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EDITORIAL COMMENT

Calculate Your Risk of Heart Attack After Hematopoietic Cell Transplantation*

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Hematopoietic cell transplantation (HCT) is a curative treatment for a variety of hematologic diseases. Advances in transplantation technology have reduced early transplant-related mortality,[1] and there is a growing number of HCT survivors, estimated to be more than half a million worldwide.[2] Many recent studies have shown that HCT survivors suffer from significant late effects that adversely affect morbidity, mortality, and quality of life.[3] Cardiovascular diseases have been increasingly recognized among these late effects.[4,5] Several previous studies have shown that HCT survivors have a higher incidence of cardiovascular disease than the general population.[5,6] Although cardiovascular disease after HCT includes coronary heart disease (CHD), cardiomyopathy, heart failure, stroke, and peripheral vascular disease, most of the previous studies combined all these events for analysis because of the limited number of events. In this issue of *JACC: CardioOncology*, Gangaraju et al[7] specifically focused on CHD after HCT using a large study population of the BMTSS (Bone Marrow Transplant Survivor Study). The study cohort included 6,677 patients who survived 2 years after HCT, and 249 CHD events were observed with a long median follow-up time of 9.2 years among survivors.

The strengths of this study are the large multicenter cohort specifically designed for HCT survivors, detailed information, and a long follow-up. Importantly, data were also collected from siblings of survivors and were used as the general population for comparison of incidence and risks of CHD. The odds ratio of CHD compared with siblings was 1.61 in this study, which was a similar value to the HR of 1.6 reported in a previous study using a different cohort and design.[5] Furthermore, consistent with a previous study,[8] HCT patients had more cardiovascular risk factors (CVRFs) such as diabetes and dyslipidemia than the general population, indicating an opportunity for early intervention to treat these modifiable risk factors.

The higher incidence of CHD after autologous HCT compared with allogeneic HCT in this study contrasts with the results of a previous study.[4] As discussed by the authors, the discrepancy could be attributed to the difference in the event definition (ie, most previous studies combined all cardiovascular diseases for analysis) and the older patient age in this study than in the previous study. One potentially overlooked possibility is the small number of patients at risk later than 10 years after autologous HCT (Supplemental Figures 2 and 3), resulting in overestimation of the cumulative incidence after 10 years. Furthermore, the mechanisms of developing CHD events would differ after autologous HCT and allogeneic HCT. Particularly, graft-versus-host disease (GVHD) that occurs after allogeneic HCT may directly injure the vascular endothelium, or treatment for GVHD may contribute to the development of CVRFs.[9] Associations of GVHD with arterial events after HCT have been reported.[10] Although the authors did not find a statistically significant association between GVHD and the risk of CHD in this study, differences in the risk of CHD between autologous and allogeneic HCT and associations of GVHD with CHD events require further investigation.

As acknowledged by the authors, there are several caveats in the interpretation of the results of this study. First, the cumulative incidence reported in this study (5.45% at 20 years) might have been

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underestimated because only CHD events requiring intervention were included and subclinical or milder cases might not have been captured. The cumulative incidence of CHD was 8% at 14 years after HCT in a study using International Classification of Diseases codes to identify CHD events requiring hospitalizations.[5] Second, more than 2,000 patients were lost to follow-up or refused participation. Older, non-Hispanic Whites, autologous HCT recipients, and patients undergoing HCT before 2000 were more likely to participate in this study. Lastly, the study design was unique in that different data collection methods were applied for living and deceased participants at the last follow-up.

The simple nomogram proposed by the authors will be useful to identify patients who might benefit from early intervention for their CVRFs. Because cardiovascular risk scores developed in the general population may not be adequate for HCT survivors,[11] the nomogram included HCT-specific therapeutic exposures such as radiation history. Interestingly, the authors found a dose effect of chest radiation on CHD risk (the risk increased by 21% for every 10-Gy increase with autologous HCT), indicating that the radiation dose could be also incorporated for an accurate prediction of CHD risk. Although risk assessment before HCT is fundamental, the prediction of dynamic risk of CHD after HCT will be also important. For example, it is well-known that many patients develop CVRFs after HCT, and patients may change their lifestyle after HCT.[8,12] Future research could aim at developing algorithms to predict dynamic CHD risk after HCT by incorporating post-HCT covariates such as "current" CVRFs and cardiac medications. Future studies are also necessary to demonstrate whether any prospective intervention to treat CVRFs decreases the risk of CHD among HCT survivors.

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