Management of Cancer Therapeutics–Related Cardiac Dysfunction

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KEYWORDS

• Cancer therapy–mediated cardiotoxicity • Chemotherapy-induced cardiomyopathy • Anthracyclines • HER2-targeted therapies • Trastuzumab • Radiotherapy-induced cardiotoxicity • β-Blockers • Renin-angiotensin inhibitors

KEY POINTS

- Cancer therapies are associated with different cardiac adverse effects. Cardiotoxicity is a well-known dose-limiting adverse effect of anthracyclines. Trastuzumab-related cardiomyopathy is dose independent and usually reversible.
- Vascular endothelial growth factor signaling pathway inhibitors include monoclonal antibodies (eg, bevacizumab), which block vascular endothelial growth factor, as well as small molecule inhibitors (eg, sunitinib, pazopanib, vandetanib). Apart from hypertension, these drugs can cause ventricular dysfunction, heart failure, and myocardial ischemia.
- The goal of cardio-oncology is to ensure optimal cancer therapy while limiting adverse effects with an emphasis on early recognition and treatment of cancer therapeutics–related cardiac dysfunction.
- Pre–cancer therapy evaluation begins with the assessment of cardiovascular disease burden and risk stratification of each patient. Intra–cancer therapy evaluation involves close follow-up, monitoring, and treatment according to specific surveillance protocols and consensus guidelines.

INTRODUCTION

Improvements in the detection and treatment of cancer have resulted in a significant increase in the number of patients who are long-term survivors of cancers. In 2016, the estimated number of cancer survivors was more than 15.5 million.[1] However, cancer survivorship comes with long-term risk of adverse effects of cancer therapies. Complications caused by cancer therapies include cardiomyopathy, heart failure (HF), pericardial and valvular disease, arrhythmias, vascular disease, ischemic heart disease, and hypertension.[2] This article discusses the pathophysiology and mechanisms underlying cancer therapeutics–related cardiac dysfunction (CTRCD) and presents an approach to the evaluation and treatment of these patients.

DEFINITIONS

Different criteria have been used to define CTRCD but no single definition is universally accepted.[3] In

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a preliminary study evaluating doxorubicin-mediated cardiomyopathy, moderate cardiotoxicity was described as a greater than or equal to 15% decrease in left ventricular ejection fraction (LVEF) to less than 45% on serial radionuclide angiocardiography.[4] According to the US Food and Drug Administration (FDA) package insert, doxorubicin-mediated cardiotoxicity is defined as either (1) greater than 20% absolute decline in LVEF or (2) greater than 10% decrease in LVEF to less than the lower limit of normal or absolute value of less than 45%.[5] The definition of trastuzumab-mediated cardiomyopathy, as determined by cardiac review and evaluation committee in trastuzumab trials, was either a greater than or equal to 10% decline in absence of symptoms or greater than or equal to 5% decrease in symptomatic patients to a final LVEF of less than 55%.[6,7] In the Herceptin Adjuvant (HERA) trial, LVEF decline by at least 10% from baseline to a value less than 50% was considered a significant LVEF decrease. New York Heart Association class III or IV symptoms with significant LVEF decrease was designated as symptomatic congestive HF.[8] The American Society of Echocardiography (ASE) defined CTRCD as greater than or equal to 10% decline in LVEF to a final value less than 53% confirmed on subsequent imaging performed 2 to 3 weeks after the initial measurement. If criteria for CTRCD were not met, greater than 15% relative decline in global longitudinal strain (GLS) compared with baseline strain was considered as subclinical left ventricular (LV) dysfunction. If there was less than 8% relative decline in GLS, LV dysfunction was unlikely.[9]

SELECTED CANCER THERAPEUTICS

Anthracyclines

Anthracyclines (eg, doxorubicin, daunorubicin, and epirubicin) are a group of chemotherapeutic agents that are very effective for the treatment of solid malignancies, lymphomas, and leukemias.[10] However, cardiotoxicity is a well-known dose-limiting adverse effect of anthracyclines that negatively affects their therapeutic efficacy.[11]

The exact pathophysiologic basis of anthracycline-related cardiotoxicity is not clear. According to one hypothesis, generation of reactive oxygen species and formation of iron complexes results in anthracycline-mediated cardiomyopathy. In cardiac myocytes, the quinone group of anthracyclines is reduced to a semiquinone form, which donates an electron to the oxygen molecule resulting in the production of superoxide ion, which in turn leads to the formation of hydrogen peroxide and reactive oxygen species. In the presence of reduced iron (Fe^{2+}), the oxidative potential of these compounds is greatly enhanced.[12] Anthracyclines can also form iron complexes that play a role in redox reactions in the cardiac myocytes.[12] These series of events result in lipid peroxidation, protein sulfhydryl oxidation, and injury to the mitochondrial DNA.[12,13] Dysfunction of oxidative phosphorylation and reduction of ATP production adds to the mitochondrial damage.[12,13] Anthracyclines bind to topoisomerase II, which negatively affects DNA repair and decreases protein production.[14] Inhibition of topoisomerase II-α in rapidly proliferating cancer cells results in tumoricidal effects. Inhibition of topoisomerase II-β in cardiomyocytes is probably responsible for cardiac damage.[15] According to a recently proposed theory, binding of anthracyclines to topoisomerase II-β induces breaks to double stranded DNA, causes alterations in transcriptome, damages the mitochondrial DNA, and results in the production of reactive oxygen species, all of which together may lead to cardiotoxicity (**Fig. 1**).[16]

The risk of HF exists at doses of doxorubicin less than 250 mg/m^2 and there is no clear dose threshold.[17] However, the risk of anthracycline-mediated cardiotoxicity is dose dependent. A pooled analysis of 3 studies revealed that the incidence of doxorubicin-induced symptomatic HF was 1.7%, 4.7%, 15.7%, and 48% at cumulative doses of 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, and 650 mg/m^2 respectively.[18] Conventional cardiovascular risk factors, simultaneous or sequential treatment with other cardiotoxic therapies such as trastuzumab, and radiotherapy further increase the risk of cardiotoxicity.[19]

ALKYLATING AGENTS

Alkylating agents (eg, cyclophosphamide, ifosfamide, and melphalan) negatively affect DNA transcription, which in turn results in downregulation of protein production.[20] Cyclophosphamide is an integral part of combination chemotherapy used for treatment of leukemias, lymphomas, and solid tumors.[20] The incidence of symptomatic cardiomyopathy and fatal cardiotoxicity with cyclophosphamide has been estimated to be ~22% and 11% respectively.[21] Cardiotoxicity is dose dependent, with a dose ~180 to 200 mg/kg over a period of 48 to 96 hours associated with a significant risk. The dose based on body surface area is a good predictor of the cardiotoxicity, with a 25% risk of cardiomyopathy at 1.5 g/m^2/d or higher.[21] The exact mechanism underlying cyclophosphamide cardiotoxicity is not known. According to commonly accepted theory, injury to the endothelial layer causes leakage of potentially toxic