Chemotherapy Induced Cardiotoxicity

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ABSTRACT

Treatment for cancer has improved and the number of cancer survivors is expected to increase from 11.7 million in 2007 to 18 million by 2020. However, chemotherapy and radiation therapies for cancer can have long lasting effects for patients. One notable side effect is cardiotoxicity, commonly caused by anthracycline chemotherapeutic agents. The most promising diagnostic procedure has been tracking the decline of Left Ventricular Ejection Fraction (LVEF). The only approved treatment by the FDA is Dexrazoxane, though it is only approved for patients under 16 years old. Adult patients are treated prophylactically with organic heart failure medications. Efficient detection and rapid treatment have become a high priority due to the increasing number of cancer survivors and therefore increased number of patients who will experience cardiotoxicity.

TABLE 1: Risk factors for cardiotoxicity

Risk Factors	Parameters
Age	<4 and >65 years old
Total cumulative dose of anthracycline	At a cumulative dose >550mg/m^2 the risk of cardiotoxicity is five times higher than lower cumulative doses
Intravenous bolus administration	Bolus administration compared to prolonged infusion has increased risk for toxicity
Radiation therapy	Previous mantel mediastinal radiation
Higher single doe	Higher individual doses are associated with increased toxicity
Sex	Female greater than male
The use of other concomitant agents known to have cardiotoxic effects	Such as cyclophosphamide, trastuzumab, and paclitaxel may increase susceptibility to cardiotoxicity
Increased length of time since anthracycline completion[2]	

INTRODUCTION

Early detection and treatment are key to reducing morbidity and mortality in chemotherapy induced cardiotoxicity. Anthracycline chemotherapy is the most effective treatment for breast cancer, soft tissue sarcomas, lymphomas, leukemias, and childhood solid tumors.[1] With anthracyclines being so widely used, it is imperative to fully understand the cardiac complications that can arise. Since 1960, when anthracycline agents were first introduced, providers have seen cardiotoxic side effects, sometimes years after administration.[2] Combination chemotherapeutics like anthracycline and Trastuzumab, a leading treatment for breast cancer, can have an additive cardiotoxic effect making the most effective treatments also potentially the most harmful.[3] There are many risk factors (Table 1) that contribute to a patient developing cardiotoxicity, but the most prominent is age.

PATHOPHYSIOLOGY

Anthracycline chemotherapeutics cause dose dependent, cumulative, irreversible cardiomyocyte damage and loss.[1] The damage occurs most often by cardiomyocyte oxidative stress and cell death from free radical injury that leads to DNA damage.[1] Cardiac myocyte death and sarcomere disruption are also associated with anthracycline use. The heart is slow to repair itself and therefore repeated use of anthracyclines can lead to cumulative toxicity causing left ventricular dysfunction and heart failure.[2] This cumulative damage usually begins as diastolic heart failure and develops into systolic cardiac dysfunction.[4] Anthracycline agents can also cause apoptosis of cardiomyocytes using the same mechanism of action the drug uses on cancer cells.[4] All of these mechanisms can be occurring in tandem, leaving those with predisposing risk factors or those receiving high doses of chemotherapeutics, to potentially develop indefinite heart failure.

DIAGNOSIS

The biggest indicators for future heart failure were the anthracycline dose and LVEF prior to the last treatment. In 98% of cases, cardiotoxicity occurred within the first year, though cardiotoxicity has been identified up to 11 years after completed treatment.[5] Cardiac markers for organic heart failure, like BNP, cannot be used to detect chemotherapy induced cardiotoxicity due to the difference in the mechanism of destruction. There are specific biomarkers being researched for chemotherapy induced cardiotoxicity like peptide SAA-1525, but these biomarkers are not yet widely used.[6] The most common imaging modalities are multigated acquisition and echocardiography with strain imaging to detect cardiac changes, specifically to reduced ejection fraction.

TABLE 2: Management of cardiotoxicity

	Method of action	Common Medications and Dosages	Adverse Effects	Contraindications	Monitoring
Dexrazoxane	The agent binds iron in blood before entering cardiomyocytes preventing formation of an iron-anthracycline complex thereby preventing the formation of free radicals and thus decreasing cardiac damage[7]	• 10:1 ratio dexrazoxane: chemotherapeutic agent given by IV	• Severe nausea • Vomiting • Easy bruising • Unusual bleeding • Blood stool • Long term loss of fertility[7]	• Breastfeeding during tx and for 2wk after • Caution if CrCl <40 • Caution if hepatic impairment • Caution if myelosuppression	• Cr • Pregnancy test at baseline • CBC w/ diff • LFTs at baseline and before each dose • Cardiac fxn at baseline, then periodically
Beta Blockers	The agent treats diastolic heart failure, because it slows the heart rate and allow more time for your heart to fill with blood. This allows the left ventricle to fill more completely and increases the ejection fraction	• Bisoprolol 10 mg daily • Metoprolol ER 200 mg daily • Carvedilol 50mg daily	• Bradycardia • Heart block • Raynaud phenomenon • Bronchospasm • Headache • URI • Dizziness	• Beta blockers may be considered in patients who have reactive airway disease with caution • Caution if marked bradycardia (HR<55) or marked hypotension (systolic < 80 mm Hg)	• Cr at baseline • BP • HR
Statins	The agent promotes improvement of endothelial function, attenuation of cardiac hypertrophy, the inhibition of neurohormonal activation, and the reduction of proinflammatory activation	• Rosuvastatin10 mg/day • Simvastatin 10mg	• Tendon rupture • Rhabdomyolysis • Acute renal failure • Hepatotoxicity • Pancreatitis • Headache • Constipation	• Pregnancy • Myopathy • Unexplained elev. LFTs • Active hepatic dz • Caution if alcohol abuse	• Cr at baseline • LFTs at baseline, then as clinically indicated • CK at baseline if myopathy risk, then as clinically indicated
ACE Inhibitors	The agent blocks the action of an enzyme that causes blood vessels to narrow. As a result, blood vessels relax and widen. This lowers blood pressure and makes it easier for the heart to pump blood	• Captopril50 mg tid • Enalapril 10 mg bid • Lisinopril 10-40 mg qd	• Cough- common • Renal Insufficiency • Angioedema • Hypotension • Dizziness • Fatigue • Hyperkalemia	• Pregnancy • Angioedema	• Hyperkalemia (> 5.0 mEq/L) • Renal Insufficiency (Scr > 3.0 mg/dl) • Hypotension (systolic < 80 mm Hg) • Bilateral RAS

CONCLUSIONS

Chemotherapy induced heart failure is a common side effect of anthracycline chemotherapy use and there are no universal guidelines for detection and treatment of these patients. Diagnosis using echocardiography with strain imaging to detect decreased LVEF is used most, but the prospect of biomarkers is hopeful for early detection of damage. Prophylactic treatment is currently best, but the proper dosing and timeline for administration has yet to be standardized. Beta blockers are the most studied agent in adult patients and have been shown to reduce the rate of developing heart failure. Dexrazoxane is the only medication to be specifically approved by the FDA for chemotherapy induced cardiotoxicity, though its use is limited to those under 16 years old. A summary of treatment options are listed in Table 2. As the numbers of cancer survivors rise, it is imperative to have more trials and published guidelines to best protect these survivors and help them live a healthy life after cancer.

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