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Pharmacogenetics of Chemotherapy-Induced Cardiotoxicity

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Abstract

Purpose of Review—The goal of this review is to summarize current understanding of pharmacogenetics and pharmacogenomics in chemotherapy-induced cardiotoxicity.

Recent Findings—Most of the studies rely on in vitro cytotoxic assays. There have been several smaller scale candidate gene approaches and a handful of genome-wide studies linking genetic variation to susceptibility to chemotherapy-induced cardiotoxicity. Currently, pharmacogenomic testing of all childhood cancer patients with an indication for doxorubicin or daunorubicin therapy for RARG rs2229774, SLC28A3 rs7853758, and UGT1A6*4 rs17863783 variants is recommended. There is no recommendation regarding testing in adults.

Summary—There is clear evidence pointing to the role of pharmacogenetics and pharmacogenomics in cardiotoxicity susceptibility to chemotherapeutic agents. Larger scale studies are needed to further identify susceptibility markers and to develop pharmacogenomics-based risk profiling to improve quality of life and life expectancy in cancer survivors.

Keywords

Chemotherapy-induced cardiomyopathy; Chemotherapy-induced cardiotoxicity; Pharmacogenetics of cancer; Pharmacogenomics of cancer

Introduction

Despite recent advances in cancer treatment, cardiotoxicity can result from traditional chemotherapy agents such as anthracyclines, as well as newer targeted therapies, such as trastuzumab, leading to significant morbidity and mortality [1–4]. Radiation therapy alone

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and in combination with chemotherapy can also contribute to cardiotoxicity [5, 6]. These adverse effects can occur early or late, with early effects occurring within 1 year after exposure and late effects occurring a year or more after exposure. Now that patients with cancer are living longer, these cardiotoxicity effects are becoming increasingly recognized and cardio-oncology is emerging as a multidisciplinary field to advance our ability to diagnose, treat, and prevent these potentially devastating side effects.

The most common sign of chronic cardiotoxicity is asymptomatic systolic or diastolic dysfunction, leading to irreversible heart failure and even death [2], which makes close long-term monitoring by experienced healthcare providers critical. In one trial evaluating trastuzumab, cardiotoxicity was defined as one or more of the following: [1] cardiomyopathy characterized by a decrease in cardiac 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 [3]. However, cardiotoxic effects can range from coronary heart disease, pericardial disease, valvular disease, cardiomyopathy, and arrhythmias [7] and there are no standardized definitions or diagnostic criteria for cardiotoxicity.

Furthermore, conventional biomarkers show changes only after damage to the heart has been done. Once CHF develops, mortality increases to 50%. Standardized guidelines on how to best screen patients are much needed, as well as the identification of novel predictive biomarkers and genetic risks prior to chemotherapeutic treatment or development of heart failure symptoms and signs. This review summarizes the types of chemotherapeutic agents associated with cardiotoxicity, the known pharmacogenetics of chemotherapy-induced cardiotoxicity, and presents the future role of genomics.

Materials and Methods

A literature review was performed using PubMed to identify articles and case reports in the English literature between August 1973 and August 2017 on the clinical description, molecular mechanism, genetics, and treatment of chemotherapy-induced cardiomyopathy. Combinations of search terms including chemotherapy and cardiotoxicity, anthracycline and cardiomyopathy, antibody or targeted treatment and cardiotoxicity, mechanisms of cardiac dysfunction and chemotherapy and radiation, risk factors for cardiotoxicity and chemotherapy and radiation, pharmacogenetics or pharmacogenomics and cardiotoxicity, and screening for cardiotoxicity were used. Identified articles and case reports were reviewed, and the related reference lists were also searched to include additional studies. Studies pertaining to pharmacogenetics of chemotherapy-induced cardiotoxicity are included in this review.

Chemotherapeutic Agents that Cause Cardiotoxicity

Different chemotherapy agents cause cardiotoxicity through a wide variety of mechanisms, causing not only cardiomyopathy but also hypercoagulable states, arrhythmia, and

inflammation [4]. Anthracyclines such as daunorubicin, doxorubicin, and mitoxantrone are the most well-studied and cause dose-dependent cardiomyopathy and congestive heart failure [1, 5–8]. These agents work against cancer by cross-linking topoisomerase II α to DNA and directly intercalating with DNA, resulting in DNA damage, apoptosis, mitochondrial injury, increased reactive oxygen species [6], and programmed cell death [9]. Interestingly, cardiomyocytes do not express topoisomerase II α like tumor cells, but topoisomerase II β which can similarly complex with anthracyclines and result in cell death and decreased mitochondrial biogenesis [10, 11]. This is important because dexrazoxane is a cardioprotectant that has been shown to decrease incidence and severity of cardiotoxicity from anthracycline exposure [12–14] and acts through inhibition of both isomers of topoisomerase II as well as by chelating free iron and decreasing free radical generation [15–17].

Trastuzumab is a targeted antibody against Her2/neu amplification in certain breast cancers [18, 19]. It also has direct toxic effects on the heart and can potentiate anthracycline-mediated damage [10, 11]. The Her2 pathway is known to be involved in normal development of cardiomyocytes and conditional mutations of the HER2 receptor in cardiomyocytes lead to dilated cardiomyopathy [20]. Furthermore, trastuzumab has been shown to downregulate autophagy in primary cardiomyocytes leading to increased reactive oxygen species [21].

Taxanes such as paclitaxel and docetaxel act by disrupting microtubule formation. They can primarily cause arrhythmias, bradycardia, and myocardial ischemia [22, 23] thought to be due to abnormalities in calcium handling [24] and histamine release, resulting in conduction abnormalities [25]. The effect of taxanes has been found to worsen when administered with Her2 inhibitors and anthracyclines [26, 27].

Tyrosine kinase inhibitors such as imatinib, dasatinib, and nilotinib disrupt signaling pathways responsible for cancer progression by competing with the ATP binding site of oncogenic tyrosine kinases that are constitutively active often through mutation or translocation [28, 29]. A mouse model for imatinib-induced cardiotoxicity suggests effects in mitochondrial function and cardiomyocyte death through c-Jun N-terminal kinase activation and cardiomyocytes exposed to imatinib in culture undergo both apoptosis and necrosis [30].

Angiogenesis inhibitors such as bevacizumab and multi-targeted tyrosine kinase inhibitors such as sunitinib and dasatinib, intended at least in part to target tumor vasculature, can cause QT prolongation with progression to torsade de pointes (TdP) and sudden death [31]. Angiogenesis inhibitors can also lead to hypertension by inhibiting NO synthase, causing a decrease in NO production and subsequently vasoconstriction [32–34].

Fluoropyrimidines, such as 5-fluorouracil (5-FU), capecitabine, and gemcitabine, are anti-metabolites that inhibit thymidylate synthase [35]. This class of chemotherapy agents can cause chest pain, myocardial infarction, arrhythmia, CHF, and cardiogenic shock and sudden death [36, 37]. 5-FU seems to induce vasoconstriction while capecitabine causes coronary artery thrombosis, arteritis, or vasospasm [38–40]. Other proposed mechanisms include

endothelial damage, such as dilated or ruptured vessels, thrombosis, and effects on red blood cells potentially leading to a thrombogenic state [39, 41, 42].

Evidence in Support of the Role of Genetics in Cardiotoxicity

Known risk factors for cardiotoxicity include cumulative dose (e.g., for anthracycline), concomitant cardiac irradiation, higher individual doses, shorter infusion time, older than 65 years of age, female sex, and cardiovascular comorbidity. Of these, cumulative dosage and irradiation with cardiac involvement are the strongest independent risk factors [43]. According to the 2017 American Society of Clinical Oncology Clinical Practice Guideline on the Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers, patients who received the following types of treatments are considered to be at increased risk for developing cardiac dysfunction: (1) high-dose anthracycline (e.g., doxorubicin 250 mg/m², epiuribin 600 mg/m²), (2) high-dose radiotherapy (RT 30 Gy where the heart is in the treatment field), (3) low-dose anthracycline in combination with low-dose radiotherapy where the heart is in the treatment field, (4) low-dose anthracycline or trastuzumab plus any of the following risk factors, including cardiovascular risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia, and obesity), age 60, and compromised cardiac function (e.g., borderline LV EF 50 to 55%, history of myocardial infarction, and moderate valvular heart disease), (5) low-dose anthracycline followed by trastuzumab (sequential therapy) [44]. According to the International Late Effects of Childhood Cancer Guideline Harmonization Group on long-term surveillance, pediatric patients who receive anthracycline dose of 100 mg/m² and chest radiation dose 15 Gy are at moderate to high risk of developing cardiomyopathy long-term [45]. Yet, chemotherapy dosages that lead to toxic responses vary considerably among individual patients. For instance, doxorubicin dosages of 1000 mg/m² are tolerated by some patients, whereas others develop acute cardiotoxicity after 200 mg/m². Such findings demonstrate that there is likely no “safe” anthracycline dose where cardiotoxicity will not occur. Anthracycline-induced cardiotoxicity can occur idiosyncratically in patients without known risk factors. Cardiomyopathy has been reported in survivors who received doses well below 250 mg/m² [46]. The wide variation in the inter-individual susceptibility to anthracyclines begs the question of whether genetic determinants or predisposition plays a role in chemotherapy-induced cardiotoxicity.

Studies Examining Heritability and Genetic Determinants of Chemotherapy-Induced Cytotoxicity

In vitro studies minimize interindividual variability due to complex interactions on the whole organism level. Frick et al. developed a drug screening platform using a panel of genetically diverse mouse inbred strains. The aim was to examine interstrain differences in normal, noncancerous immune cell viability following chemotherapeutic cytotoxic insult. Drug effects were investigated by comparing selective chemotherapeutic agents, such as BEZ-235 and selumetinib, against conventional cytotoxic agents targeting multiple pathways, including doxorubicin and idarubicin. Splenocytes were isolated from 36 isogenic strains of mice. Cells were incubated with chemotherapeutic compounds of different

with breast cancer [53]. Although there were no differences using left ventricular ejection fraction as the primary outcome, the Ala1170Pro homozygous *ERBB2* genotype was associated with a lower risk of cardiotoxicity. Of note, previous studies looking at the Ala1170Pro *ERBB2* SNP have shown conflicting results with at least one study with similar results and a smaller retrospective study showing no correlation with the Ala1170Pro *ERBB2* SNP and cardiotoxicity in breast cancer patients [54, 55].

Studies of Chemotherapy-Induced Cardiotoxicity in Mice and Humans

Indeed, there is increasing evidence in mice and humans supporting the roles of genetics and in oncologic drug response and toxicity. For example, overexpression of the multiple drug resistance gene MDR1 protects the heart from the toxic effect of doxorubicin [56].

Linschoten et al. described two women with breast cancer who developed severe heart failure within months after chemotherapy. Genetic screen revealed truncating frameshift mutations in *TTN*, encoding the myofilament titin, in both women. Truncations in *TTN* are the most common cause of the familial and sporadic dilated cardiomyopathy. These findings suggest that a genetic predisposition to dilated cardiomyopathy may be an important contributor to chemotherapy-induced cardiomyopathy [57].

The variation in susceptibility to chemotherapy-induced cardiotoxicity has been postulated to be due to common polymorphisms in genes related to the metabolism of chemotherapy or iron levels, sensitivity to cell cycle inhibitor, cytoskeleton, or direct toxicity. There have been close to a dozen studies linking candidate genetic variation to cardiotoxicity [58, 59, 60, 61, 62, 63–65]. The general approach is described as follows. In one of the largest candidate approach studies, involving 1697 subjects, genes involved in metabolism of reactive oxygen species, drug transport and metabolism, DNA repair, endothelial physiology, the renin-angiotensin-aldosterone system, muscle contraction and structure, inflammation, and cell cycle were selected [65]. Polymorphisms for 73 genes were genotyped from peripheral blood lymphocytes of patients with non-Hodgkins lymphoma and tested for association with acute and chronic cardiotoxicity. A total of six variants showed nominal statistically significant ($P < 0.05$) association with anthracycline cardiotoxicity. Chronic ACT was associated with a variant in the NAD(P)H oxidase subunit NCF4, which is responsible for down regulation of the enzyme. Acute ACT was associated with two SNPs in other subunits of the same enzyme: p22phox and RAC2. In addition, acute ACT was associated with three polymorphisms in the transmembrane efflux transporters of anthracyclines, multi-drug resistance protein 1 (*MRP1*) and multi-drug resistance protein 2 (*MRP2*). The authors addressed the problem with multiple testing using a permutation analysis to see what are the chances of observing five associated genes nested within two functional groups. The overall P value was 0.08, indicating that the findings could be generated by chance in < 1 of 12 replicas of the study. Nonetheless, the authors concluded that a significant association between anthracycline-induced cardiotoxicity and genetic polymorphisms of the NAD(P)H oxidase and efflux transporters (*MRP1* and *MRP2*) was found. Overall, most candidate gene studies are limited by small patient numbers, lack of replication studies and functional data (66). A systemic review of 28 candidate gene association studies examined 84 different genes and 147 single nucleotide polymorphisms

[67]. Three risk variants in genes *ABCC2*, *CYBA*, and *RAC2* significantly increased the risk for anthracycline-induced cardiotoxicity.

One of the first genome-wide association studies for anthracycline-induced cardiotoxicity was published in 2015. The discovery cohort consisted of 280 patients of European ancestry treated for childhood cancer. The study identified a nonsynonymous variant (rs2229774, p.Ser427Leu) in *RARG* as being significantly associated with anthracycline-induced cardiotoxicity ($P = 5.9 \times 10^{-8}$) [66••]. This finding was replicated in similar cohorts of 96 European and 80 non-European patients. *RARG* is highly induced in mouse cardiocytes after injury [68] and is known to bind the topoisomerase II β promoter [69]. This finding suggests that *RARG* could be a clinically significant biomarker for anthracycline-induced cardiotoxicity.

Another genome-wide association study was conducted in childhood cancer survivors with and without cardiomyopathy [70••]. A modifying SNP rs1786814 on the *CELF4* gene was identified as an independent risk factor for anthracycline-induced cardiotoxicity in those in the treatment group ($P = 1.14 \times 10^{-5}$), possibly via a pathway that involves the expression of abnormally spliced *TNNT2* variants.

Linschoten et al. recently published a review article that assessed the body of literature by ten criteria, including assessment of population stratification, statistical methodology, and replication of findings [71]. They identified 40 studies: 34 exploring genetic risk factors for anthracycline-induced cardiotoxicity ($n = 9678$) and six studies related to trastuzumab-associated cardiotoxicity ($n = 642$). The majority (35/40) of studies had a candidate gene approach, whereas five genome-wide association studies have been performed. They identified 25 genetic variants in 20 genes and two intergenic variants reported significant at least once. The overall validity of studies was limited, with small cohorts, failure to assess population ancestry and lack of replication. The authors concluded that the SNPs with the most robust evidence up to this point are *CELF4* rs1786814 (sarcomere structure and function), *RARG* rs2229774 (topoisomerase-2 β expression), *SLC28A3* rs7853758 (drug transport), *UGT1A6* rs17863783 (drug metabolism), and one intergenic variant (rs28714259) (Table 1). All but the intergenic variant rs28714259 is found on popular direct-to-consumer genotyping service, such as 23andme's genotyping platform. Existing evidence supports the hypothesis that genetic variation contributes to chemotherapy-related cardiac dysfunction. Although many variants identified by this systematic review show potential to improve risk stratification, future studies are necessary for validation and assessment of their value in a diagnostic and prognostic setting. A summary of the evidence for genetic variants modulating chemotherapy-related cardiac dysfunction is outlined in a table in Linschoten et al. [71].

Recommendations for Genetic Testing

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Practice Recommendations Group examined individual genetic markers for the level of evidence in support of its role in discriminating individuals at low, moderate, or high risk of anthracycline-induced cardiotoxicity. They concluded that three SNPs in three genes

currently have the strongest evidence as pharmacogenomic markers for anthracycline-induced cardiotoxicity. These associations have been replicated at least twice in large well-characterized patient populations with clinically relevant effect sizes (OR > 3 or < 0.3). They recommended pharmacogenomic testing in all childhood cancer patients with an indication for doxorubicin or daunorubicin therapy for *RARG*rs2229774, *SLC28A3*rs7853758, and *UGT1A6**4 rs17863783 variants [72]. Based on an overall risk stratification, taking into account genetic and clinical risk factors, a number of management options including increased frequency of echocardiogram monitoring, follow-up, as well as therapeutic options within the current standard of clinical practice can be initiated. As most of the studies so far have been performed in pediatric patients, receiving doxorubicin and daunorubicin, the generalizability of these findings to adults and other anthracycline is unknown. As such, pharmacogenomic testing is currently not recommended in adult patients and in children receiving other types of anthracyclines. Further research in adults and other chemotherapeutic agents is needed to improve the diagnostic and prognostic role in predicting chemotherapy-induced cardiotoxicity. Outcomes studies will also be needed to demonstrate that such early risk stratification and intervention lead to a meaningful difference in hard clinical endpoints such as the development of cardiac morbidity and mortality.

Conclusions: Future Avenues

The number of survivors of cancer is growing at an increasing pace. Chemotherapy-induced cardiotoxicity will represent an increasing health burden for the foreseeable future. Chemotherapeutic agents cause cardiotoxicity through multiple mechanisms that are subject to genetic influences. Understanding the pharmacogenomics holds the promise of maximizing benefits and minimizing harm.

This review has described the initial identification of risk-associated genetic polymorphisms. Larger studies will be needed to confirm existing and identify novel associations. A major barrier to the advance of the field has been small cohort sizes. Typically, large consortia supported by substantial funding will be required.

Genetic polymorphisms described above are present on most whole-genome arrays. Institutions pioneering precision healthcare already have access to genotype data. The general approach is to superimpose genotypes and clinical data over a large number of patients across an entire health system. This approach can quickly increase cohort sizes and to study additional cardiotoxic agents, such as trastuzumab, tyrosine kinase inhibitors, and immunotherapy. If multiple such institutions collaborate, replication of findings in clinical applications such as genomic risk profiling can be done quickly.

In spite significance advances, gaps in the understanding of cardiotoxicity mechanisms remain. Risk modifying polymorphisms shed light on mechanisms of toxicity. Most of polymorphisms affecting chemotherapy-induced cardiotoxicity are expected to be common. Thus, polymorphism-specific therapeutic options may be possible.

As we build knowledge around the genetic polymorphisms that account for the interindividual differences in cardiotoxicity, we will be better at assessing risks of chemotherapeutic options and individualizing treatment plans. We will march one step closer to the promise of optimized care for each patient.

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Genetic polymorphisms that are clinically relevant to chemotherapy-induced cardiotoxicity

Table 1

Gene	SNP	Biological function	Clinical relevance	Relevant chemotherapy
CELF4 [70••]	rs1786814	Sarcomere structure and function	The GG genotype conferred a 10.2-fold (95% CI, 3.8- to 27.3-fold; $P < 0.001$) increased risk of cardiomyopathy compared with those who had GA/AA genotypes	> 300 mg/m ² of anthracyclines in childhood
RARG [66••]	rs2229774	Topoisomerase-2 β expression	A nonsynonymous variant (rs2229774, p.Ser427Leu) in RARG was highly associated with ACT ($P = 5.9 \times 10^{-8}$, odds ratio (OR) (95% confidence interval) = 4.7 (2.7–8.3)).	Anthracycline in childhood
SLC28A3 [64]	rs7853758	Drug transport	rs7853758 ($P = 0.058$, OR 0.46) in SLC28A3 was associated with ACT (replication study combined $P = 1.6 \times 10^{-5}$).	Anthracycline in childhood
intergenic variant [73••]	rs28714259	Unknown	rs28714259 was associated with borderline increased CHF risk ($P = 0.04$, OR = 1.9) and decreased left ventricular ejection fraction ($P = 0.018$, OR = 4.2).	Anthracycline in adult breast cancer patients
UGT1A6 [64]	rs17863783	Drug metabolism	rs17863783 in UGT1A6 was associated with ACT ($P = 0.0062$, odds ratio (OR) 7.98).	Anthracycline in childhood