INTRODUCTION
Cytotoxic chemotherapeutic agents, immunotherapy and, most recently, antiangiogenic preparations may have potential cardiovascular events associated with their use, from minor ECG changes in asymptomatic patients to cardiovascular collapse in acute, subacute or chronic clinical settings. In addition, cardiovascular complications associated with malignancy can pose problems in diagnosing and treating patients and may host a systemic, metabolic, paraneoplastic or other major organ system dysfunction that often accompanies advanced disease.\(^1\)

To minimize potential cardiovascular problems, oncologists must consider numerous therapeutic issues — including drug dosage, rate of administration, single or combination agent sequencing and possible overlapping side effects — while employing drugs with different mechanisms of antitumor activity. Likewise, cardiologists must consider issues such as infection, fever, volume status, electrolyte abnormalities, age, sex, pregnancy, prior radiation and pre-existing heart disease when considering testing modalities.

ANTHRYCYCLINES

Anthracyclines are commonly employed to treat malignancies of the breast, lung and bladder as well as sarcomas and myeloproliferative states in adults and children.

Above a cumulative dose of 450-500 mg/m\(^2\) of adriamycin, cardiomyopathy and congestive heart failure (CHF) are common.\(^2\) Epirubicin and mitoxantrone doses over 900-1000 mg/m\(^2\) both reflect a wider safety range. The incidence of CHF is estimated at 3% or less with a total cumulative dose of 400 mg/m\(^2\), 7% at 550 mg/m\(^2\) and 18% with doses of adriamycin at 700 mg/m\(^2\). Patients treated with higher total doses of adriamycin may have a mortality risk as high as 50% after the first episode (Figure 1).

Infusion times of 72-96 hours have been intermittently successful in delaying the onset of cardiomyopathy but not enough to be recommended for general use. Historically, other anthracyclines such as rubidazone appeared less cardiotoxic but also displayed less antitumor effect.\(^3\)

Acute cardiotoxicity occurs during or following IV administration of adriamycin and is usually short lived: prolonged QT interval and nonspecific ST-TW changes may be seen; transient arrhythmias and even CHF may require little or no treatment; and pericarditis-myocarditis syndrome is rare. Endomyocardial biopsy, however, has detected chronic cardiotoxicity — including the onset of CHF, a decrease in LVEF more than 10-20% below baseline studies and occasionally myopathy with cumulative doses as low as 200 mg/m\(^2\) and without major clinical evidence of cardiac dysfunction.\(^4\)

Levels of troponin and B-natriuretic peptide from myocytes in both symptomatic and asymptomatic patients with left ventricular dysfunction at any level are frequently elevated, but specific guidelines for serial determinations are not yet available.\(^5,6\) At the Methodist DeBakey Heart Center, three patients on 5-Fluorouracil (5-FU) and platinoids who have severe coronary artery disease had elevated baseline levels of B-natriuretic peptide that further increased on therapy — without

![Figure 1](cumulative-doxorubicin-dose-at-onset-on-study-or-off-study-of-doxorubicin-related-congestive-heart-failure-in-630-patients-who-were-randomized-to-receive-a-doxorubicin-containing-regimen-plus-placebo.png)

Figure 1.
Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo.
detectable clinical worsening—and returned to baseline after infusion was completed. Prospective studies correlated with newer echodoppler techniques, as described by W. Zoghbi, could better outline the course of cardiotoxicity.

Pathogenesis of cardiotoxicities is thought to be associated with formation of free radicals and super oxides created by iron complexes that lead to “oxidative stress” in myocytes. Biopsy studies have shown distorted and fractured mitochondria, leading to diminished myocyte energy regulation and production in the presence of fewer muscle fibers surrounded by fibrosis, inflammatory cells and progressive cell death. Figure 2 is an electron microscopic view of adriamycin myocardiopathy showing total disarray of muscle fibers and cellular organelles (Figures 2 and 3). Changes in mitochondrial calcium transport also contribute to cell injury and death, and immunogenic reaction to drug-induced myocyte damage further compromises heart function. Dexrazoxane, an iron chelator, interferes with the formation of the anthracycline complex and muscle fibers and can mute or delay the onset of myocardial damage. Table 1 illustrates several clinical studies where adriamycin, epirubicin, 5-FU, cytoxan (CTX) and taxanes have been studied with and without dexrazoxane, as described by F. Roila.

Lastly, the time range from anthracycline exposure to clinical toxicity ranged from weeks to as long as 20 years in follow-up studies on pediatric patients.8

**ALKYLATING AGENTS**

The major alkylating agents associated with cardiac problems are CTX, ifosfamide (IFM), nitrogen mustard, alkeran and platinum compounds and mitomycin. CTX and IFM are converted in the liver to active cytotoxic efficacy as phosphoramid mustard. While cardiac injury is not as well understood as with anthracyclines, there appears to be an increase in intracellular oxide radicals. Doses of CTX are well tolerated in most combination regimens, but in the high doses used in bone marrow transplant programs, 2-10% of patients experience cardiotoxicity ranging from reversible systolic dysfunction to acute CHF and cardiomyopathy.
Early observations by oncologists at Baylor College of Medicine and The Methodist Hospital in 1979 reported that platinoids could be linked to myocardial infarction and other cardiac events as mentioned previously. Enhanced platelet aggregation increased thromboxanes and appeared to activate arachidonic acid activity. In addition, endothelin, a powerful vasoconstrictor peptide, may play a role in several alkylating agents that cause coronary spasm. Cardiovascular collapse has been acute in other settings, causing hypotension and vasodilatation that necessitate vasopressors and close monitoring; partial or complete reversal may require hours of treatment. This has occurred in successive patients on several separate occasions in our experience, warranting permanent discontinuance of drugs.

**ANTIMETABOLITES**

5-FU and its oral preparation have been associated with angina, infarction, arrhythmias, CHF and even sudden death. Continuous 96-hour infusions seem less risky — possibly because of the dilutional effect as opposed to bolus administration. As seen with CTX, endothelin has been implicated in vasoconstriction. Recurring cardiac events have required discontinuance of treatment.

The folic acid antagonist methotrexate (MTX) and its analogues can occasionally cause cardiac difficulties. For example, within several seconds of IV-MTX, one of our patients experienced atrial flutter with 4:1 block that was easily reversed with carotid massage on three successive occasions.

Methotrexate lung syndrome can cause cor pulmonale and attendant cardiac sequelae that vary in severity depending on current or post exposure to cardiac cancer drugs. The same situation has been seen with drugs in other categories (e.g., bleomycin) in which acute drug-induced pneumonitis (Figure 4) progresses to diffuse pulmonary fibrosis and cor pulmonale with combined cardiorespiratory failure if the drug is not discontinued.

**TAXANES**

These preparations, mainly taxol or taxotere, have negative effects on the heart both alone and when combined with platinoids. Hypotension, brady-tachy arrhythmias, coronary ischemia and conduction problems have occurred in 5% of patients in Phase I and II studies at Johns Hopkins. Previous or current anthracyclines-taxanes or combinations have also resulted in CHF, and it is suspected that taxane toxicity is associated with both histamine release and myocyte damage by effecting subcellular organelles.

**IMMUNOTHERAPY**

Interleukin (IL-2) alone or coupled with interferon, platinoids, dacarbazine and vinca alkaloids as commonly employed in melanoma protocols frequently causes hypotension and sometimes shock. Such patients may require treatment and monitoring in an intensive care unit. Capillary leak syndrome is the extension of this clinical complex.

Herceptin (Trastuzumab) and other monoclonal antibodies used in breast cancer protocols, employed alone or in combinations with anthracyclines, CTX, 5-FU or platinoids, have resulted in cardiac dysfunction in 5-28% of patients. Herceptin treatment is directed toward the HER-2 receptor protein in breast cancer cells and may result in CHF in an acute setting.
MISCELLANEOUS AGENTS

A host of antiangiogenic drugs are now available and have activity versus neovasularity associated with primary and metastatic tumors. Acute events include hypertensive crisis and stroke, and chronic cardiotoxicity information is not yet available. All individuals on treatment require close observation because the toxicity spectrum of cardiac events is incomplete at the present. Other agents including vinca alkaloids, fludarabine and busulphan may have cardiotoxic sequelae.

Future pharmacologic targets may utilize drug metabolic inhibitors, selective delivery modalities, analogue development and improved cardiac therapeutics beyond the current applicability of ACE-inhibitors, calcium channel active agents and vasopressors.

REFERENCES


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Table 1.
Randomized Clinical Trials with Dexrazoxane.
A reduction in the LVEF to <45% or ≥20% reduction in LVEF from baseline and/or a ≥2-point increase in the Billingham biopsy score
LVEF = resting left ventricular ejection fraction
RR = objective response rate
*Including clinical signs of CHF
** cumulative doxorubicin dose 400 to 499 mg/m²


