CHAPTER 3

Principles of chemotherapy

Ray Page, DO, PhD, and Chris Takimoto, MD, PhD

The effective use of cancer chemotherapy requires an understanding of the principles of tumor biology, cellular kinetics, pharmacology, and drug resistance. Thanks to the development of new, effective chemotherapeutic agents, coupled with our expanding knowledge about the administration and combination of these agents, we now are able to cure almost 20% of all new cases of cancer through chemotherapy alone.

This chapter focuses on the principles responsible for the development of modern combination chemotherapy regimens. This discussion is followed by descriptions of the major classes of chemotherapeutic drugs and their mechanisms of action.

Cellular kinetics

Cytokinetic studies have shown how the kinetics of cellular growth defines the characteristics of tumor growth and, in part, explains the biological behavior and heterogeneity of tumors.

Normal cell cycle

Inherent to cytokinetic principles is the concept of the cell cycle. Daughter cells formed as a result of mitosis consist of three subpopulations: (1) cells that are nondividing and terminally differentiated, (2) cells that are continually proliferating, and (3) cells that are resting but may be recruited into the cell cycle (ie, stem cells). All three populations exist simultaneously in tumors.

The cell cycle is composed of four phases during which the cell prepares for and effects mitosis. Cells that are committed to divide again enter the G_1 phase. Preliminary synthetic cellular processes occur that prepare the cell to enter the DNA synthetic (S) phase. Specific protein signals regulate the cell cycle and allow replication of the genome where the DNA content becomes tetraploid (4N). After completion of the S phase, the cell enters a second resting phase, G_2, prior to undergoing mitosis. The cell progresses to the mitotic (M) phase, in which the chromosomes condense and separate and the cell divides, producing two daughter cells.

Chemotherapeutic agents can be classified according to the phase of the cell cycle in which they are active (Table 1). Agents that are cell-cycle-phase–

TABLE 1: Cell-cycle-phase–specific drugs

S phase–dependent	M phase–dependent
Antimetabolites	Vinca alkaloids[a]
Capecitabine	Vinblastine
Cytarabine	Vincristine
Doxorubicin	Vinorelbine
Fludarabine	Podophyllotoxins
Floxuridine	Etoposide
Fluorouracil	Teniposide
Gemcitabine	Taxanes
Hydroxyurea	Docetaxel
Mercaptopurine	Paclitaxel
Methotrexate	**G_2 phase–dependent**
Prednisone	Bleomycin
Procarbazine	Irinotecan
Thioguanine	Mitoxantrone
	Topotecan
	G_1 phase–dependent
	Asparaginase
	Corticosteroids

[a] Have greatest effects in S phase and possibly late G_2 phase; cell blockade or death, however, occurs in early mitosis.

Adapted, with permission, from Dorr RT, Von Hoff DD (eds): The Cancer Chemotherapy Handbook, 2nd ed, p 5. East Norwalk, Connecticut, Appleton & Lange, 1993.

nonspecific (eg, alkylating agents) have a linear dose-response curve; that is, the greater the dose of drug, the greater is the fraction of cell kill. However, cell-cycle-phase–specific drugs have a plateau with respect to cell killing ability, and cell kill will not increase with further increases in drug dosage.

Tumor kinetics

The rate of growth of a tumor is a reflection of the proportion of actively dividing cells (the growth fraction), the length of the cell cycle (doubling time), and the rate of cell loss. Variations in these three factors are responsible for the variable rates of tumor growth observed among tumors of differing histologies, as well as among metastatic and primary tumors of the same histology.

Tumors characteristically exhibit a sigmoid-shaped Gompertzian growth curve, in which tumor doubling time varies with tumor size. Tumors grow most rapidly at small tumor volumes. As tumors become larger, growth slows based on a complex process dependent on cell loss and tumor blood and oxygen supply.

In order to have the best chance for cure, chemotherapy must achieve a fractional cell kill in a logarithmic fashion (ie, 1-log-kill is 90% of cells, 2-log-kill is 99% of cells). From these concepts, chemotherapy models have been developed utilizing alternating non–cross-resistant therapies, induction-intensification approaches, and adjuvant chemotherapy regimens.

Principles of combination chemotherapy

Using kinetic principles, a set of guidelines for designing modern combination chemotherapy regimens have been derived. Combination chemotherapy accomplishes three important objectives not possible with single-agent therapy: (1) It provides maximum cell kill within the range of toxicity tolerated by the host for each drug; (2) it offers a broader range of coverage of resistant cell lines in a heterogeneous tumor population; and (3) it prevents or slows the development of new drug-resistant cell lines.

Selection of drugs for combination regimens

The following principles have been established to guide drug selection in combination regimens:

- Drugs known to be active as single agents should be selected for combinations. Preferentially, drugs that induce complete remissions should be included.
- Drugs with different mechanisms of action should be combined in order to allow for additive or synergistic effects on the tumor.
- Drugs with differing dose-limiting toxicities should be combined to allow each drug to be given at full or nearly full therapeutic doses.
- Drugs should be used in their optimal dose and schedule.
- Drugs should be given at consistent intervals. The treatment-free interval between cycles should be the shortest possible time for recovery of the most sensitive normal tissue.
- Drugs with different patterns of resistance should be combined to minimize cross-resistance.

Terminology used in describing chemotherapy

Chemotherapy is administered with a variety of treatment schedules designed according to the intent and responsiveness of therapy. Definitions of chemotherapy are generally based on the purpose of achieving certain therapeutic goals as described in Table 2.

Definitions of response

Tumors can be classified according to their general sensitivity to chemotherapy. Response to chemotherapy is defined precisely as complete response, partial response, minimal response (stable disease), and progression. Complete response is defined as the disappearance of all evidence of disease and no ap-

TABLE 2: Terminology used in describing chemotherapy

Induction: High-dose, usually combination, chemotherapy given with the intent of inducing complete remission when initiating a curative regimen. The term is usuallly applied to hematologic malignancies but is equally applicable to solid tumors.

Consolidation: Repetition of the induction regimen in a patient who has achieved a complete remission after induction, with the intent of increasing cure rate or prolonging remission.

Intensification: Chemotherapy after complete remission with higher doses of the same agents used for induction or with different agents at high doses with the intent of increasing cure rate or remission duration.

Maintenance: Long-term, low-dose, single or combination chemotherapy in a patient who has achieved a complete remission, with the intent of delaying the regrowth of residual tumor cells.

Adjuvant: A short course of high-dose, usually combination chemotherapy in a patient with no evidence of residual cancer after surgery or radiotherapy, given with the intent of destroying a low number of residual tumor cells.

Neoadjuvant: Adjuvant chemotherapy given in the preoperative or perioperative period.

Palliative: Chemotherapy given to control symptoms or prolong life in a patient in whom cure is unlikely.

Salvage: A potentially curative, high-dose, usually combination, regimen given in a patient who has failed or recurred following a different curative regimen.

From: Yarbro J: The scientific basis of cancer chemotherapy, in Perry MC (ed): The Chemotherapy Sourcebook, p 12. Baltimore, MD, Lippincott, Williams and Wilkins, 1996.

pearance of new disease for a specified interval (usually 4 weeks). Partial response is defined as a reduction by at least 50% in the sum of the products of the two longest diameters of all lesions, maintained for at least one course of therapy, with no appearance of new disease. Minimal response is any response less than a partial response and is usually not reported in clinical trials. Progression is defined as growth of existing disease or appearance of new disease during chemotherapy.

The NCI (National Cancer Institute) has adopted standardized response criteria and is requiring their use by all cooperative groups. These criteria, called RECIST (Response Evaluation Criteria in Solid Tumors), were developed and recently revised by the World Health Organization (WHO). The goals are consistency of evaluation and comparison of regimens within a single trial and regimens of different trials. A comparison of RECIST and WHO guidelines is listed in Table 3.

Dose intensity

Kinetic principles predict that, for drug-sensitive cancers, the factor limiting the capacity to cure is proper dosing. Reduction in dose is associated with a decrease in cure rate before a significant reduction in the complete remission rate occurs. A dose reduction of approximately 20% can lead to a loss of up to

Tariquidar (XR9576) is an investigational intravenous drug that is a potent *p*-glycoprotein inhibitor that reverses MDR associated with common chemotherapy drugs. It can be safely and conveniently administered with full doses of paclitaxel, doxorubicin, and vinorelbine with no compromise of pharmacokinetics. Phase III studies in lung cancer are ongoing to evaluate the efficacy and response of tariquidar in combination therapy *(Boniface G, Ferry D, Atsmon J, et al: Proc Am Soc Clin Oncol [abstract] 21:90b, 2002).*

50% of the cure rate. Conversely, a twofold increase in dose can be associated with a 10-fold (1-log) increase in tumor cell kill in animal models.

Overcoming chemotherapy resistance

There are multiple reasons for chemotherapy failure in cancer patients, involving a variety of anatomic, pharmacologic, and biochemical mechanisms. Tumor sanctuary sites (brain, testes) and blood flow to the tumor represent anatomic barriers; pharmacologic and biochemical explanations include altered drug activation/inactivation in normal tissues, decreased drug accumulation, increased repair of drug-induced damage to the cell, altered drug targets, and altered gene expression.

Overexpression of the MDR_1 (multidrug resistance) gene is the most notable mediator of drug resistance and encodes a 170-kd transmembrane *p*-glycoprotein. *p*-Glycoprotein is an energy-dependent pump that serves to remove toxins or endogenous metabolites from the cell. A high level of MDR_1 expression is reliably correlated with resistance to cytotoxic agents. Tumors that intrinsically express the MDR_1 gene prior to chemotherapy characteristically display poor durable responses.

TABLE 3: Comparison of RECIST and WHO guidelines

Characteristic	RECIST	WHO
Objective response (LD is the longest diameter)	**Target lesions** (change in sum of LDs, maximum 5 per organ up to 10 total [more than one organ])	**Measurable disease** (change in the sum of the products of LDs and greatest perpendicular diameters, no maximum number of lesions specified)
Complete response (CR)	Disappearance of all target lesions, confirmed at ≥ 4 weeks	Disappearance of all known disease, confirmed at ≥ 4 weeks
Partial response (PR)	≥ 30% decrease from baseline, confirmed at ≥ 4 weeks	≥ 50% decrease from baseline, confirmed at ≥ 4 weeks
Progressive disease (PD)	≥ 20% increase over smallest sum observed or appearance of new lesions	≥ 25% increase in one or more lesions or appearance of new lesions
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met (no change)

RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

TABLE 4: Advantages of liposomal drug delivery

- Provides selective passive targeting to tumor sites
- Increases efficacy and therapeutic index
- Improves delivery of hydrophobic molecules
- Reduces the toxicities of the encapsulated agent
- Avoids accumulation in vital organs and tissues
- Improves pharmacokinetics (reduced elimination, increased drug exposure time)
- Increases stability via encapsulation
- Enhances intracellular drug delivery to overcome drug resistance

Chemotherapy agents subject to MDR_1- mediated resistance include the anthracyclines, vinca alkaloids, taxanes, and topoisomerase inhibitors. Targeted therapies that inhibit *p*-glycoprotein are under evaluation in combination with cytotoxic drugs subject to MDR (see sidebar on previous page).

Liposomal formulations of chemotherapeutic drugs are a promising new approach to overcoming these resistance mechanisms. Liposomes are well-defined lipid and lipoprotein vesicles that offer immense potential for targeting drugs to tumors. The advantages of these drug carriers over the conventional administration of chemotherapy agents are described in Table 4.

FDA-approved liposomal preparations of doxorubicin (Doxil), daunorubicin (DaunoXome), cytarabine (DepoCyt), and amphotericin B (Abelcet) have proven to be attractive, less toxic alternatives to the conventional drug formulations. Liposomal daunorubicin and amphotericin B have clearly shown less cardiac and renal damage, respectively. Daunorubicin liposomal is efficacious in induction regimens for acute leukemia; cytarabine liposomal appears to be superior to intrathecal cytarabine for treatment of CNS leukemia and lymphoma.

An additional advantage of the liposomal delivery system is the ability to encapsulate and stabilize very hydrophobic molecules such as paclitaxel (Taxol). Nanoparticle, albumin-stabilized paclitaxel has allowed much higher doses of drug to be given with far fewer side effects than paclitaxel which contains the toxic carrier material cremophor. Currently, a phase III randomized study comparing the efficacy of nanoparticle paclitaxel with conventional paclitaxel in metastatic breast cancer is under way.

Several liposomal formulations of conventional anticancer drugs are currently in phase I/II evaluation, including liposomal vincristine, platinum, mitoxantrone, all-*trans* retinoic acid (ATRA), and lurtotecan. There is a strong probability that these drug carriers will allow better administration of poorly soluble cancer drugs, enhance drug delivery and uptake in the tumor, and boost dose intensity, subsequently improving antitumor response, overcoming drug resistance, and decreasing chemotherapy toxicities.

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TABLE 5: Alkylating agents and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Nitrogen mustards		
Chlorambucil *CLL, HD, NHL,* ovarian cancer, choriocarcinoma, lymphosarcoma	0.1-0.2 mg/kg PO daily for 3-6 wk as required (usually 4-10 mg/d) or intermittent 0.4 mg/kg every 3-4 wk; increase by 0.1 mg/kg until control of disease or toxicity	*Bone marrow depression,* gonadal dysfunction, leukemia, hyperuricemia, pulmonary fibrosis
Cyclophosphamide *AML, ALL, CLL, HD, and NHL, multiple myeloma, mycosis fungoides, neuroblastoma, ovarian and breast cancers, retinoblastoma,* lung, testicular, and bladder cancers, sarcoma	40-50 mg/kg IV in divided doses over 2-5 d to start, followed by 10-15 mg/kg IV every 7-10 d; or 3-5 mg/kg IV twice weekly; or 1-5 mg/kg/d PO	*Bone marrow depression,* hemorrhagic cystitis, immunosuppression, alopecia, stomatitis, SIADH
Estramustine *Prostate, renal cell carcinoma*	14 mg/kg/d PO in 3-4 equally divided doses; 300 mg/d IV for 3-4 wk, followed by 300-450 mg/wk IV over 3-8 wk	*Bone marrow depression,* ischemic heart disease, thromboembolism, thrombophlebitis gynecomastia, nausea and vomiting, hepatotoxicity
Ifosfamide *Germ-cell testicular cancer,* sarcoma, NHL, lung cancer	1.2 g/m^2/d via slow IV infusion for 5 consecutive days; repeat every 3 wk; give with mesna	*Bone marrow depression, hemorrhagic cystitis,* confusion, somnolence
Mechlorethamine *HD, NHL, CML, CLL, mycosis fungoides, bronchogenic carcinoma,* lymphosarcoma, polycythemia vera, malignant effusions (intracavitary)	0.4 mg/kg ideal body weight given as single dose or in divided doses of 0.1-0.2 mg/kg/d	*Bone marrow depression, nausea and vomiting,* local phlebitis, severe skin necrosis if extravasated, gonadal dysfunction
Melphalan *Multiple myeloma, breast and ovarian cancers, sarcoma,* testicular and lung cancers	Continuous therapy: 6 mg PO daily for 2-3 wk, no therapy for 2-4 wk, then maintenance with 2-4 mg PO daily Pulse: 10 mg/m^2 PO daily for 4 d every 4-6 wk	*Bone marrow depression,* anorexia, nausea and vomiting, gonadal testicular dysfunction, leukemia

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

continued on following page

TABLE 5: Alkylating agents and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Aziridine		
Thiotepa *Ovarian, breast, and superficial bladder cancers,* HD, CML, CLL, bronchogenic carcinoma, malignant effusions (intracavitary), BMT for refractory leukemia, lymphomas	IV: 0.3-0.4 mg/kg by rapid IV infusion Intravesical: 60 mg/60 mL sterile water instilled and retained in bladder for 2 h; repeat weekly for 4 wk Intracavitary: 0.6-0.8 mg/kg	*Bone marrow depression,* nausea and vomiting, mucositis, skin rashes
Alkyl sulfonate		
Busulfan *CML,* BMT for refractory leukemia, lymphomas	2-8 mg PO daily for remission induction; adjust dosage to WBC count; 1-3 mg PO daily for maintenance; withhold induction if WBC count < 15,000/μL; resume therapy when WBC count > 50,000/μL	*Bone marrow depression, pulmonary fibrosis,* aplastic anemia, amenorrhea, gynecomastia, skin hyperpigmentation
Nitrosoureas		
Carmustine *Brain tumor, multiple myeloma, HD, NHL,* melanoma, BMT for refractory solid tumors and lymphomas	150-200 mg/m^2 IV every 6-8 wk	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, local phlebitis, pulmonary and renal damage (high dose)
Gliadel wafers *Glioblastoma multiforme*	Up to 8 wafers placed in the brain cavity created by tumor removal	Fever, pain, and abnormal healing
Lomustine *Brain tumors, HD,* GI carcinomas, NSCLC	130 mg/m^2 PO every 6 wk; adjust dose in combination chemotherapy	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, pulmonary and renal damage, neurologic reactions, leukemia
Streptozocin *Pancreatic islet-cell,* carcinoid, colon, hepatoma, NSCLC, HD	Daily: 500 mg/m^2 IV for 5 d every 6 wk until maximum benefit or toxicity Weekly: 1,000 mg/m^2 IV weekly for first 2 wk, then escalate dose to response or toxicity, not to exceed a single dose of 1,500 mg/m^2	*Renal damage,* nausea and vomiting, diarrhea, altered glucose metabolism, liver dysfunction

Drug and its uses[a]	Dosages	Toxicities[b]
Platinum complexes		
Carboplatin *Ovarian cancer,* endometrial, head and neck, lung, testicular, and breast cancers, relapsed acute leukemia, NHL	Single agent: 360 mg/m^2 IV every 4 wk Combination: 300 mg/m^2 IV every 4 wk Calvert formula: Total dose (mg) = Target AUC × (GFR + 25)	*Bone marrow depression,* nausea and vomiting, peripheral neuropathy, ototoxicity
Cisplatin *Testicular, ovarian, bladder,* uterine, cervical, and lung cancers, squamous cell cancer of the head and neck, sarcoma, NHL	50 mg/m^2 IV or more every 3 wk; or 20 mg/m^2 IV daily for 4-5 d every 3-4 wk; give vigorous hydration before and after chemotherapy	*Renal damage,* nausea and vomiting, electrolyte disturbance, peripheral neuropathy, bone marrow depression, ototoxicity, radiosensitizer
Oxaliplatin Colorectal (second-line)	85 mg/m^2 IV over 120 min on d 1 followed by infusional 5-FU and leucovorin on d 1-2, every 2 wk	*Bone marrow depression, diarrhea,* nausea and vomiting, neuropathies exacerbated by cold exposure, pharyngolaryngeal dysesthesia
Nonclassic alkylators		
Altretamine *Ovarian,* lung, breast, and cervical cancers, NHL	4-12 mg/kg/d or 260 mg/m^2, PO divided in 3-4 doses for 14-21 d of a 28-d regimen	*Nausea and vomiting,* bone marrow depression, paresthesias, CNS toxicity
Dacarbazine *Malignant melanoma, HD,* soft-tissue sarcomas, neuroblastoma	Melanoma: 2.0-4.5 mg/kg/d IV for 10 d every 4 wk; or 250 mg/m^2/d IV for 5 d every 3 wk HD: 375 mg/m^2 IV on d 1, repeated every 15 d (single agent); 150 mg/m^2/d IV for 5 d every 4 wk (combination therapy)	*Bone marrow depression,* nausea and vomiting, flulike syndrome, transient hepatotoxicity, local irritation, facial flushing, alopecia
Procarbazine *HD,* NHL, brain tumors, lung cancer	Single agent: 4-6 mg/kg/d PO until maximum response HD (MOPP): 100 mg/m^2/d PO for 14 d	*Bone marrow depression,* nausea and vomiting, lethargy, depression, paresthesias, headache, flulike symptoms
Temozolomide *Anaplastic astrocytoma (relapsed),* renal cell cancer, melanoma	150 mg/m^2/d PO for 5 d every 28 d	*Bone marrow depression,* nausea and vomiting

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; AUC = area under the curve; BMT = bone marrow transplantation; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CMML = chronic myelomacrocytic leukemia; 5-FU = fluorouracil; GFR = glomerular filtration rate; HD = Hodgkin's disease; MDS = myelodysplastic syndromes; MOPP = mechlorethamine, Oncovin, procarbazine, and prednisone; NHL = non-Hodgkin's lymphoma; NSCLC = non–small-cell lung cancer; SIADH = syndrome of inappropriate antidiuretic hormone secretion; WBC = white blood cell

TABLE 6: Antimetabolites and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Folate analog		
Methotrexate *Breast, head and neck, GI, and lung cancers, ALL, CNS leukemia (intrathecal), gestational trophoblastic tumors, NHL (advanced stage),* Burkitt's lymphoma, osteosarcoma, mycosis fungoides	Numerous dosing schedules with combination therapy: Low dose: 2.5-5.0 mg PO daily; or 5-25 mg/m^2 PO, IM, IV twice weekly; or 50 mg/m^2 IV every 2-3 wk High dose: 1-12 g/m^2 IV with leucovorin rescue every 1-3 wk Intrathecal: 5-10 mg/m^2 (up to 15 mg) every 3-7 d	*Mucositis, GI ulceration (may produce hemorrhage or perforation), bone marrow depression, pulmonary fibrosis (previously irradiated area),* nerve root irritation and convulsion (intrathecal), liver cirrhosis and osteoporosis (chronic therapy), renal damage (high dose), diarrhea, skin erythema
Purine analogs		
Fludarabine *CLL,* AML, NHL (low-grade)	25 mg/m^2/d IV over 30 min for 5 d; repeat every 28 d	*Bone marrow depression,* nausea and vomiting, fever, malaise, pulmonary infiltrates, tumor lysis syndrome, CNS effects (high dose)
Mercaptopurine *ALL, CML, AML*	1.5-2.5 mg/kg/d PO (100-200 mg in average adult) until response or toxic effects are seen; may increase dose to 5 mg/kg/d; adjust for maintenance dose; reduce dose by 50%-75% if given with allopurinol or if renal or hepatic insufficiency ensues	*Bone marrow depression,* nausea and vomiting, anorexia, diarrhea, cholestasis
Thioguanine *AML,* ALL, CML, advanced colorectal cancer, multiple myeloma	2 mg/kg/d PO until response or toxic effects are seen; may cautiously increase to 3 mg/kg/d	*Bone marrow depression,* liver damage, stomatitis
Adenosine analogs		
Cladribine *Hairy-cell leukemia,* NHL, mycosis fungoides, AML, CML, CLL	0.09 mg/kg/d (4 mg/m^2/d) by continuous IV infusion for 7 consecutive days	*Bone marrow depression,* febrile episodes, rash, infections, septicemia
Pentostatin *Hairy-cell leukemia,* ALL, CLL, lymphoblastic lymphoma, mycosis fungoides	4 mg/m^2 IV over 30 min every other week or for 3 consecutive weeks; give vigorous hydration before and after chemotherapy	*Nephrotoxicity, CNS depression,* bone marrow depression, nausea and vomiting, conjunctivitis

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Pyrimidine analogs		
Capecitabine *Breast cancer (relapsed), colorectal cancer, and other GI malignancies*	1,250 mg/m^2 bid PO with food (2 weeks on drug, 1 week of rest)	*Diarrhea*, stomatitis, nausea and vomiting, fatigue, hand-foot syndrome, bone marrow depression (minimal)
Cytarabine *AML,* ALL, CML, NHL, CNS leukemia (intrathecal)	AML induction: 100 mg/m^2/d by continuous IV infusion on days 1-7; or 100 mg/m^2 IV every 12 h on days 1-7 Relapsed ALL: 3 g/m^2 IV over 1-3 h every 12 h for 4 doses	*Bone marrow depression,* nausea and vomiting, diarrhea, arachnoiditis (intrathecal), stomatitis, hepatic dysfunction, fever, conjunctivitis, confusion, somnolence, cerebellar toxicity
DepoCyt (liposomal cytarabine) *CNS leukemia/lymphoma*	Intrathecal: DepoCyt, 50 mg over 1-5 min every 14 d, with dexamethasone, 4 mg PO bid × 5 d	
Floxuridine *GI adenocarcinomas metastatic to liver,* including oral, pancreatic, biliary, colon, and hepatic cancers, and metastatic breast cancer	0.1-0.6 mg/kg/d over several days via continuous arterial infusion supplying well-defined tumor; treatments given over 1-6 wk	*Stomatitis and GI ulcers, bone marrow depression,* abdominal pain, nausea and vomiting, diarrhea, liver dysfunction (transient)
Fluorouracil *Colon, rectal, stomach, pancreas, breast,* head and neck, renal cell, prostate, and ovarian cancers, squamous cell carcinoma of esophagus, basal and squamous cell carcinoma of skin (topical), hepatic cancer (intra-arterial)	Numerous dosing schedules with combination therapy: Loading dose: 300-500 mg/m^2; or 12 mg/kg IV daily for 3-5 d, followed by weekly maintenance Maintenance: 10-15 mg/kg IV weekly, as toxicity permits Infusion: 20-25 mg/kg by continuous IV infusion over 24 h daily for 4-5 d, every 4 wk	*Stomatitis and GI ulcers (infusion) bone marrow depression (bolus), diarrhea,* nausea and vomiting, esophagitis, angina, cerebellar ataxia, radiosensitizer
Gemcitabine *Pancreatic cancer, lung,* ovarian, breast, and bladder cancers	1,000 mg/m^2 IV over 30 min, once weekly for up to 7 weeks (or until toxicity necessitates reducing or withholding a dose), followed by 1 week of rest Subsequent cycles: Infusions once weekly for 3 consecutive weeks out of every 4 weeks	*Bone marrow depression,* transient fever, flulike syndrome, skin rash, mild nausea and vomiting
Substituted urea		
Hydroxyurea *CML, acute leukemia (emergent treatment), head and neck cancer, ovarian cancer, melanoma,* essential thrombocytosis, polycythemia vera	Intermittent: 80 mg/kg PO every third day Continuous: 20-30 mg/kg PO daily	*Bone marrow depression,* mild nausea and vomiting, skin rashes, radiosensitizer

(See Table 5 for abbreviations)

TABLE 7: Natural products and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Antitumor antibiotics		
Bleomycin *Testicular cancer, HD, reticulum cell sarcoma, lymphosarcoma, squamous cell cancer of the head and neck, skin, cervix, vulva, and penis*	10-20 U/m^2 given IV, IM, or SC weekly or twice weekly; maximum total dose, 400 U; a 2-U test dose should be given because of a possible anaphylactoid reaction	*Pneumonitis and pulmonary fibrosis,* fever and allergic reactions, anaphylaxis, hyperpigmentation, Raynaud's phenomenon, alopecia
Dactinomycin *Testicular cancer, gestational trophoblastic tumors, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma*	0.010-0.015 mg/kg IV daily for 5 d every 3 wk (usual adult dose, 0.5 mg), or 2 mg/m^2 IV as a single dose every 3-4 wk	*Stomatitis, bone marrow depression,* anorexia, nausea and vomiting, diarrhea, alopecia, skin changes, anaphylactoid reaction
Daunorubicin *AML, ALL*	Remission induction: 30-45 mg/m^2/d IV for 3 d in combination therapy; total cumulative dose, 550 mg/m^2	*Bone marrow depression,* cardiotoxicity, alopecia, nausea and vomiting, diarrhea, stomatitis, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
DaunoXome (liposomal daunorubicin) *Kaposi's sarcoma*	Liposomal preparation: 40 mg/m^2 IV every 2 wk	
Doxorubicin *ALL, AML, breast, ovarian,* bladder cancers, HD, NHL, SCLC, gastric cancer, sarcoma, Wilms' tumor, neuroblastoma, thyroid cancer	60-90 mg/m^2 single IV injection every 21 d, 20-30 mg/m^2/d IV for 3 d every 3-4 wk, or 20 mg/m^2 IV weekly; total cumulative dose of 550 mg/m^2; reduce dose for liver dysfunction	*Bone marrow depression, cardiotoxicity, stomatitis (continuous infusion),* alopecia, nausea and vomiting, diarrhea, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
Doxil (liposomal doxorubicin) *Ovarian cancer (refractory to paclitaxel- and platinum-based regimens),* *Kaposi's sarcoma*	50 mg/m^2 IV every 4 wk 20 mg/m^2 IV every 3 wk	*Bone marrow depression,* hand-foot syndrome *Bone marrow depression,* hand-foot syndrome
Epirubicin *Breast cancer*	100 mg/m^2 IV on day 1, or 60 mg/m^2 IV on days 1 and 8 in combination therapy	*Bone marow depression, cardiotoxicity, stomatitis,* alopecia
Idarubicin *AML,* CML (blast phase), ALL	12 mg/m^2/d IV for 3 d every 3 wk in combination therapy	*Bone marrow depression,* nausea and vomiting, stomatitis, alopecia, cardiotoxicity

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Mitoxantrone *AML, prostate,* ALL, CML, breast and ovarian cancers	Remission induction: 12 mg/m^2/d IV for 3 days, in combination with Ara-C	*Bone marrow depression*, cardiotoxicity, alopecia, stomatitis, nausea and vomiting, blue urine and sclera
Mitomycin *Gastric, colorectal, pancreatic adenocarcinomas,* NSCLC, breast, uterine, cervical, and head and neck cancers	20 mg/m^2 IV every 6-8 wk as a single agent, or 5-10 mg/m^2 IV every 6 wk in combination therapy	*Bone marrow depression (cumulative),* nausea and vomiting, anorexia, alopecia, stomatitis, fever, pulmonary fibrosis
Valrubicin *Bladder*	800 mg IV once a week for 6 wk	*Local bladder symptoms*
Epipodophyllotoxins		
Etoposide *Testicular cancer (refractory), SCLC,* HD, NHL, AML, gestational trophoblastic tumors	Testicular: 50-100 mg/m^2/d IV for 5 d, or 100 mg/m^2/d IV on days 1, 3, and 5 Lung: 35-50 mg/m^2/d IV for 5 d, or 100 mg/m^2/d PO for 5 d For both indications, given with combination therapy and repeated every 3-4 wk	*Bone marrow depression,* nausea and vomiting, diarrhea, fever, hypotension with rapid infusion, alopecia, rash
Teniposide *Relapsed ALL in children,* SCLC	ALL: 100 mg/m^2 once or twice weekly, or 20-60 mg/m^2/d for 5 days in combination with Ara-C Lung: 80-90 mg/m^2/d for 5 days as a single agent	*Bone marrow depression,* nausea and vomiting, alopecia, hypotension with rapid infusion, increased liver enzymes
Microtubule agents		
Docetaxel *Breast cancer (relapsed), lung,* ovarian, pancreatic cancer, head and neck, esophagus, stomach, cervical, Kaposi's sarcoma, uterine, prostate, and bladder	60-100 mg/m^2 IV over 1 hour every 21 days; or up to 42 mg/m^2 IV every week	*Bone marrow depression,* fluid retention, hypersensitivity reaction, paresthesias, rash, alopecia, myalgias
Paclitaxel *Ovarian cancer (relapsed), NSCLC (in combination with cisplatin), Kaposi's sarcoma, breast cancer (relapsed),* head and neck, gastric, colon, esophagus, uterine, prostate, bladder cancers and melanomas	135-175 mg/m^2 by IV infusion (ranging from 3-96 h) every 3 wk; or 80 mg/m^2 IV every week	*Bone marrow depression* peripheral neuropathy, alopecia, mucositis, anaphylaxis, dyspnea, myalgias

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TABLE 7: Natural products and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Vinblastine *HD, NHL, gestational trophoblastic tumors, testicular and breast cancers, mycosis fungoides, Kaposi's sarcoma, histiocytosis X,* bladder and renal cancers, NSCLC, CML (blast crisis)	4-12 mg/m^2 IV as a single agent every 1-2 wk; titrate dose to myelosuppression; adjust for hepatic insufficiency	*Bone marrow depression,* nausea and vomiting, ileus, alopecia, stomatitis, myalgias, vesication
Vincristine *ALL, HD, NHL, rhabdomyosarcoma, neuroblastoma, Wilms' tumor,* multiple myeloma, sarcomas, breast cancer	0.4-1.4 mg/m^2 IV weekly; maximum total dose, 2 mg/wk; reduce dose for hepatic insufficiency	*Peripheral neuropathy,* ileus, abdominal pain, SIADH, bone marrow depression (mild)
Vinorelbine *NSCLC,* breast, ovarian, head and neck cancers, HD	30 mg/m^2 IV over 10 min; repeat weekly	*Peripheral neuropathy, bone marrow depression,* nausea and vomiting, hepatic dysfunction
Camptothecin analogs		
Irinotecan *Colorectal cancer,* lung, ovarian, and cervical cancers	125 mg/m^2 IV over 90 min once weekly for 4 wk; then 2 weeks rest; or 350 mg/m^2 every 21 days	*Bone marrow depression, diarrhea,* nausea and vomiting anorexia, weight loss
Topotecan *Ovarian cancer (relapsed), SCLC (relapsed),* MDS, CMML	1.5 mg/m^2 IV over 30 min for 5 consecutive days at 21-d intervals	*Bone marrow depression,* fever, flulike symptoms, nausea and vomiting
Enzyme		
Asparaginase *ALL,* CML, AML	6,000 IU/m^2 IM 3 times weekly for 9 doses, or 100 IU/kg/d IV for 10 continuous days, starting on day 22 of treatment; usually given with vincristine and prednisone	*Allergic reactions (fever, chills skin rash, anaphylaxis),* nausea and vomiting, anorexia, liver dysfunction, CNS depression, coagulopathy, hyperglycemia

(See Table 5 for abbreviations)

Chemotherapeutic agents classified by mechanism of action

Alkylating agents

The alkylating agents impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules. The most important sites of alkylation are DNA, RNA, and proteins. The electron-rich nitrogen at the 7 position of guanine in DNA is particularly susceptible to alkylation.

Alkylating agents depend on cell proliferation for activity but are not cell-cycle-phase–specific. A fixed percentage of cells are killed at a given dose. Tumor resistance probably occurs through efficient glutathione conjugation or by enhanced DNA repair mechanisms. Alkylating agents are classified according to their chemical structures and mechanisms of covalent bonding; this drug class includes the nitrogen mustards, nitrosoureas, and platinum complexes, among other agents (see Table 5).

Nitrogen mustards The nitrogen mustards, which include such drugs as mechlorethamine (Mustargen), cyclophosphamide, ifosfamide (Ifex), and chlorambucil (Leukeran), are powerful local vesicants; as such, they can cause problems ranging from local tissue necrosis, to pulmonary fibrosis, to hemorrhagic cystitis. The metabolites of these compounds are highly reactive in aqueous solution, in which an active alkylating moiety, the ethylene imonium ion, binds to DNA. The hematopoietic system is especially susceptible to these compounds.

Nitrosoureas The nitrosoureas are distinguished by their high lipid solubility and chemical instability. These agents rapidly and spontaneously decompose into two highly reactive intermediates: chloroethyl diazohydroxide and isocyanate. The lipophilic nature of the nitrosoureas enables free passage across membranes; therefore, they rapidly penetrate the blood-brain barrier, achieving effective CNS concentrations. As a consequence, these agents are used for a variety of brain tumors.

Platinum agents Cisplatin (Platinol) is an inorganic heavy metal complex that has activity typical of a cell-cycle-phase–nonspecific alkylating agent. The compound produces intrastrand and interstrand DNA cross-links and forms DNA adducts, thereby inhibiting the synthesis of DNA, RNA, and proteins. Carboplatin (Paraplatin) has the same active diamine platinum moiety as cisplatin, but it is bonded to an organic carboxylate group that allows increased water solubility and slower hydrolysis to the alkylating aqueous platinum complex, thus altering toxicity profiles. Oxaliplatin (Eloxatin) is distinguished from the other platinum compounds by a di-amino-cyclohexane ring bound to the platinum molecule, which interferes with resistance mechanisms to the drug.

Antimetabolites

Antimetabolites are structural analogs of the naturally occurring metabolites involved in DNA and RNA synthesis. As the constituents of these metabolic pathways have been elucidated, a large number of structurally similar drugs that alter the critical pathways of nucleotide synthesis have been developed.

Antimetabolites exert their cytotoxic activity either by competing with normal metabolites for the catalytic or regulatory site of a key enzyme or by substituting for a metabolite that is normally incorporated into DNA and RNA. Because of this mechanism of action, antimetabolites are most active when cells are in the S phase and have little effect on cells in the G_0 phase. Consequently, these drugs are most effective against tumors that have a high growth fraction.

Antimetabolites have a nonlinear dose-response curve, such that after a certain dose, no more cells are killed despite increasing doses (fluorouracil [5-FU] is an exception). The antimetabolites can be divided into folate analogs, purine analogs, adenosine analogs, pyrimidine analogs, and substituted ureas (see Table 6).

Natural products

A wide variety of compounds possessing antitumor activity have been isolated from natural substances, such as plants, fungi, and bacteria. Likewise, selected compounds have semisynthetic and synthetic designs based on the active chemical structure of the parent compounds, and they, too, have cytotoxic effects (see Table 7).

Antitumor antibiotics Bleomycin (Blenoxane) preferentially intercalates DNA at guanine-cytosine and guanine-thymine sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage.

Anthracyclines The anthracycline antibiotics are products of the fungus *Streptomyces percetus* var *caesius.* They are chemically similar, with a basic anthracycline structure containing a glycoside bound to an amino sugar, daunosamine. The anthracyclines have several modes of action. Most notable are intercalation between DNA base pairs and inhibition of DNA topoisomerases I and II. Oxygen free radical formation from reduced doxorubicin intermediates is thought to be a mechanism associated with cardiotoxicity.

Epipodophyllotoxins Etoposide is a semisynthetic epipodophyllotoxin extracted from the root of *Podophyllum peltatum* (mandrake). It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex; this process ultimately results in the inability to synthesize DNA, and the cell cycle is stopped in the G_1 phase.

Vinca alkaloids The vinca alkaloids are derived from the periwinkle plant *Vinca rosea.* Upon entering the cell, vinca alkaloids bind rapidly to the tubulin. The binding occurs in the S phase at a site different from that associated with paclitaxel and colchicine. Thus, polymerization of microtubules is blocked, resulting in impaired mitotic spindle formation in the M phase.

Taxanes Paclitaxel and docetaxel (Taxotere) are semisynthetic derivatives of extracted precursors from the needles of yew plants. These drugs have a novel

14-member ring, the taxane. Unlike the vinca alkaloids, which cause microtubular disassembly, the taxanes promote microtubular assembly and stability, therefore blocking the cell cycle in mitosis. Docetaxel is more potent than paclitaxel in enhancing microtubular assembly and also induces apoptosis.

Camptothecin analogs include irinotecan (CPT-11 [Camptosar]) and topotecan (Hycamtin). These semisynthetic analogs of the alkaloid camptothecin, derived from the Chinese ornamental tree *Camptotheca acuminata*, inhibit topoisomerase I and interrupt the elongation phase of DNA replication.

SUGGESTED READING

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