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FOCUS SEMINAR: CARDIO-ONCOLOGY

STATE-OF-THE-ART REVIEW

Cardiovascular Complications of Cancer Therapy

Best Practices in Diagnosis, Prevention, and Management: Part 1

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ABSTRACT

Modern cancer therapy has successfully cured many cancers and converted a terminal illness into a chronic disease. Because cancer patients often have coexisting heart diseases, expert advice from cardiologists will improve clinical outcome. In addition, cancer therapy can also cause myocardial damage, induce endothelial dysfunction, and alter cardiac conduction. Thus, it is important for practicing cardiologists to be knowledgeable about the diagnosis, prevention, and management of the cardiovascular complications of cancer therapy. In this first part of a 2-part review, we will review cancer therapy–induced cardiomyopathy and ischemia. This review is based on a MEDLINE search of published data, published clinical guidelines, and best practices in major cancer centers. With the number of cancer survivors expanding quickly, the time has come for cardiologists to work closely with cancer specialists to prevent and treat cancer therapy–induced cardiovascular complications. (J Am Coll Cardiol 2017;70:2536–51)

Heart diseases and cancer are the top 2 leading causes of death in the United States. Because these maladies share several common risk factors, many of our patients, especially the elderly, are afflicted by both cancer and heart diseases. Furthermore, cancer therapies, either radiation treatment or chemotherapy, can cause cardiovascular complications. Thus, it is important for practicing cardiologists to be familiar with the prevention, diagnosis, and management of cardiovascular complications of cancer therapy. This topic was reviewed in the *Journal* in 2009 (1). The purpose of this new State-of-the-Art Review is to provide an update in this emerging discipline that abounds with exciting new developments. Cardiovascular complications covered in this 2-part review are heart failure (HF), myocardial ischemia, myocarditis, hypertension (HTN), pulmonary HTN, pericardial diseases, thromboembolism, QT prolongation and arrhythmias, and radiation-induced cardiovascular diseases. A MEDLINE search for each of these complications was performed; clinically relevant complications were selected based on experiences at the MD Anderson Cancer Center and centers affiliated with authors of this review. Diagnostic and treatment recommendations are based on the best practices developed at MD Anderson Cancer Center and recent guidelines (2–6).

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HEART FAILURE

HF due to chemotherapy has been long recognized as a serious side effect of daunorubicin, the first anthracycline used clinically (7). Although the anthracycline class of chemotherapy agents remains the major cause of chemotherapy-induced cardiomyopathy (CIMP), newer cancer therapy, such as trastuzumab or proteasome inhibitors, can also cause cardiomyopathy (**Central Illustration, Table 1**). It should also be recognized that patients can develop signs and symptoms of clinical heart failure during chemotherapy; however, the cause of cardiac decompensation may be due to fluid overload, stress-induced cardiomyopathy, or primary cancer, but not chemotherapy (2). CIMP has been described in 1% to 5% of cancer survivors (8,9) and portends one of the worst survivals among cardiomyopathies (10). Early diagnosis and timely intervention has been shown to result in a superior clinical outcome in cancer patients treated with cardiotoxic chemotherapy (11).

DEFINITION. In the initial report by Von Hoff et al. (12), HF was defined as the presence of tachycardia, shortness of breath, neck vein distention, gallop rhythms, ankle edema, hepatomegaly, cardiomegaly, and pleural effusion (12). With the advance of cardiac imaging, echocardiography or multigated acquisition radionuclide ventriculography-based evaluation of left ventricular ejection fraction (EF) has recently been included in the diagnostic criteria (4,13). In the trastuzumab clinical trials, drug-associated cardiotoxicity is defined as 1 or more of the following: 1) cardiomyopathy characterized by a decrease in EF globally or due to regional changes in interventricular septum contraction; 2) symptoms associated with HF; 3) signs associated with HF, such as S3 gallop, tachycardia, or both; and 4) decline in initial EF of at least 5% to <55% with signs and symptoms of HF or asymptomatic decrease in EF of at least 10% to <55% (14). This definition does not include subclinical cardiovascular damage, such as diastolic dysfunction and changes in LV strain, which may occur earlier in response to some of the chemotherapeutic agents. Common Terminology Criteria for Adverse Events has also defined cardiomyopathy and/or heart failure for the purposes of uniform reporting. In Common Terminology Criteria for Adverse Events 4.03, echocardiography and biomarkers were included to provide a more precise definition of cardiotoxicity.

INCIDENCE AND PATHOGENESIS. Anthracyclines. In a retrospective review of 3 trials, the incidence of doxorubicin-related HF was found to be 5% at a cumulative dose of 400 mg/m^2, 16% at a dose of 500 mg/m^2, and 26% at a dose of 550 mg/m^2 (15). However, subclinical events occurred in about 30% of the patients, even at the doses of 180 to 240 mg/m^2, about 13 years after the treatments (16). Interestingly, histopathological changes, such as myofibrillar loss and vacuolization, can be seen in endomyocardial biopsy specimens from patients who have received as little as 240 mg/m^2 of doxorubicin (17). These findings suggest that there is no safe dose of anthracycline. Even doses as low as 100 mg/m^2 have been associated with reduced cardiac function (16,18). Nonetheless, some patients had no significant cardiac complications despite receiving doses as high as 1,000 mg/m^2 (19). Individual susceptibility is most likely due to genetic variants in genes that regulate anthracycline cardiotoxicity (20). Other risk factors for anthracycline toxicity include cumulative dose, intravenous bolus administration, higher single doses, history of prior irradiation, use of concomitant agents known to have cardiotoxicity, female sex, underlying CV disease, age (young and elderly), delayed diagnosis, and increase in cardiac biomarkers such as troponins during and after administration (9,21–23).

Doxorubicin poisons topoisomerase 2 to cause deoxyribonucleic acid (DNA) double-strand break and demise of cancer cells. In the cardiomyocytes, doxorubicin targets topoisomerase 2β to induce DNA double-strand breaks, and doxorubicin-bound topoisomerase 2β binds promoters of antioxidative and electron-transport genes to reduce their transcripts and protein expression (24,25) (**Figure 1**). Doxorubicin-treated cells have a marked increase in reactive oxygen species and are defective in mitochondria biogenesis. Thus, topoisomerase 2β accounts for the 3 hallmarks of anthracycline-induced cardiotoxicity: myocyte death, reactive oxygen species generation, and mitochondriopathy. Reduced topoisomerase 2β expression has been linked to a coding variant in the retinoic receptor γ gene, which predicts susceptibility to anthracycline-induced cardiotoxicity in childhood cancer (26).

Alkylating agents. Alkylating agents add an alkyl group to the DNA of rapidly dividing cells and, in the case of bifunctional alkylating agents, cross-link the 2 DNA strands, thereby inhibiting DNA replication and cell proliferation (27). Symptoms may include arrhythmias, conduction disorders, and fulminant HF (28,29). Alkylating agents such as cyclophosphamide

ABBREVIATIONS AND ACRONYMS

5-FU = 5-fluorouracil

ACS = acute coronary syndrome(s)

ATE = arterial thrombotic event

CAD = coronary artery disease

CIMP = chemotherapy-induced cardiomyopathy

cTnI = cardiac troponin I

CVA = cerebral vascular accident

ECG = electrocardiogram

EF = ejection fraction

FDA = U.S. Food and Drug Administration

GLS = global longitudinal strain

HF = heart failure

HTN = hypertension

MI = myocardial infarction

TDI = tissue Doppler imaging

VEGF = vascular endothelial growth factor

VSP = vascular endothelial growth factor signaling pathway