A Supplement to CareManagement

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Post-Allogeneic Hematopoietic Cell Transplantation:

Considerations for Case Management

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INTRODUCTION

Hematopoietic cell transplantation (HCT) is an intensive, potentially curative therapy for blood cancers, such as leukemia and lymphoma, and genetic and immune disorders. This treatment replaces diseased blood-forming cells in the blood and marrow with healthy cells. The treatment process is long, requiring weeks to months of preparation and months to years of recovery and follow-up care.

There are two main types of HCT: allogeneic and autologous. An allogeneic transplant uses the healthy cells from either a related or unrelated donor or an umbilical cord blood unit (CBU). For autologous transplant, the patient's own blood-forming cells are collected and returned to the patient after administration of high-dose chemotherapy. This article will describe the most prevalent physical and psychosocial complications 100+ days post-allogeneic HCT to help you identify patients at risk for complications and coordinate long-term follow-up care.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

1. Describe management of common physical complications post-allogeneic HCT.
2. Describe management of common psychosocial complications post-allogeneic HCT.
3. Identify HCT survivorship resources for patients and clinicians.

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GRAFT-VERSUS-HOST DISEASE (GVHD)

GVHD is the most common complication of allogeneic HCT. It happens when the donated immune system identifies the recipient's body as foreign and attacks it. Having a human leukocyte antigen (HLA) well-matched sibling donor helps to reduce the risk for GVHD, but it does not eliminate it. GVHD can cause mortality, morbidity, and quality of life issues for years after transplant.

There are two main classifications of GVHD: acute and chronic. Acute GVHD presents with different symptoms than chronic GVHD and often occurs during the first 100 days post-HCT. This discussion will focus on chronic GVHD, which most often presents during the first year but can develop any time after transplant. The body systems most commonly affected by chronic GVHD include the skin and mouth.[1,2] Severity can range from a mild rash affecting limited parts of the body or asymptomatic, white patches in the mouth to severe limitations in range of motion with widespread skin lesions or severe oral dryness and sores significantly reducing oral intake.[3]

Chronic GVHD affects up to half of allogeneic HCT recipients even with prophylaxis.[1,2] The source of blood-forming cells can affect a patient's risk for GVHD. Receiving cells from the donor's bone marrow, rather than peripheral blood stem cells (PBSC), may reduce the risk.[4,5] Additionally, using cells from an umbilical cord blood unit may also lower the risk.[2] Historically, cyclosporine or tacrolimus and methotrexate have been chronic GVHD prophylaxis mainstays.[6] More recent protocols aim to prevent chronic GVHD with T cell depletion, post-HCT cyclophosphamide, and rituximab.[7] Two examples of prospective randomized clinical trials within the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) are testing different drug and cell source combinations to help identify the best prophylaxis protocols.[8,9] Others outside of the BMT CTN are also researching novel strategies to lower the risk of GVHD.

After diagnosis, steroids are often the initial therapy. They are given with the intention to control symptoms and prevent more damage.[3] It may take months to years of treatment before an acceptable tolerance is developed between the donated immune system and the recipient's body. Thus, physicians must balance treatment against the immunosuppression and other toxicities caused by prolonged steroid use. And unfortunately, only about one-third of patients respond to steroids, so need for second-, third-, and fourth-line therapies is common.

Researchers are testing a variety of new and established agents for treatment of refractory chronic GVHD. One recent breakthrough is the discovery that ibrutinib is an effective treatment option. It targets donor B cells while preserving the antiviral effects of cytotoxic T cells, thus limiting overall immunosuppression.[10] The US Food & Drug Administration expanded approval of ibrutinib to include refractory chronic GVHD in August of 2017.[11]

POST-HCT CARE GUIDELINES

Even when patients are doing well after HCT, there are screening tests and immunization schedules to follow. Abbreviated guidelines are outlined in Table 1. For detailed guidelines, including special recommendations for populations such as pediatrics and patients with chronic GVHD, visit BeTheMatchClinical.org/guidelines. A patient-friendly version in plain language is available in print and online. The recommendations are based on the consensus publication by Majhail and colleagues.[14] The clinician version also includes a photo atlas to assist with screening and diagnosis of chronic GVHD.

PSYCHOSOCIAL COMPLICATIONS POST-ALLOGENEIC HCT

Anxiety and Depression

Research on psychological complications (such as distress, anxiety, depression, and post-traumatic stress disorder [PTSD]) after allogeneic HCT has shown varied prevalence rates, up to nearly 50%, depending on myriad factors including the population studied and time since transplant.[15-19] Risk factors for these complications also vary and may include chronic GVHD, persistent symptoms, younger age, and limited social support.[15-18] However, consistent psychosocial complications are identified that require routine screening and timely treatment. Signs and symptoms are no different from anxiety or depression outside of HCT survivorship, but they may be triggered by HCT-specific situations, such as treatment anniversaries, fear of relapse, or survivorship guilt.[20] Treatment options include medications and individual or group therapy led by professional mental health counselors with experience working with transplant survivors.[20]

Caregivers are also at risk for psychological complications after their loved one's transplant.[21,22] These symptoms can develop from the physical demands of caregiving, the emotional impact of bearing witness to a loved one's suffering, and a lack of self-care. Research suggests caregivers may even experience more complications and require more

TABLE 1 2018 Post-Transplant Care Recommendations

TISSUES/ORGANS	ANNUAL PREVENTIVE MEASURES FOR ALL ALLOGENEIC HCT RECIPIENTS
Immune system	• Immunizations post-transplant according to published guidelines
Ocular	• Routine ocular clinical symptom evaluation; prompt ophthalmologic examination in patients with visual symptoms
Oral	• Clinical oral assessment with particular attention to intra-oral malignancy evaluation • Check for history of xerostomia and high-risk habits and provide education about preventive oral health practices • Dental assessment. Perform thorough oral, head, and neck and dental exams
Pulmonary	• Routine clinical pulmonary evaluation • Assessment of tobacco use and counseling against smoking • Pulmonary function testing and focused radiologic assessment as clinically indicated for patients with symptoms or signs of lung compromise
Cardiovascular	• Routine clinical assessment of cardiovascular risk factors • Education and counseling on "heart healthy" lifestyle (regular exercise, healthy weight, no smoking, dietary counseling) • Early treatment of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia • Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines
Liver	• Liver function tests; may be performed more frequently as clinically indicated
Renal and genitourinary	• Blood pressure assessment with aggressive hypertension management • Assessment of renal function with serum creatinine, blood urea nitrogen (BUN) and urine protein. Further workup (kidney biopsy or renal ultrasound) for renal dysfunction as clinically indicated • Avoidance of nephrotoxins and consideration of early referral to a nephrologist for evaluation and treatment in patients with progressive chronic kidney disease
Muscle and connective tissue	• Physical activity counseling. Follow general population guidelines for physical activity
Mucocutaneous	• Education of patients to perform routine self-exam of skin and avoid excessive exposure to sunlight without adequate protection • Annual gynecologic exam in women
Skeletal	• Counseling about physical activity, vitamin D, and calcium supplementation to prevent loss of bone density
Nervous system	• Clinical evaluation for symptoms and signs of neurologic dysfunction. Diagnostic testing (eg, radiographs, nerve conduction studies) for those with symptoms or signs • Evaluation for changes in cognitive function, which may be subtle in adults
Endocrine	• Thyroid function testing—additional testing if relevant symptoms develop
Second cancers	• Counseling of patients about risks of secondary malignancies and encouragement to perform self-exam (eg, skin, testicles/genitalia); education about avoidance of high-risk behaviors (eg, smoking) • Screening for second cancers—following general population recommendations for cancer screening
Psychosocial and sexual	• Clinical assessment throughout recovery period, with mental health professional counseling recommended for those with recognized symptoms • Regular assessment of level of spousal/caregiver psychological adjustment and family functioning. Encouragement of engagement in robust support networks • Discussion with adults about sexual function
Fertility	• Sexual function assessment. Counseling of sexually active patients in the reproductive age group about birth control post-HCT
General health	• Recommended screening per general population

time for recovery than the transplant recipient.[21]

With appropriate and timely treatment of psychosocial distress, some transplant recipients and caregivers may experience enhanced coping and post-traumatic growth.[23,24] This may be evidenced by a greater appreciation for life, new priorities, and strengthened relationships.[23,24]

Financial Toxicity

Financial toxicity, hardship, and stress are terms to describe the effect of out-of-pocket costs for medical care and treatment on families.[25] This may be especially pronounced for allogeneic HCT recipients and their families because of the intensity and duration of HCT and post-HCT care. The treatment course involves many oral medications, frequent clinic visits, tests, exams, and procedures over the first 6 months post-HCT. With a limited number of hospitals providing this specialty care, many patients must travel long distances to undergo HCT, often having to temporarily relocate for a minimum of 100 days following HCT. The extended timeframe for post-HCT care and the need for a full-time caregiver often result in decreased income as one or more family members must reduce or eliminate work hours. One study found that the median out-of-pocket costs during the first 3 months after allogeneic HCT were $2,440, and roughly half of patients studied reported some type of financial burden, such as a decrease in household income over 50% or withdrawing money from retirement savings.[26] Complications, such as chronic GVHD, only increase the financial demands and extend the impact of financial hardship.

While a family's financial situation may improve over time after HCT with recipient and caregiver able to return to work, Denzen and colleagues[27] found that only two-thirds of families felt confident in meeting their household financial obligations 2 years after transplant.

RESOURCES FOR SUPPORT

Be The Match® Patient Support Center offers free one-on-one telephone counseling and support groups to help patients, caregivers, and families cope with the transplant process and recovery. Individual counseling is an opportunity for patients and their loved ones to get support during difficult times. A licensed social worker can help them to identify and resolve social and emotional problems related to illness and transplant recovery. Counseling can help improve coping skills and quality of life for your patients and their loved ones. Joining a support group may help patients and their loved ones connect with others, learn practical tips, and reduce stress. Support groups are safe spaces for them to share their fears, joys, and frustrations without feeling judged. To learn more about the free support programs for patients and families, call 1 (888) 999-6743, email patientinfo@nmdp.org, or visit BeTheMatch.org/one-on-one.

Be The Match also offers two grants for families after transplant. For both grants, patients must have had a transplant through the Be The Match Registry® and meet financial eligibility requirements. These grants can be paid directly to patients, a caregiver, or a family member.

Transplant Support Assistance Grant helps with direct and indirect costs of post-transplant care, including copays, transportation, gas, and housing. To qualify patients must have had transplant less than 12 months ago.

John and Caryn Camiolo Survivorship Grant helps with direct costs of medications and treatment that insurance does not cover. To qualify patients must have had transplant more than 1 year ago, have chronic GVHD, and receive care at the transplant center at least once a month.

A third grant, **the *Drs. Jeffrey and Isabel Chell Clinical Trials Travel Grant*** provides financial help to qualified patients who need help paying travel costs necessary to enroll in a clinical trial. This grant supports patients and families seeking trials through the Jason Carter Clinical Trials Program, offered by Be The Match. Transplant is not a requirement for this grant program. Learn more at JCCTP.org.

Applications for all three grants must be submitted by someone from the patient's transplant or clinical trials team. Learn more about the grants and access the applications.

CONCLUSION

All aspects of a patient's quality of life and all family members can be affected by the allogeneic HCT recovery process. While the benefit of transplant is great—extended life without disease—there are real risks. But these can be managed and in some cases prevented with well-coordinated care. ■

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Questions

1. Hematopoietic cell transplantation (HCT) is an intensive, potentially curative therapy for blood cancers, such as leukemia and lymphoma, and genetic and immune disorders.
a. True
b. False

2. Graft-versus-host disease (GVHD) is the most common complication of allogeneic HCT.
a. True
b. False

3. GVHD can cause:
a. Mortality
b. Morbidity
c. Quality-of-life issues
d. All of the above

4. There are two main classifications of GVHD: acute and chronic.
a. True
b. False

5. Symptoms of chronic GVHD may include:
a. Mild rash
b. Limitations in range of motion
c. Oral dryness
d. All of the above

6. Chronic GVHD affects up to how many allogeneic HCT recipients even when prophylaxis is provided?
a. 20%
b. 35%
c. 50%
d. 60%

7. The risk of chronic GVHD may be reduced by:
a. Receiving cells from the donor's bone marrow
b. Using cells from an umbilical cord blood unit
c. Receiving prophylaxis using cyclosporine or tacrolimus and methotrexate
d. All of the above

8. Annual preventive measures for all allogeneic HCT recipients include:
a. Clinical assessment of cardiovascular risk factors
b. Blood pressure assessment with aggressive hypertension management
c. Assessment of neurological dysfunction
d. All of the above

9. Risk factors for psychosocial complications post-allogeneic HCT may include:
a. Persistent symptoms
b. Younger age
c. Limited social support
d. All of the above

10. Contributing factors to psychological complications among caregivers after a loved one's transplant include:
a. Physical demands of caregiving
b. Emotional impact of witnessing the recipient's suffering
c. Lack of self-care
d. All of the above

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Answers

May 2018

1. Describe management of common physical complications post-allogeneic HCT. _____
2. Describe management of common psychosocial complications post-allogeneic HCT. _____
3. Identify HCT survivorship resources for patients and clinicians. _____

Please indicate your answer by filling in the letter:

1. ____ **2.** ____ **3.** ____ **4.** ____ **5.** ____ **6.** ____ **7.** ____ **8.** ____ **9.** ____ **10.** ____

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