HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2017 January ; 23(1): 6–9. doi:10.1016/j.bbmt.2016.10.020.

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

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Abstract

Continual advances in hematopoietic cell transplantation (HCT) have greatly improved early transplant 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 post 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 healthcare and research infrastructure to manage this growing population. To address these needs, the National Cancer Institute (NCI) and National Heart, Lung and Blood Institute (NHLBI) co-sponsored 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 healthcare 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.

Keywords

Late Effects; Hematopoietic Cell Transplantation; Survivorship

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Introduction

Allogeneic and autologous hematopoietic cell transplantation (HCT) is potentially curative for many disorders including hematologic malignancies (e.g. leukemias, lymphomas, multiple myeloma), marrow failure states, hemoglobinopathies, primary immunodeficiencies, genetic metabolic disorders (e.g. mucopolysaccharidoses), autoimmune conditions and select solid cancers (e.g. germ cell tumors). HCT volumes show continued growth; more than 65,000 HCTs are being performed worldwide annually with the one-millionth 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 non-relapse mortality (NRM), in recent years [2, 3]. In the United States alone, the current population of >100,000 survivors is projected to increase five-fold by 2030, with 14% of the population aged <18 years and 25% aged ≥ 60 years at transplant [4]. Many transplant survivors will achieve a cure of their underlying malignancy or hematologic disorder but are susceptible to life-long health problems.

Improvements in Early Safety after HCT

Since its inception six 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, 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/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 two to three years following HCT. It is now common for centers to report NRMs 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), 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 (QOL) studies have documented a multitude of changes spanning physical, psychological, financial and social domains of health.

Late mortality in the allogeneic transplant setting was assessed in the large Bone Marrow Transplant Survivor Study (BMTSS) 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% CI 8.7–11.2)[9]. Relative mortality decreased with time from HCT, but remained significantly elevated even at 15 years after HCT (standardized mortality ratio [SMR] = 2.2). Subsequent large retrospective studies confirm that if an allogeneic transplantation recipient is alive at 2 years, then relapse mortality is uncommon but they are still likely to have an ~20% risk of late mortality over the next 15–20 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 survivor's 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 transplant center. Unfortunately, late complications often do not receive the attention they deserve—non-lethal late effects or those with a long latency of onset are liable to be ignored in the context of a busy transplant clinic or relegated to a non-transplant 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] & 2014[12]) and establishment of the consortium (2008) that have successfully improved characterization of incidence, manifestations and outcomes of patients, 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 CAD 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 due to the lack of dedicated long term follow up (LTFU) clinics for HCTsurvivors 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 healthcare provider (transplant-physician versus internist versus allied health professional-led) and location of care (community versus transplant center-based). Development of a viable business model for a community based LTFU multi-disciplinary clinic could be limited by reimbursement issues (e.g. 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 transplant 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, impact of inflammatory states on arterial disease, endocrinopathy and carcinogenesis. The actual prevalence of many late effects and effectiveness of prevention is unknown. Although preventive guidelines for screening recommendations for long term survivors of HCT were published in 2012, many of the recommendations were not based on evidence derived from randomized or other controlled trials, but were supported by retrospective studies that had identified specific complications in long-term survivors and their associated risk factors[14]. Thus a lack of an organized approach to evaluate the biology and clinical outcomes of specific late effects of HCT is evident. There are methodologic challenges in integrating adequately powered studies of important late effects, which may occur decades after HCT, with biological sampling while leveraging existing infrastructure. Understanding the prevalence, mechanisms and risk of late effects will inform timely screening and interventions as an attempt to reduce late effect development and related morbidity and mortality after HCT. These goals can be accomplished by coordinating late effects research across multiple transplant centers globally and by integrating late effects into prospective HCT trials. A well-coordinated approach that has the potential to improve outcomes andpatient reported outcomes of HCT survivors is urgently needed. To assess, monitor, and enhance the quality of medical care, patient experiences, and clinical outcomes at all levels (patients, providers, institutions, and health care systems), a comparative effectiveness approach is needed.

Justification and Goals for Organizing a Late Effects Initiative in HCT

Recognition that HCT survivorship is challenged by significant late complications, growing interest in exploring their underlying biological drivers, and the perceived lack of coordination of efforts in the basic, translational and clinical research, led to the emergence of an effort to catalyze an international initiative. The initiative goals were to: 1) develop a core working committee and specialized multidisciplinary working groups based on international expertise to have a global representation for this international effort; 2) identify gaps in understanding and prioritize research in areas of key late effects among HCT survivors; and 3) evaluate the current data infrastructure capabilities of various agencies and institutions to help in assimilating a robust framework for research methods.

Methods

The National Cancer Institute (NCI) and National Heart, Lung, and Blood Institute (NHLBI) sponsored a 12-month initiative comprised of a steering committee and six working groups, culminating in a workshop titled “NIH Blood and Marrow Transplant Late Effects Consensus Conference” in June 2016 in Bethesda, MD. The proposal evoked keen support from the community of transplant health care workers and researchers, patient advocacy organizations and other stakeholders such as the Center for International Blood and Marrow Transplantation Research (CIBMTR), American Society for Blood and Marrow Transplantation (ASBMT), European Society for Blood and Marrow Transplantation (EBMT) and the NCI’s National Clinical Trials Network (CTN).

For the BMT Late Effects Initiative, HCT survivors were defined as pediatric or adult, autologous or allogeneic HCT recipients who survived for one year or longer after transplantation. One year was selected as the initial time-point because most relapses occur before this landmark and many late effects have their genesis early.

A steering committee of HCT clinicians across federal and non-federal agencies was established to coordinate the initiative. The identification of the six priority areas for working groups (Table 1) was achieved through review of CIBMTR working group reports, literature and NIH active grant funding. In selection of the six priority working areas, the Steering Committee focused on survivorship problems unique to the field of HCT. In doing so, some important but non-unique aspects of HCT, such as gonadal failure and infertility, were relegated to other oncologic initiatives. Areas of overlap with the NIH chronic GVHD consortium, such as chronic inflammation and pulmonary failure, were avoided.

The six working groups were charged with identifying research gaps and formulating research and practice recommendations within the assigned content area. Co-chairs were identified for each of the content areas and charged with outlining the working group’s scope based on critical knowledge gaps in June 2015--topics focused on the most critical challenges that could improve health, advance the science or change clinical care (Table 1).

Working group membership was comprised of HCT and non-HCT clinicians, administrators, researchers and advocates across federal and non-federal groups and met virtually over a one-year period[15]. The working group co-chairs and steering committee teleconferenced

monthly to monitor progress and manage overlap between content areas. The working groups wrote draft manuscripts identifying knowledge gaps and recommendations for practice and research. Each manuscript was distributed to the June 2016 public meeting attendees, as well as to two external content reviewers who provided expert commentary during the meeting. Meeting attendees included multidisciplinary HCT team members, administrators, researchers, professional societies, advocates and survivors. Each working group topic was presented and discussed during a 90-minute session with ample time for comment and feedback on the recommendations[15]. The manuscripts were revised based on public comment prior to submission for publication[16–21].

Summary

Over the following months a summary of each Working Group's findings and recommendations will be presented in the *Biology of Blood and Marrow Transplantation*. These reports from the NIH Late Effects Consensus Initiative will provide a thorough scientific review, identify critical barriers and knowledge gaps, stimulate discussion and identify and prioritize efforts to address this important clinical problem.

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Table 1

Working Groups and Scope

Working Group	Scope
Research Methodology and Study Design	• Methodological challenges across HCT survivor research • Historical transplantation strategies in retrospective analysis • Database and bio specimen requirements for future HCT survivorship studies
Subsequent Neoplasm	• Magnitude of risk for subsequent neoplasm • Subsequent neoplasm pathogenesis, transplant- and non-transplant-related risk factors and outcomes
Patient Centered Outcomes	• HRQOL dimensions (physical, psychological, social, and environmental, adherence to treatment and health behaviors) affected by HCT • Interventions tested to improve these outcomes • Methodological issues that restrict progress in this field
Immune Dysregulation and Pathobiology	• Trends in late infections among HCT survivors • Immune reconstitution in the laboratory setting • Interventions to improve immune function across survivorship
Cardiovascular Disease and Associated Risk Factors	• Arterial disease (e.g. coronary artery, cerebrovascular, peripheral artery) • Cardiac dysfunction (e.g. heart failure, valvular, arrhythmia) • Cardiovascular risk factors (e.g. hypertension, hyperglycemia, dyslipidemia, sarcopenic obesity)
Health Care Delivery	• Health care models • Coverage and Value