Bone Marrow Transplantation

Neda Kalhor, MD
The collection and transplantation of hematopoietic stem cells

1950s and 1960s, 200 allogeneic transplants

1968, first successful allogeneic transplant
Features of stem cells

- **Regenerative capacity**
- **Ability to home** to the marrow space following intravenous injection
  - Selectins (BM endothelial cells) and integrins (stem cells)
- **Ability of the stem cell to be cryopreserved**
Sources of stem cells

- **Bone marrow** stem cells
- **Peripheral blood** stem cells (PBSC)
- Umbilical **cord** blood
Types of transplants

- Autologus
- Allogenic
  - Syngeneic (identical twin)
  - Related
  - Unrelated
Autologous Tx

- Removal and storage of the patient's own stem cells with subsequent reinfusion after high-dose myeloablative therapy
- No risk of graft rejection
- Can be contaminated with tumor cells, leading to relapse
- No need for growth factors
Indications

1- **Replace** an abnormal but nonmalignant lymphohematopoietic system

2- **Treat malignancy** by allowing the administration of high-dose chemotherapy with stem cell rescue (HDC/SCR)
Non-malignant diseases

- Inherited immune disorders
  - Severe combined immunodeficiency
  - Wiskott-Aldrich syndrome
  - Chédiak-Higashi syndrome
  - Chronic granulomatous disease
  - Kostmann’s syndrome
- Marrow failure states
  - Fanconi's anemia
  - Severe aplastic anemia
Inherited red cell disorders
- Thalassemia major
- Sickle cell anemia

Autoimmune diseases (experimental)

Storage diseases
- Gaucher's disease
- Hurler's syndrome
- Hunter's syndrome
Malignant disorders

- **Hematopoietic** neoplasms
  - Acute Leukemia
  - Chronic Leukemia
  - Myelodysplasia
  - Lymphoma
  - Myeloma

- **Solid Tumors**
  - Breast cancer
  - Ovarian cancer
  - Testicular cancer
Histocompatibility

- Human Leukocyte Antigen (HLA) typing for allogeneic transplants
  - Class I: HLA-A, -B, -C
  - Class II: HLA-DR, -DP, DQ
- Chromosome 6
- HLA –A, -B and –DR are the most relevant loci
- -A and –B by serology and –DR by molecular methodology
The genes encoding HLA antigens are highly polymorphic ($10^{23}$).

Inherited as haplotypes, with only rare crossovers between them.

The odds that any one sibling will match a patient are one in four.

Within different races, certain haplotypes are far more common.

More problematic for African-American to find an acceptable donor.
Obtaining HLA-matched marrow

- **National Marrow Donor Program (NMDP)** with 4 million potential donors
- Identifying and typing >3 million volunteers, 50% chance of finding HLA-matched donor
- 6 cord blood banks in the U.S. have been set up under a National Institutes of Health initiative.
Bone marrow Harvest

- Aspirated from the donor's iliac crests, under general or spinal anesthesia
- **5-10 mL/kg** of marrow is aspirated, placed in heparinized media, and filtered, to remove fat and bony spicules.
- 2-5% of a person's bone marrow, which the body replaces in four weeks.
- 1.5 to $5 \times 10^8$ nucleated marrow cells per kilogram
Bone marrow stem cells

- Further processings:
  - Removal of red cells in ABO-incompatible transplants
  - Removal of donor T cells to prevent GVHD
  - Removal of contaminating tumor cells in autologous transplantation
BMT procedure

- Chemo-radiation (conditioning or preparative regimen)
- 1-2 days following conditioning
- In the patient's room
- Stem cells infused through a large-bore central venous catheter
- Usually well tolerated, occasionally fever, cough, or shortness of breath
Engraftment

- **2-4 weeks** post-transplant
  - 10-14 d for marrow
  - 7-12 with PBSCs
  - 24 days for cord
BMT complications

- **Early** complications:
  - Rejection
  - Acute GVHD
  - Infections; HSV, CMV, PCP

- **Late** complications:
  - Chronic GVHD
  - Prolonged immunodeficiency
  - Relapse
Graft-Versus-Host Disease

- Donor T cells transferred, reacting with host cells
- A major complication to allogenic tx
- Much less frequent in fully-matched txs
GVHD

- **Acute** (<3 months posttransplant); fever, exfoliative dermatitis, anorexia, vomiting and diarrhea, hepatitis
  - Usually requires skin, liver, or GI biopsy for confirmation

- **Chronic** (>3 months); resembles an autoimmune disorder with skin, liver and GI involvement and less commonly arthritis and obliterative bronchiolitis
GVHD

- Cyclosporine
- Removal of T cells with monoclonal Abs
- Higher incidence of engraftment failure and relapse with GVHD prevention
  - Cytokines promote stem cell multiplication and maturation
  - T cells involved in graft—vs.-tumor effect
Peripheral blood stem cells

- 4 or 5 days of hematopoietic growth factor, G-CSF or GM-CSF

- One or two 4-h apheresis sessions
Umbilical cord stem cells

- Related and unrelated allogeneic
Umbilical cord stem cells

- **Engraftment** at a **slower** pace than seen with a marrow
- Low cell content, limited use as a source of stem cells for adult patients.
- Less GVHD
Umbilical cord blood

- Not requiring the exact match
  (marrow asks that 6/6 protein markers be exact, umbilical cord blood bank needs only 4 and when the donor is a sibling of the recipient, only 3)

- If a child has a serious genetic disease, umbilical cord blood from a sibling born within two years may be able to correct it.