The first goal of therapy is to eradicate or control the malignancy. Late treatment consequences are, indeed, testimony to the increasing success of such treatment. Their occurrence sharply underlines the necessity to develop more effective therapies with less long-term morbidity and mortality. At the same time, a sense of perspective and relative risk is necessary; fear of long-term complications should not prevent the application of effective, particularly curative, cancer treatment.

CARDIOVASCULAR DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Cardiovascular toxicity of cancer chemotherapeutic agents includes dysrhythmias, cardiac ischemia, cardiomyopathic congestive heart failure (CHF), pericardial disease, and peripheral vascular disease. Because these cardiac toxicities are difficult to distinguish from disease that is not associated with cancer treatment, clear etiologic implication of cancer chemotherapeutic agents may be difficult. Cardiovascular complications occurring in an unexpected clinical setting in patients who have undergone cancer therapy are often important in raising suspicion. Dose-dependent myocardial toxicity of anthracyclines with characteristic myofibrillar dropout is pathologically pathognomonic on endomyocardial biopsy. Anthracycline cardiotoxicity occurs through a root mechanism of chemical free radical damage. Fe^{3+}-doxorubicin complexes damage DNA, nuclear and cytoplasmic membranes, and mitochondria. About 5% of patients receiving >450–550 mg/m^2 of doxorubicin will develop CHF. Cardiotoxicity in relation to the dose of anthracycline is clearly not a step function, but rather a continuous function, and occasional patients are seen with CHF at substantially lower doses. Advanced age, other concomitant cardiac disease, hypertension, diabetes, and thoracic radiation therapy are all important cofactors in promoting anthracycline-associated CHF. The risk of cardiac failure appears to be substantially lower when doxorubicin is administered by continuous infusion. Anthracycline-related CHF is difficult to reverse and has a mortality rate as high as 50%, making prevention crucial. Some anthracyclines such as mitoxantrone are associated with less cardiotoxicity, and continuous-infusion regimens and liposomally encapsulated doxorubicin are associated with less cardiotoxicity. Dexrazoxane, an intracellular iron chelator, may limit anthracycline toxicity, but the concern of limiting chemotherapeutic efficacy has somewhat limited its use. Monitoring patients for cardiac toxicity typically involves periodic gated nuclear cardiac blood pool ejection fraction testing (multigated acquisition scan [MUGA]) or cardiac ultrasonography. More recently, cardiac magnetic resonance imaging (MRI) has been used, but MRI is not standard or widespread. Testing is performed more frequently at higher cumulative doses, with additional risk factors, and certainly for any newly developing CHF or other symptoms of cardiac dysfunction.

After anthracyclines, trastuzumab is the next most frequent cardiotoxic drug currently in use. Trastuzumab is frequently used as adjuvant breast cancer therapy, sometimes in conjunction with anthracyclines, which is believed to result in additive or possibly synergistic toxicity. In contrast to anthracyclines, cardiotoxicity is not dose-related, is usually reversible, is not associated with pathologic changes of anthracyclines on cardiac myofibrils, and has a different biochemical mechanism inhibiting intrinsic cardiac repair mechanisms. Toxicity is typically routinely monitored every three to four doses using functional cardiac testing as mentioned earlier for anthracyclines.

Other cardiotoxic drugs include lapatinib, phosphoramide mustards (cyclophosphamide), ifosfamide, interleukin 2, ponatinib, imatinib, and sunitinib.

RADIATION THERAPY

Radiation therapy that includes the heart can cause interstitial myocardial fibrosis, acute and chronic pericarditis, valvular disease, and accelerated premature atherosclerotic coronary artery disease. Repeated or high (>6000 cGy) radiation doses are associated with greater risk, as is concomitant or distant cardiotoxic cancer chemotherapy exposure. Symptoms of acute pericarditis, which peaks about 9 months after treatment, include dyspnea, chest pain, and fever. Chronic constrictive pericarditis may develop 5–10 years following radiation therapy. Cardiac valvular disease includes aortic insufficiency from fibrosis or papillary muscle dysfunction resulting in mitral regurgitation. A threefold increased risk of fatal myocardial infarction is associated with mantle field radiation with accelerated coronary artery disease. Carotid radiation similarly increases the risk of embolic stroke.

TREATMENT CHEMOTHERAPEUTIC/RADIATION-INDUCED CARDIOVASCULAR DISEASE

Therapy for chemotherapeutic/radiation-induced cardiovascular disease is essentially the same as therapy for disease not associated with cancer treatment. Discontinuation of the offending agent is the first step. Diuretics, fluid and sodium restriction, and antiarrhythmic agents are often useful for acute symptoms. Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors or, in some cases, β-adrenergic blockers (carvedilol) often is of significant benefit, and digitalis may be helpful as well.

A hybrid discipline of "cardio-oncology" has been developing in clinics to expressly follow chemotherapy-treated patients for cardiotoxicity. The goals are early intervention using more sensitive techniques, management of cardiotoxicity before it becomes symptomatic, and using clinical trials to identify cardioprotective strategies.

PULMONARY DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Bleomycin generates activated free radical oxygen species and causes pneumonitis associated with a radiographic or interstitial ground-glass appearance diffusely throughout both lungs, often worse in the lower lobes. A nonproductive cough with or without fever may be an early sign. This toxicity is dose-related and dose-limiting. The diffusion capacity of the lungs for carbon dioxide (DL_{CO}) is a sensitive measure of toxicity and recovery, and a baseline value is generally obtained for future comparison prior to bleomycin therapy. Additive or synergistic risk factors include age, prior lung disease, and concomitant use of other chemotherapy, lung irradiation, and high concentrations of inspired oxygen. Other chemotherapeutic agents notable for pulmonary toxicity include mitomycin, nitrosoureas, doxorubicin with radiation, gemcitabine combined with weekly docetaxel, methotrexate, and fludarabine. High-dose alkylating agents, cyclophosphamide, ifosfamide, and melphalan are frequently used in the hematopoietic stem cell transplant setting, often with whole-body radiation. This therapy may result in severe pulmonary fibrosis and/or pulmonary venoocclusive disease.

RADIATION THERAPY

Risk factors for radiation pneumonitis include advanced age, poor performance status, preexisting compromised pulmonary function, and radiation volume and dose. The dose "threshold" is thought to be in the range of 5 to 20 Gy. Hypoxemia and dyspnea on exertion are characteristic. Fine, high-pitched "Velcro rales" may be an accompanying physical finding, and fever, cough, and pleuritic chest pain are common symptoms. The DL_{CO} is the most sensitive measure of pulmonary functional impairment, and ground-glass infiltrates often correspond with relatively sharp edges to the irradiated volume, although the pneumonitis may progress beyond the field and even occasionally involve the contralateral unirradiated lung.