Models of Heart Failure Based on the Cardiotoxicity of Anticancer Drugs

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ABSTRACT

Heart failure (HF) is a complication of oncological treatments that may have dramatic clinical impact. It may acutely worsen a patient's condition or it may present with delayed onset, even years after treatment, when cancer has been cured or is in stable remission. Several studies have addressed the mechanisms of cancer therapy-related HF and some have led to the definition of disease models that hold valid for other and more common types of HF. Here, we review these models of HF based on the cardiotoxicity of antineoplastic drugs and classify them in cardiomyocyte-intrinsic, paracrine, or potentially secondary to effects on cardiac progenitor cells. The first group includes HF resulting from the combination of oxidative stress, mitochondrial dysfunction, and activation of the DNA damage response, which is typically caused by anthracyclines, and HF resulting from deranged myocardial energetics, such as that triggered by anthracyclines and sunitinib. Blockade of the neuregulin-1/ErbB4/ErbB2, vascular endothelial growth factor/vascular endothelial growth factor receptor and platelet-derived growth factor /platelet-derived growth factor receptor pathways by trastuzumab, sorafenib and sunitinib is proposed as paradigm of cancer therapy-related HF associated with alterations of myocardial paracrine pathways. Finally, anthracyclines and trastuzumab are also presented as examples of antitumor agents that induce HF by affecting the cardiac progenitor cell population. (*J Cardiac Fail 2016;22:449–458*)

Key Words: Heart failure, antineoplastic drugs-induced cardiotoxicity, anthracyclines, receptor tyrosine kinase.

Recent advances in antineoplastic treatments have rendered cancer curable in a sizable percentage of subjects, which is likely to further increase in the next years. In many other cases, prolonged remission is achieved, leaving patients free of disease for a considerable time. Unfortunately, these improvements take their toll in terms of emerging chronic side effects of antineoplastic agents, which can predominate once a tumor is eliminated or durably controlled.[1] Asymptomatic reduction in left ventricular (LV) function and heart failure (HF) are prototypical complications of cancer therapies that may have long-lasting impact.[2] Much effort has been expended in trying to pinpoint the mechanisms of cancer therapy-related HF (CTHF). This substantial body of work has allowed the identification of potential approaches to tackle the cardiotoxicity of antitumor agents, and additional ones are expected to be investigated in the next future. On the other hand, such an approach has also contributed to uncover important insights into the pathogenesis of HF in general. Among the many mechanisms that have been reported for CTHF, here we focus on those that have proven to be also relevant for other, more common forms of HF. We classify them as cardiomyocyte-intrinsic and paracrine, depending on whether they primarily affect cardiomyocytes or paracrine signals regulating cardiomyocytes, respectively. Furthermore, we propose disturbance of the cardiac progenitor cell (CPC) compartment as a third, stand-alone potential event in CTHF that may apply to other types of HF (Table 1). Each model is discussed referring to the anticancer agents that typically cause it, although it may also explain the cardiotoxicity of other drugs.

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Table 1. Chemotherapeutic Agents Commonly Associated with Cardiotoxicity

Proposed Mechanisms	Chemotherapeutic Drug
Cardiomyocyte intrinsic	Anthracyclines, sunitinib
Paracrine	Trastuzumab, sunitinib, sorafenib
Effects on cardiac progenitor cells	Anthracyclines, trastuzumab

Cardiomyocyte-Intrinsic Mechanisms

Oxidative Stress and DNA Damage

Anthracyclines currently constitute key components of chemotherapeutic regimens for the treatment of different adult and pediatric cancers, such as leukemias and lymphomas as well as many solid tumors, including breast cancer.[3] These agents are among the most cardiotoxic anticancer drugs. Anthracycline cardiotoxicity can manifest acutely, early after infusion, requiring either modification or withdrawal of anticancer regimens.[4] Luckily, this is a relatively rare complication of chemotherapy, occurring in less than 9% of all patients treated with anthracyclines, and recent evidence clearly demonstrates that anthracycline side effects are usually dose-dependent and more frequently detected within the first year after completing the treatment.[5,6] Preexistent heart diseases and advanced age represent major risk factors for CTHF and recent studies also highlight the existence of a gender-related predisposition. Interestingly, a significantly higher risk for subclinical cardiotoxicity has been found in females than in males[7–9]; this could be ascribed, at least in cellular models, to testosterone-mediated protection from anthracycline-induced senescence of cardiomyocytes[10] (see Table 2 for a comprehensive list of risk factors).

Table 2. Risk Factors for Cancer-Related Heart Failure

Risk Factor	References
Age	6
Cumulative anthracycline dose	6–8
End-chemotherapy LVEF	6
Family history of coronary artery disease	6
Younger age at treatment	7
Female gender	6,7,9

LVEF, left ventricular ejection fraction.

Cardiotoxicity is a well-known adverse effect of anthracyclines and the research performed in the past 50 years has started to shed light on the molecular pathways involved. From a pathophysiological point of view, anthracyclines induce cardiomyocyte death, primarily apoptosis and necrosis, through several molecular mechanisms, including but not limited to induction of oxidative stress, activation of DNA damage responses and impairment of mitochondrial biogenesis and metabolism (Fig. 1).[11] The maladaptive changes occurring in surviving myocytes as well as those occurring in the extracellular matrix eventually lead to pathological LV remodeling, with dilatation and impairment of contractility, up to decline in systolic function and development of clinical HF.

Anthracycline-mediated myocyte damage has traditionally been attributed to the production of reactive oxygen species (ROS) with a subsequent increase in oxidative stress, which in turn causes membrane lipid peroxidation, vacuolization, irreversible damage, and myocyte replacement by fibrous tissue.[2,3,12–18] This primarily stems from the susceptibility of anthracyclines to be rapidly reduced to unstable metabolites

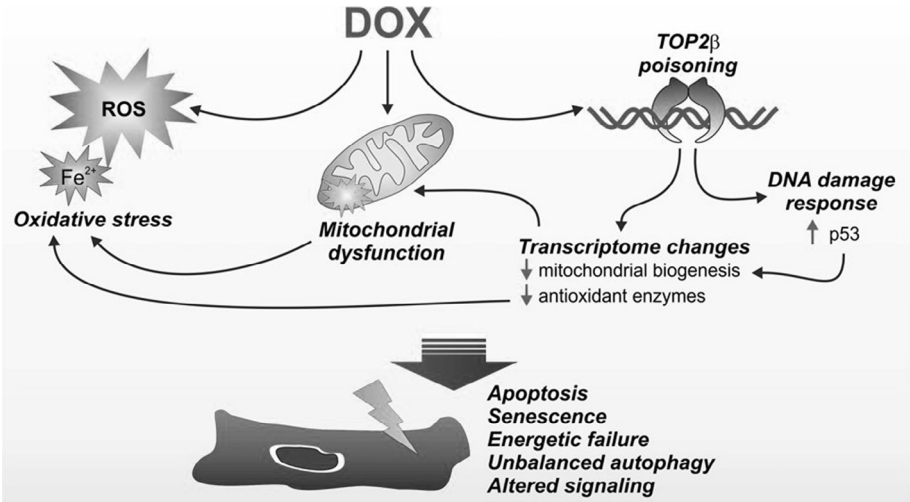

Fig. 1. Cardiomyocyte-intrinsic molecular mechanisms underlying anthracycline cardiotoxicity.
Anthracyclines, such as doxorubicin (DOX), lead to cardiotoxicity by promoting the production of reactive oxygen species (ROS), via direct (unstable DOX metabolites, such as DOX-semiquinone, react with oxygen and generate hydrogen peroxide and superoxide) and indirect (DOX chelates free iron and modulates the activity/expression of major iron-transporting/binding proteins) mechanisms. Alternatively, DOX can interact with cardiomyocyte topoisomerase 2β (Top2β), an enzyme responsible for managing DNA tangles and supercoils, thus inducing DNA double-strand breaks. DNA damage, in turns, activates the tumor suppressor protein p53, which is responsible for the activation of DNA repair proteins, but also of repression of genes involved in mitochondrial biogenesis/recycling and oxidative phosphorylation pathways. Finally, DOX can accumulate within mitochondria of cardiomyocytes and exacerbate metabolic failure of these organelles. Altogether, these molecular events contribute to cardiomyocyte death and ultimately to cardiac dysfunction.

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