TABLE 103e-3 CURABILITY OF CANCERS WITH CHEMOTHERAPY

A. Advanced Cancers with Possible Cure
- Acute lymphoid and acute myeloid leukemia (pediatric/adult)
- Hodgkin's disease (pediatric/adult)
- Lymphomas—certain types (pediatric/adult)
- Germ cell neoplasms
  - Embryonal carcinoma
  - Teratocarcinoma
  - Seminoma or dysgerminoma
  - Choriocarcinoma
- Gestational trophoblastic neoplasia
- Pediatric neoplasms
  - Wilms' tumor
  - Embryonal rhabdomyosarcoma
  - Ewing's sarcoma
  - Peripheral neuroepithelioma
  - Neuroblastoma
- Small-cell lung carcinoma
- Ovarian carcinoma

B. Advanced Cancers Possibly Cured by Chemotherapy and Radiation
- Squamous carcinoma (head and neck)
- Squamous carcinoma (anus)
- Breast carcinoma
- Carcinoma of the uterine cervix
- Non-small-cell lung carcinoma (stage III)
- Small-cell lung carcinoma

C. Cancers Possibly Cured with Chemotherapy as Adjuvant to Surgery
- Breast carcinoma
- Colorectal carcinoma[a]
- Osteogenic sarcoma
- Soft tissue sarcoma

D. Cancers Possibly Cured with "High-Dose" Chemotherapy with Stem Cell Support
- Relapsed leukemias, lymphoid and myeloid
- Relapsed lymphomas, Hodgkin's and non-Hodgkin's
- Chronic myeloid leukemia
- Multiple myeloma

E. Cancers Responsive with Useful Palliation, But Not Cure, by Chemotherapy
- Bladder carcinoma
- Chronic myeloid leukemia
- Hairy cell leukemia
- Chronic lymphocytic leukemia
- Lymphoma—certain types
- Multiple myeloma
- Gastric carcinoma
- Cervix carcinoma
- Endometrial carcinoma
- Soft tissue sarcoma
- Head and neck cancer
- Adrenocortical carcinoma
- Islet cell neoplasms
- Breast carcinoma
- Colorectal carcinoma
- Renal carcinoma

F. Tumors Poorly Responsive in Advanced Stages to Chemotherapy
- Pancreatic carcinoma
- Biliary tract neoplasms
- Thyroid carcinoma
- Carcinoma of the vulva
- Non-small-cell lung carcinoma
- Prostate carcinoma
- Melanoma (subsets)
- Hepatocellular carcinoma
- Salivary gland cancer

[a]Rectum also receives radiation therapy.

natural history of most metastatic cancers, *palliative care* or *hospice-based* approaches, with meticulous and ongoing attention to symptom relief and with family, psychological, and spiritual support, should receive prominent attention as a valuable therapeutic plan (Chaps. 10 and 99). Optimizing the quality of life rather than attempting to extend it becomes a valued intervention. Patients facing the impending progression of disease in a life-threatening way frequently choose to undertake toxic treatments of little to no potential value, and support provided by the primary caregiver in accessing palliative and hospice-based options in contrast to receiving toxic and ineffective regimen can be critical in providing a basis for patients to make sensible choices.

Cytotoxic Chemotherapy Agents Table 103e-4 lists commonly used cytotoxic cancer chemotherapy agents and pertinent clinical aspects of their use, with particular reference to adverse effects that might be encountered by the generalist in the care of patients. The drugs listed may be usefully grouped into two general categories: those affecting DNA and those affecting microtubules.

DIRECT DNA-INTERACTIVE AGENTS DNA replication occurs during the synthesis or S-phase of the cell cycle, with chromosome segregation of the replicated DNA occurring in the M, or mitosis, phase. The G_1 and G_2 "gap phases" precede S and M, respectively. Historically, chemotherapeutic agents have been divided into "phase-nonspecific" agents, which can act in any phase of the cell cycle, and "phase-specific" agents, which require the cell to be at a particular cell cycle phase to cause greatest effect. Once the agent has acted, cells may progress to "checkpoints" in the cell cycle where the drug-related damage may be assessed and either repaired or allowed to initiate apoptosis. An important function of certain tumor-suppressor genes such as *p53* may be to modulate checkpoint function.

Alkylating agents as a class are cell cycle phase–nonspecific agents. They break down, either spontaneously or after normal organ or tumor cell metabolism, to reactive intermediates that covalently modify bases in DNA. This leads to cross-linkage of DNA strands or the appearance of breaks in DNA as a result of repair efforts. "Broken" or cross-linked DNA is intrinsically unable to complete normal replication or cell division; in addition, it is a potent activator of cell cycle checkpoints and further activates cell-signaling pathways that can precipitate apoptosis. As a class, alkylating agents share similar toxicities: myelosuppression, alopecia, gonadal dysfunction, mucositis, and pulmonary fibrosis. They differ greatly in a spectrum of normal organ toxicities. As a class, they share the capacity to cause "second" neoplasms, particularly leukemia, many years after use, particularly when used in low doses for protracted periods.

Cyclophosphamide is inactive unless metabolized by the liver to 4-hydroxy-cyclophosphamide, which decomposes into an alkylating species, as well as to chloroacetaldehyde and acrolein. The latter causes chemical cystitis; therefore, excellent hydration must be maintained while using cyclophosphamide. If severe, the cystitis may be prevented from progressing or prevented altogether (if expected from the dose of cyclophosphamide to be used) by mesna (2-*m*ercapto-*e*thanesulfo*na*te). Liver disease impairs cyclophosphamide activation. Sporadic interstitial pneumonitis leading to pulmonary fibrosis can accompany the use of cyclophosphamide, and high doses used in conditioning regimens for bone marrow transplant can cause cardiac dysfunction. Ifosfamide is a cyclophosphamide analogue also activated in the liver, but more slowly, and it requires coadministration of mesna to prevent bladder injury. Central nervous system (CNS) effects, including somnolence, confusion, and psychosis, can follow ifosfamide use; the incidence appears related to low body surface area or decreased creatinine clearance.

Several alkylating agents are less commonly used. Nitrogen mustard (mechlorethamine) is the prototypic agent of this class, decomposing rapidly in aqueous solution to potentially yield a bifunctional carbonium ion. It must be administered shortly after preparation into a rapidly flowing intravenous line. It is a powerful vesicant, and infiltration may be symptomatically ameliorated by infiltration of the affected site with 1/6 *M* thiosulfate. Even without infiltration, aseptic thrombophlebitis is frequent. It can be used topically as a dilute solution or ointment in cutaneous lymphomas, with a notable incidence of hypersensitivity reactions. It causes moderate nausea after intravenous administration. Bendamustine is a nitrogen mustard derivative with evidence of activity in chronic lymphocytic leukemia and certain lymphomas.

Chlorambucil causes predictable myelosuppression, azoospermia, nausea, and pulmonary side effects. Busulfan can cause profound myelosuppression, alopecia, and pulmonary toxicity but is relatively "lymphocyte sparing." Its routine use in treatment of CML has been curtailed in favor of imatinib (Gleevec) or dasatinib, but it is still used in transplant preparation regimens. Melphalan shows variable oral bioavailability and undergoes extensive binding to albumin and α_1-acidic glycoprotein. Mucositis appears more prominently; however, it has prominent activity in multiple myeloma.

Nitrosoureas break down to carbamylating species that not only cause a distinct pattern of DNA base pair–directed toxicity but also can covalently modify proteins. They share the feature of causing relatively delayed bone marrow toxicity, which can be cumulative and long-lasting. Procarbazine is metabolized in the liver and possibly in tumor cells to yield a variety of free radical and alkylating species. In addition to