Anthracycline-induced cardiomyopathy: The search continues

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Anthracyclines are not only some of the most effective, but also the most toxic, chemotherapeutic agents. Their use is associated with a dose-dependent, progressive, dilated cardiomyopathy. To date, there is no specific laboratory or imaging approach to proactively identify patients who will develop anthracycline-induced cardiotoxicity. Echocardiography and radionuclide ventriculography have been employed to measure left ventricular ejection fraction as chemotherapy progresses, and once decreases in function are identified, chemotherapy dosage or frequency is modified, or the chemotherapy is stopped. Unfortunately, overt cardiomyopathy is a late manifestation of injury due to anthracyclines,¹ and thus prediction of which patients may develop anthracycline-induced cardiac toxicity is an important goal, especially since these agents are frequently used in children and young adults.

The developing hearts of children and adolescents are particularly vulnerable to the adverse effects of anthracyclines. Although the exact mechanism of cardiotoxicity is not known, the key step in its pathogenesis appears to be the generation of reactive oxygen species, which leads to increased apoptosis, disruption of mitochondrial structure and function, and energy depletion.^{2–6} Recent studies have demonstrated a critical role of topoisomerase 2 β in anthracycline-induced DNA

double strand breaks, which lead to mitochondrial dysfunction and formation of reactive oxygen species.^{7,8} In addition, anthracyclines can disrupt intracellular calcium processing,⁹ impair pro-survival signaling pathways,¹⁰ and damage cardiac progenitor cells.¹¹ These pathways hinder normal myocardial growth during childhood and adolescence. The hearts of children exposed to anthracyclines have been found to have decreased left ventricular wall thickness and mass, left ventricular dilation, and increased end-systolic wall stress.¹²

Evidence of left ventricular remodeling and reduced ejection fraction is a late finding in the pathogenesis of anthracycline-induced cardiomyopathy. During, or soon after, anthracycline exposure, subtle molecular, and biochemical changes in cardiomyocyte structure and function have already begun. An important goal in the field of cardio-oncology is to discover or develop a highly sensitive diagnostic test to accurately detect the subclinical changes of cardiac injury before there is overt clinical manifestation.¹³ Load-independent measures of left ventricular systolic function, such as measures of cardiac strain and strain rate and tissue Doppler imaging of systolic and diastolic function are showing some promise in the early detection of cardiotoxicity.^{14–17} In addition, serum biomarkers, particularly high-sensitivity cardiac troponins and NT-proBNP, may be useful in predicting the development of cardiac dysfunction.¹⁸

Changes to the adrenergic system could potentially be involved in the development of anthracycline-induced cardiac dysfunction. Using radiotracer technology, over 20 years ago, small studies demonstrated that myocardial iodine-123 *meta*-iodobenzylguanidine (I-123 MIBG) uptake is decreased in patients receiving anthracyclines in a dose-dependent way.^{19–22} In some studies, the changes in MIBG uptake appeared earlier than alterations in left ventricular ejection fraction, but this was not a universal finding. One confounding variable is that normal MIBG

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uptake appears to be related to age,²³ which was not considered in these early studies. In addition, many of the subjects of these earlier studies received multiple chemotherapeutic agents, and some had adjuvant radiation therapy. Finally, most of these earlier studies looked at MIBG uptake early during the course of anthracycline chemotherapy rather than several years later.

The tracer, MIBG, is used to image the function of sympathetic nerve terminals. It is considered an analog of guanethedine, a “false” neurotransmitter that is structurally similar to the physiological neurotransmitter, norepinephrine. Currently, I-123 MIBG is used primarily for the assessment of sympathetic innervation in patients with heart failure as well as for evaluation of tumors of the neuro-endocrine system such as pheochromocytoma and carcinoid. Recent reviews have summarized the mechanism by which I-123 MIBG is taken up by the nerve terminal, the utility of this agent, and the technical aspects of its imaging.²⁴⁻²⁷

One of the strengths of the current study by dos Santos²⁸ is that all of the subjects were relatively young (mean age of 16), when identification of early anthracycline-induced cardiomyopathy would be most critical. The subjects were a median of 5.3 years out from their chemotherapy. In addition, the study was carefully done in a relatively large sample with equal gender distribution and results compared to young adult controls. Radionuclide ventriculography was used to determine left ventricular ejection fraction (LVEF). While patients receiving chemotherapy had a small, but statistically significant, reduction in LVEF compared to controls (60.4% compared with 64.1%), there was no difference in early or late heart to mediastinal uptake ratios or washout rates of MIBG between patients and controls. Only the cumulative dose of anthracycline was shown to have an effect on LVEF, as is known. Of equal interest, detailed parameters of systolic and diastolic function by radionuclide ventriculography also showed no difference between patients and controls. The potentially more sensitive echocardiographic parameters of myocardial strain and strain rate or Doppler-derived indices of diastolic function were not performed in this study.

It cannot be said definitively that neurohumoral transmission does not play a role in anthracycline-induced cardiomyopathy because of the inherent limitations of a cross-sectional study and also because MIBG only interrogates one aspect of sympathetic innervation. However, the current study appears to support the fact that MIBG imaging, which targets presynaptic sympathetic function, is not useful to define cardiac toxicity in patients who have previously received anthracyclines. It is likely that MIBG uptake will be reduced once anthracycline-induced cardiac

toxicity occurs and results in reduced cardiac function or overt heart failure. To confirm this hypothesis, long-term prospective studies that provide longitudinal assessment of cardiac function and MIBG uptake in patients undergoing treatment with anthracyclines are necessary.

Several approaches to delineate cardiotoxicity induced by chemotherapy are under active study.²⁹ The data by dos Santos suggest that MIBG imaging is not helpful in predicting who will exhibit anthracycline cardiotoxicity. Future studies will need to concentrate on other markers of the pathways that lead to cardiomyopathy. One would expect that as these pathways are better defined, molecular markers will become available to identify changes before irreversible damage occurs. Thus, the search continues for a biomarker or imaging approach that is useful in this important iatrogenic disease.

Disclosure

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