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Cardiotoxic effects of chemotherapy: A review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system

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ABSTRACT

Cardiotoxic effects of chemotherapy and targeted drugs are ubiquitous and challenging in the field of oncology therapeutics. The broad spectrum of toxicities ranging from ischemic, hypertensive, cardiomyopathic, and arrhythmic complications can present as a significant challenge for clinicians treating cancer patients. If early diagnosis and intervention of cardiotoxic complications is missed, this can lead to delay or abrogation of planned treatment, which can potentially culminate to significant morbidity due to not only the cardiotoxic complications but also the progression of cancer. Hence, full knowledge of cardiovascular complications of chemotherapeutic agents, essential diagnostics tests to order, and appropriate management is paramount to oncologist, oncology pharmacists, and scientific clinical investigators. The aforementioned is particularly true in the current oncology era of plenteous early clinical trials studying several pathway/molecular-targeting agents with an increased cardiotoxic potential and the rapid expedited approval of those drugs by the FDA. Herein, we present a review discussing cardiotoxic effects of drugs and guidelines for management of the toxicities to assist the medical field in general managing patients with cancer.

1. Introduction

Chemotherapy, while highly effective in treating some cancers, can be self-limiting due to toxicity. Cardiac toxicity has long been associated with traditional cytotoxic agents including anthracyclines, anthraquinolones, antimetabolites, antimicrotubules, vinca alkaloids, tyrosine-kinase inhibitors, and other miscellaneous drugs. A conservative estimate of the occurrence of symptomatic clinical heart failure (HF) with these agents is in the range of 1–5% with asymptomatic reduction in left ventricular function in the range of 5–20% (Shakir and Rasul, 2009). A growing body of research is studying cardiotoxicity related to chemotherapy, however, clear definition of chemotherapy-induced cardiotoxicity (CIC) is lacking. In this review, CIC will be used to refer to both chemotherapy and targeted drugs-induced cardiotoxicity. CIC is a general term that implies toxicity that affects the heart from antineoplastic drugs. This occurs due to direct effect of the drug on the cardiovascular system or indirect due to both thrombogenic status or hemodynamic flow alterations (Albini et al., 2010). A cardiac review committee evaluating trastuzumab clinical trials defined CIC as one or more of the following: 1) reduction of LVEF, either global or specific in the interventricular septum; 2) symptoms or signs associated with heart failure (HF); 3) reduction in LVEF from

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baseline to ≥5%– < 55% in the presence of signs or symptoms of HF, or a reduction in LVEF ≥10%– < 55% without signs or symptoms of HF (Seidman et al., 2002). The aforementioned is actually the definition by the Cardiac Review and Evaluation Committee on trastuzumab-associated cardiotoxicity and the ESMO Clinical Practice Guidelines and used for all other drugs by oncologists (Anon., 2017). In general, cardiotoxicity is defined by the National Cancer Institute as "the toxicity that affects the heart". This incorporates not only the direct-effect on the heart but also the indirect effect that occurs due to change in hemodynamic flow or thrombotic events (Brana and Tabernero, 2010).

Newer molecularly targeted agents like Sunitinib, bevacizumab, imatinib, and lapatinib also show chemotherapy-induced HF while other targeted agents such as cabozantinib and vandetanib have been associated with QTc prolongation (Ghatalia et al., 2015). The causes of toxicity vary based on both the chemotherapeutic mechanism of action or the targeted site of kinase inhibition or due to multifactorial causes. Traditional chemotherapy can damage cardiac myocytes by causing inflammation in the myocardium or injuring myocardial cell surface receptors while kinase inhibitors may affect numerous cardiac cell-signaling targets leading to myocyte loss and decreased cardiac function (Ghatalia et al., 2015). Herein, we review the cardiac toxicity profile of various antineoplastic agents and discuss potential management strategies. In addition to the aforementioned, radiation therapy is a common treatment modality as approximately 50% of cancer patients are treated with radiotherapy (Yusuf et al., 2011). From a cardiac toxicity profile, radiation can lead to coronary artery disease, pericardial, myocardial, and endocardial disease in addition to conduction abnormalities. Early diagnosis is essential for appropriate treatment, for example some patients with hodgkin's disease who received mediastinal radiation are at risk of developing complete heart block and go on to receive permanent pacemakers, hence early recognition of complications and early treatment can lead to positive outcomes. Moreover, certain malignancies can predispose patients to cardiac complications; an example is primary mediastinal large B-cell lymphoma, which has the propensity to infiltrate the heart leading to many complications such as valvular heart disease and arrhythmia (Rogowitz et al., 2013). The data in this review was compiled from primary literature, include data sourced from the original clinical trials in addition to outcome evaluations of real world data. Data was selected from pubmed and selected from the literature evaluating cardiac side effects with chemotherapy and was reviewed in its entirety.

2. Traditional cytotoxic chemotherapy

Cardiotoxicity is a potential adverse effect of a number of antineoplastic drugs. The risk of cardiotoxicity is dependent upon several factors, including the type of chemotherapy agent, administered dose and administration rate (continuous infusion versus bolus) of the drug, advanced or young age, female gender, co-morbidities such as hypertension and pre-existing heart disease, concurrently administered agents, previous exposure to other cardiotoxic agents, and/or radiation exposure such as mediastinal radiation (Shakir and Rasul, 2009; Ghatalia et al., 2015). Chemotherapy-related cardiac dysfunction (CRCD) can be classified as Type I or Type II (Ewer and Lippman, 2005). Type I cardiotoxicity is generally thought to result in permanent and irreversible damage, while Type II can be reversible. Table 1 reviews the different characteristics of type I and type II chemotherapy-induced HF.

2.1. Anthracycline and anthracenedione agents

Anthracyclines are among the most widely utilized antineoplastic agents and include doxorubicin, liposomal doxorubicin, daunorubicin, idarubicin, and epirubicin. These agents are frequently used in curative and palliative regimens for breast cancer, lymphomas, sarcomas, acute leukemias, and other cancers. Anthracycline-induced cardiotoxicity was first reported as early as 1967 in children receiving doxorubicin (Tan et al., 1967). Due to the lack of consistent reporting, however, estimates of the global prevalence of anthracycline cardiotoxicity are lacking.

The exact etiology of anthracycline-induced cardiotoxicity remains unclear, but free radical formation after binding to iron is thought to be the primary mechanism (Giantris et al., 1998). Other proposed mechanisms include direct DNA damage, blockage of mitochondrial adenosine triphosphate generation, and apoptotic protein release. The myocardium is more susceptible to free radical damage than other tissues as its has less free-radical scavenging enzymes namely superoxide dismutase and catalase activity in addition to the suppression of glutathione peroxidase by anthracyclines, its major defense against free radical damage (Doroshow, 1983). In addition, superhydroxide free radicals accumulate and cause severe lipid peroxidation causing extensive destruction of the mitochondria, endoplasmic reticulum, and nucleic acid. Moreover, circulating pro-inflammatory cytokines such as histamine, tumor necrosis factor alpha (TNF-A), and interleukin-2 from macrophages and monocytes have been implicated as well in the pathogenesis (Ehrke et al., 1986). Systolic dysfunction occurs by a number of mechanisms including increase in myocardial interstitial pressure causing a decreases in coronary blood flow culminating to cardiac ischemia (Yeh et al., 2004). In addition to the aforementioned, conversion of anthracyclines to secondary alcohol metabolites in cardiac myocytes leads to poor clearance and greater accumulation in the heart. This in turn contributes to cardiotoxicity both during and for a protracted period of time after completion of chemotherapy (Geisberg and Sawyer, 2010). A new interesting pre-clinical study showed that cardiomyocyte-specific deletion of *Top2b* (encoding topoisomerase-IIß) protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes which cause defective mitochondrial biogenesis. In the preclinical study the aforementioned deletion protected mice from the development of doxorubicin-induced heart failure suggesting that cardiotoxicity is mediated by topoisomerase-IIß in cardiomyocytes (Zhang et al., 2012).

Many potential risk factors have been identified for anthracycline-induced cardiotoxicity as previously mentioned in addition to lifetime cumulative dose, intravenous bolus administration, high single doses, history of cardiovascular disease, diabetes mellitus (DM), and excessive alcohol intake, longer time since therapy completion, and increased cardiac biomarkers (e.g., troponins and natriuretic peptides) during and after treatment (Shakir and Rasul, 2009).

Three categories of anthracycline-induced cardiotoxicity have been proposed: acute, early-onset chronic progressive, and late-onset chronic progressive (Curigliano et al., 2012). Occurring in less than one percent of patients', acute cardiotoxicity is seen immediately after drug infusion and is described as a transient, often reversible decline in myocardial contractility. Arrhythmias could be a presentation in the acute category and hence patients should be closely monitored. Early- and late-onset chronic cardiotoxicity can present as dilated cardiomyopathy in adults, resulting in potentially severe symptomatic HF. Early-onset chronic progressive cardiotoxicity occurs in approximately 1.6–2.1% of patients during therapy or within 1 year after completion of treatment. The late-onset occurs at least one year beyond therapy completion and has been reported in up to 1.6–5% of patients, with some patients experiencing clinical symptoms ten to twenty years after administration (Curigliano et al., 2012).

Doxorubicin-associated cardiotoxicity is the best characterized of all the anthracyclines. Apparent cardiotoxicity is unusual in adults at cumulative doxorubicin doses < 300 mg/m^2. The incidence of HF is about 7–26% at 550 mg/m^2 and increases to 18–48% at a cumulative dose of 700 mg/m^2 (Curigliano et al., 2012; Bielack et al., 1989). As such, the recommended lifetime maximum cumulative anthracycline dose is 400–550 mg/m^2 for adults. Pediatric patients have been shown to develop cardiotoxicity at lower cumulative doses, where cumulative doses ≥300 mg/m^2 correlate to an 11-fold increased risk of HF (Shankar et al., 2008).