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EDITORIAL COMMENT

Examining Cardiotoxicity With HER2 Therapies*

Neelima Denduluri, MD

HER2-targeted therapies dramatically improve outcomes in early and advanced HER2 positive breast cancer (1). Cardiotoxicity is a major concern for patients with HER2 positive breast cancer. Trials have shown an approximate 4% heart failure risk with trastuzumab, primarily in patients who received an anthracycline. Guidelines generally recommend some form of regular monitoring, but data suggest inconsistent adherence. Reasons for nonadherence are not well elucidated (2,3).

In this issue of *JACC: CardioOncology*, Yu et al. (4) sought to determine if there is an association between adherence to current guidelines for routine left ventricular ejection fraction (LVEF) surveillance during targeted HER2 therapy and treatment-induced heart failure. In this case-control study, 53 patients with stage I to IV breast cancer who were treated between 2005 and 2015 developed heart failure (New York Heart Association functional classes III or IV) or cardiac death during trastuzumab-based treatment and were compared with 159 patients who received trastuzumab and did not develop cardiotoxicity. Patients were matched by age, anthracycline exposure, and year of treatment. There was approximately 60% adherence to cardiac surveillance guidelines with echocardiography compared with 36% in previous reports (3). The investigators noted that adherence to surveillance guidelines during the observation period or during the first 6 months of treatment was not associated with a lower risk of heart failure. In multivariable-adjusted analyses, LVEF <55% at any timepoint or during the final surveillance timepoint was associated with subsequent development of heart failure. Compared with control subjects, a greater percentage of the affected cases had a higher body mass index, African American ancestry, and lower baseline LVEF, which are known risk factors for heart failure (5-7).

The rates of heart failure in this analysis of patients treated up to 15 years ago might be less relevant due to changes in anthracycline use patterns for HER2 positive breast cancer. Yu et al. (4) reported that 81% of the patient population received anthracyclines, greater than what would be currently expected because of the reported decrease in anthracycline use in the HER2-positive population in the United States (8). There was also a lower incidence of symptomatic heart failure and LVEF decline in patients who received trastuzumab without an anthracycline (9,10). These lower rates of cardiotoxicity without anthracycline use suggested that we might be able to explore less rigorous cardiotoxicity monitoring and focus resources on those at highest risk.

The investigators showed that a modest reduction in LVEF <55% was predictive of heart failure. Although recognizing this is important, there are a few studies that suggested that early intervention might lead to clinically meaningful benefit. The CECCY (Carvedilol for Prevention of Chemotherapy-Related Toxicity) trial attempted to use beta-blockers for prevention of cardiotoxicity, but the trial did not beneficially affect the early onset of LVEF reduction (11). The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) and MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trials each showed modest reductions in LVEF declines

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From the Virginia Cancer Specialists, The US Oncology Network, Arlington, Virginia, USA. Dr. Denduluri has received research funding to his institution from Daiichi, AstraZeneca, Pfizer, Novartis, Immunomedics, and Seattle Genetics; and is on the advisory board for Seattle Genetics. The author attests they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

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with various cardioprotective agents, including beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (12,13). Another small trial showed fewer interruptions in trastuzumab use in patients who received lisinopril or carvedilol over placebo (14). The SAFE-HeaRt study showed that HER2-targeted therapy could be safely continued in patients with mildly decreased LVEF with intense monitoring and intervention (15).

Although these data are instructive, a number of questions remain regarding the optimal surveillance method, interval, and duration of monitoring for patients who receive HER2-targeted therapy. The current cardiac imaging modality and interval were largely adopted for monitoring because this was the strategy used in the first generation of adjuvant HER2-targeted therapy trials (1). Data suggested that cardiac magnetic resonance imaging might provide high reproducibility and sensitivity to detect cardiotoxicity (16). Biomarkers in lieu of imaging (e.g., troponin, natriuretic peptides, and myeloperoxidase) might also predict cardiotoxicity (17,18). Alternative and complementary testing to echocardiography and LVEF monitoring should be further explored, especially if there is an opportunity for early and effective intervention. Optimal timing of testing for decreased LVEF has not been well-established. Thirteen-year registry data showed that decreases in LVEF during the first 3 months predicted heart failure. Patients who had decreased LVEF were more likely to have received anthracyclines and have a lower LVEF at baseline; no trastuzumab-related cardiac deaths were reported. Similarly, the current analysis found no association between surveillance adherence and heart failure (19).

Trastuzumab-induced cardiotoxicity generally occurs during the treatment period; long-term follow-up of early adjuvant therapy trials suggested that this is largely reversible (1). In contrast, a more recent study showed a slightly higher risk of heart failure at short- and long-term follow-up in patients who received trastuzumab, albeit in a population in which >85% of patients received anthracyclines in varying doses. Mortality was similar (20). This is particularly important considering the improved outcomes of patients with HER2 positive breast cancer, including those with advanced stage disease (21).

Looking to the future, designing clinical trials that standardize cardiotoxicity reporting and develop alternatives to echocardiography, including biomarkers and other imaging modalities, are needed. To improve the therapeutic index of HER2-targeted therapy, we must focus cardioprotective interventions on those at highest risk of cardiotoxicity. Preventing progression to heart failure in those with early declines in LVEF may improve both quality of life and mortality.

ADDRESS FOR CORRESPONDENCE: Dr. Neelima Denduluri, Virginia Cancer Specialists, The US Oncology Networkm 635 N. George Mason Drive, Suite 170, Arlington, Virginia 22205. E-mail: neelima.denduluri@usoncology.com. Twitter: @ndenduluri1.

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