membranes, and mitochondria. These cardiotoxic effects may also be mediated by topoisomerase IIB. Approximately 5% of patients receiving >450–550 mg/m^2 total dose of doxorubicin will develop CHF, but it can also develop at substantially lower doses in some patients. Anthracycline-related CHF is often irreversible and carries a high mortality rate, making prevention crucial. Genome-wide association studies have identified multiple genetic polymorphisms associated with a higher risk of cardiotoxicity, but our ability to risk-stratify is limited. The risk of cardiac failure appears to be related to the route of administration, and regimens that use continuous infusion of doxorubicin or liposomally encapsulated doxorubicin are associated with less cardiotoxicity. Baseline assessment of cardiac function with multigated acquisition scan (MUGA) or transthoracic echocardiograms is commonly performed, and a patient who develops symptoms suggestive of CHF should be tested immediately while therapy is held. Periodic surveillance testing during therapy is often done in asymptomatic patients with preexisting risk factors.

Trastuzumab is a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2) that is also associated with CHF. It is used in combination with chemotherapy as both adjuvant therapy and as treatment of metastatic breast cancer, and it is sometimes combined 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 on cardiac myofibrils, and has a different biochemical mechanism inhibiting intrinsic cardiac repair mechanisms. Monitoring for cardiac toxicity is typically performed every three or four doses using functional cardiac testing, and treatment is interrupted when ejection fractions significantly decline from baseline. Other potentially cardiotoxic chemotherapy agents include phosphoramide mustards (cyclophosphamide) at high doses and ifosfamide.

Small-molecule inhibitors, including tyrosine kinase inhibitors, are novel classes of molecularly targeted anticancer agents that have become routinely applicable across a variety of malignancies. Although the overall tolerability of these drugs is often better than