Overview of Hematopoietic Cell Transplantation for the Treatment of Hematologic Malignancies

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KEYWORDS

• Allogeneic hematopoietic cell transplantation • Hematologic malignancies
• Graft-versus-host disease • Complications

KEY POINTS

- Allogeneic hematopoietic cell transplantation (HCT) is a curative-intent therapy for patients with certain hematologic malignancies.
- The efficacy of allogeneic HCT is driven by allo-immune graft-versus-tumor (GVT) immunotherapy; this activity also leads to toxicity in the form of graft-versus-host disease (GVHD).
- The balance between efficacy and toxicity is managed by manipulation of pretransplant conditioning, HLA matching, donor selection, and graft source to encourage GVT while minimizing risks.
- Advances in HLA typing, donor sources, and supportive and posttransplant care have improved outcomes. Newer approaches using molecular targeted therapies also promise improved efficacy.
- Patients treated with allogeneic HCT require intensive long-term care to monitor and manage the wide-ranging medical complications and psychosocial needs resulting from this high-stakes therapy.

BACKGROUND: SELF OR NON-SELF

Hematopoietic cell transplantation (HCT) refers to 2 distinct therapies from 2 distinct transplant sources: autologous (self) and allogeneic (non-self). Autologous HCT can be used as part of the treatment of several hematologic malignancies, including various lymphomas and multiple myeloma, and involves the administration of high-dose chemotherapy followed by infusion of previously collected autologous hematopoietic stem cells. The efficacy of this therapy is determined by the conditioning regimen itself, which may include myeloablative doses of radiation as well as chemotherapy. The doses of chemotherapy and radiation used in this setting would otherwise result in long-term or even permanent marrow ablation, and thus delivery of these regimens would be impossible without reconstitution of the marrow. As such, autologous hematopoietic cell "transplantation" can be more appropriately referred to as a "hematopoietic cell rescue," with the goal of cell infusion being to repopulate the marrow to ensure physiologic hematopoiesis. The toxicity of this therapy is thus limited to the toxicity of the high-dose chemotherapy. Allogeneic transplantation, on the other hand, is a fundamentally different therapy, and carries with it the

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complications associated with immunosuppression to prevent graft rejection present in solid organ transplantation, as well as the added complications of transplanting a donor immune system, referred to broadly as graft-versus-host disease (GVHD). Allogeneic transplant and its complications are the focus of this article.

WHAT IS THE GOAL OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION?

The history of allogeneic HCT (alloHCT), from the first infusion in 1957 to today, has taught us a great deal about how and why this therapy works, and has been the basis of the development of cell-based immunotherapy for cancer. The original studies investigating the feasibility of transplanting donor bone marrow (BM) were driven by the search for a therapy for radiation toxicity in the post-World War II era.[1] It was later recognized that radiation also killed leukemia cells,[2] and allogeneic BM transplantation was used as a means of stem cell rescue.[3] The next 2 decades saw many preclinical and clinical studies of allogeneic transplant for leukemia, and a study published in 1979 fundamentally changed our understanding of this therapy. Patients who received alloHCT from unrelated donors (and experienced GVHD) had a nearly 2.5-fold increased likelihood of long-term remission compared with those who received transplants from an identical twin.[4] This observation pointed out the role of the transplanted graft itself in determining response to therapy. Subsequently, it was demonstrated that relapse rates are higher when T cells were removed from the allograft,[5] and that relapse could successfully be treated by infusion of donor lymphocytes[6] or withdrawal of T-cell–directed immunosuppression.[7] Together, these findings led to the understanding that a fundamental mechanism of disease-directed activity in alloHCT is donor T-cell killing of host malignancy, a concept referred to as graft-versus-tumor or graft-versus-leukemia (GVL). Thus, although traditional cytotoxic chemotherapy and radiation therapy work by directly killing tumor cells, alloHCT is the first example of an immune-mediated cancer therapy, the goal of which is to promote a donor immune response against host malignancy.

WHO RECEIVES AN ALLOGENEIC TRANSPLANT?

Indications for Allogeneic Hematopoietic Cell Transplantation

The 2 broad categories of patients who are considered for alloHCT are those with malignant diseases and those with nonmalignant diseases. AlloHCT is curative for many genetic conditions, including immunodeficiencies, inborn errors of metabolism, and hemoglobinopathies.[8] These transplants are most often done during childhood, and will not be discussed in this review.

In adults, malignant indications for alloHCT are limited to the hematologic malignancies and severe aplastic anemia. Based on risk profiling, patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), and various myeloproliferative diseases (including chronic myelogenous leukemia) are considered for alloHCT as part of therapeutic management. AlloHCT can also be considered in patients with chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphomas, and multiple myeloma refractory to standard therapeutic regimens.

Eligibility for Allogeneic Hematopoietic Cell Transplantation

Eligibility for allogeneic transplantation varies a bit by institution, but age and comorbid diseases are of primary concern when considering this therapy. For younger patients, disease risk is the primary consideration, whereas in older patients, comorbidities play a greater role in decision making. Historically, age greater than 50 to 55 years was a contraindication to transplantation. More recently, however, several factors have led to increases in alloHCT for older patients. The Center for International Blood and Marrow Transplantation Research reported the results of 1080 patients with AML who received alloHCT, demonstrating 2-year survival rates for patients aged 40 to 54 years of age of 44%, 55 to 59 years of age of 50%, 60 to 64 years of age of 34%, and greater than 65 years of age of 36%.[9] Performance status before transplantation correlated with survival, leading the authors to conclude that age itself should not be the primary determinant of alloHCT eligibility. Several scoring systems have been developed to quantify the significance of comorbid disease on transplant outcomes.[10–14] Although these metrics can be helpful, none have been adopted as standard by the allogeneic transplant community, and a thoughtful and thorough consideration by the transplant physician is vital. Finally, strong social support structures are essential for success in the posttransplant period.[15] Immunosuppressive regimens are highly complex, and transplant-related complications are unfortunately quite common.

DONOR SELECTION

HLA Matching

The fundamental component in identification of an appropriate HCT donor is immune matching.