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EDITORIAL COMMENT

Partnering Teams to Optimize the Care of Patients With HER2-Positive Breast Cancer*

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Human epidermal growth factor receptor 2 (HER2)-positive breast cancer, defined by the overexpression of HER2 on the cancer cell or amplification of the HER2 gene, represents approximately 20% of all breast cancer. This translates to approximately 50,000 cases of HER2-positive disease diagnosed every year in the United States. With greater understanding of the biology and function of HER2, there has been substantial progress in the development of HER2-targeted therapies, with 2 new agents approved in 2020 (tucatinib and trastuzumab deruxtecan) joining at least 5 established targeted therapies for this subtype of breast cancer (1,2). Despite the proliferation of newer agents, the HER2-targeting monoclonal antibody trastuzumab remains the most commonly used therapy for this subtype of breast cancer, particularly in the early stage and curative settings. Trastuzumab has well-demonstrated, substantial benefits in reducing cancer recurrence, progression, and death and generally is very well tolerated. However, this therapy confers some risk for cardiac toxicity, ranging from asymptomatic reduction in left ventricular systolic function to the development of clinically apparent congestive heart failure. As a result, interval monitoring with echocardiography is recommended for all patients receiving this agent. Contemporary guidelines (3,4) have described a recommended frequency of monitoring and evaluation, including periodic cardiovascular assessments, with a goal to reduce morbidity associated with the use of trastuzumab and to maximize its anticancer potential.

Over the past several years, with the recognition of cardiac toxicity related to trastuzumab and other cancer therapies, the field of cardio-oncology has emerged as a subspecialty designed to provide multidisciplinary management for oncology patients. The objectives of this multidisciplinary involvement include minimizing the potential morbidity of anticancer therapies and optimizing the health of the growing population of cancer survivors, including optimal management of inherent or treatment-associated cardiovascular disease (5). The field of cardio-oncology has been of particular value for patients with HER2-positive breast cancer, both for clinical guidance in the setting of acute cardiac toxicity and for research partnerships. Early prospective studies have suggested that the astute administration of common cardiovascular medications may attenuate or prevent drug-related cardiac toxicities (6,7). Additionally, several large ongoing prospective trials are currently evaluating strategies designed to reduce cardiac toxicity from breast cancer treatments, ranging from prophylactic administration of statin medications (PREVENT [Preventing Anthracycline Cardiovascular Toxicity With Statins]; NCT01988571) to the exploration of the safety of HER2-targeted therapies in patients with pre-existing cardiovascular disease (SAFE-HEaRt [Cardiac Safety Study in Patients With HER2 + Breast Cancer]; NCT01904903).

In this issue of *JACC: CardioOncology*, Demissei et al. (8) from the University of Pennsylvania, report their single-center retrospective evaluation of the

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relationship between cardiologist consultation and clinical outcomes in more than 1,000 patients with HER2-positive breast cancer treated with trastuzumab over the past decade. The investigators reviewed electronic health records and identified that 28% of the patients in their study population were comanaged with the involvement of a cardiologist. Patients in whose care a cardiologist was involved at baseline or longitudinally were more likely to have pre-existing cardiac diagnoses, including congestive heart failure or atrial fibrillation. The investigators identified that patients who interacted with cardiologists prior to the initiation of trastuzumab therapy received care that more closely adhered to guideline recommendations for echocardiographic monitoring and demonstrated slight improvements in cardiovascular parameters, including systolic blood pressure and body mass index. There was no survival difference measured between patients who received specialty care from cardiologists compared with those who did not. This study is one of the first rigorously conducted assessments to demonstrate that multidisciplinary care, involving a cardiology specialist, may confer clinical benefits for patients with breast cancer, particularly in the context of multiple cardiovascular risk factors.

Overall, the investigators should be congratulated on conducting an expansive and comprehensive review of the care of this patient population. The methodologic attributes of this type of study do present some limitations. First, as was well described by the investigators, the retrospective review of electronic medical records may be confounded by missing or incorrect diagnosis codes, especially if patients received care in multiple medical systems. Second, this study constitutes a single-institution experience at a U.S. cancer center with one of the most well-developed cardio-oncology programs in the country. The prevalence of cardiology involvement in the care of patients with breast cancer in the United States treated in community settings, where the majority of oncology care is provided, and the outcomes of patients in these settings are not known, limiting the generalizability of these findings. It is not known whether the outcomes of patients receiving care from general cardiologists may differ from those treated by cardiologists with cardio-oncology specialty training. Furthermore, it is not clear from this analysis whether all patients who received cardiology involvement prior to the initiation of trastuzumab therapy were being evaluated longitudinally for pre-existing cardiovascular conditions or whether the subspecialty care was specifically requested for the prevention of trastuzumab-related cardiotoxicity. The finding that cardiologists were more frequently involved in the care of patients with cardiovascular-related diagnoses suggests that the engagement of subspecialty care may not have been specifically related to the cancer diagnosis or treatment strategy. Similarly, the relative improvement in cardiovascular parameters measured in patients followed by cardiologists may reflect the fact that there was active management of recognized, diagnosed cardiovascular conditions, whereas in the other patients, these conditions may not have been recognized or actively addressed.

Considering the results of this study, one may question the extent to which cardiology subspecialty care should be offered to patients with HER2-positive breast cancer. From the findings, a case can be made that patients with pre-existing cardiovascular disease, or those who have high risk for adverse cardiovascular events, should receive multidisciplinary care involving a cardiologist from baseline. However, for young, otherwise healthy patients with breast cancer with few or no cardiovascular risk factors, the benefits of subspecialty care may be less clear. Furthermore, the rationale supporting the recommended frequency of cardiac monitoring in this healthy patient population may not be as compelling, given the very low incidence of baseline cardiac dysfunction or cardiac events in this group, particularly when treated with non-anthracycline regimens (9,10). Certainly, further study is required to develop more nuanced risk stratification that will guide the frequency with which cardiovascular monitoring and subspecialty care will be of clinical benefit.

Providing multidisciplinary care is a hallmark of contemporary oncology treatment, and cancer clinicians are increasingly engaging specialists from multiple medical and surgical specialties to optimize care. The evolution of the subspecialty field of cardio-oncology has been highly beneficial in the care of patients with cancer and cancer survivors. The value of this partnership is especially highlighted given the rapid development of novel therapies for a variety of malignancies, which may be associated with significant cardiovascular complications. Recent developments in this respect include the identification of myocarditis associated with immuno-oncology agents (11), as well as heart failure seen with carfilzomib (12), a proteosome inhibitor approved for treatment of patients with multiple myeloma. Additionally, given the growing number of cancer survivors globally, subspecialty attention to optimizing cardiovascular parameters will be beneficial and may improve overall survival for this expanding patient population. The findings of this clinical investigation

by Demissei et al. (8) support the premise that subspecialty cardiovascular care may improve health in patients with breast cancer, particularly those with HER2-positive breast cancer and concomitant cardiovascular diagnoses. Caring for the growing population of oncology patients in both the acute and the survivorship settings will require expansion of a cardio-oncology workforce (13), a process supported by the American College of Cardiology Cardio-Oncology Section. Overall, a continued focus on measuring the benefits of cardio-oncology care for patients with cancer, and support for training the next generation of subspecialty providers, is heartily welcome.

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