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EDITORIAL COMMENT

Not So Young at Heart*

Long-Term Cardiac Dysfunction in Young Adult Hematopoietic Cell Transplantation Survivors

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Cardiomyopathy and heart failure are well described late complications of allogeneic hematopoietic cell transplantation (HCT). By the time they clinically manifest, significant and irreversible damage to the myocardium has already occurred with resultant substantial morbidity and mortality. A standardized screening tool that may identify early harbingers of cardiac injury in high-risk HCT recipients is currently lacking. Based on studies in childhood cancer survivors where subtle abnormalities have been shown to be associated with subsequent heart failure, echocardiography is frequently used for monitoring pediatric HCT survivors, although this modality is not widely used for the follow-up of adult recipients. More advanced technology such as 3-dimensional imaging and speckle tracking echocardiography may lead to greater sophistication in detecting early cardiac dysfunction, which may possibly lead to earlier interventions to mitigate risks of clinically manifest heart failure.

In this issue, Massey et al. (1) present a cross-sectional study of cardiovascular function in a cohort of long-term allogeneic survivors with malignant and nonmalignant disorders who underwent HCT as children, adolescents, and young adults. Cardiovascular function was measured through clinical, laboratory, and transthoracic echocardiography assessments in 104 survivors and 55 healthy controls irrespective of their cardiovascular risk-factor profile. At a median time of 17.2 years since HCT, survivors had significantly higher burden of left ventricular systolic dysfunction (LVSD), including decrease in 2-dimensional left ventricular ejection fraction and in global longitudinal strain compared to controls. Left ventricular ejection fraction and global longitudinal strain impairments correlated with greater cumulative anthracycline exposure. The investigators also found significantly higher prevalence of modifiable risk factors such as hypertension and hypercholesterolemia among survivors.

Most prior studies on cardiomyopathy and heart failure have primarily focused on either childhood cancer survivors or older adults with malignancy undergoing autologous or allogeneic HCT, and their extrapolation to adolescent and young adult HCT survivors including patients with nonmalignant diseases is challenging. Moreover, self-reported or registry-level data have been mostly used to study an overt and severe phenotype of cardiomyopathy/heart failure. Hence, this study is novel as it helps us understand the magnitude of subclinical LVSD among HCT survivors including recipients with nonmalignant diseases. They show a higher prevalence of LVSD with advanced echocardiographic imaging technology than what has been previously reported; especially in a cohort of HCT recipients who did not receive total body irradiation (TBI)-based conditioning regimens. Importantly, nearly three-

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quarters of survivors with LVSD were asymptomatic. As noted by the investigators, the actual magnitude of the problem may be different because only 66% of study-eligible survivors completed the assessments; additionally, nearly 45% of HSCT recipients had died before the study initiation. Notwithstanding the limitations, these findings have several implications in survivorship care and warrant further discussion.

First, this study highlights the role of cardiovascular surveillance using echocardiograms in HCT survivors. Heart failure is recognized as a progressive disorder where patients move from subclinical dysfunction to overt heart failure over a variable period (2). It is important to detect and intervene during an earlier stage because the course is largely irreversible once heart failure has progressed to an advanced stage. However, there is no clear guidance regarding the need for routine screening, its frequency, or duration among HCT survivors. Routine use of serial echocardiograms in childhood, adolescent, and young adult cancer survivors exposed to anthracyclines and/or radiation with potential impact to the heart is endorsed by the Children's Oncology Group long-term follow-up guidelines and International Late Effects of Childhood Cancer Guideline Harmonization Group. In contrast, the international guidelines for screening and preventive practices for HCT survivors do not provide any specific recommendations regarding echocardiographic surveillance (3). Recent publications have questioned the cost-effectiveness and reproducibility of echocardiograms in surveillance (4,5). This is especially relevant when considering cost- and resource-based challenges associated with performing routine serial echocardiograms for the entire and increasing numbers of HCT survivor population. The investigators do not tell us whether better technology adds substantially to the time-tested and widely available 2D echocardiography in identifying LVSD. Also, this study was not designed to tell us how and when to use echocardiography to screen for early cardiac dysfunction, and how often and in which patients these early changes progress to overt heart failure. However, the high prevalence of LVSD, especially in asymptomatic patients, makes the case for continued discovery of interventions to identify and mitigate progression of early cardiomyopathy.

This study provides an opportunity to discuss approaches to prevent occurrence of cardiomyopathy or heart failure in HCT survivors. Since anthracyclines and chest radiation have known association with these complications (6), several primary preventive interventions are under study to reduce their exposure in pediatric and young adult oncology population. The use of dexrazoxane as a cardioprotective agent has shown promise in mitigating anthracycline-induced cardiotoxicity in the short-term and warrants longer follow-up to understand its effects on reducing late cardiovascular dysfunction (7). Ongoing trials are investigating less cardiotoxic chemotherapy regimens (e.g., liposomal preparation of daunorubicin and cytarabine [CPX-351]) and radiation-free preparative regimens. For survivors with prior exposure to cardiotoxic therapies, similar to those in current study, emphasis must be placed on secondary preventive interventions. Angiotensin-converting enzyme inhibitors and beta-blockers have been used for this purpose in cancer survivors with variable degree of success and require further work in HCT population. It is also important to understand the role of modifiable risk factors such as hypertension, dyslipidemia, diabetes mellitus, and obesity in the development of late cardiac toxicity, for which HCT survivors are at increased risk due to conditioning regimen exposure and graft-versus-host disease (8). This study also highlights the question about why patients with similar HCT-related exposures have varying risks for developing LVSD and heart failure. A growing body of literature has shown the role of genetic risk factors in development of cardiotoxicity in childhood cancer survivors (9).

How can we apply the findings of this study and existent literature to pragmatically care for young adult allogeneic HCT survivors while we await high-quality evidence on appropriate screening and preventive interventions against cardiac late effects? First and foremost, these patients need life-long follow-up and high vigilance for early symptoms of cardiomyopathy and heart failure. Surveillance must be individualized with a focus on those who are particularly at high-risk (e.g., exposure to high anthracycline doses and TBI). This study shows that HCT survivors who get non-TBI-based conditioning but have prior anthracycline exposure also have a high prevalence of LVSD. Young-adult survivors can be screened with echocardiography using the schedule suggested by pediatric-focused guidelines. If resources do not allow screening of all survivors, imaging can be focused on patients with high-risk exposures. Routine screening and aggressive management of modifiable risk factors and counseling to

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adopt healthy diet, regular exercise, and minimize high-risk behaviors should be performed in clinical survivorship care, and probably has greater impact in reducing cardiac morbidity than general screening with imaging.

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