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Validating the pharmacogenomics of chemotherapy-induced cardiotoxicity: What is missing?

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ABSTRACT

The cardiotoxicity of certain chemotherapeutic agents is now well-established, and has led to the development of the field of cardio-oncology, increased cardiac screening of cancer patients, and limitation of patients' maximum cumulative chemotherapeutic dose. The effect of chemotherapeutic regimes on the heart largely involves cardiomyocyte death, leading to cardiomyopathy and heart failure, or the induction of arrhythmias. Of these cardiotoxic drugs, those resulting in clinical cardiotoxicity can range from 8 to 26% for doxorubicin, 7–28% for trastuzumab, or 5–30% for paclitaxel. For tyrosine kinase inhibitors, QT prolongation and arrhythmia, ischemia and hypertension have been reported in 2–35% of patients. Furthermore, newly introduced chemotherapeutic agents are commonly used as part of changed combinational regimens with significantly increased incidence of cardiotoxicity. It is widely believed that the mechanism of action of these drugs is often independent of their cardiotoxicity, and the basis for why these drugs specifically affect the heart has yet to be established. The genetic rationale for why certain patients experience cardiotoxicity whilst other patients can tolerate high chemotherapy doses has proven highly illusive. This has led to significant genomic efforts using targeted and genome-wide association studies (GWAS) to divine the pharmacogenomic cause of this predilection. With the advent of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), the putative risk and protective role of single nucleotide polymorphisms (SNPs) can now be validated in a human model. Here we review the state of the art knowledge of the genetic predilection to chemotherapy-induced cardiotoxicity and discuss the future for establishing and validating the role of the genome in this disease.

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1. Introduction

Despite the substantial improvement in cancer care, which has resulted in the increase in 5-year survival rate from 35% in the early 1950s to 70% in 2006–2012, the extensive use of chemotherapeutic agents is concordant with a higher incidence of adverse drug events

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(ADE). ADEs are one of the leading causes of death worldwide. According to the US Food and Drug Administration (FDA) adverse drug events reporting system (FAERS), about 1 million serious (including death) ADEs were reported in 2014 in the USA alone (fda.gov). Cardiotoxicity is a common ADE for multiple anti-cancer agents, constituting a significant clinical and economic burden, resulting in the establishment of the field of cardio-oncology to elucidate this phenomenon. Chemotherapy-induced cardiotoxicity (CIC) can be defined as subclinical or clinical, causing manifestations that include disturbance in ventricular de/repolarization and QT interval, arrhythmia, bradycardia, tachycardia, decreases in left ventricular ejection fraction (LVEF) and fractional shortening (FS), and irreversible congestive heart failure (CHF), all of which lead to increased morbidity and mortality. In addition, cardiotoxicity may be classified as early-onset acute (developed directly or up to 1 year after treatment) or late-onset chronic (detected at 1 to 20 years after starting chemotherapy), making the situation even more complex, as lifelong follow-up monitoring of patients is a substantial clinical burden. The childhood cancer survivor study (CCSS) is a large multi-center, long-term effort to follow ~10,000 cancer survivors diagnosed in the period between 1960 and 1986. 30 years after initial diagnosis, the accumulative incidence of severe chronic health conditions, including myocardial infarction and CHF, was 73.4%. After adjustments for age, sex, and ethnicity, survivors showed an 8.2-fold higher risk of developing severe chronic health conditions (Grade 3 and Grade 4) compared to their siblings who did not receive any cancer treatments (Oeffinger et al., 2006). Hence, identifying risk factors for CIC that make certain patients more susceptible than others, as well as identifying and understanding the underlying mechanism of ADEs, is essential to improving clinical outcome of chemotherapy treatment regimens. In this review we will focus on genetically-dependent inter-patient variability in susceptibility to CIC and the extent to which identified genetic polymorphisms are linked to the mechanisms of CIC with an emphasis on doxorubicin pharmacogenomics.

2. Cardiotoxicity of anti-cancer therapeutics

2.1. Anthracyclines

Anthracyclines are anticancer agents initially isolated from natural sources. Daunorubicin and doxorubicin (DOX) are anthracyclines isolated from *Streptomyces peucetius*, a soil-dwelling bacterium, and from a mutated strain of the same bacterium, respectively (Arcamone et al., 1969; Di Marco et al., 1981). Other commonly used anthracyclines include epirubicin and idarubicin (Espinosa et al., 2003). Anthracyclines exert their action primarily through topoisomerase 2-α (TOP2A) inhibition. Topoisomerases are enzymes that cause double stranded DNA breaks that serve to relax DNA supercoiling during DNA replication and transcription. Anthracyclines prevent TOP2A from dissociating from DNA after making a cut, preventing re-ligation. Anthracyclines also directly intercalate with DNA, induce the formation of reactive oxygen species, and modulate histone-DNA binding. Together these effects ultimately lead to programmed cell death (Champoux, 2001).

DOX has been in use for over five decades as the backbone of chemotherapy treatment regimens for a wide range of adult and pediatric cancers such as breast cancer, leukemia, and lymphomas. Although DOX treatment has contributed to an increase in the 5-year survival rate in children to more than 80% (Lipshultz et al., 2008), severe dose-dependent cardiotoxicity occurs in about 50% of treated patients (Swain et al., 2003) and leads to dose limitation or treatment discontinuation. About 26% of patients treated with an accumulative DOX dose of 550 mg/m^2 experienced heart failure, and the maximum life time cumulative dose is thus limited to 400 to 550 mg/m^2, decreasing the benefits that patients may receive form this potent drug (Swain et al., 2003; Wouters et al., 2005). Notably, up to 65% of pediatric cancer survivors treated with DOX develop measureable impairment in cardiac function, even when treated with less than the maximum recommended DOX doses (van der Pal et al., 2010). As many as 16% of children with these abnormalities will develop subsequent clinical heart failure with a mortality rate as high as 72%. Although DOX has been used for more than 50 years, the mechanism by which it induces cardiotoxicity remains unclear.

2.2. Small molecule tyrosine kinase inhibitors (TKIs)

The protein kinase gene family comprises one of the biggest gene families in the human genome, with more than 538 identified protein kinase encoding genes. Protein kinases play a crucial role in various cellular processes including metabolism, transcription, cell movement, and intercellular communication. With more than 90 members, tyrosine kinases (TKs) constitute a large sub-family of protein kinases; TKs are enzymes responsible for physiologically reversible polypeptide phosphorylation through the transfer of a phosphate moiety from ATP to tyrosine residues, and thus regulate signaling pathways involved in cancer progression (Manning et al., 2002; López-Otín & Hunter, 2010). Based on this fact, several TK inhibitors (TKIs) have been developed as anti-cancer agents to treat a wide range of cancers including leukemia, breast cancer, renal cell carcinoma, and gastrointestinal stromal tumors. Cardiovascular toxicity has been observed in patients treated with a wide-range of TKIs, and 25 of the 27 currently FDA approved oncology TKIs have some type of cardiovascular toxicity-related warning in their package insert (accessdata.fda.gov).

Imatinib was one of the first small molecules developed to inhibit TKs, targeting the fusion protein breakpoint cluster region-ABL proto-oncogene 1 (BCR-ABL1) tyrosine kinase. Imatinib was approved in 2001 to treat Philadelphia chromosome positive (Ph^+) chronic myeloid leukemia (CML), contributing to a better than 90% 5-year survival rate (Druker et al., 2001, 2006). The first cardiovascular adverse effect associated with imatinib therapy was reported by Kerkelä et al. They showed that ten individuals who had normal left ventricular function before receiving imatinib, experienced class 3–4 heart failure approximately 7 months after imatinib therapy (Kerkelä et al., 2006). Studies performed in mouse models showed that one possible mechanism for imatinib-induced cardiotoxicity may occur via endoplasmic reticulum stress response-induced pro-death pathway activation including c-Jun N-terminal kinases (JNKs) activation, which leads to subtle alterations in mitochondrial function and cardiomyocyte death. Since the initial report, several studies have implicated imatinib in cardiovascular adverse events (Demetri, 2007; Herman et al., 2011; Toubert et al., 2011).

Imatinib was followed by second generation TKIs including dasatinib, nilotinib, and bosutinib. Dasatinib, a second generation BCR-ABL1 TKI was introduced following the dasatinib versus imatinib comparison study in treatment-naive CML patients (DASISION), which demonstrated that dasatinib (100 mg once daily) resulted in faster and deeper molecular responses compared with imatinib (400 mg once daily). However, this did not translate into better overall survival rate (Jabbour et al., 2014). Acquired resistance to TKIs is caused by the formation of a polymorphic BCR-ABL1 oncogene, which decreases the binding affinity of TKIs. On that basis, Griffin et al. successfully developed a second generation BCR-ABL1 TKI, nilotinib, which is 30-fold more potent than imatinib. While its role as a first line of treatment is still under investigation, it is an excellent therapeutic candidate for patients harboring imatinib-resistant BCR-ABL1 mutants (Weisberg et al., 2005). Importantly, analysis of 2200 electrocardiograms from patients recruited in a dose escalation phase l study of nilotinib showed prolonged QT intervals, ranging from 5 to 15 ms, and thus close monitoring of arrhythmia and QT intervals has been recommended for patients treated with nilotinib (Kantarjian et al., 2006). Prolonged QT intervals could be explained by the inhibitory effect of nilotinib on human Ether-à-go-go-Related Gene (hERG or KCNH2), which encodes the alpha subunit of potassium ion channel (K_v11.1). K_v11.1 is responsible for delayed-rectifier K^+ current in cardiac tissue, and blocking this ion channel by nilotinib results in QT wave disturbance (Shopp et al.,