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Cardiac Toxicity From Systemic Cancer Therapy: A Comprehensive Review

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Abstract Cardiovascular toxicity is a potential short- or long-term complication of anticancer therapy. Exposure to chemotherapy medications, primarily the anthracycline class, can lead to potentially irreversible clinically significant cardiac dysfunction. The advent of novel biologic agents, including monoclonal antibodies and tyrosine kinase inhibitors, has revolutionized the treatment of several types of malignancies. Although targeted therapies are considered less toxic and better tolerated by patients compared with classic chemotherapy agents, rare serious complications have been observed; and longer-term follow-up is needed to determine the exact profile of related cardiac adverse effects. Cardiac toxicity associated with cancer therapies can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary left ventricular ejection fraction decline, to life-threatening events such as congestive heart failure or acute coronary syndromes. Assessment of the prevalence, type, and severity of cardiac toxicity caused by various cancer treatments is a critical topic for patient management and specifically for new drug development. Guidelines for monitoring cardiac adverse effects have been formulated; however, appropriate supportive evidence remains limited. Given the rate of new drug development designed to fulfill unmet oncologic needs, efforts are needed to promote strategies for cardiac risk detection and management and to avoid unintended consequences potentially impeding development of, regulatory approval for, and patient access to novel therapies. These advances require ongoing research to assess and manage the cardiovascular safety of patients treated with anticancer agents, as well as a well-organized collaboration between oncologists and cardiologists. The aim of this review is to summarize potential cardiovascular toxicities for a range of cancer chemotherapeutics and to review general mechanisms of cardiovascular toxicity for each agent. (Prog Cardiovasc Dis 2010;53:94-104)

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Abbreviations and Acronyms

5-FU = 5-fluorouracil

AI = aromatase inhibitor

ATO = arsenic trioxide

CHF = congestive heart failure

ECG = electrocardiogram

EGFR = epidermal growth factor receptor

LVD = left ventricular dysfunction

LVEF = left ventricular ejection fraction

NO = nitric oxide

TdP = torsades de pointes

VEGF = vascular endothelial growth factor

VEGFR = vascular endothelial growth factor receptor

with cancer therapies can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary left ventricular ejection fraction (LVEF) decline, to life-threatening events such as congestive heart failure or acute coronary syndromes. Assessment of the prevalence, type, and severity of cardiac toxicity caused by various cancer treatments is a critical topic for patient management and specifically for new drug development. Guidelines for monitoring cardiac adverse effects have been formulated; however, appropriate supportive evidence remains limited. Given the rate of new drug development designed to fulfill unmet oncologic needs, efforts are needed to promote strategies for cardiac risk detection and management and to avoid unintended consequences potentially impeding development of, regulatory approval for, and patient access to novel therapies. These advances require ongoing research to assess and manage the cardiovascular safety of patients treated with anticancer agents, as well as a well-organized collaboration between oncologists and cardiologists. The aim of this review is to summarize potential cardiovascular toxicities for a range of cancer chemotherapeutics and to review general mechanisms of cardiovascular toxicity for each agent.

Cardiac toxicity induced by anticancer agents

Left ventricular dysfunction

Left ventricular dysfunction (LVD) is associated with exposure to several anticancer therapies. An early definition of the effect of cancer therapy on LV function has been promulgated by the Cardiac Review and Evaluation Committee supervising trastuzumab (Herceptin) clinical trials.[1] According to this definition, cardiomyopathy is characterized by a "decrease in cardiac left ventricular ejection fraction (LVEF) that was either global or more severe in the septum; (2) symptoms of congestive heart failure (CHF); (3) associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms." Recent definitions have varied and include a larger change in LVEF to less than the lower limit of normal or LVEF less than 50%. As a result, a clear understanding of the degree of LV dysfunction with different therapies can be problematic.[2] The use of specific chemotherapeutic agents and molecular targeted therapies can affect the cardiovascular system, either through a direct effect on heart function or peripherally through hemodynamic flow alteration (hypertension and/or thrombotic events).

Anthracyclines

Anthracyclines are a class of chemotherapeutics widely used in the management of multiple malignancies, most prominently in adjuvant therapy for breast cancer as well as systemic treatment of sarcomas, lymphomas, and leukemias.[3] Formal estimates of the worldwide prevalence of anthracycline cardiotoxicity are lacking.[4] Differences among pediatric, adult, and elderly populations and the lack of universal criteria for detecting and reporting cardiac events make such estimates even more challenging.[4,5]

Anthracycline-induced cardiotoxicity can develop in an acute, subacute, or chronic manner.[3] Acute cardiotoxicity occurs in less than 1% of patients immediately after infusion of the anthracycline and manifests as an acute, transient decline in myocardial contractility, which is usually reversible. The early-onset chronic progressive form occurs in 1.6% to 2.1% of patients during therapy or within the first year after treatment and is dose dependent as well. Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy in 1.6% to 5% of patients.[3] Both the subacute and chronic forms of anthracycline-mediated cardiotoxicity tend not to be reversible. The risk of clinical cardiotoxicity increases with cumulative dose of anthracycline.[3] Studies evaluating cumulative probability of doxorubicin (Adriamycin)-induced HF have found rates in the range of 3% to 5% at 400 mg/m^2, 7% to 26% at 550 mg/m^2, and 18% to 48% at 700 mg/m^2. Importantly, in a retrospective review of 3 trials, the incidence of HF was found to be 26% with cumulative doses of 550 mg/m^2. For this reason, the recommended maximum lifetime cumulative dose for doxorubicin is 400 to 550 mg/m^2.[3] A somewhat lower incidence of HF has been observed for the related anthracyclines epirubicin or idarubicin.[6]

Risk factors for anthracycline toxicity include cumulative dose; intravenous bolus administration; higher single doses; history of prior irradiation; the use of other concomitant agents known to have cardiotoxic effects