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Review

Lost in Transition: The Essential Need for Long-Term Follow-Up Clinic for Blood and Marrow Transplantation Survivors

Shahrukh Hashmi [1,*], Paul Carpenter [2], Nandita Khera [3], André Tichelli [4], Bipin N. Savani [5]

[1] Division of Hematology, Mayo Clinic, Rochester, Minnesota
[2] Department of Hematology Oncology, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington
[3] Division of Hematology/Oncology, Mayo Clinic, Phoenix, Arizona
[4] Diagnostic Hematology, University Hospital Basel, Basel, Switzerland
[5] Division of Hematology/Oncology, Vanderbilt University, Nashville, Tennessee

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A B S T R A C T

Because of expanding indications and improvements in supportive care, the utilization of blood and marrow cell transplantation (BMT) to treat various conditions is increasing exponentially, and currently more than 60,000 BMTs are performed annually worldwide. By the year 2030, it is projected that the number of BMT survivors will increase 5-fold, potentially resulting in one half of a million survivors in the United States alone. As the majority of survivors now live beyond the first 2 years after BMT, they are prone to a unique set of complications and late effects. Until recently, BMT experts assumed responsibility for almost all of the care for these survivors, but now oncologists/hematologists, pediatricians, and internists are involved frequently in offering specialized care and preventive services to these survivors. To integrate and translate into clinical practice the unique BMT survivorship issues with current preventive guidelines, a team effort is required. This can be facilitated by a dedicated "long-term-follow-up (LTFU)" clinic that provides lifelong care for BMT survivors. In this review, we first illustrate with clinical vignettes the need for LTFU and then focus upon the following: (1) types of LTFU clinic models, (2) challenges and possible solutions to the establishment of LTFU clinic, and (3) vulnerable transition periods.

INTRODUCTION

The term *cancer survivor* typically refers to any individual who has been diagnosed with cancer, and the journey of survivorship begins at diagnosis and includes all curative and palliative treatments [1]. Similarly, we define *blood and marrow transplantation (BMT) survivor* as any individual who has undergone a BMT, with BMT survivorship beginning on the day of transplantation (day 0 of stem cell infusion).

Because of the expanding indications for BMT and improvements in supportive care leading to decreased mortality [2], the use of BMT for treating various malignant and nonmalignant diseases is increasing exponentially [3]. Currently, more than 60,000 BMTs are performed annually worldwide. It is projected that the number of BMT survivors will increase 5-fold, to a total of 500,000 by the year 2030 in the United States alone [4].

As the majority of survivors are living beyond the first 2 years after BMT, they are prone to a unique set of complications and late effects that reflect the complex interplay between their cancer diagnosis (or their immune/genetic disorder), prior immunotherapies and/or chemotherapies, conditioning therapy, and graft-versus-host disease (GVHD). This leads to a multitude of changes in physical, psychological, financial, and social domains. Let's now consider, as an example, 1 of 2 BMT survivors.

Peter, a widowed 55-year-old male information technology specialist with acute lymphoblastic leukemia in second complete remission, was conditioned immediately before transplantation with 12 Gy total body irradiation (TBI) and cyclophosphamide and then infused with a related peripheral blood stem cell allograft. Because of multiple pretransplantation relapses, his cumulative anthracycline exposure now totals a substantial 450 mg/m^2. He is 2 years after BMT and has developed severe uncontrolled dyslipidemia and advanced chronic GVHD, for which he is being treated with corticosteroids, cyclosporin, statins, and prophylactic antibiotics. He lives alone in New York City and is unable to use his computer because of GVHD-associated

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* Correspondence and reprint requests: Shahrukh Hashmi, 200 First Street S.W., Rochester, MN 55905.
E-mail address: shahrukh@mayo.edu (S. Hashmi).

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wrist contractures that limit his ability to work and impair his quality of life.

The second survivor is Rong, a 19-year-old Vietnamese woman who underwent BMT at age 13 for marrow failure associated with Fanconi anemia. She was conditioned with 2 Gy TBI and fludarabine and then infused with bone marrow. She recently underwent neck dissection for oral cancer and is struggling with depression. Before BMT, Rong received multiple red cell transfusions and now has abnormal liver function that is presumably due to iron overload. She lives with her very supportive parents in rural western United States and believes in the curative potential of Chinese herbal medications for all ailments.

Although these patients differ with respect to age, sociodemographic profile, and current medical conditions, they each demonstrate several late effects that can characterize BMT survivorship. The common late effects range from TBI-associated hypothyroidism (with up to 20% of survivors eventually becoming hypothyroid after full-dose TBI) [5]; financial burden including unemployment [6]; post-traumatic stress disorder [7,8]; cutaneous carcinomas (mainly due to BMT conditioning, but GVHD is an additional risk factor) [9,10]; cataracts (mainly due to TBI, but steroid exposure increases this risk) [11]; and metabolic syndromes (mainly due to BMT, but immunosuppressive therapy is an additional risk factor) [12], as well as many other complications (particularly infections). However, certain risks are more specific to each of these patients.

Peter's risk of heart failure and coronary artery disease is substantial [13,14] because of his exposure to TBI, anthracyclines, and because of metabolic syndrome, including medication-induced diabetes and hypertension. His chronic GVHD has been significantly disabling because of deep fasciitis, which has severely restricted the range of motion in his wrists and ankles. He also remains at risk of lung cancer due to BMT [15] and a history of cigarette smoking; suicide, due to BMT and loneliness [16]; chronic kidney disease due to cyclosporin, GVHD, and diabetes [17]; and osteoporosis, due to complications of glucocorticoids [18,19]. He requires extensive services from physiatry, especially occupational therapy for musculoskeletal GVHD; clinical psychology, to evaluate for psychiatric comorbidities; cardiology and nephrology, for late effects surveillance; and endocrinology, to consult on the management of iatrogenic diabetes, bone health, and secondary adrenal insufficiency. Dermatology and ophthalmology are consulted for skin cancers and cataract screening, respectively. Social workers are often called to provide essential additional support relevant to their expertise. Individualized care plans are the overall goal of coordinated long-term follow-up. Lastly, the struggle with chronic GVHD as an orphan disease for which no FDA-approved therapies exist often delays the recovery for a number of BMT survivors like Peter.

For Rong, 6 years after BMT at a young age, the risk of new head and neck cancers remains extremely high as a consequence not only of BMT but also as a result of her underlying Fanconi anemia [20,21]. Infertility primarily due to TBI [22-24] and complications due to secondary hemochromatosis [25,26] are other very relevant late effects. Because her post-transplantation survival is expected to be high, Rong's lifetime risk for developing a conditioning treatment–related myeloid neoplasm is considerably higher than Peter's. An individualized multidisciplinary approach for Rong will include the services of psychology, hepatology, gynecology, and dermatology. In addition to ongoing monitoring for suicidal ideation and sexual dysfunction, she will be offered well-defined interval screening for hepatomas, breast cancer, cervical cancer, head and neck cancers, and skin cancers. She will also see complementary and alternative medicine experts to discuss the pros and cons of their suggested therapies because she behaves similarly to the 90% of cancer survivors who utilize complementary and alternative medicine for a variety of symptoms [27-29]. She still wants to continue seeing her primary transplantation physician, a pediatric hematologist, but at some future time point, her care will typically be transitioned to an adult provider or a long-term follow-up (LTFU) clinic that provides care to adult BMT survivors.

Each 1 of these survivors is very illustrative of the need for well-coordinated multidisciplinary care to help optimize BMT outcomes. Such care is possible only through collaborations between BMT experts, physicians, and allied health professionals (AHP) in the fields of oncology, hematology, pediatrics, and internal medicine. Collaborations often need to span long distances because a sizeable proportion of survivors do not live close to the BMT center. Thus, it is important for all relevant academic and community-based clinicians to understand the basics of late effects [30], coordination of care models, and the role of an organized clinic that is dedicated to providing specialized care to these survivors to optimize the long-term benefits of BMT.

Late effects in cancer literature are defined as complications arising months to years after cancer treatment is over [31]. Specific late effects preventive guidelines have been published for BMT survivors [32]. Other areas of BMT survivorship continue to be actively studied, particularly caregiver health [33-35], quality of life with GVHD [36-38], psychosocial burden [39-41], integration of care models [42,43], and health care utilization/financial toxicity [6,44,45]. To integrate aforementioned BMT survivorship issues and current preventive guidelines into clinical practice, a team effort, that can be facilitated by a dedicated LTFU clinic that follows BMT survivors lifelong, is required.

Although the data on late effects in BMT survivors are rapidly accumulating, research on the value of LTFU clinics for this population is lacking. In this review, we highlight the following: (1) basics of LTFU clinic models, (2) challenges faced in establishing LTFU clinics and proposed solutions; and (3) vulnerable transition periods in BMT survivorship longitudinal care.

LONG-TERM FOLLOW-UP CLINIC MODELS

Compared with a 5-decade history of BMT [46], the field of BMT survivorship is still in its infancy. The Children's Oncology Group has assimilated comprehensive guidelines on childhood cancer survivors, which include risk-adapted management guidance for specific late effects [47]. The Children's Oncology Group has also described various LTFU models of care for pediatric cancer survivors. BMT survivors' needs differ from those of general cancer survivors, as illustrated by the cases of Peter and Rong: they can easily overwhelm the management capacity of a single health care provider. Comprehensive care requires specific knowledge and expertise of late (>6 months after BMT) and very late effects (>5 years after BMT) due to a multitude of physical and psychological insults before, during, and after transplantation.

Dedicated LTFU clinics are operational at a minority of the centers that currently perform BMT; models of care differ by center as described below and in Table 1. We do not propose