Understanding Bone Marrow Transplantation: Where Are We Now and What's Coming?

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Dr. E. Donnell-Thomas
1920 – 2012
Recipient of the 1990 Nobel Prize in Physiology and Medicine
for the development of bone marrow transplantation

Outline
• History
• Hematopoietic Cell Transplantation Fundamentals
• Donor Search and Graft Sources
• Preparing for a Transplant
• Conditioning Regimens
• The Transplant Process
• Early Post-Transplant Period
• Long-term Recovery
• Future Directions

A Brief History
**Principle of Marrow Grafting**

- **High-Dose Chemo-Radiation Therapy**
  - Destroys diseased marrow
  - Suppresses patient’s immune cells so that marrow graft will be accepted

- **Healthy Marrow Graft**
  - Replaces diseased marrow
  - Alloimmune reactions (GVT/GVL) contribute to the elimination of malignant disease

**Types of Hematopoietic Cell Transplant: Autologous**

- Stem cell infusion as “rescue” from high dose chemotherapy given at “marrow lethal dose”

- Works well for chemotherapy sensitive malignant diseases:
  - Hodgkin Lymphoma
  - High-grade Non-Hodgkin Lymphoma in remission
  - Multiple Myeloma

- Immune system “reset” for non-malignant, autoimmune disorders
  - Scleroderma
  - Multiple Sclerosis
  - Amyloidosis

**Types of Hematopoietic Cell Transplant: Allogeneic**

- Replacing bone marrow, as an organ: aplastic anemias, bone marrow failure syndromes, hemoglobin disorders (sickle cell anemias, etc)

- Utilizing donor immune system to control malignant disease: acute and chronic leukemias, low-grade lymphomas, MDS, myeloproliferative disorders, etc

- Allogeneic Donor Sources:
  - Syngeneic (identical twins)
  - HLA-identical siblings
  - HLA-matched unrelated donors
  - HLA-mismatched unrelated donors
  - HLA-haploidentical family members
  - Umbilical Cord Blood (usually HLA-mismatched)

**Location of Centers Participating in the CIBMTR 2015**
Multidisciplinary Team Approach

- Nursing (nurse coordinators, inpatient BMT RNs, ICU RNs, outpatient team RNs, home infusion RNs, research RNs)
- Advanced Practice Providers (NPs and PAs)
- Physicians
- Pharmacists (Team Pharm D)
- Dietitians/Nutritionists
- Social Workers
- Research Staff
  - Caregiver
- Consultants
  - Infectious Disease
  - Pulmonary
  - Gastroenterology
  - Others (ICU, Neurology, Psychiatry, etc.)
Donor Search: HLA-typing

- **Major Histocompatibility Complex (MHC):**
  A set of cell surface proteins essential for the immune system to recognize foreign molecules in vertebrates, which, in turn, determines histocompatibility
- **Human Leukocyte Antigen (HLA) system:**
  A gene complex encoding MHC proteins in humans

Donor Search – HLA typing

- **Match:**
  - Genotypic match = patient and donor have SAME PARENTS. Example: siblings
  - Phenotypic match = patient and donor share alleles, but do NOT have same parents. Example: all matched unrelated pairings, cousins
- **Degree of Match**
  - "6 of 6": HLA-A, B, and DRB1 alleles (3 pairs x 2 codominant alleles each = 6 codominant antigens or alleles)
  - "10 of 10": HLA-A, B, and DRB1 plus HLA-C and DQB1 (5 pairs x 2 alleles each, all codominant)

The MHC gene expression is **co-dominant**
Acquisition of HLA-haplotypes Follows Mendelian Rules of Inheritance.

Donor Search – HLA-typing

- Only ~25-30% of potential allogeneic stem cell transplant recipients will have an HLA-identical sibling donor.
- In the absence of a matched sibling donor, MSKCC considers an 8/8 (HLA-A, -B, -C, -DRB1) unrelated donor (URD) the gold standard stem cell source.
- Alternative Donor Sources:
  - HLA-mismatched unrelated donors
  - Umbilical cord blood
  - HLA-haploidentical ("half"-matched donors)

Effect of HLA-Matching on Graft Rejection and Graft-versus-Host Disease

<table>
<thead>
<tr>
<th>HLA-MATCH</th>
<th>GRAFT FAILURE (%)</th>
<th>GRADE III-IV aGVHD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic Match</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Phenotypic Match</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mismatch – 1 locus</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Mismatch – 2 or 3 locus</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>Matched unrelated</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>Mismatched unrelated – 1 locus</td>
<td>5</td>
<td>51</td>
</tr>
</tbody>
</table>

Overview of Donor Search Process

- Preliminary Search
  - 24-48 hrs
  - Entering search into NMDP database
- Preformal Search
  - 1-2 weeks
  - Siblings, family members HLA-typed
- Formal Search
  - 2-4 weeks
  - Number of possible fully matched, mismatched unrelated donors, umbilical cord units identified
  - Donors contacted
  - HLA-typing confirmed
  - Primary and backup donor or umbilical cord units identified
- Donor Workup
  - 2-4 weeks
  - Donor availability confirmed
  - Infectious disease screening, other testing as needed
- Transplant
  - Donor physical exam
Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017

Pre-transplant Care - Donor

- Donor evaluation (FACT requirement: separate team and physician)
- PBSC mobilization and collection – daily RN contact
- Education
- Symptom relief (diffuse bone pain and ache)

Graft Sources

- Bone Marrow
- Peripheral Blood Stem Cells: mobilized by G-CSF +/- plerixafor +/- chemotherapy
- Umbilical Cord Blood (single vs. double)

Umbilical Cord Blood Units
Pre-transplant Care

- First interface: initial consult
- Nursing coordinators, unrelated donor coordinators
- Pre-transplant workup and testing (patient and donor)
- Consenting
- Patient education

Pre-Transplant Testing

- Marrow biopsy to confirm disease status
- Infectious disease markers
- Chest CT scan, Sinus CT scan
- Pulmonary Function Tests
- Cardiac Function Tests: 2D Echo or MUGA scan
- Dental Evaluation
- Health Care Maintenance: colonoscopy, mammogram, PAP smear results
- Specific Health Issues – depending on medical history
## Transplant Timeline

<table>
<thead>
<tr>
<th>1-2 wks</th>
<th>4-6 days</th>
<th>14-21 days</th>
<th>2-3 months</th>
<th>Day 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Transplant Process Conditioning</td>
<td>HCT</td>
<td>Pre-engraftment</td>
<td>Early Post-engraftment</td>
<td>Long-term Recovery</td>
</tr>
<tr>
<td>Outpt.</td>
<td>Inpatient (Outpatient)</td>
<td>Outpatient</td>
<td></td>
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</tbody>
</table>

- Chemotherapy +/- Total Body Irradiation
- Immunosuppressive Therapy
- Infectious Disease Prevention
- Graft-vs.-host Disease Prevention

## Hematopoietic Cell Transplantation

### Vascular Access
- **Need:** reliable long-term venous access
- Externally tunneled catheters: Hickman-Broviac (single-, double-, triple lumina)
- Apheresis catheters
- Implantable subcutaneous ports
- PICC

### Transplant Process - Conditioning
- Chemotherapy and/or radiation therapy based
- Acute toxicities – symptom management
- Vigilant monitoring
- Initiation of GVHD prophylaxis
- Patient and caregiver support – physical and emotional
- Outpatient teaching
Conditioning Regimens

- Purpose – in patients with malignant disease:
  - Sufficient immunoablation to prevent graft rejection
  - Reduce tumor burden
- Traditional approach: otherwise supralethal doses of TBI and chemotherapy with non-overlapping toxicities
- Contribution of GVT effects recognized
  - Reduced-intensity conditioning
  - Nonmyeloablative conditioning

RIC and NMA Regimens

- Patients with acute and chronic GVHD had improved RFS
- Lower relapse rates associated with unmodified grafts vs. autologous, syngeneic or T-cell depleted grafts
  
  Immunologic GVT effects contribute to the cure of malignant disease

- Host-vs.-graft and graft-vs.-host reactions are both primarily mediated by T-lymphocytes
  
  Modulation of host-vs.-graft reactions would contribute to the prevention of GVHD

Conditioning Regimens: Definitions

- **Mycloablative or High-dose Regimens:**
  Expected to ablate marrow hematopoiesis, not allowing autologous hematologic recovery

- **Nonmyeloablative regimens:**
  Cause minimal cytopenias, do not require stem cell support

Conditioning Regimens: Definitions

- **Reduced-intensity Conditioning (RIC) Regimens:**
  - Do not fit the definition for myeloablative or nonmyeloablative conditioning
  - Result in potentially prolonged cytopenias
  - Require hematopoietic stem cell support
  - Dose of alkylating agent or TBI is generally reduced, by at least 30% (when compared to MA regimens)
  - Intensity of RIC regimens represents a continuum
**Conditioning Regimens**

**High-dose Conditioning Regimens**

12-16 Gy TBI, usually fractionated, combined with chemotherapy, most commonly CY (based on its antineoplastic and immunomodulatory properties).

**TBI-based Regimens**

- CY + TBI (≥ 12 Gy)
- tBU + CY (+ ATG)
- CY + iBU
- BU + Melphalan
- FLU + Melphalan
- FLU + Treosulfan + TBI (2 Gy)
- TBI (2 Gy) + FLU (90-250)
- tBU + CY (> 12 Gy)
- BU + Melphalan
- FLU + Melphalan

**Modified from HJ Deeg**

**High-dose Chemotherapy-based Regimens: tBU/CY**

- Steady-state BU plasma concentrations can be achieved rapidly and can be predicted from first dose kinetics
- IV BU: less individual variation in PK
- Standard high-dose regimen: BU/CY Tutschka et al., Blood, 1987

**Allogeneic Transplants Registered with the CIBMTR**

- By Conditioning Regimen Intensity

- Reduced Intensity
- Myeloablative
Commonly Used RIC Regimens: FLU/MEL

- **FLU**: 25-30 mg/m²/day
- **MEL**: 100-140 mg/m²
- **ATG**: +3 +1 +6 +11 +56 +180
- **HCT**
- **Tacrolimus BID**
- **Methotrexate 5 mg/m²/dose**

2 yr OS: 66% for patients in CR
40% active disease without circulating blasts
23% active disease with circulating blasts
4 yr OS: 71% in CR at the time of HCT

Oran et al., BBMT, 2007
Popat et al., BMT, 2012

Cyclophosphamide and ATG Conditioning for Patients with Aplastic Anemia with HLA-identical Sibling Donors

Nonmyeloablative Conditioning: The “Seattle Regimen”

- **FLU**: 30 mg/m²/day
- **2 Gy TBI**
- **PBSCT**
- **CSP/TAC BID**
- **MMF BID / TID**
- **Chimerism Analyses**

Day 0: Transplant Process

- Stem-cell product infusion
- Cryopreserved products: DMSO
- Infusion reactions

Storb et al., JCO 2013

Gren et al., BBMT 2007
Popat et al., BMT 2012
Pre-engraftment

- Toxicities and symptom management
- Early detection and management of complications
- Infection prevention
- Neutropenia precautions
- Transfusion support
- Pain management
- If outpatient daily visits (some/most can be RN visits)
- Ongoing patient education

Hematopoietic Cell Transplantation Complications

1. Infections
   - Bacterial
   - Fungal
   - Viral

2. Regimen-Related Toxicities
   - Marrow Aplasia
   - Mucositis
   - Other Organ Toxicities

3. GVHD
   - Acute vs. Chronic
   - Skin, Gut, Liver

Days

- TBI or BU
- Cy
- HCT
- Methotrexate
- Calcinuerin Inhibitor (CSP or TAC)

Early Post-engraftment

- Detection of early complications: GVHD
- Infection prevention/treatment
- Supportive care
- Oral intake monitoring
- Communication with inpatient staff, if/when needed
- Caregiver support
- Preparation for long-term recovery
- Discharge education

Regimen Related Toxicity

- Regimen intensity¹
  - Myeloablative
  - Reduced intensity
  - Nonmyeloablative

- Common Toxicities
  - Side effects of radiation and chemotherapy
  - Organ Toxicity
    - Mucositis
    - Bone marrow
    - Lung
    - Heart
    - Kidney
    - Liver
    - Nervous system

¹Bacigalupo A et al, Biol Blood Marrow Transpl. 2009, 15:1628-1633
Causes of HCT Morbidity and Mortality

Early
- Mucositis
- Infection due to neutropenia
- Hemorrhagic cystitis
- Cardiomyopathy
- Sinusoidal obstruction disease
- Graft rejection
- Graft-Versus-Host Disease
- Opportunistic infections

Late
- EBV-PTLD
- Disease Recurrence
- Endocrine: growth delay, infertility, cataracts, caries
- Secondary Malignancies

Graft vs. Host Disease (GVHD)

Host versus Graft and Graft versus Host Reactions

Pathophysiology of Graft vs. Host Reactions
# GVHD

- Traditional description of acute GVHD: syndrome of cutaneous, hepatic and gastrointestinal inflammation within 100 days of HCT
- Currently defined by clinical features rather than timing
- Acute GVHD: cutaneous, gastrointestinal and hepatic manifestations
- Chronic GVHD: presents 3 – 24 months after allogeneic HCT, approximately 50% develop within the first 6 mo
- Chronic GVHD: skin, mouth, eyes, liver, lungs, GI tract, musculoskeletal system, female genital organs
- Chronic GVHD can overlap with acute form
- Therapy: calcineurin inhibitors, corticosteroids
- Approximately 85% of patients who survive beyond 5 years are able to discontinue systemic therapy

# Acute GVHD

- Grade II-IV acute GVHD develops in approx. 50-60% of unmodified allogeneic stem cell transplant recipient
- Risk Factors:
  - Donor-recipient HLA-mismatch
  - Unrelated donor vs sibling
  - Multiparous female
  - PBSC vs BM
  - Intensity of transplant conditioning
  - Unable to tolerate calcineurin inhibitor or subtherapeutic drug levels

## Acute GVHD: Skin

- Most common affected organ
- Maculopapular rash with possible blistering/ulceration
- Pathology: apoptosis at base of epidermal rete pegs, crypt loss, perivascular lymphocytic infiltration in the dermis

## Acute GVHD: Gut

- Symptoms: nausea, vomiting and/or diarrhea
- **Diarrhea** is the most dangerous and hard to treat
- Lower treatment response (only 42%).
- ↑ Risk of death
- Worse quality of life
Chronic GVHD

• Common complication after HSCT.
• 2-year cumulative incidence requiring systemic treatment is 30-40%
• Manifestations typically appear within the 1st year of transplant
• Common onset: immunosuppression taper
• Can begin as early as 2 mo and as late as 7 yrs
• Onset > 1 year HSCT is only 10%

First Line Therapy of Chronic GVHD

Corticosteroids!
• Recommended ≥ 1 year for patients with moderate to severe disease
• Patients should also receive:
  – Infection prophylaxis
  – Vit D 1000 IU/day
  – Calcium 1500 mg/day

Second Line Agents in Chronic GVHD

• Extracorporeal Photophoresis
• Mycophenolate Mofetil
• Sirolimus (Rapamycin)
• Rituximab
• Pentostatin
• Low-dose methotrexate
• Imatinib
• Ruxolitinib
• Ibrutinib
Chronic GVHD Outcomes

• 50% will be cured within 7 years after starting systemic therapy
• 10% continue on systemic treatment beyond 7 years
• 40% have recurrence of malignancy or die of cGVHD complications

GVHD Summary

• Is unknown which patients will develop graft-versus-host disease but certain risk factors can increase the likelihood of this complication
• Acute GVHD is common after transplant (30-60%)
• Chronic GVHD is also common and frequently affects the skin and oral mucosa
• GVHD may affect the patient quality of life
• New approaches minimizing corticosteroids exposure are underway

Long-term Recovery

• Diagnosis and treatment of chronic GVHD
• Screening for long-term side effects (osteoporosis, cataracts, etc)
• Screening for secondary cancers
• Health maintenance (colonoscopy, mammography, PAP smears, etc.)
• Transplant RN: liaison between the transplant team and referring physician

Future Directions

• Graft manipulation, cellular therapy
• Maintenance therapy to prevent relapse of malignant disease
• GVHD prevention and therapy
• Radioimmunotherapy
• Microbiome-based interventions
• Homebound transplants
HLA-matched Related Marrow Grafts for Patients with Aplastic Anemia Conditioned with CY/ATG

Commonly Used Conditioning Regimen in MDS: Targeted Busulfan and Cyclophosphamide
Impact of 5-Group Karyotype

N = 1007 patients with MDS
Underwent allogeneic HCT at the FHCRC
Through June 2010
Deeg et al., Blood, 2012

Impact of Conditioning Regimen

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