Delivering Care to Long-Term Adult Survivors of Hematopoietic Cell Transplantation

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ABSTRACT

This review highlights long-term and late consequences of hematopoietic cell transplantation (HCT) as well as strategies to manage or prevent complications that are more prevalent after HCT than most other cancer treatments. Chronic graft-versus-host disease stands out as a unique late effect of allogeneic HCT that is not seen after other types of cancer treatment. However, many other complications seen after solid tumor treatments are also common after HCT, including infections, second cancers, bone loss, and cardiovascular, pulmonary, renal, and endocrine dysfunction. Symptoms and syndromes that are reported after HCT include sexual dysfunction, cognitive problems, fatigue, insomnia, musculoskeletal symptoms, emotional distress, anger, and depression. Addressing these complex potential or actual complications requires diligent routine health care to intervene early or, when possible, to prevent late complications. To accomplish early detection and prevention of life-threatening complications, HCT survivors should undergo an annual comprehensive physical examination that includes screening for functional and psychosocial consequences of treatment and encouraging healthy lifestyle behaviors. Clinicians can link survivors to numerous online, print, and video resources to help them advocate for their health needs.

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INTRODUCTION

Among adult cancer treatments, hematopoietic cell transplantation (HCT) is notable for high rates of long-term and late effects. Chemotherapy agents used in preparative regimens for HCT are similar to those used in other cancer treatments. In HCT, however, these treatments are often administered at myeloablative doses within a 1-week time span and may be accompanied by total-body irradiation. Most HCT recipients have had previous cancer treatment that adds to the cumulative exposure to chemotherapy and may account for some of the consequences attributed to HCT long-term effects. The goal of this article is to summarize the long-term and late complications of HCT as a framework for the processes we propose for enhancing the delivery of care to HCT survivors.

Major progress has been made in improving survival after HCT, particularly for allogeneic recipients.¹⁻³ Similarly, toxicities during treatment have been reduced by improved supportive care, thereby making both autologous and allogeneic transplantation more widely available, even to older populations.^{2,3} As a result, more than 10,000 people undergo autologous transplantation and more than 6,000 undergo allogeneic transplantation annually in the United States.³ These survivors have a long-

term elevated probability of mortality, relative to age-adjusted population norms. This risk extends throughout life after transplantation, with a four- to nine-fold greater mortality risk, even for those who have survived for more than 5 years.⁴⁻⁶ These risks are related to the long-term complications after HCT (Fig 1) and therefore highlight the importance of ongoing health surveillance. Two thirds of adult long-term survivors have at least one chronic health condition, and approximately 20% have at least one severe or life-threatening condition.⁷

Chronic graft-versus-host disease (GVHD) represents a unique late effect of allogeneic HCT that is not seen after other types of cancer treatment. This autoimmune-like complication can affect multiple organ systems and causes some of the most severe deficits in medical, symptom, and quality of life outcomes after HCT. Nonetheless, on average, physical and emotional function after resolution of chronic GVHD are similar to what is reported by patients who never had the disease.^{8,9}

Much of the research on long-term and late effects has been performed among patients receiving myeloablative treatments. However, allogeneic transplantation is increasingly performed with non-myeloablative therapies, thereby reducing acute toxicities. This approach relies on immunologic effects of donor cells to eliminate malignant cells in the

Fig 1. Subsequent causes of death for adult (A) allogeneic and (B) autologous transplant recipients who survived without recurrent malignancy at least 5 years after transplantation. There were 219 subsequent deaths among 1,625 allogeneic patients and 65 subsequent deaths among 342 autologous patients. All patients were treated at Fred Hutchinson Cancer Research Center from 1970 through 2002. GVHD, graft-versus-host disease.

recipient. Late complications of HCT with nonablative treatments are generally similar to those observed with myeloablative treatments, but precise estimates await longer follow-up among more patients.

MEDICAL COMPLICATIONS AFTER HCT

Patients surviving after autologous or allogeneic HCT have higher risks of medical problems compared with the general population or other cancer survivors.⁴⁻⁶ These problems include infections, second cancers, bone loss, and cardiovascular, pulmonary, renal, and endocrine dysfunction.^{7,10-12} Many factors contribute to the risks of late complications after HCT, including the antineoplastic treatments received before HCT, damage or adverse effects caused by the underlying disease, the chemotherapy and irradiation regimens used for conditioning before HCT, and medications such as corticosteroids, antibiotics, or calcineurin inhibitors used for years after HCT. Organ damage from infections or other complications during or after the transplantation process contribute to the increased risk of mortality.

Recent reviews have summarized the incidence of late complications after HCT, associated risk factors, recommended prevention

strategies, screening tests that can be used for early detection of complications, and management approaches for treatment of specific problems.^{13,14} Other articles in *Journal of Clinical Oncology (JCO)* describe many of these complications, which also occur in HCT survivors. Here we focus on complications that have not been associated with other types of cancer treatment. A number of these problems are related to chronic GVHD and the slow pace of immune reconstitution after HCT.

Chronic GVHD

Chronic GVHD occurs in 10% to 50% of those undergoing allogeneic HCT, with a median onset at 4 to 6 months after transplantation and a median treatment duration of 2 to 3 years.¹⁵ Chronic GVHD is usually treated with a calcineurin inhibitor, such as cyclosporine or tacrolimus, together with prednisone initially at 1 mg/kg per day, followed by tapering to the lowest dose that controls manifestations of the disease. Long-term high-dose glucocorticoid treatment for chronic GVHD has a profound adverse effect on recovery. In particular, patients treated for chronic GVHD require monitoring and management of hyperglycemia, hypertension, hyperlipidemia, renal impairment, and osteoporosis.¹⁶ Steroid treatment also can cause avascular necrosis in joints, bone mineral density loss, and other long-term effects. Muscle loss can be reduced with an exercise program. Alternate-day administration of prednisone is an important strategy used to minimize many harmful effects of treatment. This approach can be especially useful in minimizing the risk of adrenal insufficiency when steroid treatment is withdrawn at the end of treatment for chronic GVHD.

Patients with chronic GVHD require prophylactic administration of medications to prevent opportunistic infection with encapsulated organisms, *Pneumocystis jirovecii*, and varicella virus, throughout the duration of immunosuppressive treatment. Patients with previous cytomegalovirus (CMV) infection may require monitoring for viral reactivation. When CMV reactivation is detected, pre-emptive treatment is needed to prevent progression to CMV disease.

Endocrine Effects of HCT

The spectrum of late effects shifts over time after HCT. Concerns about chronic GVHD and infection wane after approximately 3 to 5 years in most patients but are replaced by other concerns that extend throughout life. These concerns include endocrine dysfunction, cardiovascular disease, and second malignancies, which are risks for both autologous and allogeneic patients. Approximately 10% to 15% of patients treated with high-dose fractionated total-body irradiation or chemotherapy-based pretransplantation conditioning regimens develop hypothyroidism at a median of 4 years after HCT.¹⁷ Patients should be screened for thyroid-stimulating hormone elevation at annual intervals, and replacement therapy should be started if the diagnosis is confirmed. High-dose conditioning regimens cause gonadal dysfunction in most patients. Most men have azoospermia, although testosterone concentrations are often normal. In some men, even low normal levels of testosterone may be associated with poor libido or erectile problems. Women rarely retain ovarian function after high-dose treatment. Premature menopause can be treated with hormone replacement therapy until the age of normal menopause, in the absence of contraindications such as cardiovascular disease, liver disease, or elevated breast cancer risk.

Cardiovascular Risks

Recent reports have described increased risks of premature cardiovascular disease after HCT.¹⁸⁻²¹ The increased risks include cardiovascular death, ischemic heart disease, cardiomyopathy or heart failure, stroke, vascular disease, and rhythm disorder. Patients younger than 60 years of age have increased risks in comparison with age- and sex-matched controls, more so than those older than age 60 years. In addition, the risks of cardiovascular complications are exacerbated in patients who had recurrent malignancy after HCT.²⁰ Risks of cardiovascular disease are likely to be attenuated by treatment for hypertension and hyperlipidemia.²² Patients should be encouraged to participate in preventing cardiovascular complications through adherence to an exercise program and healthy diet.

Screening and Surveillance

General population recommendations for cancer screening are appropriate for patients who have undergone HCT, except that mammographic screening should begin at age 25 years or at 8 years after irradiation to fields involving the breast, whichever occurs later, but no later than age 40 years. Particular attention should be given to the skin, oropharynx, and thyroid during physical examination, because cancer rates in these organs are increased in HCT survivors.^{23,24} Patients should be reminded to avoid ultraviolet exposure to decrease the risk of skin cancer, and smoking cessation programs should be prescribed for patients who use tobacco.

Once complications are detected, the management strategies for most conditions are similar to approaches used for the general population, and patients can be treated by nontransplantation oncologists or primary care physicians. Those with chronic GVHD, who may benefit from evaluation by transplantation specialists with expertise in management of this complication, are the exception.

Vaccinations

After HCT, patients can lose immunity to previous vaccinations. A comprehensive schedule of immunizations is used to restore protection against vaccine-preventable diseases.^{25,26} The schedule of immunization is similar to the program used for infants and children, except that live vaccines, such as measles, mumps, and rubella, attenuated influenza, or varicella zoster virus vaccines, should not be used if the patient has recently been receiving immune suppressive medications.

SYMPTOMS AND SYNDROMES

Frequent long-term symptoms after other cancer treatments occur even more often after HCT. These include sexual dysfunction, cognitive problems, fatigue, musculoskeletal symptoms that include cramps, myalgias, arthralgias and weakness, insomnia, emotional distress, and depression. Most survivors, even with these symptoms, adapt to the changes in their lives and maintain a high quality of life. A high proportion return to full-time work.^{9,27}

Sexual Function

Impaired sexual function causes problems for both men and women after HCT (Fig 2).²⁸⁻³⁰ Most men recover when testosterone levels return to normal by 1 to 2 years after treatment. In contrast, up to 45% of women do not return to sexual activity at any time after

Fig 2. Overall quality and quantity of sexual function over 5 years from before to after hematopoietic cell transplantation, with case-matched controls at 5 years and including non-relapse-free survivors (non-RFS) before transplantation. Data adapted.²⁸

treatment.²⁸ Interventions for women ideally start during the first year after transplantation, because hypothalamic-pituitary-gonadal axis hormone levels generally do not return to normal after myeloablative treatment. Hormone therapy is crucial for those who are prematurely postmenopausal, not only for bone health, but also because lack of ovarian function rarely allows return to normal sexual function in the absence of hormone therapy. Sexual satisfaction and improved function can be facilitated by relatively brief interventions. These include communication training between sexual partners to address physical changes and altered relationships, behavioral strategies that prioritize and plan time for sexual intimacy, and the use of water- or silicone-based lubricants for women. An annual gynecologic examination is necessary to evaluate vaginal changes that might need intervention, screen for cancers or chronic GVHD, and assess any pain or postcoital bleeding. For men, testosterone and follicle-stimulating hormone concentrations should be measured if libido or erectile dysfunction inhibits sexual satisfaction. Testosterone replacement and phosphodiesterase type 5 inhibitors can be considered if not contraindicated by cardiovascular or other safety considerations. Concerns about fertility should be discussed with survivors who are interested in exploring their parenthood options.

Cognitive Function

Mild neurocognitive deficits remain even after 5 years in approximately 25% of those who undergo myeloablative HCT; for another 15%, these deficits will be moderate to severe.³¹ Short-term memory deficits that predate HCT and motor dexterity are the most common areas of long-term difficulty. Although self-report is not a reliable indicator of neurocognitive dysfunction, complaints that memory or concentration difficulties are disrupting quality of life more than 1 year after treatment warrant neuropsychological and mental health evaluation. No strategies thus far have been shown to prevent or reverse these deficits, although psychostimulants have shown some promise in improving cognitive function and in alleviating severe fatigue, which may limit cognitive capacity. Cognitive rehabilitation and behavioral strategies have helped survivors compensate for limitations.³²

Fatigue and Musculoskeletal Symptoms

Up to 70% of patients surviving for at least 5 years after HCT report moderate to severe symptoms of fatigue, muscle weakness, cramps, myalgias, or arthralgias.³³⁻³⁵ Exercise improves physiologic outcomes after HCT and reduces fatigue as well as some musculoskeletal symptoms in survivors after other cancer treatments.³⁶⁻³⁸ Fatigue has many potential causes, and symptoms that worsen or do not resolve with exercise require further evaluation.

Psychological Adjustment

Those who undergo HCT are highly resilient, and most cope well with the demands of treatment and survivorship. At the same time, emotional demands on survivors are wide ranging and include the stress of living with uncertainty, fear of relapse, hypervigilance about symptoms, anxiety with surveillance testing, clinical and subclinical depression, anger, and post-traumatic stress. At the other end of the emotional continuum, post-traumatic growth and new appreciation for life are reported by up to 90% of survivors. Emotional recovery is a longer process than physical recovery after HCT, taking 2 years or even much longer, particularly in patients with persistent chronic GVHD.^{9,39} Approximately 20% to 45% of long-term survivors have at least some emotional distress.^{40,41} Clinical depression is reported in 9% to 20% of long-term survivors.⁴²⁻⁴⁵ Those more vulnerable to emotional difficulties long term after HCT include survivors with more traumatic transplantation experience, less than college education, lower income, and poorer mental health before HCT.^{46,47} Previous medical factors have little influence on later psychosocial outcomes, whereas persisting chronic GVHD and poorer health at the time of assessment are associated with more severe psychological symptoms.

Less than half of survivors with psychological needs are treated for these problems.⁴⁸ Unfortunately, those with greater need for services have more social, emotional, and financial constraints as barriers to care and are less likely to mention their needs during medical appointments. For this reason, psychosocial symptoms, sexuality, and other persistent symptoms should be addressed yearly. Few treatments specifically targeted to psychosocial needs after HCT have been tested. Telephone-based cognitive behavioral treatment has improved depression, general distress, and post-traumatic stress symptoms in HCT survivors.⁴⁹

HEALTH AND LIFESTYLE IMPACTS

Health behaviors, including exercise, diet, obesity, smoking, alcohol use, and health surveillance behaviors, affect not only quality of survival but also the risk of recurrence and mortality, as demonstrated in many cancer survivorship studies. Exercise programs have demonstrated clear benefits during the first several months after HCT, although no adequately powered studies have tested outcomes specifically in HCT long-term survivors.^{36,50,51} Obesity confers added risk for late effects of diabetes, metabolic syndrome, and cardiovascular disease after transplantation.^{20,52} High-risk behaviors such as smoking and alcohol use may be less common in HCT survivors than in the general population, but they are more likely in younger adult survivors. These problems require attention, because they increase the risks of second cancers and poorer health outcomes.⁵³ Transplantation survivors are at higher risk for medical problems, yet they are no

more likely than controls to maintain routine health screening, clearly indicating a need for improved education among both survivors and their providers.⁵¹ Recommendations for a healthy lifestyle and strategies for addressing these issues with survivors are similar to those used for other cancer survivors. Other articles in this special issue of *JCO* address these strategies in more detail.

DELIVERING SURVIVORSHIP CARE TO PATIENTS AFTER HCT

In 2012, Majhail et al¹³ updated the international recommendations for screening and preventive practices for HCT survivors. This publication and the supportive materials for physicians and patients are available through the National Marrow Donor Program to provide a timetable and guidance for survivorship care. Savani et al¹⁴ have also summarized specific suggestions for managing late effects in HCT survivors. These recommendations are intended to help both oncologists and primary care providers in addressing the medical and psychosocial needs of survivors after HCT.

As one example of how survivorship care can be delivered, we have found it helpful to apply the following systems organization principles to follow-up after HCT at the Fred Hutchinson Cancer Research Center:

One. We dedicate one visit each year to a comprehensive evaluation.⁵⁴ We begin with a thorough screening, from the patient's perspective, of recent medical history, symptoms and other complications, and health behaviors (Data Supplement). A focused evaluation ensures that all required tests are performed. Anchoring this evaluation to the date of transplantation or to the patient's birthday helps everyone to remember when tests should be performed, because testing that occurs throughout the year can be difficult to track. Components of a comprehensive medical evaluation include laboratory work (complete blood count with differential, liver function tests, creatinine, thyroid function tests), complete physical examination (blood pressure, evaluation for chronic GVHD, oral, skin, breast, and thyroid examinations as well as other cancer screening for second malignancies), other relevant monitoring tests (dual-emission x-ray absorptiometry bone scan, pulmonary function tests, iron studies), immunizations if needed (influenza A/B, childhood vaccinations), and evaluation by other specialties (ophthalmology, gynecology, and oral medicine). If testing is completed in advance of the visit, results will be available for review. Most of the visit can then be dedicated to discussing the results of testing and planning for subsequent assessment or the next routine testing. With this system, the results of the comprehensive testing, their interpretation, and the dates of next testing are available to all providers in one place in the medical record.

Two. Patients are concerned about finances and copayments, and we address these concerns proactively to ensure that patients follow through with recommended screening tests.¹¹ We educate survivors about their risks of medical complications to encourage them to report changes in their health and adhere to recommendations.^{5,51}

Three. Late effects are generally managed in a manner similar to the approach recommended for the general population. For late effects that are not reversible, we advocate aggressive symptom control and close monitoring.

Four. Ancillary services such as physical therapy, occupational therapy, neurocognitive training, rehabilitation services, and psychotherapy can improve functioning and teach patients valuable coping

strategies. Evaluation for these needs is an essential part of the comprehensive annual review. Brief online or paper screening measures of a patient's medical, physical, and emotional functioning can save time during the clinic visit to focus on specific areas of need (Data Supplement provides an example of our screening form).

Five. A summary of the evaluation and recommendations is sent to all other providers involved in the care of the patient. Interested patients also receive a copy of the letter.

Most HCT survivors want to understand and acquire the resources to advocate for their health needs. Programs designed to meet these needs include the Blood and Marrow Transplant Information Network, the National Marrow Donor Program, and the National Bone Marrow Transplant Link. Additional resources could emerge from recent studies that have evaluated the efficacy of telephone and online interventions in meeting the psychosocial and physical health needs of both adult survivors and the parents of pediatric patients.^{49,55,56}

CONCLUSIONS AND FUTURE DIRECTIONS IN HCT SURVIVORSHIP CARE AND OUTCOMES

The HCT survivor population is growing rapidly and is expected to have a relatively high rate of long-term and late complications. Opti-

mizing the health of this population requires application of known screening and management strategies as well as clear communication with survivors and their caregivers to ensure that everyone is aware of survivors' increased risks and the importance of specific health behaviors. Future research should focus on the best ways to achieve this communication and to support survivors who are usually under the care of internists and oncologists, despite the complex medical needs associated with transplantation. In addition, research should investigate whether changes in transplantation approaches can decrease the rates of long-term and late complications.

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