



Managing Survivorship after Hematopoietic Cell Transplantation

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Abstract

Purpose of Review With improvement in survival after hematopoietic cell transplantation (HCT), it has become important to focus on the late complications experienced by the survivors that may lead to late mortality and morbidity to be able to provide patient-centered care across the transplant continuum. The goals of this article are to describe the status of literature on late complications in HCT survivors; offer a brief overview of the status of the screening, prevention, and management of these complications; and identify opportunities for future practice and research.

Recent Findings This is an exciting time for the field with increasing awareness about survivorship issues. Studies are moving beyond description to examining pathogenesis of these late complications and identifying biomarkers. The eventual goal is to promote changes in our transplant techniques to decrease the incidence of these complications as well as help develop interventions targeting these late effects. There is also an emphasis on improving health care delivery models to provide optimal post-HCT management for medical and psychosocial complications through close coordination between multiple stakeholders and leveraging technology to help address the barriers in delivery of care to fulfill the unmet needs in this area.

Summary The increasing population of HCT survivors with their burden of late effects underscores the need for concerted efforts to improve long-term medical and psychosocial outcomes for this group.

Keywords Hematopoietic cell transplantation · Survivorship · Late effects

Introduction

The current population of > 100,000 hematopoietic cell transplantation (HCT) survivors in the USA is projected to increase fivefold by 2030, with 14% of the population with age < 18 years and 25% with age ≥ 60 years at transplantation [1]. The physical, psychological, and social sequelae of HCT have an adverse impact on mortality and morbidity of these survivors even many years after HCT [2–8, 9••, 10].

The goal of this article is to summarize the current information about medical and psychosocial complications and review the current status of screening and management of these complications to facilitate better care of HCT survivors. I also briefly overview the unique physiological and psychosocial challenges of survivorship

in the pediatric and adolescent young adult population. I do not discuss chronic graft vs host disease which is a major complication after allogeneic HCT and a risk factor for a host of other sequelae, in detail in this review. I also highlight the barriers and models of care delivery to address these complications and identify areas of focus for future research priorities and clinical practice.

Medical Complications After HCT

There is an extensive literature on the occurrence of late medical complications/chronic health conditions including diseases of the cardiovascular, pulmonary, and endocrine systems, renal and hepatic dysfunction, infertility, iron overload, bone and metabolic problems, infections, and secondary cancers after HCT. Additionally, there are abundant reports on physical sequelae affecting the survivors such as chronic pain, fatigue, sexual dysfunction, and cognitive impairment. Table 1 outlines these complications, frequency of occurrence, and risk-adapted screening measures.

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Table 1 Late complications after hematopoietic cell transplantation

Late complications	Frequency	Risk-adapted screening
Cardiovascular	Up to 15%	<ul style="list-style-type: none"> • BMI assessments • Lipid profile assessments • Echo/EKG
Metabolic syndrome	31 to 49%	<ul style="list-style-type: none"> • BMI assessments • Lipid profile assessments • Blood pressure assessments
Kidney disease	4 to 80%	<ul style="list-style-type: none"> • Blood pressure assessments • Renal function/urinalysis
Endocrine and gonadal dysfunction	5 to 40%	<ul style="list-style-type: none"> • Thyroid function tests • LH/FSH/testosterone and estrogen levels
Infection	Variable depending on the type of infection	<ul style="list-style-type: none"> • Lymphocyte subsets • Immunoglobulin levels • Hepatitis and HIV tests • CMV/EBV monitoring • Fungal tests if high suspicion
Liver complications	4 to 80%	<ul style="list-style-type: none"> • Liver function tests • Viral testing • Liver biopsy in those at risk
Iron overload	25 to 50%	<ul style="list-style-type: none"> • Serum ferritin • MRI liver
Pulmonary complications	30 to 60%	<ul style="list-style-type: none"> • Pulmonary function tests • Radiologic evaluation as needed
Bone disease	Up to 50%	<ul style="list-style-type: none"> • DEXA scan • MRI for avascular necrosis
Secondary cancers	2 to 11%	<ul style="list-style-type: none"> • History and physical • Breast MRI/mammogram • Skin exam • Colonoscopy
Ocular problems	4 to 50%	<ul style="list-style-type: none"> • Ophthalmologic testing including Schirmer's
Oral complications	Up to 80%	<ul style="list-style-type: none"> • Dental examination
Neuropsychological	10 to 40%	<ul style="list-style-type: none"> • Neuropsychological testing • MRI brain as indicated
Psychological problems	12 to 40%	<ul style="list-style-type: none"> • Clinical assessment/distress testing
Sexual dysfunction	Up to 70%	<ul style="list-style-type: none"> • Genital exam • Questionnaires for sexual dysfunction
Sleep problems	14 to 50%	<ul style="list-style-type: none"> • Screen for sleep disorders

Abbreviations: *BMI* body mass index, *EKG* electrocardiogram, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *HIV* human immunodeficiency virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *MRI* magnetic resonance imaging

Figure 1 highlights the traditionally known risk factors associated with these late effects. The spectrum of late effects may continue to evolve along with changes in the conditioning regimens such as higher use of reduced intensity regimens, decreased use of TBI-based regimens, donor sources, and GVHD prophylaxis regimens such as use of post-transplant cyclophosphamide [11, 4]. Studies are starting to examine the mechanistic aspects of these late effects including the role of microbiome, accelerated aging with telomere shortening, shift in body fat distribution, endothelial dysfunction, and chronic inflammation/immune dysregulation in producing these late effects [12–16]. Improved knowledge about underlying mechanism can inform the development of personalized risk-reduction

strategies and set the stage for much-needed tailored interventions to prevent and treat these complications.

Psychosocial Complications After HCT

Psychological sequelae following allogeneic HCT have been described in detail such as depression, anxiety, perceived stress, adverse coping, social isolation, poor mental functioning, financial burden, and inability to return to work. Table 2 describes the prevalence and risk factors for these complications. The recent COVID-19 pandemic has exacerbated the susceptibility to adverse biobehavioral sequelae [17]. HCT survivors and their caregivers

Fig. 1 Risk factors that influence occurrence and prevalence of late effects after survivorship

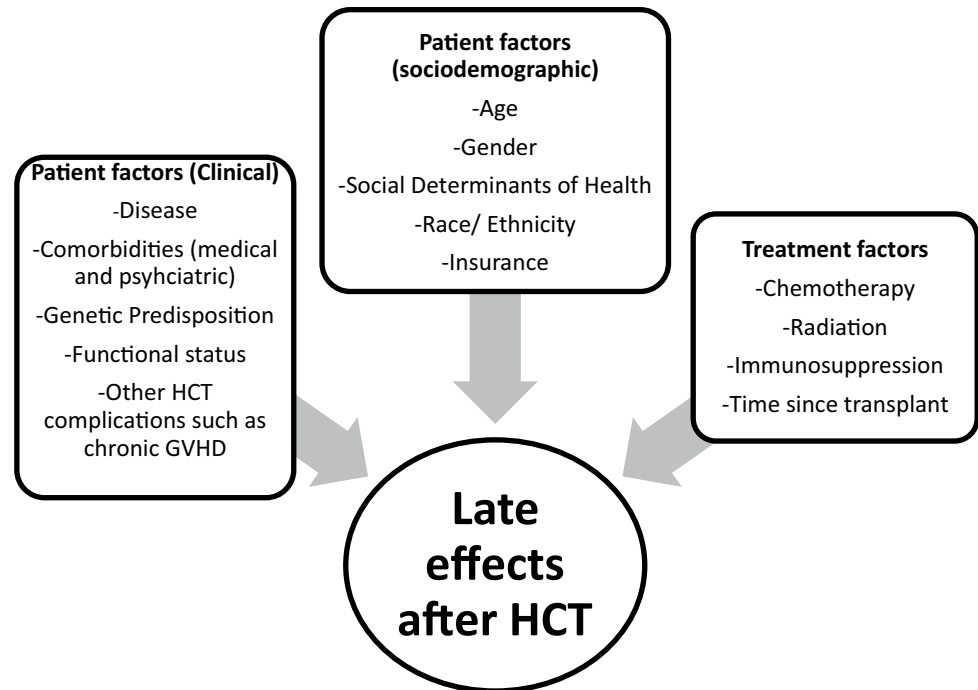


Table 2 Prevalence and risk factors for psychosocial problems after HCT

Complication	Prevalence	Risk factors
Depression/anxiety	5 to 40%	<ul style="list-style-type: none"> • Younger age • Female sex • Lower household income • Poor health status • Use of steroids • Poor social support
Post-traumatic stress disorder	3 to 19%	<ul style="list-style-type: none"> • History of depression or anxiety at HCT • Younger age • Marital status-single • Low social support
Psychologic distress	3 to 40%	<ul style="list-style-type: none"> • Active chronic GVHD • Use of steroids • Lower household income • Low social support
Financial burden	20 to 70%	<ul style="list-style-type: none"> • Younger age • Low household income • Poor physical and mental functioning • Chronic GVHD
Inability to return to work	15 to 40%	<ul style="list-style-type: none"> • Lower physical function • Multimorbidity • Female sex • Use of peripheral blood as stem cell source • Pre-HCT unemployment/disability • Active GVHD

Abbreviations: *HCT* hematopoietic cell transplantation, *GVHD* graft vs. host disease

have identified these concerns as critical focus areas to be focused on during care delivery for post-HCT period [18].

A multitude of studies has reported the impact of these medical and psychosocial complications on the quality

of life for HCT survivors. Guidelines for post-HCT care recommend periodic screening and counseling for psychosocial difficulties and deficits especially depression after transplant, at 6 and 12 months, and annually

thereafter [19]. They also recommend regular assessments of spousal/caregiver psychological adjustment and family functioning as a caregiver is now identified as an integral part of a patient's transplant journey. Universal screening for financial distress should be added to the usual patient-reported outcomes assessments since it is prevalent and affects patient outcomes [20].

Specific Considerations for Pediatric/Adolescent and Young Adult (AYA) Populations

Pediatric and AYA patients and survivors of pediatric HCT have a high burden of chronic health conditions such as endocrine abnormalities including growth hormone deficiency, impaired fertility, neurocognitive deficits, cardiopulmonary and renal problems, infectious complications, and secondary cancers [21]. Though good outcomes have been reported after allogeneic HCT in pediatric and adolescent patients with non-malignant disorders, the risk for secondary neoplasms is high especially in patients with Fanconi's Anemia and marrow failure syndromes [22].

Adverse psychosocial outcomes including greater symptom burden, cognitive and academic deficits, depression, anxiety, and post-traumatic stress are also quite common in this vulnerable group of survivors as compared to healthy peers. HCT and its sequelae may limit the AYA survivors to achieve milestones such as graduating college, selecting a career, establishing employment, and achieving socioeconomic independence from parents [23, 24].

The unique challenges of pediatric and AYA survivors of HCT indicate the need to develop screening programs and interventions specifically tailored to them [25–27].

Prevention and Treatment of Late Effects After HCT

Many large studies show that the life expectancy for HCT survivors continues to lower than that of their age- and gender-matched peers from the general population indicating the high burden of late effects [5, 28]. This underscores the need for evidence-based preventive and therapeutic interventions specific for HCT survivors with the goal of mitigating the risks and improving outcomes following HCT. Comprehensive guidelines for screening and prevention have been published and are in the process of being updated soon [19]. A recent trial examining the role of individualized survivorship care plans generated using registry data showed reduced distress and improved mental domain of quality of life among 1–5-year HCT survivors [29].

Table 3 describes current preventive practices and treatments for these complications. Continued surveillance for specific complications for early diagnosis and treatment, adequate psychosocial support, and encouraging healthy lifestyle behaviors may help in reducing the long-term morbidity associated with these complications. Vaccinations are an important component of the preventive care for these patients. Vaccines for SARS-CoV-2 likely have positive risk benefit but more studies are needed to understand short and long-term protection with it.

Survivorship Care Delivery Models

Given the increased risk of developing a wide range of adverse late effects, there is an urgent need to develop and implement effective models for delivering survivorship care. The overall goal of survivorship care is early diagnosis of treatment-related complications, potentially allowing for early intervention leading to reduction in morbidity and mortality. These models should be based on the three-step approach to prevention for these complications. The first step or primary prevention would include health promotion activities including using transplant as a “teachable moment” for promoting healthy behaviors, increasing awareness, and preemptively trying to address risk factors including altering therapeutic exposures for these complications. Secondary prevention would include screening for early detection of late effects and instituting appropriate treatments. Screening should be individualized based on sociodemographic and clinical factors. Tertiary prevention would be targeted at decreasing the morbidity and mortality from these complications such as rehabilitation strategies and disability limitation.

Implementing the above approach requires integration of all the relevant stakeholders such as transplant team, primary care or oncology physician, psychologist or psychiatrist, other medical specialists, social workers, and financial counselors. Figure 2 outlines the barriers in the ability to deliver accessible, equitable, and affordable survivorship care. Establishment of multidisciplinary long-term follow-up clinic can help deliver guideline-driven screening and management of late effects; however, the challenges and lack of standardization for such clinics was highlighted by a survey done by the American Society for Blood and Marrow Transplantation (ASBMT) Practice Guidelines Committee [30]. A more recent survey carried out by the British Society of Blood and Marrow Transplantation and Cellular Therapy data registry reflected on growth of survivorship efforts possibly driven by increasing recognition of late effects and survivorship by clinicians, health service policy, and JACIE accreditation standards mandating survivorship care though challenges specially with resource constraints and availability of specialists persist [31••].

Table 3 Prevention and treatment for late complications

Late complication	Prevention	Treatment
Cardiovascular	<ul style="list-style-type: none"> • Reduce modifiable risk factors, such as obesity, smoking, hypertension, and dyslipidemia 	<ul style="list-style-type: none"> • Angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors and beta blockers
Metabolic syndrome	<ul style="list-style-type: none"> • Lifestyle modifications such as diet (low fat, high fiber), exercise (or other regular physical activities), weight reduction, smoking cessation, and limiting alcohol intake 	<ul style="list-style-type: none"> • Lipid-lowering therapy especially fibrate • Nicotinic acid for high triglycerides • Treat high BP • Treat hyperglycemia
Kidney disease	<ul style="list-style-type: none"> • Avoid nephrotoxins 	<ul style="list-style-type: none"> • Taper or stop calcineurin inhibitors • Treat high BP
Endocrine and gonadal dysfunction		<ul style="list-style-type: none"> • Treat hypothyroidism • Testosterone replacement • Hormone replacement for premenopausal women • Consider stress doses steroids during acute illness for patients on chronic steroids
Infection	<ul style="list-style-type: none"> • Preventive antimicrobials • Endocarditis prophylaxis • Vaccinations • Intravenous immunoglobulins 	<ul style="list-style-type: none"> • Treatment of specific infections
Liver complications	<ul style="list-style-type: none"> • Antiviral agents for hepatitis • Minimize hepatotoxins 	<ul style="list-style-type: none"> • Treat specific infections
Iron overload	<ul style="list-style-type: none"> • Iron free vitamin supplementation • Minimize transfusion by using erythropoietin supplementation if feasible 	<ul style="list-style-type: none"> • Treat iron overload with phlebotomy or chelators
Pulmonary complications	<ul style="list-style-type: none"> • Avoid smoking • Influenza and pneumococcal vaccines • Prophylactic antimicrobials 	<ul style="list-style-type: none"> • Prompt treatment of pulmonary infections • Steroids and bronchodilators
Bone disease	<ul style="list-style-type: none"> • Encourage physical activity • Calcium and vitamin D intake • Hormone replacement 	<ul style="list-style-type: none"> • Bisphosphonates • Pain management and surgery for avascular necrosis • Treatment of fractures
Secondary cancers	<ul style="list-style-type: none"> • Avoid high-risk behaviors • Follow age and gender appropriate general population screening guidelines • Vaccinations (such as human papillomavirus vaccine) 	<ul style="list-style-type: none"> • Treatment plan for specific cancer
Ocular problems	<ul style="list-style-type: none"> • Lens shielding during TBI 	<ul style="list-style-type: none"> • Treatment of specific complication
Oral complications	<ul style="list-style-type: none"> • Prevention of infection • Maintain good oral hygiene • Avoidance of sugar-containing drinks 	<ul style="list-style-type: none"> • Use of sialogogues and fluoride supplements
Neuropsychological	<ul style="list-style-type: none"> • Avoid neurotoxic agents 	<ul style="list-style-type: none"> • Medications, such as methylphenidate or modafinil • Rehabilitation strategies
Psychological problems	<ul style="list-style-type: none"> • Exercise • Psychotherapy • Integrative therapies 	<ul style="list-style-type: none"> • Pharmacologic agents for depression/anxiety/fatigue/pain • Cognitive behavioral therapy
Sexual dysfunction	<ul style="list-style-type: none"> • Hormone replacement • Treat depression 	<ul style="list-style-type: none"> • Multimodal interventions
Sleep problems	<ul style="list-style-type: none"> • Encourage sleep hygiene 	<ul style="list-style-type: none"> • Pharmacologic agents • Multimodal exercise interventions

Abbreviations: *BP* blood pressure, *TBI* total body irradiation

With the increased focus on virtual medicine because of the pandemic, there is an opportunity to leverage virtual technologies to deliver well-rounded risk stratified survivorship care to HCT survivors incorporating psychosocial screening and interventions [32]. This can help encourage health-related self-efficacy in patients,

increase health system capacity, and promote adaptive HCT survivorship. Online programs may help address some of the barriers in providing medical care such as distance, varying needs and lack of standard follow-up care. Recently, the INSPIRE (an INternet-based Survivorship Program with Information and Resources) study found no differences

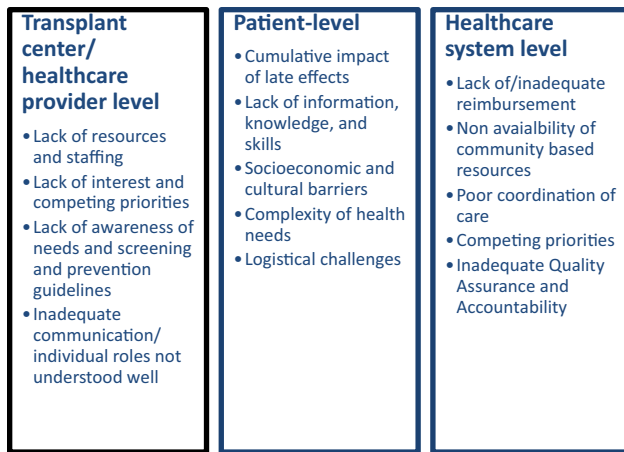


Fig. 2 Barriers to transplant survivorship care delivery

between the study arms on the primary endpoint of aggregated outcomes of cancer and treatment distress, depressive symptoms, physical dysfunction, and fatigue though there was significant improvement in distress alone for those in the INSPIRE + problem-solving treatment arm [33].

Areas of Focus for Future Research Priorities and Clinical Practice

Future studies in large, representative samples with more focus on special populations—children, adolescent and young adults, older adults, racial/ethnic minority patients are needed to describe the changing landscape of late effects with the ongoing changes in transplant practice. MOSA study is a great example of a well-designed matched cohort study of late effects after HCT and includes a matched cohort representing the general population allowing direct comparisons [34•]. There is an urgent need to identify biomarkers for detection and prognostication of the late effects. Leveraging Artificial Intelligence and Machine Learning techniques develop predictive models for risk using transplant- or patient-related factors including social determinants of health can help with earlier diagnoses of some of these late effects, improve clinical decision-making, and ultimately lead to better health outcomes for HCT survivors. More research is also required to develop and test effective ways of reducing long-term toxicity of HCT, early prevention and rehabilitation strategies, and social and financial support (emotional, informational, and logistical) interventions. HCT caregivers are a vulnerable group with persistent unmet psychosocial, medical, financial, and daily activity needs throughout the transplant continuum. Research is needed to address their needs and better support them to improve outcomes for HCT survivors, caregivers, and survivor-caregiver dyads.

In routine clinical practice, there is a compelling need to create robust community-based resources that coordinate with transplant centers to help deliver care at point of need to HCT survivors. Workforce recruitment/retention/training and infrastructure development is essential to provide optimal care and address the needs of a growing pool of HCT survivors. Educational initiatives to improve awareness about the late effects targeting different stakeholders can help improve engagement and improve resilience and coping. Partnerships with payers will be required to test and implement new models of care delivery for HCT survivors including application of technology or use of patient navigators.

Conclusions

With advances in treatment practices and survival after HCT, there is an increasing recognition of the medical and psychosocial complications which continue to increase in incidence after HCT. Multiple initiatives in the field of HCT are beginning to identify the gaps in practice and research and recognize the importance of integrating patient-centered outcome screening and interventions with the goal to improve long-term health outcomes after HCT [18, 35]. The role of educational initiatives to empower and engage patients and their caregivers in improving their psychosocial health is extremely valuable. An individualized, risk-adapted, and multidisciplinary approach is required for follow-up care for HCT survivors.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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