

## Cancer Chemotherapy

Cytotoxic drugs, hormones, antihormones, and biologic agents have become increasingly effective means of treating cancer. Many patients are treated on protocols to provide optimal therapy for refractory or poorly responsive malignancies. Treatment may be inadequate or ineffective because of drug resistance of the tumor cells. This has been attributed to spontaneous genetic mutations in subpopulations of cancer cells prior to exposure to chemotherapy. After chemotherapy has eliminated the sensitive cells, the resistant subpopulation grows to become the predominant cell type (Goldie-Coldman hypothesis). This has been the basis of alternating non-cross-resistant chemotherapy regimens.

Molecular mechanisms of drug resistance are now the subject of intense study. In many instances, specific drug resistance results from an amplification in the number of gene copies for an enzyme inhibited by a specific chemotherapeutic agent. A more general form of "multidrug resistance" (MDR) has been described in association with expression of a gene (MDR1) encoding a transmembrane glycoprotein of MW 170 (P-glycoprotein) on tumor cells. This protein is an energy-dependent transport pump that facilitates drug efflux from tumor cells and promotes resistance to a broad spectrum of unrelated cancer drugs. Acquired multidrug resistance in multiple myeloma and lymphoma has been reversed clinically by adding the calcium channel blocker verapamil to chemotherapy regimens. Unfortunately, the doses of verapamil required to overcome drug resistance are associated with cardiovascular side effects. High doses of cyclosporine appear to increase the cytotoxicity of etoposide both in vitro and in vivo, probably by inhibiting the function of P-glycoprotein. The use of cyclosporine to enhance the effect of etoposide in purging resistant tumor cells in vitro from autologous bone marrow is under investigation. Cyclosporine has also been shown to enhance the cytotoxic effect of multiagent chemotherapy against resistant multiple myeloma. Verapamil and cyclosporine increase the accumulation and cytotoxicity of daunorubicin in myeloid leukemia cells, enhancing cell kill. MDR modulators will need to be both less toxic and more potent to be clinically useful. An example is the cyclosporine analog PSC 833, with little of the immunosuppressive effects or renal toxicities of cyclosporine but with five- to tenfold greater MDR-modulating activity.

Chemotherapy is used to cure a small percentage of malignancies, as adjuvant therapy to decrease the rate of relapse or improve the disease-free interval, and to palliate symptoms in some patients with incurable malignancies. In addition, chemotherapy may play a role as preoperative or "neoadjuvant" therapy to reduce the size and extent of the primary tumor, thereby allowing complete excision at the time of surgery. Chemotherapy was first shown to be curative in the treatment of advanced stages of choriocarcinoma in women. It is also curative in Hodgkin's disease, diffuse large-cell and some high-grade lymphomas (including Burkitt's), carcinoma of the testis, some cases of acute leukemia, and embryonal rhabdomyosarcoma. When combined with initial surgery—and in some instances with irradiation—chemotherapy increases the cure rate in Wilms' tumor and increases the rate of long-term control and cure of breast cancer, colon cancer, rectal cancer, and osteogenic sarcomas. Combination chemotherapy provides palliation and prolongation of survival in adults with Hodgkin's disease, non-Hodgkin's lymphoma, mycosis fungoides, multiple myeloma and macroglobulinemia, acute and chronic leukemias, and breast, ovary, and small-cell lung carcinoma as well as carcinoid. Patients with incurable tumors who desire aggressive treatment should be referred for experimental protocol therapy. Tumor cell vaccines combined with immune adjuncts are under investigation as specific immunotherapy for chemotherapy-resistant tumors such as malignant melanoma.

High-dose chemotherapy followed by bone marrow transplantation is curative therapy for various types of leukemia, multiple myeloma, and high-risk lymphoma and testicular cancer. Allogeneic or autologous bone marrow or peripheral blood stem cells with or without ex vivo purging is used depending on the disease. The use of growth factors and blood stem cells has decreased the toxicity and cost of bone marrow transplantation. Autologous transplantation may now be used with low morbidity and mortality on selected patients up to age 70. In addition, dose-intense chemotherapy regimens with autologous bone marrow or peripheral blood progenitor cell rescue are currently being investigated in the high-risk adjuvant or early relapse setting for patients with carcinoma of the breast and ovaries. A small study suggests that intensive doses of chemotherapy followed by bone marrow or peripheral blood stem cell infusion in incurable diseases such as metastatic breast cancer may prolong survival. It is possible that this aggressive approach may be useful even when "cure" is not the objective.

While most anticancer drugs are used systemically, there are selected indications for local or regional administration. Regional administration involves direct infusion of active chemotherapeutic agents into the tumor site (eg, intravesical therapy, intraperitoneal therapy, hepatic artery infusion with or without embolization of the main blood supply of the tumor). These treatments can result in palliation and prolonged survival.

A summary of the types of cancer responsive to chemotherapy and the current treatments of choice is offered in Table 4–3. In some instances (eg, Hodgkin's disease), optimal therapy may require a combination of therapeutic resources, eg, radiation plus chemotherapy rather than either modality alone. Patients with stages I, II, and IIIA Hodgkin's disease are often treated with radiation alone, avoiding the potential toxicity of systemic chemotherapy. A small percentage of these patients may require chemotherapy later for disease recurrence.

Table 4–3. Treatment choices for cancers responsive to systemic agents.

Diagnosis	Current Treatment of Choice	Other Valuable Agents and Procedures
Acute lymphocytic leukemia	Induction: Combination chemotherapy. Adults: Vincristine, prednisone, daunorubicin, and asparaginase. Children: Vincristine, prednisone with or without asparaginase. Consolidation: Multiagent alternating chemotherapy. Allogeneic bone marrow transplant for young adults or high-risk disease or second remission. CNS prophylaxis with intrathecal methotrexate with or without whole brain radiation. Remission maintenance: Methotrexate, thioguanine.	Doxorubicin, cytarabine, cyclophosphamide, etoposide, teniposide (VM-26), <sup>1</sup> allopurinol, <sup>2</sup> autologous bone marrow transplantation
Acute myelocytic and myelomonocytic leukemia	Induction: Combination chemotherapy with cytarabine and an anthracycline (daunorubicin, idarubicin). Tretinoin for acute promyelocytic leukemia. Consolidation: High-dose cytarabine. Autologous (with or without purging) or allogeneic bone marrow transplantation for high-risk disease or second remission.	Mitoxantrone, idarubicin, etoposide, mercaptopurine, thioguanine, azacitidine, <sup>1</sup> amsacrine, <sup>1</sup> methotrexate, doxorubicin, tretinoin, allopurinol, <sup>2</sup> leukapheresis, prednisone
Chronic myelocytic leukemia	Hydroxyurea, alpha interferon. Allogeneic bone marrow transplantation for young patients.	Busulfan, mercaptopurine, thioguanine, cytarabine, plicamycin, melphalan, autologous bone marrow transplantation, allopurinol <sup>2</sup>
Chronic lymphocytic leukemia	Chlorambucil and prednisone or fludarabine (if treatment is indicated).	Vincristine, cyclophosphamide, doxorubicin, Cladribine (2-chlorodeoxyadenosine; CdA), androgens, <sup>2</sup> allopurinol <sup>2</sup>
Hairy cell leukemia	Cladribine (2-chlorodeoxyadenosine; CdA).	Pentostatin (deoxycoformycin), alpha interferon
Hodgkin's disease (stages III and IV)	Combination chemotherapy: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) or mechlorethamine, vincristine, prednisone, procarbazine (MOPP) or alternating MOPP/ABVD or MOPP/ABV, autologous bone marrow transplant for high-risk patients or relapsed disease.	Carmustine, lomustine, etoposide, thiotepa, autologous bone marrow transplantation
Non-Hodgkin's lymphoma	Combination therapy depending on histologic classification but usually including cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) with or without other agents. Autologous bone marrow transplantation in high-risk first remission or first relapse.	Bleomycin, methotrexate, etoposide, chlorambucil, fludarabine, lomustine, carmustine, cytarabine, thiotepa, amsacrine, mitoxantrone, autologous or allogeneic bone marrow transplantation
Multiple myeloma	Combination chemotherapy: melphalan and prednisone or melphalan, cyclophosphamide, carmustine, vincristine, doxorubicin, and prednisone. Autologous bone marrow transplantation in first complete or partial remission. Allogeneic bone marrow transplantation for young patients with poor prognosis disease.	Etoposide, cytarabine, alpha interferon, dexamethasone, autologous bone marrow transplantation
Waldenström's macroglobulinemia	Chlorambucil versus combination chemotherapy: cyclophosphamide, vincristine, prednisone. Allogeneic bone marrow transplantation for high-risk young patients.	Etoposide, alpha interferon, doxorubicin, dexamethasone, plasmapheresis, autologous bone marrow transplantation
Polycythemia vera	Hydroxyurea, phlebotomy	Busulfan, chlorambucil, cyclophosphamide, alpha interferon, radiophosphorus <sup>32</sup> P
Carcinoma of lung Small cell Non-small cell <sup>3</sup>	Combination chemotherapy: cisplatin and etoposide. Palliative radiation therapy. Advanced disease: cisplatin, vinorelbine Localized disease: cisplatin, vinblastine	Cyclophosphamide, doxorubicin, vincristine  Doxorubicin, etoposide, mitomycin
Carcinoma of the head and neck <sup>3</sup>	Combination chemotherapy: cisplatin and fluorouracil	Methotrexate, bleomycin, hydroxyurea, doxorubicin, vinblastine
Carcinoma of the esophagus <sup>3</sup>	Combination chemotherapy: fluorouracil, cisplatin, mitomycin	Methotrexate, bleomycin, doxorubicin, mitomycin
Carcinoma of the stomach and pancreas <sup>3</sup>	Stomach: etoposide, leucovorin, <sup>2</sup> fluorouracil (ELF) Pancreas: fluorouracil or ELF, gemcitabine	Carmustine, mitomycin, lomustine, doxorubicin, gemcytidine. Doxorubicin, methotrexate, cisplatin, combinations for stomach
Carcinoma of the colon and rectum <sup>3</sup>	Colon: fluorouracil plus levamisole (adjuvant) or with leucovorin. <sup>2</sup> Rectum: fluorouracil with radiation therapy (adjuvant)	Methotrexate, mitomycin, carmustine, cisplatin, floxuridine
Carcinoma of the kidney <sup>3</sup>	Floxuridine, vinblastine, IL-2, alpha interferon	Alpha interferon, progestins, infusional FUDR, fluorouracil
Carcinoma of the bladder <sup>3</sup>	Intravesical BCG or thiotepa. Combination chemotherapy: methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin (M-VAC) or CMV alone	Cyclophosphamide, fluorouracil
Carcinoma of the testis <sup>3</sup>	Combination chemotherapy: etoposide and cisplatin Autologous bone marrow transplantation for high-risk or relapsed disease.	Bleomycin, vinblastine, ifosfamide, mesna, <sup>2</sup> carmustine, carboplatin
Carcinoma of the prostate <sup>3</sup>	Estrogens or LHRH analog (leuprolide) plus an antiandrogen (flutamide)	Ketoconazole, doxorubicin, aminoglutethimide, progestins, cyclophosphamide, cisplatin, estramustine, vinblastine, etoposide, suramin <sup>1</sup>
Carcinoma of the uterus <sup>3</sup>	Progestins or tamoxifen	Doxorubicin, cisplatin, fluorouracil, ifosfamide
Carcinoma of the ovary <sup>3</sup>	Combination chemotherapy: cyclophosphamide and cisplatin (or carboplatin) or paclitaxel and cisplatin/ carboplatin	Docetaxel, topotecan
Carcinoma of the cervix <sup>3</sup>	Combination chemotherapy: methotrexate, doxorubicin, cisplatin, and vinblastine; or mitomycin, bleomycin, vincristine, and cisplatin	Carboplatin, ifosfamide, lomustine
Carcinoma of the breast <sup>3</sup>	Combination chemotherapy: cyclophosphamide, doxorubicin, fluorouracil, or cyclophosphamide, methotrexate, fluorouracil. Tamoxifen for estrogen/progesterone receptor-positive tumors. Adjuvant therapy for high-risk patients and for limited metastatic disease:	Mitoxantrone, vinblastine, paclitaxel, docetaxel, topotecan, thiotepa, vincristine, carboplatin, cisplatin/carboplatin, mitomycin, vinorelbine, progestins, androgens, aminoglutethimide

Choriocarcinoma (trophoblastic neoplasms) <sup>3</sup>	Dose intensification or autologous bone marrow transplantation. Methotrexate or dactinomycin (or both) plus chlorambucil	Vinblastine, cisplatin, mercaptopurine, doxorubicin, bleomycin, etoposide
Carcinoma of the thyroid gland <sup>3</sup>	Radioiodine (131I)	Doxorubicin, cisplatin, bleomycin, melphalan
Carcinoma of the adrenal gland <sup>3</sup>	Mitotane	Doxorubicin, suramin <sup>1</sup>
Carcinoid <sup>3</sup>	Fluorouracil plus streptozocin with or without alpha interferon	Doxorubicin, cyclophosphamide, octreotide, cyproheptadine, <sup>2</sup> methysergide <sup>2</sup>
Osteogenic sarcoma <sup>3</sup>	High-dose methotrexate, doxorubicin, vincristine	Cyclophosphamide, ifosfamide, bleomycin, dacarbazine, cisplatin, dactinomycin
Soft tissue sarcoma <sup>3</sup>	Doxorubicin, dacarbazine	Ifosfamide, cyclophosphamide, etoposide, cisplatin, high-dose methotrexate, vincristine
Melanoma <sup>3</sup>	Dacarbazine, alpha interferon, IL-2	Carmustine, lomustine, melphalan, thiotepa, cisplatin, paclitaxel, <sup>1</sup> tamoxifen, vincristine
Kaposi's sarcoma	Vincristine alternating with vinblastine or vincristine alone. Palliative radiation therapy.	Alpha interferon, bleomycin, etoposide
Wilms' tumor (in children) <sup>3</sup>	Combination chemotherapy: vincristine and dactinomycin with or without doxorubicin after surgery and radiation therapy	doxorubicin
Neuroblastoma <sup>3</sup>	Combination chemotherapy: variations of cyclophosphamide, cisplatin, vincristine, doxorubicin, dacarbazine	Cyclophosphamide, methotrexate, etoposide, cisplatin
		Melphalan, ifosfamide, autologous or allogeneic bone marrow transplantation

<sup>1</sup>Investigational agent. Treatment is available through qualified investigators and centers authorized by the National Cancer Institute and Cooperative Oncology Groups.

<sup>2</sup>Supportive agent; not oncolytic.

<sup>3</sup>These tumors are generally managed initially with surgery with or without radiation therapy with or without adjuvant chemotherapy. For metastatic disease, the role of palliative radiation therapy is as important as that of chemotherapy.

Table 4–4 sets forth the currently used dosage schedules and toxicities of the most commonly used cancer chemotherapeutic agents. The dosage schedules given are for single-agent therapy. Combination therapy is used for many diseases, including advanced-stage Hodgkin's disease, non-Hodgkin's lymphoma, and testicular carcinoma. Hematologic or other toxicity may limit the therapeutic effectiveness of chemotherapy. It is possible to avoid the need for dose reductions or delay in therapy by using granulocyte colony-stimulating factor (G-CSF; filgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim). Scroll right to see more columns.

**Table 4–4. Single agent dosage and toxicity of anticancer drugs.**

<u>Drug</u>	<u>Dosage</u>	<u>Acute Toxicity</u>	<u>Delayed Toxicity</u>
Alkylating agents Mechlorethamine	6–10 mg/m <sup>2</sup> IV every 3 weeks	Severe vesicant; severe nausea and vomiting	Moderate suppression of blood counts. Melphalan effect may be delayed 4–6 weeks. Excessive doses produce severe bone marrow suppression with leukopenia, thrombocytopenia, and bleeding.
Chlorambucil	0.1–0.2 mg/kg/d orally (6–12 mg/d) or 0.4 mg/kg pulse every 4 weeks	None	Alopecia and hemorrhagic cystitis occur with cyclophosphamide, while busulfan can cause hyperpigmentation, pulmonary fibrosis, and weakness (see text). Ifosfamide
Cyclophosphamide	100 mg/m <sup>2</sup> /d orally for 14 days; 400 mg/m <sup>2</sup> orally for 5 days; 1–1.5 g/m <sup>2</sup> IV every 3–4 weeks	Nausea and vomiting with higher doses	is always given with mesna to prevent cystitis. Acute leukemia may develop in 5–10% of patients receiving prolonged therapy with melphalan, mechlorethamine, or chlorambucil; all alkylators probably increase the risk of secondary malignancies with prolonged use. Most cause either temporary or permanent aspermia/amenorrhea.
Melphalan	0.25 mg/kg/d orally for 4 days every 6 weeks	None	
Busulfan	2–8 mg/d orally; 150–250 mg/course	None	
Carmustine (BCNU)	200 mg/m <sup>2</sup> IV every 6 weeks	Local irritant	Prolonged leukopenia and thrombocytopenia . Rarely hepatitis. Acute leukemia has been observed to occur in some patients
Lomustine (CCNU)	100–130 mg orally every 6–8 weeks	Nausea and vomiting	receiving nitrosoureas. Nitrosoureas can cause delayed pulmonary fibrosis with prolonged use.
Procarbazine	100 mg/m <sup>2</sup> /d orally for 14 days every 4 weeks	Nausea and vomiting	Bone marrow suppression, mental suppression, MAO inhibition, disulfiram-like effect
Dacarbazine	250 mg/m <sup>2</sup> /d IV for 5 days every 3 weeks; 1500 mg/m <sup>2</sup> IV as single dose	Severe nausea and vomiting; anorexia	Bone marrow suppression; flu-like syndrome

Cisplatin	50–100 mg/m <sup>2</sup> IV every 3 weeks; 20 mg/m <sup>2</sup> IV for 5 days every 4 weeks	Severe nausea and vomiting	Nephrotoxicity, mild otic and bone marrow toxicity, neurotoxicity.
Carboplatin	360 mg/m <sup>2</sup> IV every 4 weeks	Severe nausea and vomiting	Bone marrow suppression, prolonged anemia; same as cisplatin but milder.
Structural analogs or antimetabolites			
Methotrexate	2.5–5 mg/d orally; 20–25 mg IM twice weekly; high-dose: 500–1000 mg/m <sup>2</sup> IV every 2–3 weeks; 12–15 mg intrathecally every week for 4–6 doses	None	Bone marrow suppression, oral and gastrointestinal ulceration, acute renal failure; hepatotoxicity, rash, increased toxicity when effusions are present. Note: Citrovorum factor (leucovorin) rescue for doses over 100 mg/m <sup>2</sup> .
Mercaptopurine	2.5 mg/kg/d orally; 100 mg/m <sup>2</sup> /d orally for 5 days for induction	None	Well tolerated. Larger doses cause bone marrow suppression
Thioguanine	2 mg/kg/d orally; 100 mg/m <sup>2</sup> /d IV for 7 days for induction	Mild nausea, diarrhea	Well tolerated. Larger doses cause bone marrow suppression
Fluorouracil	15 mg/kg/d IV for 3–5 days every 3 weeks; 15 mg/kg weekly as tolerated; 500–1000 mg/m <sup>2</sup> IV every 4 weeks	None	Nausea, diarrhea, oral and gastrointestinal ulceration, bone marrow suppression, dacryocystitis.
Cytarabine	100–200 mg/m <sup>2</sup> /d for 5–10 days by continuous IV infusion; 2–3 g/m <sup>2</sup> IV every 12 hours for 3–7 days; 20 mg/m <sup>2</sup> SC daily in divided doses	High-dose: nausea, vomiting, diarrhea, anorexia	Nausea and vomiting; cystitis; severe bone marrow suppression; megaloblastosis; CNS toxicity with high-dose cytarabine.
Hormonal agents			
Testosterone propionate	100 mg IM 3 times weekly	None	Fluid retention, masculinization, leg cramps. Cholestatic jaundice in some patients receiving fluoxymesterone.
Fluoxymesterone	20–40 mg/d orally	None	Gynecomastia, hot flushes, decreased libido, mild gastrointestinal side effects.
Flutamide	250 mg 3 times a day orally	None	Fluid retention, feminization, uterine bleeding, exacerbation of cardiovascular disease, painful gynecomastia, thromboembolic disease.
Diethylstilbestrol	1–5 mg/d orally in divided doses	Occasional nausea and vomiting	?Increased risk of venous thrombosis; anovulation
Ethinyl estradiol	3 mg/d orally	None	
Tamoxifen	20 mg/d orally in 2 divided doses	Transient flare of bone pain	
Megestrol acetate	40 mg orally 4 times daily	None	
Anastrozole	1 mg orally daily	None	
Hydroxyprogesterone caproate	1 g IM twice weekly	None	Occasional fluid retention; rare thrombosis, weight gain.
Medroxyprogesterone	100–200 mg/d orally; 200–600 mg orally twice weekly	None	
Adrenocorticosteroid			
Prednisone	20–100 mg/d orally or 50–100 mg every other day orally with systemic chemotherapy	Alteration in mood	Fluid retention, hypertension, diabetes, increased susceptibility to infection, "moon facies," osteoporosis, electrolyte abnormalities, gastritis.
Aromatase inhibitor			
Aminoglutethimide	500 mg/d orally, along with hydrocortisone, 40 mg/d orally	Initial drowsiness	Transient skin rash, which usually subsides with continued therapy; weight gain, fluid retention, leg cramps; cholestatic jaundice.
GnRH analogs			
Leuprolide	7.5 mg IM (depot) once a month; 1 mg/d SC	Local irritation, transient flare of symptoms	Hot flushes, decreased libido, impotence, gynecomastia, mild gastrointestinal side effects
Goserelin acetate	3.6 mg SC monthly	Transient flare of symptoms	.
Biologic response modifiers			
Interferon alfa-2a	3–5 million units	Fever, chills, fatigue, anorexia	General malaise, weight loss, confusion
Interferon alfa-2b	SC 3 times weekly or daily		
Aldesleukin (IL-2)	600,000 IU/kg IV over 15 minutes every 8 hours for 14 doses, repeated after 9-day rest period. Some doses may be withheld or interrupted because of toxicity. Caution: High doses must be administered in an ICU setting by experienced	Hypotension, fever, chills, rigors, diarrhea, nausea, vomiting, pruritus, liver, kidney, and CNS toxicity, capillary leak (primarily at high doses), pruritic skin rash, infections (can be severe)	Hypoglycemia, anemia

Peptide hormone inhibitor Octreotide acetate	personnel. 100–600 mg/d SC in 2 divided doses	Local irritant; nausea and vomiting	Diarrhea, abdominal pain, hypoglycemia.
Natural products and miscellaneous agents			
Vinblastine	0.1–0.2 mg/kg or 6 mg/m <sup>2</sup> IV weekly	Mild nausea and vomiting; severe vesicant	Alopecia, peripheral neuropathy, bone marrow suppression, constipation, SIADH, areflexia.
Vincristine	1.5 mg/m <sup>2</sup> (maximum: 2 mg weekly)	Severe vesicant	Areflexia, muscle weakness, peripheral neuropathy, paralytic ileus, alopecia (see text), SIADH.
Vinorelbine	30 mg/m <sup>2</sup> IV weekly	Mild nausea and vomiting, fatigue, severe vesicant	Granulocytopenia, constipation, peripheral neuropathy, alopecia
Paclitaxel	135 mg/m <sup>2</sup> by continuous infusion over 24 hours every 3 weeks	Hypersensitivity reaction (premedicate with diphenhydramine and dexamethasone), mild nausea and vomiting	Peripheral neuropathy, bone marrow suppression, fluid retention.
Docetaxel	60–100 mg/m <sup>2</sup> IV every 3 weeks		
Dactinomycin	0.04 mg/kg IV weekly	Nausea and vomiting; severe vesicant	Alopecia, stomatitis, diarrhea, bone marrow suppression.
Daunorubicin	30–60 mg/m <sup>2</sup> daily IV for 3 days, or 30–60 mg/m <sup>2</sup> IV weekly	Nausea, fever, red urine (not hematuria); severe vesicant; acute cardiotoxicity	Alopecia, stomatitis, bone marrow suppression, late cardiotoxicity. Risk of cardiotoxicity increases with radiation, cyclophosphamide.
Idarubicin	12 mg/m <sup>2</sup> daily IV for 3 days		
Doxorubicin	60 mg/m <sup>2</sup> IV every 3 weeks to a maximum total dose of 550 mg/m <sup>2</sup>		
Liposomal Doxorubicin	20 mg/m <sup>2</sup> IV every 3 weeks		
Daunorubicin	40 mg/m <sup>2</sup> IV every 2 weeks		
Etoposide	100 mg/m <sup>2</sup> /d IV for 5 days or 50–150 mg/d orally	Nausea and vomiting; occasionally hypotension	Alopecia, bone marrow suppression.
Plicamycin (mithramycin)	25–50 mg/kg IV every other day for up to 8 doses	Nausea and vomiting	Thrombocytopenia, diarrhea, hepatotoxicity, nephrotoxicity, stomatitis.
Mitomycin	10–20 mg/m <sup>2</sup> every 6–8 weeks	Severe vesicant; nausea	Prolonged bone marrow suppression, rare hemolytic-uremic syndrome.
Mitoxantrone	12–15 mg/m <sup>2</sup> /d IV for 3 days with cytarabine; 8–12 mg/m <sup>2</sup> IV every 3 weeks	Mild nausea and vomiting	Alopecia, mild mucositis, bone marrow suppression.
Bleomycin	Up to 15 units/m <sup>2</sup> IM, IV, or SC twice weekly to a total dose of 200 units/m <sup>2</sup>	Allergic reactions, fever, hypotension	Fever, dermatitis, pulmonary fibrosis.
Hydroxyurea	500–1500 mg/d orally	Mild nausea and vomiting	Hyperpigmentation, bone marrow suppression.
Mitotane	6–12 g/d orally	Nausea and vomiting	Dermatitis, diarrhea, mental suppression, muscle tremors.
Fludarabine	25 mg/m <sup>2</sup> /d IV for 5 days every 4 weeks	Nausea and vomiting	Bone marrow suppression, diarrhea, mild hepatotoxicity, immune suppression.
Cladribine (CdA)	0.09 mg/kg/d by continuous IV infusion for 7 days	Mild nausea, rash, fatigue	Bone marrow suppression, fever, immune suppression.
Topotecan	1.5 mg/kg IV daily for 5 days every 3 weeks	Nausea, vomiting, diarrhea, headache, dyspnea	Alopecia, bone marrow suppression.
Tretinoin	45 g/m <sup>2</sup> by mouth until remission or for 90 days	Retinoic acid syndrome (fever, dyspnea, pleural or pericardial effusion) must be treated emergently with dexamethasone; headache, dry skin rash, flushing.	
Gemcitabine	1000 mg/m <sup>2</sup> every week up to 7 weeks, then 1 week off, then weekly for 3 out of 4 weeks	Nausea, vomiting, diarrhea, fever, dyspnea	Bone marrow suppression, rash, fluid retention, mouth sores, flu-like symptoms, paresthesias.
Supportive agents			
Allopurinol	300–900 mg/d orally for prevention or relief of hyperuricemia	None	Rash, Stevens-Johnson syndrome; enhances effects and toxicity of mercaptopurine when used in combination.
Mesna	20% of ifosfamide dosage at the time of ifosfamide administration, then 4 and 8 hours after each dose of chemotherapy to prevent hemorrhagic	Nausea, vomiting, diarrhea	None

Leucovorin	cystitis 10 mg/m <sup>2</sup> every 6 hours IV or orally until serum methotrexate levels are below 5 × 10 <sup>-8</sup> mol/L with hydration and urinary alkalization (about 72 hours)	None	Enhances toxic effects of fluorouracil.
Amifostine	910 mg/m <sup>2</sup> IV daily, 30 minutes prior to chemotherapy	Hypotension, nausea, vomiting, flushing	Decrease in serum calcium.
Dexrazoxane	10:1 ratio of anthracycline IV, before (within 30 minutes of) chemotherapy infusion	Pain on injection	Increased bone marrow suppression.
Pilocarpine hydrochloride	5–10 mg orally 3 times daily	Sweating, headache, flushing; nausea, chills, rhinitis, dizziness, and urinary frequency at high dosage	None
Pamidronate	90 mg IV every month	Symptomatic hypoglycemia (rare), flare of bone pain, local irritation	None
Epoetin alfa (erythropoietin)	100–300 units/kg IV or SC 3 times a week	Skin irritation or pain at injection site	Hypertension, headache, seizures in patients on dialysis (rare).
Filgrastim (G-CSF)	5 mg/kg/d SC or IV	Mild to moderate bone pain, mild hypotension (rare), irritation at injection sites (rare)	?Unknown risk of tumor cell stimulation.
Sargramostim (GM-CSF)	250 mg/kg/d as a 2-hour IV infusion (can be given SC)	Fluid retention, dyspnea, capillary leak (rare), supraventricular tachycardia (rare), mild to moderate bone pain, irritation at injection sites	

Hormonal therapy also plays an important role in cancer management. Hormonal therapy or ablation is important in treatment and palliation of breast and prostatic carcinoma, while added progestins are useful in suppression of endometrial carcinoma. Women with metastatic breast cancer who show objective improvement with hormonal therapy have tumors that contain cytoplasmic estrogen and progesterone receptors. Antiestrogens (eg, tamoxifen) and aromatase inhibitors (eg, anastrozole or megestrol acetate) that block peripheral conversion of adrenal androgens into estrogens have substantial additive effects to—or may obviate the need for—oophorectomy in premenopausal women whose tumors are estrogen- or progesterone receptor-positive. Hormonal approaches are also available to treat prostate cancer, though androgen receptors remain difficult to measure. These include the use of estrogen therapy, gonadotropin-releasing hormone agonists (eg, leuprolide), aromatase inhibitors (eg, aminoglutethimide), and antiandrogens (eg, flutamide). The use of leuprolide plus flutamide can be considered as an alternative to orchiectomy but also causes impotence. High-dose ketoconazole has been used to rapidly suppress adrenal production of steroids in crises such as cord compression. Use of this agent requires hydrocortisone supplementation.

Several recombinant growth factors have been shown to be effective in the treatment of malignancy. Recombinant alpha interferon has marked antitumor effects in hairy cell leukemia and chronic myelogenous leukemia, moderate effects in lymphomas, in the epidemic (AIDS-associated) form of Kaposi's sarcoma, in multiple myeloma, and as adjuvant therapy for malignant melanoma. Alpha interferon has some utility also in metastatic melanoma, renal cell carcinoma, and carcinoid syndrome. Patients with chronic myelogenous leukemia may benefit from treatment with alpha interferon and achieve both a hematologic and cytogenetic remission. Patients with a cytogenetic response to interferon (about 30% of treated patients) have longer survival than patients treated with standard oral chemotherapy. The addition of alpha interferon to systemic chemotherapy for multiple myeloma appears to enhance the degree of cytoreduction achieved as compared with chemotherapy alone; toxicity is additive. Use of alpha interferon for myeloma following chemotherapy or autologous bone marrow transplant has prolonged remission duration, though overall survival may not be altered. Another cytokine, interleukin-2, when administered alone or in combination with lymphocyte-activated killer cells or tumor-infiltrating lymphocytes, exhibits marked antitumor activity in a minority of patients with melanoma or renal cancer, though its use is associated with marked toxicity.

In addition to cytokines, other agents have recently been shown to be efficacious in the treatment of some tumors. For chronic lymphocytic leukemia and low-grade lymphomas, fludarabine phosphate, cladribine (2-chlorodeoxyadenosine; CdA), and pentostatin (2-deoxycoformycin) are effective. Studies using cladribine to treat hairy cell leukemia have resulted in a high remission rate that is durable with tolerable toxicities after a 1-week course of therapy. Pentostatin has been approved for use in hairy cell leukemia. Paclitaxel is a novel agent isolated from the Pacific yew tree that has been found to be effective in reducing tumor size in 20–35% of patients with refractory metastatic ovarian cancer, though most patients experienced rapid disease progression after an initial response; paclitaxel combined with carboplatin appears to be more effective than cyclophosphamide plus carboplatin in the

adjuvant setting. Dose intensification as well as intraperitoneal instillation may also be helpful. The toxicity of paclitaxel is primarily hematologic and neurologic. The hematologic toxicity is dose-dependent and can be ameliorated by the use of myeloid growth factors. Effectiveness has been demonstrated in metastatic carcinoma of the breast as well as in other cancers. Docetaxel, a synthetic analog of paclitaxel, has recently been approved and is effective also in the treatment of advanced malignancies, especially breast cancer. Toxicities are similar to those of paclitaxel. Vinorelbine, a semisynthetic vinca alkaloid, has recently been approved for use in treating advanced non-small-cell lung cancer. Response rates of 30% have been observed when vinorelbine is used as a single agent in this poorly responsive tumor. Current studies are evaluating combination chemotherapy, including vinorelbine, in the treatment of metastatic breast cancer and other tumors. Newer experimental cancer therapies are discussed briefly at the end of this chapter.

10040:7:1 Berkowitz RS, Goldstein DP: Chorionic tumors. *N Engl J Med* 1996;335:1740. (Review of the clinical presentation and treatment of this curable tumor.)

10040:7:2 Chabner BA: Biological basis for cancer treatment. *Ann Intern Med* 1993;118:633. (A discussion of cancer biology as the basis of drug discovery research and a review of novel cancer therapies.)

10040:7:3 O'Brien S, del Giglio A, Keating M: Advances in the biology and treatment of B-cell chronic lymphocytic leukemia. *Blood* 1995;85:307. (Fludarabine treatment results in high complete remission rates and may allow more aggressive subsequent therapy.)

10040:7:4 Philip T et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995;333:1540. (Bone marrow transplantation for chemotherapy-sensitive relapsed lymphoma markedly improves event-free survival over standard salvage chemotherapy [46% versus 12% at 5 years].)

10040:7:5 Pritchard RS, Anthony SP: Chemotherapy plus radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer: A meta-analysis. *Ann Intern Med* 1996;125:723. (Fourteen articles with 2589 patients suggested a 2-month mean gain in life expectancy when chemotherapy was added to radiation therapy.)

10040:7:6 Rowinsky EK, Donehower RC: Paclitaxel (Taxol). *N Engl J Med* 1995;332:1004. (A thorough review, including mechanisms of action, toxicity, and antitumor effects.)

10040:7:7 Saven A, Piro LD: Treatment of hairy cell leukemia. *Blood* 1992;79:1111. (Current and investigational treatments of hairy cell leukemia, including interferon, deoxycoformycin, and cladribine.)

10040:7:8 Yuen A, Sikic BI: Multidrug resistance in lymphomas. *J Clin Oncol* 1994;12:2453. (Review of multidrug resistance in lymphomas and status of ongoing trials using modulating agents.)

## Adjuvant Chemotherapy for Micrometastases

One of the most important roles of cancer chemotherapy is as adjuvant therapy to eradicate or suppress minimal residual disease after primary field treatment with surgery or irradiation. Failure of primary field therapy to eradicate tumor is due principally to occult micrometastases of tumor stem cells outside the primary field. These distant micrometastases are more likely to be present in patients with positive lymph nodes at the time of surgery (eg, breast cancer), in patients with tumors known to have a propensity for early hematogenous spread (eg, osteogenic sarcoma, Wilms' tumor), and in patients with certain pathologic or molecular risk factors (eg, high proliferative index, vascular invasion, oncogene amplification). Given specific risk factors, the risk of recurrent or metastatic disease can be extremely high (> 80%). Only systemic therapy can adequately prevent micrometastases.

Chemotherapeutic regimens that have been shown to be effective in inducing regression of advanced cancers may be curative when combined with surgery for high-risk "early" cancer.

More data are now available to support the use of adjuvant therapy in several neoplasms. Prolongation of survival times has been shown for women (especially premenopausal women) with breast cancer and positive or negative axillary lymph nodes (stages I, II, and III) from combination chemotherapy following surgical resection; there are several useful regimens. Node-negative patients are treated with CMF (cyclophosphamide, methotrexate, and fluorouracil) or variants, whereas high-risk, node-positive patients are generally treated with regimens that include doxorubicin. Neoadjuvant (preoperative) and perioperative chemotherapy are also used and may improve surgical resectability or time to disease progression. The antiestrogen tamoxifen is used routinely either with or without antecedent chemotherapy if receptors for estrogen and progesterone are present. The role of amplification of the c-erbB-2 or Her-2/neu oncogene in tamoxifen-resistant breast cancer is a subject of current research. In postmenopausal women, tamoxifen alone may be used. The main challenge in treating women with node-negative (stage I) breast cancer is to identify prognostic factors to determine which patients are at higher risk and therefore more likely to benefit from adjuvant therapy.

Adjuvant chemotherapy with fluorouracil plus levamisole is now indicated in Dukes C (node-positive) colon cancer and has been

shown to reduce the risk of cancer recurrence. Earlier clinical trials employing semustine (methyl-CCNU) appeared to result in an increased risk of both leukemia and renal insufficiency. The omission of semustine from combination regimens still results in enhanced cure rates with decreased local and overall tumor recurrence.

Other tumors that have been shown to respond to adjuvant therapy include osteogenic sarcoma, ovarian cancer, and malignant melanoma. Adjuvant therapy remains investigational and unproved for a number of common tumors, including non-small-cell lung cancer and pancreatic cancer. Patients with Hodgkin's disease or testicular carcinoma do not benefit from adjuvant therapy. Although adjuvant therapy has been shown to reduce the rate of recurrence for some cancers, there is still a high failure rate (up to 80% in high-risk breast cancer despite adjuvant therapy). In most cases, tumor recurrence signifies incurability. There is clear evidence of a dose-response effect of adjuvant chemotherapy in some cancers; however, doses have been limited by bone marrow toxicity. Current studies are investigating the use of dose-intense chemotherapy regimens with or without autologous bone marrow or peripheral blood progenitor cell rescue in the high-risk adjuvant setting for patients with carcinoma of the breast, testis, and ovaries. Otherwise incurable patients with testicular cancer have been cured by this intensive treatment approach. Nonrandomized studies suggest efficacy with tolerable side effects of high-dose chemotherapy with stem cell support in the setting of high-risk breast cancer (more than ten positive lymph nodes). Multicenter trials are now in progress comparing aggressive adjuvant chemotherapy with autologous bone marrow transplantation for high-risk breast cancer. The use of marrow transplantation for high-risk ovarian cancer remains controversial, though long-lived responses in otherwise incurable patients have been documented. Patients with advanced ovarian cancer at high risk for recurrence may now be considered for treatment in a multicenter randomized study comparing transplantation with standard adjuvant chemotherapy. Young patients with high-risk malignancies should be considered for entry into clinical trials investigating this aggressive, potentially curable therapy.

10040:8:1 [Physicians' Data query: Information on cancer treatment] [http://cancernet.nci.nih.gov/h\\_treat.htm](http://cancernet.nci.nih.gov/h_treat.htm)

10040:8:2 Bonadonna G et al: Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. *N Engl J Med* 1995;332:901. (Long-term improvement in survival in patients with node-positive breast cancer randomized to receive adjuvant chemotherapy following mastectomy.)

10040:8:3 Cannistra SA: Cancer of the ovary. *N Engl J Med* 1993;329:1550. (A review of risk factors, presentation, staging, surgical treatment and chemotherapy, and prognosis.)

10040:8:4 Gradishar WJ, Tallman MF, Abrams JS: High-dose chemotherapy for breast cancer. *Ann Intern Med* 1996;125:599. (A review of this controversial but widely used therapy.)

10040:8:5 Moertel CG: Chemotherapy for colorectal cancer. *N Engl J Med* 1994;330:1136.

10040:8:6 Trimble EL et al: Neoadjuvant therapy in cancer treatment. *Cancer* 1993;72:3515. (Increasing indications.)

## Toxicity and Dose Modification of Chemotherapeutic Agents

A number of cancer chemotherapeutic agents have cytotoxic effects on rapidly proliferating normal cells in bone marrow, mucosa, and skin. Still other drugs such as the vinca alkaloids produce neuropathy, and hormones often have psychologic effects. Acute and chronic toxicities of the various drugs are summarized in Table 4-4. Appropriate dose modification usually minimizes these side effects, so that therapy can be continued with relative safety.

### Bone Marrow Toxicity

Depression of bone marrow is usually the most serious limiting toxicity of cancer chemotherapy. Autologous bone marrow or peripheral blood progenitor cell transplantation or rescue can reduce the myelosuppressive toxicity of high-dose chemotherapy; however, cost and toxicity limit its general use. Growth factors that stimulate myeloid proliferation (eg, granulocyte colony-stimulating factor [G-CSF; filgrastim] and granulocyte-macrophage stimulating factor [GM-CSF]; sargramostim) or erythroid proliferation (erythropoietin [epoetin alfa]) are now used to ameliorate bone marrow toxicity. G-CSF and GM-CSF have been shown to shorten the period of neutropenia following both standard and high-dose chemotherapy. Mucosal toxicity is also reduced. The myeloid growth factors are also used to stimulate circulation of progenitor cells in the peripheral blood either at steady state or during white blood cell recovery following myelosuppressive chemotherapy. These cells are then harvested using an apheresis machine and frozen for later use. When stimulated peripheral blood progenitor cells are used instead of or in conjunction with bone marrow for autologous transplantation following high-dose chemotherapy and radiotherapy, recovery of both neutrophils and platelets may be hastened by as much as 7-10 days as opposed to the use of bone marrow alone.

Epoetin alfa (erythropoietin) has been shown to improve anemia associated with malignancy. Patients must have adequate iron stores to respond to this agent, and even patients with marrow infiltration with tumor may benefit. Higher doses are necessary for patients with cancer than for patients with renal failure (100-150 units/kg compared with 50 units/kg). It is useful to check the level

of erythropoietin before instituting therapy. Very high levels (> 500 ng/mL) predict a poor response. Erythropoietin is usually given by subcutaneous injection three times a week.

Thrombocytopenia remains a problem with high doses of or prolonged exposure to chemotherapeutic agents and may limit therapy. Several agents may help with this problem. Interleukin-3 stimulates myeloid growth and, to a lesser extent, platelet recovery. The megakaryocyte growth factor thrombopoietin has been cloned and is the subject of intense study. Clinical trials using thrombopoietin in a variety of circumstances are under way.

Commonly used short-acting drugs that affect the bone marrow are the alkylating agents (eg, cyclophosphamide, melphalan, chlorambucil), procarbazine, mercaptopurine, methotrexate, vinblastine, fluorouracil, dactinomycin, and doxorubicin. In general, it is preferable to use alkylating agents in intensive "pulse" courses every 3–4 weeks rather than to administer the drugs in continuous daily schedules. This allows for complete hematologic (and immunologic) recovery between courses rather than continuously suppressing the bone marrow with a cytotoxic agent. Pulse therapy reduces side effects to some degree but does not reduce therapeutic efficacy. The standard dosage schedules required to produce tumor responses with these agents often induce bone marrow depression. Continuing some drugs in the face of falling blood counts may result in severe bone marrow aplasia with pancytopenia, bleeding, or infection. Simple guidelines for treatment and follow-up can usually prevent severe marrow depression. With long-term chemotherapy, counts should be obtained initially at weekly intervals; the frequency of counts may be reduced only after the patient's sensitivity to the drug can be well predicted (eg, 3–4 months) and cumulative toxicity excluded.

In patients with normal blood counts as well as normal liver and kidney function, drugs should be started in full dosages. Bone marrow toxicity is cumulative over time, and this must be anticipated during follow-up. Patients with bone marrow involvement may tolerate chemotherapy poorly initially, with improved counts on future cycles as the tumor burden is reduced.

Drug dosage can usually be modified as a function of the peripheral white blood count or platelet count (or both). These modifications assume that the blood counts are checked shortly before the next course of chemotherapy is to be administered.

Dosage modifications are used primarily for repeated courses of oral alkylator or antimetabolite therapy but should be avoided when possible if treatment is given with curative intent. A scheme for dosage modification is presented in Table 4–5. Alternatively, the interval between drug courses can be lengthened, thereby permitting more complete hematologic recovery and repetition of full-dose chemotherapy. Both dosage modification and delay of chemotherapy limit the efficacy of treatment.

**Table 4–5. A common scheme for dose modification of cancer chemotherapeutic agents.<sup>1</sup>**

<b>Granulocyte Count</b>	<b>Platelet Count (/mL)</b>	<b>Suggested Drug Dosage (% of full dose)</b>
> 2000/ $\mu$ L	> 100,000/ $\mu$ L	100%
1000–2000/ $\mu$ L	75,000–100,000/ $\mu$ L	50%
< 1000/ $\mu$ L	< 50,000/ $\mu$ L	0%

<sup>1</sup>In general, dose modification should be avoided if full recovery is expected within 1–2 weeks.

Chemotherapy can be delayed and given after recovery at full dosage to maintain therapeutic efficacy.

10040:9:1 ASCO Ad Hoc Colony-Stimulating Factor Guideline Expert Panel: American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based clinical practice guidelines. *J Clin Oncol* 1994;12:2471. (Standard practice guidelines.)

10040:9:2 Kaushansky K: Thrombopoietin: The primary regulator of megakaryocyte and platelet production. *Thromb Haemost* 1995;74:521. (A review of current preclinical data.)

10040:9:3 Vose JM, Armitage JO: Clinical applications of hematopoietic growth factors. *J Clin Oncol* 1995;13:1023.

### **Chemotherapy-Induced Nausea & Vomiting**

A number of cytotoxic anticancer drugs induce nausea and vomiting. In general, these symptoms are thought to originate in the central nervous system rather than peripherally. Parenteral administration of agents such as doxorubicin, etoposide, or cyclophosphamide frequently is associated with mild to moderate nausea and vomiting, whereas nitrosoureas, dacarbazine, and particularly cisplatin usually cause severe symptoms. Combination chemotherapy can also cause severe symptoms. Antiemetics clearly reduce and often eliminate nausea and vomiting associated with these drugs and are especially useful in conjunction with cisplatin.

Metoclopramide is a particularly useful agent, especially when administered parenterally at a dosage of 1–2 mg/kg both 30 minutes before and again 30 minutes after the administration of chemotherapy. Extrapyramidal signs may be induced with this drug but frequently can be suppressed with 25–50 mg of oral or parenteral diphenhydramine. Dexamethasone has antiemetic effects when administered at a dosage of 6–10 mg either as a single dose prior to or both prior to and every 6 hours following the administration

of chemotherapy for two to four total doses. Both of these drugs are more potent than conventional agents such as prochlorperazine, diphenhydramine, and thiethylperazine. Prochlorperazine is given at a dose of 10 mg orally or intravenously every 6 hours. The total dose given over 24 hours should not exceed 40 mg. A 25 mg rectal suppository is available and may be useful for patients who are too nauseated to swallow pills without experiencing further emesis. Unfortunately, all phenothiazines can induce extrapyramidal side effects. Thiethylperazine is given at a dose of 10 mg every 8 hours by mouth and is also available at the same dose in a rectal suppository. Lorazepam has both antiemetic and sedating effects and is administered at a dose of 0.5–1 mg every 4–6 hours by the sublingual route, making it particularly useful in the outpatient setting. Older patients may have intolerable psychologic side effects. Combinations of antiemetics (eg, metoclopramide with dexamethasone and lorazepam) are often more effective than maximal doses of any one agent for blocking cisplatin-induced vomiting.

5-Hydroxytryptamine-3 receptor antagonists (ondansetron, granisetron) have now replaced high-dose metoclopramide in the treatment and prevention of emesis. A new and very potent class of antiemetics, these drugs are serotonin receptor-blocking agents that have few side effects. They are both more effective and less toxic than metoclopramide in cisplatin-treated patients. They are also effective against radiation-induced and postanesthetic vomiting as well as for patients with refractory nausea and vomiting following administration of other chemotherapeutic agents. Ondansetron is administered by the parenteral route at a dose of 0.15 mg/kg for three doses or orally at a dose of 8 mg every 8 hours. The first dose is given 30 minutes before the start of chemotherapy; subsequent doses are given 4 and 8 hours after the first dose. A typical antiemetic regimen might include ondansetron combined with 0.5–1 mg of lorazepam (sublingual) or 10 mg of prochlorperazine orally or intravenously and dexamethasone (10 mg orally), omitting both metoclopramide and diphenhydramine. For less emetogenic regimens, ondansetron alone may be no more effective than metoclopramide and dexamethasone and is usually used only for failure to control nausea with less expensive combination regimens. Granisetron is a long-acting serotonin receptor antagonist that is given as a single dose of 10 mg/kg intravenously 30 minutes before chemotherapy or orally at a dosage of 1–2 mg/d. The half-life of granisetron is 9 hours, and 24-hour dosing is recommended by the manufacturer. Ondansetron may also be effective in a single daily parenteral dose of 32 mg. Both agents appear to be more effective when given in conjunction with dexamethasone.

Dronabinol (D9-tetrahydrocannabinol) is effective in some patients at a dose of 5 mg/m<sup>2</sup> prior to and then every 2–4 hours following chemotherapy for a total of four to six doses a day. Dronabinol may cause undesirable side effects such as dysphoria, and it is available only for oral administration. A patient receiving antiemetics (eg, lorazepam, prochlorperazine, metoclopramide) along with chemotherapy on an outpatient basis must be escorted to and from the clinic, since the antiemetics often induce marked sedation and transient impairment of balance and reflexes. Antiemetics are more effective when given prophylactically. Therefore, regular dosing of an agent such as lorazepam or prochlorperazine is recommended after chemotherapy until the emetogenic effects have dissipated. This is dependent on the patient as well as on the type of chemotherapy administered. One problem with all combinations of antiemetic agents is the development of tachyphylaxis over 4–5 days with continuing highly emetogenic chemotherapy. This limits the effectiveness of any regimen.

10040:10:1 Grunberg SM et al: Control of chemotherapy-induced emesis. *N Engl J Med* 1993;329:1790. (Mechanisms and treatment.)

10040:10:2 Perez EA: Review of the preclinical pharmacology and comparative efficacy of 5-hydroxytryptamine-3 receptor antagonists for chemotherapy-induced emesis. *J Clin Oncol* 1995;13:1036. (This is a highly effective class of antiemetic agents, and all three studied appear to be relatively equivalent.)

### **Gastrointestinal & Skin Toxicity**

Since antimetabolites such as methotrexate and fluorouracil act only on rapidly proliferating cells, they damage the cells of mucosal surfaces such as the gastrointestinal tract. Methotrexate has similar effects on the skin. These toxicities are at times more serious than bone marrow suppression, and they should be looked for routinely when these agents are used.

Erythema of the buccal mucosa is an early sign of mucosal toxicity. If therapy is continued beyond this point, oral ulceration will develop. In general, it is wise to discontinue therapy at the time of appearance of early oral ulceration. This finding usually heralds the appearance of similar but potentially more serious ulceration at other sites lower in the gastrointestinal tract. Therapy can usually be reinstated when the oral ulcer heals (7–10 days). The dose of drug used may need to be modified downward at this point, with titration to an acceptable level of mucosal toxicity. Adequate mouth care with antimicrobial mouthwashes and attention to dental hygiene are essential and may prevent severe toxicity. Common mouthwashes include the microbicidal oral rinse chlorhexidine and a mixture of salt and bicarbonate of soda in warm water, which aids in debridement of dead mucosa. A prophylactic antifungal mouthwash such as nystatin oral suspension may also be used. High doses of methotrexate require special consideration as noted in the following section.

Radiation therapy may cause xerostomia, which can lead to difficulty in swallowing, discomfort, and gum disease. Pilocarpine hydrochloride, 5–10 mg orally three times a day, can relieve symptoms of dry mouth but must be used regularly.

### **Miscellaneous Drug-Specific Toxicities**

The toxicities of individual drugs have been summarized in Table 4–4. Several of these warrant additional mention, since they occur with commonly administered agents, and special preventive measures are often indicated.

**A. Hemorrhagic Cystitis Induced by Cyclophosphamide or Ifosfamide:** Metabolic products of cyclophosphamide that retain cytotoxic activity are excreted into the urine. Some patients appear to metabolize more of the drug to these active excretory products. If their urine is concentrated, the toxic metabolite may cause severe bladder damage. Patients receiving cyclophosphamide must be advised to maintain a high fluid intake. Early symptoms of bladder toxicity include dysuria and frequency despite the absence of bacteriuria. Such symptoms develop in about 20% of patients who receive the drug chronically. If microscopic hematuria develops, it is advisable to stop the drug temporarily or switch to a different alkylating agent, increase fluid intake, and administer a urinary analgesic such as phenazopyridine. With severe cystitis, large segments of bladder mucosa may be shed and the patient may have prolonged gross hematuria. Such patients should be observed for signs of urinary obstruction and may require cystoscopy for removal of obstructing blood clots. The risk of developing hemorrhagic cystitis is dose-related. For high doses of cyclophosphamide, preventive continuous bladder irrigation with 0.9% saline solution is used during the period of drug administration and for the following 24 hours.

The cyclophosphamide analog ifosfamide can cause severe hemorrhagic cystitis when used alone. However, when it is used in conjunction with a series of doses of the neutralizing agent mesna, bladder toxicity can be prevented. Mesna can also be used to prevent cystitis in patients receiving cyclophosphamide in high doses.

**B. Vincristine-Induced Neuropathy:** Neuropathy is a toxic side effect that is peculiar to the vinca alkaloid drugs, especially vincristine. The peripheral neuropathy can be sensory, motor, autonomic, or a combination of these effects. In its mildest form, it consists of paresthesias of the fingers and toes. Occasional patients develop acute jaw or throat pain after vincristine therapy. This may be a form of trigeminal or glossopharyngeal neuralgia. With continued vincristine therapy, the paresthesias may extend to the proximal interphalangeal joints, hyporeflexia can appear in the lower extremities, and weakness may develop in the quadriceps muscle group. At this point, it is wise to discontinue vincristine therapy until the neuropathy has subsided. A useful means of judging whether peripheral motor neuropathy is severe enough to warrant stopping treatment is to have the patient attempt to do deep knee bends or rise from a chair without using the arm muscles.

Constipation is the most common symptom of autonomic neuropathy associated with vincristine therapy. Patients receiving vincristine should be started on stool softeners and mild cathartics when therapy is begun; otherwise, severe impaction may result along with an atonic bowel.

More serious autonomic involvement can lead to acute intestinal ileus with signs indistinguishable from those of an acute abdomen. Bladder neuropathies are uncommon but may be severe. These two complications are absolute contraindications to continued vincristine therapy. The majority of symptoms from vincristine are mild and resolve slowly after therapy has been completed. Paclitaxel, cisplatin, carboplatin, and vinorelbine can also cause peripheral neuropathy, though as a rule symptoms improve gradually after treatment is stopped.

**C. Methotrexate Toxicity and Citrovorum Rescue:** In addition to standard uses of methotrexate for cancer chemotherapy, this drug is also used in very high doses that could lead to fatal bone marrow toxicity if given without an antidote. High-dose methotrexate therapy with leucovorin rescue is routinely used to treat osteogenic sarcoma, acute lymphocytic leukemia, and some cases of non-Hodgkin's lymphoma.

The bone marrow and mucosal toxicity of methotrexate can be prevented by early administration of leucovorin. Serum levels of methotrexate are usually monitored and doses of leucovorin adjusted accordingly. Rescue is required for methotrexate doses over 80 mg/m<sup>2</sup> and is usually begun within 4 hours after completing treatment. Up to 100 mg/m<sup>2</sup> of leucovorin is given initially every 6 hours, with further doses adjusted for the serum methotrexate level. Rescue is usually continued orally for 3 days or longer until the serum methotrexate level is below 0.05 mmol/L. If an overdose of methotrexate is administered accidentally, leucovorin therapy should be initiated as soon as possible, preferably within 1 hour. Intravenous infusion should be employed for larger overdoses to ensure adequate drug delivery. It is generally advisable to give leucovorin repeatedly in this situation.

Vigorous hydration and bicarbonate loading also appear to be important in preventing crystallization of high-dose methotrexate in the renal tubular epithelium. Serum creatinine is determined before beginning therapy and daily thereafter, since methotrexate excretion is slowed by renal insufficiency and toxicity will be enhanced. In high doses, methotrexate can itself cause renal injury. Methotrexate doses are reduced in renal insufficiency. Concomitant use of certain drugs will slow methotrexate excretion, and they are avoided during therapy. These drugs include aspirin, NSAIDs, penicillins, sulfonamides, and probenecid.

**D. Busulfan Toxicity:** The alkylating agent busulfan, occasionally used for the treatment of chronic myelogenous leukemia, has curious delayed toxicities, including increased skin pigmentation, a wasting syndrome similar to that seen in adrenal insufficiency, and progressive pulmonary fibrosis. Patients who develop either of the latter two problems should be switched to a different drug (eg, melphalan) when further therapy is needed. The pigmentary changes are innocuous and will usually regress slowly after treatment is discontinued. Long-term treatment with busulfan also results in an increased risk of secondary leukemias.

E. Bleomycin Toxicity: This antibiotic has found increasing application in cancer chemotherapy in view of its activity in squamous cell carcinomas, Hodgkin's disease, non-Hodgkin's lymphomas, and testicular tumors. Bleomycin can produce edema of the interphalangeal joints and hardening of the palmar and plantar skin. More serious toxicities include an anaphylactic or serum sickness-like reaction and a potentially fatal pulmonary fibrotic reaction (seen especially in elderly patients receiving a total dose of over 300 units). If a nonproductive cough, dyspnea, and pulmonary infiltrates develop, the drug is discontinued, and high-dose corticosteroids are instituted as well as empiric antibiotics pending cultures. Fever alone or with chills is an occasional complication of bleomycin treatment and is not an absolute contraindication to continued treatment. The fever may be avoided by hydrocortisone administration just prior to the injection. Fever alone is not predictive of pulmonary toxicity. About 1% of patients (especially those with lymphoma) may have a severe or even fatal hypotensive reaction after the initial dose of bleomycin. In order to identify and treat such patients, it is wise to administer a test dose of 5 units of bleomycin first and to have adequate monitoring and emergency facilities available. Patients exhibiting a hypotensive reaction should not receive further bleomycin therapy.

F. Doxorubicin-Induced Cardiomyopathy: The anthracycline antibiotics doxorubicin and daunomycin both have acute and delayed cardiac toxicity. The problem is greater with doxorubicin because it has a major role and is used in repeated doses in the treatment of sarcomas, breast cancer, lymphomas, acute leukemia, and certain other solid tumors. Studies of left ventricular function and endomyocardial biopsies indicate that some changes in cardiac dynamics occur in most patients by the time they have received 300 mg/m<sup>2</sup> of doxorubicin. The multiple-gated ("MUGA") radionuclide cardiac scan is the most useful noninvasive test for assessing toxicity. Doxorubicin should not be used in elderly patients with intrinsic cardiac disease. In general, patients should not receive a total dose in excess of 550 mg/m<sup>2</sup>, and 1–10% of patients who receive this dose develop cardiomyopathy. Patients who have had prior chest or mediastinal radiotherapy may develop doxorubicin heart disease at lower total doses. The appearance of a high resting pulse may herald the appearance of cardiac toxicity. Unfortunately, the toxicity may be irreversible and frequently fatal at dosage levels above 550 mg/m<sup>2</sup>. At lower doses (eg, 350 mg/m<sup>2</sup>), the symptoms and signs of cardiac failure generally respond well to digitalis, diuretics, and cessation of doxorubicin therapy. Recent evidence suggests that cardiac toxicity can be correlated with high peak plasma levels obtained with intermittent high-dose bolus therapy (eg, every 3–4 weeks). Use of weekly injections or low-dose continuous infusion schedules appears to delay the occurrence of cardiac toxicity. Current laboratory studies suggest that cardiac toxicity may be due to a mechanism involving the formation of intracellular free radicals in cardiac muscle. Pretreatment with dexrazoxane, an iron chelator that decreases free radical formation, appears to protect the myocardium from anthracycline-induced injury but may also reduce the anticancer efficacy of the anthracycline. Dexrazoxane is now approved for the prevention of cardiomyopathy in women with metastatic breast cancer receiving cumulative doxorubicin doses > 300 mg/m<sup>2</sup>. Liposomally encapsulated doxorubicin and daunorubicin have been FDA-approved and appear to have minimal cardiac toxicity. Their main use to date has been to treat Kaposi's sarcoma. Newer anthracycline analogs include idarubicin, which has shown efficacy against acute nonlymphocytic leukemia and breast cancer when used in combination with other agents. Idarubicin appears to have a similar potential for causing cardiotoxicity when compared with other anthracyclines, though a maximum lifetime dosage recommendation has not yet been made.

G. Cisplatin Nephrotoxicity and Neurotoxicity: Cisplatin is effective in the treatment of testicular, bladder, and ovarian cancer as well as in several other types of tumor. Nausea and vomiting are common, but nephrotoxicity and neurotoxicity are more serious. Vigorous hydration with or without mannitol diuresis may substantially reduce nephrotoxicity. Renal function must be carefully monitored during cisplatin therapy, as should serum magnesium, which may fall during therapy with this agent. Ototoxicity is a potentially serious neurotoxicity that can result in deafness. The neurotoxicity of this drug is delayed and is more common after a total dose of 300 mg/m<sup>2</sup>. Other manifestations include peripheral neuropathy of mixed sensorimotor type that may be associated with painful paresthesias. These supportive measures do not appear to reduce the therapeutic effectiveness of cisplatin. The second-generation platinum analog carboplatin is now available and has been shown to be as effective as cisplatin in ovarian cancer. Carboplatin is less nephrotoxic and causes less severe nausea or vomiting, but it does induce myelosuppression. Amifostine, an organic thiophosphate initially developed as a radioprotective agent, has efficacy in preventing renal toxicity from cisplatin. It has recently been approved to reduce cumulative renal toxicity associated with repeat administration of cisplatin in advanced ovarian cancer. In addition, amifostine may reduce cytotoxic chemotherapy-induced hematologic toxicity and neurotoxicity. Glutathione also appears to be a promising agent in preventing cisplatin neurotoxicity. Glutathione was given at a dose of 1.5 g/m<sup>2</sup> intravenously before cisplatin administration, then at a dose of 600 mg by intramuscular injection on days 2–5.

H. Alpha Interferon Toxicities: While alpha interferon is generally tolerated in the standard doses listed in Table 4–4, it has increasing toxicity with increasing doses and is more toxic in elderly patients. Even standard doses may be intolerable to some patients. Fever and chills are initial side effects but are infrequent after continued treatment. These symptoms may be ameliorated or prevented by premedication with acetaminophen and bedtime dosing. However, anorexia, fatigue, and weight loss can be cumulative and with time may become severe. These symptoms may be dose- or treatment-limiting. Thirty percent or more of patients are intolerant of interferon therapy even at low doses. In some patients, central nervous system symptoms develop, usually manifested as confusion or somnolence. Reduction in peripheral blood counts can develop, but this abnormality is usually not clinically important

and may even be a desired effect in the treatment of chronic myelogenous leukemia. These interferon-induced side effects are sometimes confused with the symptoms of progressive cancer. The side effects usually clear within 1 week after cessation of interferon therapy.