

Hematopoietic Progenitor Cell (HPC) Transplantation Basics

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1. Our friend the stem cell
 - a. These cells are present in small quantities in everyone's bone marrow and in lower quantities in circulating blood
 - b. They are "totipotent", meaning that they can differentiate into hematopoietic cells of all three cell lines (erythroid, myeloid, and megakaryoblastic)
 - c. Stem cells are identified by surface expression of the CD34 antigen
 - 1) They are thought to also have Human Leukocyte Antigen (HLA) complexes on their surface, but they do NOT carry ABO blood group antigens
2. Basic principle: Harvest progenitor cells from a donor and infuse those cells into a recipient who has had their bone marrow deliberately wiped out. The idea is to replace the bad marrow and cells with good marrow and cells.
3. The general category of HPC transplantation includes three main types of transplantation:
 - a. **Peripheral Blood Progenitor Cell (PBPC) Transplantation**
 - 1) Progenitor cells are harvested from the circulation of a donor using apheresis equipment
 - 2) Currently the most popular type of HPC transplantation; has mostly replaced traditional bone marrow harvesting
 - 3) Reasons:
 - a) No general anesthesia required
 - b) Faster recovery and engraftment
 - c) Can potentially work with patients with marrow involvement of their malignancy
 - d) Apheresis equipment is already in widespread use
 - b. **Bone Marrow Transplantation**
 - 1) Over one liter of marrow harvested from a donor, often from multiple iliac aspirations
 - 2) For obvious reasons, requires general anesthesia
 - 3) Still done in some places but declining for reasons above
 - c. **Umbilical Cord Blood Transplantation**
 - 1) Blood from umbilical cord blood is rich in stem cells (as well as in progenitor cells that are cell-line committed); this blood can be harvested at the time of delivery and stored
 - 2) Much excitement a few years ago, has yet to realize as widespread use as PBPC transplant
 - 3) Potential advantages:
 - a) No risk to donor
 - b) Widespread availability (with a little bit of planning)
4. Three main types of HPC transplant can be done, based on the source of the stem cells
 - a. **Autologous** HPC transplantation
 - 1) The donor and recipient are the same person
 - 2) Most commonly used for metastatic or recurrent solid tumors and/or marrow malignancies

- b. **Syngeneic** HPC transplantation
 - 1) The donor and recipient are identical twins
- c. **Allogeneic** HPC transplantation
 - 1) The donor and recipient are different people that are not genetically identical
 - 2) Most commonly used in leukemias, but also in aplastic anemia, hemoglobinopathies, and immune deficiencies (see next item)
- 5. HPC transplantation is increasing in popularity and is being used as treatment for many different diseases, such as:
 - a. Malignant diseases (most common indication)
 - 1) Acute leukemias
 - 2) Chronic Myelogenous Leukemia (*most common matched unrelated transplant indication*)
 - 3) Lymphomas (Hodgkin's and non-Hodgkin's)
 - 4) Breast cancer (*most common autologous transplantation indication along with lymphoma*)
 - 5) Childhood solid tumors (Wilm's, Ewing sarcoma, neuroblastoma, etc.)
 - b. Immune deficiencies
 - 1) Severe Combined Immunodeficiency Disease (SCID)
 - 2) Aplastic anemia
 - 3) Wiskott-Aldrich syndrome
 - c. Inborn disorders
 - 1) Mucopolysaccharidoses
 - 2) Lysosomal disorders (Niemann-Pick, Gaucher's)
 - 3) Adrenoleukodystrophy
 - d. Others
 - 1) Multiple sclerosis
 - 2) Paroxysmal nocturnal hemoglobinuria
- 6. **Allogeneic HPC transplantation**
 - a. Choosing a donor
 - 1) General considerations
 - a) HLA compatibility is paramount in HPC transplantation; a "perfect" match has compatibility at HLA-A, HLA-B, and HLA-DR antigens (called a "six-antigen match" because there are two of each of the above).
 - b) ABO compatibility is secondary
 - c) Best chance of finding compatible donor is in family members
 - 2) CMV status is also a consideration (better is CMV-seronegative)
 - 3) Donors are fully infectious-disease screened
 - b. Donor procedures (specifically for PBPC transplants)
 - 1) Mobilization
 - a) Cytokines like granulocyte colony-stimulating factor (G-CSF) can increase circulating PBPCs enough (15- to 30-fold) to harvest them by apheresis
 - c) Measure by checking number of CD34+ cells by flow cytometry or by counting colony-forming units (CFU) by cell culture
 - 2) Harvest
 - a) Collection via standard apheresis machines modified for PBPC collection
 - b) Target a specific quantity of cells (commonly 2.0×10^6 CD34+ cells/Kg)
 - c) Up to four separate collections often required

- 3) Processing
 - a) Product may be processed to reduce amount of red cells and/or plasma (especially useful in ABO incompatible allogeneic transplants)
 - b) May also process to reduce T-cells to reduce risk of graft vs host disease
 - c) Methods being investigated to isolate and purify the CD34+ cells
 - d) Frozen most commonly using dimethylsulfoxide (DMSO) as cryoprotectant
- c. Recipient procedures
 - 1) Myeloablation
 - a) Generally accomplished with high-dose chemotherapy with or without total body irradiation
 - 2) Infusion
 - a) Generally thawed at bedside and infused immediately to prevent DMSO toxicity
 - 3) Engraftment
 - a) In general, roughly three weeks following infusion
- d. Special considerations
 - 1) ABO issues
 - a) **Major incompatibility**
 - Defined as the introduction of an incompatible red cell *antigen* into a recipient, such as with a group A donor and a group O recipient (see table below for more examples)
 - Initial consideration: The incompatible red cells infused with the HPC product may be hemolyzed by the native ABO antibody in the recipient, so process the HPC's to decrease the number of accompanying RBCs
 - Secondary consideration: The recipient ABO antibodies that may persist can hemolyze the new, incompatible red cells formed by engrafting marrow (see "Transfusion Therapy" section below).
 - Until all original recipient RBCs are gone, patient may test in a chimeric pattern on routine testing (has been reported as far out as two years)
 - b) **Minor incompatibility**
 - Defined as the introduction of an incompatible donor red cell *antibody* into an HPC recipient, such as with a group O donor and a group A recipient (see table below for more examples)
 - Initial consideration: The incompatible plasma in the HPC product may hemolyze the recipient's red cells, so process the HPC's to remove as much plasma as possible.
 - Secondary consideration: Engrafting lymphocytes may start making antibody that is incompatible with recipient's red cells before all the red cells are gone from the circulation (see "Transfusion Therapy" section below).
 - c) **Major and minor incompatibility**
 - Defined as the introduction of both incompatible donor *red cells and antibodies* into a recipient; this occurs only in two situations:
 - Group A donor/group B recipient
 - Group B donor/group A recipient

- Initial consideration: A combination of the above initial considerations, as hemolysis of both donor red cells and recipient red cells can occur at the same time.
 - See “Transfusion Therapy” section below for more information on how to transfuse these patients
- 2) Rh issues
 - a) Rh incompatibility is not a contraindication to transplantation, though Rh antibodies may be induced when a D-negative donor engrafts in a D-positive recipient
 - 3) Graft-vs-Host Disease
 - a) Acute and chronic forms
 - Acute: first 100 days, presents with skin, GI tract, and liver involvement
 - Chronic: generally after day 50, has autoimmune symptoms (like Sjogrens and systemic sclerosis) in addition to acute problems above
 - Chronic GVHD seen in 30-40% of long-term survivors
 - b) Paradoxically, GVHD may be associated with *better* survival in leukemic patients (see next item)
 - 4) Graft-vs-Leukemia effect
 - a) In leukemic patients, a little bit of GVHD actually is a good thing, with the transplanted lymphocytes attacking the residual malignant cells, leading to better survival and decreased recurrence
 - b) Difficult to balance, because severe GVHD can be deadly
7. **Autologous HPC transplant:**
- a. Since the donor and recipient are the same person, the processes are similar to those outlined above, but they are occurring in one patient
 - b. Mobilization/Myeloablation
 - 1) Ablative chemotherapy can both wipe out marrow elements and cause increase in circulating PBPCs
 - 2) Ablative chemo and cytokines like G-CSF work together to increase PBPCs by 100-200 times baseline level
 - b. Harvest
 - 1) As with allogeneic, though the target may not be quite as high as with allogeneic donors
 - c. Processing
 - 1) Product may be processed as for allogeneic collections
 - 2) In addition, may process using specialized methods to purge tumor cells
 - d. Reinfusion
 - 1) As for allogeneic
 - e. Engraftment
8. **Transfusion therapy in HPC transplantation**
- a. Three phases
 - 1) Pre-transplant
 - 2) Peri-transplant
 - a) From beginning of myeloablation until engraftment
 - 3) Post-transplant
 - a) Defined as after engraftment has occurred

b. The pre-transplant phase

- 1) Two main concerns are pre-eminent:
 - a) Preventing alloimmunization
 - Generally done via use of leukocyte reduced blood products
 - Also, avoid family member transfusions to prevent exposure to family HLA antigens
 - b) Preventing graft vs host disease
 - All patients in this phase should receive irradiated blood products due to their upcoming immunodeficiency
- 2) Other concerns
 - a) CMV; use CMV negative or leukoreduced products

c. The peri-transplant phase

- 1) Continue support as above, but may have special concerns in ABO-mismatched allogeneic transfusions
- 2) See chart below for recommendations for ABO types of transfused products in this phase, remembering the principles mentioned above.
- 3) Though some people wash red cells to remove incompatible plasma, most do not feel it is necessary to do so.

Recipient Type	Donor Type	Mismatch	Red Cell Type	FFP Type
O	A	Major	O	A, AB
O	B	Major	O	B, AB
O	AB	Major	O	AB
A	AB	Major	A	AB
B	AB	Major	B	AB
A	O	Minor	O	A, AB
B	O	Minor	O	B, AB
AB	O	Minor	O	AB
AB	A	Minor	A	AB
AB	B	Minor	B	AB
A	B	Major & Minor	O	AB
B	A	Major & Minor	O	AB

(NOTE: After AABB *Technical Manual*, 14th ed)

d. The post-transplant phase

- 1) After the patient’s original ABO antibodies have disappeared (which may take several months after engraftment), patient may be transfused with ABO-identical blood (identical to the patient’s *new* ABO type, that is)
 - a) May utilize simple crossmatch technique to detect residual “old” ABO antibodies in a donor who has a new ABO type; i.e., if the patient’s serum does not react with red cells of the new ABO type at all (a negative crossmatch), it is safe to begin using the new type
 - b) Until that happens, however, it is safer to use the recommendations in the table above.