a form of regional chemotherapy, intrathecal administration has the advantage of delivering very high drug concentrations to the CSF and meninges with low doses and therefore with minimal systemic toxicity. However, there are disadvantages to intralumbar administration. Repeated lumbar punctures are painful, inconvenient, and may be technically challenging. In 10% of intralumbar injections, the drug is not delivered into the subarachnoid space but is instead injected or leaks into the subdural or epidural space. Because of the slow circulation of the CSF, distribution of drugs within the subarachnoid space, specifically to the ventricles, is not uniform. Ventricular MTX concentrations after an intralumbar dose are highly variable and are less than 10% of ventricular concentrations after direct intraventricular injection.[33] The depth of penetration of effective drug concentrations into the brain parenchyma is limited to a few millimeters for commonly used intrathecal agents. As a result, intrathecal therapy is not likely to be effective for parenchymal brain tumors.[34] Intrathecal therapy is also associated with unique toxicities, such as chemical arachnoiditis.

The distribution of drug from the lumbar sac to the ventricles can be improved by positioning the patient prone for 60 minutes after intralumbar injection. In animals, ventricular MTX concentrations after intralumbar drug administration were more than 20-

fold higher when they were placed in the prone position compared to keeping them upright.[35] Many of the problems associated with intralumbar injection can be overcome with direct intraventricular administration using an Ommaya reservoir or a similar device.[36] Intraventricular therapy is more convenient, less painful, allows for more frequent injections, ensures that the drug is delivered to the subarachnoid space, and results in better drug distribution throughout the CSF.[33] Better drug distribution and more frequent drug administration may account for the improved therapeutic results from intraventricular therapy compared with intralumbar administration in the treatment of recurrent or refractory meningeal leukemia.[37] Ventricular access devices, which, generally, are reserved for patients with relapsed leptomeningeal disease, allow for more flexible drug administration schedules, such as the concentration × time (C×T) schedule (daily for 3 consecutive days). C×T MTX and cytarabine proved to be effective for inducing and maintaining CSF remission in patients with multiply recurrent leptomeningeal leukemia.[38]

There are a limited number of agents that are routinely administered intrathecally. The most commonly used agents are MTX, cytarabine, and hydrocortisone. Less commonly used are thiotepa and topotecan. Details of intrathecal administration of these drugs are included in the description of the systemic use of each drug.

Pharmacogenetics

Genetic factors can influence interpatient variability and impact the efficacy of a drug and the likelihood and severity of toxicity. The field of pharmacogenetics encompasses the study of the influence of germ line genetic variation (polymorphisms) on drug disposition (absorption, distribution, metabolism, and excretion), sensitivity to toxic drug effects,[39] and the effect of somatic gene alterations in the tumor on drug efficacy.

Pharmacogenetically based variability in response to drugs is more apparent for drugs that have a narrow therapeutic index, such as cytotoxic drugs. Phase I enzymes include the cytochrome p450 (CYP) superfamily of enzymes that catalyze oxidation and demethylation reactions. The CYPs are responsible for 70% to 80% of all phase I drug metabolism. The CYP1, CYP2, and CYP3 families are primarily responsible for hepatic drug and xenobiotic metabolism in humans, with CYP3A accounting for the metabolism of nearly half of all drugs (Fig. 10.3). CYP genes known to have functionally relevant polymorphisms include CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2D6. Loss-of-function polymorphisms in CYP3A4 are very rare.[40]

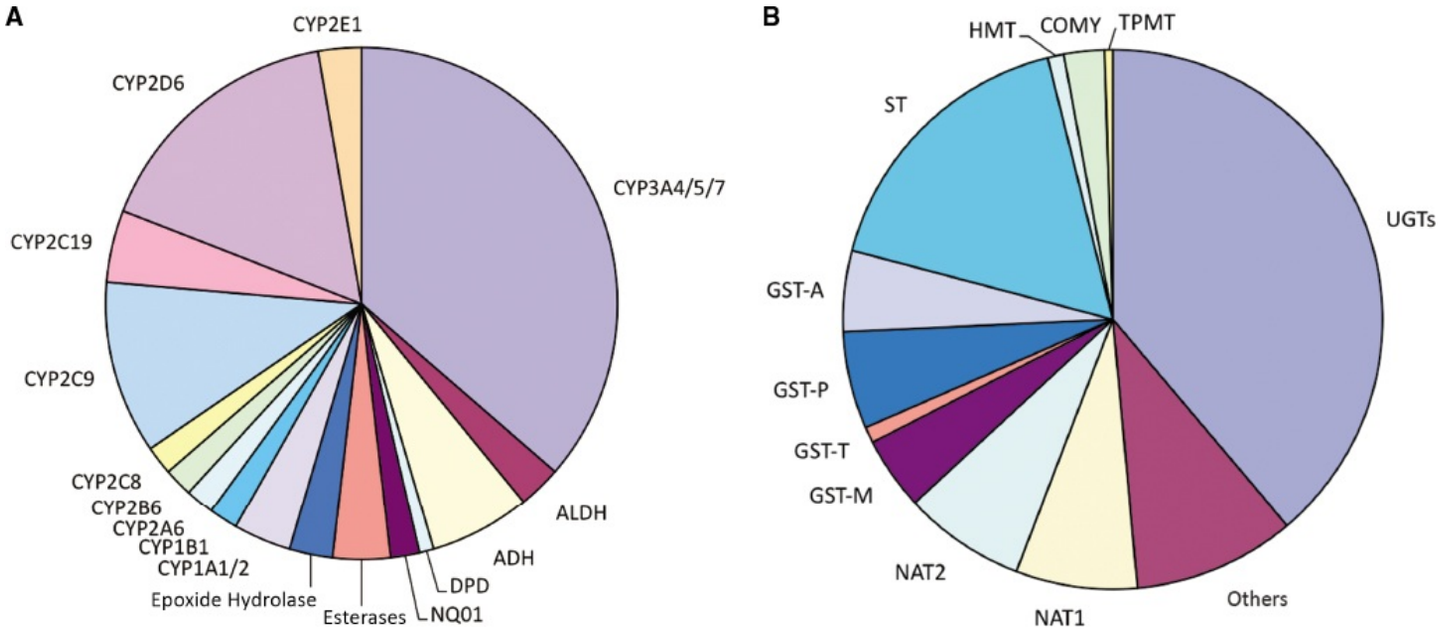


Figure 10.3 **(A)** Phase I and **(B)** Phase II enzymes involved in drug metabolism. Almost all of the major human enzymes responsible for modification of functional groups or conjugation with endogenous substituents exhibit common polymorphisms at the genomic level. The percentage of phase I and phase II metabolism of drugs that each enzyme contributes is estimated by the relative size of each section of the corresponding chart. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; COMT, catechol *O*-methyltransferase; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; GST, glutathione *S*-transferase; HMT, histamine methyltransferase; NAT, *N*-acetyltransferase; NQO1, NADPH:quinone oxidoreductase or DT diaphorase; STs, sulfotransferases; TPMT, thiopurine methyltransferase; UGTs, uridine 59-triphosphate glucuronosyltransferases. (Republished with permission of American Association for the Advancement of Science from Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286(5439):487-491; permission conveyed through Copyright Clearance Center, Inc.)

Phase II enzymes also have functionally relevant polymorphisms (Fig. 10.3). Thiopurine methyl transferase (TPMT), which is the enzyme that methylates the thiol group on mercaptopurine and thioguanine, is the classic example of anticancer drugs. Since the original description of enhanced drug toxicity associated with this genetic variation in TPMT, the identification of the gene encoding the enzyme and the DNA sequence variations associated with this inherited trait have been identified[41] and studied in diverse populations. Another example is irinotecan, the toxicity of which is a function of the pharmacogenetic variation observed in the phase II enzyme UDP-glucuronosyl-transferase.[42]

Variability in the severity of drug-induced toxicities may be related to genetically determined variation in tissue sensitivity to the drugs. For example, germ line variants in several genes, such as CELF4 and RARG, are associated with susceptibility to chemotherapy-induced cardiotoxicity.[43] Genetic differences may also have indirect effects on drug response, as has been observed with methylation of the methylguanine methyltransferase (MGMT) gene promoter. The expression of the DNA repair protein, MGMT, in tumor modulates the response of high-grade gliomas in adults to temozolomide.[44]

Toxicity

Actively dividing normal host cells, such as those in the bone marrow or the mucosal epithelium, are sensitive to the cytotoxic effects of anticancer drugs. The nonselective

mechanisms of action and resulting low therapeutic indices of cytotoxic chemotherapy mean that a high incidence of potentially severe toxicities must be tolerated to administer effective doses. Acute toxicities common to many anticancer drugs include myelosuppression, nausea and vomiting, alopecia, orointestinal mucositis, liver function abnormalities, allergic or cutaneous reactions, and local ulceration from subcutaneous drug extravasation. These acute toxicities occur over hours to weeks after a dose and are usually reversible. Many drugs also have unique toxicities affecting specific organs or tissues, such as cardiotoxicity associated with the anthracyclines; hemorrhagic cystitis associated with cyclophosphamide and ifosfamide; peripheral neuropathy from vincristine, cisplatin, and paclitaxel; nephrotoxicity from cisplatin and ifosfamide; ototoxicity from cisplatin; and coagulopathy from L-asparaginase. Many of these latter toxicities are cumulative (i.e., occur after multiple doses), and, in some cases, they are not completely reversible (e.g., anthracycline cardiotoxicity).

The toxicity profile of molecularly targeted tyrosine kinase inhibitors (TKIs) differs from that of conventional cytotoxic anticancer drugs. TKIs are usually not myelosuppressive, and common toxicities include fatigue, anorexia, nausea, vomiting, diarrhea, abdominal pain, edema, hypertension, and skin rashes including hand-foot skin reactions. Many TKIs have also been associated with thyroid dysfunction[45] and cardiotoxicity.[46]

A significant portion of an oncologist's time is spent in providing supportive care for patients experiencing acute and long-term drug toxicities. A number of therapeutic approaches have evolved to attenuate these toxicities, to make the therapy more tolerable, and to safely increase the dose intensity of regimens by circumventing dose-limiting toxicities. HSCT to rescue patients from myeloablative doses of anticancer drugs is an example of this rescue approach. Other widely used forms of rescue include the administration of leucovorin or glucarpidase to counteract the toxicities of HDMTX, the use of antiemetics to block nausea and vomiting, the use of mesna to prevent the hemorrhagic cystitis caused by the oxazaphosphorines, the use of colony-stimulating factors (e.g., filgrastim, peg-filgrastim) to alleviate myelosuppression, and the use of dexrazoxane to prevent anthracycline cardiotoxicity.

The toxicity of anticancer drugs has a major impact on the dosing of these agents. The endpoint of the phase 1 dose-finding studies for most cytotoxic anticancer drugs is the identification of the MTD, which is considered the optimal dose. The dosing interval (every 21 to 28 days) for cytotoxic anticancer drugs is determined by the duration of acute toxicities, and dose modifications are usually based on the severity or duration of toxicities on the prior treatment cycle. The lifetime cumulative dose of the anthracyclines and bleomycin is limited to prevent cardiotoxicity and pulmonary toxicity.

The severity, incidence, and time course of toxicities are important factors in designing optimal drug combinations or adjusting doses to avoid overlapping toxicities. For example, nonmyelosuppressive agents such as vincristine, prednisone, L-asparaginase, and HDMTX with leucovorin rescue can be administered with traditional myelosuppressive drugs without compromising the dose of myelosuppressive agents. Some regimens administer nonmyelosuppressive agents during the period of marrow suppression from myelotoxic drugs to ensure continuous exposure of the tumor to cytotoxic therapy.

The long-term side effects of cancer chemotherapy are also of particular concern to the

pediatric oncologist because of the high cure rates and the long life spans of successfully treated patients. The adverse late effects of chemotherapy on growth, development, and reproductive function; possible permanent cardiac, pulmonary, or renal damage; and possible carcinogenic and teratogenic effects are discussed in Chapter 45.

Drug Interactions

In addition to being administered in combination regimens, anticancer drugs are administered with antiemetics, antibiotics, analgesics, stool softeners, and other agents used to alleviate the toxicity of chemotherapy or the underlying cancer. This polypharmacy introduces a significant risk of drug interactions. Clinicians must be aware of potential drug interactions, which can alter the disposition of anticancer drugs or alter their effects at the target site in tumor or normal tissues, to avoid unexpected or severe toxicities or antagonism that can diminish a drug's antitumor effect.

Many commonly used anticancer drugs, such as the vinca alkaloids, oxazaphosphorines, epipodophyllotoxins, and taxanes, are metabolized by the CYP3A subfamily of drug-metabolizing enzymes. Drugs (e.g., fluconazole) and some foods (e.g., grapefruit juice) can inhibit or induce the activity of CYP3A and other drug-metabolizing enzymes and thereby alter the metabolism and clearance of anticancer drugs. In the case of cyclophosphamide, which is a prodrug that is activated through hydroxylation by CYP3A4, inhibition of this enzyme may reduce the formation of the active metabolite of cyclophosphamide.

Drug Resistance

Although toxic effects of anticancer drugs are usually predictable, the response of any given tumor to individual agents is not. Clinical resistance to anticancer drugs is the primary reason for treatment failure in childhood cancers. Drug resistance can be present at the outset of treatment or can become clinically apparent under the selective pressure of drug exposure. The magnitude of the problem of drug resistance was appreciated early in cancer chemotherapy for childhood cancers.

The development of most forms of drug resistance has a genetic or epigenetic basis.[4,47] The inherent genetic instability of tumor cells results in the spontaneous generation of drug-resistant clones as a consequence of a mutation, deletion, gene amplification, translocation, chromosomal rearrangement, or alterations in gene expression. These alterations are presumed to be random events, which may account for the variability in response. This genetic and epigenetic basis for drug resistance means that resistance can be inherited by subsequent generations of tumor cells, and under the selective pressure of drug exposure, drug-resistant cancer cells become the predominant subpopulation. At a biochemical level, there are a variety of mechanisms by which tumors become drug resistant. In most cases, these alterations in cellular metabolism can be related to an increase, a decrease, or an alteration in some gene product, for example, the upregulation of asparagine synthase enzyme as the most common mechanism of resistance to asparaginase. Mechanisms of resistance to molecularly targeted receptor and nonreceptor TKIs include point mutations in the kinase domain that lower drug affinity or activation of downstream effectors or

alternative signaling pathways through epigenetic alterations.[48,49]

Genetically based molecular or biochemical alterations in cancer cells can produce anticancer drug resistance that is specific to a single agent or class of agents or provides protection from a broad range of anticancer drugs. In the latter form of resistance, termed multidrug resistance, a single cellular alteration conveys resistance simultaneously to multiple unrelated drugs, including drugs to which the cancer has not been exposed.[50] The best-studied multidrug-resistant phenotypes are associated with decreased intracellular drug accumulation and an increase in plasma membrane, adenosine triphosphate (ATP)-dependent drug efflux pumps such as P-glycoprotein (Pgp) or multidrug resistance protein (MRP).[51]

Other mechanisms for multidrug resistance include an enhanced capacity to repair DNA damage produced by alkylating agents; the detoxification of chemically reactive forms of alkylating agents and anthracyclines by glutathione; decreased levels of topoisomerase II, the target enzyme of the anthracyclines, epipodophyllotoxins, and dactinomycin; and suppression of apoptotic pathways. The loss of DNA mismatch repair activity results in multidrug resistance by impairing the cancer cell's ability to detect DNA damage and activate apoptosis. Intrinsic and acquired resistance to targeted agents include specific kinase mutations that decrease binding to the ATP pocket, mutation in kinase domains, and activation of redundant signaling pathways.[52]

The mechanism of drug resistance is an important consideration in selecting agents to be included in combination regimens or as second-line therapy in patients with a relapse. Ideally, drug combinations should be composed of non–cross-resistant agents, and relapse treatment regimens should avoid the use of drugs that are cross-resistant with drugs used in the frontline regimen. With advances in our understanding of the mechanisms of drug resistance, specific treatment approaches may be devised to prevent the development of or overcome drug resistance in tumor cells.

In the remainder of this chapter, the pharmacologic characteristics of the anticancer drugs used to treat childhood cancers are reviewed. Tables summarize the general pharmacologic properties (Table 10.4) and pharmacokinetic parameters (Table 10.5) of the commonly used anticancer drugs.

TABLE 10.5 Pharmacokinetic Parameters of the Commonly Used Anticancer Drugs

abcdefgiiihhhhhhhhhhhh

Drug	Clearance[a] (mL/min/m^2)	Half-Life[b]	Route of Elimination[c]	Volume of Distribution (L/m^2)[d]	Protein Binding (%)	Bioavailability (% Absorbed)	CSF: Plasma Ratio (%)[e]
Alkylating Agents							
Mechlorethamine		<1 min	D, M				
Cyclophosphamide							
Parent	35–95	2.5–6.5 h	M, r	15–20	20	90	50
4-OH-cyclophosphamide		4 h	M, R		50		10–20
Thiotepa	250–500	2.5 h	M	30	10–20		
Ifosfamide							
Parent	50–130	1–5 h	M, r	20		95	30
4-OH-ifosfamide		4 h	M, R				10–20
Melphalan	200–400	0.5–2 h	D, r	20–30	20–30	32–100	10
Lomustine	(Parent drug ND in plasma)		D, M		>90	50–>90	
Carmustine	1,500–2,000	20 min	D, M	90	65–75		>90
Busulfan	70–100	2.5 h	M, d	10–20	30	70	>95
Cisplatin							
Ultrafiltrate	250	40 min	D, r	12	0	<10	<10
Total platinum	3–6	2–5 d	R		>95		<10
Carboplatin							
Ultrafiltrate	70–120	2–3 h	R, d	10	0	10	20–30
Total platinum		2–5 d	R		20–50		

Dacarbazine	450	40 min	M, R	17	20	Variable	15
Temozolomide	90	1.8 h	D	14		100	30
Procarbazine		<10 min	M			Complete	
Antimetabolites							
Methotrexate	100	8–12 h	R, m	11	60	Variable	2–3
Mercaptopurine	800	<1 h	M, r	22	20	<20 (variable)	25
Thioguanine	1,000–2,000	2 h	M			Low and variable	18
Fludarabine phosphate	70	6–30 h	R	44	20–30	75	
Clofarabine	480	5 h	R, m	170	47		
Nelarabine	4,300	30 min	M, r	197	<25		
ara-G metabolite	175	3 h	M, r	50	<25		
Cytarabine	1,000	2–3 h	M	30	10	<20	20
Gemcitabine	2,200	14–62 min	M	16–27	<10		
Fluorouracil							
Bolus dose	800	10 min	M	15	<10	0–74 (variable)	48
Infusion	3,600		M				10–20
Topoisomerase Inhibitors							
Doxorubicin	500–1,000	30 h	B, M	800	75	Not absorbed	ND in CSF
Daunomycin	1,000	15–20 h	B, M	1,000		Not absorbed	ND in CSF
Idarubicin	1,000	15–20 h	B, M	1,000		20%–30%	ND in CSF[f]
Mitoxantrone	200–600	75 h	B, M	>1,000	78	Not absorbed	Poor
Dactinomycin		36 h	R, B	Large			<10
Etoposide	20–25	2–6 h	M, R	5–10	95	50 (variable)	<5
Topotecan (Lac + HA)[g]	150	3 h	R, m	30	20	30 (variable)	30
Irinotecan (Lac + HA)	250–1,000	4–12 h	M, B, r	90–150	65		15
SN-38 (Lac + HA)		12 h	M, B		96		<10
Tubulin Inhibitors							
Vincristine	450	18 h	M, B	350	75	Poor	5
Vinblastine	400	24 h	M, B	800	75	Poor	
Vinorelbine	800	15 h	M, B	550	80–90	25–40 (variable)	
Paclitaxel	150	20 h	M, B	50–100	88–98		ND in CSF
Docetaxel	350	12 h	M, B	100	80		
Miscellaneous							
Arsenic trioxide		12 – >24 h	M		75		
Asparaginase							
E. coli	1.4	24 h	M	3		Not absorbed	ND in CSF[i]
Erwinia	3.4	10 h	M	5		Not absorbed	ND in CSF[i]
PEG-asparaginase	0.15	5–7 days	M	2		Not absorbed	ND in CSF[i]
Bleomycin	40	3 h	R, m	10		Not absorbed	
Dexamethasone	200–250	4 h	M	50	70	85	15
Prednisolone	250	2.5 h	M	50	70–>95	85	<10
All-*trans*-retinoic acid	300–4,800 (day 1 only)	45 min	M		>99		<10
13-*cis*-retinoic acid	90	10–20 h	M	31	>99	50–75	
Trabectedin	300	105–175 h	M	>2,500	97	—	
Small-Molecule Pathway Inhibitors							
Imatinib	180	9–15 h	M, r	165	95	98	
Dasatinib	3,000	2–3 h	M, r	>1,000[h]	96		

Ruxolitinib	140	2.5–3 h	M, r	35	97	95	
Crizotinib	700	36 h	M, r	980[h]	91	45	
Ceritinib[h]	300	41 h	M	>1,000	97		
Lorlatinib[h]	160	24 h	M, R	170	66	81	
Larotrectinib	900	2.9 h	M, r	27	70	35	
Vemurafenib[h]	12	57 h	M	60	99		
Selumetinib	110	5–10 h	M		98	65	14 (unbound)
Sorafenib	65[h]	35h[h]	M		99.5	40	3 (unbound)
Sunitinib	375[h]	50h[h]	M, r	>1,000[h]	95		
Pazopanib	5	31 h	M		99		
Vandetanib	100	19 d	M, R	>1,000[h]	93		
Monoclonal Antibodies							
Rituximab[h]	0.13	18 d		1.7			
Dinutuximab	0.15	10 d		5.4			
Bevacizumab	0.1	12 d		2			
Gemtuzumab ozogamicin	3.2 (antibody)	60–90 h	M (calicheamicin)	12 (antibody)	97 (calicheamicin)		
Brentuximab vendotin		4–6 d (total) 3–4 d (MMAE)	B, R (MMAE)	5–7 (total)	68–82 (MMAE)		
Inotuzumab ozogamicin	0.3 (total)	12.3 d (total)	M (calicheamicin)	6 (total)	97 (calicheamicin)		
Blinatumomab		2 h	M	2.5			

[a]For oral drugs, the apparent clearance is reported.

[b]Post-distributive or terminal half-life; min, minutes; h, hours.

[c]D, spontaneous chemical decomposition; M, metabolism (biotransformation); R, renal excretion; B, biliary excretion; RES, reticuloendothelial system; a lower case letter (d, m, r, b) indicates that this is a minor route for elimination of the drug.

[d]Volume listed is the steady-state volume of distribution.

[e]CSF, cerebrospinal fluid; ND, not detectable.

[f]The active metabolite idarubicinol is detectable in CSF.

[g]HA, hydroxy acid; Lac, lactone. The combination represents total drug.

[h]Parameter estimate from adult studies.

[i]Asparaginase is ND in CSF, but CSF asparagine is depleted with systemic administration of asparaginase.

ALKYLATING AGENTS

The alkylating agents have a broad range of clinical activity in childhood cancers. These drugs are chemically reactive compounds that exert their cytotoxic effect through the covalent bonding of an alkyl group to important cellular macromolecules (Fig. 10.4). Although a number of nucleophilic macromolecules and their precursors are potential targets for alkylation intracellularly, damage to the DNA template and the resulting induction of apoptosis appears to be the major determinant of cytotoxicity. With the bifunctional alkylating agents that have two alkylating groups, this damage appears to result primarily from interstrand and intrastrand DNA–DNA and DNA–protein cross-links.[53]

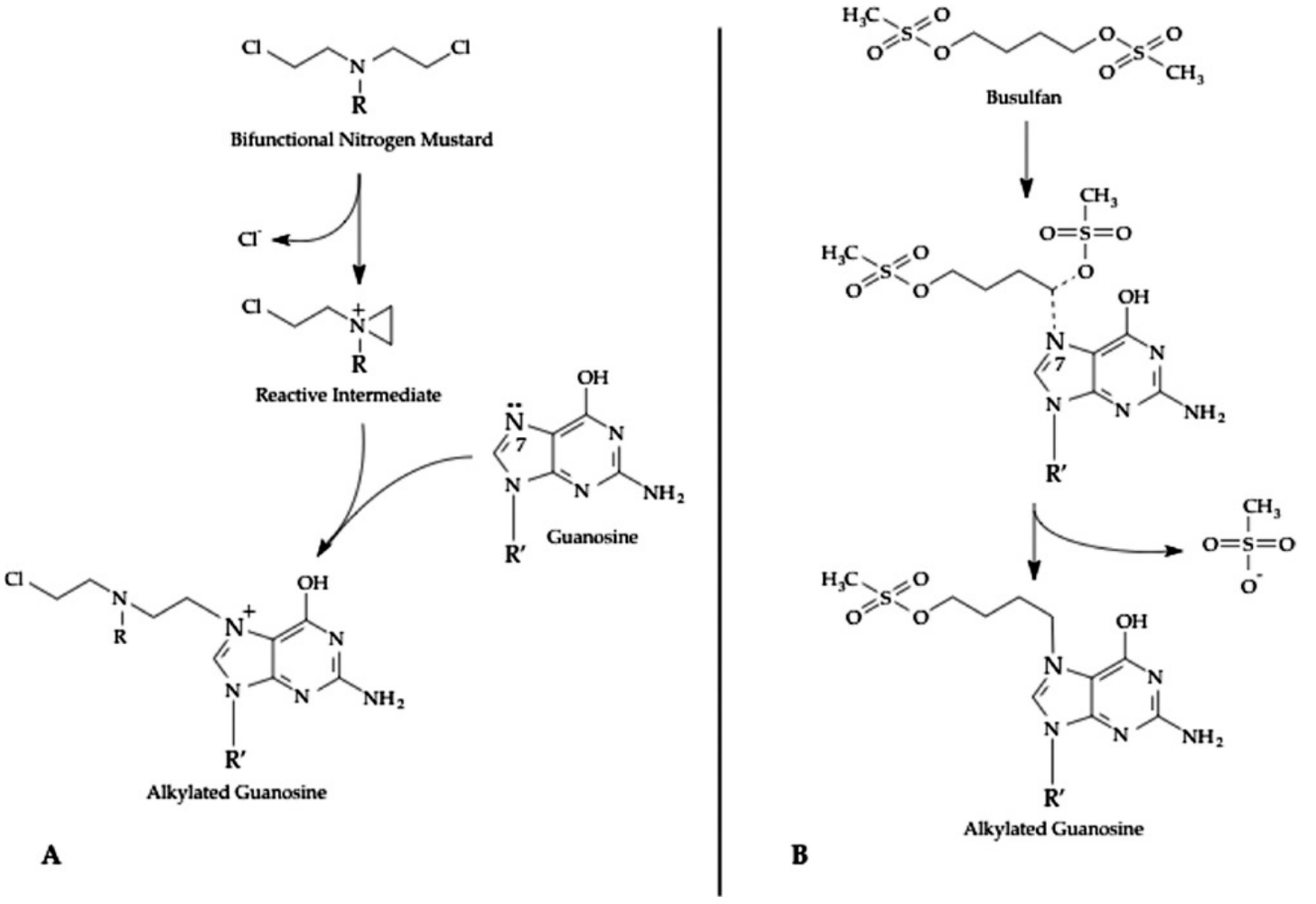


Figure 10.4 Mechanisms of alkylation of the nucleophilic N^7 position of guanosine. **(A)** The bifunctional nitrogen mustard illustrates the S_N1 type of alkylation reaction, in which a reactive intermediate forms spontaneously and then rapidly reacts with the nucleophilic group. The rate-limiting step for S_N1 alkylation is the formation of the reactive intermediate, and thus the reaction exhibits first-order kinetics (i.e., independent of the target nucleophile concentration). If the second chloroethyl group also reacts with another nucleotide base, a cross-link is formed. **(B)** Busulfan exemplifies an S_N2 reaction, characterized by a bimolecular nucleophilic displacement. In this case, the methylsulfonate group on either end of busulfan is displaced by the nucleophilic group on guanosine. The rate of S_N2 alkylation reactions depends on the concentration of the alkylating agent and the target nucleophile, and it therefore follows second-order kinetics.

Alkylating agents have steep dose–response curves in experimental model systems. A log-linear relationship exists between tumor cell killing and the concentration of the alkylating agent, and this correlation is maintained through 4 to 5 orders of magnitude of cell killing. This steep dose–response relationship for alkylating agents provides a strong rationale for their use in high-dose therapy regimens. Because of the significant myelosuppressive effects of these drugs, high-dose alkylator therapy is generally administered in conjunction with HSCT to prevent permanent bone marrow aplasia.

Myelosuppression is the major dose-limiting toxicity for most alkylating agents. Other common acute toxic effects include nausea and vomiting, alopecia, allergic and cutaneous reactions, and gastrointestinal and neurologic toxicity at high doses. Of particular concern are the potential long-term effects of alkylator therapy such as gonadal atrophy that permanently affects reproductive function. The nitrogen mustards and the nitrosoureas have been linked to

pulmonary fibrosis, and nephrotoxicity of the nitrosoureas, cisplatin, and ifosfamide can permanently impair renal function. These agents are also highly carcinogenic, mutagenic, and teratogenic.

The pharmacokinetics of the alkylating agents has been difficult to study because the chemical reactivity and inherent chemical instability of the active alkylating species make their measurement in biologic fluids difficult. Spontaneous hydrolysis of alkylating agents or their active metabolites in solution can be a major route of drug elimination. Most alkylating agents also undergo some degree of enzymatic metabolism, which can produce active and inactive metabolites.[54]

Of the various classes of alkylating agents, the nitrogen mustards and the nitrosoureas are most frequently used in the treatment of the childhood cancers. The chemical structures of these agents and several nonclassical alkylators are shown in Figures 10.4 to 10.7, 10.9, and 10.11.

Nitrogen Mustards

The nitrogen mustards were the first class of alkylating agents used to treat cancer and remain the most widely used for childhood cancers. Mechlorethamine (nitrogen mustard), introduced into clinical trials in 1942, was the first drug demonstrated to be effective in the treatment of human cancers. Synthetic nitrogen mustard analogs with greater chemical stability and other pharmacologic advantages have largely supplanted mechlorethamine in clinical practice. Cyclophosphamide and its isomer ifosfamide are the most widely used in pediatric oncology (Fig. 10.5).

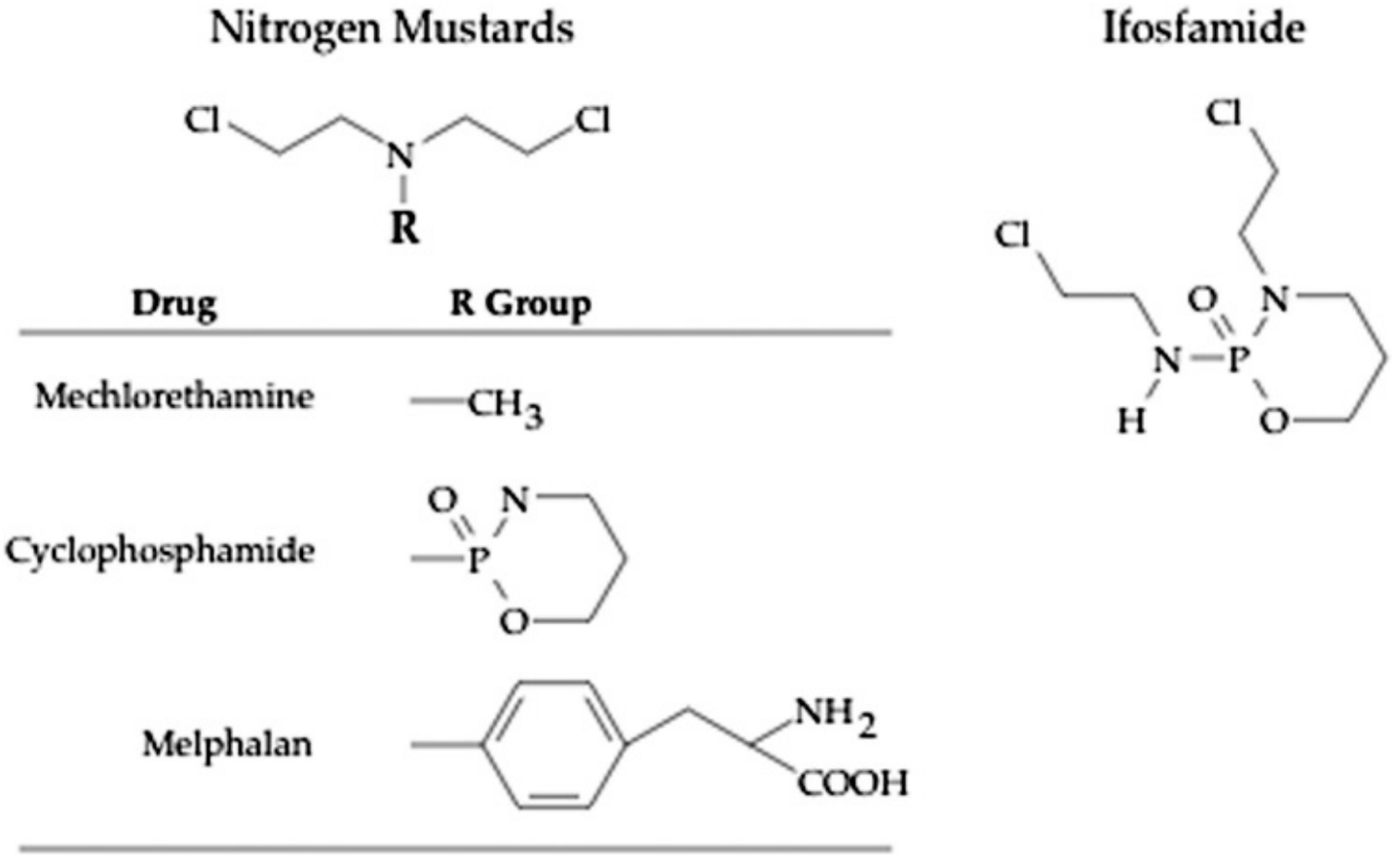


Figure 10.5 Chemical structures of the nitrogen mustard alkylating agents and the cyclophosphamide isomer, ifosfamide.

Mechlorethamine

The chemical reactions of bifunctional alkylators can be exemplified by mechlorethamine (Fig. 10.4). The spontaneously formed alkylating intermediate is highly chemically reactive and rapidly undergoes hydrolysis, leading to inactivation, or it alkylates a wide variety of molecules, with a propensity to react with the N^7 position on guanosine.[53]

Mechlorethamine has been used primarily in combination with vincristine, prednisone, and procarbazine (MOPP) for the treatment of Hodgkin lymphoma, but the MOPP regimen has been supplanted as standard therapy for this disease. The pharmacokinetics of mechlorethamine in humans has not been well delineated. In animals, the drug disappears from plasma in seconds.[54] In addition to its rapid spontaneous hydrolysis, mechlorethamine is rapidly metabolized (N-demethylated) in the liver. As a result of this rapid degradation, renal excretion is not likely to play a role in drug clearance.

In addition to its major clinical toxicities of myelosuppression, nausea, and vomiting, mechlorethamine has an anticholinergic effect, leading to diaphoresis, lacrimation, and diarrhea. Neurotoxicity in the form of an acute or delayed encephalopathy has been reported with the use of high doses of mechlorethamine. It is a potent vesicant, producing a sclerosing thrombophlebitis above the site of administration and severe local tissue damage if extravasated. If extravasation occurs, sodium thiosulfate should be injected into the area as rapidly as possible to neutralize the drug.[55]

Bendamustine

Bendamustine, a bifunctional molecule with both alkylating and antimetabolic properties, has been used for many years in Europe and was approved by the U.S. Food and Drug Administration (FDA) in 2008 for the treatment of indolent B-cell lymphoma.[56] It is also indicated for adults with chronic lymphoblastic leukemia and non-Hodgkin lymphoma (NHL). Because of this unique bifunctionality, bendamustine is thought to have a distinct activity and resistance profile that differentiates bendamustine from other alkylating agents. Bendamustine is extensively metabolized to active metabolites and excreted by both the liver and the kidneys; clearance is rapid and the steady-state volume of distribution is limited, and, as such, the reported half-life is less than 1 hour.[57] Dose-limiting toxicity includes myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, and skin reactions.

Thiotepa

Thiotepa, an ethylenimine-type alkylator, is chemically related to nitrogen mustards and capable of cross-linking DNA. Release of ethylenimine radicals results in the disruption of DNA bonds, primarily initiated by the alkylation of guanine at the N^7 position. Limited pharmacokinetic data in adults suggest that when administered intravenously, the elimination half-life is approximately 2.5 hours. Metabolism is primarily through CYP2B6 and CYP3A4.

The major metabolite, TEPA, is also cytotoxic, and is found in both serum and urine. In children, the pharmacokinetics of thiotepa is similar to that of adults.[58] Adverse events include bone marrow suppression, occasionally severe, liver toxicity, and pulmonary toxicity. Sinusoidal obstructive syndrome (SOS) has been reported. Severe desquamation has been reported, including in children.[59]

Intrathecal Thiotepa

Thiotepa can be safely administered intrathecally at a dose of 10 mg and is sometimes used as a second-line agent for childhood meningeal cancers, although it does not appear to be of substantial benefit.[60] Thiotepa toxicity is similar to that of intrathecal MTX. However, thiotepa is highly lipophilic and diffuses rapidly out of the CSF, leading to limited drug distribution within the subarachnoid space. After intraventricular administration, thiotepa is rapidly cleared from the CSF at a rate 10-fold higher than that of CSF bulk flow and exposure in the lumbar CSF is less than 10% of that achieved in the ventricle.[61]

Oxazaphosphorines

Cyclophosphamide/Ifosfamide

The oxazaphosphorines, cyclophosphamide and ifosfamide, are inactive prodrugs that require biotransformation by hepatic microsomal oxidative enzymes before expressing alkylating activity.[62] Cyclophosphamide is a true nitrogen mustard derivative with a bifunctional bischloroethylamine side chain. Ifosfamide is also bifunctional but has one chloroethyl group shifted to a ring nitrogen (Fig. 10.5). Cyclophosphamide is one of the most widely used anticancer drugs, with a broad range of clinical activity that includes the acute leukemias and a variety of solid tumors (Table 10.1). It is also used in preparative regimens before HSCT and as an immunosuppressant in nonmalignant disorders. Ifosfamide has activity as a single agent or in combination with etoposide in sarcomas (e.g., Ewing sarcoma, rhabdomyosarcoma, osteosarcoma), lymphoma, germ cell tumors, Wilms tumor, and neuroblastoma.

Cyclophosphamide is usually administered as a single-dose bolus or in fractionated doses over 2 to 5 days. Ifosfamide is administered in a fractionated schedule over 5 days, because in the initial trials, the single-dose schedule produced intolerable nephrotoxicity, cystitis, and neurotoxicity. Ifosfamide has also been administered as a continuous 5-day infusion. The maximally tolerated total dose of ifosfamide is approximately three- to fourfold higher than an equitoxic dose of cyclophosphamide.[63]

Biotransformation

The metabolic pathways of cyclophosphamide and ifosfamide are shown in Figure 10.6. The steps in the biotransformation of these two drugs are qualitatively identical. However, quantitatively, the rate of activation of cyclophosphamide is greater than that of ifosfamide, and this difference in the rate of activation accounts for the difference in clinical pharmacokinetics and MTD of the two isomers.[64]

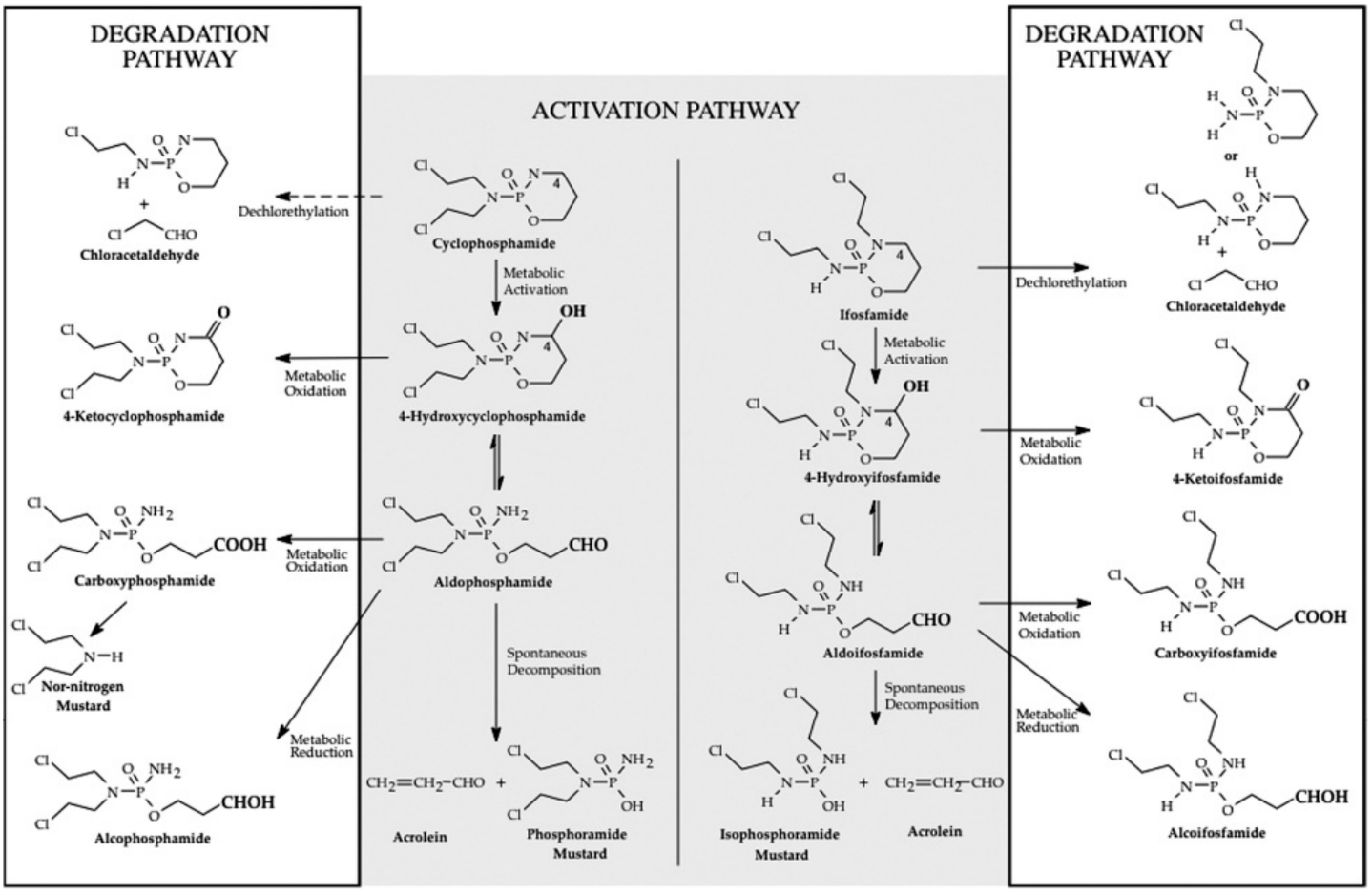


Figure 10.6 Metabolic pathways for the oxazaphosphorines, cyclophosphamide and ifosfamide. Both compounds must undergo hydroxylation at the 4-position before expressing alkylating activity; this reaction is catalyzed by hepatic microsomal enzymes. The 4-hydroxy metabolites are in spontaneous equilibrium with the open-ring aldehydes (aldophosphamide or aldoifosfamide), which can release acrolein and form the active alkylating mustards (phosphoramide mustard or isophosphoramide mustard). Further oxidation at the 4-position of the primary metabolites leads to the formation of inactive metabolites (ketocyclophosphamide and carboxyphosphamide or ketoifosfamide and carboxyifosfamide), which are excreted in the urine. The open-ring aldehyde metabolites can be chemically reduced to an alcohol (alcophosphamide or alcoifosfamide). Inactivation by dechlorethylation leads to formation of the potentially toxic by-product chloracetaldehyde. This is a minor pathway for cyclophosphamide but more active with ifosfamide.

Further oxidation of the hydroxyl group at the 4-carbon position on primary metabolites by aldehyde dehydrogenase leads to inactivation. 4-Ketocyclophosphamide and carboxyphosphamide are the principal urinary metabolites of cyclophosphamide. Aldehyde dehydrogenase is found in a wide variety of tissues and in cancer cells. The chloroethyl side chain can also be enzymatically cleaved by CYP3A4. Less than 10% of the administered dose of cyclophosphamide is metabolized via this pathway, but up to 50% of the ifosfamide is dechlorethylated, resulting in a greater rate of production of the potentially toxic by-product chloracetaldehyde compared with cyclophosphamide.[64,65]

Pharmacokinetics

The pharmacokinetic behavior of unchanged cyclophosphamide and ifosfamide has been well described. When administered orally in low doses, 75% to 95% of the cyclophosphamide is absorbed. The minimal first-pass metabolism after oral administration

indicates that the hepatic extraction ratio for cyclophosphamide is low. Plasma concentrations of the active metabolites, 4-hydroxycyclophosphamide and phosphoramide mustard, after oral administration are equivalent to those achieved with IV administration.[66] The oral bioavailability of ifosfamide is greater than 95%.[67] Peak concentrations of 4-hydroxy-ifosfamide and chloracetaldehyde were twofold higher than those achieved with the same dose administered intravenously.[68]

Cyclophosphamide and ifosfamide are eliminated primarily by hepatic biotransformation to active and inactive metabolites, which are excreted mainly in the urine. Less than 20% of the dose is excreted as unchanged drug in the urine, and biliary excretion of unchanged drug is minimal.[69] The total body clearance in adults is 30 to 35 mL/min/m^2 and 60 to 80 mL/min/m^2 for cyclophosphamide and ifosfamide, respectively.[70,71] Total clearance of cyclophosphamide in children (40 to 50 mL/min/m^2) appears to be higher than it is in adults. The plasma half-life in children (3 to 4 hours) is also reported to be shorter than that in adults (6 to 8 hours). Ifosfamide clearance in children ranges from 50 to 130 mL/min/m^2, similar to that reported in adults, and the half-life of ifosfamide in children is 1 to 5 hours.

Cyclophosphamide and ifosfamide can rapidly induce their own metabolism. With infusional or fractionated dosing, there is a decrease in the plasma half-life and an increase in clearance of the parent prodrugs and an increase in metabolite concentrations. Cyclophosphamide exposure induces the expression of CYP2C9 and CYP3A4 enzyme levels in human hepatocytes. The increase in the rate of metabolism occurs within 12 to 24 hours of the first dose, and a new steady state is achieved by 48 to 72 hours.[72] Over a 5-day course of ifosfamide, the parent drug half-life decreases and the clearance increases by 30% to 50%. Although several studies have found that the apparent clearance of ifosfamide and its metabolites is greater when the drug is administered as a continuous infusion,[73] an observation that would favor administration of the drug on a fractionated schedule, a crossover study in adult patients could not find a significant difference in drug disposition between the two schedules of administration.[74]

The fraction of the cyclophosphamide dose that is converted to active metabolites appears to be constant (60% to 70% of the dose), and there is no evidence of saturation of the activating enzymes over a broad dosage range of 100 to 3,000 mg/m^2. However, at doses of 4,000 mg/m^2 used in autologous bone marrow preparative regimens, saturation of drug-activating enzymes becomes apparent.[75] Saturation (nonlinearity) of ifosfamide metabolism has also been described at doses exceeding 2,500 mg/m^2. The half-life was prolonged to 15 hours, a higher percentage of the drug is excreted in the urine unchanged, and the AUC of ifosfamide metabolites do not increase in proportion to the dose.[69]

The activated metabolites of cyclophosphamide and ifosfamide appear in plasma rapidly, reach a peak by 2 hours after the dose, and have a half-life of approximately 4 hours.[66] At equivalent doses, the plasma concentrations of alkylating metabolites of ifosfamide are approximately one-third that generated from cyclophosphamide, presumably because of a difference in the rate of enzymatic activation.[64,65] Plasma concentrations of the active metabolites are considerably lower than those of the parent prodrug, because of the chemical instability and reactivity of the active 4-hydroxy metabolites. The plasma concentration of the active 4-hydroxy metabolites is approximately 1% to 3% of that of the parent drug.[76]

Patients with severe renal function impairment (i.e., creatinine clearance less than 20 mL/min) have moderately higher parent drug concentrations[77] and significantly higher plasma alkylating activity. However, in a single anuric patient, no change in the disposition of cyclophosphamide and its activated metabolite was found,[78] and ifosfamide disposition did not appear to be altered in an anuric child.[79] The degree of cyclophosphamide-related hematologic toxicity does not correlate with the severity of renal insufficiency. There is no strong evidence to support dosage modifications of cyclophosphamide in patients with renal dysfunction; however, ifosfamide dosage adjustment may be indicated because of the increased risk of neurotoxicity in patients with renal dysfunction.[79,80] Cyclophosphamide and ifosfamide can be efficiently removed from blood by dialysis.[81] The hemodialysis extraction efficiency for 4-hydroxyifosfamide is lower than it is for the parent drug.[79] Hepatic dysfunction may alter the rate of drug activation and the rate of elimination. With hepatic damage, the half-life of cyclophosphamide is prolonged, and peak concentrations of alkylating activity in plasma are lower.[82]

Toxicity

Myelosuppression is the major dose-limiting toxicity of the oxazaphosphorines, but unlike the lipid-soluble alkylating agents, such as the nitrosoureas, they rarely cause cumulative marrow damage. Nausea, vomiting, and alopecia occur in most patients.[62,83]

Hemorrhagic cystitis is a toxicity that is unique to the oxazaphosphorines. It may range from mild dysuria and frequency to severe hemorrhage from bladder epithelial damage. The reported incidence of this complication ranges from 5% to 10% for cyclophosphamide and 20% to 40% for ifosfamide. This toxic effect is dose related and appears to be caused by the activated metabolites and by the biologically active by-products, such as acrolein (Fig. 10.6). The incidence and severity of chemical cystitis can be lessened by aggressive hydration and frequent emptying of the bladder, by bladder irrigation, or by the concurrent administration of mesna (2-mercaptoethane sulfonate). After administration, mesna is rapidly oxidized in plasma to a chemically stable and pharmacologically inert disulfide, which is then rapidly excreted by the kidneys and converted back to its chemically reduced active form during tubular transport. It is therefore only active in urine and does not interfere with the antitumor effects of cyclophosphamide or ifosfamide.[84] Although the dose and schedule of mesna varies, it is commonly administered at a dose equal to 60% of the total ifosfamide dose, divided into three doses and administered at 0, 4, and 8 hours after ifosfamide. Mesna can be administered orally or intravenously. Mesna also reduces the incidence of oxazaphosphorine-induced bladder cancers in rats, a complication that has been reported in humans.

The oxazaphosphorines are nephrotoxic. Cyclophosphamide can have a direct renal tubular effect that can result in water retention.[85] Ifosfamide produces proximal tubular damage resembling Fanconi syndrome, with glucosuria, amino aciduria, and phosphaturia. Animal studies suggest that it is the ifosfamide metabolite chloracetaldehyde, acting on mitochondrial NADH:uqiquinone oxioreductase in the renal tubule, which is the primary mediator of nephrotoxicity.[86] Rickets has been observed in younger children.[87] Decreased glomerular filtration rate (GFR) and distal tubular damage manifested by concentrating defects and renal tubular acidosis also have been reported. Comprehensive follow-up

evaluation of glomerular and tubular function in children previously treated with ifosfamide revealed dysfunction in 78%, including 28% with moderate or severe nephrotoxicity.[88] Cumulative doses of 45 to 80 g/m^2 or greater appear to be the primary risk factor,[89] with young children appearing to be at higher risk for proximal renal tubular damage.

Other toxic effects of ifosfamide include reversible neurotoxicity characterized by somnolence, disorientation, and lethargy in about 10% to 40% of patients and, more rarely, hallucinations, coma, and seizures.[90] The incidence of neurotoxicity was 50% with oral administration, presumably the result of first-pass metabolism of ifosfamide to neurotoxic metabolites. The neurotoxicity has been attributed to the metabolite chloracetaldehyde (Fig. 10.6), which results from dechlorethylation of ifosfamide.[91] The dechlorethylation pathway accounts for 50% of ifosfamide metabolism but less than 10% for cyclophosphamide. The incidence of neurotoxicity also appears to be greater in children who previously received high cumulative doses of cisplatin. Neurotoxicity may be reversible or preventable with methylene blue,[92] but its actual efficacy remains uncertain. Transient hepatic dysfunction has also been reported with ifosfamide. Cardiac toxicity has been observed in patients treated with high doses (≥100 to 200 mg/kg) of cyclophosphamide. Ifosfamide has also been implicated as a cause of cardiomyopathy and arrhythmias at doses of 10 to 18 g/m^2 in an HSCT setting.

Although pulmonary toxicity is not commonly associated with the oxazaphosphorines, cases of early- and late-onset interstitial pneumonitis from cyclophosphamide and ifosfamide have been reported. Factors that appear to augment oxazaphosphorine lung damage include administration of cyclophosphamide in combination with other cytotoxic drugs or irradiation.

Drug Interactions

Compounds known to alter the activity of p450 microsomal enzymes can affect the rate of activation and elimination of the oxazaphosphorines. Phenobarbital pretreatment enhances the rate of metabolism of cyclophosphamide and its activated metabolites in animals and in humans[93]; similar induction may also occur with phenytoin. When cyclophosphamide is administered less than 24 hours after a dose of busulfan, as can be done in HSCT preparatory regimens, busulfan can block the conversion of cyclophosphamide to its active metabolite.[94] The neurokinin-1 receptor antagonist aprepitant, a moderate inhibitor of CYP3A4,[95] can inhibit metabolism of cyclophosphamide and thiotepa, but the overall impact is small relative to the overall variability observed.[96] Aprepitant may be associated with increased ifosfamide neurotoxicity.[97]

Melphalan

Melphalan (L-phenylalanine mustard, Fig. 10.5) is a rationally designed anticancer drug that has the bischloroethylamine moiety attached to the amino acid phenylalanine, with the intention that it would be taken up preferentially by melanin-producing cancers. Although this agent has a broad range of clinical activity in adult cancers, its use has been limited in the treatment of childhood cancers. At high but nonmyeloablative doses (35 mg/m^2), melphalan is active against rhabdomyosarcoma. The administration of bone marrow ablative

doses (140 to 220 mg/m^2) of melphalan followed by rescue with autologous HSCT has resulted in high response rates in children with neuroblastoma, Ewing sarcoma, and acute leukemia[98] and has been used in reduced-intensity conditioning regimens in children with acute leukemia.[99] Melphalan has also been administered intra-arterially by isolated perfusion for cancers localized to an extremity or the liver,[100] as well as intraocularly for retinoblastoma, either alone or in combination with other agents such as topotecan.[101]

As with other chemically reactive compounds, melphalan is rapidly cleared from the body. It is inactivated after spontaneous hydrolysis or alkylation reactions with plasma or tissue proteins. Melphalan does not appear to undergo any appreciable enzymatic degradation. The absorption of melphalan after oral administration has been reported to be incomplete and highly variable. The fraction of a dose absorbed usually ranges from 32% to 100%, but patients with no detectable drug in plasma and urine after an oral dose have been reported.[102] The incidence of myelosuppression is lower with oral than with IV melphalan, and poor therapeutic response may be attributable in part to poor absorption in some patients receiving oral melphalan. The disposition of melphalan after IV administration in children and adults is similar.[103] With standard parenteral doses, the terminal half-life ranges from 60 to 120 minutes, with a total clearance exceeding 200 mL/min/m^2. Pharmacokinetic parameters in patients receiving high-dose therapy (up to 220 mg/m^2) are similar to those found at standard doses.[104]

Renal excretion is a minor route of melphalan elimination, accounting for 20% to 30% of total drug clearance. However, patients with renal dysfunction have a higher incidence of hematologic toxicity.[105] In a group of patients with a wide range of renal function, drug clearance after high-dose melphalan was correlated with creatinine clearance, but the decrease in melphalan clearance in patients with renal dysfunction was insignificant compared with the high degree of interindividual variation in drug disposition.[106] In children previously treated with carboplatin, melphalan clearance was approximately two-third of that observed in other children.[107]

At standard doses (5 to 35 mg/m^2), myelosuppression is the primary toxicity, and cumulative marrow damage has been observed with repeated doses. Pulmonary fibrosis and secondary leukemia are late effects associated with the chronic administration of melphalan. At high doses with autologous bone marrow or stem cell reinfusion, gastrointestinal toxicity (e.g., mucositis, esophagitis, diarrhea) becomes dose limiting.

Nitrosoureas

Carmustine/Lomustine

The nitrosoureas are a group of lipid-soluble alkylating agents (Fig. 10.7) that are highly active in experimental tumor models, including intracranially implanted tumors. The 2-chloroethyl derivatives, carmustine (BCNU) and lomustine (CCNU), are the nitrosoureas most widely used in pediatric oncology. Rapid spontaneous chemical decomposition of these compounds in solution generates an alkylating intermediate (chloroethyldiazohydroxide) and an isocyanine moiety that can carbamoylate amine groups on proteins. Alkylation, including

cross-linking of DNA by the monofunctional lomustine and the bifunctional carmustine, is generally accepted as the primary mechanism of action of the nitrosoureas. However, the isocyanates can inhibit DNA repair of alkylator damage and may contribute to the antitumor activity and the toxicity of the nitrosoureas. The nitrosoureas alkylate the N^3 position on cytidine and the N^7 and O^6 positions on guanosine,[53] but the primary factor determining tumor cell resistance to the nitrosoureas is the capacity to enzymatically repair O^6-alkyl-guanosine.[108]

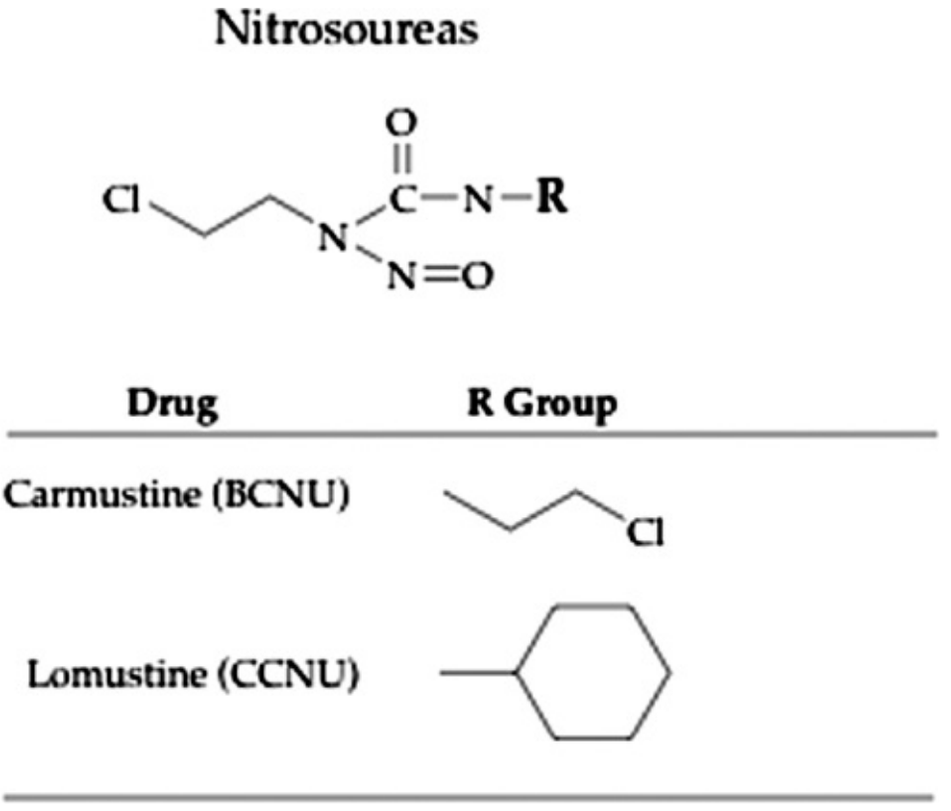


Figure 10.7 Chemical structures of the nitrosoureas, carmustine and lomustine.

The nitrosoureas have been used primarily to treat patients with brain tumors or lymphomas, and high-dose carmustine has been incorporated into HSCT preparative regimens. Delayed and cumulative myelosuppression and other serious long-term cumulative renal and pulmonary toxic effects, which are particularly concerning in children, limit the clinical utility of these agents in combination regimens.[109] Carmustine has been incorporated into biodegradable polymer wafers that can be implanted into the tumor cavity after surgical resection for brain tumors. Drug is released slowly from the polymer wafer over 2 weeks, providing prolonged sustained exposure to high concentrations of carmustine locally with a lower risk of systemic toxicity.[110]

Biotransformation and Pharmacokinetics

In addition to their rapid spontaneous decomposition, nitrosoureas undergo significant hepatic metabolism. As a result of this rapid spontaneous and enzymatic degradation, the clearance of nitrosoureas from plasma is extremely rapid. In early studies of carmustine and lomustine, the parent drug could not be detected in plasma after IV or oral administration.[111]

With high-dose carmustine administered by IV infusion, the half-life was 22 minutes, and clearance exceeded 2,000 mL/min/m^2.[112] Similar results have been reported with standard doses of the drug (half-life, 22 minutes; clearance, 1,700 mL/min/m^2).[113] The half-life of the active 4-hydroxy metabolites of lomustine is 3 hours.[114] When administered orally, the nitrosoureas are well absorbed, and lomustine is extensively converted to hydroxylated metabolites presystemically during its first pass through the liver. These results confirm that the metabolites of lomustine are primarily responsible for the drug's antitumor activity. Although carmustine is also well absorbed, severe vomiting after oral administration frequently precludes adequate absorption.[115]

The lipid-soluble nitrosoureas are widely distributed and readily penetrate into the CNS. After equilibration, drug concentrations in the CSF approximate those in plasma, which in part accounts for the activity of this group of drugs in treating brain tumors. Implantation of carmustine-containing polymer wafers into the tumor bed for brain tumors bypasses the BBB and provides local drug concentrations that are higher than those achieved with systemic administration. However, the depth of penetration into the brain parenchyma from the wafer is very limited (5 mm at 30 hours) because of the rapid diffusion of drug into capillaries.[116]

Toxicity

Gastrointestinal toxicity (i.e., nausea and vomiting) and cumulative delayed myelosuppression are the most consistent side effects of the nitrosoureas. The nadir of blood counts occurs 4 to 5 weeks after administration, and the platelet count tends to be the most affected. With repeated dosing, chronic marrow hypoplasia develops. Cumulative doses (≥1,500 mg/m^2) of carmustine are associated with renal atrophy[117] and progressive and frequently fatal pulmonary toxicity characterized by cough, dyspnea, tachypnea, and a restrictive-type ventilatory defect. Carmustine-induced pulmonary toxicity can vary substantially in manifestations, outcome, and histopathologic appearance, with the risk of developing significant pulmonary symptoms remaining elevated for many years following completion of therapy. Females appear to be more susceptible to the complication than are males, and a history of atopy may increase the risk of pulmonary complications.[118] Pulmonary fibrosis appears less frequent with lomustine. CNS toxicity has been reported rarely. High-dose carmustine (300 to 750 mg/m^2) can produce hypotension, tachycardia, flushing, and confusion.[113]

Dimethanesulfonates

Busulfan

The bifunctional alkylating agent busulfan is an alkyl alkane sulfonate. The busulfan alkylation reaction occurs by nucleophilic displacement of the methylsulfonate group on either end of the molecule (Fig. 10.4). Busulfan has a greater propensity to alkylate thiol groups on amino acids and proteins than do the nitrogen mustards, but it also can alkylate the N^7 position on guanosine.

Busulfan is not water soluble and is commercially available as oral and IV formulations.

Busulfan has been used in conventional doses (1.8 mg/m^2/d) as palliative therapy for chronic myelogenous leukemia, and high-dose busulfan (16 mg/kg or 600 mg/m^2, in 16 divided doses every 6 hours) is an important component of many HSCT preparative regimens, usually in combination with cyclophosphamide.[119]

The pharmacokinetics of oral busulfan is highly variable and age dependent.[120] Oral busulfan is rapidly absorbed, peaking 1 to 2 hours after the dose, with an average bioavailability of 70% (range, 40 to >90%). On the every-6-hour oral dosing schedule, busulfan trough plasma concentrations exhibited a marked circadian rhythm, with the highest troughs occurring at 6:00 AM. Pharmacokinetic studies of the IV formulation in children suggest that interpatient variability is decreased with this route of administration.[121,122] Children heterozygous or homozygous for the glutathione *S*-transferase variant GSTA1*B appear to have decreased busulfan clearance,[123] but this finding requires confirmation in larger studies.

Busulfan is a small lipophilic compound that penetrates well across the BBB. CSF concentrations at steady state are equivalent to those in plasma.[124] The primary route of busulfan elimination appears to be glutathione conjugation, which is catalyzed by an isoform of glutathione-*S*-transferase (GSTA1-1).[125] Busulfan has a short half-life of 2.5 hours and a clearance in children of 80 mL/min/m^2. These pharmacokinetic parameters appear to be linear over the wide dosage range used. Compared with adults, busulfan's apparent clearance is more rapid in children, especially in those younger than or 5 years of age.[126] The busulfan AUC in young children treated with 1 mg/kg is less than half the AUC in adults receiving the same dose (Fig. 10.8).[120] The higher apparent clearance in young children is the result of more rapid glutathione conjugation rather than of lower bioavailability.[127]

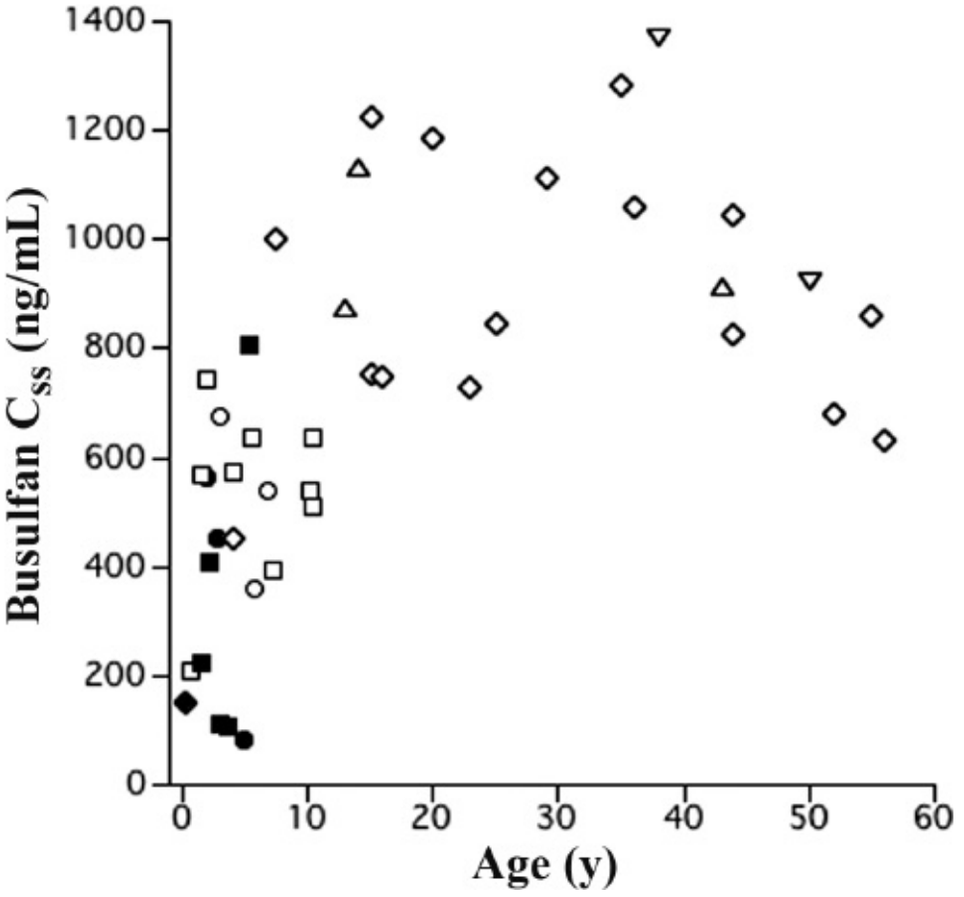


Figure 10.8 Plasma busulfan steady-state concentrations (C_{ss}) as a function of age. C_{ss} is derived by dividing the AUC by the dosing interval (6 hours). Patients were treated with 16 to 30 mg/kg of busulfan in combination with cyclophosphamide before HSCT. Triangles represent patients who rejected their graft or had a mixed chimera. Patients who experienced grade 0 treatment-related toxicity are designated in green, grade 1 toxicity in dark blue, grade 2 toxicity in orange, grade 3 toxicity in red, and grade 4 toxicity in black. Young children had substantially lower C_{ss}, less toxicity, and were at greater risk for graft rejection. (From data presented in Tables 1, 2, and 3 in Slattery JT, Sanders JE, Buckner CD, et al. Graft rejection and toxicity following HSCT in relation to busulfan pharmacokinetics. *Bone Marrow Transplant* 1995;16:31.)

The variability in the disposition of busulfan after oral dosing can result in a 20-fold range in systemic drug exposure among patients treated with a fixed dose. Factors contributing to this variability include age-dependent clearance, variable bioavailability, hepatic dysfunction, drug interactions (e.g., phenytoin), and circadian rhythmicity.[128]

In the HSCT setting, busulfan plasma concentrations appear to be predictive of hepatic toxicity and graft rejection, and, in at least one model, may also predict for efficacy. In adults, the risk of developing severe SOS is higher when the busulfan AUC exceeds 1,500 μM•min (C_{ss} of 1,000 ng/mL).[126] In children, targeting a C_{ss} of 600 to 900 ng/mL has been associated with improved engraftment,[129] but the upper threshold for increased risk of toxicity has not been well defined. The busulfan AUC or C_{ss} associated with SOS or graft rejection appears dependent on the prior therapy administered, the preparative regimen, and the underlying disease.[120] Therapeutic drug monitoring is now commonly performed following the initial dose of busulfan, because this appears to successfully maintain C_{ss} or AUC in a safe and effective range.

Myelosuppression is the primary toxicity from busulfan. Gastrointestinal toxicity, which is

only observed at high doses, includes nausea, vomiting, and mucositis. Busulfan can rarely produce pulmonary toxicity (busulfan lung) that is characterized by diffuse interstitial fibrosis and bronchopulmonary dysplasia. Busulfan lung presents with cough, fever, rales, and dyspnea and usually progresses to respiratory failure. Hepatic SOS, which may be severe in 25% of affected patients, is observed in up to 40% of patients who are treated with high-dose busulfan without pharmacokinetically guided dosing. Seizures have also been reported with high-dose therapy, but they are preventable with prophylactic anticonvulsants. Girls who receive high-dose busulfan have a high incidence of severe and persistent ovarian failure.

NONCLASSICAL ALKYLATING AGENTS

Platinum Compounds

Cisplatin/Carboplatin/Oxaliplatin

Cisplatin, carboplatin, and oxaliplatin are heavy metal coordination complexes (Fig. 10.9) that exert their cytotoxic effects by platination of DNA, a mechanism of action that is analogous to alkylation. Reactive equated intermediates are formed in solution in a manner similar to that of the nitrogen mustards (Fig. 10.4). Chloride is the leaving group replaced by a water molecule in cisplatin; dicarboxycyclobutane is the leaving group in carboplatin; and oxalate is the leaving group in oxaliplatin. These reactive intermediates covalently bind to DNA (N^7 position of adenine and guanine) and form intrastrand and interstrand DNA cross-links.[130] The rate of reaction of these platinum analogs with water to form reactive intermediates is an important determinant of the stability of the compounds in solution and influences the drugs' pharmacokinetics.[131] Cisplatin is more reactive than is carboplatin and is less stable in aqueous solution. The stability of oxaliplatin is intermediate. Chloride-containing solutions such as 0.9% NaCl are required to stabilize cisplatin before administration.

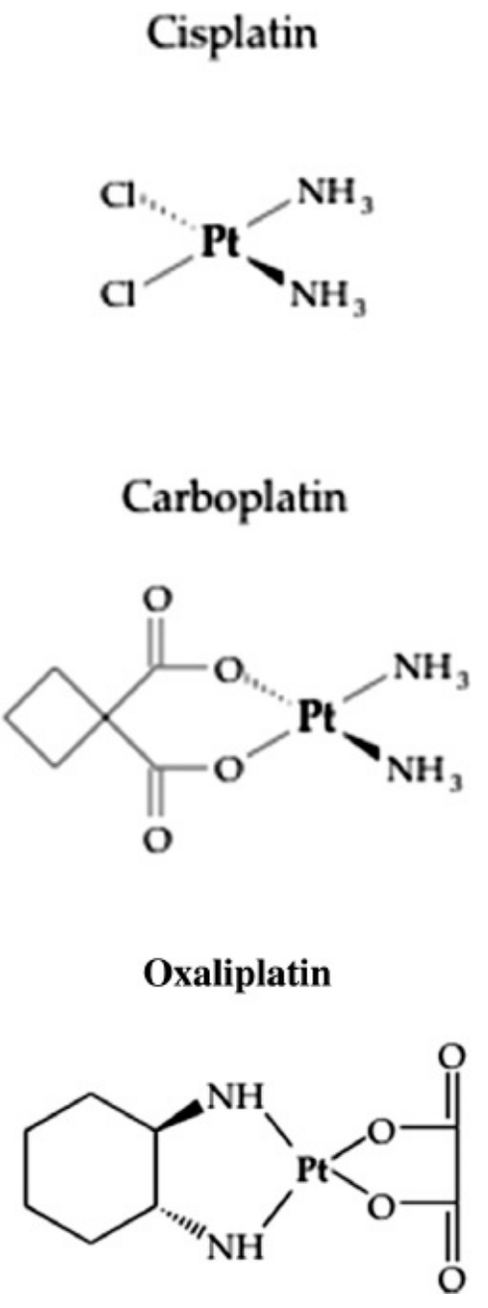


Figure 10.9 The chemical structures of cisplatin, carboplatin, and oxaliplatin, which platinate DNA in a manner analogous to alkylation by the nitrogen mustards. Reactive intermediates are formed after spontaneous elimination of chloride (cisplatin), dicarboxylatecyclobutane (carboplatin), or oxalate (oxaliplatin).

Cisplatin is an effective agent for the treatment of testicular tumors and has demonstrated activity against osteosarcoma, neuroblastoma, Wilms tumor, germ cell tumors, and brain tumors. It is administered intravenously on a variety of schedules, including a single dose, infused over 4 to 6 hours; divided doses, usually daily for 5 days; and by continuous infusion for up to 5 days. The divided dose and continuous-infusion schedules may lessen the gastrointestinal and renal toxicities.

The spectrum of antitumor activity of carboplatin is similar to that of cisplatin in adults, although it may be less efficacious in several solid tumors including testicular cancer.[130] Carboplatin is active against brain tumors, neuroblastoma, sarcomas, and germ cell tumors. The pharmacokinetic and toxicity profiles of cisplatin and carboplatin are quite different

(Tables 10.4 and 10.5).[132] In children, carboplatin is administered as a bolus dose of 400 to 600 mg/m^2 or in divided doses of 400 mg/m^2 on 2 consecutive days or 160 mg/m^2 daily for 5 days, every 4 weeks. Adaptive doing formulas that individualize carboplatin dose for children depending on the GFR are described later.

As a single agent, oxaliplatin is usually administered at a dose of 130 mg/m^2 every 3 weeks, a dose that is also the recommended in children.[133] This drug does not currently have a role in the frontline treatment of childhood cancers.

Pharmacokinetics

The chemical stability (reactivity) of the platinum analogs is a critical determinant of their pharmacokinetics. The reactive intermediates of cisplatin and carboplatin are rapidly and covalently bound to plasma protein and tissue. After binding with plasma or tissue proteins, the reactive platinum intermediates are inactivated. Only the free (unbound) platinum species (including the parent drug) are cytotoxic. This interaction of platinum compounds with protein is time dependent. For cisplatin, more than 90% of total platinum in plasma is protein bound and inactivated within 2 to 4 hours. This represents the major route of drug elimination. Oxaliplatin, as is cisplatin, is highly protein bound, with more than 80% of platinum species bound to plasma proteins 1 hour after administration.[134] The major route of excretion of oxaliplatin is renal, and there is no evidence of cytochrome p450–mediated metabolism. Carboplatin is more chemically stable than are cisplatin and oxaliplatin. Only 20% to 40% of total platinum is protein bound at 2 hours following carboplatin administration, and this slowly increases to 50% over 24 hours.[135] Tissue-bound platinum may be retained in the body for a prolonged time and is still measurable in plasma for 10 to 20 years after treatment.[136]

The pharmacokinetic behavior of bound, and unbound, active forms of platinum differ appreciably. For cisplatin, after an initial rapid decay, total platinum (≥95% protein bound) persists in plasma and can be detected in the urine for many days. The terminal half-life of total platinum ranges from 1 to 5 days. In contrast, the unbound, active platinum species have a much more rapid decline, with a half-life of less than 1 hour, which is primarily a reflection of the chemical reactivity of cisplatin and the avid binding of the reactive intermediates to tissue and plasma protein. In children receiving cisplatin, the half-lives of total and ultrafilterable (unbound) platinum are 44 hours and 40 minutes to 1.5 hours, respectively.[137]

Approximately 50% of the platinum administered as cisplatin is excreted in the urine over 4 to 5 days, primarily in an inactive form. Initially, total platinum clearance equals or exceeds creatinine clearance, reflecting excretion of unbound platinum species, but as protein binding becomes extensive, renal clearance of total platinum drops to only a small fraction of creatinine clearance. The renal clearance of the unbound, ultrafilterable species of platinum can actually exceed creatinine clearance, suggesting tubular secretion. In children, the clearance of cisplatin is not related to the GFR.[137] Approximately 25% of unbound platinum species is excreted in the urine, and the degree of renal excretion is schedule dependent (greater with short infusions). In patients with impaired renal function, the peak concentration of active, unbound platinum was elevated, but the terminal half-life was not prolonged, presumably because of the rapid reaction of these active species with plasma and

tissue protein leading to inactivation. However, dosage reductions in patients with renal dysfunction may be indicated because of cisplatin's nephrotoxic effects, which could further impair renal function.

The disposition of carboplatin is characterized by a lower rate and degree of protein binding than for cisplatin. As a result, the terminal half-life of unbound carboplatin is longer (2 to 3 hours), and renal excretion is the primary route of elimination. By 24 hours, as much as 70% of the total platinum from carboplatin is excreted in the urine, mostly as parent drug. Carboplatin is dialyzable in patients with severe renal insufficiency.[138,139]

Pharmacokinetic parameters for carboplatin in children are similar to those in adults.[139] In children younger than 5 years of age, carboplatin clearance may be increased (120 mL/min/m^2), but in children younger than 1 year of age, the clearance is 75 mL/min/m^2.[140] These age-related differences in carboplatin clearance appear to be related to differences in the GFR. The variability in carboplatin clearance supports the use of the adaptive dosing formulas based on GFR, described subsequently.

The total clearance of carboplatin is highly correlated with creatinine clearance (Fig. 10.10), and patients with renal dysfunction and higher carboplatin AUCs have a greater probability of experiencing dose-limiting hematologic toxicity. These associations allowed the development of adaptive dosing formulas for individualizing carboplatin dose based on creatinine clearance in adults and children,[141–144] which decrease the variability in systemic drug exposure (AUC) and reduce the incidence of severe thrombocytopenia.[145] However, caution must be exercised when using these formulas, because the results are expressed either as an absolute dose (mg) or as a dose normalized to body surface area (mg/m^2). In addition, nuclear medicine–based estimates of renal function in children with cancer are highly variable and subject to potential systematic errors, placing children at risk for underdosing or excessive toxicity from adaptive dosing formulas that incorporate nuclear medicine–based estimates of glomerular filtration.[146] High-dose carboplatin regimens in children utilized adaptive dosing based on glomerular filtration[147] and monitoring of platinum-DNA adducts to achieve desired exposures. Additional study of the pharmacokinetics of carboplatin in infants is needed, because an analysis of carboplatin exposures achieved in patients younger than 1 year of age suggests that clearance of this drug may be different in very young patients.[148]

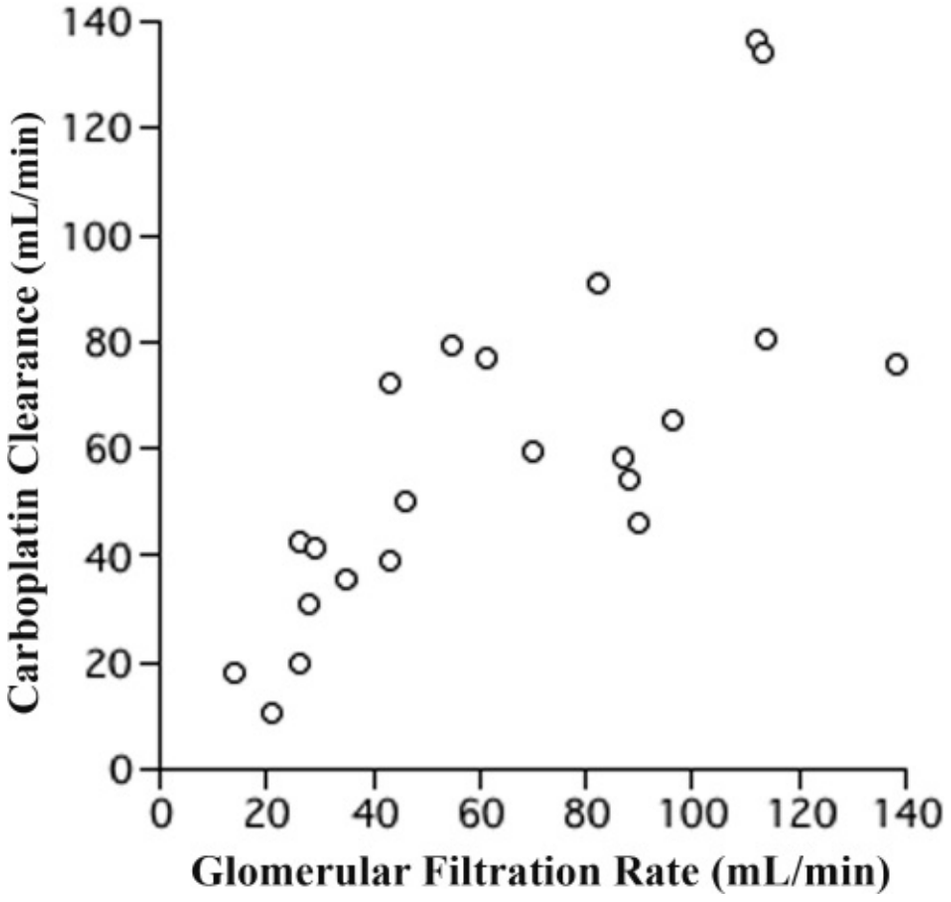


Figure 10.10 Relationship between carboplatin clearance and glomerular filtration rate as measured by ^{51}Cr-EDTA clearance in 22 children. (Adapted from Newell DR, Pearson ADJ, Balmanno K, et al. Carboplatin pharmacokinetics in children: the development of a pediatric dosing formula. *J Clin Oncol* 1993;11:2314.)

The pharmacokinetics of oxaliplatin is similar in adults and children.[133,134,149] Oxaliplatin is rapidly hydrolyzed in a nonenzymatic manner to a large number of reactive intermediates. Dose reduction does not appear to be necessary in patients with moderate renal or hepatic dysfunction.[150,151]

Toxicity

The toxicity profiles of the platinum analogs are strikingly different. Cisplatin is associated with only mild myelosuppression but produces significant and potentially irreversible nephrotoxicity, ototoxicity, and neurotoxicity. The dose-limiting toxicity of carboplatin is hematologic toxicity, primarily thrombocytopenia, and the nonhematologic toxicities observed with cisplatin are only seen at doses of carboplatin exceeding 800 mg/m^2. Dose-limiting toxicities of oxaliplatin include neurotoxicity, thrombocytopenia, and neutropenia.

Nephrotoxicity, manifested as azotemia and electrolyte disturbances (especially hypomagnesemia requiring oral supplementation), was the dose-limiting toxicity in the initial clinical trials with cisplatin. The exact mechanism of cisplatin nephrotoxicity is not defined, but patients experience a reduction in renal blood flow and GFR and a loss of tubular function. Pathologic changes are seen primarily in the renal proximal and distal tubule epithelium and collecting ducts. Renal damage from cisplatin is cumulative. As a result of its nephrotoxic effects, cisplatin can alter its own elimination rate and that of other drugs, such

as MTX, that rely on renal excretion.[152] In one series, the renal clearance of ultrafilterable platinum fell from almost 500 mL/min with the first course to 150 mL/min by the fourth course in patients receiving repeated doses, probably due to decreased renal tubular secretion of the drug.[153]

IV fluid hydration with normal saline before and after the infusion of cisplatin reduces the severity of nephrotoxicity. Diuresis with mannitol and furosemide has been used in an effort to decrease cisplatin-induced nephrotoxicity, but randomized studies have not shown a clear and reproducible benefit associated with the use of diuretics. The use of hypertonic sodium chloride solutions to promote chloruresis and the coadministration of amifostine remain controversial.[154] Because cisplatin-associated renal dysfunction may be augmented in patients exposed to concomitant aminoglycosides, concurrent administration of nephrotoxic medications such as nonsteroidal anti-inflammatory drugs, iodinated contrast agents, and aminoglycosides should be avoided in patients receiving cisplatin.[155] Although these measures have reduced the incidence and severity of cisplatin-induced nephrotoxicity, moderate and permanent reductions in the GFR of patients receiving cisplatin have been documented. However, in a long-term follow-up study of children who received a median of 500 mg/m^2 of cisplatin, most patients with end-therapy decreases in GFR partially recovered, with a median increase in GFR of 13 mL/min/m^2.[156]

As methods to prevent nephrotoxicity have allowed the administration of higher single and cumulative doses of the drug, ototoxicity and peripheral neuropathy have become more prominent. Cisplatin causes a reversible sensory peripheral neuropathy (i.e., numbness, tingling, and paresthesias) at cumulative doses of 300 to 600 mg/m^2. Lhermitte sign (an electric shock sensation when the neck is flexed) is common at high cumulative doses of cisplatin.[157] Symptoms may progress after discontinuation of cisplatin and persist for months to years. Seizures and encephalopathy have also been reported in children receiving intensive cisplatin therapy. The irreversible hearing loss is in the high-frequency range and appears to be related to a cumulative dose of cisplatin of greater than 400 mg/m^2.[158] Children younger than 5 years of age also appear more likely to develop cisplatin-related hearing loss compared with older children.[159] Genetic differences may explain some of the variability in platinum-associated neurotoxicity in adults, although the significance of germ line variants in genes such as TPMT and catechol O-methyltransferase (COMT) is a subject of debate in the literature.[160] Amifostine decreases the incidence and severity of platinum-related neurotoxicity and ototoxicity in adults.[161] In a study of children with average-risk medulloblastoma, amifostine appeared to have provided some otoprotection,[162] but protective effects have yet to be observed in other pediatric studies.[163–165] Sodium thiosulfate has been studied as an otoprotectant.[166] In one study, sodium thiosulfate conferred hearing protection in children with localized hepatoblastoma and no effects on survival were observed[167,168]; however, these results have not been replicated in other studies with more heterogeneous populations. Further studies of sodium thiosulfate as well as intratympanic dexamethasone or N-acetylcysteine are needed to understand their role in ameliorating cisplatin-related ototoxicity.[169] Additional toxic effects associated with cisplatin include prominent nausea and vomiting, mild myelosuppression, Raynaud phenomenon, and hypersensitivity reactions.

Carboplatin’s myelosuppressive effects are delayed, affecting the frequency by which the

drug can be administered. Platelet nadirs are typically seen up to 3 weeks after the dose and milder granulocyte nadirs are observed 3 to 4 weeks after carboplatin administration. Some patients require 5 to 6 weeks for complete count recovery. Not only are the nephrotoxicity, ototoxicity, and peripheral neuropathy from carboplatin milder than that associated with cisplatin, but the nausea and vomiting, which can be dose limiting with cisplatin, are also less severe. High cumulative doses of carboplatin are associated with a small drop in GFR and serum magnesium, but these changes are usually not clinically significant. Hypersensitivity reactions to carboplatin are relatively common and the risk increases after multiple cycles of therapy.[170]

Myelosuppression due to oxaliplatin is usually mild, and the dose-limiting toxicity in adults is a cumulative peripheral neuropathy. Oxaliplatin is also associated with an unusual acute neurologic toxicity, pharyngolaryngeal dysesthesia, in which patients report difficulty in breathing or swallowing in the absence of laryngeal obstruction, probably related to transient sensory disturbances.[171] The sensory neuropathy associated with oxaliplatin is exacerbated by cold in children, as in adults.[133] Although more than one-third of patients enrolled in a study of oxaliplatin in children with CNS tumors developed a sensory neuropathy, it was severe in less than 5% of the patients.[149]

Hydrazines

Procarbazine

Procarbazine is a methylhydrazine analog that was originally synthesized as a monoamine oxidase inhibitor but was discovered to have antitumor activity. Procarbazine is used for the treatment of Hodgkin lymphoma and is also active against brain tumors. Procarbazine is a prodrug that requires metabolic activation in vivo to express its antitumor activity. This activation yields methylating and free radical intermediates, which appear to produce the drug’s antitumor effect.

The spontaneous chemical decomposition and biotransformation of procarbazine is complex. Metabolic activation probably occurs in the liver and is catalyzed by the cytochrome P-450 enzyme complex (Fig. 10.11).[172] In liver perfusion studies, procarbazine is extensively converted to its active metabolite.[173]

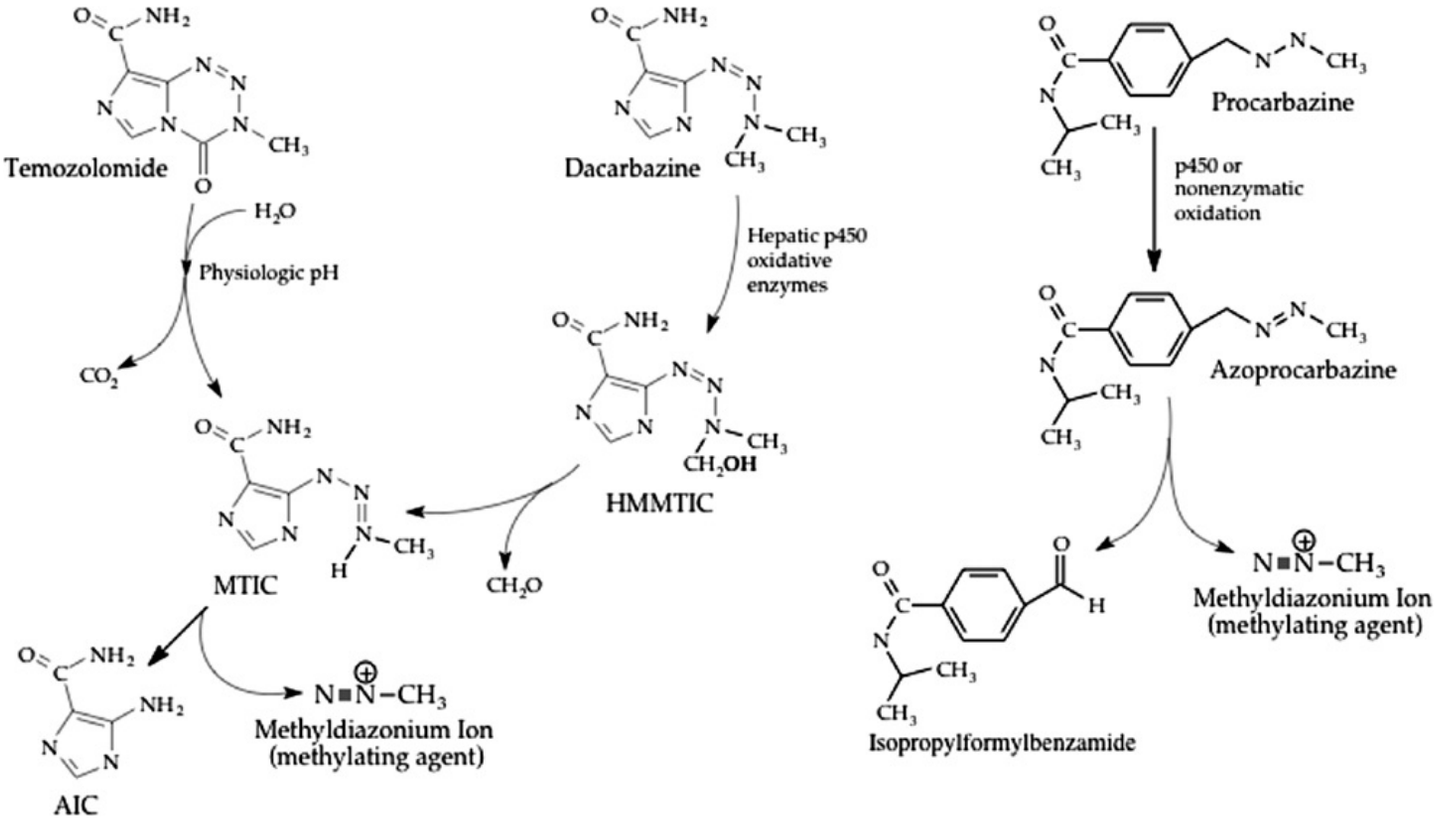


Figure 10.11 Chemical structures and activation pathways of the methylating agents, dacarbazine, temozolomide, and procarbazine, which are prodrugs. Dacarbazine requires enzymatically catalyzed activation and temozolomide undergoes spontaneous chemical conversion in solution at physiologic pH to the active metabolite, MTIC (MTIC, methyltriazenyl-imidazole carboxamide; HMMTIC, hydroxymethyl-methyltriazenyl-imidazole carboxamide; AIC, amino-imidazole carboxamide). The metabolic pathway for procarbazine is highly complex and incompletely shown. In addition to the methyldiazonium ion, free radicals can also be generated from azoprocarbazine.

The disposition of procarbazine and its active intermediates has not been well characterized in humans. The drug is rapidly and completely absorbed from the gastrointestinal tract,[174] and it undergoes complete first-pass conversion to cytotoxic metabolites, which probably accounts for the activity of the drug when administered orally. After IV administration, procarbazine is rapidly metabolized and has a half-life of less than 10 minutes. The metabolites of procarbazine are excreted primarily in the urine. Procarbazine or unidentified metabolites enter the CSF readily. Drugs such as phenobarbital and phenytoin that are capable of inducing hepatic microsomal enzymes can increase the rate of procarbazine activation. Procarbazine can inhibit the biotransformation of the barbiturates, phenothiazines, and other sedatives, resulting in potentiation of their sedative effects. The inhibition of monoamine oxidase by procarbazine can put patients at risk for hypertensive reactions from foods high in tramline (e.g., bananas, wine, cheese). Procarbazine also appears to alter its own metabolism over a 14-day course of therapy. The plasma concentrations of procarbazine metabolites differ markedly between days 1 and 14 of treatment.[175]

The primary toxicities of procarbazine include nausea, vomiting, and myelosuppression. Some patients develop evidence of neurotoxicity consisting of paresthesias, somnolence, depression, or agitation. Neurotoxicity is prominent with high-dose IV administration. Patients are also at risk for the long-term toxicities, including azoospermia, ovarian failure,

and teratogenic and carcinogenic effects.

Tetrizines

Dacarbazine

Dacarbazine (Fig. 10.11) is a prodrug that undergoes hepatic microsomal metabolic activation (N-demethylation), which is catalyzed primarily by CYP1A2, to the active metabolite, methyltriazenyl-imidazole carboximide (MTIC).[176] MTIC then spontaneously decomposes into a reactive methylating species (methyldiazonium ion) and the primary circulating metabolite aminoimidazole carboxamide (AIC).

Dacarbazine is generally administered intravenously (150 to 250 mg/m^2) on a divided once-daily dosage schedule for 5 days. Absorption after oral administration is slow, incomplete, and variable.[177] After IV administration, the drug is rapidly cleared from the plasma. One-half of the dose is excreted unchanged in the urine, and renal clearance exceeds the GFR, suggesting the drug is also eliminated by renal tubular secretion. The remainder of the dose presumably undergoes biotransformation. The half-life and renal clearance of the metabolite AIC are similar to that of the parent drug.[178] Methylated DNA adducts in white blood cells of patients treated with dacarbazine (250 to 800 mg/m^2) increase rapidly during the first hour after treatment but then decline with a more prolonged half-life (72 hours) than that in the parent drug.[179]

Gastrointestinal toxicity, consisting of moderate to severe nausea and vomiting, is the primary toxicity and is frequently dose limiting. Tolerance usually develops over the 5-day course of administration. At standard doses, myelosuppression is mild. Other side effects include a flulike syndrome with malaise, fever, and myalgias; mild hepatic dysfunction; and local pain at the site of IV injection. Rare cases of liver failure and death from SOS and hepatic vein thrombosis (Budd–Chiari syndrome) have been associated with dacarbazine.

Temozolomide

The methylating agent temozolomide is structurally and mechanistically related to dacarbazine. As is dacarbazine, temozolomide is a prodrug, but temozolomide does not require enzymatic activation in the liver. In solution at physiologic pH, temozolomide spontaneously decomposes to MTIC, the same active metabolite that is derived by enzymatic N-demethylation of dacarbazine (Fig. 10.11).[180]

Temozolomide is insoluble in aqueous solution and was initially only available in capsules for oral administration. A study comparing a 90-minute IV infusion with an equivalent oral dose of temozolomide demonstrated exposure equivalence. Temozolomide is available for IV administration and as an oral solution for patients who are unable to tolerate capsules.[181] Preclinical studies and early clinical trials demonstrated that the divided dosing schedule had greater antitumor effect than does a single bolus dose.[182] The recommended dose for children is 150 to 200 mg/m^2/d (up to 1,000 mg/m^2/course) when administered as a single agent, although doses as high as 260 mg/m^2/d given daily for 5 days have been well tolerated in children with leukemia.[183–185] A continuous daily dosing schedule is also used, and a dose of

75 to 100 mg/m^2/d appears to be tolerable for 6 to 7 weeks.[186] Temozolomide is used in children primarily for the treatment of brain tumors, but it has also been studied as part of combination regimens for a number of childhood solid tumors.

Absorption of temozolomide from the gastrointestinal tract is rapid and complete.[187] The peak concentration is achieved in plasma within 1.5 hours of the dose.[183] When administered with food, the bioavailability is slightly lower but remains greater than 90%. Temozolomide is rapidly eliminated; its half-life is 1.8 hours.[180] Decomposition to the active metabolite, MTIC, is the primary route of elimination for temozolomide. A pharmacokinetic study of radiolabeled temozolomide confirmed that AIC, which is the end product of temozolomide decomposition to MTIC, is a primary urinary metabolite. In children, 5% to 15% of the dose of temozolomide was recovered in urine as unchanged drug.[183] The apparent clearance of temozolomide in children is approximately 100 mL/min/m^2 and the terminal half-life is similar to that observed in adults.[185] The active metabolite, MTIC, is much less stable and has an estimated half-life of 2.5 minutes and clearance exceeding 5,000 mL/min/m^2.[188] There is some evidence that temozolomide clearance is lower in younger children.[189] Temozolomide is widely distributed in tissues and penetrates well across the BBB.[187]

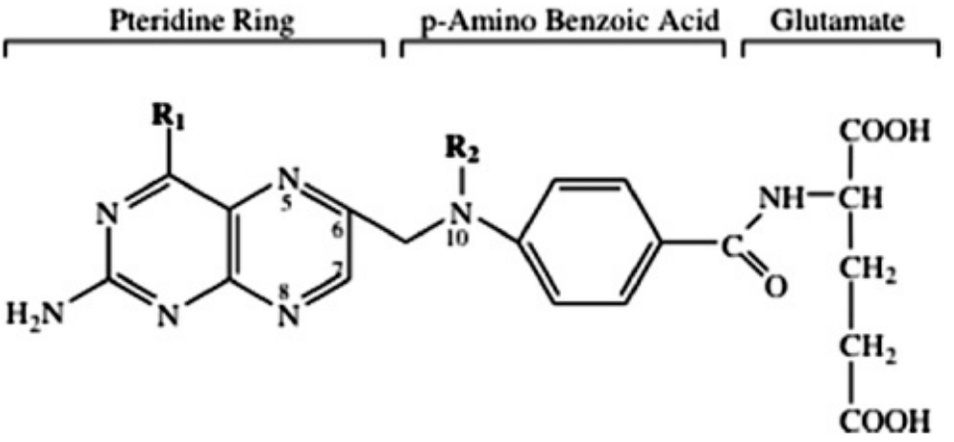
Myelosuppression is the dose-limiting toxicity of temozolomide. Nadir neutrophil and platelet counts typically occur 21 days after the start of therapy, and recovery of blood counts may take 7 to 10 days. This delayed myelosuppression may necessitate administering temozolomide on a 28-day schedule. The myelosuppression from temozolomide does not appear to be cumulative.[182] Nonhematologic toxicities are mild and include nausea and vomiting, headache, fatigue, constipation, and serum transaminase elevations.[187]

The DNA repair protein, O^6-alkylguanine-DNA alyltransferase (MGMT), removes the methyl adduct from the O^6-position of guanine. Although this adduct accounts for only 5% of DNA adducts formed by temozolomide, it is thought to be the primary cytotoxic lesion. Tumor cell lines with high levels of this repair protein are resistant to the cytotoxic effect of temozolomide. Administration of temozolomide itself depletes MGMT.[190] Loss of DNA mismatch repair capacity enhances to resistance to temozolomide.

ANTIMETABOLITES

The antimetabolites are structural analogs of vital cofactors or intermediates in the biosynthetic pathways of DNA and RNA. By acting as fraudulent substrates for the enzymes in these pathways, antimetabolites inhibit synthesis of the nucleic acids and their building blocks or are incorporated into DNA or RNA, resulting in a defective product. Antimetabolites that are used in the treatment of pediatric cancers include the folate analog MTX (Fig. 10.12); the pyrimidine analogs cytarabine, gemcitabine, and fluorouracil (Fig. 10.13); and the purine analogs mercaptopurine, thioguanine, fludarabine, clofarabine, and nelarabine (Fig. 10.14).

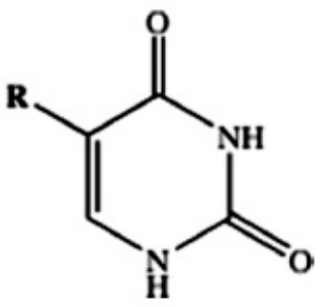
FOLATE ANTIMETABOLITES



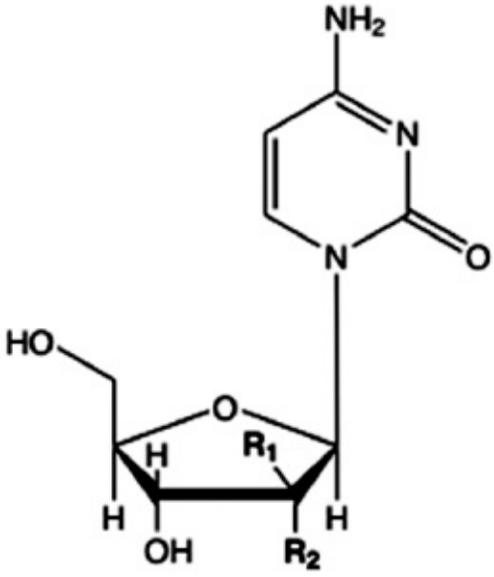
	R_1	R_2
Folic Acid	OH	H
Methotrexate	NH_2	CH_3

Figure 10.12 Chemical structures of the antifolate methotrexate compared with the structure of folic acid.

PYRIMIDINE ANTIMETABOLITES



	R
Uracil	H
5-Fluorouracil	F



	R_1	R_2
Cytidine	H	OH
Cytarabine	OH	H
Gemcitabine	F	F

Figure 10.13 Chemical structures of commonly used pyrimidine antimetabolites compared with the structures of corresponding endogenous compounds, of which they are analogs.

In general, the clinical pharmacology of these agents is similar to that of the endogenous compounds that they structurally resemble. The absorptive, metabolic, and excretory pathways are frequently shared by the endogenous compound and the antimetabolite. The rate of elimination of the antimetabolites is usually rapid. Most of the antimetabolites are prodrugs that require metabolic activation within the target cell to express their cytotoxic effects. The purine and pyrimidine analogs, for example, require intracellular conversion to phosphorylated nucleotides, which are the active forms of these drugs. Because most antimetabolites interfere directly with DNA synthesis, they are cell-cycle and S-phase specific; the maximum cytotoxic effect occurs in cells that are synthesizing DNA. This partially explains the schedule dependence of this class of anticancer drugs. More prolonged drug exposure that results from administering these agents by continuous infusion or by chronic daily dosing increases the chance of exposing a higher proportion of the tumor cell population to the drugs during active DNA replication.

Antifolates

Methotrexate

MTX is the most widely used antimetabolite in childhood cancers. It is effective in the treatment of ALL, NHL, the histiocytoses, and osteosarcoma. MTX is administered on an intermittent schedule by a variety of routes, including oral, intramuscular, subcutaneous, intrathecal, and IV. Chronic oral or intramuscular therapy is administered weekly at a dose of 20 mg/m^2. With IV therapy, an extraordinarily wide range of doses has been employed, ranging from a 10-mg bolus to 33,000 mg/m^2 as a 24-hour infusion. Doses above 300 mg/m^2, which are usually administered by continuous infusion, must be followed by a course of the rescue agent leucovorin (5-formyl-tetrahydrofolate) to prevent the development of severe toxicities.

The loading and infusion doses required to achieve a desired steady-state plasma concentration ($[MTX]_{plasma}$) can be estimated from the following formulas[191]:

$$\text{Loading dose } (mg/m^2) = 15 \bullet [MTX]_{plasma}\ (\mu M)$$

$$\text{Infusion dose } (mg/m^2/h) = 3 \bullet [MTX]_{plasma}\ (\mu M)$$

For example, to achieve a steady-state plasma concentration of 10 µM, the loading dose would be 150 mg/m^2, followed by an infusion of 30 $mg/m^2/h$. Infusion durations of up to 42 hours are tolerable when followed by leucovorin rescue. In clinical practice, infusion durations range from 4 to 36 hours depending on the type of cancer being treated. Patients who are treated with an HDMTX infusion must be adequately hydrated and alkalinized to prevent precipitation of MTX in acidic urine, and routine monitoring of urinary output, serum creatinine, and plasma MTX concentrations is mandatory to determine the duration of leucovorin rescue. For most infusion regimens, 12 to 15 mg/m^2 of leucovorin should be continued every 6 hours until plasma MTX concentration decreases to 0.05 to 0.1 µM.

Mechanism of Action

MTX is a structural analog of folic acid, a required cofactor for the synthesis of purines and thymidine. As a result of the substitution of an amino group for the hydroxyl group at the 4-position on the pteridine ring of folic acid (Fig. 10.12), MTX is a tight-binding inhibitor of dihydrofolate reductase (DHFR), the enzyme responsible for converting folates to their active, chemically reduced (tetrahydrofolate) form.[192] In the presence of MTX, intracellular tetrahydrofolate pools are depleted, leading to depletion of purines and thymidylate and inhibition of DNA synthesis. Accumulation of partially oxidized dihydrofolic acid, resulting from the inhibition of DHFR, appears to contribute to the inhibition of de novo purine synthesis.[193] A critical determinant of MTX cytotoxicity is the rate of thymidylate synthesis, because the synthesis of thymidylate from uridylate is the only reaction that oxidizes the tetrahydrofolate cofactor to the inactive dihydrofolate form. Another determinant is achieving an intracellular MTX concentration that is in excess of DHFR binding sites, because intracellular levels of this target enzyme are 20- to 30-fold higher than required to maintain tetrahydrofolate pools.[192]

MTX shares membrane transport processes and intracellular metabolic pathways with the naturally occurring folates. It competes with the tetrahydrofolates for an energy-dependent transport system for cell entry. On entry, MTX is rapidly and tightly bound to DHFR, and uptake into the target cell is essentially unidirectional until the enzyme binding sites are saturated, allowing for even greater intracellular accumulation of drug.[192]

With the accumulation of free intracellular drug in excess of DHFR binding sites, MTX, as with the naturally occurring folates, is metabolized intracellularly to polyglutamated derivatives, which cannot readily efflux from the cell. MTX polyglutamate formation enhances the cytotoxicity of the drug by allowing greater accumulation of free intracellular drug and retention of the drug within the cell, even after extracellular drug is cleared. MTX polyglutamate formation is optimal in vitro when cells are exposed to high concentrations for prolonged periods. MTX polyglutamates are more potent inhibitors of DHFR and are capable of directly inhibiting other enzymes in the synthetic pathways for thymidine (thymidylate synthase) and purines.[194]

Pharmacokinetics

At oral doses of 7.5 to 20 mg/m^2, the rate and extent of absorption of MTX is highly variable. Peak plasma concentrations can occur from 0.5 to 5 hours after oral administration, and the percentage of the dose that is absorbed ranges from 5% to 97%. The AUC of oral MTX ranged from 0.63 to 12 μM•h at a dose of 18 to 22 mg/m^2, and over a broader dosage range, the AUC correlated poorly with the dose. Absorption of MTX is saturable, and as the dose is increased, the fraction of the dose that is absorbed diminishes.[195] Simply increasing the dose in patients who have low plasma concentrations after standard oral doses may not overcome poor bioavailability. The bioavailability of oral MTX can also be significantly reduced when administered with food.[196] When administered intramuscularly or subcutaneously, MTX is completely absorbed.[195]

The disposition of MTX in children differs from that in adults.[197] In one study, children had

lower plasma concentrations of MTX and excreted the drug in the urine more rapidly after a 6-hour infusion than did adults.[198] The volume of distribution was also greater in children. Within the pediatric age group, the clearance of MTX is also age dependent.[199] Children younger than 10 years of age had a clearance of 160 mL/min/m^2, compared with 110 mL/min/m^2 in those older than 10. Infants (<1 year old) have a slightly lower clearance rate than do children,[24] with somewhat more pronounced differences observed in very young (<3 months) infants.[200]

The plasma disappearance of MTX is multiphasic, with a terminal half-life of 8 to 12 hours.[191] Retention of the drug in large extravascular fluid collections, such as ascites or pleural fluid, is associated with prolongation of the half-life as a result of slow release of retained drug into the circulation. This prolonged exposure to the drug can increase the risk of toxicity. Patients who have large extravascular fluid collections and are receiving MTX should have their MTX concentrations monitored closely.

MTX is eliminated primarily by renal excretion, undergoing glomerular filtration and renal tubular reabsorption and secretion.[201] Approximately 70% to 90% of a dose is excreted unchanged in the urine, most within the first 6 hours. Mutations in the drug transporter adenosine triphosphate-binding cassette (ABC) gene *ABCC2* have been associated with impaired MTX elimination. The renal clearance of MTX can exceed the rate of creatinine clearance. In patients with significant renal dysfunction, MTX clearance is delayed, resulting in prolonged drug exposure and a greater risk of severe toxicities. HDMXT should not be given to patients with a creatinine clearance of less than 50% to 75% of normal. Low-dose therapy should be withheld in patients with a serum creatinine level greater than 2 mg/dL. Any patient who is suspected of having renal dysfunction and who receives MTX should have the plasma concentrations closely monitored and receive leucovorin if drug clearance is delayed.

MTX is also metabolized in the liver to 7-hydroxy-methotrexate. Although this is a minor route of elimination, plasma concentrations of 7-hydroxy-methotrexate can be equivalent to or exceed those of MTX after high-dose infusions, because of the slower clearance of the metabolite.[202] Polyglutamated, 7-hydroxy-methotrexate appears to be able to bind to and inhibit DHFR.[192] MTX clearance is not significantly altered with hepatic dysfunction, but modification of the MTX dose in patients with abnormal liver function tests may be indicated to avoid additional hepatic damage.

Total renal and metabolic MTX clearance is approximately 100 mL/min/m^2, but it may vary widely among patients. In patients with normal creatinine clearance, there is not a good correlation between MTX clearance and creatinine clearance.[203] Renal tubular dysfunction, which is not measured by creatinine clearance, may account for this disparity. A small test dose of MTX can accurately predict the kinetics and steady-state concentration of a high-dose infusion.[204] Optimal management dictates that each course of HDMTX be closely monitored by following renal function and plasma MTX concentration to determine the dose and duration of leucovorin rescue.

Penetration of systemically administered MTX into the CSF is only 3% in patients without meningeal tumor spread,[205] but is 20% in patients with leptomeningeal carcinomatosis.[206] When the infusion rate exceeds 3,500 mg/m^2 over 24 hours, the CSF MTX concentration is

typically >1 μM[206]; and HDMTX infusion regimens are effective for treating and preventing leptomeningeal leukemia.[207]

Toxicity

The primary toxic effects of MTX are myelosuppression and orointestinal mucositis, which occur 5 to 14 days after the dose. The development of toxic reactions is related to the concentration of drug and the duration of exposure.[191] In patients receiving a 6-hour infusion of MTX, a 48-hour MTX concentration above 1 μM was associated with the development of significant toxicity. These toxicities can be prevented by administration of leucovorin. With the use of therapeutic drug monitoring and continuation of leucovorin rescue until plasma MTX concentration has fallen below 0.05 to 0.1 μM, the toxicity of HDMTX can be avoided in most patients. Despite these measures, however, nephrotoxicity still occurs in almost 2% of patients receiving HDMTX infusions.[208]

Nephrotoxicity observed with HDMTX can delay MTX clearance and markedly intensify the drug's other toxic effects. An early rise in serum creatinine (1.5 times baseline) within the initial 24 hours can help identify a population of patients at increased risk for delayed MTX elimination.[209] The renal damage may be related to precipitation of MTX or 7-hydroxy-MTX in acidic urine or to direct toxic effects on the renal tubule. Aggressive hydration and alkalinization as well as increasing the sodium content of the hydration fluids[210] can prevent drug precipitation and result in enhanced excretion of MTX.

The development of renal dysfunction during HDMTX is a medical emergency. Patients must be closely monitored and the leucovorin dose increased in proportion to the plasma MTX concentration.[211] Hemodialysis and charcoal hemoperfusion have not proved useful for drug removal in patients with renal dysfunction, unless they are used repeatedly.[212] Glucarpidase (carboxypeptidase-G_2), a recombinant bacterial enzyme that catabolizes MTX to the inactive metabolite, 4-amino-4-deoxy-N^{10}-methylpteroic acid (DAMPA),[213] rescues patients who develop MTX nephrotoxicity by providing an alternative route of elimination.[214] Glucarpidase is well tolerated and results in a 95.6% to 99.6% reduction in plasma MTX concentrations within minutes. Unlike dialysis, there is minimal rebound of plasma drug concentrations after glucarpidase.[215] Consensus guidelines for the use of glucarpidase for HDMTX-induced acute kidney injury have been published.[216]

Hepatic toxicity consisting of transient elevations of serum transaminase and, less commonly, hyperbilirubinemia, has been associated with standard and high doses of MTX but is more common and more severe with high-dose therapy. Hepatic fibrosis has been observed primarily in patients receiving chronic low-dose MTX.[197] Other side effects include a dermatitis characterized by erythema and desquamation, allergic reactions, and acute pneumonitis. MTX osteopathy is a cumulative toxicity that causes bone pain, osteoporosis, and an increased risk of fractures. Neurotoxicity from HDMTX includes an acute, stroke-like encephalopathy, seizures, and chronic leukoencephalopathy, particularly in association with cranial irradiation.[217] Hispanic ethnicity may be associated with increased risk of MTX neurotoxicity[218] and polymorphisms in genes related to neurogenesis may contribute to susceptibility to MTX-related neurotoxicity.[219]

Drug Interactions

Several drugs have been associated with increase in toxicity when coadministered with MTX. The most significant interactions involve agents that interfere with MTX excretion, primarily by competing for renal tubular secretion. These drugs include probenecid; salicylates; sulfisoxazole; penicillins; ciprofloxacin; the nonsteroidal anti-inflammatories indomethacin, ketoprofen, and ibuprofen; and the proton pump inhibitors omeprazole, rabeprazole, and pantoprazole. Nephrotoxic drugs, such as the aminoglycosides, vancomycin and cisplatin, may also alter the clearance of MTX.[93,220] Pharmacodynamic interactions resulting in synergistic cytotoxic effects have been reported with MTX and fluorouracil or cytarabine.[221] The synergistic effects of MTX and asparaginase are sequence dependent: asparaginase administration should always follow MTX administration. Administering asparaginase before or concomitant with MTX can directly antagonize MTX's effectiveness.[222,223]

Intrathecal Methotrexate

Intrathecal MTX has been in clinical use for more than 50 years, primarily for the treatment of the meningeal spread of cancer, especially leukemia and lymphoma. It is also administered adjuvantly to patients with newly diagnosed ALL to prevent meningeal relapse. Acute and delayed neurotoxic reactions to intrathecal MTX have been reported. An acute chemical arachnoiditis characterized by headache, nuchal rigidity, vomiting, fever, and CSF pleocytosis can present several hours to days after a dose. A subacute encephalopathy, which may be irreversible in some patients, presents with extremity paresis and cranial nerve palsies, ataxia, visual impairment, seizures, and coma. This syndrome is associated with elevated CSF drug concentrations.[224] An ascending radiculopathy with loss of primarily motor function resembling Guillain–Barre syndrome is also associated with intrathecal MTX, as well as cytarabine, and occurs days to weeks following a course of therapy.[225] A chronic, progressive demyelinating encephalopathy (i.e., leukoencephalopathy) that appears months to years after intrathecal MTX leads to dementia, spastic paralysis, seizures, and coma in more advanced cases. Severe, often fatal, reactions can result from the inadvertent administration of excessive doses of MTX or the administration of the wrong agent (e.g., vincristine) intrathecally. Intrathecal MTX overdose has been treated with CSF drainage and ventriculolumbar perfusion. Intrathecal instillation of glucarpidase (carboxypeptidase-G_2) has also been reported.[226]

MTX elimination from the CSF after intrathecal injection is biphasic, with a terminal half-life of 14 hours. MTX is eliminated by passive diffusion out of the CSF, bulk resorption of CSF, and a nonspecific active transport system.[26] Conditions associated with delayed clearance of MTX from the CSF include meningeal leukemia, communicating hydrocephalus, or the lumbar puncture syndrome.

When MTX is administered intrathecally, the volume of the CSF is the initial volume in which the drug is distributed. In young children, CSF volume increases much more rapidly than does the body surface area, reaching 80% of the adult volume by the age of 3 years. An intrathecal dose based on body surface area would underdose young children and overdose

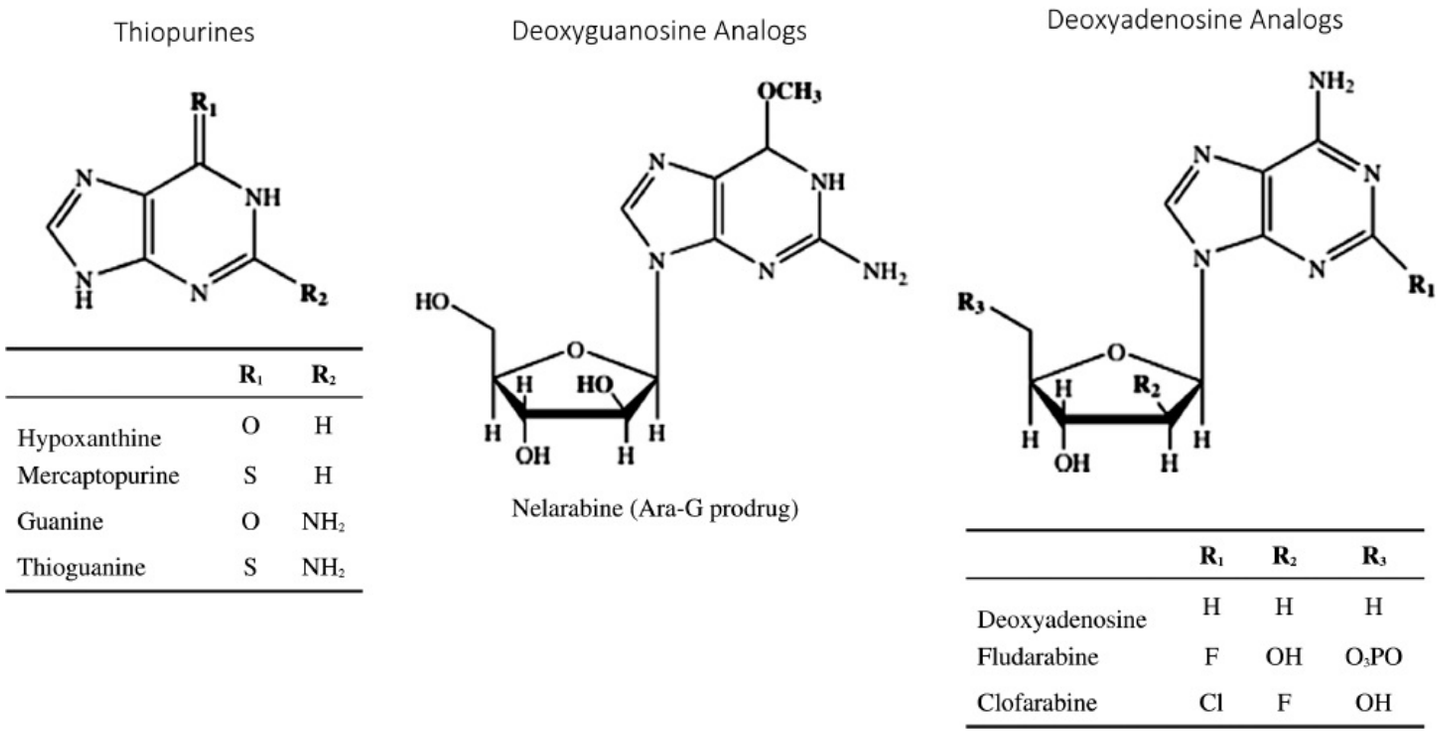
adolescents. Therefore, the intrathecal dosage schedule for MTX is based on age instead of body surface area.[227] This regimen has been less neurotoxic, and because this dosing scheme was incorporated into frontline leukemia protocols, the CNS relapse rate has declined from 12% to 7%. The greatest decline was observed in the youngest patients, the group in whom the intrathecal MTX dosage was increased with the age-adapted dosing regimen.[228]

PURINE ANTIMETABOLITES

Thiopurines

Mercaptopurine/Thioguanine

Mercaptopurine and thioguanine are thiol-substituted derivatives of the naturally occurring purine bases hypoxanthine and guanine (Fig. 10.14). Mercaptopurine has been used in the treatment of ALL for five decades, primarily for the maintenance of remission. In standard maintenance regimens, mercaptopurine is administered orally at a dose of 60 to 75 mg/m^2/d with upward or downward dose adjustments based on the degree of myelosuppression. Ensuring that patients are receiving their MTD of mercaptopurine appears to be an important factor in the outcome for children with ALL.[9] In a retrospective analysis, when the actual dose of mercaptopurine received increased by 22% as a result of more aggressive prescribing guidelines, the relapse-free survival improved by 18%.[229] Although high-dose IV infusions of mercaptopurine (1,000 mg/m^2 over 6 to 24 hours) have been evaluated as an approach to circumvent the pharmacokinetic limitations of oral dosing, this route of administration does not offer an advantage over oral dosing in children with ALL.[230] Thioguanine has been used in the treatment of acute myelocytic leukemia and is administered orally in doses of 75 to 100 mg/m^2 daily for 5 to 7 days or in doses of 40 to 60 mg/m^2 daily for more prolonged courses.



	R_1	R_2
Hypoxanthine	O	H
Mercaptopurine	S	H
Guanine	O	NH_2
Thioguanine	S	NH_2

	R_1	R_2	R_3
Deoxyadenosine	H	H	H
Fludarabine	F	OH	O_3PO
Clofarabine	Cl	F	OH

Figure 10.14 Chemical structures of commonly used purine antimetabolites compared with the structures of corresponding endogenous compounds of which they are analogs.

The thiopurines are prodrugs that must be converted intracellularly to thioguanine nucleotides to exert a cytotoxic effect. The metabolic pathways for activation of mercaptopurine and thioguanine are outlined in Figure 10.15. The active intracellular metabolites are phosphorylated thiopurine nucleotides, which inhibit de novo purine synthesis and purine interconversion and are incorporated into DNA. Incorporation of thioguanosine into DNA appears to be the critical determinant of thiopurine cytotoxicity, but there is evidence that for mercaptopurine, methylated metabolites also appear to contribute to its overall antiproliferative effects.[231] Thioguanine is 10-fold more potent and less schedule dependent than is mercaptopurine against lymphoblastic leukemia cell lines and lymphoblasts from patients with ALL in vitro, and can achieve cytotoxic drug concentrations within the CSF with oral dosing.[232] Despite preliminary clinical data suggesting an advantage of thioguanine over mercaptopurine for the treatment of children with ALL,[233] randomized clinical trials failed to demonstrate an overall event-free survival advantage.[234,235]

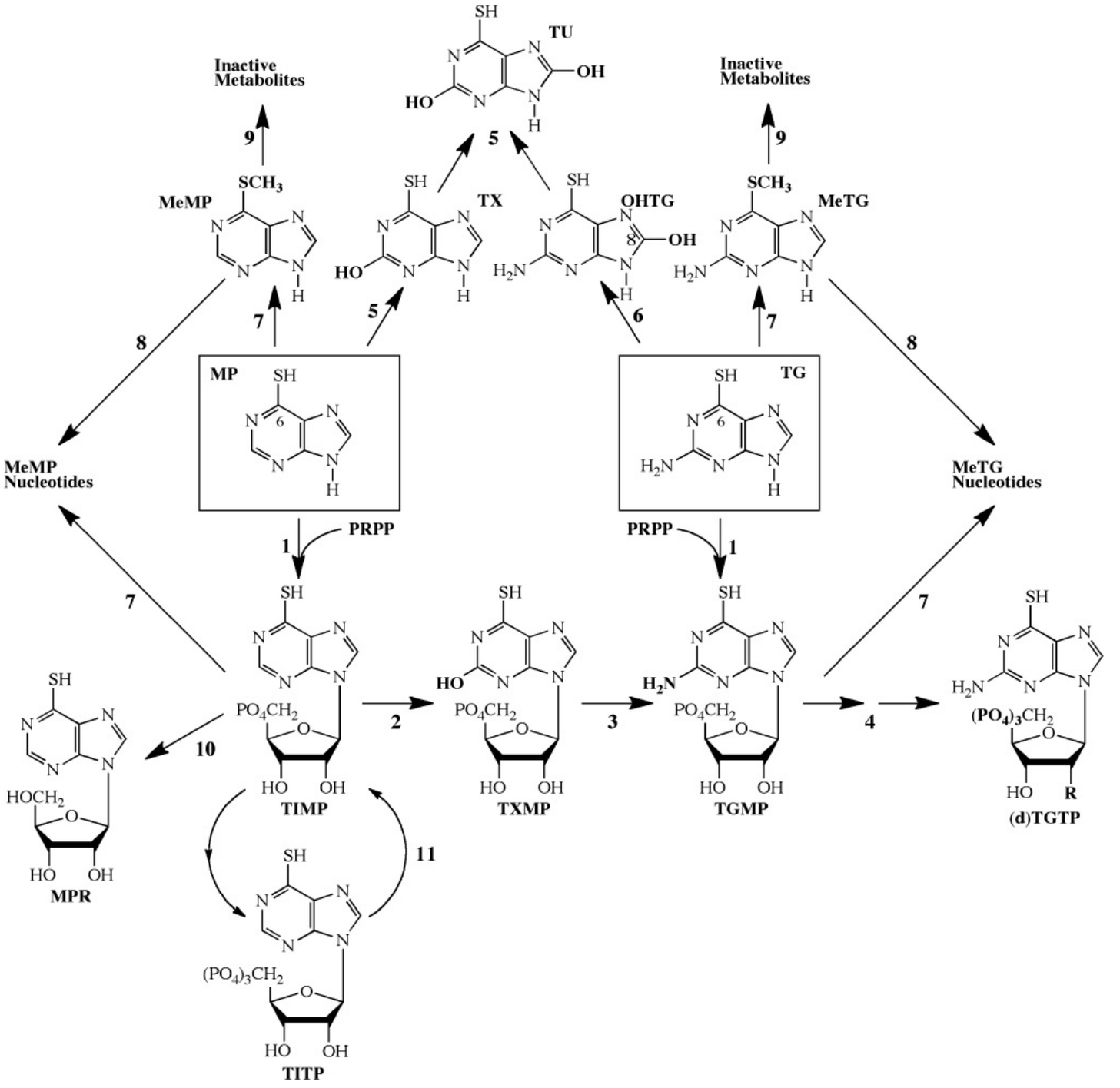


Figure 10.15 Metabolic pathways of mercaptopurine (MP) and thioguanine (TG). Intracellular activation of these prodrugs involves conversion to thioguanine nucleotides. For mercaptopurine, this is a three-step process, starting with conversion to thioinosine monophosphate (TIMP), catalyzed by the enzyme hypoxanthineguanine phosphoribosyl transferase or HGPRT (1). Phosphoribosylpyrophosphate (PRPP) is a required cofactor in this reaction. TIMP is converted to thioxanthosine monophosphate (TXMP) by inosine monophosphate dehydrogenase (2) and then to thioguanine monophosphate (TGMP) by guanosine monophosphate synthetase (3). Thioguanine is converted directly to TGMP by HGPRT. TGMP is phosphorylated by kinases to TGTP (R = OH) and converted to the deoxyribonucleotide dTGTP (R = H) by ribonucleotide reductase (4). dTGTP can then be incorporated into DNA (not shown). There are competing catabolic pathways for the thiopurines, including oxidation to the inactive metabolite, thiouric acid (TU). For MP, this is catalyzed in a two-step reaction by xanthine oxidase (5). The initial oxidation step from TG to 8-hydroxy-thioguanine (OHTG) is catalyzed by aldehyde oxidase (6). The thiopurines also undergo S-methylation, catalyzed by thiopurine methyltransferase or TPMT (7). Methylmercaptopurine (MeMP) and methylthioguanine (MeTG) can be converted to methylated thionucleotides along the same pathways as the parent drug (8). TPMT can also convert TIMP and TGMP to methylated

thionucleotides. MeMP and MeTG can also be oxidized or desulfurated to inactivate metabolites (9). Dephosphorylation of TIMP to mercaptopurine riboside is another inactivating step that is catalyzed by several intracellular enzymes (10). Inosine triphosphate pyrophosphatase (ITPA) catalyzes thiol-ITP back to thiol-IMP (11).

Biotransformation

The thiopurines are extensively metabolized in vivo to active and inactive metabolites (Fig. 10.15). The activation pathway for thioguanine, which is converted to the nucleotide thioguanosine monophosphate in a single step, is more direct than that for mercaptopurine, which undergoes a three-step conversion to the thioguanine nucleotide. The primary degradative pathway for mercaptopurine is conversion to the inactive metabolite thiouric acid by the enzyme xanthine oxidase. The oxidation of thioguanine to thiouric acid follows a different metabolic pathway, initially being converted by aldehyde oxidase to 8-hydroxy-thioguanine, the primary circulating metabolite of thioguanine.[236]

The thiopurines are also subject to S-methylation by the enzyme thiopurine methyltransferase (TPMT). The level of intracellular TPMT activity is an important determinant of the availability of thiopurines for conversion to active thioguanine nucleotides, and, as a result, TPMT regulates the cytotoxic effect of these thiopurines. The activity of this enzyme is controlled by a common genetic polymorphism, resulting in a trifocal distribution of intracellular enzyme levels: normal, intermediate, and deficient. One in 300 patients is deficient of TPMT activity and extremely sensitive to the cytotoxic effects of mercaptopurine, thioguanine, and azathioprine. TMPT activity is inversely related to the erythrocyte thioguanine nucleotide concentration (Fig. 10.16) and the severity of neutropenia, suggesting that TPMT modulates the cytotoxic effect of mercaptopurine.[237]

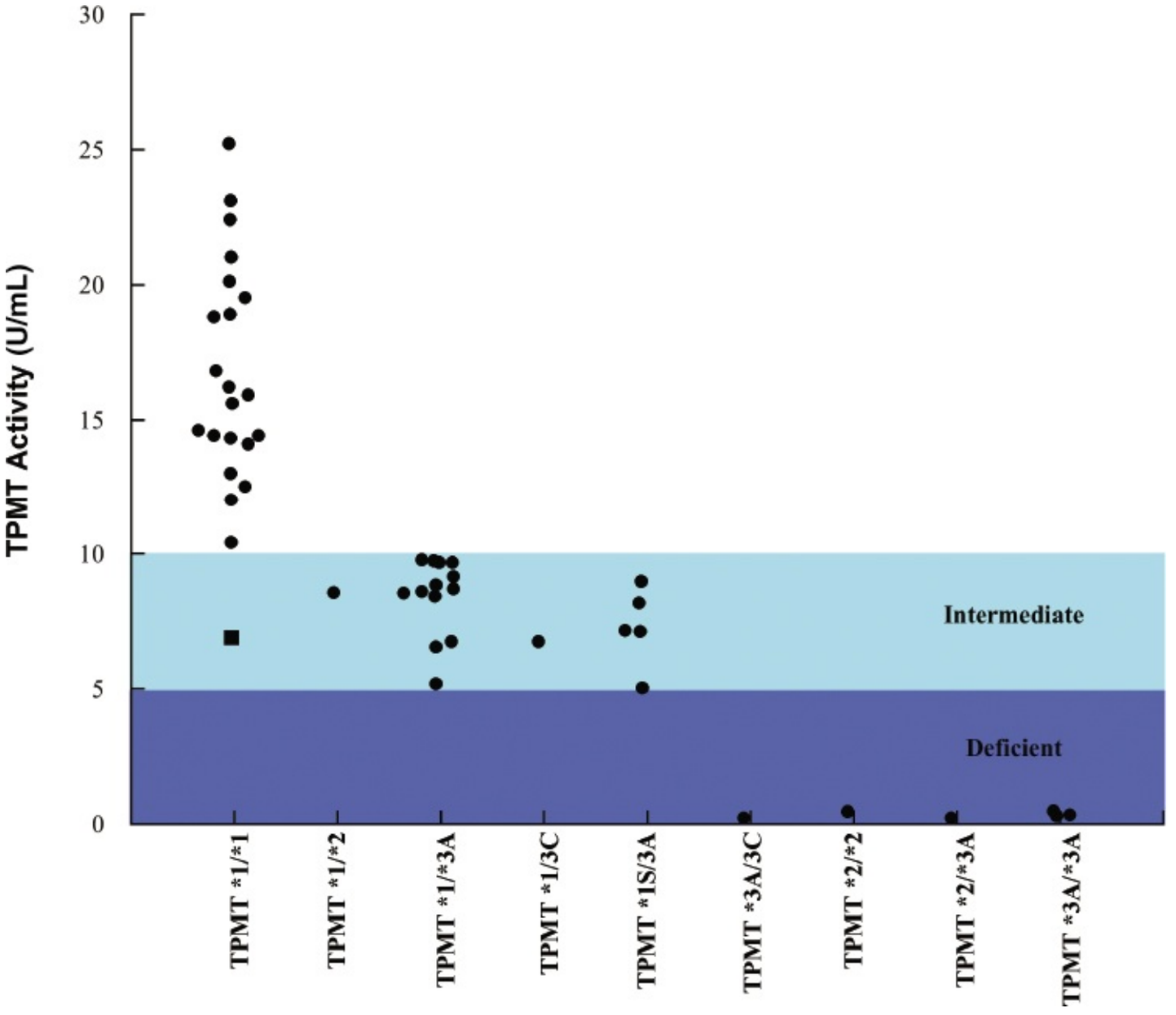


Figure 10.16 Thiopurine S-methyltransferase (TPMT) activity in patients with different genotypes. The heavily shaded area depicts the range of TPMT activity in erythrocytes that defines TPMT deficiency (<5 U/mL of packed red blood cells), the lightly shaded area depicts intermediate activity that defines TPMT heterozygous phenotypes (5 to 10 U/mL of packed red blood cells), and the unshaded area depicts the range of TPMT activity in patients who have homozygous wild-type phenotypes. Black circles indicate patients with concordant genotype and phenotype; the black square indicates one patient with discordant genotype and phenotype. (From Yates CR, Krynetski EY, Loennechen T, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med*. 1997;126(8):608-614. Copyright © 1997 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.)

It is well known that differences in TPMT activity alone cannot account for the wide interpatient variation observed in thiopurine disposition and effect. Polymorphisms in nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) have also been identified as determinants of thiopurine intolerance. NUDT15 is a nucleoside diphosphate that converts thioguanosine triphosphate (TGTP) to the inactive monophosphate thioguanosine nucleotide (TGMP), preventing the incorporation of TGTP into DNA and decreasing the cytotoxicity of

the thiopurines. Patients with loss-of-function alleles in NUDT15 have elevated thiopurine metabolites and increased sensitivity to the cytotoxic effects of mercaptopurine.[238,239] Of the other enzymes involved in thiopurine metabolism, there is conflicting data as to whether polymorphisms in inosine triphosphate pyrophosphatase (ITPA), which catalyzes conversion of inosine triphosphate (ITP) to inosine monophosphate (IMP) can contribute to observed variations in thiopurine pharmacology. Children with ALL with an ITPA polymorphic variation accumulate higher concentrations of methylated mercaptopurine metabolites than do children with the normal variant.[240]

Pharmacokinetics

The bioavailability of oral mercaptopurine is less than 20% and the resulting plasma drug concentrations are highly variable.[241] Only one-third of patients achieve plasma concentrations of mercaptopurine above 1 μM.[242] With oral doses ranging from 65 to 85 mg/m^2, the median peak plasma concentration was 0.59 μM (range, 0.13 to 2.3 μM) and the median AUC was 1.8 μM•h (range, 0.39 to 4.8 μM•h). Plasma mercaptopurine AUC is not predictive of erythrocyte thioguanine nucleotide concentrations. The bioavailability of mercaptopurine is limited by the extensive first-pass metabolism of the drug by xanthine oxidase in the liver and intestinal mucosa. When mercaptopurine is coadministered with the xanthine oxidase inhibitor allopurinol, the fraction of the dose absorbed increases fivefold and a dose reduction of oral mercaptopurine is recommended.[242]

The bioavailability of oral thioguanine is poor; plasma concentrations are variable, with a 30- to 50-fold range in peak plasma concentration and AUC.[243] The mean (±S.D.) peak plasma concentration was 0.46 ± 0.68 μM and the AUC ranged from 0.18 to 9.5 μM•h. Bioavailability was diminished further in nonfasting patients and patients experiencing nausea and vomiting. Plasma thioguanine AUC after an oral dose did not correlate with erythrocyte thioguanine nucleotide concentrations,[232] and although food may incrementally decrease the absorption of the drug, it does not appear to have any impact on the overall accumulation of thioguanine nucleotides.[244]

Pharmacogenetics

TMPT deficiency is the most common inherited form of thiopurine intolerance in people of European, African, or Hispanic descent in whom the frequency of variant alleles is approximately 10%. The molecular basis for polymorphic TPMT activity has been defined,[245] with at least 22 functional variant alleles being described (Fig. 10.18).[246] These alleles contain single-nucleotide polymorphisms (SNPs), leading to substitution, premature stop codons, or destruction of a splice site. The TPMT*3C, *3A, and *2 account for more than 95% of inherited deficiency. In children who are homozygous TPMT deficient, even a short course of thiopurine administration can result in profound myelosuppression, and erythrocyte thioguanine nucleotide levels in these TPMT-deficient patients are markedly elevated. Very low doses of mercaptopurine (5% to 10% of the standard dose) are tolerable in TPMT-deficient patients.[247] The 11% of patients who are heterozygous at the TPMT locus and have intermediate enzyme activity levels require more frequent mercaptopurine dose reductions

for toxicity than do homozygous patients with full enzyme activity. In children with ALL, the risk of relapse appears to be related to TPMT, with a lower rate of relapse observed in heterozygotes.[248]

The p.R139C missense variant was the first identified germ line variant of NUDT15 to be associated with increased sensitivity to mercaptopurine in children with ALL.[238,249] In contrast to TMPT, NUDT15 mutations are most common in people of Asian and Native American descent.[250] In a study of children with ALL, those who were homozygous and heterozygous for the p.R139C missense variant demonstrated increased sensitivity to mercaptopurine. Patients who were heterozygotes for both TMPT and NUDT15 received lower doses of mercaptopurine than did those who were heterozygotes for only TMPT or NUDT15, and none of the dual heterozygotes were able to tolerate more than 50% of the prescribed mercaptopurine. Guidelines for recommended starting doses of thiopurines for patients with TMPT and NUDT15 mutations have been published.[249]

Toxicity

The common toxic effects of mercaptopurine include myelosuppression, hepatic dysfunction (elevated transaminases, cholestatic jaundice), and mucositis. Myelosuppression is the primary toxic effect of thioguanine. Thioguanine has also been associated with a reversible form of SOS.[233] The 7-year event-free survival for children with standard-risk ALL who experience SOS or disproportionate prolonged thrombocytopenia, a subclinical form of SOS, was the same as in patients without SOS or disproportionate thrombocytopenia (85% vs. 84%, $p = 0.36$).[251] However, a subset of children who experience thioguanine-associated SOS appear to be at risk for developing portal hypertension.[252]

Drug Interactions

The classic example of a drug interaction in cancer chemotherapy is the effect of the xanthine oxidase inhibitor allopurinol on the catabolism of mercaptopurine to thiouric acid. When these two agents are administered concurrently, the hematologic toxicity of mercaptopurine is significantly enhanced.[253] Allopurinol pretreatment results in a fivefold increase in bioavailability of the oral dose of mercaptopurine,[254] and thus the mercaptopurine dose should be reduced by 75% when coadministered with allopurinol. Because the first step in the oxidation of thioguanine is catalyzed by aldehyde oxidase rather than by xanthine oxidase, the coadministration of allopurinol and thioguanine does not require a dose modification. MTX and folates also inhibit xanthine oxidase, and MTX can minimally enhance mercaptopurine bioavailability.[255]

Deoxyadenosine Analogs

Fludarabine/Clofarabine

Fludarabine and clofarabine (Fig. 10.14) are analogs of deoxyadenosine and are examples of agents originally developed through rational drug design on the basis of the observation that patients with adenosine deaminase (ADA) deficiency accumulate deoxyadenosine, which is

directly cytotoxic to lymphocytes. The deoxyadenosine analogs have proved particularly useful in adult patients with chronic lymphocytic leukemias and childhood acute leukemias. These drugs are prodrugs that undergo deoxycytidine kinase (DCK)-catalyzed activation to the triphosphate form. The deoxyadenosine analogs inhibit DNA synthesis via inhibition of DNA polymerase and ribonucleotide reductase, and via incorporation into DNA.

After IV administration, fludarabine phosphate is rapidly converted to fludarabine (F-ara-A). F-ara-A has a variable half-life in adults, ranging from 6 to 30 hours, and is primarily excreted unchanged in the urine.[256] With conventional fludarabine phosphate doses, myelosuppression and immunosuppression are dose limiting. At high doses, irreversible neurotoxicity can be observed, manifested as cortical blindness, optic neuritis, encephalopathy, and seizures.[257] In children with solid tumors, dose-limiting myelosuppression was observed.[258] Plasma steady-state concentrations of F-ara-A increase in proportion to the dose.

Synergy with cytarabine occurs via fludarabine potentiation of intracellular phosphorylation of cytarabine and more rapid accumulation of ara-CTP,[259] a finding that has been the basis for a number of regimens that combine these agents in the treatment of leukemias.[260] In addition, because of its profound immunosuppressive effects, fludarabine phosphate is used as a component of HSCT conditioning regimens, particularly in reduced-intensity conditioning regimens.[261]

In an effort to further increase the acid stability and improve the solubility of deoxyadenosine analogs, clofarabine (Fig. 10.14) was developed. In children with the leukemia, hepatotoxicity and skin rash were dose limiting, resulting in an MTD of 52 $mg/m^2/d \times 5$ days. In a phase 2 trial, 20% of children with refractory ALL achieved a response (7 complete responses, 5 complete responses without platelet recovery).[262] The most commonly reported adverse events included hypokalemia, hepatic dysfunction, and infections, with greater than or equal to grade 3 infections occurring in approximately 70% of children including 20% who developed sepsis or shock.

Deoxyguanosine Analogs

Nelarabine

Nelarabine is a water-soluble prodrug of arabinofuranosylguanine (ara-G). In the presence of ADA, nelarabine is demethoxylated to ara-G, which is subsequently catabolized intracellularly to a cytotoxic metabolite, ara-GTP.[263] Initial phase 1 and 2 trials focused on patients with T-cell malignancies because of the enhanced accumulation of ara-GTP in T versus B lymphoblasts.[264] These studies showed that nelarabine had antitumor activity in patients with recurrent or refractory T-cell malignancies with a response rate greater than 50% for children with T-cell leukemia in first relapse.[265]

Nelarabine is administered at doses of 400 to 650 mg/m^2 as a 1-hour infusion daily for 5 consecutive days every 3 weeks.[266] Neurotoxicity, primarily in the form of reversible somnolence and peripheral neuropathy, occurs in approximately 20% of patients. Severe CNS toxicities associated with nelarabine, although rare, include a Guillain–Barre-like

ascending paralysis. The plasma C_{max} and AUC of nelarabine and ara-G increase linearly with dose. The elimination of both agents is monoexponential. The clearance of ara-G is somewhat higher in children versus adults (0.3 L/h/kg vs. 0.2 L/h/kg) with a corresponding shorter half-life in children versus adults (2.1 hours vs. 3.0 hours).[267]

PYRIMIDINE ANTIMETABOLITES

Deoxycytidine Analogs

Cytarabine

Cytarabine (cytosine arabinoside, ara-C), an arabinose nucleoside analog of deoxycytidine (Fig. 10.13), is active in the treatment of acute leukemias and lymphoma. After intracellular metabolic activation, cytarabine interferes with DNA replication and repair through inhibition of DNA polymerase and through incorporation into DNA. Depending on the dose and schedule of cytarabine used, incorporation into DNA is thought to inhibit chain elongation, result in chain termination, or cause DNA strand breaks. Inhibition of DNA synthesis or incorporation into DNA by ara-CTP can only occur during the DNA synthesis phase (S phase) of the cell cycle, and more prolonged exposure to cytarabine allows the drug to be incorporated into a larger fraction of the cells as they pass through the S phase. Cytarabine incorporation into DNA may also be enhanced by timed retreatment with cytarabine after recruitment of leukemic cells into an active phase of DNA synthesis after the first treatment cycle and the simultaneous administration of cytarabine and colony-stimulating factors, which stimulate leukemic cells into the S phase.

A wide range of doses and schedules for cytarabine has been employed. The standard dose is 100 to 200 mg/m^2 as a bolus injection every 12 hours or by continuous infusion and it is usually administered daily for 5 to 7 days. High-dose regimens (3 g/m^2 every 12 hours for 4 to 12 doses or as a continuous infusion) have also been used with the intention of overcoming resistance mechanisms. Low-dose cytarabine regimens (5 to 20 mg/m^2/d over several weeks) are used for the treatment of myelodysplastic syndromes.

Cytarabine:daunorubicin liposome (CPX-351) is a dual-drug formulation of cytarabine and daunorubicin, packaged at a fixed 5:1 molar ratio within a liposomal carrier. The novel design was developed to optimize both a constant drug ratio of 5:1 found to have the highest proportion of synergy and lowest antagonism as well as to increase drug exposure while minimizing toxicity.[268] Response rates for CPX-351 are higher than that for standard-of-care cytarabine and daunorubicin chemotherapy. The approved adult dose of CPX-351 is 100 units/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) administered as a 90-minute infusion on days 1, 3, and 5[269]; higher doses have been studied in children.

Biotransformation

After entering cells by the carrier-mediated nucleoside transport system, cytarabine is converted to the active nucleotide, cytosine arabinoside triphosphate (ara-CTP), by three sequential phosphorylations catalyzed by intracellular kinases.[270] Ara-CTP then competes

with the natural substrate deoxycytidine triphosphate (dCTP) for DNA replicative and repair enzymes. The primary route of elimination of cytarabine and ara-CMP is catabolized to the inactive by-products uridine arabinoside (ara-U) and ara-UMP by a ubiquitous enzyme, cytidine deaminase.

Pharmacokinetics

The pharmacokinetics of cytarabine is directly related to the activity of the major degradative enzyme, cytidine deaminase. The bioavailability of oral cytarabine is less than 20% because of extensive presystemic metabolism by high levels of this enzyme in the gastrointestinal epithelium and liver. The hepatic extraction ratio for cytarabine is estimated to be as high as 80%. Subcutaneously injected cytarabine is completely absorbed.[271]

Drug elimination is rapid with IV dosing. Metabolism to ara-U accounts for 80% to 90% of total cytarabine clearance, and renal clearance accounts for less than 10% of total clearance. The ara-U formed is excreted in the urine. Because of the ubiquity of cytidine deaminase (e.g., liver, gastrointestinal tract, plasma, leukocytes), hepatic dysfunction does not significantly alter the rate of elimination of cytarabine. With high-dose prolonged IV infusions, the mean steady-state plasma concentration of cytarabine was 5 µM at a dose of 2 g/m^2/d, and the steady-state concentration of ara-U was 10-fold higher (60 µM).[29] In these patients, plasma clearance appeared to decrease with increasing dose, suggesting saturation of deaminases at the higher dose levels. In children receiving an infusion of 5 g/m^2/d, total clearance was 555 mL/min/m^2,[272] and at steady state, ara-U plasma concentrations are more than 10-fold higher than are steady-state cytarabine concentrations in children.[273]

The liposomal formulation of CPX-351 results in a prolonged half-life and decreased clearance of both the cytarabine and daunorubicin components. The terminal half-life of the cytarabine when given as the liposomal product is approximately 35 hours, 10 times that of the nonliposomal formulation. There is also more than a 1,000-fold reduction in clearance in the liposomal formulation compared to the nonliposomal cytarabine. This prolonged exposure does appear to be associated with increased nonhematologic toxicity, suggesting that the cytarabine and daunorubicin components are retained within the liposome.[268,269,274]

The pharmacokinetics of cellular ara-CTP, the active intracellular metabolite of cytarabine, has been characterized in the leukemic blasts from patients receiving high-dose cytarabine. After a 3 g/m^2 dose administered as a short infusion, there was considerable interpatient variability in the amount of ara-CTP accumulated in blasts. However, there was no correlation between the pharmacokinetics of the parent drug in plasma and the cellular concentrations of ara-CTP in leukemic blasts.[275]

Pharmacogenetics

Population-specific variants may be an important determinant in susceptibility to cytarabine cytotoxicity. On the basis of the results of an unbiased whole-genome approach in lymphoblastoid cell lines, unique pharmacogenetic signatures of four SNPs in persons of European ancestry and of five SNPs in persons of African ancestry explain more than half of the variability in sensitivity to this agent.[276] Sequencing studies have shown that genetic

polymorphisms in DCK, the rate-limiting enzyme in the activation of pyrimidine analogs such as cytarabine, may impact the levels of the active (triphosphate) form of the parent drug.[277] In children with Down syndrome and acute myeloid leukemia (AML), particularly the acute megakaryoblastic subtype, host genetic polymorphisms as well as alterations in leukemic blast gene expression that impact leukemia sensitivity to cytarabine are believed to positively contribute to the outcome following treatment with cytarabine-containing regimens. Increased levels of cystathionine-β-synthetase (CBS), a gene localized to 21q22.3, and altered expression of *GATA1* in megakaryoblasts, which impacts cytidine deaminase levels, are contributing factors.[278]

Toxicity

The primary toxicities of cytarabine are myelosuppression, nausea and vomiting, and gastrointestinal mucosal damage, including life-threatening bowel necrosis.[279] A syndrome of high fever, malaise, myalgias, joint or bone pain, rash, conjunctivitis, and chest pain has also been reported in children receiving cytarabine.[280] Coadministration of corticosteroids appears to relieve these symptoms. Neurotoxicity from cytarabine has been primarily associated with high-dose therapy. The most common manifestation of neurotoxicity is an acute cerebellar syndrome manifesting 3 to 8 days after initiation of therapy, but seizures and encephalopathy have also been reported. Nystagmus, ataxia, dysarthria, dysmetria, and dysdiadochokinesia are the classic cerebellar manifestations. In most cases, these neurologic symptoms resolve within a week, but as many as 30% of patients do not regain full cerebellar function.[281] Neuropathologic findings include loss of Purkinje cells and a reactive gliosis in the cerebellum. In addition to dose, other risk factors for the development neurotoxicity include advanced age and hepatic or renal dysfunction. Lowering the dose of cytarabine from 3,000 to 2,000 mg/m^2 and administering the drug daily instead of every 12 hours is recommended for patients with renal dysfunction.[282] The drug should be immediately withdrawn if nystagmus or ataxia occurs. Skin and ocular toxic effects have also been observed on high-dose regimens.[279]

Intrathecal Cytarabine

Intrathecally administered cytarabine is valuable in the treatment and prevention of meningeal leukemia. The clinical pharmacology of intrathecal cytarabine is quite different from that seen with systemic administration of this agent. With an intraventricular dose of 30 mg, peak concentrations exceed 2 mM and remain above 1 μM for 24 hours. Levels of cytidine deaminase, the enzyme that metabolizes cytarabine to ara-U, are low in the brain and CSF, and metabolism to ara-U is therefore only a minor pathway of elimination. The ratio of ara-U to cytarabine in the CSF is only 0.08. The terminal half-life of cytarabine is 3.5 hours, and the clearance is 0.42 mL/min, similar to the CSF bulk flow rate.[283] Plasma concentrations of cytarabine after an intrathecal 30 mg dose are less than 1 μM. Leukemic cells in the CSF were found to accumulate significant levels of intracellular ara-CTP after intrathecal cytarabine, and this active metabolite was retained in cells longer (half-life of 8 to 36 hours) than it was in peripheral lymphoblasts.[284] Neurotoxicity from intrathecal cytarabine includes

arachnoiditis, radiculopathy, seizures, encephalopathy, or myelopathy.[25]

Triple intrathecal therapy (ITT) consists of MTX, cytarabine, and hydrocortisone. ITT decreased the incidence of CNS relapse but did not improve event-free survival in children with standard-risk ALL.[285] No differences in neurocognitive functioning were identified in comparison of ITT to MTX as a single intrathecal agent.[286]

Gemcitabine

Gemcitabine (dFdC, Gemzar), a difluorinated analog of deoxycytidine (Fig. 10.13), is approved for use as frontline therapy for adult patients with pancreatic cancer and in combination with cisplatin for patients with non–small cell lung cancer (NSCLC). In contrast to cytarabine, gemcitabine has activity against a wide range of solid tumors including breast cancer, bladder carcinoma, ovarian cancer, head and neck cancer, testicular carcinoma, and a variety of sarcomas. Although gemcitabine has activity against leukemia and NHL in adults, it is not active in children with recurrent or refractory leukemias.[287] Gemcitabine as a single agent does not have a clearly defined role in the treatment of childhood solid tumors.[288] In combination with vinorelbine, there is substantial antitumor activity in recurrent Hodgkin lymphoma,[289] and in combination with docetaxel, there is modest antitumor activity in refractory sarcomas of bone.[290]

Biotransformation

Gemcitabine is a prodrug that requires intracellular activation by DCK for its cytotoxic effects. Gemcitabine diphosphate (dFdCDP) inhibits ribonucleotide reductase and gemcitabine triphosphate (dFdCTP) inhibits DNA polymerase. Intracellular drug concentrations of cells exposed to equimolar concentrations of gemcitabine and cytarabine are up to 20-fold higher for gemcitabine. The intracellular half-life of dFdCTP is 16 hours, which is significantly longer than that of ara-CTP (0.7 hours).[291] Gemcitabine is an S-phase cell cycle–specific agent that causes cells to accumulate at the G_1-S phase boundary. Gemcitabine is converted by cytidine deaminase to an inactive uridine metabolite, dFdU.

The most commonly used dose of gemcitabine is 1,000 mg/m^2 administered as a 30-minute infusion weekly × 3 weeks every 28 days. However, in one study comparing a standard dosing regimen (2,200 mg/m^2 over 30 minutes) to a fixed dose rate infusion regimen (10 mg/m^2/min over 150 minutes), there was a statistically significant increase in median survival for patients who received the fixed dose rate infusion. Furthermore, there was a twofold increase in intracellular gemcitabine triphosphate concentrations for patients receiving the fixed dose rate versus the standard dose.[292]

Pharmacokinetics

Gemcitabine clearance in children may be dose dependent.[293] However, in adults, there is no evidence of dose-dependent clearance over a wide dosage range (53 to 2,500 mg/m^2/dose).[294] Pharmacokinetic parameters in children and adults are otherwise similar. The half-life and volume of distribution of distribution are schedule dependent. In children receiving a 30-minute infusion, the half-life is 14 minutes, whereas in children receiving a 6-hour infusion,

the terminal half-life is 62 minutes. The volume of distribution is greater with longer infusion durations. The elimination half-life for the inactive deaminated metabolite, dFdU, is approximately 650 minutes. Mild to moderate renal insufficiency does not appear to have a significant impact on the pharmacokinetics of gemcitabine.[295]

Pharmacogenetics

Germ line mutations in the gene encoding for cytidine deaminase may impact its activity, leading to decreased activity and/or increased toxicity following gemcitabine administration.[296]

Toxicity

The primary toxicities associated with gemcitabine administration include myelosuppression, nausea, vomiting, increased serum transaminases, fatigue, fever, diarrhea, mucositis, flulike symptoms, rash, swelling, and alopecia.[297] Rarely, gemcitabine may cause somnolence, hypotension, severe pulmonary toxicity, or a thrombotic microangiopathy.[293] Gemcitabine has also been implicated in cases of radiation recall involving the skin and internal organs.[298]

Uracil Analogs

Fluorouracil/Capecitabine

The fluorinated pyrimidine fluorouracil (Fig. 10.13) is one of the few rationally designed cytotoxic anticancer drugs. It has been widely used in the treatment of carcinomas of the gastrointestinal tract, breast, ovary, and head and neck, but its use in children, in general, is limited to germ cell and hepatic tumors. Fluorouracil is administered intravenously as a bolus injection (500 mg/m^2), usually on a daily-for-5-days schedule, or as a continuous infusion (800 to 1,200 mg/m^2 over 24 hours).

Biotransformation

Fluorouracil is a prodrug and must be converted intracellularly to nucleotides before expressing cytotoxicity.[299] There are several possible pathways for the anabolism of fluorouracil to active intracellular metabolites, and the relative importance of each pathway is tissue- and tumor dependent.[300] The deoxyribonucleotide 5-FdUMP is a potent inhibitor of thymidylate synthase, leading to depletion of the DNA precursor, thymidine; and the ribonucleotide FUTP is incorporated into RNA. Inhibition of thymidylate synthase by FdUMP is thought to be the primary mechanism of action in most tumors.[301]

Pharmacokinetics

Bioavailability of oral fluorouracil is highly variable, in part because of a saturable first-pass elimination process.[302] Therefore, fluorouracil should not be administered by the oral route.[303] Bioavailable fluorouracil prodrugs, such as capecitabine, have been developed for oral administration. Capecitabine is converted to fluorouracil after absorption and provides

prolonged drug exposure, similar to that in a prolonged IV infusion.[304] Subcutaneously administered fluorouracil is well tolerated and has nearly complete bioavailability.[305]

Fluorouracil is eliminated primarily by biotransformation. The degradative pathway is the same as that for the naturally occurring pyrimidines uracil and thymine.[303] Less than 10% of the drug is excreted unchanged in the urine. With standard bolus dosing, the elimination of fluorouracil is rapid; total clearance is greater than 1,000 mL/min.[306] For a continuous-infusion schedule, the pharmacokinetics differs significantly, with clearance values as high as 5,000 mL/min. In children treated with 80 $mg/m^2/h$ for 12 hours, the mean steady-state concentration of fluorouracil was 6.7 μM and the clearance was 2,500 $mL/min/m^2$.[307] This schedule-dependent clearance is consistent with a dose-dependent or saturable clearance process. Although the liver is thought to be the principal site of drug catabolism, the high clearance values with infusions exceed the rate of hepatic blood flow, indicating that biotransformation must also be taking place in other organs.[306]

Circadian dependency of fluorouracil toxicity appears to be related to rhythmic 3- to 25-fold fluctuations in plasma drug concentrations over the course of the day.[308] During a continuous IV infusion, the plasma fluorouracil concentrations were highest in the late morning and lowest shortly before midnight; and plasma concentrations of fluorouracil were inversely related to the activity of the catabolic enzyme, dihydropyrimidine dehydrogenase (DPD), in peripheral blood mononuclear cells.[309]

Pharmacokinetic studies following administration of a rapidly disintegrating tablet formulation of capecitabine, a prodrug of fluorouracil designed to preferentially generate 5-fluoruacil in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase, demonstrated that the plasma exposures (area under the curve) for capecitabine and its metabolites were slightly lower in children than in adults at equivalent dose levels.[310]

Pharmacogenetics

Inherited partial deficiency of the catabolic enzyme DPD in 1% to 3% of the population is associated with severe fluorouracil toxicity. The intronic variant, *DPYD*2A*, which is associated with DPD deficiency, has been found in approximately half of patients who develop severe neutropenia. In patients with DPD-deficiency, fluorouracil half-life is markedly prolonged with no evidence of drug catabolism.[311] Genetic polymorphisms in other genes that have been associated with fluorouracil-related treatment outcomes include thymidylate synthase, *TYMS*, and the methylenetetrahydrofolate reductase, *MTHGR*, genes.

Toxicity

The incidence and severity of clinical toxicities of fluorouracil depend on the dosing schedule. With IV bolus dosing, myelosuppression is the primary toxicity, but if the drug is given as a continuous infusion, myelosuppression is less prominent and stomatitis and diarrhea become dose limiting. Protracted low-dose infusions can produce palmar-plantar dysesthesia (hand-foot syndrome). Reversible neurologic toxicity characterized by somnolence, cerebellar ataxia, and headache; ocular toxicity consisting of conjunctivitis and

ectropion; dermatitis; and, rarely, cardiotoxicity, which can include chest pain, arrhythmias, and ischemic changes on ECG, are also reported.[312]

Drug Interactions

Folates are required for the stable binding of 5-FdUMP to its target enzyme, thymidylate synthase, and the combination of leucovorin and fluorouracil is synergistic in experimental systems. This combination has been studied in a large number of clinical trials, primarily in adults with gastrointestinal tumors. In randomized clinical trials, the combination results in higher response rates than in fluorouracil alone.[313]

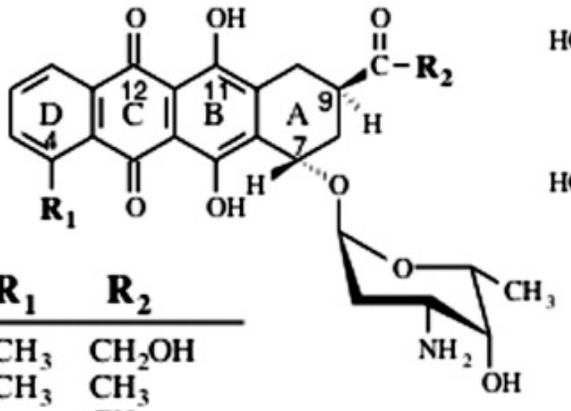
TOPOISOMERASE INHIBITORS

Topoisomerases are nuclear enzymes that regulate the three-dimensional shape of DNA by cleaving and religating DNA during replication, transcription, repair, and recombination. Topoisomerase I catalyzes cleavage and religation of single strands of DNA, whereas topoisomerase II regulates breakage and rejoining of both strands. Topoisomerase inhibitors appear to facilitate stabilization of cleavable complexes and block ligation of disrupted strands of DNA. Accumulation of strand breaks results in cell death.

Anthracyclines

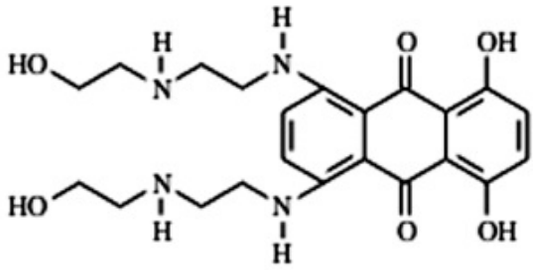
Doxorubicin/Daunomycin/Idarubicin

The anthracyclines, doxorubicin, daunomycin (daunorubicin), and idarubicin, are highly pigmented compounds (Fig. 10.17). Doxorubicin has a wide range of clinical activity against pediatric cancers, including the acute leukemias, lymphomas, sarcomas of soft tissue and bone, Wilms tumor, neuroblastoma, and hepatoblastoma. The use of daunomycin and idarubicin is currently limited to the acute leukemias.

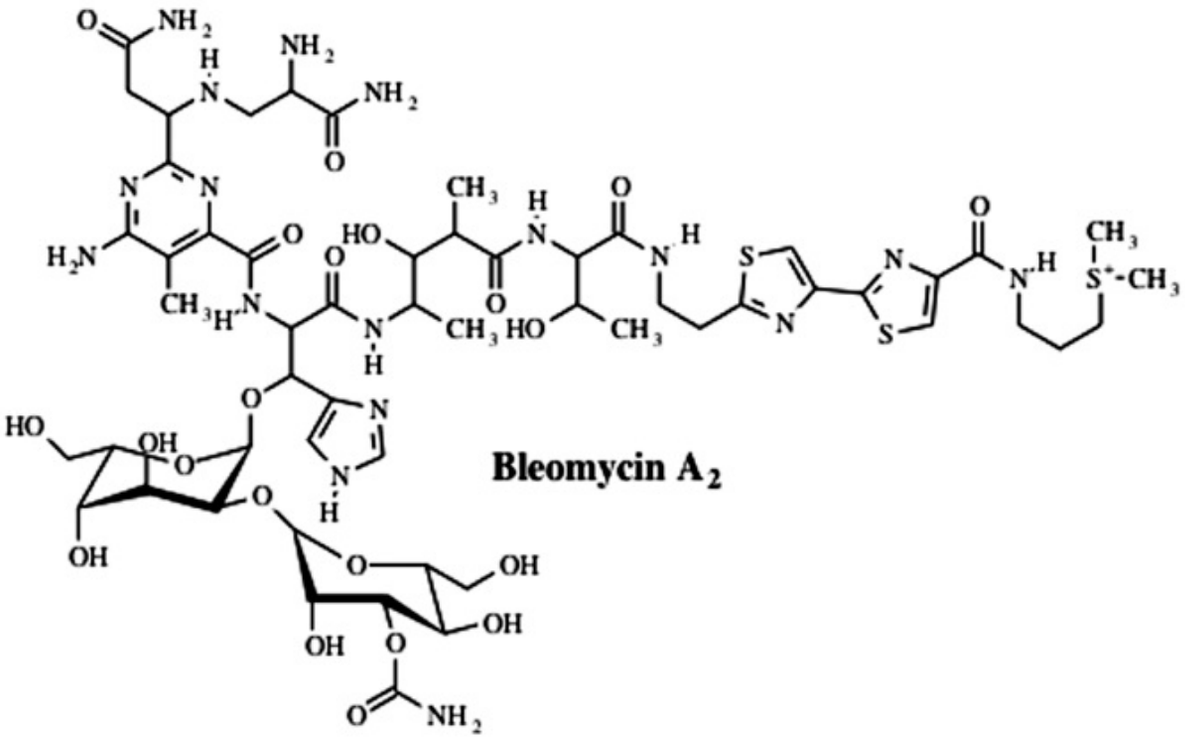


Anthracyclines

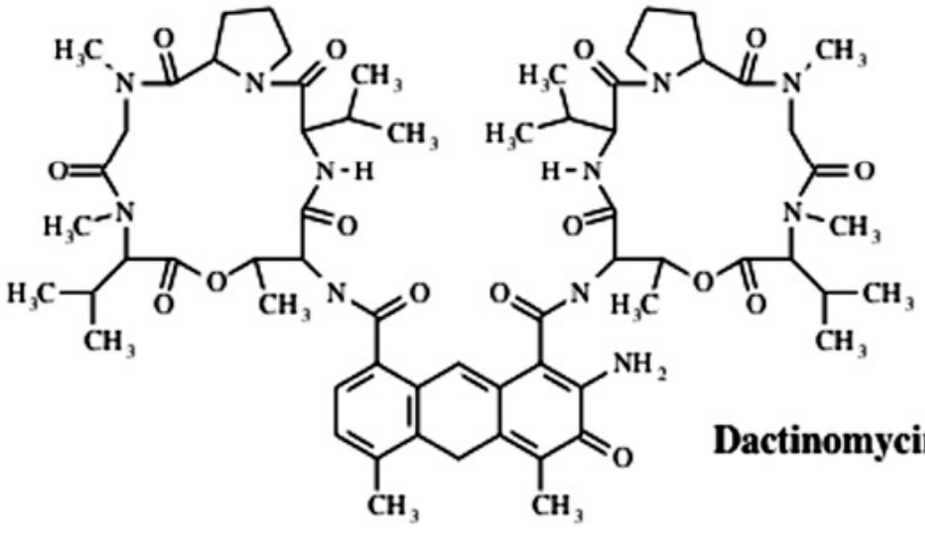
	R_1	R_2
Doxorubicin	OCH_3	CH_2OH
Daunomycin	OCH_3	CH_3
Idarubicin	H	CH_3



Mitoxantrone



Bleomycin A_2



Dactinomycin

Figure 10.17 Chemical structures of the antitumor antibiotics commonly used in the treatment of childhood cancers: the anthracyclines, doxorubicin, daunomycin, and idarubicin; mitoxantrone; bleomycin A_2; and dactinomycin. Doxorubicin and daunomycin differ only in the presence or absence of a hydroxyl group on the carbonyl side chain at ring position 9. The structure of idarubicin (4-demethoxydaunomycin) is identical to that of daunomycin except for the absence of a methoxy group at ring position 4. Mitoxantrone differs from the anthracyclines by virtue of its three-ring nucleus, its symmetrical aminoalkyl side chains, and its lack of a glycosidic substituent, which is important for water solubility of the anthracyclines.

Several mechanisms for the antitumor activity of anthracyclines have been proposed. These agents intercalate into DNA and induce topoisomerase II–mediated single- and double-strand breaks in DNA. Topoisomerase II–mediated DNA cleavage may also occur by nonintercalative mechanisms.

Although experimental evidence indicates that topoisomerase-mediated DNA damage is the most important mechanism of anthracycline action, agents in this class also block helicase-catalyzed dissociation of duplex DNA into single strands and oxidize DNA bases. The anthracyclines can undergo chemical reduction, yielding reactive free radical intermediates. Transfer of an electron from these unstable radicals to molecular oxygen yields superoxide radicals that can oxidative damage to cellular macromolecules. The interaction of anthracyclines with iron plays a role in free radical formation. Anthracyclines may also exert cytotoxic effects through a direct interaction with the cell membrane.[314]

The anthracyclines are administered by a wide range of schedules, including bolus injection daily, weekly, or every 3 to 4 weeks, short infusions of up to 6 hours, continuous infusion over 24 to 96 hours, and long-term, low-dose infusions over weeks to months. The antitumor effect does not appear to be influenced by these variations in the schedule of administration. However, the schedule can significantly influence toxicity. Administering doxorubicin weekly or by infusion appears to reduce nausea and vomiting but enhances mucositis.[315] Although some data suggest that prolonged infusion may decrease anthracycline-associated cardiotoxicity, no difference was observed when cardiac toxicity in children with ALL who received doxorubicin via bolus dosing was compared to that observed in children who received 48-hour doxorubicin infusions.[316]

Biotransformation

The principal metabolites of the anthracyclines are the corresponding alcohols (13-dihydroderivative), doxorubicinol, daunomycinol, and idarubicinol, formed by the action of aldoketoreductase.[317] Doxorubicinol and daunomycinol retain cytotoxic activity but are considerably less active than are the parent drugs, but idarubicinol is as potent as idarubicin.[318] Anthracycline free radical species can be generated by several reactions. Anthracyclines avidly chelate iron; the resulting drug–iron complex can undergo reduction to yield free radicals by cellular reducing systems (e.g., glutathione, NADH cytochrome P-450 reductase) or by auto-oxidation of the anthracycline molecule. Anthracyclines may be inactivated by conjugation with sulfate or glucuronide after demethylation (i.e., doxorubicin and daunomycin) of the methoxy group at the 4-position on the ring.

Pharmacokinetics

Instability of doxorubicin and daunomycin in an acid environment prevents their oral administration. Idarubicin can be administered orally and has a bioavailability of 20% to 30%.[319] The severe vesicant properties of the anthracyclines prohibit intramuscular or subcutaneous administration.

After an IV injection, there is an initial rapid decline in plasma concentration, which is generally attributed to the rapid and avid binding of these drugs by tissues.[320] This extensive binding also accounts for the very large volumes of distribution (>500 L/m^2). Tissue anthracycline concentrations can be up to 100-fold higher than are plasma drug concentrations, and tissue concentrations persist longer. The distributive phase is followed by a long terminal elimination phase, with half-lives of 30 hours for doxorubicin and 15 to 20 hours for daunomycin and idarubicin. Despite the fact that drug concentrations at the start of the terminal phase are 1/50 the peak concentrations, 66% to 80% of the total drug exposure occurs during this terminal phase. The anthracyclines are eliminated by biotransformation (primarily hepatic) and biliary excretion. Renal excretion accounts for only 5% to 15% of total drug clearance. The total clearance exceeds 500 $mL/min/m^2$, and in children, clearance corrected for body surface area is independent of age. The pharmacokinetic parameters appear to be linear over a wide range of dosage schedules.[321] One pediatric study reported age-dependent pharmacokinetic parameters for doxorubicin when the parameters are normalized for body weight; however, when clearance and volume of distribution are normalized for body surface area, there are no age-dependent differences. Nonetheless, the mean systemic clearance for children is significantly greater than the values reported for adults.[322] In a study of infants treated with daunomycin, clearance did not differ from that of older children overall; however, a 15-fold difference in clearance was observed within the relatively small group of infants evaluated.[323]

The alcohol metabolites of the anthracyclines are also detectable in plasma. Exposure to doxorubicinol as measured by AUC is approximately half that of doxorubicin. In contrast, aldoketoreductase has a higher affinity for daunomycin and idarubicin, and the terminal half-lives of daunomycinol (20 to 40 hours) and idarubicinol (50 to 80 hours) are longer than those of their respective parent drugs. As a result, exposure to daunomycinol and idarubicinol is twofold and fivefold higher than it is to daunomycin and idarubicin, respectively. There is accumulation of idarubicinol with daily administration of idarubicin.

Dosage modifications are usually not required for doxorubicin and daunomycin in patients with renal dysfunction, although doxorubicin clearance is delayed in patients on hemodialysis.[324] Idarubicin clearance is correlated with creatinine clearance and appears to be reduced with renal impairment.[325] Delayed clearance of doxorubicin associated with an increase in myelosuppression and mucositis has been reported in adults and children with hepatic dysfunction.[320] Abnormal liver function test results do not correlate well with doxorubicin clearance. The best recommendation is that dose reduction be reserved for patients with multiple liver function test abnormalities or direct bilirubin elevations, although this guideline may significantly underdose some patients.[326]

Obese patients (>130% of ideal body weight) appear to eliminate doxorubicin more slowly than do nonobese patients, and therefore have a twofold higher drug exposure than do nonobese patients.[327] Substantially higher doxorubicin exposure was observed in obese

women compared to that in lean controls or in men.[328] However, it appears that obese women do not experience increased anthracycline-related toxicity when actual rather than ideal body weight is used for drug dosing.[329] Doxorubicinol clearance is decreased in children with more than 30% body fat.[330] However, in children with AML treated with an anthracycline-based induction regimen, the time to neutrophil recovery and the time to entry to course two therapy were not significantly increased in obese patients compared with that in children of normal weight.[331] Therefore, the data at present do not appear to support empiric anthracycline dose modification for obese patients.

Toxicity

The acute toxicities of the anthracyclines include myelosuppression, mucositis (less prominent with daunomycin), nausea, vomiting, diarrhea, and alopecia.[332] Extravasation of these agents leads to severe local tissue damage and deep ulcerations, which heal very slowly and are difficult to skin graft. In a prospective clinical trial of topical dimethyl sulfoxide (DMSO, 99% solution), no ulcerations occurred in 20 patients with suspected anthracycline extravasation when DMSO was applied twice and allowed to air dry, 6 times/d for 14 days.[333] When administered within 6 hours of an extravasation event, dexrazoxane has been shown to decrease the need for surgical intervention in adults.[334] In severe cases, consideration should be given to early surgical excision of the affected tissues followed by full-thickness skin graft or skin flap coverage.[335]

Anthracyclines can potentiate radiation reactions in many tissues, including skin, liver, esophagus, lungs, and heart, and the concurrent use of these two modalities should be avoided. A radiation-recall phenomenon can be observed if an anthracycline is administered in the post-irradiation period.[332]

Anthracyclines can cause acute and chronic cardiac toxicity.[336] The acute form is characterized by arrhythmias and conduction abnormalities, but there can also be an acute drop in left ventricular function, reaching a nadir at 24 hours, followed by variable recovery.[337] Rarely, this acute toxicity is manifested as the myocarditis-pericarditis syndrome, which in its severest form is characterized by the rapid onset of congestive failure associated with pericarditis.[338] In general, the acute asymptomatic cardiac changes are transient and do not prevent further use of anthracyclines.

Late effects of chemotherapy including anthracycline-related cardiotoxicity are presented in Chapter 45. Chronic anthracycline-associated cardiac disease has been linked to several risk factors. Higher cumulative doses of anthracycline have been linked to an increased risk of cardiac disease; however, it should not be assumed that lower “safe” doses have been defined, particularly in children. Patients exposed to anthracycline doses as low as 101 to 150 mg/m^2 have been shown to be at increased risk for cardiomyopathy compared to children who were not treated with these agents. Children appear to be at higher risk for cardiac toxicity than are adults, and those younger than 5 years are at higher risk than are older children. Girls have a significantly higher incidence of abnormal cardiac findings at any given cumulative dose of doxorubicin than do boys.[339] Additional factors that are reported to increase the risk of the development of a cardiomyopathy include prior or concurrent mediastinal irradiation and preexisting cardiac disease. Lowering peak concentrations of

anthracycline by administering the drugs on a lower dose weekly schedule or by 6- to 96-hour continuous infusions may reduce the cardiotoxic effects in adults without compromising the antitumor effect. However, prolonged infusions of anthracyclines and divided dosing schedules may not protect children from late cardiotoxicity.[340]

The primary pathologic change in the myocardium is the destruction and loss of myofibrils and sarcoplasmic vacillation. Myocardial damage appears to result from the generation of free radicals of the drug or secondary oxygen free radicals. The myocardium has limited ability to withstand this oxidative stress because of its low levels of catalase, which detoxifies peroxides. Cardiac doxorubicin and doxorubicinol concentrations in human hearts at autopsy were significantly higher than were concentrations in skeletal muscle and smooth muscle organs (i.e., bladder and uterus).[341] The synthesis of anthracycline alcohol metabolites in humans is modulated by carbonyl reductases (CBRs), and case–control studies suggest a link between a polymorphism in *CBR3* and an increased risk of cardiomyopathy following low to moderate doses of anthracyclines in children. Other SNP-associated risks, either increased or decreased, of anthracycline-associated cardiomyopathy include variants in the *SLC28A3*, *SLC28A1*, *UGT1A6*, *CAT*, *ABCB1*, *ABCB4*, *ABCC1*, *ABCC5*, and *NOS3* genes.[342]

The cardiac function in children receiving anthracycline therapy should be closely monitored during treatment. Echocardiograms or radionuclide cineangiography is generally recommended before starting therapy and then periodically before courses of anthracyclines.

Approaches to the prevention of anthracycline cardiac toxicity include coadministration of agents that protect the myocardium from the cardiotoxic effects of anthracyclines and development of potentially less cardiotoxic anthracycline analogs (such as idarubicin and epirubicin) and liposomal formulations of doxorubicin. The most studied cardioprotective drug is a chelating agent, dexrazoxane (Zinecard). This drug undergoes hydrolysis intracellularly to a compound that is similar in structure to EDTA and tightly binds iron, a cofactor in anthracycline free radical reactions. The dexrazoxane dose is determined from the doxorubicin dose as a ratio of 10 mg of dexrazoxane for each 1 mg of doxorubicin. Clinical and subclinical cardiac toxicity, as measured by incidence of congestive heart failure, decline in left ventricular ejection fraction on radionuclide cineangiography, and endomyocardial biopsy, was significantly reduced in patients receiving dexrazoxane. The cardioprotective effect of dexrazoxane has been demonstrated in children.[343] In a randomized trial of children with ALL treated with 300 mg/m^2 of doxorubicin, patients treated with doxorubicin alone were more likely than were those who received dexrazoxane and doxorubicin to have elevated troponin T levels (50% vs. 21%, $p < 0.001$) and extremely elevated troponin T levels (32% vs. 10%, $p < 0.001$). Importantly, event-free survival at 2.5 years was 83% in both groups, indicating that dexrazoxane does not diminish the antileukemic effect of doxorubicin. Although a greater than anticipated incidence of second malignant neoplasms was observed in children with Hodgkin lymphoma treated with dexrazoxane as a component of multiagent therapy including administration of other topoisomerase II inhibitors,[344] no increased risk has been observed in adult trials and no such risk was observed in clinical trials in children with leukemia.[345–347] In 2011, the European Medicines Agency (EMA) restricted the use of dexrazoxane in children with cancer because of concerns for increased risk of second malignant neoplasms. However, in 2017, the EMA amended the

contraindication to permit the use of dexrazoxane in children and adolescents receiving higher cumulative doses of anthracyclines. Systematic reviews including studies in children found that dexrazoxane administration was associated with significant decreases in cardiotoxicity and had no negative impact on survival.[348,349] Less cardiotoxic anthracycline analogs such as idarubicin or liposomal formulations of anthracyclines such as liposomal daunorubicin have also been incorporated into clinical trials by cooperative groups.[350,351]

Drug Interactions

Doxorubicin-related toxicity is also significantly enhanced when the drug was administered in combination with cyclosporine.[352] The mechanism of this interaction is likely to be related in part to inhibition of P-glycoprotein in the biliary tract and decreased excretion of doxorubicin and doxorubicinol into the bile.

Epipodophyllotoxins

Etoposide

Etoposide (VP-16) is a semisynthetic analog of the natural product, podophyllotoxin, an antibiotic agent that binds to tubulin. However, the epipodophyllotoxins do not act as microtubule inhibitors.[353] Instead, the antitumor effect, through stabilization of the normally transient covalent intermediates formed between the DNA substrate and topoisomerase II, leads to single- and double-strand DNA breaks (Fig. 10.18).[354] Activity of etoposide has been observed against the acute leukemias, Hodgkin leukemia and NHL, neuroblastoma, rhabdomyosarcoma, soft-tissue sarcomas, Ewing sarcoma, germ cell tumors, and brain tumors.

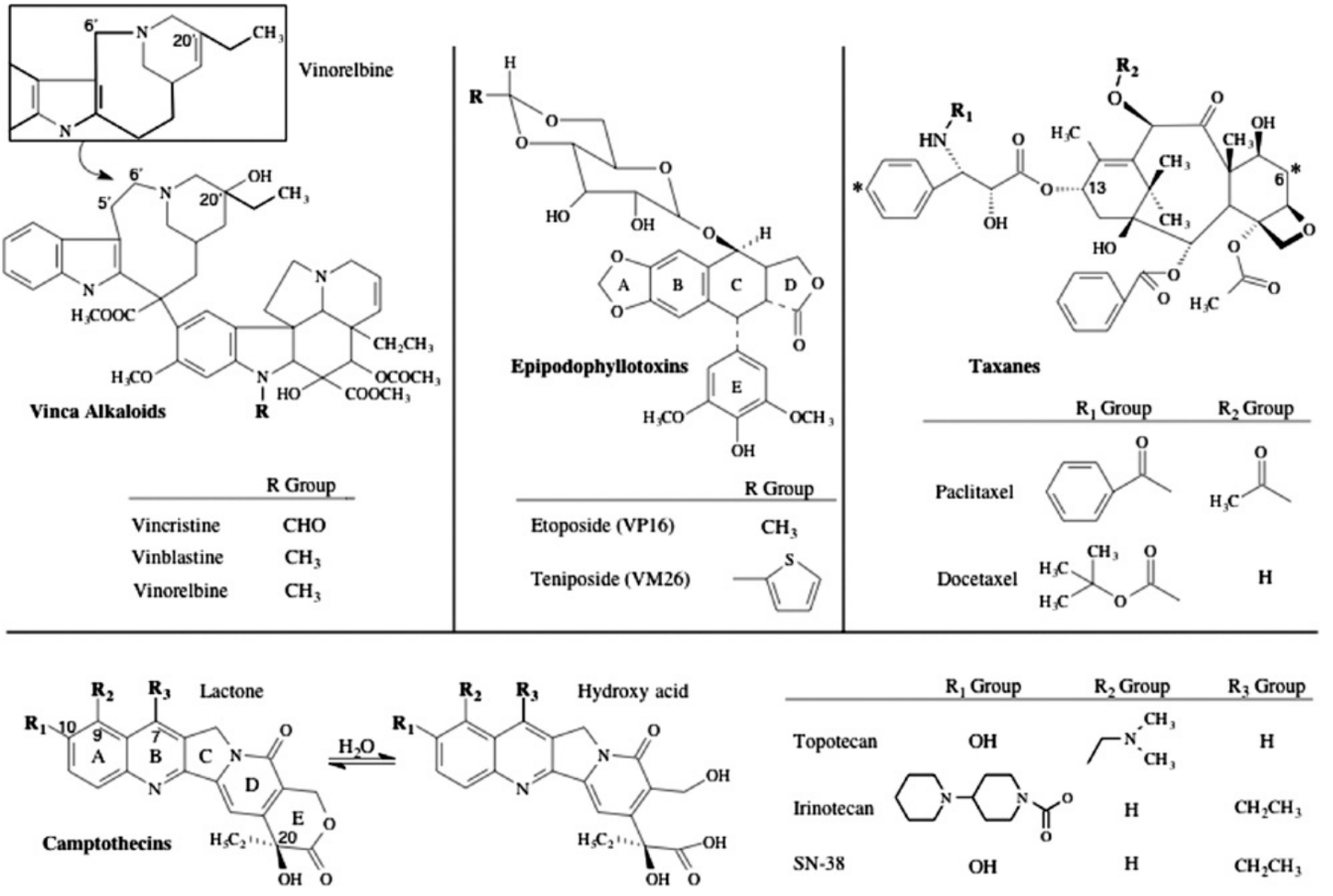


Figure 10.18 Chemical structures of the plant alkaloids commonly used in the treatment of childhood cancers: the vinca alkaloids, vincristine and vinblastine, extracted from the periwinkle plant; the epipodophyllotoxin, etoposide, a synthetic derivative of the natural product podophyllotoxin, which is derived from the mandrake plant (May apple); the taxanes, paclitaxel and docetaxel, derived from the yew tree; and the camptothecins, topotecan and irinotecan, derived from the stem wood of *Camptotheca acuminata*. Vincristine and vinblastine are identical except for the substituent at the R position, whereas the catharanthine ring of vinorelbine is modified. The *asterisks* on the taxane structure are hydroxylation sites. The hydroxyl group on the 10-position of SN-38 is the site of glucuronidation.

Because the solubility of the epipodophyllotoxins in water is poor, both are supplied in nonaqueous formulations. Etoposide is formulated in polysorbate 80, polyethylene glycol, and alcohol. Before IV administration, these agents are diluted in 5% dextrose in water or in 0.9% saline to a concentration of less than 0.4 mg/mL and infused over 30 to 60 minutes to avoid the hypotension associated with rapid injections. Etoposide phosphate is a water-soluble prodrug of etoposide that overcomes the formulation difficulties of the parent drug. Etoposide phosphate is rapidly converted to etoposide in vivo by plasma phosphatases and has a toxicity profile, MTD, and pharmacokinetic profile similar to that of etoposide.[355]

Etoposide is usually administered on a daily schedule for 3 to 5 days at a dose of 60 to 120 mg/m^2/d or a single high-dose schedule (up to 800 mg/m^2 of etoposide); etoposide (2,400 mg/m^2) has also been incorporated into HSCT preparative regimens. A chronic oral low-dose (50 mg/m^2/d) schedule of etoposide has been incorporated in a number of combination metronomic regimens.[356]

Etoposide antitumor activity is dose- and schedule dependent. In adults with small cell

lung cancers, the response rate in patients treated on a daily-for-5-days schedule is significantly higher than in patients treated with same total dose infused over 24 hours.[357]

Biotransformation

The disposition of the epipodophyllotoxins is characterized by a significant degree of intrapatient and interpatient variability. The bioavailability of oral etoposide is nonlinear, approximately 50% at doses of 200 mg/m^2 or less, but it ranges from 10% to 80%, and there is considerable dose-to-dose variation within each patient. At higher doses (>200 mg/m^2), the fraction of the dose absorbed decreases.[357] Because oral absorption is erratic, dose dependent, and associated with increased toxicity, the clinical usefulness of oral administration of standard doses of etoposide has been limited. However, the more efficient absorption of lower doses of etoposide (bioavailability, 70%) suggests that the chronic oral low-dose schedule may circumvent some of these limitations.[358] The epipodophyllotoxins are extensively metabolized in part by CYP3A4 and CYP3A5, mediated O-demethylation to the active catechol form, which can be oxidized to a reactive quinone.

Pharmacokinetics

Renal clearance accounts for 30% to 40% of the total systemic clearance of etoposide (Table 10.4). Biliary excretion is not a major route of elimination for etoposide, accounting for less than 10% of total drug elimination in most studies.[359] Penetration of the epipodophyllotoxins into the CSF is limited, but the concentrations achieved may be cytotoxic.[360]

The clearance of etoposide is highly variable, the median clearance in children is 26 mL/min/m^2 (range 14 to 54 mL/min/m^2). Cyclosporine, a modulator of the P-glycoprotein, diminishes the renal and nonrenal elimination of etoposide, resulting in an increase in plasma exposure (AUC) to the drugs and an increase in toxicity. The concomitant administration of anticonvulsants with etoposide in children results in a two- to threefold increase in clearance and a proportional decrease in systemic drug exposure, which could reduce the drug's efficacy.[361] The enhanced clearance is presumably the result of induction of hepatic metabolism.

Etoposide pharmacokinetic parameters, including drug clearance, are dose independent for doses up to 3,000 mg/m^2. In infants 3 to 12 months of age, the median clearance was 19 mL/min/m^2, and in children older than 1 year of age, the median clearance was 18 mL/min/m^2.[362] Therefore, no special dosing guidelines are required for treating infants, and all patients should receive a dose calculated from body surface area. In children receiving 5 consecutive days of etoposide therapy, the maximum plasma concentration and AUC for total and free etoposide decrease slightly on day 5 versus day 1, the AUC for etoposide catechol is much greater on day 5 than on day 1.[363] Etoposide clearance was significantly delayed in patients with renal insufficiency, putting them at higher risk for toxicity. There was a correlation between creatinine and etoposide clearance, suggesting that etoposide dose modifications could be based on the creatinine clearance. Etoposide clearance was not delayed in patients with abnormal hepatic function. The protein binding of etoposide is highly variable in cancer patients (range, 76% to 97%), and the degree of binding is

correlated with the serum albumin level.[364] Patients with low serum albumin experience more severe hematologic toxicity from etoposide, presumably because of higher free-drug concentrations. A 30% to 40% dosage reduction may be indicated in these patients. The fraction of etoposide bound to protein is higher in pediatric cancer patients than in adults with cancer.[365]

Toxicity

The primary dose-limiting toxicity of etoposide is myelosuppression. Other toxicities include alopecia, nausea, vomiting, phlebitis, mild peripheral neuropathy, hepatic enzyme elevations, and mucositis. Arrhythmias are relatively rare. Diarrhea was the dose-limiting toxicity in children treated with etoposide on the chronic oral dosing schedule, but myelosuppression and mucositis occur frequently.[366] Non–dose-limiting hypersensitivity reactions, characterized by urticaria, flushing, rash, and angioedema, are common and related to the cumulative dose of etoposide. Severe hypersensitivity reactions, such as bronchospasm and anaphylaxis, can occur.[367]

A distinctive form of secondary acute leukemia, characterized by a short latency period (median time to presentation, 30 months), chromosomal translocations of the *KMT2A* gene at chromosome band 11q23, and M4 or M5 FAB morphologic subtype (monocytic or myelomonocytic), occurs in epipodophyllotoxin-treated patients.[368] The cumulative risk of developing this form of secondary leukemia has been estimated to be 5% to 12% in children with ALL treated with high cumulative doses of epipodophyllotoxins on a weekly or twice-weekly schedule. In contrast, the incidence of this form of secondary AML in survivors of germ cell cancers who were treated with etoposide is less than 1%. The 6-year cumulative incidence of secondary leukemia and myelodysplastic syndrome in patients who were treated on 12 pediatric cooperative group clinical trials was 3.3%, 0.7%, and 2.2% for cumulative etoposide doses of <1.5 g/m^2, 1.5 to 2.99 g/m^2, and ≥ 3 g/m^2, respectively. Thus, epipodophyllotoxin cumulative dose does not appear to be a significant risk factor for development of secondary leukemia.[369]

Camptothecins

Topotecan and irinotecan are semisynthetic, water-soluble camptothecin analogs (Fig. 10.18) that produce DNA strand breaks by forming a ternary complex with DNA and topoisomerase I. In aqueous solutions, the camptothecins exist in equilibrium between the active lactone form and the relatively inactive hydroxy-acid form, which results from reversible hydrolysis of the E-ring. The inactive form predominates at physiologic pH, although the ratio of lactone:hydroxy acid varies for topotecan (10%), irinotecan (25% to 30%), and its active metabolite SN-38 (50% to 65%).

Topotecan

Topotecan is active against neuroblastoma, rhabdomyosarcoma, Ewing family tumors, medulloblastoma, and Wilms tumor but is inactive in osteosarcoma. Topotecan is now used in combination with multiagent chemotherapy in frontline therapy for patients with high-risk

neuroblastoma and is commonly used as in a number of solid tumors such as rhabdomyosarcoma or Ewing sarcoma.

Topotecan is usually administered intravenously for 5 days at a dose of 1.4 mg/m^2/d every 21 days or 2.0 mg/m^2/d for 5 days followed by filgrastim. The injectable form of topotecan has also been administered orally once daily for 5 days for 2 consecutive weeks every 28 days at a dose of 1.8[370] or 0.5 mg/m^2/d twice daily for 21 days.[371] Continuous-infusion schedules of 1 to 21 days' duration have also been studied. The pharmacokinetics of intraventricular topotecan has also been evaluated; a dose of 0.2 mg of intraventricular topotecan administered daily for 5 consecutive days with concomitant administration of dexamethasone resulted in CSF topotecan lactone concentrations above 1 ng/mL for 8 hours.[372]

The dose of topotecan must be substantially reduced when administered in combination with cisplatin, carboplatin, or cyclophosphamide because of enhanced hematologic toxicity.[373] Myelosuppression is the most common topotecan toxicity. Diarrhea becomes dose limiting with more protracted schedules or with oral dosing.[374] Other toxicities associated with topotecan include nausea and vomiting, alopecia, mucositis, elevated hepatic transaminases, and rash.[375] Typhlitis has also been reported in patients with refractory acute leukemia.[376]

The bioavailability of oral topotecan in children is approximately 30%, but there is marked interpatient variability in absorption.[370] With IV administration, the clearance of the lactone form of topotecan is also highly variable.[377] Renal excretion is the primary route of elimination (60% to 70% of total dose).[378] Impaired renal function decreases topotecan clearance, necessitating a dosage reduction.[379] N-demethylation is a minor metabolic pathway, and mild to moderate hepatic dysfunction does not appear to impact drug disposition.[380] Systemically administered topotecan penetrates into the CSF better than do other topoisomerase I inhibitors. Although topotecan penetrates into pleural and ascitic fluid, it is not sequestered in the fluid accumulation and the drug has thus been safely given to patients with large effusions.[381]

Intrathecal Topotecan

A phase II trial of intrathecal topotecan administered twice weekly in children with leptomeningeal dissemination of CNS or solid tumors was not associated with an adequate progression-free survival[382]; thus a phase I trial evaluating daily × 5 schedule of intraventricular topotecan was performed to determine a pharmacokinetic optimal dose. Although safe and well tolerated, objective antitumor activity was not observed in the small number of treated patients.[372]

Irinotecan

Irinotecan is a prodrug that is converted by carboxylesterases in the liver and intestinal tract to the active metabolite, 7-ethyl-10-hydroxy camptothecin (SN-38), which is 100- to 1,000-fold more potent than is irinotecan.[383] Irinotecan has activity in children with neuroblastoma, hepatoblastoma, and some pediatric CNS tumors. In formal phase II trials, irinotecan was

active in children with rhabdomyosarcoma and medulloblastoma. Irinotecan and temozolomide has been combined with the anti-GD2 monoclonal antibody dinutuximab and granulocyte-macrophage colony-stimulating factor (GM-CSF) in a randomized trial in relapsed and refractory neuroblastoma showing potent activity.[384]

In adults, irinotecan is administered as a 90-minute IV infusion weekly for 4 weeks at a dose of 125 mg/m^2/d. In children, irinotecan has been administered on a number of different schedules, but is most commonly administered as a 60-minute IV infusion daily for 5 days at a dose of 50 mg/m^2/d.[385] A randomized trial in children with relapsed rhabdomyosarcoma found no benefit of the daily for 5 days on 2 consecutive weeks (daily × 5 × 2) every 21 days over the daily × 5 day schedule.[386] The concomitant administration of an oral cephalosporin has permitted successful escalation of the dose of orally administered irinotecan to 90 mg/m^2/d for 5 consecutive days.[387]

Pharmacokinetics

Oral irinotecan is rapidly absorbed and more efficiently converted to SN-38 because of first-pass metabolism, but plasma drug and metabolite concentrations are highly variable.[388] The conversion of irinotecan to SN-38 appears to be dose dependent with inefficient (<10% of the dose) conversion after administration of a high, intermittent doses[389] and greater conversion to SN-38 (~50% of the dose) after protracted low-dose administration.[390] Oxidation of the dipiperidine side chain by CYP3A subfamily enzymes also yields two minor metabolites (APC, 7-ethyl-10-4-N-S-aminopentanoic acid and NPC 7-ethyl-10-4-amino-1-piperidino carbonyloxycamptothecin).[391] Induction of these CYP3A catabolic pathways by anticonvulsants can enhance the clearance of irinotecan and reduce the production of SN-38.[392] Irinotecan and its metabolites are eliminated primarily by biliary excretion.[391] Adults with elevated direct bilirubin who received irinotecan intravenously every 3 weeks had increased exposure and toxicity, particularly myelosuppression. Irinotecan dose reductions should be considered for patients with elevated direct bilirubin receiving bolus doses of irinotecan.[393] Renal excretion of the parent drug accounts for 15% to 25% of the dose.

SN-38 is conjugated to SN-38 glucuronide (SN-38G) by hepatic uridine diphosphate glucuronosyltranferase 1A1 (UGT1A1), the enzyme responsible for bilirubin conjugation. Newborns, patients who have partial UGT1A1 deficiency (Gilbert or Crigler Najjar syndromes), and patients receiving drugs that inhibit UGTA1A, such as valproic acid, are at risk for increased drug-related toxicity.[394] SN-38G is secreted into the bile and deconjugated to SN-38 by beta-glucuronidase in the gut. This intraluminal formation of SN-38 may be responsible for the delayed diarrhea from irinotecan. The product of the irinotecan AUC and the ratio of SN-38 and SN-38G AUCs (biliary index) is higher in adults with severe diarrhea after receiving irinotecan on a weekly dosing schedule.[395] However, there does not appear to be an association between the severity of diarrhea and the biliary index in patients treated on an intermittent dosing schedule.[391] When administered on protracted dosing schedules, cephalosporins (cefixime, cefpodoxime) allow for greater dose escalation of irinotecan by preventing deglucuronidation by intestinal flora of SN-38G to SN-38.[387,396]

Pharmacogenetics

Adults with the *UGT1A1*28* genotype are at increased risk for neutropenia following administration of high doses of irinotecan. An initial dose reduction was previously recommended for patients known to be homozygous for the UGT1A1*28 allele.[276] However, excess toxicity was not observed in adults with the UGT1A1*28 genotype when lower doses of irinotecan were administered. In pediatric studies, an association between genotype and toxicity has not been observed, which may be because the lower, more protracted dosing schedules used in pediatric regimens result in less significant neutropenia than in high-dose intermittent schedules.[397] Other genetic polymorphisms that may contribute to the wide interpatient variability in drug disposition and action are the ABC and solute-linked carrier (SLC) transporter genes.[398]

Toxicity

Myelosuppression and diarrhea are the most common irinotecan-associated toxicities in children and adults. Diarrhea, diaphoresis, and abdominal cramping that are associated with the drug infusion[385] are responsive to atropine, and delayed diarrhea is responsive to loperamide.[399] Other toxicities include nausea and vomiting, transient elevations of hepatic transaminases, asthenia, alopecia, malaise, and electrolyte abnormalities.[400,401] The combination of irinotecan and oxaliplatin was associated with expected severe diarrhea but unexpected elevations in pancreatic enzymes.[402]

Drug Interactions

Administration of irinotecan in patients who receive chronic treatment with strong inducers of CYP3A4 result in lower exposures to irinotecan and its active metabolites.[403] Administration of the moderate CYP3A4 inducer dexamethasone does not appear to alter irinotecan exposure; however, strong inhibitors of CYP3A4 have been shown to increase irinotecan exposures, and, therefore, medications such as ketoconazole should not be prescribed in patients receiving irinotecan.

Other Topoisomerase Inhibitors

Dactinomycin

Dactinomycin (actinomycin-D) has been in clinical use for more than 60 years. It has a role in the treatment of Wilms tumor and rhabdomyosarcoma. Dactinomycin is composed of a planar tricyclic ring chromophore (phenoxazone), to which two identical cyclic polypeptides are attached (Fig. 10.17). The drug intercalates between DNA bases, preferentially binding to the base sequence d(ATGCAT). Dactinomycin binding to DNA causes topoisomerase-mediated single- and double-strand breaks in DNA and blocks replication and transcription of the DNA template.

Dactinomycin is administered intravenously, traditionally on a daily-for-5-days schedule at a dose 15 mcg/kg/d. A single bolus dose of 45 to 60 mcg/kg is also used for Wilms tumor. This schedule is more convenient, is equally effective, and is no more toxic than the protracted regimen.[12] A daily for 3 days schedule on weeks 1, 2, 4, and 5 was more

hepatotoxic.[404]

Pharmacokinetics

After an IV bolus injection, plasma dactinomycin concentrations decrease rapidly as a result of its avid tissue binding.[405] This distributive phase is followed by a prolonged elimination phase, during which renal and biliary excretion occur, although it is estimated that only 30% of the administered dose is recovered in the urine and stool. Only a small fraction of the dose appears to be metabolized. Overall, considerable variability in drug exposure was observed.

Toxicity

The primary toxicities of dactinomycin are myelosuppression, orointestinal mucositis, and severe nausea and vomiting. Extravasation of this drug can result in severe local tissue damage and ulceration. An analysis of toxicities associated with administration of dactinomycin in patients with Wilms tumor and rhabdomyosarcoma enrolled on six Children's Oncology Group (COG) trials demonstrated that compared to older children, infants younger than 1 year of age experienced a higher rate of toxicity.[406] Of particular concern among patients with Wilms tumor is actinomycin-associated hepatic SOS. SOS usually occurs during the first 10 weeks of treatment and is characterized by fever, hepatomegaly, ascites, weight gain, jaundice, elevated serum transaminases, and thrombocytopenia. The incidence of SOS in Wilms tumor is approximately 5% and risk factors include low body mass, young age, and concomitant radiation.[404] Dactinomycin is a radiation sensitizer that can enhance the local toxicity of radiation therapy, particularly pneumonitis, if administered concurrently.[407] It can also cause a radiation-recall effect if administered up to 2 years after irradiation.

Mitoxantrone

Mitoxantrone is a synthetic anthracenedione that has a planar tricyclic nucleus with two symmetrical para-aminoalkyl side chains, but no glycosidic substituent (Fig. 10.17). Mitoxantrone induces topoisomerase II–mediated DNA strand breaks similar to the anthracyclines,[408] Mitoxantrone is currently used in some regimens for the acute leukemias and lymphomas. It is usually administered on a daily for 3 to 5 days, weekly, or an every 3-week schedule.

The plasma concentration–time profile of mitoxantrone resembles that of the anthracyclines, with an initial rapid decline ($t_{1/2}$ 10 minutes) and a prolonged terminal elimination phase ($t_{1/2}$ >24 hours).[408] Mitoxantrone is metabolized by oxidation of the terminal hydroxyl groups on the side chains to the inactive mono- and dicarboxylic acids.[409] Biliary excretion appears to be a major route of elimination for mitoxantrone with renal excretion of parent drug accounting for <10% of the administered dose. Mitoxantrone is avidly tissue bound. It has a volume of distribution of 500 to greater than 3,000 L/m^2 and can be detected in tissues for weeks after a dose.[410] Mitoxantrone clearance is variable.[408]

The acute toxicities of mitoxantrone include myelosuppression, mucositis, mild nausea and vomiting, diarrhea, and alopecia. Patients may also notice a bluish discoloration of the sclera,

fingernails, and urine. Tissue damage from extravasation of mitoxantrone is uncommon. Mitoxantrone has a diminished capacity to undergo redox reactions compared to the anthracyclines and, therefore, was previously considered less cardiotoxic compared to anthracyclines.[411] However, long-term mitoxantrone cardiotoxicity, evaluated in an international collaborative study in survivors of childhood cancer, indicates that mitoxantrone is associated with significant risk of cardiotoxicity. Prior cardiotoxic equivalence ratios relative to doxorubicin underestimated the cardiotoxicity of mitoxantrone.[412]

TUBULIN INHIBITORS

Tubulin inhibitors have a broad range of antitumor activity in pediatric malignancies, including a clinical role in the frontline treatment of ALL as well as many solid and CNS tumors. Microtubules, which are an integral component of the cytoskeleton, play important roles in a variety of cellular functions including mitosis, cellular transport, maintenance of cell shape, polarity, and cell signaling. Traditional tubulin inhibitors include the vinca alkaloids, which are microtubule-destabilizing agents, and the taxanes. New tubulin inhibitors, such as eribulin, that both bind directly to the microtubules and induce tubulin aggregates,[413] have been evaluated clinically and have begun evaluation in the pediatric population.[414,415]

Vinca Alkaloids

Vincristine/Vinblastine/Vinorelbine

The vinca alkaloids, vincristine, vinblastine, and vinorelbine, are structurally similar alkaloids composed of two multiring subunits, vindoline and catharanthine (Fig. 10.18). Despite their structural similarity, these agents, which act as mitotic inhibitors, have differing clinical and toxicologic properties. The vinca alkaloids exert their cytotoxic effect by binding to tubulin, a dimeric protein that polymerizes to form microtubules. The resulting disruption of the intracellular microtubular system interferes with a number of vital cell functions, including mitosis, maintenance of the cytostructure, membrane trafficking, and transmission of receptor signals, and transport of p53 to the nucleus.[416] The cytotoxic effect is related to inhibit mitotic spindle formation, causing metaphase arrest during mitosis. The vinca alkaloids are subject to multidrug resistance, and alterations in the alpha- and beta-tubulin subunits also confer resistance.

Vincristine has a wide spectrum of clinical activity and is currently used in the treatment of ALL, Hodgkin lymphoma, and NHL, rhabdomyosarcoma, soft-tissue sarcomas, Ewing sarcoma, Wilms tumor, brain tumors, and neuroblastoma. Vinblastine has been used in the treatment of histiocytosis, testicular cancer, and Hodgkin disease. Vinorelbine has been used in combination with gemcitabine in the treatment of relapsed/refractory Hodgkin disease[289] and in the treatment of sarcomas, in particular rhabdomyosarcoma.[417]

Pharmacokinetics

Vincristine and vinblastine are poorly absorbed if administered orally and are therefore administered intravenously as a bolus injection. Oral vinorelbine is bioavailable (29% ± 22%), but the resulting plasma concentrations are variable, with the apparent oral clearance and volume of distribution substantially higher in children than in adults receiving similar doses.[418] The standard dose for vincristine is 1 to 2 mg/m^2, administered every 1 to 3 weeks. For infants younger than or equal to 1 year of age, vincristine dose is scaled to body weight (0.03 to 0.05 mg/kg) or doses determined by infant dosing.[419] Many regimens limit the total single dose of vincristine to 2 mg on the basis of reports of increased neurotoxicity at doses above 2 mg, especially on the weekly schedule. However, this practice of capping the dose may underdose some patients, because there is substantial interpatient variation in the plasma pharmacokinetics of vincristine, with a greater than 10-fold variation in the AUC.[420] Escalation of the dose beyond the 2 mg maximum may be well tolerated by some patients. Vinblastine doses range from 3.5 to 6.0 mg/m^2, administered in 1- to 3-week cycles. Vinorelbine is most commonly administered as a 10-minute infusion at a dose of 30 mg/m^2 weekly for up to 6 weeks.

After bolus administration, the vinca alkaloids manifest a rapid initial decline in plasma concentration (initial half-life of 5 to 10 minutes), followed by a prolonged terminal elimination phase with half-life of approximately 12 to 40 hours. The long terminal half-life and the large steady-state volume of distribution (Table 10.5) are consistent with avid and extensive tissue binding that is characteristic of these drugs. Vincristine and vinorelbine clearance is more rapid in children than in adults, and adults have a more than twofold longer terminal half-life. Vincristine disposition in children is highly variable, resulting in a wide interpatient range in drug exposure at a standard dose of 1.5 mg/m^2.[418] Vincristine enters the CSF after IV administration, although the CSF concentrations are only 3% to 5% of the corresponding plasma concentrations.[421]

Dosage modifications of the vinca alkaloids are generally recommended in infants and in patients with delayed biliary excretion as evidenced by an elevated direct bilirubin. Infants appear to manifest increased toxicity with standard doses of vincristine depending on body surface area. Infants and younger children have a relatively larger ratio of body surface area to weight, and in a randomized crossover study in infants comparing dosing of vincristine depending on body surface area (1.5 mg/m^2) to dosing by body weight (0.05 mg/kg), the dose calculated from body surface area resulted in greater systemic drug exposure (AUC).

Pharmacogenetics

CYP3A4 and CYP3A5 are involved in the metabolism of the vinca alkaloids.[422,423] The CYP3A5*1 allele, which is required for the production of functional enzyme, is believed to mediate 80% of the CPY3A metabolism of vincristine for individuals with high CYP3A5 expression. This may in part explain the large interpatient variability in vincristine pharmacokinetics as well as in the finding that vincristine neurotoxicity is less common in African Americans than in Caucasians. Approximately 70% of African Americans express the CYP3A5*1 allele; in contrast, the most common allelic variants in Caucasians are CYP3A5*3, CYP3A5*6, and CYP3A5*7.[424] CYP3A5*6 and CYP3A5*7 allelic variants result in little to no active CYP3A5 enzyme and the CYP3A5*3 allele possesses an SNP that

results in a premature termination codon.[425] The functional effect is that genotypes other than the CYP3A5*1 allele are effectively void of active enzyme.

Biotransformation

Hepatic metabolism and biliary excretion are the principal routes for elimination of the vinca alkaloids. From 70% to 75% of the radioactivity from a radiolabeled dose of vincristine appears in the feces by 72 hours, and slightly more than 10% of the radioactivity is excreted in the urine. Half of the radiolabeled material in urine and feces represents metabolites.

Toxicity

Neurotoxicity is the dose-limiting toxicity of vincristine. It is related to the cumulative dose and occurs more commonly on a weekly schedule. Manifestations of the peripheral sensory and motor neuropathy include loss of deep tendon reflexes, neuropathic pain (muscular cramping, jaw pain), paresthesias, and wrist and foot drop. Cranial motor nerves may be affected, and autonomic nerve involvement may be responsible for constipation, paralytic ileus, and urinary retention. In most cases, these symptoms are reversible on withdrawal of the drug. Vincristine neurotoxicity can be markedly accentuated in children with Charcot–Marie–Tooth disease.[426] Accidental intrathecal administration of vincristine has been reported and is usually fatal. Other toxicities associated with vincristine include alopecia, inappropriate antidiuretic hormone syndrome, seizures, and orthostatic hypotension. Nausea and vomiting and myelosuppression are rarely encountered. Vincristine can increase the platelet count.

Myelosuppression is the dose-limiting toxic effect of vinblastine and vinorelbine. Vinblastine also frequently causes mucositis. Neurotoxicity with vinblastine is minimal and is less prominent with vinorelbine than with vincristine.[427] Vinorelbine causes constipation in 30% of patients. Vinca alkaloids are vesicants; extreme care must be taken to avoid extravasation during their administration. Ulcerations from vinca alkaloid extravasation were prevented in animal models with the local injection of hyaluronidase and the application of local warming.[55] Hydrocortisone injection and local cooling increased ulcerations in these studies.

Drug Interactions

Drugs that induce CYP3A4, such as anticonvulsants, corticosteroids, and drugs that inhibit CYP3A4, such as azoles antifungal agents, can alter the disposition of the vinca alkaloids.[428]

Taxanes

Paclitaxel/Docetaxel

The taxanes, paclitaxel and docetaxel, are complex diterpenes (Fig. 10.18) that exert their cytotoxic effect by interfering with microtubule function. Taxanes increase microtubule stability by preventing depolymerization, which results in tubulin bundling. Taxane-induced

cytoskeletal changes lead to cell-cycle arrest in the G_2 (premitotic) and M (mitotic) phases and cell death by apoptosis. Because paclitaxel arrests cells in the G_2/M phase, the most radiosensitive phase of the cell cycle, it is also a potent radiosensitizer.[429,430]

Paclitaxel is insoluble in water and is formulated in Cremophor EL and ethanol, which has been implicated in the hypersensitivity reactions. Because this formulation leaches plasticizers (phthalate) from polyvinylchloride IV infusion bags, paclitaxel must be mixed and stored in glass, polypropylene, or polyolefin containers and administered through polyethylene-lined infusion sets. Docetaxel is formulated in polysorbate 80 and ethanol. A novel nanoparticle albumin-bound paclitaxel (nab-paclitaxel) formulation has been developed and is approved for several adult cancers, but it has had very limited activity in pediatric trials.[431] Docetaxel may have limited activity in bone tumors, including Ewing sarcoma, primarily in combination with gemcitabine.[290,432,433]

Paclitaxel has been administered as a 1-, 3-, 24-, or 96-hour IV infusion. The standard adult dose of paclitaxel is 135 or 175 mg/m^2 infused over 3 hours, although doses of up to 250 mg/m^2 are tolerable. Longer infusions appear to be more myelosuppressive. The recommended dose of paclitaxel administered as a 24-hour infusion every 3 weeks in children is 350 mg/m^2.[434] The recommended dose of paclitaxel administered as a 3-hour infusion twice weekly × 6 doses, every 28 days, is 50 mg/m^2/dose.[435] Docetaxel is administered as a 1-hour infusion every 3 weeks at a dose of 100 to 125 mg/m^2, but higher doses may be tolerable with filgrastim support.

Pharmacokinetics

Paclitaxel pharmacokinetics is dose dependent and probably schedule dependent, and complex pharmacokinetic models incorporating capacity-limited elimination and capacity-limited distribution have been devised to describe the disposition of the drug.[436] Paclitaxel is extensively tissue bound, accounting for its large volume of distribution. Hepatic metabolism (hydroxylation) by CYP2C8 at the C6 position on the ring and by CYP3A4 on the C13 side chain (Fig. 10.19) followed by biliary excretion is the primary route of paclitaxel elimination (80% of the dose is recovered as parent drug or metabolites in feces).[437,438]

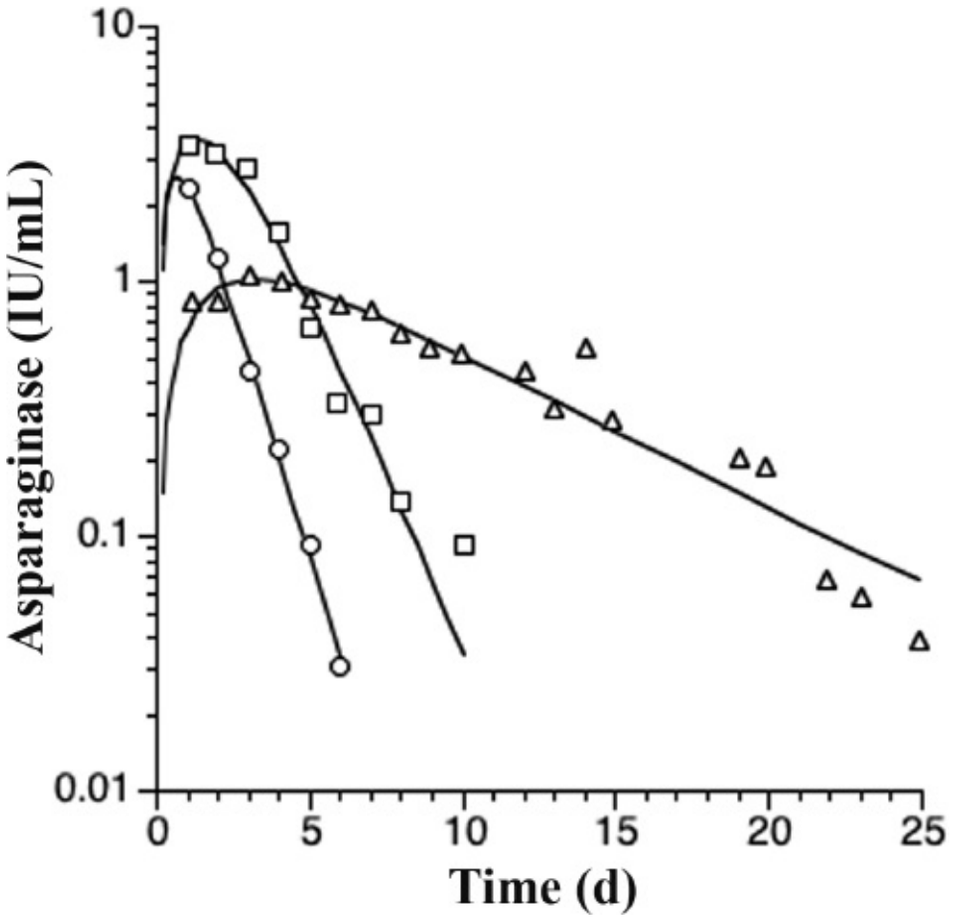


Figure 10.19 Disposition of serum asparaginase activity in 10 patients treated intramuscularly with 25,000 IU/m^2 of native *Escherichia coli* asparaginase (*squares*), 10 patients treated intramuscularly with 25,000 IU/m^2 of native *Erwinia* asparaginase (*circles*), and 10 patients treated intramuscularly with 2,500 IU/m^2 of PEG-asparaginase (*triangles*). Points represent the mean. (Adapted from Asselin BL, Whitin JC, Coppola DJ, et al. Comparative pharmacokinetic studies of three asparaginase preparations. *J Clin Oncol* 1993;11:1780.)

Docetaxel also undergoes hepatic metabolism primarily mediated by CY3A4.[439] At high concentrations, CYP2C8 may play a role in docetaxel elimination. Patients with hepatic tumor involvement or biochemical evidence of liver dysfunction (elevated bilirubin or transaminases) are at increased risk for paclitaxel toxicity, presumably because of delayed paclitaxel clearance; dose reductions are recommended for these patients.[440] Renal excretion accounts for only 5% of total drug clearance.[441]

Pharmacogenetics

Several retrospective studies have evaluated the impact of genetic variants in enzymes involved in taxane metabolism and transport to assess whether there were correlates between the variants and toxicity and/or survival. No statistically significant correlates have been identified to date.[442,443] Germ line polymorphisms in the proximal promoter of beta-tubulin IIA that protect against paclitaxel-induced peripheral neuropathy have recently been identified.[444]

Toxicity

Myelosuppression is the primary dose-limiting toxicity of paclitaxel.[445] Neurotoxicity is also prominent in children and is characterized by a stocking-glove peripheral neuropathy (paresthesias, diffuse myalgias, and loss of fine motor control) and seizures.[434] Acute encephalopathy and irreversible coma are also associated with paclitaxel. Ethanol in the formulation can cause toxicity if high doses of paclitaxel are infused over a short period of time.[446] The incidence of acute hypersensitivity reactions (hypotension, urticaria, and bronchospasm) occurring within minutes of the start of the infusion has been reduced by administering paclitaxel as a more prolonged infusion and by premedicating patients with corticosteroids and antihistamines (H_1 and H_2 blockers). Cardiac arrhythmias (bradycardia, atrioventricular conduction disturbances), alopecia, mucositis, radiation-recall dermatitis, pneumonitis, and phlebitis at the injection site are also caused by paclitaxel.[430]

Docetaxel produces neutropenia without significant thrombocytopenia. Other toxicities include malaise, myalgias, skin rashes (including palmar-plantar erthrodysesthesia), nausea and vomiting, mucositis, diarrhea, alopecia, interstitial pneumonitis, and transient elevations of serum transaminases.[447,448] Neurotoxicity is less prominent with docetaxel, but fluid retention associated with weight gain, edema, and, in some cases, scleroderma-like skin changes, is a cumulative toxicity that occurs in 20% of patients. Hypersensitivity reactions, rashes, and fluid retention may be ameliorated by premedication with an antihistamine and corticosteroid.

MISCELLANEOUS AGENTS

Arsenic Trioxide

Arsenic is one of the oldest drugs in both Western as well as in traditional Chinese medicine. In the late 18th century, Fowler solution (potassium bicarbonate–based solution of arsenic) was used to treat a number of diseases including chronic myelogenous leukemia. In the 1970s in the Northeastern region of China, a crude solution of arsenic trioxide (ATO; As_2O_3) was introduced into the treatment of acute promyelocytic leukemia (APL),[449] and in the 1990s, results from prospective clinical trials of pure arsenic trioxide emerged.

Numerous investigators have found that ATO induces complete, durable remissions in 70% to 90% of adults with newly diagnosed or relapsed APL.[450,451] The FDA-approved dose for ATO in both adults and children with APL for remission induction is 0.15 mg/kg daily, administered intravenously, for up to 60 doses. Subsequent efforts to improve outcome for patients with APL have focused on reducing anthracyclines. The combination of ATO with *all-trans* retinoic acid (ATRA) in adult patients with standard-risk APL yielded an event-free survival of 97.3% and an overall survival of 99.2%. In children with newly diagnosed APL, two cycles of IV ATO administered in combination with oral ATRA in the first consolidation phase resulted in significant reduction in anthracycline and comparable event-free and overall survival to anthracycline-based treatment regimens.[452] Oral arsenic is being evaluated in clinical trials.

Toxicity

In adult patients, adverse events frequently associated with ATO administration include elevated hepatic transaminases, abdominal pain, musculoskeletal pain, peripheral neuropathy, hypokalemia, hyperglycemia, and dermatitis. Nearly 40% of adult patients experience cardiac conduction abnormalities, most commonly QT_c interval prolongation.[453] The APL differentiation syndrome, clinically similar to retinoic acid syndrome with fever, dyspnea, pleural effusion, pulmonary infiltrates, and weight gain, occurs in up to 30% of adult patients.[454] In long-term follow-up of adults treated with IV ATO, there were no sudden deaths attributable to cardiac dysfunction, no clinical evidence of cardiac dysfunction, no second malignancies, and no hepatotoxicity. No formal assessment of fertility was completed. Others have reported mild hepatic dysfunction but no major chronic adverse events.[455]

The toxicity profile of ATO in children appears similar to that observed in adults. In a pediatric phase 1 trial, frequent non–dose-limiting toxicities observed included elevated serum hepatic transaminases, nausea/vomiting, abdominal pain, constipation, hypomagnesemia, hypocalcemia, hyperglycemia, dermatitis, infection, and headache.[456] Eight percent of cycles were associated with prolonged QTc interval and 3% with APL differentiation syndrome.

Pharmacokinetics

The major metabolic pathway of ATO is biomethylation and involves the reduction of pentavalent arsenic (As^V) to trivalent arsenic (As^{III}) by arsenate reductase, and methylation of trivalent arsenic to monomethylarsonic acid and dimethylarsinic acid by methyltransferases. Results of human pharmacokinetic studies are difficult to interpret owing to the differing analytic methodologies employed. The concentration of trivalent inorganic arsenic (As^{III}) may be the most effective and toxic species.[457] In one adult study following administration of 0.15 mg/kg As_2O_3, total peak plasma arsenic concentrations averaged 6.9 µM and the mean terminal half-life averaged 12 hours. A more recent study found that although the maximum concentration of As^{III} and As^V were similar (0.17 ± 0.11 and 0.13 ± 0.05 µM, respectively), the AUC of As^V was approximately twice that of As^{III}.[458] With repeated administration, approximately 60% of the dose was excreted in the urine as inorganic arsenic and methylated species. In children, following an IV dose of 0.15 mg/kg, the median (range) peak total arsenic concentration was 0.26 (0.11 to 0.37) µM, with a terminal half-life exceeding 24 hours.[456]

Asparaginases

Asparaginase is a bacterial enzyme that rapidly depletes the circulating pool of asparagine by catalyzing the conversion of this amino acid to aspartic acid and ammonia. In most tissues, asparagine is synthesized from aspartic acid and glutamine by the enzyme asparagine synthase, and normal tissues respond to asparagine depletion by upregulation of asparagine synthase. In contrast, sensitive lymphoid cancers do not upregulate asparagine synthase and, therefore, depend on exogenous circulating asparagine for protein synthesis. Asparaginase-resistant lymphoid tumor cells often have high levels of asparagine synthase, rendering them

capable of synthesizing their own asparagine. Thus, asparaginase has a selective antileukemic effect.[459]

The native (unmodified) forms of asparaginase are derived from *Escherichia coli* or *Erwinia chrysanthemi (Dickeya dadantii)* and are administered intravenously or intramuscularly at doses of 6,000 to 25,000 IU/m^2 on an intermittent schedule (usually 3 times each week). In the United States, production of native *E. coli* asparaginase ceased in 2012, and PEG-asparaginase, produced by the conjugation of poly(ethylene glycol) to *E. coli* asparaginase, has replaced native *E coli.* asparaginase. Owing to the poly(ethylene) glycol, PEG-asparaginase has lower immunogenicity and a longer half-life, allowing for less frequent administration (2,500 IU/m^2 every 2 to 4 weeks).[460] Erwinaze (asparaginase *E. chrysanthemi*) is indicated for the treatment of ALL in patients who have developed hypersensitivity or development of antiasparaginase neutralizing antibodies in the absence of clinical symptoms of allergic reaction (silent inactivation) of *E. coli*–derived asparaginase.[461] Pegcrisantapase, PEGylated recombinant *Erwinia crysanthemi* asparaginase, has been evaluated in children with ALL; however, it was associated with hypersensitivity and anti-PEG IgG antibodies, indicating PEG-mediated immune response in a small population of patients with a prior history of hypersensitivity to asparaginase.[462] IV administration of PEG-asparaginase has a toxicity profile, frequency of hypersensitivity reactions, and efficacy similar to that of native *E. coli* L-asparaginase administered intramuscularly.[463] In a large retrospective analysis, the frequency of serious hypersensitivity reactions was lower after administration PEG-asparaginase intravenously compared to intramuscular administration, 3.2% versus 5.4% ($p < 0.0001$).[464]

Depletion of asparagine is associated with improved outcome for children with ALL.[465] The continual production and release of asparagine by normal tissues into the blood stream requires plasma asparaginase activity exceeding 0.1 IU/mL to suppress the concentration of asparagine below the critical level of 1 to 3 μM.[466] Serum asparagine concentration is challenging to accurately measure because of ongoing hydrolysis of asparagine after the blood sample has been obtained. In a randomized trial in standard-risk ALL, asparaginase plasma concentrations were more prolonged with a single dose of PEG-asparaginase than with 9 to 12 doses of native *E. coli* asparaginase.[467] Serum asparagine concentration is inversely related to asparaginase activity; therefore, measurement of asparaginase activity is a surrogate for asparagine depletion.[468] Measurement of asparagine activity by commercially available assays can be used to detect silent inactivation. Target thresholds for asparaginase activity are influenced by formulation of asparaginase (native vs. PEGylated), route of administration (IV vs. intramuscular), and time point for sample collection.[469]

Pharmacokinetics

Parenteral administration of asparaginase is required because of denaturation and peptidase digestion within the intestinal tract. Peak concentrations with intramuscular injection are approximately half those achieved with IV dosing. The time to peak concentration (rate of absorption) after intramuscular injection is 24 to 48 hours for *E. coli* asparaginase, less than 24 hours for *Erwinia* asparaginase, and 72 to 96 hours for PEG-asparaginase. The half-lives

for *E. coli* asparaginase, *Erwinia* asparaginase, and PEG-asparaginase are 24 to 36 hours, 10 to 15 hours, and 5 to 7 days, respectively (Fig. 10.20).[470]

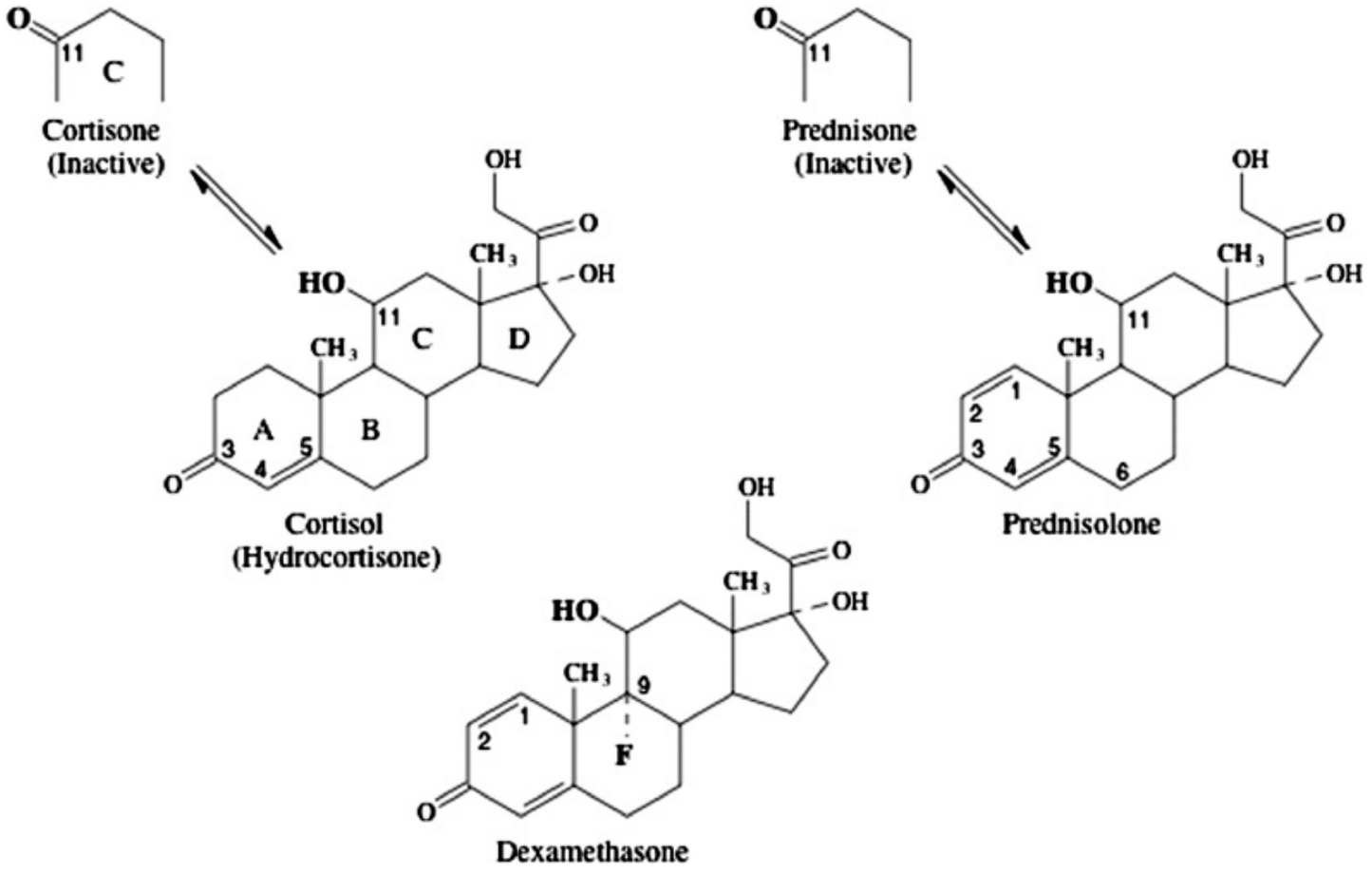


Figure 10.20 Chemical structures of the naturally occurring and synthetic corticosteroids commonly used in treating childhood cancers. Reduction of the keto group (cortisone, prednisone) to a hydroxyl group (cortisol, prednisolone) at the 11 position is necessary for activity. Addition of the 1,2-double bond (prednisolone, dexamethasone) and the fluorine group at the 9-position (dexamethasone) increases glucocorticoid activity.

Plasma concentrations of asparagine fall to undetectable levels within 24 hours of a dose of asparaginase. The duration of depletion of circulating asparagine is related to the rate of asparaginase elimination; consequently, it is shorter with *Erwinia* asparaginase than with native *E. coli* asparaginase.[471] PEG-asparaginase depletes serum asparagine for at least 14 days.[472] Even though asparaginase distributes primarily within the intravascular space, its effects are more wide reaching. For example, asparaginase cannot be detected in the CSF after systemic administration, but CSF levels of asparagine are depleted for long periods.[473]

Patients who develop antibodies to asparaginase have a rapid fall in the plasma concentrations of the native enzyme, indicating that the antibody interferes with the therapeutic effects of asparaginase.[474] PEG-asparaginase elimination is more rapid in one-third of patients who have previously experienced hypersensitivity reactions to native *E. coli* asparaginase.[470,475] Many patients who have high antibody titers do not have a history of clinical hypersensitivity reaction. Consequently, weekly dosing of PEG-asparaginase is recommended in children previously treated with native asparaginase. Development of antibody to poly(ethylene glycol) may develop and is associated with increased clearance of

PEG-asparaginase and PEG-crisantapase.[476]

Toxicity

The principal side effects of asparaginase are related to sensitization to a bacterial protein or decreased protein synthesis. Hypersensitivity reactions and the development of neutralizing antibodies impact asparaginase activity. Allergic reactions range from local erythema and swelling at the injection site to urticaria, laryngeal edema, bronchospasm, or anaphylaxis. Diphenhydramine, epinephrine, and other resuscitative measures must be available when administering this agent, even for the initial dose. The overall incidence of hypersensitivity reactions in children is 10% to 30% with native *E. coli* asparaginase. In patients treated with PEG-asparaginase, the incidence of hypersensitivity reactions is 3% to 24% and hypersensitivity reactions are more common in patients previously exposed to native *E. coli* asparaginase. The incidence of hypersensitivity reactions is lower (10%) in patients receiving combination chemotherapy than in those receiving *E. coli* asparaginase as a single agent (40%), presumably because of the immunosuppressive effects of the other drugs in the regimen. *E. coli* and *Erwinia* asparaginase are minimally cross-reactive, so those patients experiencing hypersensitivity reactions to one can be safely switched to maintain efficacy.[477] The incidence of hypersensitivity in patients receiving *Erwinia* asparaginase is 3% to 37%. PEG-asparaginase has also been administered safely to patients who were hypersensitive to the native *E. coli* enzyme or Erwinia asparaginase.[478] The FDA-approved dose of Erwinia asparaginase to substitute for each planned dose of PEG-asparaginase is 25,000 IU/m^2 administered intramuscularly or intravenously 3 times a week for six doses. To avoid prolonged interruption of asparagine depletion, patients with hypersensitivity should begin treatment with alternative asparaginase as soon as possible (48 to 72 hours) after the hypersensitivity event if symptoms of reaction have resolved. Development of hypersensitivity to both *E. coli* and *E. chrysanthemi* formulation should have asparaginase therapy discontinued.[479]

Coagulopathies resulting from deficiencies or imbalances in coagulation factors (fibrinogen, II, V, VII, VIII-X, antithrombin III, and protein C) can lead to clotting and hemorrhagic complications, including stroke. The thromboembolic events reflect a decreased capacity to inhibit thrombin resulting from the acquired antithrombin III deficiency. The incidence of symptomatic thrombosis is 3% to 7% and is more prevalent during induction and may be a multifactorial attribution including central venous catheters, corticosteroids, and asparaginase. Decreased serum albumin, insulin, and lipoproteins or increased ammonia levels are also associated with asparaginase therapy. Other toxicities include an encephalopathy characterized by somnolence, disorientation, seizures, and coma, which have been related to hyperammonemia in some patients. Acute pancreatitis, which can progress to hemorrhagic pancreatitis, has been reported in 2% to 18% of patients receiving asparaginase therapy, and severe or life-threatening pancreatitis occurs in 5% to 10%. Patients with mild pancreatitis can be rechallenged if the patient has mild lipase and amylase elevations and no clinical symptoms. However, recurrence rates for pancreatitis exceed 50% in some populations. Formulation does not appear to be related to the incidence of pancreatitis.

Hepatotoxicity characterized by hyperbilirubinemia and elevated serum transaminases including alkaline phosphatase occur in 5% to 8% of patients and rarely can be life-threatening. Myelosuppression and gastrointestinal toxicity (with the exception of nausea and vomiting) are usually associated with multimodality leukemia therapy.

Drug Interactions

Asparaginase can rescue patients from the toxic effects of MTX and cytarabine. Antagonism has been observed if asparaginase is administered before these antimetabolites.[480]

Bleomycin

Bleomycin is a unique antibiotic that is a mixture of 11 low-molecular-weight (1,500 Daltons), water-soluble, glycopeptides. The major species is bleomycin A_2 (Fig. 10.17), which accounts for 65% of the commercial preparation. Bleomycin chelates divalent redox-active transition metal ions, such as iron, cobalt, zinc, nickel or copper, but it is only active in the ferrous form. The bleomycin–iron complex binds tightly to DNA, with partial intercalation between guanosine-cytosine base pairs. After binding to DNA, the bleomycin–iron complex produces single- and double-strand DNA breaks by a Fe^{2+}-O_2–catalyzed free radical reaction. The bleomycin•Fe coordination complex oxygenates the C4′ hydrogen of deoxyribose, and cuts DNA in the minor groove, predominately at the CpT and GpC sequences in actively transcribed chromatin domains.[481]

Bleomycin can be administered intravenously, intramuscularly, or subcutaneously at doses of 10 to 20 U/m^2. A unit is a measure of the drug's cytotoxic activity in bacteria and is equivalent to about 1.2 to 1.7 mg of peptide. The drug is active against Hodgkin lymphoma, lymphomas, testicular cancer, and other germ cell tumors. Bleomycin has been administered regionally into the pleural space for malignant pleural effusions and intravesicularly for bladder tumors.

Pharmacokinetics

Bleomycin is not administered orally because it would probably be enzymatically degraded in the intestinal tract. Absorption after intramuscular and subcutaneous injection is almost complete, and plasma concentrations with a continuous subcutaneous infusion closely simulate those after an IV infusion. With IV bolus dosing in children, the drug has a biphasic plasma disappearance curve with a terminal half-life of about 3 hours. Total clearance is 41 mL/min/m^2, and renal clearance accounts for 65% of total drug clearance.[482] Patients with renal failure have prolonged terminal drug half-lives, higher plasma concentrations, and delayed clearance.[483] Concurrent use of other nephrotoxic drugs may impair bleomycin elimination and augment toxicity. A 45% to 65% dosage reduction has been recommended for patients with a creatinine clearance of less than 30 mL/min/m^2. In patients undergoing hemodialysis, bleomycin was not detected in the dialysate.

The primary determinants of bleomycin cytotoxicity are cellular uptake, DNA repair activity, concurrent medications that alter DNA conformation (e.g., intercalating agents), and

the level of activity of bleomycin hydrolase. The latter is a cysteine proteinase that is found in normal tissues and tumor cells. This proteinase hydrolyzes a terminal carboxamide group within the bleomycin molecule to form an inactive metabolite.[481] Lung and skin, the tissues with the greatest susceptibility to bleomycin damage, have the lowest levels of this enzyme. In contrast, liver, spleen, intestine, and bone marrow, sites that are less susceptible to bleomycin toxicity have high levels of this enzyme. Bleomycin-resistant cells lines have an increased capacity to hydrolyze bleomycin and an enhanced capacity to repair DNA damage.

Pharmacogenetics

In men with nonseminomatous testicular cancer treated with bleomycin a polymorphism, homozygous variant G/G of SNP A1450G of bleomycin hydrolase (*BLMH*) is associated with an increased risk for disease progression.[484]

Toxicity

Unlike most other anticancer drugs, bleomycin is not myelosuppressive. The dose-limiting toxicity is an interstitial pneumonitis that can lead to pulmonary fibrosis. Below a total cumulative dose of 450 U, pulmonary toxicity is sporadic with an incidence of 3% to 5%. At cumulative doses above 450 U, the incidence increases with dose. Patients with pulmonary toxicity present with a persistent dry cough and exertional dyspnea that can progress to tachypnea, hypoxia, and death. The chest x-ray typically shows reticulonodular infiltrates at the lung bases. A decline in the single breath diffusing capacity for carbon monoxide is the most sensitive measure of subclinical damage, but it may not delineate those patients who are at highest risk to develop clinically symptomatic toxicity. Pulmonary irradiation and the use of supplemental oxygen may enhance the risk of pulmonary toxicity in patients receiving bleomycin,[485] but others have found that serum creatinine and age older than 30 years may be predictors of pulmonary toxicity. Concurrent use of filgrastim does not appear to enhance bleomycin pulmonary toxicity.[486] Bleomycin-associated pathologic changes in the lung include edema and cellular infiltration in the perivascular interstitial space, followed by damage to alveolar lining cells and formation of hyaline membranes and fibrosis. These changes may progress even after the drug is stopped. Pulmonary function monitoring has been performed in the past; however, computed tomography of the lungs performed in patients receiving bleomycin has been proposed in adults with germ cell tumors.[487] Bleomycin should be discontinued at the first sign of lung damage.

Dermatologic toxicity from bleomycin is common. Linear hyperpigmentation of the skin is the most common finding, but other mucocutaneous reactions include erythema, induration, desquamation, and sclerosis of the skin; alopecia; nail hyperpigmentation and deformities; and mucositis.[488] Other side effects include nausea and vomiting, fever, hypersensitivity reactions, and Raynaud phenomenon.

Corticosteroids

Prednisone/Prednisolone/Dexamethasone

Although generally not considered anticancer drugs because of the diversity of their other clinical uses, the corticosteroids (prednisone, prednisolone, dexamethasone) play a significant role in the treatment of ALL, lymphoma, and Hodgkin lymphoma and have been incorporated into treatment regimens for the histiocytoses and brain tumors. In addition, they are useful in managing some of the complications of cancer, including hypercalcemia, increased intracranial pressure, anorexia, and chemotherapy-induced nausea and vomiting.

Glucocorticoids induce apoptosis by binding to intracellular glucocorticoid receptors. The receptor–glucocorticoid complex translocates to the nucleus, dimerizes, and binds to specific DNA response elements, modulating expression of many genes. Continuous saturation of the receptor by the steroid for many hours to days is needed to induce apoptosis in sensitive cell lines; and in children with ALL, thrice-daily administration is more effective than are intermittent schedules.[489] Glucocorticoid receptor content on leukemic blasts and the duration of receptor occupancy appear to be the critical determinants of response to corticosteroid therapy in vitro and in vivo. A loss of or defect in the glucocorticoid receptor can lead to drug resistance in vitro. Children with ALL and low levels of glucocorticoid receptor on their lymphoblasts have a poor prognosis when treated on corticosteroid-based regimens. Other mechanisms of glucocorticoid resistance may include modulation of apoptosis-associated proteins, BCL-2 (B-cell lymphoma 2), BCL-2–associated X protein (BAX), and BCL-2–interacting mediator of cell death (BIM).[490]

The chemical structures of the most commonly used synthetic analogs of cortisol, prednisone, prednisolone, and dexamethasone are shown in Figure 10.19. The addition of the 1,2-double bond in prednisolone and dexamethasone increases the glucocorticoid and anti-inflammatory potency fourfold and decreases mineralocorticoid activity; addition of the fluorine at position 9 in dexamethasone enhances the activity another fivefold. Prednisone is an inactive prodrug analogous to cortisone and requires chemical reduction of the ketone group at position 11 to a hydroxyl group, yielding prednisolone. This activation occurs in the liver. Prednisolone and dexamethasone are eliminated by the catabolic enzymes that inactivate cortisol.[491]

Pharmacokinetics

The absorption of orally administered prednisone, prednisolone, and dexamethasone is almost complete (>80%). Prednisone is rapidly converted to prednisolone, which is the predominant form in plasma after an oral dose of prednisone. In children, variable absorption of prednisone and prednisolone has been reported.[492] The elimination half-lives are 2.5 hours for prednisolone and 4 hours for dexamethasone, reflecting differences in the rate of catabolism. Hepatic metabolism is the primary route of elimination; renal clearance accounts for 10% or less of total clearance. The clearance of prednisolone, due to concentration-dependent plasma protein binding, is dose dependent and increases with increasing dose.[491] At low concentrations, prednisolone, just like cortisol, is more than 95% bound to transcortin, but this specific carrier protein is saturated at higher prednisolone concentrations, so that the relative amount of free drug available for metabolic degradation increases.

Dexamethasone is not bound to transcortin, and the degree of protein binding is concentration independent. Up to a 10-fold range in systemic exposures have been observed

following a dexamethasone dose of 8 mg/m^2/d, with apparent clearances being greater in younger children.[493] The lower rate of meningeal relapse in children treated with dexamethasone compared with prednisone may in part be explained by this difference in protein binding.[494] The concentration of prednisolone and dexamethasone in the CSF is equivalent to the free-drug concentration in plasma, and because prednisolone, unlike dexamethasone, is tightly and extensively bound to transcortin at low concentrations, its free plasma and CSF concentrations are lower at equipotent doses.

The capacity to activate prednisone to prednisolone is not impaired in patients with severe hepatic dysfunction, and prednisolone concentrations are elevated in this group, because of delayed catabolism. Unbound prednisolone concentration is also elevated in patients with severe renal dysfunction.[491]

Toxicity

The corticosteroids have some effect on almost every organ and tissue in the body, and the side effects of these agents are protean. Significant common toxicities include increased appetite, centripedal obesity, immunosuppression, myopathy, osteoporosis, avascular necrosis of bone, peptic ulceration, pancreatitis, psychiatric disorders, cataracts, hypertension, precipitation of diabetes, growth failure, amenorrhea, impaired would healing, and atrophy of subcutaneous tissue. Although the use of dexamethasone may be associated with fewer thrombotic events than when prednisone is used in intensive leukemia induction regimens,[495] its use may increase the rate of serious infections.[496] Osteonecrosis of weight-bearing joints is a serious complication that occurs in children with leukemia treated with corticosteroids. Risk factors include age older than 10 years, female gender, treatment with two rather than one 21-day course of dexamethasone, elevated body mass index (BMI), and simultaneous administration of dexamethasone and L-asparaginase. A polymorphism in plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis, has recently been associated with an increased risk of developing osteonecrosis[497] and in a genome-wide association study in children with ALL, inherited variations near the glutamate receptor genes were associated with osteonecrosis.[498]

Drug Interactions

Ketoconazole interferes with the elimination of non–protein-bound prednisolone by inhibiting the catabolic enzyme, 6-beta-hydroxylase, leading to a 50% increase in the AUC of unbound prednisolone. Estrogen-containing oral contraceptives increase transcortin and lower free prednisolone concentrations. Drugs such as phenytoin, rifampicin, carbamazepine, and barbiturates induce hepatic microsomal enzymes that catabolize prednisolone and result in enhanced prednisolone clearance.[491] Asparaginase also inhibits dexamethasone clearance, likely through impairing hepatic synthesis of proteins required for drug clearance.[493]

Retinoids

13-*cis*-Retinoic Acid/All-*trans*-Retinoic Acid

Retinoids have an established role in the treatment of patients with APL[499] and children with high-risk neuroblastoma.[500] The actions of retinoids are mediated through the nuclear retinoid receptors, which are members of the steroid/thyroid/retinoid hormone receptor family. Retinoid receptors act as ligand-inducible transcription factors that enhance the transcription of target genes by binding to retinoic acid response elements (RAREs) in the promoter region of retinoid-responsive genes. Two families of retinoid nuclear receptors have been described, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). The RARs bind the naturally occurring retinoid ATRA with high affinity (Fig. 10.21), whereas the RXRs bind 9-*cis*-retinoic acid (9*c*RA), a naturally occurring, biologically active isomer of ATRA[501] that is capable of binding and transactivating both the RXRs as well as the RARs. Mutations in the ligand-binding domain of PML-RARα in patients with AML may result in selection of ATRA-resistant clones and subsequent disease relapse.[502] 13-*cis*-retinoic acid (13*c*RA) binds neither class of receptors with high affinity and likely acts a prodrug for other isomers.

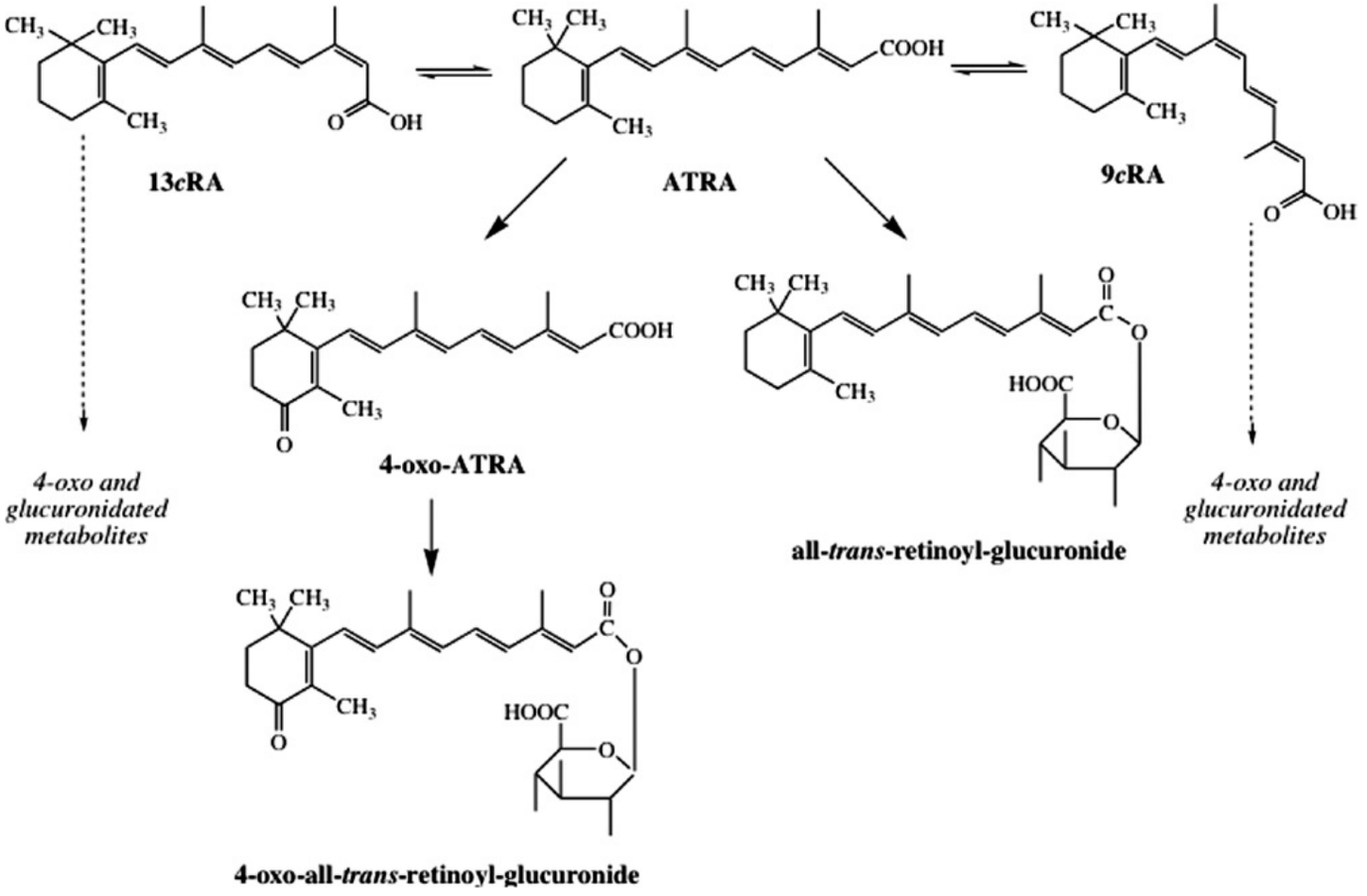


Figure 10.21 Chemical structures of the retinoids 13-*cis*-retinoic acid (13*c*RA), all-*trans*-retinoic acid (ATRA), and 9-*cis*-retinoic acid (9*c*RA). All three geometric isomers of retinoic acid undergo CYP-mediated oxidation, primarily at the 4-position, to 4-hydroxy (not shown) and 4-oxo retinoic acid. The parent isomers and their oxidated metabolites also undergo glucuronidation.

As a single agent, daily doses of 45 mg/m^2 of ATRA result in complete response rates of 70% to 92% of patients with newly diagnosed or relapsed APL. The addition of ATRA to chemotherapeutic regimens for adults[503] and children[504] with APL has been responsible for a

dramatic improvement in survival, with 5-year disease-free survival ranging from 75% to 85%.

Although 13*c*RA has very limited activity in children with recurrent neuroblastoma,[505] 13-cRA, in combination with high-dose chemotherapy and bone marrow rescue, improves 3-year survival for children with high-risk neuroblastoma,[500] a survival advantage that unfortunately does not appear to be maintained over time.[506] 13-cRA (isotretinoin) is a component of post-HSCT immunotherapy therapy with dinutuximab, GM-CSF, and interleukin-2 (IL-2) that has improved the event-free and overall survival of children with high-risk neuroblastoma.[507]

Pharmacokinetics

The pharmacokinetics of 13*c*RA following oral administration is highly variable, with peak plasma concentrations occurring within approximately 4 hours and terminal elimination averaging 10 to 20 hours in adult patients with cancer. The primary 4-oxo metabolite is formed rapidly and, during chronic administration, its concentration exceeds that of the parent drug by four- to fivefold.[508] In children, the half-life of elimination appears to be shorter than that observed in adult patients.[509] The pharmacokinetics of ATRA[510] differs substantially from 13cRA. Following a 45 mg/m^2 oral dose of ATRA, peak plasma concentrations on the first day of treatment are approximately 1 μM. The elimination of ATRA is significantly more rapid than that of 13*c*RA, with a terminal half-life of only approximately 45 minutes.[511] Furthermore, with daily dosing, there is a significant decrease in plasma ATRA concentrations within days of the start of therapy.[512] The rapid decrease in plasma drug exposure is related to autoinduction of enzymes CYP2C8, and to lesser extents by CYP3A4, CYP2C9,[513] and members of the retinoic acid specific CYP26 family[514] responsible for the 4-hydroxylaton of the drug (Fig. 10.21). Intermittent schedules of administration can partially overcome the increased clearance of ATRA.[504,510]

Toxicity

The embryotoxic and teratogenic effects of retinoids have been well documented and include a characteristic pattern of malformations involving craniofacial, cardiac, thymic, and CNS structures.[515] A prescriber education program developed to minimize pregnancies among women treated for acne[516] has been implemented and is required education for physicians prescribing 13*c*RA.

The most common symptoms associated with retinoid administration include cheilitis, conjunctivitis, dry mouth, xerosis, pruritus, headache, bone and joint pain, epistaxis, and fatigue. Common laboratory abnormalities include elevated sedimentation rates, elevated triglycerides, and, less commonly, elevations in hepatic transaminases. In children with cancer receiving 13*c*RA doses of 100 to 200 mg/m^2/d, hypercalcemia was dose limiting.[517]

The major adverse effect of ATRA, occurring in 25% of ATRA-treated patients with APL in the absence of prophylactic measures, is the retinoic acid syndrome, clinically similar to APL differentiation syndrome, manifests with weight gain, respiratory distress, serous effusions, and cardiac and renal failure. It is associated with increasing leukocyte counts and

subsequent cytokine release by maturing blast cells. Prophylaxis, consisting of dexamethasone and, in case of rapidly increasing leukocyte counts, cytotoxic chemotherapy, has reduced drug-related mortality to approximately 1%.[518]

Children appear more susceptible to the CNS effects of ATRA, manifested by headaches and the development of pseudotumor cerebri. Doses of 45 mg/m^2/d are generally well tolerated by children, but very young children may remain at increased risk for pseudotumor cerebri even at this dose.

Trabectedin

Trabectedin is a tetrahydroisoquinoline alkaloid derived from the sea tunicate *Ecteinascidia turbinata*. In the United States, it is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma after anthracycline therapy.[519] In Europe, trabectedin is authorized for use in adults with advanced soft-tissue sarcoma who have relapsed after anthracyclines and ifosfamide, and it is approved in combination with liposomal doxorubicin for patients with relapsed cisplatin-sensitive ovarian cancer. Trabectedin has a unique mechanism of action. It interacts with DNA by reversible alkylation of the guanine N2 in the DNA minor groove, forming adducts and triggering a cascade of events that can affect the activity of DNA-binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death. In the laboratory, trabectedin blocks DNA binding of the transcription factor FUS-CHOP, promoting cellular differentiation and reversing the oncogenic phenotype of cancer cells.[520] Trabectedin also inhibits the oncogenic protein EWS-FLI1 by removing the SWI/SNF chromatin remodeling complex from chromatin, redistributing EWS-FLI1 in the nucleus, subsequently suppressing EWS-FLI1–mediated target genes.[521]

In adults, trabectedin is administered as an IV infusion at a dose of 1.5 mg/m^2 over 24 hours every 3 weeks. Dose reduction is recommended in patients with moderate hepatic dysfunction and trabectedin is contraindicated in patients with severe hepatic dysfunction. Trabectedin is approximately 97% protein bound. Metabolism is primarily through hepatic CYP3A4, and excretion is primarily fecal. The elimination half-life is 180 hours.[522] Adverse events include nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache; severe adverse events include neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and capillary leak syndrome; and trabectedin shows embryo-fetal toxicity. Trabectedin is thought to have a narrow therapeutic window.[523]

A phase I study of trabectedin in children with refractory solid tumors defined a 3-hour infusion schedule every 3 weeks and a recommended dose of 1.1 mg/m^2. Dose-limiting toxicities included one patient with neutropenia at 1.1 mg/m^2, and two patients with transaminitis at 1.3 mg/m^2. One patient with metastatic Ewing sarcoma experienced a complete response. In a second phase I trial, trabectedin was administered as a 24-hour infusion. The half-life was 105 hours.[524] In a phase II study in children with sarcoma,[525] trabectedin (1.3 or 1.5 mg/m^2) was administered as a 24-hour infusion every 3 weeks. Dose-limiting toxicity included fatigue and gamma glutaminase (GGT) elevation. Efficacy was

limited; one patient with rhabdomyosarcoma experienced a partial response. Trabectedin evaluation in children has been limited, despite its indication in adults with sarcoma.

SMALL-MOLECULE PATHWAY INHIBITORS

Protein kinases are enzymes that catalyze the transfer of the terminal phosphate of ATP to substrates that usually contain tyrosine, serine, and threonine residues. Phosphorylation of these protein targets leads to activation of signal-transduction pathways that regulate critical processes including growth, differentiation, adhesion, metabolism, and apoptosis. Normal regulation of kinase function may be altered in cancer cells because of mutation, overexpression, or translocation of proto-oncogenes (see Chapter 11). This section focuses on the pharmacology of drugs that inhibit these kinases. Constitutive activity of these kinases by the formation of fusion oncoproteins makes cancer cells particularly vulnerable to inhibitors, making kinases rational targets for anticancer therapeutics. The most common pharmacologic approaches taken to targeting signal-transduction pathways include the development of small-molecule inhibitors that target the ATP-binding domain of tyrosine kinases and the development of monoclonal antibodies against the relevant receptors.

The success of imatinib mesylate (STI-571; Gleevec) for the treatment of patients with chronic myeloid leukemia (CML) in chronic phase[526] resulted in a paradigm shift in oncology drug development and ushered in the era of molecularly targeted cancer chemotherapy. As of 2018, the FDA has approved 48 small molecules that inhibit protein kinases. Ninety percent of these new approvals include malignancy as an indication; 96% are orally bioavailable. The most common targets are anaplastic lymphoma kinase (ALK), mitogen-activated protein kinase (MAPK) pathway including BRAF and mTOR, break point cluster region-Abelson kinase (BCR-Abl), epidermal growth factor (EGRF), and vascular endothelial growth factor receptor (VEGF-R).[16] In November 2018, the FDA issued a landmark approval that was age and tissue agnostic, for larotrectinib, an oral NTRK inhibitor for children and adults with metastatic or unresectable solid tumors that harbor NTRK gene fusions.

Kinases of particular interest for the treatment of childhood cancer include BCR-ABL in Ph-positive leukemias[526]; MAPK pathway inhibitors including mTOR, BRAF, and MEK inhibitors[527–529]; FLT3 in acute myelogenous leukemia[530]; ALK in anaplastic large-cell lymphoma (ALCL) and neuroblastoma[531,532]; and VEGF-R for a spectrum of pediatric solid tumors. In addition, inhibition of NTRK in rare pediatric cancers including infantile fibrosarcoma has produced dramatic, complete, and durable responses in tumors harboring NTRK fusions.[533,534]

Oral dosing and concern for potential food effects contribute to significant variability in exposure of many of these inhibitors.[535] Most of these agents are labeled with the provision that the drug should be administered on an empty stomach. In addition, appropriate oral formulations for children who cannot swallow tablets or capsules remain a considerable challenge for administration of these drugs.

Break Point Cluster Region-Abelson Kinase Inhibitors

Imatinib Mesylate

Imatinib received accelerated FDA approval for use in adults with Philadelphia chromosome–positive CML in 2001 followed by children in 2003. Large trials demonstrate that first-line therapy with imatinib in children with newly diagnosed CML is highly effective.[536] In 2013, the FDA also approved imatinib to treat children with newly diagnosed Philadelphia chromosome–positive ALL.

Although imatinib targets BCR-ABL, its effects on PDGF-R and c-kit have also been exploited. Imatinib inhibits mutant KIT, which is present in gastrointestinal stroma tumors (GIST) in adults.[537] On the basis of responses observed in adults with KIT-positive GIST,[538] the drug was approved for use in such patients in 2002. Activating mutations of c-kit are rare in pediatric solid tumors, but expression of the target protein or its ligand is found in a number of cancers in children. In a phase II trial of imatinib in children with these types of tumors, only one objective response was observed among 59 evaluable patients.[539]

Mechanisms of imatinib resistance have been explored extensively, particularly in the setting of CML. The most common mechanisms include BCR-ABL kinase domain mutations, BCR-ABL amplification and overexpression, impairment of drug transport, and clonal evolution with activation of additional signaling pathways.[540] Approximately 90 different BCR-ABL mutations that result in alterations in phosphate-binding loop and the activation loop have been identified in adults with imatinib-resistant CML. The majority of these mutations affect six specific amino acid residues, including Gly250, Tyr253, Glu255, Thr315, Met351, and Phe359.[541]

Imatinib dosing varies with indication. Adults with CML in chronic phase and adults with GIST are typically treated with a dose of 400 mg/d, whereas adults with CML in blast crisis or accelerated phase are treated 600 mg/d administered on a daily basis. Phase I data in children demonstrated that comparable doses of 260 mg/m^2/d or 340 mg/m^2/d are well tolerated and result in drug exposures similar to those observed in adults.[542] The recommended dose for children with newly diagnosed Philadelphia chromosome–positive CML is 340 mg/m^2/d, whereas the dose for children with chronic-phase CML recurring post-HSCT or post-interferon therapy is 260 mg/m^2/d.

Pharmacokinetics

Imatinib is well absorbed following oral administration and is highly protein bound. Imatinib exposure (AUC) is dose proportional over a 25 to 1,000 mg dose range. Imatinib is metabolized predominantly by CYP3A4. Peak plasma concentrations of the N-demethylated piperazine derivative of imatinib (CGP74588) are reached within 2 to 4 hours of dosing. Imatinib and CGP74588 are excreted mainly in feces, with only a small amount of the drug excreted in urine. Wide interpatient variability in the clearance of imatinib is observed in children and adults.[543] Imatinib penetrates poorly into the CNS,[544] and, thus, recurrence of disease in this sanctuary site can occur. Drug exposure following imatinib administration in patients with mild and moderate liver dysfunction did not differ significantly from that in patients with normal liver function, but exposures were increased in adults with mild or moderate renal insufficiency.[545,546]

Toxicity

The most frequently reported drug-related toxicities in adults are nausea, vomiting, fatigue, diarrhea, musculoskeletal pain, and fluid retention. Although edema is rarely severe, significant fluid retention can occur, manifested as pleural effusion, pericardial effusion, pulmonary edema, ascites, or superficial edema with rapid weight gain. The most common adverse events reported in children were nausea, vomiting, fatigue, diarrhea, and transaminitis.[542] Hemorrhagic pleural effusions have been described.[539]

Dasatinib

Point mutations in the kinase domain of the BCR-ABL fusion protein may alter the conformation of the protein, affecting imatinib binding and causing resistance to this agent. Dasatinib, a second-generation kinase inhibitor, binds to the ABL kinase in both its active and inactive conformations.[547] Dasatinib retains kinase inhibitory activity in cells harboring clinically relevant imatinib-resistant BCR-ABL isoforms. The drug also decreases disease burden in in vivo models of CML, including an imatinib-acquired resistance model. In addition to binding to the kinase domain of BCR-ABL, dasatinib competes with ATP for binding to additional kinases and kinase families, including the SRC family kinases, c-kit, EPHA2, and PDGF receptor.[548] Dasatinib is approved for use in adults with newly diagnosed Philadelphia chromosome–positive ALL or CML in chronic phase and for adults with Philadelphia chromosome–positive ALL or CML in any phase who have resistance or intolerance to previous therapy. Recommended doses in adults are 100 mg daily for chronic-phase CML and 140 mg daily for accelerated- or blast-phase CML or for Ph-positive ALL. In children, doses between 60 and 85 mg/m^2 daily have been well tolerated,[549] and dasatinib is safe and effective in children with CML in chronic phase.[550] Dasatinib is approved by the FDA and EMA for children older than 1 year with Philadelphia chromosome–positive CML in chronic phase and for children with newly diagnosed Philadelphia chromosome–positive ALL, dasatinib is approved for use in combination with chemotherapy. In children, the dose of dasatinib is weight based and the dose may be escalated in individual children who have minimal toxicity but do not achieve hematologic or cytogenic response.

Pharmacokinetics

Unlike other small-molecule TKIs, dasatinib has a short half-life (<4 hours) in adults. In children, the mean terminal half-life is 2.2 hours.[549,551] Following oral administration of dasatinib, exposure increases proportionally with dose, although there is considerable interpatient variability in exposure, particularly at higher dose levels. Dasatinib crosses the BBB.[552] The drug is extensively metabolized by hepatic CYP3A4 and most metabolites are excreted in feces. Daily dosing is associated with similar efficacy but fewer side effects compared with twice-daily dosing.[553] Dosage adjustment does not appear to be necessary in adults with hepatic impairment. Less than 4% of dasatinib and its metabolites are excreted by the kidney[554] and renal dysfunction does not alter the pharmacokinetics of dasatinib.

Toxicity

Dasatinib-associated toxicities in adults include thrombocytopenia and pleural effusion.[553] Other adverse events include pericardial effusion, generalized edema, dyspnea or pulmonary edema, rash, flushing, headache, and fatigue.[555] In children, dose-limiting toxicities were diarrhea, headache, and hypokalemia.[549] In children with CML in chronic phase, no dasatinib-related pleural or pericardial effusion, pulmonary edema, or pulmonary arterial hypertension occurred in a large phase II trial. However, bone growth and development events were reported in 4% of patients.[550] Overall, safety, tolerability and drug disposition were similar to that of adults.[551,556]

Other Break Point Cluster Region-Abelson Kinase Inhibitors

Owing to the development of resistance or intolerance to imatinib and dasatinib, second- and third-generation BCL-ABL inhibitors have been developed and recently FDA approved for use in children. Ponatinib, a third-generation kinase inhibitor, was developed to overcome resistance to the gatekeeper mutation T315I in BCL-ABL kinase in CML and Ph-positive ALL. Development of cardiovascular thrombotic events in 8% of adults treated with ponatinib and risk of hepatotoxicity are associated with ponatinib in adults. Nilotinib is effective in resistance-conferring mutations, except in T351I. Guidelines for selection of BCL-ABL inhibitors in adults have been developed and can be utilized to assist in selection of agents in children.[557] Generally, the toxicity profile of these drugs is similar to that in adults; however, emerging data indicates endocrine and bone growth monitoring may be warranted for children receiving BCR-ABL inhibitors.

Janus-Associated Kinase/Signal Transducers and Activator of Transcription Pathway Inhibitors

The Janus-associated kinase/signal transducers and activator of transcription (JAK/STAT) is critical to normal hematopoiesis. Aberrant activation of the JAK/STAT pathway occurs in inflammatory conditions, hematologic malignancies, and solid tumors.

The FDA and EMA have approved ruxolitinib for patients with intermediate or high-risk myelofibrosis. The most common hematologic adverse effects are thrombocytopenia and anemia; nonhematologic toxicity includes bruising, dizziness, and headache. Ruxolitinib is rapidly absorbed after oral dosing, and the peak concentration and exposure increase in proportion to dose. Plasma protein binding is 97% and apparent volume of distribution at steady state is 53 to 65 L in adults. Ruxolitinib is extensively metabolized by CYP3A4 to active metabolites, excreted in urine, and, to lesser extent, in feces. The half-life is 3 to 6 hours. Dose reductions are recommended for patients with moderate and severe renal and any degree of hepatic dysfunction in conjunction with thrombocytopenia. Ruxolitinib is not removed by dialysis.

In a phase I trial in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative disorders, dose-limiting toxicity included neutropenia and creatinine phosphokinase elevation; one child with a relapsed solid tumor developed multiorgan failure. No MTD was established; the recommended dose of ruxolitinib in children is 50 mg/m^2/dose administered orally, twice daily. Toxicity and pharmacokinetics were similar to that in

adults.[558] Clinical trials of ruxolitinib in children are ongoing.

Anaplastic Lymphoma Kinase Inhibitors

ALK is a receptor tyrosine kinase that is mutated, fused, or overexpressed in several cancers, including ALCL, NSCLC, and in a select group of patients with neuroblastoma.[532,559] In NSCLC, the most common ALK fusion is with EML4 (echinoderm microtubule-associated protein 4, EML4-ALK). ALK-positive ALCL occurs primarily in younger patients and harbors the NPM-ALK t(2;15) translocation with fusion of the nucleophosmin and ALK genes. In neuroblastoma, ALK gain-of-function mutations include R1275, F1174, or F1245 and, rarely, ALK amplification can occur. ALK may be overexpressed in inflammatory myofibroblastic tumors (IMTs). Each of these molecular aberrations influences the sensitivity of these cancers to ALK inhibitors.

Crizotinib

Crizotinib is an oral inhibitor selective for ALK and MET[560] that has substantial efficacy in patients with NSCLC harboring ALK gene rearrangements.[561] In 2013, the FDA-approved crizotinib for the treatment of ALK-positive metastatic NSCLC.

Crizotinib has been studied in children with refractory ALCL, neuroblastoma, and solid tumors with known translocations, mutations, or amplifications in the *ALK* gene.[562] Toxicities included dizziness; intracranial hemorrhage; increase in alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and gamma-glutamyl transpeptidase; and neutrophil count decrease. In children and adults with relapsed ALCL receiving crizotinib 250 mg twice daily (older than 18 years) or 165 mg/m^2/dose twice daily (younger than 18 years), objective responses were achieved in 67% of patients. The recommended dose of crizotinib in children with solid tumors (280 mg/m^2/dose twice daily) was well tolerated and is significantly higher than the recommended dose in adults. Pharmacokinetics in adults and children is dose proportional after oral dosing twice a day. The mean steady-state trough concentrations in adults receiving crizotinib 250 mg twice daily was approximately 250 ng/mL, and demonstrated a terminal half-life of 43 to 51 hours. At the recommended dose in children, the mean steady-state peak concentrations of crizotinib was 717 ng/mL, mean trough concentration was 480 ng/mL, and the time to reach peak concentration was 4 hours.[563] In adults with severe renal impairment or moderate hepatic dysfunction, dose modifications are recommended.

Other Anaplastic Lymphoma Kinase Inhibitors

In adults with NCSLC, development of acquired resistance to ALK inhibitors is common and may be associated with specific ALK fusion variants. Second- and third-generation ALK inhibitors have been developed to overcome resistance and improve CNS penetration of the drugs. Ceritinib, a second-generation ALK inhibitor that lacks MET-binding properties but may inhibit insulin-like growth factor (IGF-1) receptor and ROS1, is approved by the FDA for patients with ALK-positive NSCLC that has progressed during treatment with crizotinib.

Gastrointestinal adverse events and fatigue are common; serious adverse events include hepatotoxicity, interstitial lung disease, prolonged QTc, bradycardia, hyperglycemia, and pancreatitis.[564] In children, the recommended dose of ceritinib is 500 to 550 mg/m^2 daily. The toxicity profile is similar to that in adults. In early-phase trials, responses were observed in ALCL and IMT.

Lorlatinib is a third-generation ALK inhibitor approved for adults with ALK-positive NSCLC whose disease has progressed during therapy with a first- or second-generation ALK inhibitor. The recommended dose in adults, 100 mg daily, is associated with hypertriglyceridemia, hypercholesterolemia, edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. Hepatotoxicity is associated with concomitant administration of strong CYP3A4 inhibitors. CNS side effects (all grades) occur in 54% of patients typically within 1.2 months of starting lorlatinib. These include seizures (3%), hallucinations, changes in cognitive function (29%), mood (24%) and suicidal ideation, speech (14%), mental status, and sleep (10%). In treatment-naive patients with ALK-positive NSCLC, the response rate was 90% versus 40% in patients who had previously been treated with an ALK inhibitor.[565] Lorlatinib is rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours after oral administration. The half-life is 19 to 29 hours in adults. There was no difference in exposure in the fasted or fed state. Human plasma protein binding is 67%. The mean CSF concentration of lorlatinib is 75% of the unbound plasma concentration.[566] The dose of lorlatinib has not been established for patients with severe hepatic or renal dysfunction. Lorlatinib has increased affinity for ALK mutations present in neuroblastoma and in vivo activity in crizotinib-resistant mouse models of neuroblastoma (Th-ALK^{F1174L}/MYC); clinical trials are ongoing.

Neurotrophic Receptor Tyrosine Kinase Inhibitors

Neurotrophic tyrosine receptor kinase (NTRK 1/2/3) genes encode tropomyosin-related kinase (TRK) receptors involved in growth regulation, differentiation, and apoptosis of neurons. A number of cancers including infantile fibrosarcoma, glioblastoma, secretory breast carcinoma, salivary gland cancer, and some sarcomas harbor NTRK fusion oncoproteins. Larotrectinib, an NTRK 1/2/3 inhibitor, is FDA approved for adults and children with solid tumors that have NTRK gene fusions if the cancer is progressive, metastatic, or unresectable. The most common adverse events were fatigue, nausea, dizziness, vomiting, increased hepatic transaminases, cough, constipation, and diarrhea. In children, larotrectinib 100 mg/m^2 twice daily provides exposure similar to that of adults receiving 100 mg twice daily. Larotrectinib is rapidly absorbed. The absolute bioavailability of capsules is 34% and is similar in the oral solution; however, the $C_{max}$of the oral solution is 36% greater than that observed with capsules. The half-life of larotrectinib is 2.9 hours. It is metabolized primarily by CYP3A4 and is 70% plasma protein bound. Larotrectinib is also detectable in CSF. Dose modifications are recommended for patients with moderate or severe hepatic dysfunction. In the pivotal study that enrolled both children and adults, all 15 patients with tumors harboring NTK fusions had decrease in tumor burden. The overall response rate was 75% (95% CI 61, 85%).[567]

Mitogen-Activated Protein Kinase Inhibitors

The classical MAPK pathway (RAS-RAF-MEK1/2-ERK1/2) regulates multiple key cellular processes and is one of the most frequently dysregulated signaling pathways in cancer. Lymphoid malignancies, rhabdomyosarcoma, low-grade glioma, glioblastoma, neuroblastoma, malignant peripheral nerve sheath tumors, melanoma, and Langerhans cell histiocytosis in children can harbor aberrations in the MAPK pathway.[568] Vemurafenib is approved for advanced metastatic melanoma harboring $BRAF^{V600E}$ mutations. In adults, the half-life of vemurafenib is approximately 57 hours. It is metabolized by CYP3A4 and is an inhibitor of a number of cytochrome P450 enzymes. Common side effects include arthralgia, rash, alopecia, fatigue, photosensitivity, nausea, pruritus, and skin papilloma. Rare but serious side effects include QTc prolongation, retinal vein occlusion, and cutaneous squamous cell carcinoma due to paradoxical activation of MAP kinase signaling in BRAF wild-type cells after exposure to BRAF inhibitors. In a small clinical trial in adolescents with melanoma, the toxicity profile and pharmacokinetics were similar to that in adults.[569] Selumetinib, a MEK inhibitor, was granted breakthrough designation by the FDA for children with neurofibromatosis type 1–related plexiform neurofibromas and is being investigated in children with low-grade gliomas and adults with hepatocellular carcinoma. In children, toxicities include elevated lipase and amylase, headache, mucositis, acneiform rash, and a decrease in left ventricular ejection fraction. There was no effect on growth. In both adults and children, selumetanib is rapidly absorbed after oral dosing and has a half-life of 6 to 7 hours.[570,571] Trametinib alone and in combination with dabrafenib is approved in adults with $BRAF^{V600E}$ melanoma. Side effects are similar to that of other inhibitors of the MAPK pathway. Investigations of trametinib alone and in combination with dabrafenib are ongoing in children.

PI3K/AKT/mTOR Inhibitors

Sirolimus/Everolimus/Temsirolimus/Ridaforolimus

The mammalian target of rapamycin (mTOR) is a serine/threonine phosphatidylinositol-3-kinase (PI3K)–related kinase, of which several inhibitors have been developed. Rapamycin (sirolimus) and its analogs exert their action through inhibition of the TOR complex 1 or complex 2 (TORC 1 and 2) receptors, which themselves are effectors within the PI3K/AKT pathway.[572] Rapamycin was first used as an antifungal agent, isolated from *Streptomyces hygroscopidcus*. Several rapalogs have been developed with differing pharmacokinetic properties including temsirolimus, everolimus, and ridaforolimis.

Pharmacokinetics

Sirolimus and temsirolimus are oral and IV forms of rapamycin. Pediatric studies in patients with neurofibromatosis type 1 with sirolimus demonstrated a clearance of 11.8 L/h at a dose of 2 mg/m^2 twice daily by mouth, and a terminal half-life of 10 to 24 hours.[573] Studies of temsirolimus given intravenously at doses of 75 to 150 mg/m^2 weekly every 3 weeks found

rapid formation of the active metabolite sirolimus with time to maximum exposure ranging from 2 to 6 hours.[574] The clearance of both sirolimus and temsirolimus appears to increase with increasing dose, suggesting saturation of drug binding the peripheral blood compartment.

Everolimus is a water-soluble ester of sirolimus created in an attempt to improve the oral bioavailability of sirolimus. In adults, everolimus is absorbed rapidly, and steady state is reached within 7 days. Everolimus is primarily metabolized by CYP3A4, 3A5, and 2C8, and it is affected by the P-glycoprotein efflux pump. Pharmacokinetics demonstrates a large mean steady-state volume of distribution, with saturable drug distribution at high doses. Clearance increases with increasing dose, and the terminal half-life has been estimated at 22 to 34 hours.[575] There is evidence to suggest that dose adjustment is required in the adult patient with hepatic impairment.[576] In children, clearance was estimated at 15.2 L/h/m^2, which was comparable to the pharmacokinetics seen in adults.[577,578] In 2012, the FDA-approved everolimus tablets for oral suspension for the treatment of patients with subependymal giant cell astrocytoma.

In a study of ridaforolimus in children with refractory solid tumors,[579] the pharmacokinetic profile was consistent with that of adults.

Toxicity

In adult phase I studies of everolimus, adverse events have consisted mainly of fatigue, rash, stomatitis, nausea, vomiting, and anorexia.[575,580] In children, dose-limiting toxicities included diarrhea, mucositis, and alanine aminotransferase elevation. Limited other grade 3 or 4 toxicities have been seen.[577] In the phase I study of ridaforolimus, no dose-limiting toxicities were observed and the most common grade 3 or 4 events were thrombocytopenia, anemia, neutropenia, lymphopenia, hypokalemia and hyponatremia.[579]

Copanlisib

Phosphatidylinositol 3-kinases (PI3K) are lipid kinases that phosphorylate inositol rings of phosphoinositides to generate second messengers to control cell proliferation, survival, and motility. Deregulation and constitutive activation of the PI3K pathway in cancer is most commonly due to activating point mutations in PI3K, inactivation of tumor suppressor PTEN, and amplification of the *Akt* gene. Activation of the PI3K/AKT pathway has been demonstrated in neuroblastoma, Ewing sarcoma, rhabdomyosarcoma, osteosarcoma, medulloblastoma, and other solid tumors.[581]

Copanlisib, a PI3K inhibitor, administered intravenously on a weekly schedule, is FDA approved in adults with relapsed follicular lymphoma and evaluation in hematologic and solid tumors in adults is ongoing. Early-phase clinical trials in children are ongoing. In adults, toxicity includes hyperglycemia, hypertension, infection, and neutropenia. Noninfectious pneumonitis and severe cutaneous reactions have been reported. In adults, the pharmacokinetics of copanlisib is dose proportional, the terminal half-life is 39 hours, clearance 17.9 L/h. No accumulation is observed on weekly IV dosing schedule. Human plasma protein binding of copanlisib is 84%, the volume of distribution is 871 L in adults. Up

to 50% of the drug is excreted unchanged in feces and urine, 40% is excreted as an oxidate metabolite. Metabolism of copanlisib is primarily by CYP3A4. The primary routes of elimination are biliary and renal. Drug interactions and dose modifications are recommended when copanlisib is administered in combination with strong CYP3A inducers and inhibitors.[582]

Vascular Endothelial Growth Factor Receptor and MultiTyrosine Kinase Inhibitors

As the role of new blood vessel formation in cancer emerged, considerable efforts have been made to develop TKIs that alter the function of angiogenesis-associated kinases. Many of these drugs are potent inhibitors of multiple tyrosine kinases, including c-Kit, FLT3, RET, c-Met, and FGFR, that may be relevant in cancer in children and in young adults.

Small-molecule multitargeted TKIs that target VEGF, PDGRF, and c-Kit include sunitinib, pazopanib, axitinib, and regorafenib. Sunitinib is approved for use in adults with renal cell carcinoma and GIST. Pazopanib is approved for use in adults with renal cell carcinoma and soft-tissue sarcoma. Axitinib is approved as a second-line treatment for adults with advanced renal cell carcinoma. Regorafenib has been approved in adults with progressive metastatic colorectal cancer. Sorafenib inhibits VEGFR1/2/3, PDGFR, c-Kit, RAF, and FLT3. It is approved in adults with renal cell carcinoma and advanced hepatocellular carcinoma. Cabozantinib is a pan-TKI for VEGFR-1/2/3, c-Kit receptor, c-Met, and FLT-3 approved for adults with medullary thyroid cancer as well as for adults with hepatocellular carcinoma refractory to sorafenib. Vandetanib is a VEGFR, EGFR, and RET inhibitor currently labeled for the treatment of advanced or progressive medullary thyroid carcinoma. Early-phase clinical trials of each of these drugs have been completed in children and adolescents with cancer. Pharmacokinetics, safety, tolerability, and toxicity spectrum have been established; however, a role for this class of agents in cancers in children and adolescents has not been established.

Pharmacokinetics

The primary metabolic pathway for most drugs in this class is hepatic metabolism, primarily via CYP3A4, and excretion in the feces, with a small percentage excreted in urine. An exception is vandetanib, which is metabolized by the liver to N-desmethylvandetanib and vandetanib N-oxide, and is excreted by both the liver and kidneys.[583] Adjustment of sunitinib dosing is not required for adults with mild hepatic impairment,[584] but data regarding the pharmacokinetics of sunitinib in patients with severe liver dysfunction or patients with renal impairment have not been published. Pazopanib was tolerated in patients with mild liver dysfunction at the FDA-labeled daily dose; however, patients with moderate and severe liver dysfunction did not tolerate this dose. In patients with moderate hepatic dysfunction, dose adjustments may be required or alternatives considered; in patients with severe liver dysfunction pazopanib is not recommended.[585] For sorafenib, dose adjustments do not appear to be required in patients with mild hepatic or renal dysfunction, but dose modification has been recommended for patients with moderate and severe organ dysfunction.[584]

Sunitinib has a long half-life of approximately 40 to 80 hours, with evidence of drug accumulation with multiple doses.[586] Pazopanib is administered once a day, and the drug has a mean half-life of approximately 31 hours in adults. Following administration of sorafenib on a twice-daily schedule, peak plasma concentrations and drug exposure did not appear to increase in proportion to dose.[587] In adults, the drug has a mean half-life of 24 to 35 hours, and accumulates with multiple doses.[588,589] A small pediatric study of vandetanib in children with MTC has demonstrated a median apparent steady-state clearance of 5.9 (3.9 to 7.3) $L/h/m^2$.[590]

Toxicity

Toxicities that are associated with antiangiogenic agents are consistent with the mechanism of action of VEGF inhibition and include hypertension, fatigue, asthenia, diarrhea, nausea/emesis, mucositis, rash, hand-foot syndrome, and bleeding. Similar to adults, hypothyroidism and reversible cardiac dysfunction requiring medical therapy have occurred. VEGF receptors are present in osteoclasts and osteoblasts; therefore, VEGFR inhibition can impact the growth plate and can impact linear long bone growth or healing of bone.[591] Vandetanib is associated with prolonged cardiac repolarization, which manifests as prolonged Q-T interval on electrocardiogram and increases the risk for *torsades de pointes*, a ventricular arrhythmia.

THERAPEUTIC ANTIBODIES

Monoclonal Antibodies

Monoclonal antibodies (MoAbs) are genetically engineered, targeted biologic agents that produce an anticancer effect by the following:

- Stimulation of an immune response to cancer cells through Fc-mediated complement-dependent cytotoxicity (CDC) (e.g., rituximab) or antibody-dependent cell-mediated cytotoxicity (ADCC) (e.g., dinutuximab) and through induction of adaptive immunity from the release of tumor antigens[592]
- Modulation of critical cell signaling pathways by binding to cell surface receptors (e.g., estimated glomerular filtration rate [EGFR]) and acting as agonists or antagonists; or binding to ligands (e.g., vascular endothelial growth factor [VEGF]) of the receptors
- Targeted delivery of conjugated radionuclides (e.g., ^{131}I-tositumomab), cytotoxic small molecules (e.g., brentuximab vedotin), or protein toxins (e.g., moxetumomab pasudotox)

A MoAb's mechanism of action influences its dosing schedule. MoAbs that modulate signaling pathways may require more frequent (e.g., weekly) administration to optimize receptor or ligand binding throughout the dosing interval, whereas MoAbs that work through immune mechanisms or antibody-drug conjugates (ADCs) may be less schedule dependent, allowing for less frequent administration.

The first therapeutic MoAbs were murine and were limited by immunogenicity, rapid elimination because of their weak affinity for the FcRn receptor (see later), and weak stimulation of CDC and ADCC. Chimeric MoAbs were generated through genetic engineering by grafting the murine variable (Fab) domain that recognizes the target antigen to the human constant (Fc) domain, yielding an antibody that is 65% human. Chimeric MoAbs are less immunogenic and have longer half-lives than do murine antibodies, but patients frequently develop endogenous antichimeric antibodies (human antichimeric antibodies [HACA]). Humanized MoAbs, which are 95% human, include only the murine hypervariable regions of the Fab domain, and newer technologies now allow for the development of fully human MoAbs.[593] The Fc region of MoAbs can be genetically engineered to enhance or decrease effector function by altering binding affinity for FcγR (ADCC effector) or C1q (CDC effector).

MoAbs' names provide information about the target and source of the antibody. The nomenclature scheme includes four key elements—the prefix, which is used to create a unique name for the MoAb; the target/disease inflix (*tu* or *t* for tumor or *li* for immune system); the source inflix (*o* for murine, *xi* for chimeric, *zu* for humanized, and *u* for fully human); and the stem or suffix (*mab* for MoAbs or antibody fragments). For ADCs, the payload is a separate word (e.g., brentuximab vedotin).

The distribution and elimination of MoAbs differ substantially from small molecules. Diffusion of large, polar proteins, such as antibodies, across the capillary endothelium and into tissue is slow, and convection, rather than diffusion, accounts for transport of MoAbs into tissues. MoAb concentration in tissue interstitial fluid is substantially lower than that in plasma, and the volume of distribution of MoAbs often approximates plasma volume. MoAbs are eliminated primarily by fluid-phase or receptor-mediated endocytosis or phagocytosis, followed by intracellular catabolism. Receptor-mediated elimination is saturable depending on the finite number of receptor binding sites, and dose-dependent elimination of MoAbs has been observed (e.g., rituximab and gemtuzumab). Endocytosed, endogenous IgG is protected from catabolism through its pH-dependent interaction with the FcRn (Brambell) receptor in the endosome. The FcRn-IgG complex is redirected to the cell surface where the IgG is recycled.[594,595] Endogenous IgG clearance is 10-fold higher in FcRn-deficient animal models,[594] and the rapid clearance of murine MoAbs in humans is likely related to the low affinity of human FcRn for murine IgG.

MoAbs are often dosed using body weight rather than BSA, but clearance of MoAbs normalized to body weight is higher in younger children, resulting in lower drug exposures (AUCs) in younger children.[596] Dosing MoAbs using BSA results in more uniform drug exposures across the pediatric age range.

Rituximab

Rituximab is a chimeric anti-CD20 MoAb that was initially approved for low-grade and follicular B-cell NHL but is also used to treat B-cell chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and post-HSCT lymphoproliferative disorder, as well as a variety of autoimmune disorders, including opsoclonus myoclonus/ataxia syndrome associated with

neuroblastoma. Rituximab depletes normal B cells and antibody production, exerting its therapeutic effect primarily through CDC and ADCC, although a number of intracellular signaling pathways are also altered by rituximab binding to CD20.[597]

The standard rituximab dose is 375 mg/m^2 administered weekly for up to four doses. This dose can also be safely administered in combination with chemotherapy,[598] usually as a single dose per treatment cycle. Premedication with diphenhydramine and acetaminophen, infusing rituximab at an initial slow rate (e.g., 0.5 mg/kg/h), and gradually increasing the infusion rate as tolerated, lowers the risk of infusion-related reactions to rituximab.[598,599] Rituximab may also be administered intrathecally for meningeal disease.[600]

Pharmacokinetics

In adults with B-cell malignancies, the pharmacokinetics of rituximab is characterized by substantial interpatient variability as well as an increase in the half-life and decrease in clearance with repeated doses, presumably related to a decrease in CD20-mediated elimination from depletion of CD20 expressing normal and malignant cells.[601–603] The half-life of rituximab in children is 26 to 29 days, which is similar to the 19-day half-life reported in adults.[603,604]

Toxicity

Infusion-related reactions and lymphopenia are common rituximab toxicities. Mild to moderate infusion-related reactions, such as fever, chills, and flulike symptoms, occur in a majority of patients during the first infusion, but decrease in frequency with subsequent infusions. Bronchospasm, hypotension, and angioedema are observed in up to 10% of patients and respond to interruption of the infusion and supportive measures.[601] Infusion-related reactions associated with cytokine release syndrome can rarely be fatal. Lymphopenia is the result of depletion of normal CD20 expressing B cells, with recovery in 9 to 12 months after the drug is stopped[605]; hypogammaglobulinemia and opportunistic infections are uncommon. Other rare but serious toxicities associated with rituximab include severe mucocutaneous reaction, such as Stevens–Johnson syndrome, and interstitial lung disease.[601,606]

Dinutuximab (ch14.18) and Dunituximab beta (ch14.18/CHO)

Dinutuximab is a chimeric MoAb directed against the ganglioside G_{D2}, which is expressed on the cell surface of neuroblastoma, as well as neurons, melanocytes, and peripheral pain fibers. The antitumor effect of dinutuximab in neuroblastoma appears to be primarily mediated through ADCC, which presumably is enhanced when dinutuximab is combined with the immunomodulating agents aldesleukin (IL-2) and sargramostim (GM-CSF).

Dinutuximab (17 mg/m^2/d) is administered over 4 days as 10-hour daily infusions (total dose 68 mg/m^2 per course), repeated every 28 days for five courses, and coadministered with sargramostim (250 mcg/m^2/d SQ daily × 14 days) on cycles one, three, and five and aldesleukin (3 × 10^6 units/m^2/d IV continuous infusion × 96 hours alone and then 4.5 × 10^6 units/m^2/d IV continuous infusion × 96 hours with ch14.18) on cycles two and four. This

regimen plus isotretinoin (80 mg/m^2/dose twice daily × 14 days) given after a dose-intensive combination chemotherapy regimen, which included high-dose myeloablative therapy with autologous stem cell rescue, significantly improved the outcome in children with high-risk neuroblastoma.[507]

Dinutuximab beta, ch14.18 cloned in Chinese hamster ovary (CHO) cell lines, is used in Europe at a dose of 20 mg/m^2 IV 8-hour infusion daily for 5 days for children with high-risk neuroblastoma. In a randomized study, children with neuroblastoma received dinutuximab beta and isotretinoin with or without subcutaneous IL-2 as consolidation therapy. Children who received dinutuximab beta and isotretinoin without subcutaneous IL-2 had less toxicity and 3-year event-free survival was 56% for patients receiving IL-2 and 60% for children who did not receive IL-2 ($p = 0.76$),[607] strongly suggesting that IL-2 is not necessary for antitumor effect.

Pharmacokinetics

In children with high-risk neuroblastoma, the peak dinutuximab concentration was 11 mcg/mL, and plasma disappearance was biexponential with an elimination half-life of 7 days. Clearance (2 L/d•m^2) was fourfold higher in children than in adults and was more rapid in younger children. Steady-state volume of distribution was 0.4 L/kg, which exceeds plasma volume. The larger volume of distribution may be related to enhanced convection-mediated tissue distribution from capillary leak syndrome. One subject who developed HACA after the first course had a 41% decrease in AUC from course one to three.[608] After administration of dinutuximab beta, the peak plasma concentration was 16.5 ± 5.9 mcg/mL and the half-life was 76.9 ± 52.5 h.[609]

Toxicity

Dinutuximab is administered in the hospital to manage potentially severe and life-threatening infusion-related toxicities including neuropathic pain (abdomen is the most common site), hypotension, hypoxia, fever, capillary leak syndrome, hypersensitivity reactions, urticaria, diarrhea, and electrolyte abnormalities.[507] Pain is more frequent during course one and decreases in severity by course five. Opioids are continuously infused concurrently with dinutuximab to alleviate pain. Capillary leak and hypersensitivity reactions are more common during courses two and four, when dinutuximab is given with aldesleukin. Some toxicities are responsive to slowing the infusion rate. Transverse myelitis has also been observed in children receiving dinutuximab.[610]

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds to all five isoforms of human VEGF ligand and blocks angiogenesis by preventing VEGF from interacting with VEGF receptors. It is approved for metastatic colorectal cancer, NSCLC, and glioblastoma, and it is often used in combination with cytotoxic chemotherapy. The dose of bevacizumab in children is 10 to 15 mg/kg administered intravenously every 2 weeks.[611] Bevacizumab has been primarily used in children for treatment of brain tumors.[612]

The clearance of bevacizumab in children was 3.1 mL/kg/d and the median half-life was 19.6 days, which are identical to adult values for these parameters.[613] The clearance was not dose dependent over the dose range of 5 to 15 mg/kg.

Bevacizumab-related toxicities include infusional reactions, rash, mucositis, proteinuria, lymphopenia, and mild increases in systolic and diastolic blood pressure in most patients. Neither bleeding or clotting complications were observed in the initial pediatric trials.[611] In children with brain tumors, bevacizumab's toxic effects included hypertension (38%), fatigue (30%), epistaxis (24%), and proteinuria (22%); approximately one-fourth of patients stopped taking bevacizumab because of intolerable toxicity.[614]

Immune Checkpoint Inhibitors

The immune system is regulated by a variety of inhibitory pathways (immune checkpoints) that are essential to maintain self-tolerance and modulate the immune response, and thereby protect normal tissues and prevent autoimmunity. Cancers can use immune checkpoints to block antitumor immunity.[615,616] Immune checkpoint inhibitors, such as ipilimumab, which target cytotoxic T-lymphocyte-antigen 4 (CTLA-4), nivolumab and pembrolizumab, which target programmed cell death receptor 1 (PD-1), and several MoAbs that target the PD-1 ligand (PD-L1), globally enhance the T-cell–mediated immune response to tumors, rather than stimulating an immune response through binding to a tumor-specific antigen on the tumor cell. This nonspecific mechanism is reflected by the rapidly growing number of FDA-approved indications for these agents in many common forms of cancer in adults. The role of immune checkpoint inhibitors in treating childhood cancers is under study.

Immune checkpoint inhibitors are humanized or human MoAbs and their pharmacokinetic behavior is characterized by limited distribution, long half-lives, and receptor-mediated elimination in adults, similar to endogenous antibodies.[617] The toxicity profile of these agents reflects the immune dysregulation that they induce, and any organ or tissue can be affected. Toxicities include pneumonitis, colitis, uveitis, hypophysitis, encephalitis, hepatitis, arthralgias, and myocarditis. Patients receiving these agents require comprehensive monitoring and may require steroids or other immunomodulatory treatments if severe immune-related toxicities develop.[618]

Antibody-Drug Conjugates

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 MoAB (hP67.6) that is conjugated to N-acetyl-γ-calcheamicin, which is a highly toxic and potent enediyne natural product.[619–621] The acid-labile linker connecting calicheamicin to hP67.6 allows for the rapid release of calicheamicin intracellularly under acidic conditions in the lysosome after antigen binding and internalization. Calicheamicin then binds to DNA and creates double-strand scission.[622]

CD33 is expressed on normal myeloid cells and on the myeloblasts in 80% of AML cases,[619] but not on hematopoietic stem cells. A splicing polymorphism in the gene encoding CD33 alters the expression of the gemtuzumab binding site on CD33. In a randomized trial, a

lower relapse rate and improved survival was observed on the GO arm only in patients with the wild-type CD33 gene that expresses the GO binding site.[623]

GO received accelerated FDA approval in the year 2000 for older adults with AML but was withdrawn from the market in 2010 after the phase III trial showed no survival advantage and more treatment-related fatal events on the GO arm.[621] The remission rate to single-agent GO in AML is approximately 30%.[624–626] Improved overall survival without an increase in early fatal events was observed in the subset of patients treated with GO at doses less than 6 mg/m^2.[624] GO has been administered to children with AML in combination with chemotherapy at dose of 3 to 5 mg/m^2 infused over 2 hours,[627–629] with improvement in event-free but not overall survival.[629]

Pharmacokinetics

GO pharmacokinetics was studied in children and adolescents with AML at doses of 6 and 9 mg/m^2. GO disposition in children was similar to that in adults. Pharmacokinetic parameters were variable, and the half-life was approximately 55 hours, clearance was 0.3 L/h, and steady-state volume of distribution was 0.3 L/kg. The half-life and AUC increased after the second dose and the clearance was lower, presumably related to a lower tumor burden and reduced receptor-mediated clearance.[630] Unconjugated calicheamicin accounted for less than 15% of total calicheamicin in plasma.

Toxicity

GO is well tolerated in children as a single agent and in combination with chemotherapy.[626,627] Infusion-related events include chills and fever, nausea and vomiting, and, less commonly, hypotension, headache, neck pain, and body pain. Myelosuppression and serious infections are common following GO. GO is also hepatotoxic, usually manifested as transient elevation of serum transaminases or bilirubin, but rarely SOS can also occur.[624]

Brentuximab Vedotin (SGN-35)

Brentuximab vedotin is an ADC that combines the anti-CD30 chimeric monoclonal SGN-30 (cAC10) and the tubulin binding agent monomethyl auristatin E (MMAE, dolastatin 10 analog) through a protease cleavable dipeptide linker.[631–633] After binding to CD30 and internalization, MMAE is released in lysosomes, and free MMAE blocks tubulin polymerization and microtubule formation. MMAE released from its MoAb carrier may also diffuse out of CD30-positive cells and affect surrounding cells.[631]

CD30 is expressed on lymphoid malignancies, and brentuximab vedotin is active in Hodgkin lymphoma and ALCL in children and adults,[634–636] with response rates of 47% for relapsed for Hodgkin lymphoma and 53% for relapsed ALCL in the pediatric population.

Brentuximab vedotin has been administered to children and adolescents at a dose of 1.8 mg/kg intravenously every 3 weeks[636] as a single agent and in combination with gemcitabine.[637]

Brentuximab vedotin has a half-life of 4 to 6 days and a clearance of 1.3 mL/h•kg in children. Younger patients have higher clearance and lower exposures (AUCs) to the ADC

when the drug is dosed depending on body weight. Pharmacokinetic simulations indicate that dosing based on body surface area rather than on weight may increase the ADC exposures across the pediatric weight range.[636,638]

The common toxicities of brentuximab vedotin include neutropenia, sensory and motor peripheral neuropathy, fatigue, fever, anorexia, and nausea and vomiting.[632,636,639] Severe infusion-related reactions are uncommon, and 10% of patients have mild infusion-related reactions. Several cases of progressive multifocal leukoencephalopathy have been reported,[640] and interstitial pulmonary infiltrates were observed in 40% of patients receiving brentuximab vedotin in combination with bleomycin.[632,639,641]

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (IO) is a humanized anti-CD22 IgG4 MoAb (G544) conjugated with ozogamicin.[642] CD22 is expressed on most B-cell malignancies, including ALL, but not on hematopoietic stem cells or nonhematopoietic cells. Adults with relapsed ALL treated with IO had a higher response rate (81% vs. 29%) and better progression-free survival (5 months vs. 1.8 months) than those treated with standard intensive chemotherapy.[643] In children with relapsed, CD22-expressing ALL, treated with IO, there was a 67% complete remission rate. SOS was observed in 11% of adults treated with IO arm. In children, SOS was only seen in those who received HSCT after IO.[644] Other toxicities in children include myelosuppression, infections, hepatotoxicity, and infusion reactions.

IO is administered to children weekly for three doses at an initial dose of 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15.[644] For subsequent cycles, 0.5 mg/m^2 is administered weekly for 3 doses. IO pharmacokinetics in adults is affected by tumor burden. The half-life was 17 hours after the first dose and 35 hours after dose one of cycle two (day 29). Similarly, the clearance was 0.27 L/h on day 1 and 0.16 L/h on day 29.[645] The more rapid clearance and shorter half-life on day 1 reflects receptor-mediated elimination of the ADC by leukemic blasts.

Bispecific T-Cell Engagers

Bispecific T-cell engagers (BiTE) technology genetically links a single-chain antigen-binding domain (scFvs) from a MoAb that binds the T-cell antigen, CD3, to a single-chain antigen-binding domain from a MoAb that targets a surface antigen on tumor cells. These bispecific 55 kDa antibody constructs link T cells to tumor cells and induce T-cell activation and proliferation, resulting in tumor cell lysis in the absence of a tumor cell antigen-specific T-cell receptor.[646]

Blinatumomab

Blinatumomab is a BiTE that targets CD19 on B-cell malignancies including ALL. It induced remission in 39% of children and 69% of adults with relapsed or refractory ALL.[647,648] The drug is administered as a continuous infusion over 4 weeks with a 2-week break between cycles at a recommended infusion rate of 5 mcg/m^2/d over the first 7 days followed by 15

mcg/m^2/d for 3 weeks. Pretreatment with dexamethasone is used to prevent cytokine release syndrome. Blinatumomab is rapidly eliminated, necessitating its administration by prolonged continuous infusion. Pharmacokinetic parameters are similar in children and adults. The clearance is 25 mL/min/m^2, which is 100-fold more rapid than is MoAbs, and the half-life is 2 hours.[455] Neurotoxicity, which ranges from mild tremor to seizures or encephalopathy, and cytokine release syndrome are the most significant blinatumomab toxicities. Fever, fatigue, myelosuppression, and edema are commonly reported, less severe toxicities.

PERSPECTIVES

Although a high proportion of children with certain types of cancer are being cured, there are still too many who do not respond or who relapse and eventually succumb to their cancer after a good initial response. Failure of multimodality therapy to cure individual patients may result from *de novo* or acquired resistance to the anticancer drugs used in their treatment regimen, or inadequate drug delivery to the cancer. The latter pharmacologic limitations of therapy can result from interpatient variability in drug disposition with poor absorption or more rapid drug clearance in a subgroup of patients limiting drug exposure or dose modifications necessitated by acute and chronic toxicity.

Cytotoxic anticancer drug dosing is toxicity based. The optimum dose of most anticancer drugs is the MTD, and after this fixed dose is administered, dose modifications are based on the severity of ensuing toxicity. A more rational approach would be to individualize drug dose and schedule based on specific patient characteristics (adaptive dosing) and on plasma drug concentration (therapeutic drug monitoring). These strategies have been successfully applied to adapting carboplatin dose for renal function and to basing leucovorin rescue on MTX plasma concentration after HDMTX therapy. Although therapeutic and toxic drug concentrations are not known for most anticancer drugs, simply defining the average plasma concentration after a standard drug dose might help identify outliers and produce rational dose modifications for patients with organ dysfunction.

Those patients who are cured are at risk for significant and often life-threatening acute and long-term toxic effects of the treatment. The severity of the toxicity of the anticancer drugs reflects their nonselective mechanisms of action and the emphasis on dose intensity to maximize tumor cell kill. Methods to circumvent or ameliorate chemotherapy-induced toxicity have improved the tolerability of chemotherapy. Examples of rescuing patients from dose-limiting toxicities include the use of hematopoietic growth factors such as filgrastim or peg-filgrastim to limit the duration of granulocytopenia after myelosuppressive therapy, the administration of mesna to block the urotoxicity of the oxazaphosphorines, leucovorin rescue from HDMTX, and the prevention of anthracycline cardiotoxicity with dexrazoxane.

The search for more selective and less toxic anticancer drugs and for more effective drug combinations must continue. Advances in our understanding the biology of pediatric cancers may ultimately identify druggable targets unique to pediatric tumors. The efficacy of molecularly targeted agents for childhood cancers is dependent on the genomic and epigenomic characterization of the individual patient's tumor. Efforts are ongoing to identify ADCs and antibodies that modulate the immune system or cellular signaling pathways as

well as molecular targets in relapsed cancer in children and adolescents. Imatinib ushered in the current era of developing agents that target a specific molecular defect. The paradigm in which the underlying transforming event involves an enzyme (*BCR-ABL* kinase), or TRK fusion oncoproteins that can be directly inhibited by a small molecule, may not be readily translated into the majority of other pediatric tumors. Therefore, the role of an expanding number of agents that target cell signaling pathways that contribute to but are not causative of the malignant process is an important therapeutic challenge for pediatric cancer drug development. Greater resources and collaborative efforts will be required to meet these challenges and will require improved integration of advances in the biologic and pharmacologic basic sciences into the design and use of therapies to cure childhood cancer.

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