Chemotherapy is most often employed in the treatment of metastatic disease for which surgery or radiation therapy is ineffective. Chemotherapy can sometimes be curative, (e.g., in certain lymphomas or testicular cancers). Even when it is not curative, chemotherapy often extends survival and improves cancer-related symptoms and quality of life.

Limitations of Chemotherapy

Chemotherapy is curative only under certain circumstances, because it is inherently limited by side effects (i.e., the dose ceiling). There are several reasons for the inability of standard doses of chemotherapy to cure cancer. First, tumor cell kinetics naturally protect against chemotherapy. When chemotherapy was initially developed, it was believed that tumors contained a percentage of cells traversing the cell cycle. However, most human tumors display Gompertzian growth kinetics—that is, the rate of tumor cell doubling *slows* progressively as tumor size increases. Therefore, the growth fraction of tumors is greatest when a tumor is clinically undetectable. Be the time the patient is symptomatic and has clinically evident disease, the growth fraction of tumors can be less than 5%. Chemotherapy can be successful in the adjuvant setting (when the burden of disease is minimal), but it rarely results in cure in the metastatic setting.

Second, cancer cells can be resistant to chemotherapy. One of the most important forms of resistance is intrinsic and is mediated by an evolutionarily conserved cell membrane efflux pump called *P-glycoprotein.* Resistance can also be acquired after a period of exposure to chemotherapy agents by a variety of mechanisms; for example, tumor cells can decrease the uptake of methotrexate by decreasing the expression of the folate transporter, or they can amplify expression of the target enzyme thymidylate synthase when treated with 5-fluorouracil.

Third, mutations in the *TP53* gene are common in various cancers. The TP53 protein causes cell-cycle arrest and mediates apoptosis when DNA damage occurs. In the absence of a functioning TP53, cancer cells are protected from chemotherapy-induced apoptosis.

Stem Cell Transplantation

One way of overcoming the limitations of chemotherapy is to increase the dose given to patients. However, delivery of higher doses can lead to life-threatening complications as a result of bone marrow suppression and other end-organ damage. Stem cell transplantation is a procedure whereby patients are given myeloablative doses of chemotherapy (sometimes with radiation therapy) and then "rescued" with infusions of peripheral blood or bone marrow stem cells that reconstitute the ablated bone marrow. The source of stem cells can be the patients themselves (*autologous* transplantation) or a human leukocyte antigen–matched related or unrelated donor (*allogeneic* transplantation). Stem cell transplantation improves survival in selected patients with chronic myelogenous leukemia (CML), relapsed Hodgkin's and non-Hodgkin's lymphoma, refractory acute myelogenous leukemia, or multiple myeloma.

Allogeneic transplantations are more successful in inducing cures than autologous transplantations, owing to the immunologic response mounted by the donor cells, termed *graft-versus-tumor* effect. Newer approaches to stem cell transplantation take advantage of this phenomenon by using lower, nonmyeloablative doses of chemotherapy and relying on the graft-versus-tumor effect to achieve tumor remissions. However, allogeneic transplantations can be offered only to a minority of patients because of the limited availability of matched donors (particularly in ethnic minority populations) and the inability of older patients and those with comorbid illnesses to tolerate this procedure. To increase the availability of donors, umbilical cord blood is being studied as a source of stem cells.

The complications of stem cell transplantation are primarily related to the toxicity of chemotherapy and radiation therapy to vital organs, including lungs and liver. Long-term morbidity and mortality after allogeneic transplantation can result from *graft-versus-host disease* and from complications of immunosuppressive agents used to treat it.

Endocrine Therapy

Cancers originating from tissues that are regulated by hormones, such as breast and prostate tissues, may to be susceptible to hormonal control mechanisms even when metastatic. Endocrine therapy includes the use of both hormonal and anti-hormonal agents that work as antagonists or partial agonists.

Many patients with metastatic breast cancer express hormone receptors (estrogen or progesterone) in tumor cells. More than 60% of these patients respond either to tamoxifen, an estrogen receptor modulator, or to aromatase inhibitors (letrozole, anastrozole, or exemestane), which inhibit adrenal steroid production. Similar responses are observed in men with metastatic prostate cancer treated with the luteinizing hormone–releasing hormone agonists leuprolide or goserelin, which decrease testosterone to castrate levels.

In selected breast and prostate cancer patients, metastatic disease can be controlled for years with only endocrine therapy. Tamoxifen and the aromatase inhibitors are also highly effective adjuvant treatment after breast cancer resection. Furthermore, tamoxifen has been shown to reduce the incidence of breast cancer by 50% in healthy women who are at high risk for developing breast cancer.

Targeted Therapy

The limitations of chemotherapy, coupled with a greater understanding of cancer cell biology, have led to the development of a new class of drugs directed against targets that are relatively specific to cancer cells: growth factors and signaling molecules that are essential for proliferation of tumor cells; cell-cycle proteins; regulators of apoptosis; and molecules mediating host-tumor interactions such as angiogenesis and tumor immunity (Fig. 55-1). These agents include monoclonal antibodies directed against cell surface antigens or growth factors, specific or multitargeted receptor tyrosine kinase inhibitors, specific pathway signal transduction inhibitors, antisense oligonucleotides, and gene therapies. Additional agents are under development. The usual side effects of chemotherapy, such as myelosuppression, nausea, emesis, diarrhea, and alopecia, are not observed with these drugs. However, other toxicities require careful monitoring and management (Table 55-4).

The best-known targeted therapy agent is imatinib, which inhibits both BCR-ABL, the constitutively active fusion product