Biol Blood Marrow Transplant 23 (2017) 184–192

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Educational Reviews

Long-Term Survivorship after Hematopoietic Cell Transplantation: Roadmap for Research and Care

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Article history:
Received 15 September 2016
Accepted 2 November 2016

Key Words:
National Institutes of Health consensus
Late effects
Hematopoietic cell transplantation
Review
Educational
2017
Survivorship

A B S T R A C T

The number of survivors after hematopoietic cell transplantation (HCT) is expected to dramatically increase over the next decade. Significant and unique challenges confront survivors for decades after their underlying indication (malignancy or marrow failure) has been cured by HCT. The National Institutes of Health (NIH) Late Effects Consensus Conference in June 2016 brought together international experts in the field to plan the next phase of survivorship efforts. Working groups laid out the roadmap for collaborative research and health care delivery. Potentially lethal late effects (cardiac/vascular, subsequent neoplasms, and infectious), patient-centered outcomes, health care delivery, and research methodology are highlighted here. Important recommendations from the NIH Consensus Conference provide fresh perspectives for the future. As HCT evolves into a safer and higher-volume procedure, this marks a time for concerted action to ensure that no survivor is left behind.

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INTRODUCTION

Significant increases in hematopoietic cell transplantation (HCT) volumes in recent years, surpassing 18,000 in the United States in 2014 alone [1], have been superimposed over steady improvement in early transplantation-related mortality [2,3]. The current population of >100,000 survivors in the United States is projected to increase 5-fold by 2030, with 14% of the population ages <18 years and 25% ages ≥60 years at transplantation [4]. HCT survivors continue to remain at risk for late effects long after the risk of malignancy relapse has abated (Figure 1). Late effect risks vary over time but tracking and management are challenging because they often occur after transition of clinical care away from the transplantation center.

Observational studies in recent years have uncovered much of what we currently understand about late effects in transplantation survivors. The spectrum of late effects impacts multiple domains of health, severity ranges from mild to lethal, the latency of onset can range from months to decades, risk patterns are unique for each late effect and dependent upon the interval after HCT, and pediatric survivors may be more vulnerable. Pathobiology is driven by therapeutic exposure, immune dysregulation, and genetic predisposition. The nature, incidence, and management of late effects have been extensively reviewed [5-10]. Although there is growing appreciation for the lasting impact of late effects, many aspects remain elusive and much further effort is necessary to understand, monitor, and integrate their management into routine survivorship care. Unresolved challenges include health care delivery, understanding the actual pathobiology driving individual late effects, the poor evidence base for screening, prevention and management guidelines in this unique population, and methodological considerations in designing adequately powered studies with biological samples.

To address shortcomings, the National Institutes of Health (NIH) sponsored a HCT late effects initiative with the objectives of defining the critical issues or barriers in the field, setting research priorities, and to create a successful organizational framework for studying late effects (biology, observational, and interventional studies). The focus was defined as critical survivorship issues occurring >1 year after autologous or allogeneic transplantation that were unique to the field of HCT. Potential areas of overlap with the chronic graft-versus-host disease (GVHD) consensus project [11,12], such as chronic inflammation and pulmonary failure, were

Financial disclosure: See Acknowledgments on page 190.

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http://dx.doi.org/10.1016/j.bbmt.2016.11.004
1083-8791/Published by Elsevier Inc. on behalf of the American Society for Blood and Marrow Transplantation.

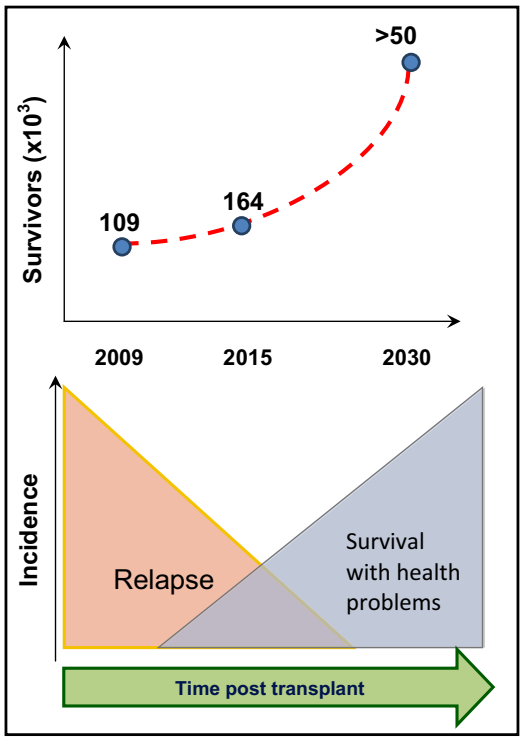

Figure 1. HCT survivorship. Projected numbers of HCT survivors and temporal course after HCT.

avoided. The scope was limited to the most important challenges that would advance the science or change guidelines/clinical care/standard approach [13]. Six broad areas of emphasis were identified, as follows: health care delivery [14]; research methodology and study design [15]; subsequent neoplasms (SN) [16]; quality-of-life and psychosocial outcomes [17]; immune dysregulation [18]; and cardiac, vascular, and metabolic events [19]. Working groups involved international experts, representation of adult and pediatrics, subject matter experts, governmental agencies, advocacy groups, and transplantation societies. Deliberations culminated in a final consensus conference in June 2016. Several important aspects of late complications not specifically covered by the final consensus conference have been the subjects of comprehensive review [7,20].

The purpose of this review is to highlight the fresh perspectives provided by the NIH consensus conference and to summarize their recommendations for a broader audience. This educational review is divided into 3 sections. The first will discuss the magnitude, pathogenesis, management, gaps, and research priorities for late events that are potentially lethal—cardiac, vascular, and metabolic events; SN; and immune dysfunction. The next will focus on patient-centered outcomes and research priorities. The last section will describe health care delivery cost versus value to survivors and unique aspects of research methodology. Table 1 summarizes the key recommendations from the conference [15-19,21].

POTENTIALLY LETHAL LATE EFFECTS

Large retrospective studies confirm that if an allogeneic HCT recipient is alive at 2 years, the recipient is unlikely to relapse but has a 20% probability of delayed mortality over the next 15 to 20 years [22-24]. This delayed nonrelapse mortality (at a rate of 4 to 9 times that of the general population) typically strikes when the recipient has left the influence of the transplantation center. The most frequent causes of delayed mortality are cardiac/vascular, SN, infections, and pulmonary [22,23]. The passage of time should not induce complacency because the standardized mortality ratio at 15 years after HCT remains elevated at 2.2-fold that of the general population [22]. Moreover, it is notable that the incidence for cardiac/vascular and SN continues to increase with time from HCT and does not peak before the completion of the second decade of survivorship. Many causes of delayed mortality are potentially surmountable if we focus research attention on understanding the unique pathobiology of HCT. Improved understanding and awareness of post-HCT physiology will also afford institution of effective early screening methods specific to the HCT population, so that pre-emptive and targeted therapies can be developed.

Magnitude of Impact, Pathogenesis, and Management

Cardiac/vascular/metabolic

It is useful to categorize 3 groups of cardiovascular complications: cardiac dysfunction, arterial disease, and metabolic risk factors. HCT survivors are at a ~4-fold higher risk of developing cardiovascular disease (CVD) compared with the general population [25], which tends to occur prematurely, with the first event such as myocardial infarction occurring ~14 years earlier than in the general population, which suggests accelerated cardiovascular aging.

The pathogenesis of elevated CVD risk has been attributed to multiple factors, including pre-HCT therapeutic exposures (eg, anthracycline chemotherapy, chest radiation), HCT conditioning, GVHD, and traditional cardiovascular risk factors (CVRFs); eg, dyslipidemia, hypertension, diabetes, sarcopenic obesity, endocrinopathy [26,27]. Endothelial damage and growth hormone deficiency are potential emerging CVD risk factors after HCT [19]. Prospective studies examining the influence of these risk factors are needed.

Current management guidelines emphasize early screening for CVRFs and high-risk lifestyle behaviors to provide opportunity for pre-emptive management of arterial disease [5,6,28,29]. While there is general consensus that screening should begin by 1 year after HCT, existing guidelines have been extrapolated from the general population and probably underestimate the risk of coronary artery disease [5,6,30,31]. The optimal initiation, frequency, and duration of screening methodologies remain undefined. Screening for asymptomatic vascular disease using imaging studies (eg, coronary artery calcium scoring, vascular intima-media thickness), or blood biomarkers of endothelial injury remains an active area of investigation [19]. Outcome after post-HCT heart failure is poor, with <50% surviving 5 years [32,33], emphasizing the need for preventive strategies. Echocardiography has been advocated for screening of asymptomatic cardiac disease, but there is little consensus regarding its cost-effectiveness [34].

SN after HCT are categorized into 3 groups: lymphoid malignancies (including post-transplantation lymphoproliferative disorder [PTLD]), myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), and solid tumors. Although lymphomas and leukemias develop relatively early after transplantation, solid tumors tend to have a longer latency, measurable in decades [35-38]. Significant methodological challenges make it difficult to provide accurate estimates of risk for each tumor type compared with the general population [16] but some generalizations can be made. Overall,