Hematopoietic Stem Cell Transplantation

Imad A. Tabbara, M.D.
Professor of Medicine
Hematopoietic Stem Cells

- Harvested from blood, bone marrow, umbilical cord blood
- Positive selection of CD34 (+) cells
- In-vitro expansion of CD34 (+) cells
Hematopoietic Stem Cell Transplantation

- Types of Transplant By Stem Cell Source
  - Bone marrow
  - Peripheral Blood
  - Cord Blood
Apheresis: Harvesting Stem Cells From Peripheral Blood

Blood-forming stem cells

Whole blood is collected from donor

Blood, minus stem cells, is returned to donor

Whole blood in  Stem cells out
Hematopoietic Stem Cell Transplantation

- **TYPES OF TRANSPLANTS BY DONOR**
  - AUTOLOGOUS
  - ALLOGENEIC:
    - related vs unrelated
    - HLA-matched vs mismatched
  - SYNGENEIC (identical twin)
Autologous Transplantation

- More than 30,000 annually
- 2/3 for MM and NHL
- High Dose Chemo
- Marrow Toxicity Otherwise Dose Limiting
- “Stem cell rescue”
Cord Blood as a Source of Stem Cells
Placental and Cord-Blood Stem Cell Transplants

After the birth of the baby, blood is collected into a special blood bag.

Stem cells transferred to a new bag.

Cryoprotectant added to minimize damage during freezing.

Virus-free, tissue-typed stem cells stored in liquid nitrogen for future transplant.
CORD BLOOD TRANSPLANTATION

Advantages
- Waste product of normal deliveries
- Readily available
- Increased availability for minorities
- Decreased transmission of viruses (e.g. CMV)

Disadvantages
- One unit rescues one patient/no DLI
- Theoretical risk of genetic disease transmission
- Theoretical risk of maternal cell contamination (GVHD)
- Efficacy in adults unknown
Using More Than One Cord-Blood Donor

Cord blood from donor 1

Cord blood from donor 2

Cells from one unit dominate the other; both attack patient’s immune system

I’m in charge!

No, I’m in charge!
BLOOD AND MARROW TRANSPLANTS WORLDWIDE 1970-2002

<table>
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<th>YEAR</th>
<th>Autologous</th>
<th>Allogeneic</th>
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<tr>
<td>2000</td>
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NUMBER OF TRANSPLANTS

YEAR

0 5,000 10,000 15,000 20,000 25,000 30,000 35,000 40,000 45,000

Autologous

Allogeneic
Contribution of Allografting to Treatment of Cancer

ESTIMATED NUMBERS OF POTENTIAL TRANSPLANT CANDIDATES vs TRANSPLANT RECIPIENTS IN U.S.

- NHL: Allografts 57,000, Autografts 13,700
- MM: Allografts 9,200, Autografts <6.5
- AML: Allografts 7,200, Autografts 4,700
- HD: Allografts 4,700, Autografts 3,600

Numbers in thousands.
DISEASES TREATED BY HEMATOPOIETIC STEM CELL TRANSPLANTATION

Aplastic anemia
Thalassemia
Sickle cell anemia
Immunodeficiency disorders
Acute myelogenous leukemia
Myelodysplastic syndrome
Multiple myeloma

Acute lymphocytic leukemia
Chronic myelogenous leukemia
Chronic lymphocytic leukemia
Non-Hodgkin’s lymphoma
Hodgkin’s disease
Auto-immune diseases
Selected solid tumors

Modified from Armitage, NEJM 1994
Stem Cell Transplantation

**GOALS**

- Restore hematopoiesis in marrow failure states
- Replace a diseased marrow by a healthy donor marrow
- As a “rescue” to reconstitute hematopoiesis following marrow-ablative chemoradiotherapy
- As a mean for treating genetic disorders
Preparative (a.k.a. Conditioning) Regimens: “Preparing” Patients for Transplant

- To suppress the patient’s immune system from rejecting the stem cells (Allogeneic)
- To eliminate the cancer (Allogeneic and Autologous).
Preparative Regimens

COMPONENTS

- Cyclophosphamide: Backbone of several regimens
  Immunopsuppression + Myelosuppression

  Cyclophosphamide + TBI = Cyclophosphamide + Busulfan
Principles of Allogeneic HSCT

• Human leukocyte antigens (HLA): major determinants of histocompatibility between donor and recipient

These antigens are cell-surface glycoproteins encoded by a series of closely linked genes located on the short arm of chromosome 6 (p21)
Principles of Allogeneic HSCT

**HLA SYSTEM**

- Two distinct types of HLA genes:
  1) Class I: HLA-A, -B, -C genes
  2) Class II: HLA-DR, -DQ, -DP genes
Principles of Allogeneic HSCT

Donor Matching (Related)

• The likelihood that any sibling of a patient will inherit the same haplotypes is 1:4

• HLA-matched sibling donors can be identified for 30-40% of individuals since the average family consists of more than two children
Principles of Allogeneic HSCT

Donor Matching (Unrelated)

- Unrelated HLA-matched donors can be found for 15-35% of patients
- Long term outcome does not significantly differ from the outcome of patients receiving a graft from HLA-compatible sibling
Principles of Allogeneic HSCT

Donor Matching (Unrelated)

- Higher morbidity due to increased incidence of acute and chronic GVHD, graft failure, and prolonged convalescence
Major Histocompatibility Complex (MHC) and Human Leukocyte Antigens (HLA)

Paternal chromosome 6
- HLA genes
  - 6 major genes
    - D
    - D
    - D
    - B
    - C
    - A

Paternal leukocyte
- 2 (of 6) major human leukocyte antigens*

Maternal chromosome 6
- HLA genes
  - 6 major genes
    - D
    - D
    - D
    - B
    - C
    - A

Maternal leukocyte
- 2 (of 6) major human leukocyte antigens*

* are MHC proteins
Three Most Important Antigens

Many Varieties of MHC “Self” Genes

3 most important antigens for tissue matching

Human leukocyte antigens (MHC proteins)
Success in HLA-Matched Unrelated Matching Varies With Population

- Asian: 50%
- Japanese: 99%
- African American: 50%
- North American Caucasian: 93%
### STEM CELL DONOR AVAILABILITY

<table>
<thead>
<tr>
<th>Donor Type</th>
<th>Availability</th>
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<tr>
<td>Identical twin</td>
<td>&lt; 1%</td>
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<tr>
<td>HLA-matched Relative</td>
<td>25-30%</td>
</tr>
<tr>
<td>Unrelated Donor</td>
<td>10-40%</td>
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<tr>
<td>Cord Blood (1-3 ag mismatch)</td>
<td>50%</td>
</tr>
<tr>
<td>HLA-mismatched Relative</td>
<td></td>
</tr>
<tr>
<td>1 Ag mismatch</td>
<td>10%</td>
</tr>
<tr>
<td>2 Ag mismatch</td>
<td>50%</td>
</tr>
<tr>
<td>3 Ag mismatch</td>
<td>90%</td>
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Factors Affecting Transplant Success

**Patient Related**
- Age
- Performance Status
- Co-morbidity

**Disease Related**
- Chemotherapy sensitivity
- Histology
- Remission status prior to transplant
HSCT COMPLICATIONS

- Regimen-related toxicity
  - Agent-specific (e.g., etoposide → mucositis); Palifermin
  - Hemorrhagic cystitis
- Infections
- Veno-occlusive disease
- Thrombotic microangiopathy
- Idiopathic interstitial pneumonitis
- Acute GVHD
- Late complications
  - Chronic GVHD; relapse; Secondary MDS/AML; developmental
Causes of Death after Transplants Done in 1998-2002

**HLA-ID SIB**
- Relapse: 38%
- Infection: 17%
- Organ toxicity: 13%
- IPn: 5%
- Other: 13%

**AUTO**
- Relapse: 75%
- Organ toxicity: 8%
- IPn: 2%
- Infection: 6%
- Other: 9%

**UNRELATED**
- Relapse: 32%
- Organ toxicity: 11%
- IPn: 7%
- Infection: 19%
- Other: 17%
- Organ toxicity: 14%
- IPn: 5%
Non-Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation
Goals of non-myeloablative Transplant

- Increased access to allografting for older and debilitated patients
- Universal engraftment
- Reduction of GVHD
- Reduction of TRM
- Long term disease control
ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Old Paradigm
The allograft is a rescue product to replace the defective stem cells following ablation with cytotoxic therapy.

New Paradigm
A major therapeutic component of an allogeneic stem cell transplant is the "graft vs. leukemia" effect mediated by T-cells in the allograft.
What is the Rationale for NST

GVHD: Cytokine Dysregulation

DONOR T CELLS

RADIATION CHEMOTHERAPY

TNFα IL-1

HOST TISSUES

DONOR MONOS (BM)

Endotoxin (LPS)

IL-4 IL-10 (Type 2)

IL-2 IFN-γ (Type 1)
TRANSPANTATION

Irradiation/Chemotherapy

Host tissues

GI-tract

Phase 1:
Recipient conditioning

Donor/Host Mononuclear Phagocyte

TNF-α
IL-1
IL-6

LPS

Host Cells (MHC I, II and/or minor H)

Donor T Cells (CD4+ or CD8+)

IL-12

Phase 2: Donor T cell activation

Phase 3: Inflammatory effectors

TNF-α
IL-1
Nitric Oxide

Target cell apoptosis
Hypothesis: Most patients after allogeneic transplantation are cured by immunotherapy NOT by cytotoxic therapy

EVIDENCE:
• Higher relapse after T-cell depleted or identical twin transplants
• Higher relapse without GVHD
• Remission after stopping immunosuppression
• Remission after donor lymphocyte infusion (DLI)
Graft-versus-Leukemia Effect

![Graph showing the Graft-versus-Leukemia Effect](image)
Nonablative BMT for AML

Cumulative Proportion Surviving

Months After Transplant

had GVHD

no GVHD

P=0.0002
Donor Lymphocyte Infusions (DLI)

- Efficacious for persistent or recurrent disease without additional cytotoxic therapy.
- Efficacy varies by histology and disease state:
  - CML (chronic phase): 50 - 80%
  - CML (advanced phase): 10 - 30%
  - AML (+/- chemo): 25 - 50%
- High incidence of GVHD (40 - 60%)
- High correlation of GVHD and response.
- Optimal dose, frequency, and timing remain undetermined.
Non-Myeloablative Regimens: Definition

• Associated with spontaneous recovery of bone marrow within 28 days without stem cell “rescue”
• Allow engraftment of transplanted donor cells (no graft rejection)
• Lead to mixed chimerism upon engraftment of donor cells
NON-ABLATIVE HEMATOPOIETIC CELL TRANSPLANT (NST)

Recipient

Donor

Mixed Chimera

Complete Chimera
A CONTINUUM OF NON-MYELOABLATIVE AND REDUCED INTENSITY CONDITIONING REGIMENS

GENETIC DISPARITY

Immunosuppression

Myelosuppression
Host vs. Graft/Graft vs. Host

“Host-versus-graft reaction” (Rejection)

“Graft-versus-Host Reaction” (Graft-versus-Host Disease and Graft-versus-Tumor Effect)
### BLOOD AND MARROW TRANSPLANTS, 1996-2002

- **North and South America** -

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<thead>
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<th>Year</th>
<th>Traditional Allogeneic</th>
<th>Non-Myeloablative Allogeneic</th>
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* Data incomplete
Percentage of solid-tumor patients achieving full donor chimerism

- T-cell chimerism
- Myeloid chimerism

Days post-transplant

Childs, 2000
NST: Promises & Accomplishments

- Increased access to allografting for older and debilitated patients: Yes
- Universal hematopoietic engraftment: Yes
- Reduction of transplant-related mortality: Yes
- Reduction of GVHD incidence and severity: Some
- Long term disease control: Mostly
- Better overall survival: Maybe
- Whether NST is better than alternative treatments for similar patients is unclear
NST Current Challenges

• Reduce GVHD, especially in unrelated donors
  – Graft modifications (T-cell depletion, T-cell exchange)
  – Antibodies (Campath-1H, ATG, anti-CD25)
  – New immunosuppressive regimens (MMF/tacrolimus, sirolimus/MTX/tacrolimus)
  – New immunosuppressants (CTLA4-Ig)

• Infections
  – Novel antifungals (voriconazole)
NST Current Challenges

• Better control of the malignant disease
  – Monoclonal antibodies that enhance efficacy without increasing toxicity
    • Anti-CD33, anti-CD20, anti-CD52
  – Enhance immunotherapy
    • vaccines
  – Novel molecular targets
    • TK inhibitors
NST Current Challenges

• How to demonstrate that NST is superior to current standard of care in a specific situation (CLL, follicular NHL, myeloma)
  – When a standard of care exists only a randomized trial will answer this question