EDITORIAL COMMENTARY

Anthracycline-induced cardiomyopathy: Is there a new light at the end of the tunnel?

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Despite introduction of novel targeted therapies and immunotherapies, cytotoxic chemotherapy with anthracyclines remains an integral part of treatment regimens for many solid and hematologic malignancies. The potential for cardiovascular toxicity with anthracyclines is well established, with the first reports of dose-dependent heart failure published in the 1970s.[1] Since then, significant effort has been spent to identify risk factors for anthracycline-induced cardiotoxicity and develop prevention strategies.[2,3] However, there is lack of clear mechanistic understanding of this potentially devastating adverse effect from this effective chemotherapeutic. Despite numerous attempts, optimal cardioprotective strategies directed against anthracycline cardiotoxicity, while maintaining its oncologic effectiveness, remain elusive. There is evidence that doxorubicin increases reactive oxygen species resulting in abnormal calcium dynamics. Perhaps strategies to improve calcium dynamics could prove cardioprotective.

Dantrolene, a skeletal muscle relaxant and ryanodine receptor stabilizer, has been used to treat muscle spasms and malignant hyperthermia.[4] It may benefit patients with catecholaminergic polymorphic ventricular tachycardia[5] and improve hemodynamics during cardiopulmonary resuscitation.[6] Preclinical data implicate calcium dysregulation in the development of dilated cardiomyopathy. Dantrolene improves sarcoplasmic calcium release, improves cardiac function in acute and chronic cardiomyopathy, and affects atrial fibrillation in animal models.[7,8] Indeed, prior work has been performed with dantrolene in anthracycline-induced cardiomyopathy; results may be dose-dependent.[9,10] Despite issues regarding dosing, dantrolene improved survival rate and preserved myocardial dystrophin, calpain levels, and cardiac function. For unclear reasons, however, evaluation of dantrolene halted several years ago.

In this issue of *Heart Rhythm O*^{2}, Azam and colleagues[11] explored utility of dantrolene as cardioprotective therapy for anthracycline-induced cardiac dysfunction in a murine model. Using a carefully and well-designed experimental protocol, the authors showed definitively that dantrolene in vivo and in a Langendorff preparation protected against deleterious myocardial effects of doxorubicin, thus preventing impairment of left ventricular ejection fraction. Their data showed improvement in calcium transient duration, calcium transient rise time, and calcium amplitude alternans ratio, suggesting a mechanistic explanation for the results. There was no effect on reduction in spontaneous diastolic calcium leak, however. These data showing improvement in calcium dynamics add to what is already known about potential benefits of dantrolene regarding cardiac contractile functioning and about potential benefits of dantrolene, specifically on unzipped ryanodine receptors. Whether lack of benefit of spontaneous diastolic calcium release is important and whether prevention of pathologic ryanodine receptor unzipping remains critical remains uncertain.

Importantly, these data provide a new ray of hope for patients with cancer who could benefit from anthracyclines. While results are intriguing, it remains to be seen whether a clinically effective cardioprotective strategy will emerge, since the role of calcium dysregulation in the pathophysiology of anthracycline-induced cardiomyopathy has yet to be established definitively and the results from a preclinical mouse model may not translate to humans of both sexes. Furthermore, there are concerns with potential adverse effects of dantrolene, including liver toxicity.

Given that left ventricular dysfunction and heart failure are the predominant manifestations of anthracycline-induced cardiotoxicity, studies have focused on neurohormonal blockade to prevent heart failure. Unfortunately, data with beta-blockers (BB) and renin-angiotensin-aldosterone blockers (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers [ARBs]) have generally been negative. In the landmark Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) trial, women with breast cancer and no significant cardiovascular disease or risk factors treated with doxorubicin were randomly assigned to either candesartan (ARB),

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metoprolol (BB), or placebo.[12] Though there appeared to be a short-term benefit with candesartan, neither BB nor ARB prevented long-term decline in left ventricular ejection fraction, calling into question the role for cardioprotective medications for cancer patients receiving anthracyclines without other indications for these therapies.[12,13] Similarly, the Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity trial (CECCY) failed to demonstrate benefit from carvedilol in preventing reduction in left ventricular function.[14]

While the study population may have impacted the results of PRADA and CECCY (the majority of the women were healthy, without baseline cardiovascular risk factors or disease), our lack of a mechanistic understanding of anthracycline-mediated cardiotoxicity certainly impacts our ability to identify the most appropriate and effective strategy for cardioprotection.

Various theories have been proposed to explain anthracycline-mediated left ventricular dysfunction, including cellular apoptosis due to reactive oxygen species, DNA damage via topoisomerase-II, impaired protein synthesis, and mitochondrial iron accumulation; however, a definitive mechanism has yet to be established.[15] Indeed, there is even a gap in our understanding of dexrazoxane's cardioprotective effects despite its being approved by the United States Food and Drug Administration to minimize potential cardiotoxicity from anthracyclines.[16] The provocative results from Azam and colleagues[11] suggest that now is the time to consider carefully controlled prospective clinical studies of dantrolene to protect against anthracycline-induced cardiotoxicity. And, hopefully, there may be a light at the end of the tunnel!

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

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