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EDITORIAL COMMENT

Angiotensin Receptor-Neprilysin Inhibition for Doxorubicin-Mediated Cardiotoxicity

Time for a Paradigm Shift*

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Nearly 17 million people in the United States are cancer survivors, a testament to the rapid advancement of cancer therapies over the last 2 decades. Longer life expectancy has led to an entire field of medicine dedicated to managing the lasting side effects of cancer therapy. Cardiovascular toxicity remains an important and common side effect of cancer therapy. Anthracyclines are the most studied class of cancer therapies known to have cardiovascular side effects. They continue to be used due to their efficacy, but use is limited by dose-dependent toxicity. In a large prospective study of anthracycline-induced cardiotoxicity, 9% of patients experienced significant decline in left ventricular ejection fraction (LVEF), the vast majority in the first year (1). Strategies for anthracycline cardiotoxicity treatment and prevention have largely focused on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, statins, and dexrazoxane, a chelator of redox-active iron (2).

Advances in guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF) has experienced a revival since the PARADIGM-HF (Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure) study demonstrated reduced mortality and heart failure hospitalization with sacubitril/valsartan (an angiotensin receptor-neprilysin inhibitor [ARNI]) over enalapril in 2014 (3). These positive trials were followed by recent studies of sodium-glucose cotransporter-2 inhibitors and soluble guanylate cyclase activators, increasing the armamentarium for effective drugs in HFrEF (4,5). These drugs have demonstrated efficacy in HFrEF broadly, but expanding the application of these therapies to populations in whom EF decline may be milder or transient, or without overt clinical heart failure manifestation, is of great interest in cardio-oncology.

In this issue of *JACC: CardioOncology*, Boutagy et al. (6) in a novel study report that ARNI therapy preserved LV function in a rodent model of doxorubicin-mediated cardiotoxicity. Their study makes several important observations. A cumulative dose of 15 mg/kg of doxorubicin or placebo was administered to male rats and doxorubicin-induced cardiotoxicity was measured by echocardiography and histologic analysis. This was followed by administered of sacubitril/valsartan, valsartan alone, or placebo to the doxorubicin-treated rats to test the hypothesis that ARNI could attenuate doxorubicin-mediated cardiotoxicity. Treatment with ARNI attenuated the decline in LVEF seen with doxorubicin treatment, while valsartan alone did not have an effect. An innovative molecular nuclear imaging platform was used to measure ^{99m}Tc-RP805 uptake. This is a radiotracer that binds to the catalytic site of several activated matrix metalloproteinases (MMPs) and can be quantitated by nuclear imaging (7). MMP activity inversely correlated to LVEF and LV end-systolic volume. ARNI therapy attenuated the rise in MMP activity seen with doxorubicin cardiotoxicity, while valsartan therapy alone did not. Fibrosis

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measured by Picrosirius red staining or smooth muscle actin staining was increased roughly 2-fold in the doxorubicin-treated mice; this was attenuated with both valsartan and ARNI treatment. Capillary density was higher in ARNI treated mice at 4 weeks but not at 6 weeks, perhaps because overall heart function had improved and the compensatory increase in capillary density was no longer activated.

The authors should be commended on their use of a novel molecular imaging technique to quantitate MMP activity in response to ARNI therapy. MMPs increase in a broad range of models of cardiovascular stress including atherosclerosis, ischemia-reperfusion, and pressure or volume overload (8). MMPs play an important role in ventricular remodeling and their inhibition is cardioprotective (9). The mechanism by which ARNI therapy reduced MMP activity is unclear, aside from broader cardioprotection and prevention of LV remodeling after doxorubicin. The cardioprotective mechanisms attributed to neprilysin are likely related to reduced degradation of natriuretic peptides and several vasoactive substances (10). Though myocardial MMP expression is known to be increased after acute cardiovascular stress in animal models, a recent study found that circulating MMP-2 and MMP-9 levels were lower than referent control values in patients with chronic HFrEF (11). It is unclear if this is due to differences in circulating levels versus myocardial expression. ARNI therapy has been shown to result in significant reduction in several circulating biomarkers related to fibrosis (11). The question remains if this due to a broader effect on LV remodeling, or a direct modulation of myocardial fibrosis via ARNI therapy. Importantly, the investigators did not report any significant adverse effects of ARNI therapy itself, other than the adverse liver injury due to intraperitoneal injections.

Though this study highlights the potential role for neprilysin inhibition in doxorubicin-mediated cardiotoxicity, several questions remain. First, only male rats were studied. Anthracyclines remain a mainstay for the treatment of breast cancer, and therefore preclinical research on anthracycline cardiotoxicity should include female animals, and clinical trials must prioritize the inclusion of women. In the PARADIGM-HF trial, women equally benefitted from sacubitril/valsartan, though they comprised only 20% of the participants (3). The subsequent trial in heart failure with preserved EF, the PARAGON-HF (Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction) trial, narrowly missed its primary endpoint (12); however, subgroup analysis suggested women derived greater benefit with sacubitril/valsartan. In a prespecified pooled analysis of the PARADIGM-HF and PARAGON-HF trials, baseline LVEF significantly modified the efficacy of sacubitril/valsartan, with women deriving benefit at higher EFs than men (13). Further investigation is needed to understand sex differences in response to ARNI therapy. Second, relatively young, healthy adult rats were used in this study that were cancer-free. The relevance to treatment of older adults with malignancy and often comorbid conditions is unknown. Third, the authors acknowledge that due to the intraperitoneal infusion of doxorubicin, liver injury was induced, leading to ascites and limiting the ability to follow the effects of ARNI therapy over a longer period of time post-doxorubicin administration. Extrapolating the present study's findings to a population receiving doxorubicin intravenously and the effects on subsequent cardiotoxicities over a longer time period is therefore limited. Ultimately, improved risk prediction tools are needed to determine which patients will benefit from ARNI therapy, which is beyond the scope of the present study.

In summary, the authors should be congratulated for their important study of ARNI therapy to prevent anthracycline-induced cardiomyopathy. Their use of in vivo molecular imaging is innovative and an important tool for assessing the target of this therapy. The present study supports a mechanistic basis for ARNI therapy to benefit patients treated with anthracycline-based therapies and adds to the growing evidence to support clinical studies of ARNI therapy for the treatment of doxorubicin-induced cardiotoxicity.

AUTHOR DISCLOSURES

Dr. Hahn has reported that she has no relationships relevant to the contents of this paper to disclose. Dr. Sharma has served as a consultant for, served on the advisory board for, and received honoraria from Novartis, Janssen, Bayer, and Bristol Myers Squibb; and has received grant support from the American Heart Association and a Johns Hopkins University Clinician Scientist Award.

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