Biol Blood Marrow Transplant 23 (2017) 6–9

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Editorial

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Developing Recommendations to Improve Survivorship and Long-Term Outcomes

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Article history:
Received 25 October 2016
Accepted 27 October 2016

Key Words:
Late effects
Hematopoietic cell transplantation
Survivorship

A B S T R A C T

Continual advances in hematopoietic cell transplantation (HCT) have greatly improved early transplantation-related mortality and broadened the applicability of this intense but curative therapy. With growing success there is increasing awareness of late complications, occurring ≥1 year after treatment, and their associated morbidity and mortality in HCT survivors. These late effects occur with a wide spectrum in terms of latency, intensity, reversibility, and lethality. There is a need to understand the biology, surveillance, management, and patient experience of HCT-related effects, as well as the health care and research infrastructure to manage this growing population. To address these needs, the National Cancer Institute and National Heart, Lung and Blood Institute cosponsored a 12-month initiative to identify barriers and knowledge gaps and to formulate research and practice recommendations. Six major areas of interest were identified: research methodology and study design, subsequent neoplasms, patient-centered outcomes, immune dysregulation and pathobiology, cardiovascular disease and associated risk factors, and health care delivery. These findings were presented during the 2016 workshop and revised based on public response. This report provides an overview of the National Institutes of Health HCT Late Effects Initiative process and recommendations.

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INTRODUCTION

Allogeneic and autologous hematopoietic cell transplantation (HCT) are potentially curative for many disorders, including hematologic malignancies (eg, leukemias, lymphomas, multiple myeloma), marrow failure states, hemoglobinopathies, primary immunodeficiencies, genetic metabolic disorders (eg, mucopolysaccharidoses), autoimmune conditions, and select solid cancers (eg, germ cell tumors). HCT volumes show continued growth: more than 65,000 HCTs are being performed worldwide annually with the 1,000,000th HCT being performed by 2013 [1]. Along with increased HCT volumes, there have been impressive improvements in HCT safety, as determined by reduction in early nonrelapse mortality, in recent years [2,3]. In the United States alone, the current population of >100,000 survivors is projected to increase 5 fold by 2030, with 14% of the population ages <18 years and 25% ages ≥60 years at transplantation [4]. Many transplantation survivors will achieve a cure of their underlying malignancy or hematologic disorder but are susceptible to lifelong health problems.

Improvements in Early Safety after HCT

Since its inception 6 decades ago, the field of allogeneic HCT bears the unfortunate distinction of having the highest procedural mortality among all elective medical/surgical procedures. The causes for improvement in the current HCT era are multifactorial: improved patient selection, accounting for comorbidities, optimization of conditioning regimens,

Financial disclosure: See Acknowledgments on page 9.

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http://dx.doi.org/10.1016/j.bbmt.2016.10.020
1083-8791/Published by Elsevier Inc. on behalf of the American Society for Blood and Marrow Transplantation.

improvements in graft source and donor selection, better graft-versus-host disease (GVHD) prophylaxis and therapy, general improvements in supportive care (particularly infectious disease), improved staff training, adoption and compliance with international standards (Foundation for the Accreditation of Cellular Therapy [FACT]/Joint Accreditation Committee ISCT EBMT), and improvements in organizational framework, all driven by research. National Institutes of Health (NIH)–sponsored consensus development efforts (initiated in 2005 and 2009, respectively) have addressed the challenges of chronic GVHD [5] and malignancy relapse [6], which are responsible for the majority of morbidity and mortality in the first 2 to 3 years after HCT. It is now common for centers to report nonrelapse mortality rates of <10% at 1 year after HCT for standard-risk acute leukemias [7]. However, HCT survivors continue to remain at risk for debilitating late complications long after the risk of malignancy relapse has abated and even without manifestations of active chronic GVHD. Addressing these late complications deserves special emphasis as we build upon the success of this field.

Understanding the Spectrum of Late Effects after HCT

Studies on pediatric cancer survivors have been seminal in drawing attention to the field of late complications in oncology [8]. However, the study of late effects in HCT survivors, specifically, is a relatively nascent field. The under-recognized burden of HCT late complications includes premature mortality and the accelerated onset of multiple age-related chronic diseases when compared to the general population. These include GVHD (allogeneic), late infections, new malignancies, cardiovascular, endocrinopathy (particularly diabetes, metabolic syndrome, hypothyroidism, osteoporosis, gonadal failure), and accelerated aging, as well as chronic morbidity from chronic pain, fatigue, musculoskeletal symptoms, insomnia, sexual dysfunction, cardiac and respiratory complications, memory loss, mood changes, vision and dental problems, and psychological stressors. The underlying pathobiology of late effects after HCT reflects the complex interplay between their underlying diagnosis or immune/genetic disorder, comorbidities, genetic predisposition, prior treatments, conditioning therapy, and immune dysregulation (which includes chronic GVHD). Observational quality-of-life studies have documented a multitude of changes spanning physical, psychological, financial, and social domains of health.

Late mortality in the allogeneic transplantation setting was assessed in the large Bone Marrow Transplant Survivor Study of 1479 HCT recipients who had survived 2 or more years after allogeneic HCT, and their relative mortality was found to be 9.9 (95% confidence interval, 8.7 to 11.2) [9]. Relative mortality decreased with time from HCT but remained significantly elevated, even at 15 years after HCT (standardized mortality ratio, 2.2). Subsequent large retrospective studies confirm that if an allogeneic transplantation recipient is alive at 2 years, then relapse mortality is uncommon but the recipient is still likely to have an ~20% risk of late mortality over the next 15 to 20 years [10,11]. The most frequent causes of delayed mortality are cardiac/vascular, subsequent neoplasms, infections, and pulmonary [9,10]. It is noteworthy that the incidence for cardiac/vascular and subsequent neoplasms continues to increase with time after HCT and does not peak before the completion of the second decade of survivorship.

The latency of onset of symptoms may be weeks (such as psychosocial challenges), months (such as metabolic complications, gonadal failure), years (infections, growth failure), or even decades (cardiovascular events and subsequent neoplasms). Their occurrence and intensity may range from frequent and mild to rare but lethal. Many are treatable and possibly preventable.

It is important to view the impact of late effects from the survivors' perspective. While they may enjoy a cure from their underlying disease state, many are dismayed by persistence of health issues for which they are rarely fully prepared. These stressors are not confined to patients but extend to caregivers and families. A further complication is organizing optimum care delivery to survivors, in a field where new knowledge is being actively discovered, coordinating multiple disciplines and at a time when many survivors may have transitioned away from their transplantation center. Unfortunately, late complications often do not receive the attention they deserve—nonlethal late effects or those with a long latency of onset are likely to be ignored in the context of a busy transplantation clinic or relegated to a nontransplantation provider.

Many of the allogeneic associated late effects are directly related to chronic GVHD. The complexities of chronic GVHD led to the development of the NIH-led chronic GVHD consensus project and conferences (2005 [5] and 2014 [12]) and the establishment of the consortium (2008) that have successfully improved characterization of incidence, manifestations, and outcomes of patients and developed and implemented universal grading systems and stimulated intervention trials. Moreover, the NIH chronic GVHD consortium and others are also embarking on identifying biomarkers that can assess risk, impending onset, diagnosis, or prognosis of chronic GVHD and its manifestations, such as cutaneous sclerosis or bronchiolitis obliterans. However, many of the late effects are either unrelated to GVHD or have a latency of 10 to 20 years, including premature coronary artery disease and new malignancies that need a different approach, which would emulate essential elements from the chronic GVHD consensus framework.

Overview of Challenges in the Field of Late Effects in HCT Survivors

Health care delivery is challenged by sporadic access to specialized health care settings because of the lack of dedicated long-term follow-up clinics for HCT survivors in most centers, although this has been proposed a FACT standard [13]. Standardized care models have not been possible because of prohibitive volumes (at large centers with a legacy of thousands of survivors), divergent models of health care provider (transplantation physician versus internist versus allied health professional), and location of care (community versus transplantation center–based). Development of a viable business model for a community-based long-term follow-up multidisciplinary clinic could be limited by reimbursement issues (eg, for multiple subspecialty visits on the same day). Pediatric survivors may be lost to follow-up when they transition to adult clinics. Universal adoption of individualized care plans and integration with national transplantation societies' advocacy groups are other challenges.

Scientific obstacles are balanced by research opportunities in the field of HCT survivorship. The current state of science is characterized mainly by retrospective or cross-sectional studies without adequate control groups, resulting in a low-level of evidence. There is a need to move beyond observational studies to understanding the actual pathobiology driving individual late effects. There is an opportunity to integrate recent advances in understanding of accelerated senescence, telomere biology, improved screening practices, and impact of