Chapter 7

Drug Induced Cardiotoxicity: Mechanism, Prevention and Management

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Abstract

Drug-induced cardiotoxicity is a major adverse effect that has been encountered for some clinically important drugs especially antineoplastic agents. This toxicity has previously led to the post-marketing withdrawal of numerous pharmacologically active drugs and limits the efficacy of other clinically useful ones. Currently, assessing the cardiotoxicity potential is a crucial parameter in drug development, and many models have been established to facilitate its prediction to avoid such toxicity. In this chapter, we will briefly discuss the mechanism of drug-induced cardiotoxicity, risk factors, how to prevent, early detection and/or management from a pharmacological and toxicological point of view.

Keywords: doxorubicin, oxidative stress, mitochondrial dysfunction, risk prediction, biomarkers

1. Introduction

Drug-induced cardiotoxicity is an important cause of attrition of compounds in preclinical and clinical development. It represents one of the most serious side effects associated with novel drug development, and it is known to be one of the major toxic effects induced by several types of drugs [1]. Cardiotoxicity is not restricted to anticancer agents, and almost all therapeutic drug classes have unanticipated cardiotoxicities. However, cardiotoxicity induced by chronically administered drugs, such as neurologic/psychiatric agents and anticancer chemotherapeutic agents, represents a major problem because toxicity may become evident only after long-term accumulation of the drug or its metabolites [2]. Assessing drug-induced cardiotoxicity risk including QT interval prolongation is considered nowadays an integral part of the standard preclinical evaluation of new chemical entities as defined by the

International Conference of Harmonization Expert Working Group for all drugs in development [3]. Strikingly, almost 10% of drugs in the last four decades have been recalled from the clinical market worldwide due to cardiovascular safety concerns, e.g., rofecoxib, tegaserod, and sibutramine, and despite the great efforts to reveal cardiotoxicity in the preclinical phase of development of medicinal products, cardiotoxicity continues to lead safety concerns mainly because of lack of sufficient knowledge of the mechanisms of cardiotoxicity [4].

Currently, cancer is shown to affect more than one in three people in their lifetime, and along with cardiovascular disease, they are the two leading causes of death in developed nations. Thanks to improvement in cancer pharmacotherapy, a current overall 10-year cancer survival stands at 50% across the 20 most common malignancies with a concomitant increase in awareness of the adverse cardiac effects of cancer treatment itself [2]. Further, the 5-year survival rate of US childhood cancers has increased from around 60% in the mid-1970s to more than 80%, and according to the data of National Health and Nutrition Examination, long cancer survivors die, 33% of them, of heart disease [5, 6]. Similarly, cardiovascular mortality has been extensively reported in patients suffering from psychiatric illness, and some antidepressants and antipsychotic drugs have a broad cardiovascular adverse effect profile that can lead to cardiovascular complications, especially cardiac arrhythmias, that have sometimes been shown fatal even to patients with no previous cardiac disease history. For instance, the use of clozapine, the most effective drug for resistant schizophrenia, has been limited due to potentially life-threatening adverse effects, including myocarditis and cardiomyopathy. Clozapine-induced myocarditis has been linked up to 24% mortality. The coexistence of a heart disease complicates the management of mental illness and worsens the illness course, and co-occurrence of psychiatric disorders in cardiac patients might affect the clinical outcome and morbidity [7–9].

Drug-induced cardiotoxicity, commonly in the form of cardiac muscle dysfunction that may progress to heart failure, represents a major adverse effect of some common traditional antineoplastic agents, e.g., anthracyclines, cyclophosphamide, 5 fluorouracil, taxanes, as well as newer agents such as biological monoclonal antibodies, e.g., trastuzumab, bevacizumab, and nivolumab; tyrosine kinase inhibitors, e.g., sunitinib and nilotinib; antiretroviral drugs, e.g., zidovudine; antidiabetics, e.g., rosiglitazone; as well as some illicit drugs such as alcohol, cocaine, methamphetamine, ecstasy, and synthetic cannabinoids. Most of the affected patients had no prior manifestation of the disease [4, 6, 10–12].

Cardiac toxicity of antineoplastic agents includes left ventricular failure, myocardial ischemia, QT prolongation, arrhythmias, pericarditis, myocarditis, hypertension, and thromboembolism. Asymptomatic diastolic dysfunction, which is a common feature observed in many cancer survivors, has been shown to be the earliest noticeable cardiac abnormality [12, 13]. Subclinical cardiotoxicity should also be kept in mind, and it is commonly defined on cardiac imaging as clinically asymptomatic left ventricular systolic dysfunction with a fall in left ventricular ejection fraction by >10% points to a value of less than <50% which is commonly used as the decision threshold to define cardiotoxicity [2]. Alternatively, cardiac dysfunction related to cancer treatment has been also defined as a decrease in left ventricular ejection fraction by ultrasound greater than 10% (from baseline) and with an absolute value

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less than 53%, confirmed by a repeat examination at 2–3 weeks. Left ventricular ejection fraction between 53 and 73% is considered normal [14]. Clinically manifested cardiotoxic effects may occur acutely at any time from the first dose of treatment till 2 weeks after it is terminated or chronically that may occur months after termination of treatment [15, 16]. The frequency to recognize such complications with cancer patients has significantly increased during the past few decades due to increased survival of those patients which has accompanied the advances in drug treatment and health care, and early detection of drug-induced cardiotoxicity is of pivotal importance to avoid further deterioration of cardiac function [17].

2. Mechanisms

The exact mechanism of antipsychotic-, anthracycline-, or drug-induced cardiotoxicity remains unclear, though it is likely to be multifactorial [2, 18]. Understanding the mechanisms of anthracycline-induced cardiotoxicity is crucial for effective cardioprotection. Several complex mechanisms have been implicated including formation of iron complexes that can react with O_2 to form $\bullet O_2^-$, which in turn dismutates to H_2O_2 and/or enters the Haber-Weiss reaction, resulting in •OH, or can react with H_2O_2 yielding directly •OH; increased production of reactive oxygen and reactive nitrogen species; lipid peroxidation; inflammation; induced cardiomyocyte apoptosis; interstitial fibrosis; abnormal signaling of epidermal growth factor as well as beta-arrestin; inhibition of nuclear topoisomerase II β; induced DNA damage; inhibition of vascular endothelial growth factor signaling; defective mitochondrial biogenesis; and calcium overloading [15, 16, 19–22]. Mitochondria have an essential role in myocardial tissue homeostasis, and deterioration in mitochondrial function eventually leads to cardiomyocyte and endothelial cell death and consequent cardiovascular dysfunction [4]. The antiretroviral nucleoside reverse transcriptase inhibitors, e.g., zidovudine, may cause cardiac mitochondrial dysfunction through inhibition of DNA polymerase-gamma and induction of mitochondrial DNA mutations leading to cardiomyopathy [23]. Two broad categories of cardiac adverse effects are known, functional and structural effects. Noteworthy, seriously altered function may be completely dissociated from structural effect, especially at an early stage [24]. Other than the functional deterioration, anthracyclines were also shown to damage several major structural proteins regulating cardiac muscle contractility including titin, the myofilament forming protein that regulates cardiac function leading to systolic and diastolic dysfunction [12]. In addition, there is a considerable interindividual variability in the susceptibility to chronic anthracycline-induced cardiotoxicity; genetic variants were suggested to have an impact on the occurrence of drug-induced cardiotoxicity; a potential role for polymorphisms in several candidate genes related to the metabolism of anthracyclines, detoxification of free radicals, or variations in body iron levels and genetic testing was recommended to reduce the incidence of anthracycline-induced cardiotoxicity [10, 21, 25, 26]. Anthracyclines are more likely to produce irreversible (type 1 drug-induced cardiotoxicity) microstructural lesions of cardiomyocytes leading to necrosis and apoptosis. Noteworthy, reversible (type 2) cardiotoxicity is associated with biological drugs targeting proteins regulating cancer cell proliferation which are also necessary for maintenance of cardiovascular homeostasis, and this toxicity can

be resolved after completion of therapy or even during its continuation, and overlap as well as addition may occur between the types while using multiple potentially cardiotoxic drugs [16, 22]. Noteworthy, some authors mention that reversible drug-induced cardiotoxic adverse effects are type 1 while irreversible ones are type 2 [2].

3. Risk factors

Patients undergoing chemotherapy have a higher risk of developing cardiovascular complications (**Table 1**), and the risk is even greater if there is a history of heart disease or concomitant radiotherapy, increasing the incidence of events by 30% compared to the general population [5, 27]. The time course of cardiotoxicity varies depending on several factors including patient age at time of exposure and the class effect of chemotherapy drugs, where childhood cancer survivors experience exponentially rising risk for delayed cardiovascular events while adult cardiovascular risk manifests earlier and depends on the number of conventional coexisting cardiac risk factors especially hypertension [2]. Patients who have a moderate to high risk of developing or are suspected to have cardiotoxicities indicated according to their medical history or abnormal imaging and biomarker levels might warrant treatment of risk factors, alternative cancer treatment options, and administration of cardioprotectants [28].

Identification of patients at risk of drug-induced cardiotoxicity is currently considered one of the main objectives for cardiologists and oncologists to personalize cancer therapy and arrange early preventive interventions. It is of key importance to optimize and standardize

Risk factors for drug-induced cardiotoxicity:
Patient age at time of exposure (below 4 years and old age)
Female gender
Black ethnicity
Class of chemotherapeutic agent
Total cumulative dose
Concomitant radiotherapy/cardiac irradiation
Abnormal cardiac imaging or biomarkers levels
History of heart disease or left ventricular dysfunction
Hypertension
Obesity
Diabetes
Dyslipidemia
Physical inactivity
Smoking
Genetic predisposition

Table 1. Risk factors for drug-induced cardiotoxicity.

the management of these patients, in a multidisciplinary approach; an integrated approach using molecular, imaging, and clinical data may allow the selection of patients at risk of developing chemotherapy-related cardiotoxicity. Risk factors also include total cumulative dose, Down syndrome, female gender, black ethnicity, age below 4 years, old age, hypertension, obesity, diabetes, dyslipidemia, physical inactivity, smoking, concomitant cardiac irradiation, concomitant treatments, previous left ventricular dysfunction or cardiovascular comorbidity, and genetic predisposition. However, drug-induced cardiotoxicity may occur idiosyncratically without obvious risk factors [6, 12, 22, 27, 29].

4. Prevention and biomarkers

Measurement of cardio-specific biomarkers can be a valid diagnostic tool for early identification, assessment, and monitoring of cardiotoxicity. Advantages of biomarkers include being minimally invasive, less expensive than echocardiography or nuclear techniques, and can easily be repeated without irradiation of the patient. Moreover, the interpretation of the results does not depend on the expertise of the operator, thus avoiding the possibility of interobserver variability [30].

Moreover, there is an increased interest on the most recent noninvasive diagnostic biomarkers to early predict and follow up anthracycline-induced cardiotoxicity allowing a potential cardioprotective intervention before irreversible damage. Currently, the most important biomarkers are cardiac troponins, brain natriuretic peptide, and N-terminal fragment of brain natriuretic peptide [16, 31]. Persistent elevation of cardiac troponin I concentrations 1 month after anthracycline therapy had more cardiac adverse events at 3 years (84%) than patients with transient or no cardiac troponin I elevations (37 and 1%, respectively). Similarly, cardiac troponin T concentrations are associated with cardiac outcomes in children receiving moderate-dose anthracyclines for high-risk acute lymphocytic leukemia, and elevated concentration of N-terminal pro-brain natriuretic peptide during the first 90 days of therapy was associated with an abnormal left ventricular thickness-dimension ratio 4 years later, suggesting pathologic left ventricular remodeling [6]. Recently, circulating microRNAs are being considered to represent promising noninvasive and specific circulating biomarkers of several cardiovascular diseases, and they were successfully tested in children and young adults treated with anthracycline chemotherapy [32]. Fatty acid-binding protein 3 is a cytosolic protein found primarily in the heart but also in the muscle, brain, and kidney with a primary role in intracellular transport of long-chain fatty acids and in regulation of gene expression via peroxisome proliferator activator receptor. It has been demonstrated to be more sensitive than cardiac troponin for detection of ischemic injury and ongoing cardiac injury associated with congestive heart failure [33, 34]. Other less commonly used biomarkers include plasma cystatin-C, galectin-3, interleukin-6, tumor necrosis factor-alpha, and high-sensitivity C-reactive protein [6]. Noteworthy, the use of the classical biomarkers of lactate dehydrogenase and creatine kinase and their isozymes as biomarkers of cardiotoxicity has been substantially limited due to lack of tissue specificity and sensitivity [35, 36]. However, circulating biochemical markers carry potential problems related to sensitivity and specificity as they can be significantly influenced

by multiple microenvironmental factors and noncardiovascular diseases. Further, troponin levels increase in the blood only after tissue damage has occurred, and thus they cannot be used as early diagnostic markers of dysfunction onset [2, 32]. Human embryonic stem cell-derived cardiomyocytes are under investigation to predict drug-induced cardiotoxicity [3].

5-fluorouracil is perhaps the second, after doxorubicin, the most common cause of chemotherapy-associated cardiotoxicity which occurs predominantly in the first 72 h of the initial treatment cycle and may include chest pain, ECG changes, arrhythmia, pulmonary edema, myocardial infarction, and, rarely, cardiac arrest. Careful clinical monitoring during 5-fluorouracil administration in patients with preexisting cardiac disease is important, and its administration should be stopped immediately in patients who develop a cardiac adverse event. These patients should not be retreated with this agent, as the risk of a subsequent, potentially more serious cardiac event increases with repeat exposure [37].

5. Management

Standard management during anthracycline-based chemotherapy involves cardiac function assessment prior to treatment, monitoring potential cardiotoxicity during the therapy, as well as a long-term follow-up after the chemotherapy is completed [12]. A risk prediction model to identify patients at increased risk for therapy-induced cardiac disease prior to starting or during therapy using patient demographics (e.g., age at treatment, gender), treatment (e.g., cumulative anthracycline dose, radiation exposure), genomics, serial biomarkers, and echocardiographic measurements at baseline and during follow-up is under progress to enable investigators with an interest in cardiac late effects resulting from childhood cancer treatments to perform further investigation in the field [38].

Cardiac damage initially occurs in a molecular phase, followed by cellular damage, asymptomatic dysfunction, and finally symptomatic clinical dysfunction. The diagnostic intervention involves monitoring left ventricular ejection fraction by ultrasound, multigated acquisition scan, or MRI, considering <53% as abnormal. Cardiac MRI is considered the reference technique for quantification of left ventricular ejection fraction. However, ultrasound offers the advantages of its availability, low cost, lack of radiation, and overview of cardiac function. Yet, 2D ultrasound depends on the quality of the image and the expertise of the operator. Furthermore, it has a reported variability of about 10%, similar to the value used for diagnosis of cardiotoxicity [39].

Doppler speckle-tracking-derived longitudinal strain echocardiography has been useful in assessing adults for cardiac damage, and cardiac MRI has characterized myocardial tissue and assessed perfusion abnormalities independent of a good transthoracic window to obtain acceptable echocardiographic images [6]. Radionuclide angiography is an alternative method to detect cardiotoxic damage, and scintigraphy is also used for heart imaging in oncology, as it enables the assessment of left ventricular function [12]. Future improvement in the modalities to early detect drug-induced cardiotoxicity may include advanced techniques in cardiac nuclear molecular imaging and photoacoustic imaging [2].

Some authors have suggested patients receiving cardiotoxic drugs to be regarded as stage A heart failure, and if they experience an asymptomatic decline in left ventricular ejection fraction, they should be treated as per stage B [40]. Several protocols have been proposed to ameliorate or treat doxorubicin-/drug-induced cardiotoxicity including the use of epirubicin which has a less cardiotoxic potential than doxorubicin, reduction of lifetime cumulative dose, avoiding bolus, the use of continuous infusion with reduced peak concentration, prolongation of infusion time, the use of non-pegylated liposomal formulation of doxorubicin to help more specific delivery to the target site which can further reduce adverse cardiac effects, and the concomitant use of the antioxidant and iron chelator dexrazoxane, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, ranolazine, metformin, and hydroxymethylglutaryl-coenzyme A reductase inhibitors which have been shown to reduce drug-induced cardiotoxicity when used in a prophylactic setting. Further, the use of antioxidants, e.g., self-nanoemulsifying formulation of quercetin, Q10 coenzyme, vitamin E, and carnitine as well as avoidance of combinations which have an augmented cardiotoxic potential like anthracyclines added to trastuzumab would help to reduce the likelihood of drug-induced cardiotoxicity [12, 19, 21, 29, 41–43]. Carvedilol beta and alpha 1 blocker with strong antioxidant properties has been also shown to inhibit anthracycline- and/or trastuzumab-induced left ventricular dysfunction by ameliorating reactive oxygen species formation, mitochondrial alterations, and cardiomyocyte-induced apoptosis. Further, the combination of enalapril and carvedilol seemed to be beneficial in treating anthracycline-induced cardiotoxicity [22]. Additionally, a telemedicine system has allowed interdisciplinary management of the patients receiving anthracyclines with an expert cardiologist, and various chronoprogrammable drug delivery systems have been developed [2, 44]. Noteworthy, dexrazoxane has been reported to augment the myelosuppressive properties of doxorubicin, and a hypothetical concern of its possibility to provide a protective benefit to the neoplastic cells has resulted in its underutilization [45]. Further, it has been recommended that clozapine dose should be titrated gradually (in up to 25 mg/day increments) over 4–6 weeks until the target dose is reached as it has been shown that the risk of clozapine-induced myocarditis may be increased with a higher cumulative dose early in clozapine titration [18].

Interestingly, epidemiological studies have demonstrated that the incidence of cardiovascular disorders in France is strikingly lower than other western countries with a fat-containing diet. This so-called French paradox has been attributed to moderate consumption of red wine containing the potent antioxidant resveratrol in France, and resveratrol was suggested to be used during early cellular damage in organ toxicity after doxorubicin treatment in cancer patients, and its combined use with doxorubicin was suggested to be a viable chemotherapeutic modality that can selectively destroy tumors while concurrently limiting cardiac damages. Resveratrol was shown to mitigate the doxorubicin-induced cardiomyocyte apoptosis, autophagy, and fibrosis [15, 46].

Remote ischemic conditioning, a noninvasive nonpharmacological treatment delivered via a blood pressure cuff as short bursts of ischemia and reperfusion in a peripheral limb, with an unclear mechanism is a potentially cardioprotective treatment that is currently under investigation in cancer patients that may involve a humoral and neural pathway that confers cardioprotection by activating innate pro-survival pathways that ultimately modulate common

mechanisms in ischemia-reperfusion injury and anthracycline cardiotoxicity such as calcium overload, lipid peroxidation, ROS generation, and mitochondrial function [2].

6. Conclusion

Cardiotoxicity is an important dose-limiting side effect of various anticancer agents. In this chapter, we have identified some of the important and commonly used chemotherapeutic and biologic agents that have been reported to be associated with cardiovascular adverse effects. We have discussed the common mechanisms thought to be involved with such toxicity as well as the most important measures used to prevent and manage drug-induced cardiotoxicity. Although cardiotoxicity can occur without any predisposing factors, various risk factors are now known and considered of utmost importance to identify and manage before and during treatment, and we have discussed them. Finally, identifying drug-induced cardiac adverse effects as early as possible will help to prevent irreversible cardiac damage and to ameliorate the long-term morbidity and mortality rates as well as to improve the patients' quality of life.

Conflict of interest

None to be declared.

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