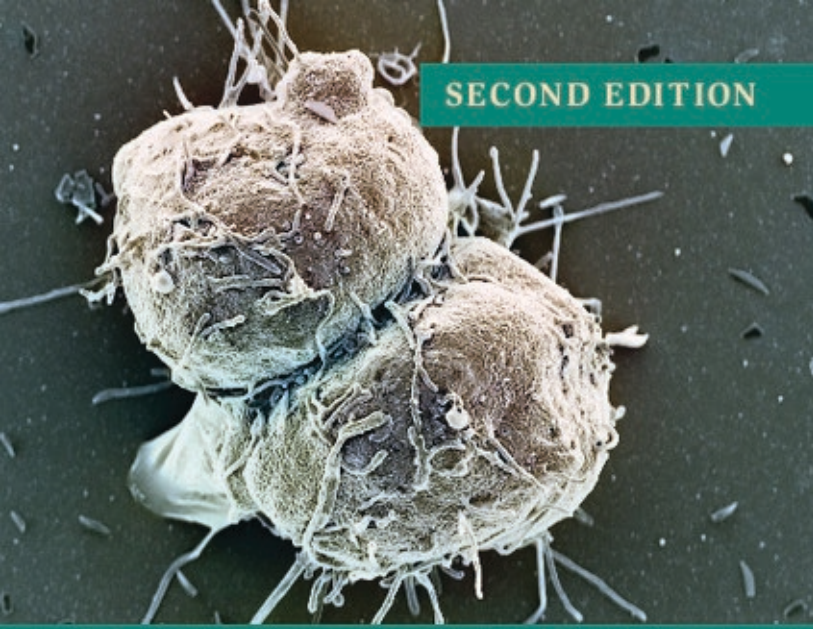


SECOND EDITION



MANUAL OF
Stem Cell AND
Bone Marrow
Transplantation

JOSEPH H. ANTIN
DEBORAH YOLIN RALEY

CAMBRIDGE

Medicine

Manual of Stem Cell and Bone Marrow Transplantation

Second Edition

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Rationale for transplantation

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. [Table 1.1](#) lists estimates of long-term survival for some of the hematologic malignancies and marrow disorders for which transplantation is commonly performed.

Table 1.1. Long-term survival rates for various diseases

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

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DFS, disease-free survival; 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.

Types of transplantation

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 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, relapse occurs usually 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 showing 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 (GVHD).

- Haploidentical transplantation (from family members matched at one HLA haplotype, that is, potentially as few as 6/12 loci) is considered investigational.
- Conditioning regimens vary in intensity and are categorized by the duration of cytopenia and on the requirement for stem cell support. There are three levels of intensity: nonmyeloablative (NMA), reduced-intensity conditioning (RIC), and high-intensity or myeloablative conditioning (MAC).

High-intensity conditioning (myeloablative – MAC) 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. Myeloablative conditioning regimens cause irreversible cytopenia and require stem cell support. 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.

Nonmyeloablative (NMA) and reduced-intensity conditioning (RIC) transplantation

Recognition of the contribution of GVL activity to disease eradication led to the development of NMA and RIC stem cell transplantation. NMA regimens cause minimal cytopenia and can be given without stem cell support if required. RIC regimens are intermediate between MAC and NMA because they cause cytopenias of variable duration and should be given with stem cell support. Cytopenia may or may not be reversible. Both conditioning regimens are used for older patients or those 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 require ablative transplantation unless they are performed when the disease is in complete remission.

The pros and cons of autologous and allogeneic transplantation are summarized in [Table 2.1](#).

Table 2.1. Pros and cons of donor sources

	Autologous	Allogeneic
Advantages	No HLA matching requirement	Stem cells have not been exposed to chemotherapy
	No GVHD	Stem cell product is free of tumor
	No need for immune suppression	Graft-versus-tumor activity
Disadvantages	Possibility of stem cell damage from prior therapy leading to delay in engraftment or MDS	Donor availability uncertain
	Possibility of contamination with tumor	GVHD
	No graft-versus-tumor effect	Higher risk of complications
	Lower risk of complications	Higher risk of complications
	Higher risk of relapse	Lower risk of relapse

GVHD, graft-versus-host disease; HLA, human leukocyte antigen; MDS, myelodysplastic syndrome.

Reference

Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 2009; 15: 1628–33.

Human leukocyte antigen matching in allogeneic transplantation

Understanding the human leukocyte antigen (HLA) system is critical for proper application of 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, -B, and -C are expressed on all cells. They are involved in antigen presentation to cytotoxic CD8+ T cells, while HLA-C is implicated in natural killer (NK) antigen recognition. In the past, HLA-A and -B were the only class I antigens routinely typed for transplantation, but it has recently 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 was 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+ T cells. They are principally expressed on B cells, macrophages, and dendritic cells, and in some other cells to a more limited degree.

- 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 $1 - (0.75)^n$, as illustrated in [Table 3.1](#).

Table 3.1. Probability of HLA match among siblings

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-, or -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.
- Newer studies of haploidentical transplantation are encouraging for patients without matched donors.

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.

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, nonmyeloablative, or reduced-intensity preparative regimens. There is no unanimity on the terminology.

- Since stem cells are difficult to identify specifically, some authors prefer the term hematopoietic cell transplantation (HCT).
- Others call the procedure hematopoietic stem cell transplantation (HSCT) to acknowledge that most transplantations 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 either minimally manipulated products or more than minimally manipulated products.

Hematopoietic progenitor cell function

Hematopoietic progenitor cells 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 [Chapter 9](#), Engraftment).

Indications

Allogeneic HPC products are intended to provide hematopoietic reconstitution after myeloablative, nonmyeloablative, 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. This 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.

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, but a simple cell count may be adequate for many marrow collections. Most centers use flow cytometric enumeration of CD34+ cells for the majority of cellular products.

Storage

Hematopoietic progenitor cell 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 2×10^8 /kg of recipient body weight.
- Marrow contains mature red cells, white cells, platelets, mast cells, fat cells, plasma cells, committed progenitors of all lineages, and HSC.
- These products are usually processed before infusion, but are sometimes infused in an unmodified state.
- The most common modifications of allogeneic HPC-M are to decrease the volume of ABO-incompatible red cells, remove ABO-incompatible plasma, isolate CD34+ progenitor cells, and remove donor T lymphocytes.

- The most common modification of autologous HPC-M is to reduce the volume by removing plasma and red cells before cryopreservation.

Hematopoietic progenitor cell, peripheral blood

Hematopoietic progenitor cell, apheresis (HPC-A) preparations contain HPCs collected from the peripheral blood by a leukapheresis procedure, usually after recombinant hematopoietic growth factor and/or chemotherapy administration.

- Mobilization regimens
 - *Granulocyte colony-stimulating factor (G-CSF)*. 5 to 10 µg/kg SC per day (4 to 10 days, depending on the concomitant use of chemotherapy).
 - *Cytosan plus G-CSF*. A single dose of 2500 to 4000 mg/m² IV with mesna (used only in autologous transplantation) plus G-CSF 5 to 10 µg/kg SC per day for 4 to 10 days.
 - *Others*. Numerous chemotherapy regimens used to treat lymphoma can be used to mobilize stem cells. Stem cells are collected on recovery of neutrophils 10 to 14 days after chemotherapy.
 - *Mozobil (plerixafor hydrochloride)*. Mozobil blocks CXCR4 (SDF-1α), facilitating release of hematopoietic progenitors and stem cells from the bone marrow into the blood.
- Processing
 - An allogeneic HPC-A may be processed to decrease the volume of ABO-incompatible red cells, remove ABO-incompatible plasma, isolate CD34+ progenitor cells, and remove donor T lymphocytes.
 - The most common modifications of autologous HPC-A are to reduce the volume by removing plasma before cryopreservation, to isolate CD34+ progenitor cells, and to wash the cells to remove dimethylsulfoxide (DMSO) after thawing.
- The minimum CD34+ cell dose is 2×10^6 /kg.

Hematopoietic progenitor cell, cord

Hematopoietic progenitor cell, cord (HPC-C) preparations contain HPCs obtained from the umbilical cord at the time of delivery. Cord blood products are used mainly for unrelated allogeneic stem cell transplantation. They may be used in family-member transplantation, particularly in children.

- Initial processing may include removal of red cells and plasma. The HPC-C products are cryopreserved after collection and initial processing.
- Cell dose is based per kilogram of recipient weight, which can be limiting. Target is 1.7 to 3.5×10^7 total nucleated cells/kg.

- In adults, single cord blood unit transplantation is associated with delayed engraftment, unless the recipient is small (below 40 kg). Combining two products seems to provide more rapid engraftment, albeit at the expense of higher rates of acute graft-versus-host disease (GVHD).

Minimally manipulated cellular therapy products

Administration

The product should be administered or cryopreserved immediately after processing (within 48 hours of collection). It is filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

Plasma-reduced products

Description

These products contain the cellular elements of the HPCs that remain after the bulk of the plasma is removed by centrifugation. Plasma depletion is performed only for minor ABO-incompatible products (O \Rightarrow A; O \Rightarrow B; O \Rightarrow AB; B \Rightarrow A; B \Rightarrow AB; A \Rightarrow AB) with plasma volume greater than 150 mL.

Indications

Plasma-reduced HPC graft is indicated

- when the donor has an antibody to one or more recipient red cell antigens, such as in minor ABO-incompatible situations;
- as a means of volume reduction for recipients who are small, fluid-sensitive, or have preexisting fluid overload, cardiac or renal compromise;
- autologous HPCs collected by apheresis are plasma-reduced to decrease volume before cryopreservation.

Red blood cell-reduced products

Description

These are the HPCs remaining after the mature red blood cells (RBCs) have been depleted by sedimentation, centrifugation, or lysis. Red blood cell depletion is performed only for major ABO-incompatible products (A \Rightarrow O; B \Rightarrow O; AB \Rightarrow O; A \Leftrightarrow B; AB \Rightarrow A; AB \Rightarrow B) or for patients with other clinically significant antibodies, and when the total RBC content is greater than 30 mL.

Indications

- The recipient may have a high-titer antibody to one or more antigens on the donor RBCs (usually major ABO incompatibility).
- Red blood cell depletion is also used to reduce the concentration of an autologous HPC product before cryopreservation.

Buffy coat-enriched products

Description

The buffy coat is the portion of an HPC product containing the nucleated cells after the bulk of the plasma and mature red cells have been removed by sedimentation or centrifugation techniques.

Indications

This procedure is indicated when a concentrated HPC product is required for further manipulation such as purging and/or cryopreservation. It may also be used when greater volume reduction is desired than can be obtained with plasma reduction alone.

Cryopreserved products

Description

Cryopreserved products are HPCs that have been frozen using cryoprotectant solutions. The most commonly used cryoprotectant is 10% DMSO and a protein additive such as human serum albumin.

Indications

Cryopreservation of cells is indicated when the product is to be stored for more than 48 hours before administration.

Administration

- The product should be administered immediately after thawing and/or processing. Cell death occurs rapidly after the product is thawed. A 2-hour expiration from time of thaw on most routine cryopreserved HPC products is reasonable but may be center dependent.
- All products should be filtered at the bedside using a 170- to 260-micron filter.
- The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused.

- If the thawed products have not been washed to remove DMSO, care should be taken not to exceed 1 mL of DMSO per kilogram of recipient weight per day administration (e.g., 100 mL of 10% solution contains 10 mL of DMSO).

CD34-enriched products

Description

CD34-enriched products contain the cellular elements of HPCs that have been enriched by CD34 selection.

Indications

A CD34-enriched HPC product may be indicated

- when circulating tumor cells are present in the peripheral blood and/or marrow and, therefore, will likely be present in the HPC product;
- as a means to reduce the number of T lymphocytes contained in the allogeneic HPC product.

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