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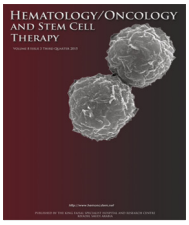

REVIEW ARTICLE

Long-term complications after hematopoietic cell transplantation

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Abstract
The prevalence of autologous and allogeneic hematopoietic cell transplantation (HCT) survivors continues to increase. Among patients whose disease remains in remission for the first 2–5 years after transplantation, it is estimated that approximately 80–90% will be alive over the subsequent 10 years. However, the relative mortality rates of such patients continue to remain higher than those of their general population peers, with late complications contributing to significant long-term morbidity and mortality. Late effects in HCT survivors include secondary cancers, organ specific complications, late infections, quality of life impairments, psychosocial issues, sexual and fertility concerns, financial toxicity, and issues around return to work/school. A patient-centric and multidisciplinary approach to HCT survivorship care with collaborative and coordinated care from transplant centers and community healthcare providers is necessary to ensure their long-term health. Lifelong follow-up of HCT survivors is recommended, with established guidelines serving as the template for providing screening and preventive care based on patient-specific exposures. This review discussed common late complications, models for care delivery, and gaps and priorities for future research in the field of HCT survivorship.

Introduction

The long-term survival probability for hematopoietic cell transplantation (HCT) recipients continues to improve with several advances in transplantation techniques and supportive care practices, and it is projected that there will be more than 500,000 HCT survivors in the United States by

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2030 [1,2]. As patients survive longer, there is an increasing recognition that pre-, peri-, and post-transplant exposures can contribute to the development of late complications that can cause substantial morbidity, impair quality of life, and can compromise life expectancy in transplant survivors. This review summarizes the contemporary literature on long-term survival after autologous and allogeneic HCT, guidelines for long-term follow-up of HCT survivors, and barriers and opportunities for their follow-up [3–5].

Long-term survival after HCT

Disease relapse is the main cause of treatment failure in the first 2–4 years after transplantation. Patients who do not suffer from disease relapse through this early time period enjoy relatively high rates of subsequent survival. Several contemporary large studies have reported on long-term survival rates in patients who have survived disease-free for 2–5 years after transplantation (Table 1) [6–15]. Although studies vary in methodology and patient characteristics, together they indicate a high probability of long-term survival in this patient population; however, their life expectancy continues to lag compared with that of their age- and gender-matched peers from the general population for at least 15–20 years after HCT. They also indicate disease recurrence, chronic graft-versus-host disease (GVHD; in allogeneic HCT recipients), organ failure, and secondary cancers, which are common causes of late deaths. Collectively, these studies highlight the need for life-long systematic follow-up for both autologous and allogeneic HCT survivors to screen for disease recurrence and late complications, and for health maintenance following transplantation.

Late complications after HCT

Late complications are medical issues that occur months to years after transplantation and can be broadly categorized as secondary cancers, organ specific complications, late infections, quality of life (QOL) impairments, psychosocial issues, sexual and fertility concerns, financial toxicity, and integration back to society. Some complications (e.g., cardiovascular complications, end-stage renal disease, bronchiolitis obliterans) contribute to late non-relapse mortality among transplant survivors. Other complications (e.g., dry eyes, xerostomia, avascular necrosis) may not directly impact mortality but can impair QOL. The genesis of these complications can be partly or completely attributed to transplant-related exposures. In addition, pre-transplant treatment exposures (e.g., disease specific chemotherapy or radiation) as well as modifiable and non-modifiable lifestyle factors (e.g., smoking, hereditary cancer risk factors) can contribute to the risk. Conditioning regimen-related chemotherapy and total body irradiation (TBI) exposures are commonly associated with risks for late complications in all HCT recipients. Among allogeneic HCT recipients, chronic GVHD and its treatment are also major contributors to late complication risks. Table 2 summarizes common late complications of transplantation and the recommendations for their screening and prevention.

Secondary cancers

Secondary cancers account for 5–10% of deaths among HCT recipients who survive 2 years or longer and can be broadly categorized as post-transplant lymphoproliferative disorders (PTLD), hematologic malignancies, and solid cancers [2,11,16,17]. PTLD is almost exclusively seen in allogeneic HCT recipients and comprises a heterogeneous group of lymphoid proliferations, primarily involving B-lymphocytes, which arise as a result of Epstein-Barr virus (EBV) infection [16,18]. It typically manifests early post transplantation with >80% cases diagnosed within the 1st year. Increase in the intensity of immunosuppression increases its risks, such as *in vivo* or *ex vivo* T-cell depletion, presence of severe GVHD and use of HLA mismatched grafts, and active surveillance for EBV reactivation in these high-risk settings with initiation of preemptive therapy is generally recommended. Secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) can be seen in 5–15% of autologous HCT recipients after a latency period of 2–5 years [17]. Characteristic cytogenetic abnormalities (e.g., balanced translocations to 11q23, monosomy of 5q and 7q) and multiple chromosomal aberrations are frequent in secondary MDS/AML and older age at transplant, use of alkylating agents prior to and during HCT, and use of TBI increases its risks. Generally, there is a latency period of 3–5 years before secondary solid cancers occur after HCT, but subsequently, their incidence continues to rise with time and a plateau in their incidence has not been observed. The reported cumulative incidence is 1–2% at 5 years, 2–6% at 10 years, and 4–15% at 15 years after HCT [17,19–21]. Lifelong cancer screening for all HCT survivors according to established guidelines is recommended [4,5,22].

Organ-specific complications

In general, any organ can be affected and major transplant-related exposures for delayed organ-specific complications include the use of TBI in conditioning, GVHD, and protracted use of corticosteroids or calcineurin inhibitors. The risk for most organ specific late complications continues to increase with time, and continued active surveillance for these problems is indicated in all HCT survivors. Table 2 highlights common complications and evaluations for their screening and prevention. For an individual patient, pre-, peri-, and post-transplant exposures need to be considered in establishing a survivorship care plan that focuses on preventive and screening practices that would be recommended based on that patient's exposures and risk factors. For example, the profile of late complications, their risk factors, and recommended long-term follow-up evaluations would be different for a young child who has received an autologous HCT without TBI for neuroblastoma compared to an older patient who has received an allogeneic HCT using TBI-based conditioning for MDS and has developed chronic GVHD. Therefore, the emphasis should be on exposures and risk factors such that the long-term follow-up care can be optimized and individualized to specific patient needs.

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