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EDITORIAL COMMENT

Ablating Late Cardiovascular Events in Modern Hematopoietic Cell Transplantation

Not There Yet*

Richard K. Cheng, MD, MSc,[a] Catherine J. Lee, MD, MS[b]

Hematopoietic cell transplantation (HCT) is a potentially curative treatment for many malignant and nonmalignant conditions. Recipients of HCT are at heighted risk for cardiovascular (CV) morbidity and mortality, with a cumulatively increasing risk with time from transplant. Reports of late CV disease (CVD) in long-term survivors of HCT emerged in the early 2000s and described an alarming 2- to 4-fold greater rate of CV-related mortality than that expected in the general population.[1] Established CV risk factors contributing to the risk include pre-existing or post-transplantation incident hypertension, dyslipidemia, or diabetes; moreover, other implicated factors include graft-vs-host disease (GVHD), long-term exposure to immunosuppressive agents, and cardiotoxic doses of anticancer drugs or radiotherapy used in initial anticancer therapy and as part of the HCT conditioning regimen.[2] Over the past decade, a refinement in HCT techniques, including novel reduced-intensity conditioning regimens and GVHD prophylaxis regimens, has improved HCT access for patients who previously would have been deemed risk prohibitive because of either older age or comorbidities, including pre-existing CVD. Although this has led to an increasing number of long-term survivors cured of their original disease, it is unknown if these innovations have changed the epidemiology of early and late CV events.

In this issue of *JACC: CardioOncology*, Vasbinder et al[3] report their retrospective analysis of a contemporary cohort of adult patients who underwent autologous or allogeneic HCT between 2008 and 2019 at 2 institutions to report on early (≤100 days post-HCT) and long-term (>100 days post-HCT) CV outcomes and their associated risk factors.[3] The primary outcome of the study was the incidence of a composite of a broad spectrum of CV events, including CV death, myocardial infarction or need for coronary revascularization, heart failure, and arrhythmias, including atrial fibrillation or flutter or sustained ventricular tachycardia. Overall, the cohort consisted of older patients, with a median age of 58 years and a range of pre-existing CV risk factors. The incidence of early CV events among all patients was relatively low at 4% and did not differ between individuals who underwent autologous vs allogenic HCT. Although the median follow-up duration was relatively short in this study (2.3 years), the investigators demonstrate a significantly higher incidence of overall CV events at 1 and 5 years in recipients of allogeneic HCT compared with autologous HCT. The risk for long-term CV events continued to increase over time, with an estimated 10-year overall cumulative incidence of 20% and 21.9% in autologous and allogeneic HCT, respectively. This signals the need for close and prolonged monitoring of CV health over decades among not only patients who underwent allogeneic HCT but also those who underwent autologous HCT.

Although atrial fibrillation or flutter was the most common CV event in both transplantation types, there was not a significant difference in the incidence

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From the [a]Division of Cardiology, University of Washington, Seattle, Washington, USA; and the [b]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA.

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between the autologous and allogenic cohorts in the early or late follow-up period. However, late events representing arterial disease, specifically myocardial infarction and stroke, as well as CV death were higher in recipients of allogeneic HCT, consistent with prior reports.[4,5] These findings underscore the potential contributions of allogeneic HCT to inflammation and accelerated atherogenesis due to a change in the patient's immunologic or endocrine milieu, as well as the onset of endothelial dysfunction. Additionally, traditional CV risk factors such as pre-existing coronary artery disease, lower left ventricular ejection fraction, and chronic kidney disease were associated with late CV events. Although graft-vs-host disease was significantly associated with CV events, it is challenging to ascertain whether the association was driven by acute vs chronic GVHD or the treatments used to mitigate GVHD. Interestingly, patients diagnosed with multiple myeloma had the highest incidence of late CV events, an observation that may be related to renal dysfunction from myeloma involvement, severe immune dysregulation from the multiple lines of immune-modifying treatments typically given for multiple myeloma, or possibly exposure to carfilzomib or other immunomodulatory agents (eg, lenalidomide, pomalidomide) in the pre-transplantation or post-transplantation maintenance period.

Although the investigators did examine the association between specific HCT conditioning regimens or pretransplantation anthracycline exposure and CV events, they did not examine other emerging drugs that are used in the peri- and post-transplantation setting to abrogate the risk for disease relapse, some of which have potential cardiotoxicity. As HCT physicians increasingly incorporate post-transplantation maintenance therapies into the treatment paradigm, this will be an important factor to incorporate in models examining risk factors for CV outcomes. In addition, transplantation experts and cardiologists alike will have to rigorously assess the association between new standard-of-care GVHD prophylactic strategies, such as high-dose post-transplantation cyclophosphamide (PTCy) and CV events. Inclusion of PTCy, commonly at a dose of 100 mg/kg divided over 2 days, as GVHD prophylaxis in both the reduced-intensity and myeloablative transplantation settings has significantly increased over the past 10 years and was recently established as the new standard of care on the basis of results from Blood & Marrow Transplant Clinical Trials Network 1703.[6] Although PTCy has been reported to correlate with early cardiac events,[7,8] longer follow-up is required to determine its association with late CV outcomes. Attributing causality of PTCy to early and late CV events is challenging because of the plethora of confounding events and multimorbidity occurring in the peri-transplantation period. Yet the available data suggest the need for the careful selection of patients who may be candidates for allogeneic HCT using a PTCy-based GVHD prophylaxis regimen.

Overall, Vasbinder et al[3] provide important and contemporary data showing that the incidence of early and late CV events has remained essentially stable despite improvements in patient selection and HCT practices over time. This static CV risk profile is attributed primarily to the increasing inclusion of older aged patients with prevalent cardiac comorbidities for HCT therapy. As their findings are limited to patients who underwent HCT at 2 institutions, the investigators may consider evaluating trends in the incidence and outcomes of CV events between earlier and later time periods within their own centers. Moreover, comparison with similar patients who did not undergo HCT would provide insights into how much incremental risk HCT adds, given that cancer treatment independent of HCT is associated with long-term risk for CVD.

To advance the field, there are several considerations on the basis of the present study.

First, these data reinforce the concept that not all cardio-oncology patients are uniform in risk. There are slight differences in risk and outcomes in those receiving autologous vs allogeneic HCT. Risk stratification needs to be individualized, and grouping all individuals receiving HCT into the same category is insufficient and can be misleading. Aligning with the concept that universal nonselective cardioprotection may not be effective against cancer therapy–induced cardiotoxicity, we must also recognize that baseline risk for individuals being evaluated for HCT differ, as well as the risk after HCT depending on type of HCT and regimen used.

Second, these data show that the totality of CV risk in this contemporary cohort undergoing HCT is not excessively high. The 5-year cumulative incidence of CV events was 13.9% but driven mostly by atrial fibrillation or flutter, which can be managed successfully in most instances. Although heart failure was the second most common long-term CV event, it is challenging to understand this in the context of the lack of a comparator group receiving cancer treatment without HCT. Regardless, we must consider the risk/benefit ratio in balancing oncologic efficacy and the

not-so-high associated CV risk. Hence, in cases in which HCT may confer a substantial oncologic benefit, the CV risk may not be prohibitive in most cases.

Third, the investigators note that although risk for CVD in the present study is similar to that in older studies, their cohort was older in age and had more baseline comorbidities. This has implications in furthering the concept that we need to iteratively reconsider strategies and thresholds by era when we consider patients for cancer therapies. Because of the shifting demographics, there is an implied trend toward taking higher risk patients for HCT successfully; however, it remains unclear what the limit should be from an age or a comorbidity standpoint, and this requires further study to delineate the thresholds.

Fourth, by recognizing specific risk factors associated with increased risk for CVD, the question of whether these risk factors are modifiable and whether intervening on them may translate to mitigation of subsequent CVD risk is unclear. Intervention studies are necessary to better understand how much we are able to optimize patients prior to HCT.

Fifth, the investigators observed that a low baseline ejection fraction was associated with long-term CV events, but not with peri-HCT events. Although this suggests that individuals with left ventricular dysfunction may tolerate HCT, we do not know the threshold ejection fraction at which it is still safe to proceed with HCT. Rather than thinking of the ejection fraction as a binary decision point for whether HCT is an option, we should probably consider it within the continuum of the overall CV risk profile for each patient.

Last, although overall CV risk was not high, it does not mean that these patients are completely without risk. These data underscore the need for serial follow-up of these patients in a survivorship clinic and within the framework of cardio-oncology programs. Historically, patients may be lost in transition once their oncologic concerns are resolved. It is imperative that these patients have lifelong surveillance and risk factor modification.

In summary, understanding the current epidemiology of CV morbidity and mortality following HCT carries implications for the prevention of CVD in long-term survivors of HCT. Addressing and intensively managing major modifiable risk factors of CVD in patients prior to HCT is likely to have the most impact in improving CV outcomes post-transplantation; however, adherence to lifelong monitoring and risk factor modification following HCT may be equally important. Understanding barriers to clinician and patient adherence to recommended prevention and screening practices will inform the development of interventions to prevent and reduce adverse CV outcomes.

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ADDRESS FOR CORRESPONDENCE: Dr Catherine J. Lee, Fred Hutchinson Cancer Center, 1100 Fairview Avenue N, Mailstop: M2-B230, Seattle, Washington 98109, USA. E-mail: cjlee@fredhutch.org. @CatherineLeeMD, @RichardKCheng2.

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