Bone Marrow Transplantation: Risks and Benefits

Aplastic Anemia and MDS International Foundation
2019 Patient & Family Conference
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Medical College of Wisconsin
Objectives

1. What is a bone marrow transplant (BMT)?
2. What are the complications of BMT?
3. Who should be considered for a BMT?
4. What are the outcomes of BMT in MDS and aplastic anemia?
5. What’s next?
What is a bone marrow transplant?
EACH DAY...
- 200 billion red cells
- 200 billion platelets
- 70 billion white cells
Bone Marrow Transplant

Aka “Stem Cell Transplant” (SCT)
Aka “Hematopoietic Stem Cell Transplant” (HSCT)

1. Cancer
   • Tool to give more chemotherapy
   • Immune therapy against more resistant cancers
     • MDS

2. Immune deficiency

3. Replace dysfunctional marrow
   • Aplastic anemia
   • PNH
Types of Transplant

I. MODALITY

• Autologous
  • Patient's own stem cells

• Allogeneic
  • Stem cells from a HLA matched donor
    • Match at HLA-A, B, C (class I MHC) AND
    • Match at DRB1, DQB1 (class II MHC)

• Syngeneic
  • Stem cells from an HLA identical donor (ie identical twin)
Annual Number of HCT Recipients in the US by Transplant Type

- Adjusted Autologous HCT
- Adjusted Allogeneic HCT

Number of Transplants

CIBMTR

Froedtert & Medical College of Wisconsin
Types of Transplant

...for allogeneic only...

II. DONOR SOURCE

• Matched related
  • Related donor at least 8/8 HLA match
  • 25% chance of full sibling

• Matched unrelated
  • Unrelated donor who is at least an 8/8 HLA match
  • Chance related to ethnicity

• Mismatched
  • Donor who is < 8/8 HLA match with recipient

• Haploidentical
  • Related donor who is mismatched at as many as 3/6 HLA loci (HLA A, B, DR) – ie siblings, children, parents

• Umbilical cord blood
  • Stem cells collected from umbilical cord + placenta after baby is born; immaturity of immune system allows for higher level of HLA mismatch, requires at least 4/6 match (HLA-A, B, DRB1)
HLA: Our Genetic “Fingerprint”

- **Human Leukocyte Antigens (HLA)** are proteins found on the surface of most cells in the body.
- The immune system uses HLA to verify that a given cell is part of the body and not foreign.
  - Grab on to foreign proteins in a way that allows immune cells to recognize and destroy them without destroying normal cells.
- There are many different HLA proteins (HLA-A, -B, -C, -DRB1, -DQ, -DP) and there are many varieties of each one.
HLA: Our Genetic “Fingerprint”

• Alleles = Genes that control HLA antigens; are on chromosome 6
• Antigens = the proteins that are on the surface of cells
HLA Inheritance

Mother

- A: 1 (9), 2
- B: 3, 4
- C: 5, 6
- DR: 7, 8

Father

- A: 9, 10
- B: 11, 12
- C: 13, 14
- DR: 15, 16

Child 1, Child 2, Child 3, Child 4

Child 1

- A: 1 (9), 11
- B: 3, 13
- C: 5, 15
- DR: 7, 16

Child 2

- A: 1 (10), 11
- B: 3, 12
- C: 5, 14
- DR: 7, 16

Child 3

- A: 2 (9), 11
- B: 4, 12
- C: 6, 13
- DR: 8, 16

Child 4

- A: 2 (10), 11
- B: 4, 12
- C: 6, 14
- DR: 8, 16
Why is HLA Matching Important?

• If donor stem cells are not the same HLA type as the recipient they will recognize the recipient as being different and attack – and vice versa
  • If the recipient cells win, you get graft rejection
  • If the donor cells win, you get graft-versus-host disease (GVHD)
Types of Transplant

...for allogeneic only...

II. DONOR SOURCE

• Matched related
  • Related donor at least 8/8 HLA match
  • 25% chance of full sibling

• Matched unrelated -- >17,000,000 people around the world!!
  • Unrelated donor who is at least an 8/8 HLA match
  • Chance related to ethnicity

• Mismatched
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• Haploidentical
  • Related donor who is mismatched at as many as 3/6 HLA loci (HLA A, B, DR) – ie siblings, children, parents

• Umbilical cord blood
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III. STEM CELL SOURCE

• Peripheral blood stem cells
  • Collected using a peripheral blood pheresis procedure after a chemokine-based or chemotherapy-based regimen
    • Common donor side effect: bony pain
    • Major side effect: low platelet counts, long term effects
Types of Transplant

III. STEM CELL SOURCE

• Bone Marrow
  • Collected directly from the bone marrow – generally no pre-procedure mobilization but requires OR and general anesthesia
    • Common donor side effect: pain
    • Major side effect: significant bone, nerve, soft tissue injury
Types of Transplant

III. STEM CELL SOURCE

• Umbilical cord blood
  • Removed from umbilical cord and placenta after normal delivery of infant donor
  • Can be stored frozen for 10+ years
    • Common donor side effects: none
    • Major donor risks: none
Transplant Logistics*

<table>
<thead>
<tr>
<th>...full medical evaluation ...</th>
<th>D-x CHEMO</th>
<th>Aka “conditioning”</th>
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<td>Rest Day</td>
<td>Day 0 HCT</td>
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<td>Day 12... counts rising</td>
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<td>Day 19... home?</td>
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- Generally inpatient for ~3 weeks *
- Need to live within ~45 minutes
- Need an adult caregiver through ~d90
Day 0 – Day of Transplant

• Stem cells from marrow or peripheral blood are collected from donor the day before and/or the day of transplant
  • Transported to patient and administered like a blood transfusion
• Cord blood units are shipped to transplant center and stored before start of preparative regimen
• Side effects are usually the same as a blood transfusion and may include fever, chills and rash
Transplant Logistics*

| ...full medical evaluation ... | D-x CHEMO  
Aka “conditioning” → | Rest Day | Day 0 HCT | Day 12... | Day 15... Engraft? | Day 19... home? |
|-------------------------------|-------------------|----------|---------|--------------|-----------------|----------------|

- Generally inpatient for ~3 weeks *
- Need to live within ~45 minutes
- Need an adult caregiver through ~d90
Recovery: Early Days after Transplant

• 14-21 days of extreme immune suppression:
  • Very low white blood cell, red blood cell & platelet counts
• At risk for serious infections, bleeding, and organ damage from the conditioning regimen
• Antibiotics given to prevent & treat infection
• Blood & platelet transfusions given as needed
• Closely monitored for organ damage and treated and supported as needed
Transplant Logistics*

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Engraftment

• Term used to refer to the establishment of new stem cells within the bone marrow as evidenced by the appearance of (in order):
  • White blood cells
  • Platelets
  • Red blood cells

• Occurs 10-28 days after transplant

• Risk for infection and bleeding decreases following engraftment
### Transplant Logistics*

| ...full medical evaluation ... | D-x CHEMO  
Aka “conditioning” → | Day 0 HCT | Rest Day | Day 12... |
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- Need to live within ~45 minutes
- Need an adult caregiver through ~d90
Getting Discharged

• You will be discharged from the hospital when:
  • You’ve engrafted – Absolute Neutrophil Count (ANC) > 500
  • No active infection
  • No active Graft Versus Host Disease (GvHD)
  • Able to take foods and meds by mouth
Life After Transplant

• The first 100 days
  • Close monitoring for complications such as GvHD and infections
  • Frequent clinic visits with possible readmission to the hospital for treatment of complications

• Don’t be discouraged by re-hospitalization: it’s very common
  • Restriction of activities
  • Need caregiver for transportation, shopping, cooking
What are the complications of BMT?
Complications

1. Low cell counts
2. Toxicity from the chemotherapy/conditioning
3. Graft failure
4. Graft-versus-host disease
5. Infection
6. Veno-occlusive disease
7. Relapse
8. Late effects
Complications

1. Low cell counts
   • Secondary to the chemotherapy prior to transplant
     • Results in fatigue, bleeding, and infectious risk
     • Will be dependent on transfusion of RBCs and platelets during chemotherapy and prior to engraftment
Complications

2. Toxicity from the chemotherapy/conditioning
   • Organ toxicity – heart/lung/liver/kidneys
   • Risk of seizure
   • Nausea/vomiting/diarrhea
   • Rash
   • Mouth sores

Higher dose chemo/XRT
Goal: Kill ALL stem cells/diseased cells -more side effects

Lower dose chemo/XRT
Goal: Suppress recipient immune system to allow donor to engraft
-usually used in patients less likely to tolerate side effects of high dose transplant
Complications

3. Graft failure

• Donor stem cells not engrafted within host marrow, fail to produce necessary hematopoietic elements
  • Primary: donor stem cells NEVER engrafted
  • Secondary: loss of donor cells after initial engraftment

• ~5% or less

• Higher risk with cord blood, reduced intensity transplants, certain disease states (ie MF)
Complications

4. Graft-versus-host disease
Complications -- GVHD

• Risk depends on:
  • Degree of HLA compatibility
    • >HLA compatibility = < GVHD
      • Related < unrelated
  • Stem cell source
    • BM < GVHD vs PBSC
  • Conditioning regimen
    • NMA/RIC < MA
Complications -- GVHD

**Acute**
- <d100
- 40-70% of patients
- Skin -- rash
- GI – upper or LOWER GI, diarrhea
- Liver – increased bilirubin

**Chronic**
- >d100
- Skin – lichen planus, sclerosis, hyper- or hypo-pigmentation
- Eyes/mouth -- dry
- Liver – abnormal LFTs
- Lungs -- BO
- MSK – fasciitis, contractures
Complications

5. Infections:

Pre-engraftment period
- Bacterial organisms from skin/oral/GI flora
- Invasive fungal infxn
- HSV

Post-engraftment period
- Impaired cell mediated immunity, humoral immunity and phagocyte function
- ?GVHD? Additional IS

Late post-transplantation period
- VIRAL – CMV, adeno, respiratory, HHV-6, BK
- Invasive fungal infxn
- PCP

?chronic GVHD – defects in cellular, humoral, barrier functions
- Skin infxn, upper and lower respiratory tract
Complications

6. Veno-occlusive disease
   • Painful hepatomegaly, ascites, jaundice, weight gain → fulminant liver failure; typically 3-21 days post-transplant
   • Progressive injury in hepatic venous endothelium with progressive occlusion of venules + sinusoids
   • Risk factors: pre-existing liver disease, hepatitis, conditioning regimen, prior treatments
   • Prevention: minimize risks, ursodiol
   • Treatment: Defibrotide
Complications

7. Relapse

• 10-40% of undergoing allogeneic HCT
  • Donor lymphocyte infusions
    • Risks: GVHD, myelosuppression
  • Additional chemotherapy
  • Second transplant
Complications

8. Late effects
   • Late relapse
   • Chronic GVHD
   • Late infection
   • Cardiovascular diseases – ischemic heart disease, cardiomyopathy
   • Pulmonary toxicity
   • Renal dysfunction
   • Endocrinopathies – DM2, thyroid disease, osteopenia, infertility, hypogonadism, hypoadrenalism
   • Treatment related malignancies
   • Increased risk for secondary solid tumors
Who should get a BMT?
Right disease, right patient...
Indications

I. Autologous
   • Malignant
     • Myeloma/other plasma cell disorders
     • Non-Hodgkins lymphoma – relapsed DLBCL, MCL, PTCL, +/- FL
     • Hodgkin’s lymphoma
     • Relapsed germ cell tumors
     • Acute promyelocytic leukemia (APL)

Transplantation of Stem Cells Allows Us to Increase the Dose Intensity of Our Treatments
Patient as Donor: Autologous Transplantation
Collect & freeze cells

Radiation/Chemo to kill the cancer

PBSC

Support until recovery

Blood stem cells to restore blood production
Indications

• Non-malignant
  • Autoimmune conditions -- ?immune re-set?
Indications

II. Allogeneic

• Malignant -- GRAFT versus TUMOR effect
  • Acute leukemias – AML, ALL (APL)
  • MDS/MPN
  • CML
  • CLL
  • Myeloma
  • NHL
  • HL

Donor’s immune cells can recognize and destroy cells of some kinds of cancer
Blood stem cells to restore blood production, **destroy cancer cells**

**Healthy Donor: Allogeneic Graft**

Conditioning may or may not kill all cancer cells

Support until recovery
Indications

• Benign – replacing diseased organ
  • *Aplastic anemia*
  • Congenital marrow failure syndromes
  • Hemoglobinopathies
  • Immunodeficiency syndromes
Indications for Hematopoietic Cell Transplant in the US, 2017

- **Allogeneic** (Total N=8,780)
- **Autologous** (Total N=14,599)

Number of Transplants

- Myeloma / PCD
- NHL
- AML
- MDS / MPN
- ALL
- HD
- Other Cancer
- Other Non-Malignant Disease
- Aplastic Anemia
- CML
- CLL
Comorbidities

- **NOT** all about age
- Cardiac disease
- Inflammatory bowel disease
- Diabetes
- CVA
- Psychiatric illness
- Liver disease
- Kidney disease
- Pulmonary disease
- Obesity
- Uncontrolled infection
- Ulcer disease
- Rheumatologic disease
- Other cancers

***These items will help determine conditioning intensity as well as candidacy for transplant overall***
When???

• For some diseases, transplant should be part of initial treatment
• For others, transplantation is appropriate when other drugs fail
• Whichever disease you have, it is good to have a consult with a transplant expert early on – to make sure that you get a transplant when you need it and when it is most likely to benefit you
What are the outcomes of BMT in MDS and aplastic anemia?
MDS
Transplants by Patient Diagnosis
Hematologic Malignancies
Unrelated Donor Transplants Facilitated by NMDP/Be The Match

Source: National Marrow Donor Program/Be The Match FY 2017
# Myelodysplastic / Myeloproliferative Diseases - Adult

Unrelated HCT Improved Survival Over Time
Transplants Facilitated by NMDP/Be The Match

## Improved Survival Over Time – MDS/MPN

<table>
<thead>
<tr>
<th>YEAR OF HCT</th>
<th>NUMBER OF CASES</th>
<th>ONE-YEAR SURVIVAL</th>
<th>TWO-YEAR SURVIVAL</th>
</tr>
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<tbody>
<tr>
<td>2013-2016</td>
<td>2,766</td>
<td>62%</td>
<td>52%</td>
</tr>
<tr>
<td>2009-2012</td>
<td>1,733</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>2004-2008</td>
<td>1,086</td>
<td>55%</td>
<td>46%</td>
</tr>
<tr>
<td>1987-2003</td>
<td>1,357</td>
<td>43%</td>
<td>37%</td>
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</tbody>
</table>

SOURCE: CIBMTR®, the research program of NMDP/Be The Match
Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2006-2016

- Early (n=1,863)
- Advanced (n=3,342)

p < 0.001
Survival after HLA-Matched Sibling HCT for Myelodysplastic Syndrome (MDS), 2006-2016

p<0.001

Early (n=1,049)

Advanced (n=1,930)
IPSS-R considers:
- degree of cytopenias
- blast percentage
- cytogenetic abnormalities

But when??

<table>
<thead>
<tr>
<th></th>
<th>Immediate Transplant</th>
<th>Transplant at Progression</th>
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<tr>
<td><strong>WAIT</strong></td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>6.51</td>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>5.16</td>
</tr>
<tr>
<td><strong>TRANSPLANT IMMEDIATELY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.2</td>
<td>2.75</td>
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Aplastic Anemia
Management of Severe Aplastic Anemia

Acquired SAA

- HLA = Sib
  - ≤40 years: Sib BMT
  - 41-60 years: ATG+CsA, no resp d+120, Sib BMT
- No HLA = Sib
  - ≤20 years: ATG+CsA, no resp d+120
  - 0-60 years: ATG+CsA, no resp d+120
  - >60 years: UD BMT, Alt Donor Tx, Second ATG+CsA, Anabolic steroids, Eltrombopag, Supportive care
Survival after Allogeneic HCT for Severe Aplastic Anemia, <18 Years, 2006-2016

- HLA Matched Sibling (n=1,013)
- Unrelated Donor (n=756)

p<0.001
Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2006-2016

- HLA Matched Sibling (n=1,426)
- Unrelated Donor (n=1,041)

p<0.001
Management of Severe Aplastic Anemia

Acquired SAA

- HLA = Sib
  - ≤40 years: Sib BMT
  - 41-60 years: ATG+CsA
    - no resp d+120: Sib BMT
    - ≥20 years: ATG+CsA
      - no resp d+120: Sib BMT
      - 0-60 years: ATG+CsA
        - no resp d+120: UD BMT
        - >60 years: ATG+CsA
          - no resp d+120: UD BMT

- No HLA = Sib
  - ATG+CsA
    - no resp d+120: Alt Donor Tx
      - Second ATG+CsA
        - Anabolic steroids
        - Eltrombopag
        - Supportive care
Survival after Allogeneic HCT for Severe Aplastic Anemia, <18 Years, 2006-2016

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Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2006-2016

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Probability, %

Years

0 1 2 3 4 5 6
What’s next?
MDS

• **BMT CTN 1102** – A Multi-Center Biologic Assignment Trial Comparing Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients with Intermediate-2 and High Risk Myelodysplastic Syndrome – completed accrual, await results

• **French study** – low/intermediate risk MDS transplant/no transplant at diagnosis based on availability of a matched related or unrelated donor -- recruiting

• **Initial Cytoreductive Therapy for Myelodysplastic Syndrome Prior to Allogeneic Hematopoietic Cell Transplantation (the ICT-HCT Study)** – intensive versus less intensive chemotherapy prior to transplant in patients with MDS
  • Mayo Scottsdale, Cleveland Clinic, Fred Hutch, Kaiser Permanente Washington

• Strategies to make transplant SAFER – GVHD prevention, changes in conditioning, etc.
Aplastic Anemia
Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP):

**BMT CTN 1502**

- Phase II pivotal trial
  - Intended to provide evidence that the curative option available to SAA patients
  - Repeated IST is of less value for patients

- Addresses key need in rare patient population
Study Design & Objectives

• **Study design:** Prospective, multicenter, phase II study in patients receiving haploidentical transplant for severe aplastic anemia

• **Primary objective:** Assess overall survival at one year post-HSCT in patients with SAA

• Secondary objectives include
  • Probability of being engrafted and alive at 1 year
  • Probabilities of GVHD
Inclusion Criteria

1. ≤ 75 years of age
2. Confirmed diagnosis of acquired SAA
3. No suitable fully matched related (6/6) or unrelated donor (8/8) available
   • Ok to forego this donor search if the clinical situation dictates urgent transplant (low likelihood of identifying a suitable donor within 6-8 weeks)
4. Refractory (at 3 months) or relapsed after at least one trial of immunosuppressive therapy directed at primary SAA
5. Available HLA haplo first degree relatives (2, 3, or 4 mismatches, but with at least one allele identical at HLA-A, -B, -C, or DRB1)
Aplastic Anemia

• A Phase II Trial of Non-Myeloablative Conditioning and Transplantation of Partially HLA-Mismatched/Haploidentical Related or Matched Unrelated Bone Marrow for Patients with Refractory Severe Aplastic Anemia and Other Bone Marrow Failure Syndromes
  • Johns Hopkins + MCW
Questions?
References


