Cardiac Dysfunction and Heart Failure in Hematopoietic Cell Transplantation Survivors

Emerging Paradigms in Pathophysiology, Screening, and Prevention

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KEYWORDS

• Cardiac dysfunction • Heart failure • Hematopoietic cell transplantation • Survivors • Pathophysiology • Screening • Prevention

KEY POINTS

- Hematopoietic cell transplantation (HCT) has been increasingly used for curative intent in patients with hematologic and nonhematologic malignancies, resulting in an increasing number of HCT survivors.
- These survivors are at risk for developing serious and sometimes life-threatening complications, including cardiovascular disease (CVD).
- This article provides an overview of CVD in HCT survivors, describing the pathophysiology of disease, emphasizing therapeutic exposures and comorbidities unique to this population.

INTRODUCTION

During the past 4 decades, hematopoietic cell transplantation (HCT) has been increasingly used as a treatment of choice for a large number of hematologic and nonhematologic diseases.[1] Patients who undergo HCT are often exposed to a combination of high-dose chemotherapy, total body irradiation, and immunosuppressive agents.[1] For many, this is in addition to therapeutic exposures (chemotherapy, radiation) they may have received before HCT.[1] Despite the relative intensity of such multimodal therapy, improvements in transplant strategy and clinical care have resulted in an incremental improvement of survival of 10% per decade.[2–4] In fact, among those who survive the first 2 years after HCT, nearly 80% of allogeneic HCT recipients and 70% of autologous HCT recipients are expected to become long-term survivors.[2–4] It is estimated that there are well over 160,000 HCT survivors living in the United States today, and that number is expected to exceed 500,000 by 2030.[5,6]

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As a result of improvements in the survival rate, important issues for HCT patients have expanded to include areas relevant to long-term survivorship, such as prevention of adverse health-related outcomes, maintenance of good health, and quality of life.[7] Studies conducted during the past 2 decades have highlighted the substantial burden of morbidity faced by HCT survivors. A report from the Bone Marrow Transplant Survivor Study[8] found that nearly two-thirds will develop a chronic health condition, and approximately 35% will develop a condition that is considered severe or life threatening; compared with sibling controls, they were twice as likely to develop a chronic health condition and nearly 4 times as likely to develop a severe or life-threatening condition. These conditions include subsequent malignancies, endocrine dysfunction, chronic kidney disease, visual impairment, and cardiopulmonary dysfunction.[8–11]

The burden of chronic health conditions is especially high in older HCT survivors, because they are dealing with the interacting effects of the biologic and physiologic changes of aging, the effects of cancer-directed therapy, after effects of cancer, and multiple chronic health conditions that develop over time.[12,13] These biologic changes are postulated to lead to physiologic consequences that can manifest by declines in organ reserve across nearly all organ systems.[12–14] In these survivors, although organ physiologic function generally remains adequate to compensate for activities required for daily living, the decline in reserves can leave HCT survivors vulnerable to premature onset of chronic health conditions, a process akin to accelerated aging.[12–14] For example, a recent report from the Bone Marrow Transplant Survivor Study[15] found that the prevalence of frailty, characterized as self-reported exhaustion, weakness, low physical activity, slow walking speed, and unintentional weight loss, in 18- to 64-year-old subjects was comparable (approximately 10%) with that documented in a community-based elderly (>65 years) population (N = 61,500). The rate of frailty was more than 8-fold higher when compared with sibling controls, with the highest risk seen in survivors transplanted for multiple myeloma, those with lower socioeconomic status, or those with chronic graft versus host disease (GVHD).

CARDIOVASCULAR AGING AND THE BURDEN OF CARDIOVASCULAR MORBIDITY

Among HCT survivors, cardiovascular disease (CVD; eg, heart failure, stroke, myocardial infarction) is a leading cause of non–relapse-related morbidity and mortality.[10] The risk of cardiovascular-related mortality is 2- to 4-fold greater than would be expected for the general population, and the incidence increases with time from HCT.[16,17] However, mortality attributed to CVD underestimates the true burden of CVD after HCT. HCT survivors have a 4-fold greater risk of developing CVD when compared with the general population,[18] adding to the already high burden of chronic health-related conditions in these survivors. Median age at first cardiovascular event such as myocardial infarction or heart failure is 53 years (range, 35–66),[19] which is much lower than would be expected in the general population (67 years).[20] The markedly increased risk of CVD, coupled with the recognition that these complications develop earlier than would be expected in the general population, suggests an accelerated cardiovascular aging phenotype that may be initiated by pre-HCT and HCT-related therapeutic exposures, and worsened by post-HCT complications such as GVHD, comorbidities (eg, hypertension, diabetes), and lifestyle behaviors (eg, physical deconditioning; **Fig. 1**).

The cardiovascular system has an inherent reserve capacity (cardiovascular reserve capacity) that is maintained by organ systems (cardiac, pulmonary, hematologic, musculoskeletal) that adapt to physiologic and/or pathologic perturbations.[21,22] However, this reserve capacity is finite and injury to 1 or more of the organ systems that maintain its integrity precipitates cardiovascular aging.[21] Moreover, repeated injuries to these systems sustained before, during, or after HCT can deplete cardiovascular reserve capacity, culminating in premature onset of CVD, or even cardiovascular death, among HCT survivors.

In clinical practice, cardiovascular risk is often determined via resting assessment of cardiac left ventricular ejection fraction (LVEF). However, the resting LVEF provides a snapshot of the heart's performance under optimal circumstances, and is a poor prognosticator of future cardiovascular events or mortality in patients undergoing HCT.[9,10] Importantly, the LVEF does not adequately evaluate or reflect cardiovascular reserve capacity, because it provides no information on the functional integrity of other organ systems that maintain cardiovascular reserve.[23–25] Peak oxygen consumption (VO_{2peak}), as derived from cardiopulmonary exercise testing (CPET), has been established as the gold standard measure of cardiovascular reserve, because it represents the integrative capacity with which multiple systems (cardiac, pulmonary, hematologic, musculoskeletal) deliver and use oxygen for ATP resynthesis. The VO_{2peak} is correlated inversely and independently with cardiovascular and all-cause mortality in a range of adult populations,