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EDITORIAL

Anthracycline-Induced Cardiotoxicity: Time to Focus on Cardioprotection Again

A.J. Croft, BSc [a], D.T.M. Ngo, B Pharm, B HealthSc, PhD [a], A.L. Sverdlov, MBBS, PhD, FRACP, FCSANZ [a,b*]

[a]Faculty of Health and Medicine, The University of Newcastle, NSW and Cardio-oncology Research Group, Hunter Medical Research Institute, Newcastle, NSW, Australia
[b]Cardiovascular Department, John Hunter Hospital, Newcastle, NSW, Australia

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Anthracyclines have been in clinical use for decades due to their anti-neoplastic effects in many cancers including breast cancer, leukaemia, lymphoma, sarcoma, lung cancer and multiple myeloma, however the effective use of these agents is limited by the danger of cardiotoxicity [1]. Incidence of cardiotoxicity in patients treated with anthracyclines varies according to cardiotoxicity definition, but has been reported as high as 26% for heart failure and 36% for left ventricular dysfunction [2,3], with the major predicting factor being anthracycline cumulative dose. Conventionally, anthracycline-induced cardiomyopathy is usually detected/monitored by assessing changes in left ventricular function using cardiac imaging (echocardiography, nuclear medicine or [magnetic resonance imaging] MRI) along with measurement of biomarkers such as cardiac troponin T [1]. With improvements in the long-term cancer survival, the cardiotoxic effects of anthracyclines are becoming an increasingly relevant problem for cancer survivors and health care system.

While anthracycline-induced cardiotoxicity has been studied for many years, we are yet to completely understand the underlying mechanisms and develop clinically proven prevention and treatment strategies. Doxorubicin has been shown to induce generation of reactive oxygen species in cardiomyocytes and endothelial cells and cause mitochondrial dysfunction to which cardiomyocytes are particularly sensitive, due to their substantial dependence on ATP [4]. Oxidative stress generated by anthracyclines also leads to cell death of both cardiomyocytes and endothelial cells via apoptosis and necrosis, which causes major and irreversible remodelling of cardiac tissue and subsequent impairment of cardiac function [4]. Cardiac fibroblasts have been demonstrated to play a role in doxorubicin-induced cardiotoxicity via cardiac remodelling and fibrosis [5].

At present, the most successful strategies to limit the cardiotoxicity of anthracyclines are to restrict the cumulative dose, use PEGylated liposomes to deliver doxorubicin more selectively to tumours or to avoid treatment of patients with cardiovascular risk factors with anthracyclines altogether [3]. Dexraxoxane, an EDTA-derived iron chelating agent, has been shown to reduce incidence of cardiotoxicity in a number of trials in patients treated with doxorubicin, but there are concerns as to whether dexraxoxane also reduces the anti-neoplastic effect of doxorubicin [6]. Antioxidants such as probucol and beta blockers such as carvedilol have shown improvements in the cardiotoxic effects of doxorubicin *in vitro* and in animal models, but these results have not yet been effectively translated into a clinical setting [7]. Angiotensin-converting-enzyme (ACE)-inhibitors and angiotensin II receptor blockers have been investigated in patients for cardioprotection with conflicting results [8]. Although the research mentioned above is showing promising results, the lack of translation of new and effective treatment options into clinical practice indicates that new prevention and treatment strategies are urgently needed to benefit patients. In order to develop effective cardioprotective agents, better understanding of basic mechanisms and pathways underlying anthracycline-medicated cardiotoxicity is necessary.

Substance P (SP) is a neuropeptide that acts through the neurokinin-1 receptor (NK1R) that has been shown to have

*Corresponding author at: University of Newcastle, John Hunter Hospital, Lookout Road, New Lambton Heights, NSW 2305, Australia. Tel. +61 2 4921 4202, fax. +61 2 4921 4210., Email: Aaron.sverdlov@newcastle.edu.au

dual roles in the heart. On one hand, the SP/NK1R axis exerts a cardioprotective effect in response to ischaemia-reperfusion [9]. However, substance P has been found to be involved in cardiomyocyte apoptosis in a myocarditis model, and may be involved in ROS generation, cardiac remodelling, hypertrophy and heart failure [10–12]. In this issue, Levick et al. investigate the repurposing of the NK1R antagonist aprepitant to act as a cardioprotective agent against doxorubicin-induced cardiotoxicity [13]. Aprepitant has previously been shown to reduce cardiomyocyte apoptosis induced by doxorubicin in a cell culture model, and it has previously been reported to attenuate cardiac fibrosis [12]. Aprepitant is already in clinical use in cancer patients receiving chemotherapy to manage emetogenic symptoms [14].

In the current study, the authors provide insights into the role of cardiac fibroblasts in remodelling of the myocardium after exposure to doxorubicin. They show evidence in doxorubicin-treated rats that enhanced collagen production in the left ventricle that was likely due to secretion by cardiac fibroblasts [13]. Moreover, while doxorubicin induced cardiomyocyte apoptosis, viability of cardiac fibroblasts was increased, consistent with their established role in cardiac injury [15]. Next, the authors investigated the effects of NK1R blockade by aprepitant on doxorubicin-induced cardiotoxicity [13]: aprepitant treatment of rats attenuated the collagen deposition in the heart induced by doxorubicin treatment; and, apreptitant reversed doxorubicin-induced apoptosis of cardiomyocytes. Conventionally, in animal and human studies, anthracycline-mediated cardiotoxicity is assessed by measuring LV systolic function (either ejection fraction or fractional shortening) [1]. Interestingly, while aprepitant had no effect on these measures of systolic function, it restored LV diastolic abnormalities induced by doxorubicin treatment [13]. This is an important observation and potentially could be explained by its effects on myocardial fibrosis, which in early stages is more commonly associated with diastolic rather than systolic changes [16].

Levick et al. add important information regarding the divergent effects doxorubicin has on different cell types in the heart [13]. A large proportion of the literature dissecting the mechanisms of doxorubicin-mediated cardiotoxicity focus on cardiomyocytes, often overlooking the role of other cell types. Cardiac fibroblasts are the major cell type involved in cardiac fibrosis in other conditions, however it is interesting to note in the present study that changes in the heart following doxorubicin treatment include increased proliferation of fibroblasts and enhanced collagen secretion, implying that doxorubicin is directly involved in this process. Targeting cardiac fibroblasts to prevent adverse cardiac remodelling may be a useful strategy in combating anthracycline-mediated cardiotoxicity.

This study suggests that aprepitant has potential to be utilised as a cardioprotective agent in the context of doxorubicin-induced cardiotoxicity. Interestingly, a retrospective study on over 5,800 cancer patients receiving chemotherapy with or without aprepitant reported a slightly lower incidence of cardiovascular-related events in patients receiving aprepitant [17]. Furthermore, studies have investigated the ability of aprepitant to kill tumour cells *in vitro* [18]. If aprepitant is indeed cardioprotective, this agent may prove to act as a double-edged sword in the treatment of cancer while protecting the heart from anthracycline-based cardiotoxicity. Additionally, as apreptitant is already in clinical use, this treatment strategy would be readily translatable into clinical practice.

The findings of the study by Levick et al. [13] provide potential insight into another potential mechanism of the anthracycline-mediated cardiotoxicty and suggest that this pathway is amenable to therapeutic intervention in an animal model. This could pave the way for further investigation and confirmation of findings in other models and rapidly translating this into human trials of cardioprotection—an area of significant unmet clinical need!

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