

Cambridge University Press

978-0-521-69975-4 - Manual of Stem Cell and Bone Marrow Transplantation

Joseph H. Antin and Deborah Yolin Raley

Excerpt

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## 1. RATIONALE FOR TRANSPLANTATION

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Hematopoietic stem cell transplantation (HSCT) has the potential to cure a variety of benign and hematologic diseases that may be incurable with conventional therapy. In its broadest form, HSCT consists of three parts: a conditioning phase, stem cell infusion, and for allogeneic procedures, a method for prophylaxis of graft-versus-host disease (GVHD). There are, however, many variations of this framework. Conditioning regimens include various combinations of chemotherapy, radiotherapy, and immunotherapeutic agents. All conditioning regimens must produce at least enough immunosuppression to prevent graft rejection; beyond this, they can vary considerably in intensity, ranging from high dose regimens that result in complete ablation of the patient's bone marrow to reduced intensity regimens that cause only mild myelosuppression. Stem cells can be obtained from bone marrow (BM), peripheral blood (PB), or umbilical cord blood (UCB). Finally, GVHD prophylaxis can be achieved through immunosuppressive medications or graft manipulation (in particular T-cell depletion). The choice of conditioning regimen, stem cell source, and GVHD prophylaxis regimens varies on the basis of patient and disease characteristics as well as donor availability. In the case of allogeneic HSCT for hematologic malignancies, one of the principal goals is to allow engraftment and development of a donor-derived immune system, that can effect an immunologic attack against the recipient lymphohematopoietic system, and in particular against the tumor cells. This graft-versus-tumor (GVT) effect is a fundamental and unique aspect of allogeneic HSCT. In autologous transplantation, the main goal is to provide an opportunity for hematologic recovery after the administration of high dose therapy.

Not surprisingly, the outcome of HSCT depends on many patient factors, such as age and comorbidities; disease factors, such as diagnosis, disease stage, and prior therapy; donor factors, including human leukocyte antigen (HLA) and gender match; and transplantation factors, including conditioning regimen, stem cell source, and GVHD prophylaxis. The following table lists estimates of long-term survival for some of the hematologic malignancies and marrow disorders for which transplantation is commonly performed.

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## Rationale for Transplantation

Disease	Approximate 5 year DFS (%)
AML/ALL	25–75 CR1 20–40 CR2 5–20 Refractory
CML	50–80 Stable phase 20–40 Accelerated phase 5–15 Blast crisis
NHL/HD/CLL	20–60 Chemosensitive relapse 10–25 Refractory disease
MDS	50–65 RA/RARS 10–35 RAEB
Multiple myeloma	10–25
Aplastic anemia	40–85

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, Hodgkin disease; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS refractory anemia with ringed sideroblasts.

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## 2. TYPES OF TRANSPLANTATION

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### AUTOLOGOUS TRANSPLANTATION

Autologous stem cell transplantation (or stem cell rescue) allows the administration of high-dose chemotherapy or chemoradiotherapy and eliminates myelotoxicity as a dose-limiting complication.

- The stem cell source can be either mobilized peripheral blood stem cells or bone marrow.
- Autologous transplantation is commonly used for lymphomas and myeloma and less commonly for leukemia.
- Autologous transplantation is also used for testicular cancer.
- In patients with leukemia and lymphoma, there is considerable concern over the reinfusion of occult tumor cells along with the marrow or peripheral blood progenitors. Therefore, numerous attempts to purge tumor cells from the stem cells have been undertaken. However, it is unclear whether such manipulation affects relapse, and tumor purging is not routinely performed. Arguments against purging include its cost and labor intensiveness. Moreover, for lymphoma and solid tumors, patients usually relapse at sites of prior bulky disease, suggesting that residual tumor within the recipient, not tumor in the stem cell product, is the primary contributor to relapse. Arguments in favor of purging include gene marking studies that show that marrow involvement can contribute to relapse.

### ALLOGENEIC TRANSPLANTATION

Allogeneic transplantation uses stem cells from either a family member or an unrelated donor. Sources include bone marrow, peripheral blood, or umbilical cord blood.

- Typically fully matched donors are preferred, but various degrees of incompatibility can be tolerated with appropriate attention to prevention of rejection and graft-versus-host disease.

## 4 Types of Transplantation

- Haploidentical transplantation (from family members matched at one HLA haplotype, that is, potentially as few as 6/12 loci) is considered investigational.

### **High-Intensity Conditioning (Myeloablative) Transplantation**

Allogeneic transplantation can control malignant disease by two distinct mechanisms. Like autologous transplantation, there is a dose-intensity component from the profound cytotoxicity of the conditioning regimen. In addition, the transplanted immune system can recognize mismatched minor histocompatibility antigens or tumor antigens expressed on tumor cells. The resultant anticancer effect is called the *graft-versus-malignancy effect* (this is commonly referred to as graft-versus-leukemia or graft-versus-lymphoma [GVL]). Thus, a myeloablative transplant is a two-pronged attack on the underlying disease and has a lower relapse rate than autologous transplantation. Unfortunately, the dose intensity of the conditioning may be prohibitively toxic for older patients or patients with comorbid disease, and early transplant-related mortality can be substantial. Moreover, dose intensity may predispose to more severe early GVHD.

### **Reduced-Intensity Conditioning Transplantation (Nonmyeloablative Transplantation)**

The recognition of the contribution of GVL activity to disease eradication led to the development of reduced-intensity conditioning stem cell transplantation. Reduced-intensity transplantation is used for older patients or patients who are not eligible for myeloablative regimens (usually by virtue of age, comorbidities, or receipt of a prior autologous transplantation). These transplants are designed not to have direct antitumor activity, but rather to provide sufficient host immunosuppression to permit engraftment of donor hematopoietic and lymphoid effector cells. These effector cells can mediate a GVL effect responsible for tumor control. This type of transplantation is most appropriate either for diseases in remission (e.g., acute myeloid leukemia (AML) in complete remission) or for diseases that tend to be more indolent (e.g., chronic lymphoblastic leukemia (CLL), follicular lymphoma, myelofibrosis). More aggressive diseases generally

## Types of Transplantation

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require ablative transplantation unless they are performed when the disease is in complete remission.

**PROS AND CONS OF EACH DONOR SOURCE**

	<i>Autologous</i>	<i>Allogeneic</i>
Advantages	<ol style="list-style-type: none"><li>1. No HLA matching requirement</li><li>2. No GVHD</li><li>3. No need for immune suppression</li></ol>	<ol style="list-style-type: none"><li>1. Stem cells have not been exposed to chemotherapy</li><li>2. Stem cells product is free of tumor</li><li>3. Graft-versus-tumor activity</li></ol>
Disadvantages	<ol style="list-style-type: none"><li>1. Possibility of stem cell damage from prior therapy leading to delay in engraftment or MDS</li><li>2. Possibility of contamination with tumor</li><li>3. No graft-versus-tumor effect</li></ol>	<ol style="list-style-type: none"><li>1. Donor availability uncertain</li><li>2. GVHD</li><li>3. Higher risk of complications</li></ol>
	Lower risk of complications Higher risk of relapse	Higher risk of complications Lower risk of relapse

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### 3. HLA MATCHING IN ALLOGENEIC TRANSPLANTATION

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Understanding the human leukocyte antigen (HLA) system is critical for properly applying allogeneic stem cell transplantation. HLA loci are found on chromosome 6, and are generally inherited as complete haplotypes. Thus, any two siblings have a 25% chance of sharing two common parental haplotypes. However, crossovers can occasionally occur during chromosomal replication.

- Class I antigens – HLA-A, -B, and -C
  - HLA-A and -B are expressed on all cells. They are involved with antigen presentation to cytotoxic CD8<sup>+</sup> T cells, while HLA-C is implicated in natural killer (NK) antigen recognition. In the past, HLA-A and -B have been the only Class I antigens routinely typed for transplantation, but recently it has been demonstrated that disparity at the HLA-C locus may be associated with higher rates of graft rejection and graft-versus-host disease (GVHD) following unrelated stem cell transplantation.
  - Serologic methods are still used to type class I antigens, but more precise molecular methods are available and have led to more precise HLA typing than were previously available through serologic typing alone. In related transplants, serology is often adequate. The one exception is homozygosity of one of the antigens. In this case, there may be allele-level differences that need to be sorted out with molecular typing. In unrelated transplants, allele-level typing is preferable.
  - Through the use of allele-level typing, disease-free survival for matched unrelated hematopoietic stem cell transplantation (HSCT) is beginning to approach that for HSCT from HLA-identical siblings. However, rates of GVHD and nonrelapse mortality are still higher for recipients of unrelated marrow.
- Class II antigens – HLA-DR, DQ, and DP
  - Class II antigens are recognized by CD4<sup>+</sup> T cells. They are principally expressed on B cells, macrophages, and dendritic cells, and in some other cells to a more limited degree.

## HLA Matching in Allogeneic Transplantation

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- It is clear that serologic typing is inadequate for class II typing, and molecular typing is employed routinely.
- HLA-DQ and DP are less important in allogeneic HSCT than HLA-DR, although some studies suggest a role for both in the pathogenesis of GVHD.

**MINOR HISTOCOMPATIBILITY ANTIGENS**

In addition to major HLA compatibility, there are also minor histocompatibility antigens that presumably have a role in GVHD, since transplantation with stem cells fully matched at both class I and class II HLA loci can still result in GVHD or rejection. Examples include HY antigens present on male but not female cells, HA1, HA2, and others.

**HLA STATISTICS**

In the United States, approximately 30% of patients have an HLA identical sibling. A smaller portion, less than 5%, will match a parent or an offspring. The likelihood of finding at least one match among  $n$  siblings is  $1 - (0.75)^n$ .

Number of Siblings	Probability of HLA Match
1	0.25
2	0.44
3	0.58
4	0.68

- The incidence of GVHD and graft failure increases with increasing HLA disparity. Generally, an unrelated donor is sought if a 5/6 HLA-A, B, DR matched relative cannot be found. There is some debate about whether a 6/6 unrelated donor is preferable to a 5/6 HLA-matched relative, but most feel that these donors are equivalent, and it is often easier from a logistic viewpoint to arrange the stem cell donation from a related donor.
- In umbilical cord blood transplantation, the immaturity of the donor immune system allows a greater degree of HLA disparity (e.g., 4/6 matches), although even here better matches are associated with better outcomes.

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HLA Matching in Allogeneic Transplantation

## HLA TYPING

Patients and their siblings should be typed first. It is sometimes useful to type the patient's parents at the outset as well, if they are available, since it helps assign haplotypes and resolve inconsistencies in the siblings' typing. In the absence of a fully matched sibling, and in addition to doing an unrelated donor search, it may be useful to occasionally type children. If the children are very young, typing the patient's spouse can be useful, since one may avoid venipuncture in a child if analysis of the parents indicates that the child cannot match. Avoid typing extended family members unless there is a reasonable possibility that they match. Sometimes typing can be obtained from buccal swabs, which are easier to obtain from potential donors in some undeveloped countries.

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## 4. STEM CELL SOURCE

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### HEMATOPOIETIC PROGENITOR CELL PRODUCTS

Hematopoietic progenitor cell (HPC) products contain hematopoietic stem and lineage-committed progenitor cells capable of providing hematopoietic and immune reconstitution after myeloablative or reduced-intensity preparative regimens. There is no unanimity on the terminology.

- Since stem cells are difficult to specifically identify, some authors prefer the term hematopoietic cell transplantation (HCT).
- Others call the procedure hematopoietic stem cell transplantation (HSCT) to acknowledge that most transplants are not successful unless stem cells are transplanted.
- The Foundation For The Accreditation of Cellular Therapy (FACT) focuses on progenitors. Cellular therapy products can be broadly categorized as being minimally manipulated products and more than minimally manipulated products.

### Hematopoietic Progenitor Cell Function

Hematopoietic progenitor cells (HPCs) administered intravenously migrate to the marrow, where they adhere, expand, self-renew (stem cells only), and differentiate. The differentiated cells are released into the blood, restoring blood counts and immunity. The time from administration of HPCs to recovery of adequate or normal blood counts is variable (see section on Engraftment).

### Indications

Allogeneic HPC products are intended to provide hematopoietic reconstitution after myeloablative or reduced intensity preparative regimens for a wide range of disease states. For some patients the product is also intended to provide a graft-versus-tumor effect. Autologous HPCs are collected and stored for use as a “rescue” following myeloablative or severely myelotoxic therapy. The high-dose therapy is intended to treat the patient’s underlying malignancy and autologous HPC products are administered to minimize morbidity and mortality due to the myelotoxic effects of the therapy.

**10 Stem Cell Source****Dosage and Administration**

The minimum number of HPCs necessary for engraftment in a myeloablated recipient has not been established. Different products have widely different numbers of progenitors and stem cells. However, eligibility criteria for some protocols usually dictate a minimum number of cells to be collected and infused.

Several methods are used to measure the number of cells in an HPC collection. Simple cell count may be adequate for many marrow collections. Most centers use flow cytometric enumeration of CD34<sup>+</sup> cells for the majority of cellular products.

**Storage**

Hematopoietic progenitor cell (HPC) products are stored using various methods depending on the required duration of storage. Products used fresh can be refrigerated for at least 24 hours before infusion. If there is a >48-hour delay before infusion, most products are frozen to maintain viability. Most frozen products are stored in the vapor phase of liquid nitrogen ( $\leq -50^{\circ}\text{C}$ ). Products may be stored for up to 10 years although no longevity limit has yet been determined. Long-term storage is generally done in the liquid phase of liquid nitrogen.

**HEMATOPOIETIC PROGENITOR  
CELL SOURCES****Hematopoietic Progenitor Cell, Marrow**

Hematopoietic progenitor cell, marrow (HPC-M) preparations contain HPCs obtained by multiple needle aspirations from the posterior iliac crest and occasionally from the anterior iliac crest or sternum of an autologous or allogeneic donor. The marrow is placed in a sterile container with an electrolyte solution and an appropriate anticoagulant. The cell suspension is passed through sterile filters to remove fat, bone particles, and cellular debris.

- The volume collected varies with the weight of the recipient, but generally ranges from 10 to 15 mL/kg of donor weight. The minimum nucleated cell dose is  $2 \times 10^8$  nucleated cells/kg of recipient body weight.