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Editorial

Corresponding author
Guilherme H. Oliveira, MD, FACC
Associate Professor of Medicine
Chief, Heart Failure Section
Director, Onco-Cardiology Program
Seidman Cancer Center
Director, Advanced Heart Failure and Transplantation Center
Harrington Heart and Vascular Institute
Case Western Reserve University School of Medicine
University Hospitals Case Medical Center
11100 Euclid Ave. Cleveland
OH 44106, USA
E-mail: guilherme.oliveira@uhhospitals.org

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Anthracycline Cardiotoxicity: Strategies for Prevention and Intervention

Chang H. Kim[1,2], Sadeer Al-Kindi[1,2] and Guilherme H. Oliveira[1,2,3*]

[1]Department of Medicine, University Hospitals Case Medical Center, Cleveland, OH, USA
[2]School of Medicine, Case Western Reserve University, Cleveland, OH, USA
[3]Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, OH, USA

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The cardiotoxic effects of anthracycline compounds, used extensively to treat malignancies such as breast cancer and lymphoma, are well known.[1,2] However, despite efforts towards cardioprotective strategies and early detection of anthracycline cardiotoxicity, defined as decline in Left Ventricular Ejection Fraction (LVEF) of ≥10% from baseline or to <50%,[3,4] there is currently no consensus on the optimal approach. Current clinical practice guidelines recommend serial LVEF monitoring to identify cardiotoxicity in high-risk patients receiving anthracyclines;[3,4] however, it has come to light that LVEF reduction may be a late manifestation of cardiotoxicity,[5,6] with potentially limited prospects for reversibility.[7-9] Recently, echocardiographic strain imaging has emerged as a promising way to detect subclinical cardiotoxicity prior to LVEF reduction,[10-13] where small reduction in Global Longitudinal Strain (GLS) has been identified as a robust predictor of future LVEF reduction and cardiac events.[14-16] The reliability of this approach in patients treated with anthracyclines has been specifically evaluated,[17-19] with reported cardiotoxicity rates ranging from <1% to 32%.[20] Recent studies have established a GLS reduction of ≥11% as a strong predictor of cardiotoxicity.[19,21-24]

Strategies to mitigate anthracycline cardiotoxicity may be classified as pre-emptive (primary prevention) *versus* reactive (secondary prevention).[2] For primary prevention, conventional treatments for heart failure, including beta-blockers and angiotensin antagonists, have been evaluated, with promising results in recent meta-analyses.[25,26] In the recently completed PRADA study, a randomized controlled trial comparing primary prevention of cardiotoxicity with metoprolol, candesartan, *versus* matched placebos in 120 patients treated with anthracyclines with or without trastuzumab for early breast cancer,[27,28] pre-emptive candesartan was shown to result in a statistically significantly attenuation in LVEF decline. In contrast, no similar effect was found with metoprolol succinate use. Additional trials and longer follow-up period are needed to confirm these findings.

Because a primary prevention strategy may needlessly expose many patients to potential adverse effects, secondary prevention strategies are of interest. The implicit assumption of such a strategy is that high risk patients would be detected early enough to be able to initiate treatment while cardiotoxicity is still reversible. In addition to echocardiographic strain, cardiac biomarkers, such as troponin and NT-proBNP, have been evaluated for this purpose. In particular, the degree and duration of troponin elevation was shown to be closely correlated with left ventricular dysfunction[29,30] and in one randomized controlled trial, initiation of enalapril in patients with early troponin leak following chemotherapy was shown to be associated with significant improvement in LVEF at 1 year follow up.[31] However, troponin elevation is not always present even in the setting of echocardiographic findings consistent with cardiotoxicity,[32-35] and thus, echocardiographic strain imaging may be a more reliable indicator for secondary prevention.

In a recent prospective observational study involving a secondary cardioprotective strategy based on strain imaging,[21] Negishi, et al. evaluated changes in strain parameters in patients undergoing treatment with anthracyclines and/or trastuzumab, where those showing ≥11% drop in GLS at 6 months were followed for an additional 6 months with or without initiation of beta blocker therapy. In the treatment group, GLS and LVEF were significantly improved at 12 months, with significant association with beta-blocker therapy in multivariable analysis. While preliminary in nature, this study is significant for being the first to utilize strain imaging in guiding initiation of cardioprotective therapy.

In conclusion, both primary and secondary cardioprotective strategies with beta-blockers and angiotensin antagonist therapy for anthracycline cardiotoxicity hold promise at this time. In adopting a secondary prevention strategy, GLS measured by echocardiographic strain imaging may be a useful and reliable indicator for timing of intervention. Additional randomized controlled trials with long term follow-up are needed in order to determine the best strategies for prevention of anthracycline cardiotoxicity.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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