CANCER DRUGS AND CARDIOVASCULAR TOXICITIES

Frank E. Smith

From Methodist OeBakey Heart Center and Baylor College of Medicine, Houston, Texas

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.

ANTHRACYCLI NES

Anchracyclines are commonly employed co 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, cardiomyopachy and congestive heart failure (CHF) are common.[2] Epirubicin and mitoxanrrone 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 coral doses of adriamycin may have a mortality risk as high as 50% after che first episode (Figure I).

Infusion rimes of 72-96 hours have been intermittently successful in delaying the onset of cardiomyopathy but not enough to be recommended for general use. Historically, ocher anthracyclines such as rubidazone appeared less cardiocoxic but also displayed less antitumor effect.3

Acute cardiocoxicity 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-myocardicis 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 dysfunccion.4

Levels of croponin and B-nacriuretic peptide from myocytes in both symptomatic and asymptomatic patients with lefr ventricular dysfunction at any level are frequendy elevated, bur specific guidelines fur serial determinations are nor 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-nacriurecic peptide that further increased on therapy - without

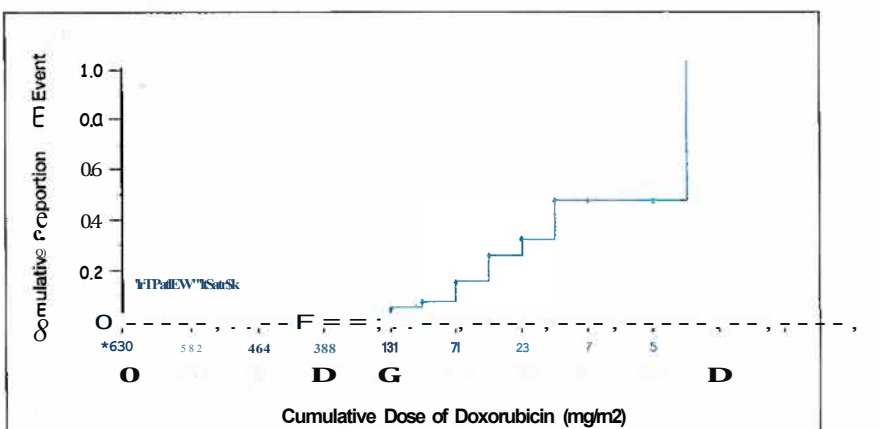

Figure 1.
Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo.

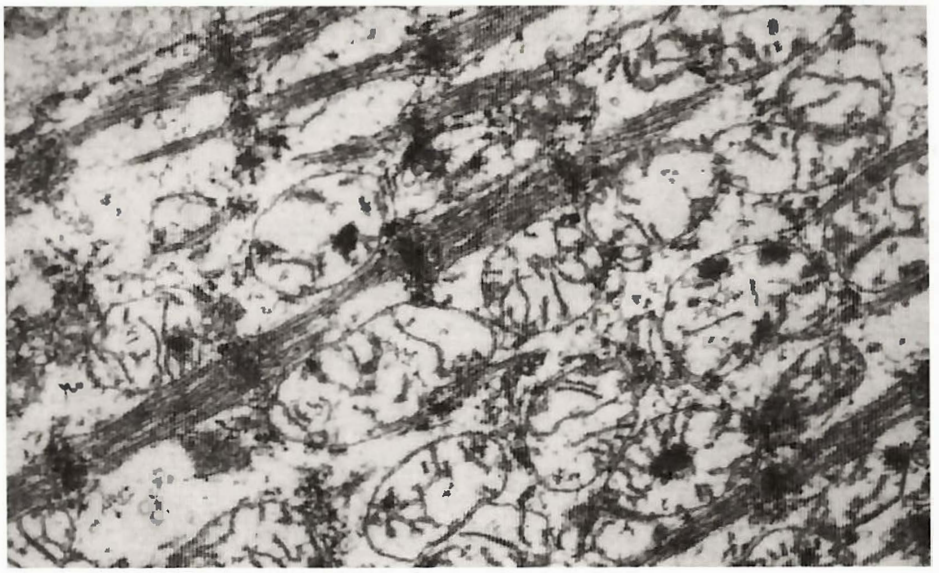

Figure 2.
An electron microscopic view of adriamycin myocardiopathy showing total disarray of muscle fibers and cellular organelles.

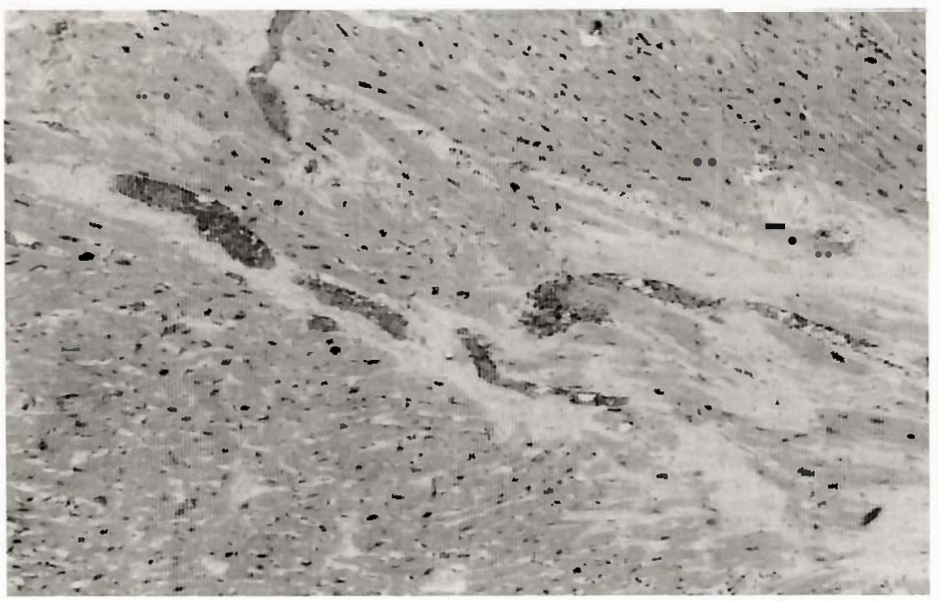

Figure 3.
The myocardium of a patient with late cardiac decompensation, showing myocyte loss with replacement by fibrosis, hypertrophy of the remaining myocytes, and no evidence of myocarditis with lymphocytic infiltration.

detectable clinical worsenmg - and returned co baseline after infusion was completed. Prospective studies correlated with newer echo-Doppler techniques, as described by W. Zoghbi, could better outline the course of cardiotoxicity.7

Pathogenesis of cardiotoxicities is thought to be associated with formation of free radicals and super oxides created by iron complexes chat lead to "oxidative stress" in myocyces. Biopsy studies have shown discorced 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 anchracycline 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 wich and without dexrazoxane, as described by F. Roila.

Lascly, the time range from anthracycline exposure co 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 phosphoramide 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 placinoids could be linked to myocardial infarction and other cardiac events as mentioned previously.9 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 senings, causing hypotension and vasodilatacion 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.

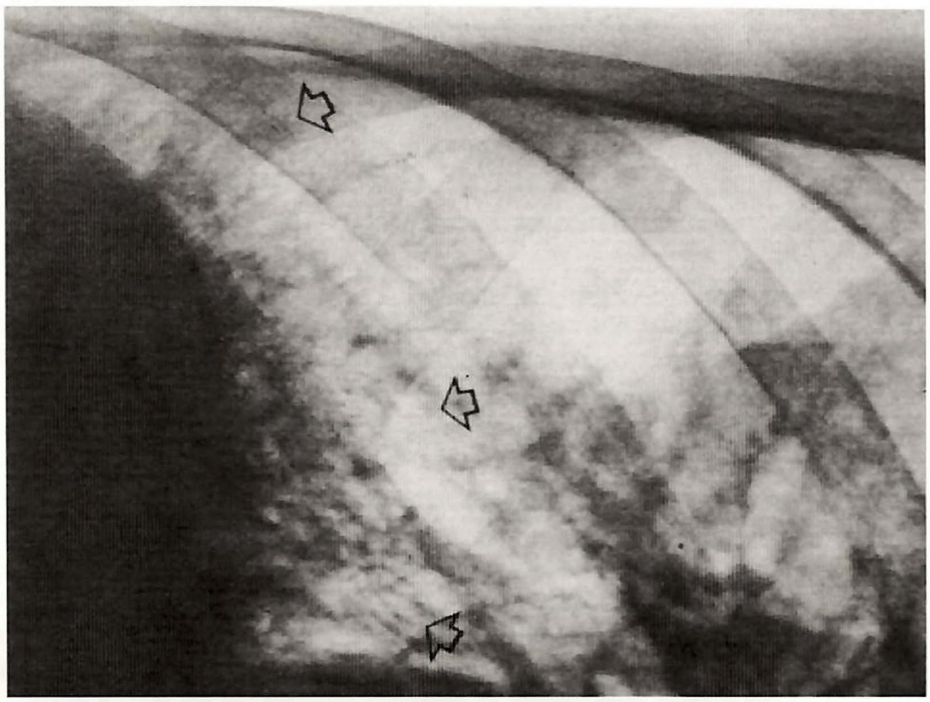

Figure 4.
Posteroanterior roentgenogram with magnified view of the right lung base. Shows fine interstitial reticulation and reticulonodularity above the diaphragm which occur in early pulmonary toxicity.

ANTI METABOLITES

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, endochelin has been implicated in vasoconscricrion. Recurring cardiac events have required discontinuance of treatment.

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

Mechocrexate lung syndrome can cause cor pulmonale and attendant cardiac sequelae chat 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 cardiorespirarory 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.[10] Previous or current anthracyclines-taxanes or combinations have also resulted in CHF, and ic is suspected chat taxane roxicity 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 creatment and monitoring in an intensive care unit. Capillary leak syndrome is the extension of chis 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.1' 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 neovascularity associated with primary and metastatic tumors. Acute events include hypertensive crisis and stroke, and chronic cardiotoxiciry information is nor yet available. All individuals on treatment require dose observation because the toxicity spectrum of cardiac events is incomplete at the present. Other agents including vinca alkaloids, fludarabine and busulphan may have cardiocoxic sequelae.

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

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Author (ref.)	No. of Points	Regimens	Anthra.	Cardiac E(o)s	LVEF (%)	CHF (%)	RR (%)	Median Overall Survival
Speyer, JL NEJM 1988;319:745	45 47	FAG FAC+DXR	No	NR NR	16** 1**	11 2	45 48	NR NR
Speyer, JL JCO 1992;10:117	74 76	FAC FAC+DXR	No	NR NR	43 7	27 2.6	41 37	16.7 months 18.3 months
Venturini, M JCO 1996;14:3112	78 82	EPI/FEC EPI/FEC+DXR	No	23.1 7.3	18 4.8	5.1 2.4	47.6 46.2	NR NR
Swain, SM JCO 1997;15:1318	181 168	FAC+PLA FAC+DXR	No	31 15	NR NR	15 0	60.5 46.8	551 days 598 days
Swain, SM JCO 1997;15:1318	104 81	FAC+PLA FAC+DXR	No	31 14	NR NR	7 2	49.3 53.7	553 days 458 days
Swain, SM JCO 1997;15:1333	99 102	FAC+PLA FAC+PLA+DXR	No	60 25	NR NR	22 3	NR NR	460 days 882 days
Lopez, M JCO 1998;16:86	49 43	EPI EPI+DXR	Yes	NR NR	12.6 1.2	4 0	67 69	19 months 29 months

Table 1.

Randomized Clinical Trails 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

CHF = congestive heart failure

NR = not reported

** cumulative doxorubicin dose 400 to 499 mg/m^2