Preparing for 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 preparation leading up to the allogeneic transplant day to help you guide your patients considering or undergoing transplant.

LEARNING OBJECTIVES

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

• Define hematopoietic cell transplantation (HCT).
• State three indications for allogeneic HCT.
• State three steps in preparing the patient for an allogeneic transplant.
INDICATIONS FOR ALLOGENEIC HCT

For adults, the most common indications for allogeneic HCT are acute leukemias and myelodysplastic syndromes (MDS).1 Cytogenetic and molecular testing results help physicians stratify these diseases by risk and plan treatment accordingly. For acute leukemias and MDS, the presence of intermediate- to high-risk features requires referral for HCT.2 Other possible indications for allogeneic HCT include chronic leukemias, lymphomas and multiple myeloma. Nongenitc indications for HCT include myelofibrosis, paroxysmal nocturnal hematuria (PNH), severe aplastic anemia, and sickle cell disease (SCD).

Like adults, children may require transplant for leukemia, lymphoma, anemias, and SCD. Transplant is the only known cure for inherited disorders of the immune system and metabolism.3,4 These diseases include adreno- leukodystrophy (ALD), Hurler syndrome, Krabbe disease, metachromatic leukodystrophy (MLD), severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

In all cases, the consulting HCT physician will assess suitability for transplant by looking at patient- and disease-related factors such as comorbidities and relapse risk.5 Recent advances in supportive care and reduced-intensity treatment regimens have improved the success of transplant for patients in their 60s and 70s.6,7

REFERRAL TIMING

Early referral to HCT is essential. Planning for allogeneic transplant takes time, and delayed referrals can result in poor survival outcomes.8 Engaging the HCT physician early ensures sufficient time for a donor search as well as time for patient and family education. Aggressive blood cancers, such as the acute leukemias and MDS, may have a short duration in complete remission (CR), and thus a short window of eligibility for HCT. Additionally, patients with poor-risk acute myeloid leukemia (AML) who undergo HCT in first CR have a significantly better relapse free survival.9 Referral timing is crucial for many nonmalignant diseases, like Hurler syndrome.1 The progressive damage caused by these diseases can be halted through HCT; however, it is not reversible with HCT.

Referral guidelines have been developed jointly by the National Marrow Donor Program® (NMDP)/Be The Match® and the American Society for Blood and Marrow Transplantation. The guidelines, updated annually, are available online. An excerpt of the guidelines, with recommended referral timing for AML, ALL, and MDS, is noted in Table 1.

TABLE 1 Recommended Timing for HCT Consultation

<table>
<thead>
<tr>
<th>ADULT LEUKEMIAS AND MYELODYSPLASIA</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute Myelogenous Leukemia (AML)</strong></td>
</tr>
<tr>
<td>High-resolution HLA typing is recommended at diagnosis for all patients</td>
</tr>
<tr>
<td>Early after initial diagnosis, all AML patients including:</td>
</tr>
<tr>
<td>• CR1 — except favorable risk AML [defined as: t(16;16), inv 16, or t(8;21) without c-KIT mutation; t (15;17); normal cytogenetics with NPM1 or isolated biallelic CEBPA mutation and without FLT3-ITD]</td>
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<tr>
<td>• Antecedent hematological disease (eg, myelodysplastic syndromes (MDS))</td>
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<tr>
<td>• Treatment-related leukemia</td>
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<tr>
<td>• Primary induction failure or relapse</td>
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<tr>
<td>• Presence of minimal residual disease after initial or subsequent therapy</td>
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<tr>
<td>• CR2 and beyond, if not previously evaluated</td>
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<tr>
<td><strong>Acute Lymphoblastic Leukemia (ALL)</strong></td>
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<tr>
<td>High-resolution HLA typing is recommended at diagnosis for all patients</td>
</tr>
<tr>
<td>Early after initial diagnosis, all ALL patients including:</td>
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<tr>
<td>• CR1</td>
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<tr>
<td>• Primary induction failure or relapse</td>
</tr>
<tr>
<td>• CR2 and beyond, if not previously evaluated</td>
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<tr>
<td>• Presence of minimal residual disease after initial or subsequent therapy</td>
</tr>
<tr>
<td><strong>Myelodysplastic Syndromes (MDS)</strong></td>
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<tr>
<td>Any intermediate or high IPSS or IPSS-R score</td>
</tr>
<tr>
<td>Any MDS with poor prognostic features, including:</td>
</tr>
<tr>
<td>• Treatment-related MDS</td>
</tr>
<tr>
<td>• Refractory cytopenias</td>
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<tr>
<td>• Adverse cytogenetics</td>
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<tr>
<td>• Transfusion dependence</td>
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<td>• Failure of hypomethylating agents</td>
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HLA, human leukocyte antigens. IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS
DONOR SEARCH
Once allogeneic HCT is determined to be the best treatment option for a patient, the donor search begins. The ideal donor or CBU will closely match the patient’s human leukocyte antigens (HLAs). HLAs are proteins on the outside of most cells that the body uses to identify self from non-self. Since HLA markers are inherited, physicians begin the donor search within the patient’s family. However, each of a patient’s biological siblings has only a 25% chance of being an HLA match, and 70% of patients won’t have a full match in their family. In these cases, the physician will search the Be The Match Registry®.

Through the registry, which includes 51 international donor centers and cooperative registries, physicians have access to nearly 29 million volunteer donors and more than 712,000 CBUs worldwide. Since HLA is inherited, patients are most likely to match a donor who shares their ethnic background. Currently, the chance of having a matched, available donor on the registry is close to 97% for whites, but for people of color, the chance is lower, ranging from 66 to 90%.

There are costs associated with the donor search that may be paid for through the patient’s health insurance policy. This includes HLA typing, first of family members and then of potential matches on the Be The Match Registry, medical exams to ensure suitability, and ultimately the collection and shipment of the blood-forming cells. Any physician can initiate a preliminary search of the Be The Match Registry for free. This will provide a snapshot of potential matches and does not include contact with or additional testing of a potential donor. Only HCT physicians within the NMDP/Be The Match network can initiate a formal search, which incurs a cost as potential donors are contacted for further evaluation and confirmatory HLA typing.

On average, it can take up to 2 weeks to identify an unrelated donor, while finding a sibling donor may be faster. Patients who may lack a suitably matched donor on the registry may have an ongoing search that continues for many months. Communication regarding the search status happens between NMDP/Be The Match case manager and the patient’s transplant center.

In some cases, a patient who doesn’t have an available matched donor may get a transplant from a haploidential, or half-matched donor. Parents are always a half-match for their children, and vice versa. Biological siblings have a 50% chance of being a half-match for each other. However, since haploidential transplant is a newer treatment, not all centers have experience with this type of transplant.

CELL SOURCES
Before an allogeneic transplant from a donor, the blood-forming cells are either collected directly from the marrow (harvest) or from the peripheral blood (apheresis). Alternatively, patients may receive blood-forming cells from a donated CBU that closely matches their HLA.

For more aggressive blood cancers with a high risk of relapse, such as AML or MDS, patients may benefit from peripheral blood stem cells (PBSC) as they have more T cells and tend to engraft quickly, thus lowering the immediate risk of graft rejection and relapse. However, the subsequent risk for chronic graft-versus-host disease (GVHD) is higher. CBUs, on the other hand, engraft more slowly but have a lower risk of GVHD. The degree of HLA match available may also influence the cell source selected. Since CBUs are made up of more naïve cells, a higher degree of HLA mismatch is better tolerated.

PREPARATION
In the days and weeks before the transplant day, patients undergo testing and central line placement, and receive the preparative (or conditioning) regimen. The preparative regimen is the chemotherapy, with or without total body irradiation (TBI), given to prepare the body to receive the new blood-forming cells. This is given during the days...
immediately before transplant day.\textsuperscript{12}

There are many different regimens and the physician chooses a regimen based on patient and disease factors. Two main categories of preparative regimens include myeloablative regimens and non-myeloablative, or reduced-intensity regimens. Typically, faster growing, more aggressive diseases respond better to myeloablative conditioning. The principle short-term risk with nonmyeloablative regimens is risk of graft failure or rejection and relapse.\textsuperscript{13} However advances in maintenance therapy and careful selection of patients for a nonmyeloablative therapy have lowered this risk.\textsuperscript{13,14} Nonmyeloablative regimens have made allogeneic HCT safer for older patients and those with co-morbidities. For blood cancers, the success of this regimen relies on the graft-versus-leukemia/lymphoma (GVL) effect.\textsuperscript{15} GVL occurs when the donor’s transplanted immune system identifies diseased cells in the patient’s body and kills them.

**TRANSPLANT DAY**

Donor cells are collected within 72 hours of transplant and transported via courier to the transplant center to be freshly infused. Frozen CBUs are shipped to the transplant center and thawed before infusion. The actual infusion of the donated blood-forming cells happens much like a standard blood transfusion and can feel somewhat anticlimactic. Patients may have minor infusion reactions related to ABO compatibility, allergy to preservatives, or fluid overload.\textsuperscript{12} Life-threatening infusion reactions are rare.\textsuperscript{12} Typically the infusion of life-saving cells is completed in a few hours or less.

After weeks to months of preparation, patients and their families may feel many emotions on transplant day. Many patients refer to this as their second “birthday.” Nurses may celebrate this milestone with patients and families before, during, and after transplant. Visit BeTheMatch.org for more information.

**REFERENCES**

6. Jantunen E, Kuitinen T, Penttilä K, Lehtonen P, Mahlamäki E, & Nousiainen T. High-dose melphalan (200 mg/m2) supported by autologous stem cell transplantation is safe and effective in elderly (greater than or equal to 65 years) myeloma patients: comparison with younger patients treated on the same protocol. Bone Marrow Transplant. 2006; 37: 917-922. doi:10.1038/sj.bmt.1705360
Questions

1. Hematopoietic cell transplantation replaces diseased blood-forming cells in the blood and marrow with healthy cells.
   a. True
   b. False

2. The allogeneic transplant uses the patient’s own blood-forming cells.
   a. True
   b. False

3. Indications for an allogeneic HCT include:
   a. Acute leukemias
   b. Myelodysplastic syndromes
   c. Multiple myeloma
   d. All of the above

4. HCT is the only known cure for inherited disorders of the immune system and metabolism.
   a. True
   b. False

5. Early referral to HCT is essential in order to ensure:
   a. Sufficient time for a donor search
   b. Time for patient education
   c. Time for family education
   d. All of the above

6. The ideal donor will closely match the patient’s human leukocyte antigens (HLAs).
   a. True
   b. False

7. Costs associated with the donor search, which may be paid by the patient’s health insurance, include:
   a. HLA typing
   b. Medical exams to ensure suitability
   c. Collection and shipping for the blood-forming cells
   d. All of the above

8. Before the transplant day, the patient will undergo:
   a. Testing
   b. Central line placement
   c. Preparative regimen
   d. All of the above

9. The preparative regimen is the chemotherapy given to prepare the patient to receive the new blood-forming cells.
   a. True
   b. False

10. The patient undergoing the infusion of donated blood-forming cells may have minor infusion reactions such as:
    a. Infusion reactions related to ABO compatibility
    b. Allergy to preservatives
    c. Fluid overload
    d. All of the above
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Answers

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2. State three indications for allogeneic HCT.

3. State three steps in preparing the patient for an allogeneic transplant.

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