Long-Term Cardiac and Pulmonary Complications of Cancer Therapy

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• Anthracyclines • Cardiac toxicity • Pulmonary toxicity
• Radiotherapy • Taxanes • Trastuzumab

Many systemically administered chemotherapeutic and biologic agents may cause late cardiovascular complications.[1,2] Late cardiac effects are most commonly related to cancer treatment by anthracyclines, mitoxantrone, paclitaxel, docetaxel, and trastuzumab. The cardiotoxicity that results from mediastinal radiotherapy is discussed in detail. Pulmonary complications of chemotherapy and radiotherapy are discussed separately.

ANTHRACYCLINE-RELATED CARDIAC TOXICITY

Anthracyclines are a group of important potent drugs used in the treatment of many pediatric and adult malignancies. Anthracycline cardiomyopathy is characterized by a dose-dependent progressive decrease in systolic left ventricular function often leading to congestive heart failure. Abnormalities in left ventricular size and function measured by noninvasive testing can be detected before the development of overt congestive heart failure. Patients who have abnormal heart function following treatment with anthracyclines may or may not have clinical symptoms.

The delayed cardiomyopathy associated with anthracycline therapy presents clinically as classic congestive heart failure, including fatigue, shortness of breath, dyspnea on exertion, sinus tachycardia, S3 gallop rhythm, pedal edema/pleural effusions, and elevated jugular venous distention. These may be subtle at onset and progress gradually.

Anthracycline cardiomyopathy risk depends on the cumulative total dose.[3] At 450 mg/m^2 for doxorubicin there is a 5% risk, and for other anthracyclines this cumulative dose is: 900 mg/m^2 for daunorubicin, 935 mg/m^2 for epirubicin, and 223 mg/m^2 for idarubicin. Mediastinal irradiation that includes the heart, older (particularly >70 years) or younger (<15 years) age, coronary artery disease, other valvular or myocardial conditions, and hypertension are cofactors in cardiomyopathy risk. When administered concurrently, trastuzumab may potentiate anthracycline cardiotoxicity. Other agents with known cardiotoxic effects may be additive.

Cardiac dysfunction is established by comparing baseline with serial left ventricular function studies. Left ventricular ejection fraction (LVEF) may be measured by echocardiography or nuclear imaging and 50% or more is considered within the normal range. A low LVEF contraindicates the use of anthracyclines.

Typical findings on echocardiograms are left ventricular diastolic/systolic dysfunction and later septal wall motion dysfunction. The left ventricle is initially not enlarged or only moderately enlarged.

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Global hypokinesis and muscle wall thinning is seen with late cardiomyopathy. Sinus tachycardia, low voltage, poor R-wave progression, and nonspecific T wave changes are noted on EKG, but these are late findings and can be nonspecific.

In pediatrics, subclinical cardiomyopathy is more common than in adults at comparable doses, resulting in progressive loss of ventricular mass, reduced cardiac output, and restrictive cardiomyopathy. There does not seem to be a threshold cumulative dose below which left ventricular dysfunction is not seen.[4–7]

Prevention of late cardiomyopathy requires the recognition of early dysfunction during chemotherapy. A decrease in ejection fraction, changes in diastolic function, and changes in troponins/brain natriuretic peptide have all been studied and are predictive in small series. The simplest is serial LVEF in susceptible patients, and discontinuing anthracycline with a significant decrease from baseline.[8–10] For doxorubicin, a repeat study should be performed at 200 mg/m^2, and all patients should have a follow-up study at 300 to 400 mg/m^2 and every 50 to 100 mg/m^2 thereafter.

Anthracycline strategies to reduce cardiovascular risk include: analogs, low-dose or infusional drug schedules, and the use of liposomal formulations.[11,12] Dexrazoxane decreases the risk for clinical cardiomyopathy with doxorubicin doses of 300 mg/m^2 or more.[13] Its role in upfront treatment regimens remains under investigation.

Anthracycline cardiomyopathy is managed like other causes of dilated cardiomyopathy with ACE inhibitors, β-blockers, and diuretics. These measures are palliative rather than curative and, unfortunately, the dysfunction may be progressive despite these agents. Cardiac transplantation provides the only curative option.

Selective cardiomyocyte apoptosis seems to play a major role in the development of anthracycline cardiomyopathy.[14] Cardiomyocyte metabolism of the anthracycline generates free radicals resulting in membrane lipid peroxidation with the consequent activation of the extrinsic and intrinsic apoptotic pathways, and cardiomyocyte intrinsic antioxidant defense is more limited than that of other organs.

Mitoxantrone is an anthracenedione, structurally related to the anthracyclines, and also causes a dose-related cardiomyopathy. Mitoxantrone cardiomyopathy is rarely seen before 100 mg/m^2 cumulative dose. LVEF should be monitored regularly thereafter and a total dose of 140 mg/m^2 should not be exceeded. Sequential use of doxorubicin followed by mitoxantrone raises cardiomyopathy risk.[15] The mechanism of cardiac damage with mitoxantrone is not fully understood.

TAXANES-RELATED CARDIAC TOXICITY

The taxanes, paclitaxel and docetaxel, are important antimicrotubule agents derived from the yew tree and their cardiotoxicity seems to be related to the taxane ring structural similarities to yew taxine.

Most of paclitaxel's cardiovascular effects are acute/subacute (asymptomatic bradycardia, hypersensitivity reactions, and life-threatening atrial or ventricular rhythm disturbances or conduction abnormalities in approximately 0.5% of patients).[16]

Congestive heart failure does not seem to be caused by paclitaxel, whereas it does seem to potentiate doxorubicin-associated cardiac dysfunction. The sequencing of paclitaxel and doxorubicin are critical in the development of cardiotoxicity [17–20] and is believed to be attributable to an interaction that results in reduced doxorubicin elimination and higher plasma levels.[21] Doxorubicin clearance is therefore paclitaxel schedule–dependent, occurring most prominently when paclitaxel immediately precedes doxorubicin or follows it by less than 1 hour. The taxane docetaxel does not seem to enhance doxorubicin cardiac dysfunction.[22] Although both taxanes increase toxic cardiomyocyte doxorubicinol production in vitro, only paclitaxel seems to be clinically cardiotoxic.

TRASTUZUMAB-RELATED CARDIAC TOXICITY

Trastuzumab is a humanized monoclonal antibody targeting p185^{HER2} (ErbB2 or HER2 receptor), a transmembrane receptor tyrosine kinase of the epidermal growth factor family. This receptor protein is overexpressed or amplified in 20% to 30% of breast cancer and trastuzumab is an important agent in the management of Her2-positive breast cancer.

Cardiac ErbB2 is essential for normal adult cardiac function; in a mouse model it has been shown that cardiac ErbB2-deficient mice develop a dilated cardiomyopathy beginning in the second postnatal month through adulthood. In addition, ErbB2-deficient cardiomyocytes are more susceptible to anthracycline toxicity.[23,24]

Trastuzumab is specific for the human ErbB2 receptor and cannot be studied directly in mice. A two-hit model, in which hemodynamic overload or anthracycline exposure with trastuzumab promotes the development of cardiomyopathy, has been proposed.[25] In a recent prospective human study, trastuzumab preceding anthracycline-based adjuvant therapy revealed no cardiac toxicity, supporting this hypothesis.[26]