Canadian Journal of Cardiology 31 (2015) 1489–1492

Training/Practice
Contemporary Issues in Cardiology Practice

A Practical Approach to the Oncology Patient With Heart Failure

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ABSTRACT

Left ventricular systolic dysfunction is a significant cause of morbidity among cancer patients in whom this unfortunate complication develops. Investigation and management of chemotherapy- and radiation-induced cardiomyopathy in the emerging field of cardio-oncology involves a multidisciplinary approach between cardiology and oncology departments. The purpose of this article is to provide a practical approach to the cardiologist's assessment and management of cancer treatment–related cardiomyopathies.

RÉSUMÉ

La dysfonction systolique du ventricule gauche est une cause importante de morbidité chez les patients atteints de cancer chez qui cette complication malencontreuse apparaît. L'examen et la prise en charge de la cardiomyopathie induite par la chimiothérapie et la radiation dans le domaine émergent de la cardio-oncologie exigent une approche multidisciplinaire entre les services de cardiologie et d'oncologie. L'objectif de cet article est de fournir au cardiologue une approche pratique à l'évaluation et à la prise en charge des cardiomyopathies liées au traitement du cancer.

Definition of Cancer Treatment-Related Cardiomyopathy

There is currently no consensus definition of chemotherapy- or radiotherapy-induced cardiomyopathy. The American Society of Echocardiography (ASE) defines cancer treatment–related cardiomyopathy as a decrease in left ventricular ejection fraction (LVEF) of $>$ 10 percentage points (%) to a value $<$ 53%, which is confirmed on repeated imaging 2-3 weeks after the initial abnormal study.[1] The cardiomyopathy can be further classified based on symptom status and reversibility.[1] According to the Cardiac Review and Evaluation Committee of Trastuzumab, treatment-related cardiomyopathy is characterized by (1) a decreased LVEF that is global or more severe in the septum, (2) symptoms of congestive heart failure (CHF), (3) signs of CHF, and (4) a decline in LVEF of 5% or 10% from baseline in symptomatic and asymptomatic patients, respectively, to a value less than 55%.[2]

Although chemotherapy has been associated with alterations in diastolic parameters, these changes do not reliably predict subsequent development of treatment-related cardiomyopathy.[1] However, mediastinal radiation can cause a treatment-related cardiomyopathy that manifests with isolated diastolic dysfunction or restriction.[3]

Differential Diagnosis of Cancer Treatment-Related Cardiomyopathy

Many oncology patients are referred to cardiologists, presenting with cardiac symptoms or an asymptomatic decrease in LVEF detected on routine surveillance imaging. For oncology patients with cardiac symptoms but without confirmed systolic dysfunction, cardiologists should consider all cardiac complications of malignancy and oncology treatments (Table 1) in addition to other cardiac and noncardiac causes of symptoms. If LV systolic dysfunction is documented, patients should be assessed for treatment- and non–treatment-related causes of cardiomyopathy (Table 1).

Evaluation of Oncology Patients With Cardiomyopathy

When evaluating oncology patients with a new diagnosis of cardiomyopathy, clinicians should determine the name, dose, and timing of all therapies, past and present, in addition to surveillance and preventive measures initiated during treatment. Clinicians should identify high-risk therapies and patient characteristics (Table 2) and assess for non–treatment-related causes of cardiomyopathy.

Received for publication February 23, 2015. Accepted May 4, 2015.

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See page 1492 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.05.002

Table 1. Differential diagnosis of cardiac symptoms and LV dysfunction in oncology patients

Cardiac complications of malignancy and oncology treatments
Complications of malignancy
Marantic endocarditis
Pericardial effusion
Cardiac metastasis
Early complications of oncology treatment
Cardiomyopathy
Myopericarditis
Pericardial effusion
Hypertension
Hypotension
Myocardial ischemia
Arrhythmias
Endocarditis (immunosuppression)
Late complications of oncology treatment
Cardiomyopathy
Coronary artery disease
Conduction abnormalities
Constrictive pericarditis
Valvular stenosis and regurgitation
Differential diagnosis of treatment-related cardiomyopathy
Chemotherapy
Anthracyclines (doxorubicin, epirubicin, idarubicin)
Monoclonal antibody–based tyrosine kinase inhibitors (trastuzumab, bevacizumab)
Alkylating agents (cyclophosphamide, ifosfamide)
Antimetabolites (clofarabine, 5-fluorouracil, capecitabine)
Antimicrotubule agents (docetaxel)
Small-molecule tyrosine kinase inhibitors (dasatinib, sorafenib, lapatinib, sunitinib)
Proteasome inhibitor (bortezomib)
Mediastinal radiation
Coronary artery disease
Valvular disease
Myocarditis
Genetic/inherited disorders
Storage disorders
Infiltrative disorders
Toxins and drugs
Nutritional deficiencies
Endocrinopathies
Infections
Idiopathic causes

LV, left ventricular.

Diagnostic Modalities

Cardiac biomarkers, 2-dimensional transthoracic echocardiography (2DE), 3-dimensional echocardiography (3DE), multigated acquisition (MUGA) imaging, cardiac magnetic resonance imaging (MRI), and endomyocardial biopsy (EMB) have been used to evaluate patients with suspected or diagnosed treatment-related cardiomyopathy. LV systolic dysfunction is typically diagnosed with 2DE or MUGA because of favorable cost and availability. Given variability in LVEF measurements and reference ranges between imaging modalities, a single modality should be used when comparing serial LVEF assessments. Although MUGA provides more accurate and reproducible LVEF measurements than does standard 2DE,[1] echocardiography has the advantage of assessing diastolic parameters, atria, valves, and pericardium. The ASE recommends 3DE over 2DE for evaluating LV function in oncology patients,[1] but availability and expertise limit its widespread use. Cardiac MRI can be used to assess LVEF when there is a discrepancy between other modalities,[1] and it is also useful for cardiac tumors, constriction, and restriction.

Table 2. Risk factors for chemotherapy- and radiation-induced cardiomyopathy

Chemotherapy risk factors
Anthracyclines
Lifetime cumulative dose (especially doxorubicin dose equivalent $\geq$ 450-500 mg/m^2)
Age ($<$ 15 and $>$ 60 y of age)
Female sex
Concurrent/previous chest irradiation
Pre-existing LV dysfunction
Traditional cardiac risk factors
Trastuzumab
Age $>$ 50 y
Previous/concurrent anthracycline use (especially if $>$ 300 mg/m^2)
Pre-existing LV dysfunction
Combination of high-risk chemotherapy regimens
Radiation risk factors
Age $<$ 15 y at time of radiotherapy
Traditional cardiac risk factors
Pre-existing coronary artery disease/LV dysfunction
Chest radiation dose $>$ 30 Gy
Dose per fraction $>$ 2 Gy/day
Large volume of heart irradiated
Longer time since exposure ($>$ 10 y)
Radiation before 1975
Combination radiotherapy and anthracyclines

EMB is the most sensitive and specific method of diagnosing anthracycline-induced cardiomyopathy.[4] It also facilitates prognostication because the extent of myocyte damage on electron microscopy directly correlates with the probability of cardiac failure with continued therapy.[4] For other chemotherapeutic agents, such as trastuzumab, EMB is less useful because histologic changes are often nonspecific or absent. Given its invasiveness, EMB is usually performed when diagnostic uncertainty remains after noninvasive assessment.

There is significant interest in noninvasive detection of early myocardial dysfunction before symptoms or clinically apparent reductions in LVEF ("subclinical cardiomyopathy"). Elevated troponin levels during chemotherapy and abnormal echocardiographic strain indices have been correlated with subsequent development of LV dysfunction.[1,2,5] Some institutions and societies have integrated these parameters into chemotherapy monitoring protocols, but optimal detection and management of subclinical cardiomyopathy remains an evolving area.[1,2,5]

Prevention of Treatment-Induced Cardiomyopathy

Prevention of chemotherapy-induced cardiomyopathy requires a multidisciplinary approach between cardiologists and oncologists. Patients with significant pre-existing myocardial dysfunction should ideally avoid chemotherapeutic agents associated with a high risk of cardiomyopathy. For anthracyclines, minimizing the total lifetime cumulative dose is one of the most important preventive strategies. Other harm reduction strategies include substituting higher-risk with lower-risk drugs (eg, doxorubicin with epirubicin), altering drug formulation (eg, liposomal doxorubicin), changing the route of administration (eg, continuous instead of bolus doxorubicin infusion), and avoiding concomitant high-risk chemotherapy regimens. Prevention of radiation-induced cardiomyopathy depends on minimizing cardiac irradiation.