Review Article

Cardiomyopathy Associated With Cancer Therapy

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ABSTRACT

Chemotherapy-associated cardiomyopathy is a well known cardiotoxicity of contemporary cancer treatment and a cause of increasing concern for both cardiologists and oncologists. As cancer outcomes improve, cardiovascular disease has become a leading cause of morbidity and mortality among cancer survivors. Asymptomatic or symptomatic left ventricular systolic dysfunction in the setting of cardiotoxic chemotherapy is an important entity to recognize. Early diagnosis of cardiac injury through the use of novel blood-based biomarkers or noninvasive imaging modalities may allow for the initiation of cardioprotective medications or modification of chemotherapy regimen to minimize or prevent further damage. Several clinical trials are currently underway to determine the efficacy of cardioprotective medications for the prevention of chemotherapy-associated cardiomyopathy. Implementing a strategy that includes both early detection and prevention of cardiotoxicity will likely have a significant impact on the overall prognosis of cancer survivors. Continued coordination of care between cardiologists and oncologists remains critical to maximizing the oncologic benefit of cancer therapy while minimizing any early or late cardiovascular effects. (*J Cardiac Fail 2014;20:841−852*)

Key Words: Cardiotoxicity, chemotherapy, congestive heart failure.

The landscape of cancer care has evolved over the past 20 years with the development of more aggressive cancer screening programs, improvements in diagnostic testing, and more effective treatment options. As a result, cancer death rates have declined 20% from 1991 (215.1 per 100,000 population) to 2009 (173.1 per 100,000 population), and the population of cancer survivors is projected to increase to nearly 18 million by 2022.[1] What has become clear, however, is that the benefit of many successful anticancer therapies is attenuated by adverse cardiotoxic effects. As cancer survival increases in the new era of improved chemotherapeutics, competing cardiac causes of morbidity and mortality will have a significant impact on long-term patient outcomes. This is an area of growing concern for both oncologists and cardiologists and has led to the development of a new field of cardio-oncology which focuses on the treatment and prevention of cardiovascular disease among cancer patients.

Chemotherapy-associated cardiomyopathy is a well known cardiotoxicity and is the primary focus of this review. A list of chemotherapeutic agents associated with cardiomyopathy is summarized in Table 1. Anthracyclines are among the oldest chemotherapeutic agents, and their cardiotoxic effects have been studied for >30 years.[16−18] Several other classes of chemotherapeutic agents also have been identified to cause significant cardiac toxicity, including alkylating agents, tyrosine kinase inhibitors, antimicrotubule agents, and monoclonal antibody−based targeted therapies.

Attempts to develop improved strategies for the diagnosis of cardiotoxicity beyond measurement of left ventricular ejection fraction (LVEF) have been a major focus of recent investigation. Biomarkers and noninvasive imaging modalities (ie, tissue Doppler imaging, speckle-tracking strain echocardiography, and cardiac magnetic resonance imaging [MRI]) have been proposed for the early detection of cardiotoxicity. Small clinical trials have shown modest success with the use of standard heart failure pharmacotherapy, including beta-blockers and angiotensin-converting enzyme inhibitors (ACE-Is), to prevent left

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Table 1. Chemotherapeutic Agents Associated With Cardiomyopathy

Chemotherapeutic Agent	Incidence (%)[2]	Proposed Mechanism of Action	Comments
Anthracyclines			
Doxorubicin	3–26	Free radical formation and increased oxidative stress, leading to apoptosis and cell death; potentially mediated by topoisomerase-II-β[3]	Acute cardiotoxicity, a rare complication, occurs immediately after infusion (<1%). Chronic cardiotoxicity can first be detected many years after exposure but not uncommonly occurs within the 1st year of treatment. Risk is dose dependent and increases with cumulative dosing >400 mg/m^2.
Liposomal doxorubicin	6–13[4–6]		
Epirubicin	0.9–3.3		
Idarubicin	5–18		
Alkylating agents			
Cyclophosphamide	7–28	Increase in free oxygen radicals; direct endothelial injury[7]	Acute cardiac toxicity is associated with high dose conditioning regimens (120–180 mg/kg) commonly used for bone marrow transplantation.
Ifosfamide	17		
Monoclonal antibodies			
Trastuzumab	2–28	Inhibition of ERBB2 signaling, activation of mitochondrial apoptotic pathway; impaired cardiac repair pathways	Associated risk factors include anthracycline exposure, age, and baseline LVEF.[8]
Bevacizumab	1.7–3	Anti-angiogenesis	CHF reported among patients with metastatic breast cancer treated with prior anthracycline.[9]
Tyrosine kinase inhibitors			
Abl kinase inhibitors			
Imatinib	0.5–1.7	Abl kinase inhibition and mitochondrial dysfunction	Most commonly seen in elderly patients with underlying cardiac risk factors (eg, diabetes, hypertension, coronary artery disease, and arrhythmia)[10]
Dasatanib	2–4		
Multikinase inhibitors			
Sunitinib	15–20[11]	Off-target kinase inhibition	Cardiomyopathy may be exacerbated by sunitinib induced hypertension.[12]
ERBB2 inhibitors			
Lapatinib	1.5–2.2	Inhibition of ERBB2 and EGFR	Lower incidence of cardiomyopathy and heart failure compared with trastuzumab[13]
Antimicrotubules			
Docetaxel	2.3–8	Increased microtubule density leading to contractile dysfunction[14]; histamine release; induction of myocyte damage by affecting subcellular organelles[7]	Potentiates the cardiotoxicity of anthracyclines when given concurrently
Paclitaxel	—		
Proteasome inhibitors			
Bortezomib	2–5	Interference with the ubiquitin proteasome system, resulting in accumulation of toxic proteins within cardiomyocytes	—
Carfilzomib	4[15]		

LVEF, left ventricular ejection fraction; CHF, congestive heart failure.

ventricular (LV) dysfunction associated with cancer therapy. However, there remains no clear consensus on the appropriate use of these therapies in the cancer setting. We will review the current evidence relating to the early detection, treatment, and prevention of cancer therapy–associated cardiomyopathy.

Clinical Criteria for Chemotherapy-Associated Cardiomyopathy

The term "cardiotoxicity" refers broadly to any cardiovascular side effect related to cancer therapy (ie, heart failure, cardiomyopathy, arrhythmias, ischemia, valvular disease, pericardial disease, hypertension, or thrombosis). For the purposes of this review, however, cardiotoxicity will be used to refer to LV dysfunction that develops as a result of chemotherapy-induced myocardial injury. Anthracycline-induced cardiomyopathy was first described in the 1970s and was defined in early trials by the presence of clinical signs and symptoms of heart failure thought to be secondary to anthracycline exposure.[19] The diagnosis can be confirmed by endomyocardial biopsy, which shows several characteristic findings including myofibrillar dropout, distortion and disruption of Z-lines, mitochondrial disruption, and intramyocyte vacuolization.[20,21] Although it is considered to be the most sensitive and specific test for anthracycline-induced cardiomyopathy, use of endomyocardial biopsy is limited in clinical practice owing to its invasive nature.

More recently, inconsistencies in the literature on the definition and criteria for cardiotoxicity pose a major challenge to the field of cardio-oncology, especially in the context of newer targeted therapies (eg, trastuzumab) that are associated with adverse cardiac effects. In 2002 a Cardiac Review and Evaluation Committee (CREC) was formed to obtain independent and unbiased estimates of trastuzumab-associated cardiac dysfunction, and the following criteria for cardiotoxicity were proposed[22]: (1) cardiomyopathy characterized by a decrease in cardiac LVEF (global or septal predominance), (2) symptoms of