Circulation: Heart Failure

EDITORIAL

Anthracycline Cardiomyopathy

The Plot Gets Thinner

See Article by Jordan et al

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Anthracycline-based chemotherapy regimens remain in wide use for treatment of many malignancies, despite the rapid growth and development of targeted pathway inhibitors and immunotherapies (both of which can be associated with a variety of cardiovascular toxicities). Discovered in the late 1960s and commonly used as a chemotherapeutic in the early 1970s, anthracycline cardiotoxicity was quickly recognized as a serious complication[1,2] and served as the canonical example of chemotherapy-associated cardiomyopathy, spurring the development of the field of cardio-oncology. The observation that left ventricular (LV) mass and growth potential are reduced after exposure to anthracycline chemotherapy was first observed in survivors of childhood cancer and the term Grinch Syndrome was coined by Lipshultz et al[3] to describe the potential evolution of reduced LV mass after anthracycline therapy to a restrictive cardiomyopathy in some patients. In adults, a reduction in LV mass has been observed several years after anthracycline-based chemotherapy and is associated with increased cardiac events.[4]

In this issue of *Circulation: Heart Failure*, Jordan et al[5] provide further details to our understanding of how anthracycline chemotherapy alters cardiac structure and function, using serial cardiac magnetic resonance imaging in a cohort of adult cancer patients. LV mass, LV systolic function, aortic stiffness, and ventricular-arterial coupling were measured in 61 adults receiving an anthracycline-based regimen at baseline and 6 months after initiation of therapy. The comparator groups included a cohort of 15 patients receiving nonanthracycline chemotherapy as well as a control group of 24 subjects without cancer. The primary findings are that there was on average a 5% decline in both LV ejection fraction and LV mass, an increase in aortic stiffness, along with changes in ventricular-arterial coupling in the anthracycline group. Decreases in LV mass, but not ejection fraction, were associated with changes in heart failure symptoms as measured by the Minnesota Living with Heart Failure Questionnaire. The authors speculate that the early decrease in LV mass may serve as an imaging biomarker of anthracycline cardiotoxicity. The authors acknowledge that their observations will need to be validated in larger studies. The time course and persistence of these changes in cardiac morphology and function will need to be established with longer follow-up, and the link to hard clinical outcomes assessed in future trials. Time will tell whether LV mass serves as a reliable marker for cardiotoxicity and predictor of long-term risk.

The relatively early reduction in LV mass does raise some intriguing questions about the mechanism of anthracycline toxicity and the potential protective pathways that may prevent or mitigate the loss of ventricular mass. Basic and clinical research has demonstrated that anthracyclines induce myocyte cell death through

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a variety of mechanisms,[6] as well as sarcopenia, both of which can contribute to reductions in myocardial mass. In addition, anthracyclines are known to target both quiescent and proliferating cells through interactions with topoisomerase, similar to the mechanism for anthracycline therapeutic actions in proliferating cancer cells. Thus, it is not surprising that anthracyclines are toxic for endothelial and cardiac progenitor cell populations.[7] Loss of endothelial cells can result in vascular damage, disrupting endothelial function, and increasing vascular stiffness. Cardiac progenitor cells have demonstrated the capability to rejuvenate the myocardium after injury and depletion of this pool halts repair mechanisms. Similarly, a growing heart depleted of progenitor cell pools would seem less likely to reach a normal size, explaining the Grinch Syndrome as a consequence of childhood anthracycline exposure.

Physiological growth of the heart during maturation and in response to increased normal demand (ie, exercise training and pregnancy) occur through other mechanisms that may also be impacted by anthracycline exposure. It is interesting that at least one of the pathways for physiological growth—neuregulin-1 and the ERBB receptor tyrosine kinase family—has known interactions with anthracycline cardiotoxicity. ERBB2-targeted cancer therapies, when given concurrently with anthracyclines, augment cardiotoxicity.[8] It is interesting that neuregulin/ERBB signaling is critical for myocardial development as well as postnatal cardiac growth, and physiological responses to exercise and pregnancy (reviewed by Odiete et al[9]). Exercise activates neuregulin,[10] and circulating levels of neuregulin are increased in people with higher fitness.[11] Circulating neuregulin levels decline with anthracycline-based chemotherapy both in adults[12] and children,[13] raising the possibility that disruption of this or other cardiac growth pathways is involved in the decline in LV mass seen by Jordan et al.[5]

The finding that anthracycline exposure increased aortic stiffness and thereby disrupt ventricular-arterial coupling makes the findings of Jordan et al[5] all the more interesting.[14,15] Increases in arterial stiffness as occur in hypertension and aging are well known to increase myocardial demand and lead to increases in LV mass. The decline in LV mass in the face of increased arterial stiffness highlights how anthracycline exposure has completely disrupted the normal physiological mechanisms that couple adaptive changes in myocardial mass to load. Thus, the clinical impact of reduced myocardial mass and impaired LV function is likely compounded with increased vascular resistance. Additional studies are needed to further characterize the dynamic relationship between the cardiac and vascular effects of anthracycline and help us better identify those at greatest risk as early in their treatment as possible.

The more we learn about anthracycline cardiotoxicity, the more the plot evolves. With >60 years of thinning hearts, we still have a lot to learn to reverse or inhibit the cardiotoxicity that is associated with anthracyclines. Basic and clinical research have uncovered numerous mechanisms involved with cardiac damage and early indicators of cardiac toxicity such as LV mass decline add to the clinical evidence base and may serve as a more accurate imaging biomarker. Perhaps one day our treatment strategies will evolve, allowing us to write the final chapter in this story. However, as suggested previously,[16] it may be worth considering how to put the cardiac effects of anthracycline to good use when progressive increases in cardiac mass becomes a clinical problem.

ARTICLE INFORMATION

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Disclosures

None.

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