ORIGINAL RESEARCH PAPER

Clinical Psychology

CARDIOMIOPATHY AND CHEMOTERAPY

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ABSTRACT

Cardiomyopathy is an adverse outcome of antineoplastic drug therapy that has become increasingly relevant in the management of cancer survivors. As the efficacy of anticancer treatments has improved, long-term outcomes are altered by the development of cardiotoxicity, which may be associated with an even worse prognosis than that of the underlying malignancy. From the research into mechanisms, prevention, and treatment, the specialized field of cardio-oncology has evolved, but the recognition and appropriate management of these patients is important for the general internist and general cardiologist as well.

INTRODUCTION

Chemotherapies are effective in most cancers; their use is limited by the potential for cardiotoxicity. These severities of these effects are related to the chemotherapy regimens and duration. Toxicity can occur early (within 1 year) or late (particularly among children, where late cardiac abnormalities are detectable in two thirds of surviving patients).

Many trials address the role of ACE inhibitors and beta-blockers, effective therapies for established LVSD, in preventing chemotherapy induced cardiotoxicity.

- Previous heart conditions or diseases that may have caused damage to your heart, such as coronary heart disease and hypertension (high blood pressure).
- Anthracyclines are a type of chemotherapy medication. They include doxorubicin, daunorubicin, epirubicin, and idarubicin.
- Trastuzumab . This type of chemotherapy medication is used to treat breast cancer and can cause cardiomyopathy. In many cases, once you stop taking it, the cardiomyopathy should partially or fully go away.
- Radiation treatment to your chest can also put you at a higher risk for developing cardiomyopathy.

Symptoms of Cardiomyopathy

The following are common signs of cardiomyopathy:

- Trouble breathing when you are active or resting. Some people might also need to sleep sitting up or with many pillows under their head to help them breathe.
- Fatigue
- Swelling in your legs, ankles, or feet.
- Coughing, which may be worse when lying down at night.
- Sudden weight gain.
- Bloating in your abdomen (belly).
- Feeling dizzy, weak, or lightheaded.
- Heart palpitations, which may feel like a fluttering or pounding feeling in your chest.

Chemotherapy induced cardiomyopathy

Cardiotoxicity may compromise the clinical effectiveness of chemotherapy, affecting the patient's survival and quality of life independently of the oncological prognosis. There are 2 types of cardiac toxicities, type I which is more serious and result in permanent damage to the myocardium and type II which is usually reversible.

Anthracyclines to play a prominent role in the treatment of a wide variety of both hematologic and solid tumors; it is now well established that anthracycline cardiotoxicity is a cumulative dose-related effect, suggesting that each administration constitutes additive or sequential damage. However, there are a number of other chemotherapy agents that cause cardiotoxicity and yet are not well recognized Cardiac events associated with chemotherapy vary in incidence and may occur acutely (during or shortly after treatment), sub-acutely (within days or weeks after completion of chemotherapy) or chronically (weeks to months after drug administration).They may also occur as late squeal, many years after the end of treatment. Cardiac events associated with chemotherapy may consist of mild blood pressure changes, thrombosis, Electrocardiographic (ECG) changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure), and congestive heart failure (CHF). The substantial limitations of using only changes in LVEF are compromised further by our knowledge that approximately half of all heart failure occurs in patients who maintain a normal LVEF; their overall cardiac outcomes are similar to those who exhibit a low LVEF.

Cardiotoxicity may depend on the dose administered during

each course or on the total cumulative dose, or may be completely independent of the dose like Anthracycline-induced cardiotoxicity which has been recognized for more than 20 years. It has been described as 3 distinct types of cardiotoxicity. Acute or sub-acute injury is a rare form of cardiotoxicity that may occur immediately after a single dose or a course of anthracycline therapy, with clinical manifestations occurring within a week of treatment. These may be in the form of transient electrophysiological abnormalities, a pericarditis, myocarditis syndrome or acute left ventricular failure. The electrophysiological abnormalities may present as nonspecific ST and T wave changes, T wave flattening, decreased QRS voltage and prolongation of QT interval. Sinus tachycardia is the most common rhythm disturbance. ECG changes may be seen in 20 to 30% of the patients. Arrhythmias, including ventricular, supraventricular and junctional tachycardia, are seen in 0.5 to 3% of patients with an overall incidence of 0.7%. More serious arrhythmias, such as atrial flutter or atrial fibrillation, are rare. Sub-acute cardiotoxicity has resulted in acute failure of the left ventricle, pericarditis or a fatal pericarditis-myocarditis syndrome in some rare cases. The ECG changes or arrhythmias do not seem related to chronic cardiomyopathy.

Chronic anthracycline-induced cardiomyopathy usually presents within a year of treatment. It may persist or progress even after discontinuation of anthracyclines therapy, and may evolve into a chronic dilated cardiomyopathy in adult patients and restrictive cardiomyopathy in pediatric patients. Late onset chronic progressive anthracycline cardiotoxicity causes ventricular dysfunction, heart failure and arrhythmias years to decades after chemotherapy has been completed. This suggests that patients who have received anthracyclines chemotherapy and survived their cancer may have undetected increases in morbidity and mortality due to cardiotoxicity. There may be a period of time, after completion of treatment, during which patients may experience no symptoms of left ventricular dysfunction or arrhythmia and cardiac function may appear normal. After the initial acute myocardial insult, there is a progressive decrease in ventricular function leading to late onset decompensation. An increased incidence of severe echocardiographic abnormalities has been seen with increased duration of follow-up. Cumulative doses of doxorubicin as low as 228 mg/m2 have shown to increase after-load or decrease contractility, or both, in 65% of patients with leukaemia up to 15 years after treatment with anthracyclines. Late onset arrhythmia and sudden death has occurred more than 15 years after anthracycline treatment.

Pathogenesis

It is probably multi-factorial. Free radicalmediated myocyte damage is one of the most thoroughly studied mechanisms by which anthracyclines have been proposed to cause cardiotoxicity. The myocardium is more susceptible to free radical damage than other tissues because it has comparatively less superoxide dismutase and catalase activity, and its major defense against free radical damage, glutathione peroxidase, is suppressed by doxorubicin. The superhydroxide free radicals accumulate and cause severe lipid peroxidation, leading to extensive destruction of the mitochondrial membranes, endoplasmic reticulum and nucleic acid. Circulating pro-inflammatory cytokines have also been implicated in anthracycline cardiotoxicity. Doxorubicin induces the release of histamine and tumour necrosis factor- from macrophages and interleukin-2 from monocytes. These cytokines have functional receptors on the myocardium and their release may result in dilated cardiomyopathy. Adrenergic dysfunction and down regulation of myocardial histamine and β-adrenergic receptors has also been proposed as a cause for an evolving and established anthracyclineinduced ventricular dysfunction.

Risk factors

Some of the risk factors cardiotoxicity have been reported. These include cumulative dose, rate of drug administration, mediastinal radiation, advanced age, younger age, female gender, pre-existing heart disease and hypertension.

Serial and post-therapy cardiac monitoring is necessary to reduce morbidity due to anthracycline- induced cardiotoxicity. Patients should be monitored for clinical signs of cardiomyopathy by physical examination, chest x-rays, ECG, echocardiogram, endomyocardial biopsy if feasible and radionuclide angiography before initiation of treatment and at periodic intervals during therapy.

Biomarkers such as B-type natriuretic peptide and troponins (I and T) are increasingly being used to stratify patients into higher and lower risk categories. This process is well established in the cardiology literature and recently has been reported in oncology patients. In fact, an elevated troponin during chemotherapy seems to correlate with increased risk for the development of cardiac toxicity.

The use of anti-oxidant agents or iron chelators finds their way in the prevention for cardiac toxicities. Probucol, vitamin E (as anti-oxidants) and carvedilol have shown promise in animal studies.

Angiotensin-converting enzyme (ACE) inhibitors (ACEIs) have been shown to slow the progression of left ventricular dysfunction in several different clinical settings, including anthracycline-induced cardiomyopathy.

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