Understanding Bone Marrow Transplant
Where we are now, and What’s Coming
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Indianapolis IN
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Stem Cell Harvest
Transplant Conditioning
Treatment 2-7 days

What is a marrow stem cell transplant delivering?

- For many malignancies, there is a dose–response effect for chemotherapy. High doses of treatment can overcome resistance, but at the price of permanent marrow failure. Marrow transplantation overcomes this problem (allogeneic and autologous)
- Allogeneic immune cells have the capacity to attack recipient cells, so establishing donor stem cells in the recipient may well decrease relapse potential (graft versus leukemia effect)

What is a marrow transplant delivering? (cont.)

- Bone marrow failure diseases (aplastic anemia) can be cured by providing a source of new marrow
- Certain inherited metabolic diseases can be overcome by marrow transplants from healthy donors by replacing the deficient enzyme

DOSE RESPONSE AND CURABILITY OF HEMATOLOGICAL MALIGNANCIES

- Other Fatal Toxicity
- Bone Marrow Toxicity
- No Limiting Toxicity

Relative Dose of Therapy Needed to Cure Tumor

Transplant conditioning regimen

- High dose treatments–myeloablative
  - Allogeneic and autologous
  - Most common are total body irradiation or busulfan and cyclophosphamide
  - Many other myeloablative alternatives
- Less intensive regimens–NMT or RIT
  - Allogeneic conditioning designed for immunosuppression rather than myeloablation—allow engraftment and graft vs. tumor effect
Applications of SCT

- Replace diseased stem cells (AML, CML, SAA, MDS, Myeloproliferative)
- Repair congenital stem cell defects (SCID, Inborn Errors, Sickle Cell, Thalassemia)
- Overcome chemotherapy cytopenia (AML, NHL, Myeloma, Hodgkins, others)
- Adoptive immunotherapy (GvL, auto-immune Dz)

Sources of HSC – The Donor

- Autologous – from the patient
- Syngeneic – from the patient’s identical twin
- Allogeneic – from a HLA tissue-matched donor –
  - MSD – matched sibling donor – full brother / sister
  - MUD – matched unrelated donor – a volunteer identified as compatible with the patient – a specific type of allogeneic donor
  - PMRD – partially matched related donor
- Haploidentical – Half matched family (parent, sibling, child)
- UCBD – umbilical cord donor (matched or mismatched)

HLA Typing

- HLA system located on chromosome 6
  - Class 1: HLA A, B, C
  - Class 2: DR, DQ, DP
  - With smaller family size, the likelihood of having a sibling match is about 30%
- Molecular diagnostic methods allow improved matching outside of the family
- Alternative donors—matched unrelated donors about 70% find a match
- Alternative donor—umbilical cord donor can find about half the time for adults
Source of Stem Cells

- Bone Marrow
  Surgical procedure, rapid, not complex, some discomfort

- Peripheral blood
  IV access issues, time consuming, more complex, less discomfort

Iliac Crest BM Aspirations

Mobilization Schema

G-CSF Alone

Daily G-CSF Injections

5 to 9 days

Apheresis

2 to 5 days

Peripheral blood stem cell collection by apheresis

Bone marrow vs. Blood stem cells

- Compared to marrow harvest, blood has
  - 10 times more mononuclear cells
  - 5.5 times more CD3+ T-cells
  - 3 times more CD19+ B-cells
  - Similar numbers of CD4+ T-helper cells
  - Higher percentage of CD8+ T-suppressor cells

Source of Stem Cells

- Recovery of blood counts is more rapid following peripheral blood stem cell transplants (autologous and allogeneic)
- Probably less chance of tumor contamination with peripheral blood stem cell transplants (autologous)
- More chronic graft versus host disease with peripheral blood transplants (allogeneic) Does this matter?

Blood versus bone marrow

- The incidence of chronic GVHD and chronic infections is higher after peripheral blood transplants.
- This decreases the success rate of low risk leukemia: childhood acute leukemia, first remission AML, and chronic phase CML.
- Greater graft vs. disease effect from blood stem cell transplants may increase the success rate of 2nd remission leukemia and other diseases in adults.

Annual Number of HCT Recipients in the US by Transplant Type

Allogeneic HCT Recipients in the US, by Donor Type

Unrelated Donor Allogeneic HCT in Patients Age ≥18 years

Trends in Allogeneic HCT in the US by Recipient Age^1

Indications for Hematopoietic Cell Transplant in the US, 2016

^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma.
Limited number of HLA identical family donors

Alternative donors include unrelated, umbilical cord blood, and haploidentical related donors

Few transplants using umbilical donor cells have been performed in adults.

Most patients will have a haploidentical related donor without HLA sensitization.
Reduced intensity haploidentical BMT with post-transplant cyclophosphamide

- In the USA most people have over 3 potential haploidentical relatives
- Post transplant cyclophosphamide decreases the risk of GVHD
- Engraftment and the risk of GVHD appears acceptable

Johns Hopkins Alternative donor BMT using post transplant cyclophosphamide in SAA

- 21 patients with refractory SAA (median f/u 24 mos (range 3–72)
  - Median age: 33 years (range 5–69)
  - 15/21 had evidence of clonality (PNH and/or cytogenetic abnormality)
  - 18 haplo 1 mmURD(9/10) 2 URD (10/10)
  - Rapid and consistent engraftment
  - ANC 15 days Reds 25 days Platelets 28 days
  - Day 60 chimerism 100% in 20/21 patients
- One primary graft failure (engrafted with 2nd BMT from different donor)
- Excellent Disease Free Survival
  - All 21 alive, transfusion-independent, without clonality (KPS 100)
  - Acute GVHD grade II-IV 2/21 (9.5%)
  - Extensive chronic GVHD 0/21
- All off IST

DeZern et al BBMT 2017

Complications – Allo BMT

- 1st three weeks (D+21):
  - Anorexia, nausea, vomiting, diarrhea
  - Mucositis
  - Pancytopenia – RBC & platelet transfusions
  - Neutropenic fever
  - Infection – bacterial, viral, fungal
  - Veno–Occlusive Disease (VOD)
  - Graft versus Host Disease (GvHD)

Factors determining immune reconstitution after allogeneic SCT

- Source of stem cells
- Age of donor and recipient
- Numbers of progenitors
- Donor matching
- Bone marrow manipulation/purging
- Intensity of prior treatment
- Presence of GVHD
- GVHD prophylaxis

Engraftment after SC infusion (days)

<table>
<thead>
<tr>
<th>Source of stem cells</th>
<th>AGC&gt;500</th>
<th>Plat&gt;20k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous BM (w/o GF)</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Autologous BM (w/GF)</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Autologous PBSC (w/o GF)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Autologous PBSC (w/GF)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Allogeneic BM (w/o GF)</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Allogeneic PBSC (w/o GF)</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

(BMT/JCCM B: 37, 2000)
Chronic GVHD
Marrow infusion
Ablative therapy begins

Complications Following Allogeneic BMT

Viral pneumonia

Fungal pneumonia post transplant

Complications – Allo BMT

- 1st three months (D+100):
  - Anorexia
  - Cytopenias – RBC & platelet transfusions
  - Infection – viral, fungal
  - Renal insufficiency
  - High blood pressure
  - Edema
  - Graft versus Host Disease (Acute GvHD)
    - skin, gut, liver

- Beyond 1st three months (>D+100):
  - Infection – viral
  - Renal insufficiency
  - High blood pressure
  - Graft versus Host Disease (Chronic GvHD)
    - skin, gut, liver, lungs, joints
  - Relapse of disease

Complications - Allo BMT

- Days after transplantation
- Months

Risk factors
- Interstitial Herpes simplex virus
- CMV
- Adeno, HHV-6
- Varicella zoster virus
- EBV
- Candida
- Aspergillus
- Gram+ Encapsulated

Days after transplantation
- Months

Complications Following Allogeneic BMT
**Graft versus host disease**
- Immune cells transplanted from a donor (graft) recognize the transplant recipient (host) as foreign causing an immune attack that causes disease in the transplant recipient.
- Acute: usually during the first 3 months, skin, liver, gastrointestinal targets
- Chronic: chronic reactions of the skin, GI tract, liver, mouth, eyes, joints usually after 3 months
- Methods to prevent GVHD are always used and include medications such as cyclosporine, tacrolimus, methotrexate, and mycophenolate.

**GVHD Risk Factors**
- Degree of HLA match, sibling vs. unrelated
- Donor/recipient gender difference
- Transplant regimen intensity/TBI
- Method used to prevent GVHD
- Cell source: bone marrow, peripheral blood, umbilical cord blood
- Age of the donor/recipient

**GVHD management**
- In spite of preventative efforts, many patients develop acute GVHD and need treatment.
- Treatment can be directed at both the target organ (topical steroids to the skin, oral non-absorbable steroids to the gastrointestinal tract) and be systemic either IV or oral medications. **Steroids** such as prednisone are the backbone of all GVHD treatments.
- Many responses are only partial, and additional drug treatments or non-drug treatments such as photopheresis are used.
CAUSES OF DEATH AFTER TRANSPLANTS

- CAUSE
  - Relapse (15%)
  - Infection (19%)
  - Organ toxicity (13%)
  - Other (7%)

AUTO

- Organ toxicity (1%)
- Infection (1%)
- Relapse (1%)
- Other (7%)

ALLO

- Relapse (15%)
- Infection (19%)
- Organ toxicity (13%)
- Other (7%)

Late Effects after Allogeneic BMT

- TBI
- Chronic GVHD
- Immune deficiency

- Damage to tissues with low repair potential
- Immune deficiency
- Late infections

- Fertility, hypogonadism
- Growth and development
- Thyroid dysfunctions
- Dental

- Cataract
- Sickle syndrome
- Osteoporosis
- Necrosis of bone
- Lung complications

Long term follow-up: Allogeneic

- Immunizations starting at 1 year if off immunosuppression
- Relapse
- GVHD and complications
  - Organ toxicity (15%)
  - Infection (19%)
- Other (7%)
- Secondary malignancies
  - Thyroid, estrogen deficiencies
  - Osteopenia/porosis
  - Skin cancer, head and neck cancer, breast cancer, lymphoma
  - Coronary artery disease?

TABLE 2: Screening and Preventative Practices for Long-Term Survivors After Allogeneic Cord Blood Transplants

- **Organs**
  - **Screening Contribution**
  - **Gastrointestinal**
    - Monitoring for infections, including MRSA
  - **Renal**
    - Monitoring for transplant rejection
  - **Endocrine**
    - Monitoring for diabetes, thyroid, adrenal, parathyroid, and pituitary function
  - **Respiratory**
    - Monitoring for respiratory infections, including pneumonia, COPD
  - **Cardiovascular**
    - Monitoring for tobacco use, cholesterol, blood pressure
  - **Malignancies**
    - Monitoring for secondary malignancies, including skin cancer, lymphoma
  - **Immunologic**
    - Monitoring for immune function, including autoimmunity
  - **Hematologic**
    - Monitoring for blood counts, including hematopoietic growth factors
  - **Psychosocial**
    - Monitoring for mood disorders, including depression

**Notes:**
- Provides evidence-based recommendations for long-term follow-up care after allogeneic cord blood transplantation.
- Includes recommendations for screening and preventative practices for long-term survivors.
- Emphasizes the importance of multidisciplinary care and patient engagement in follow-up.

**Best Transplant Outcome**

**BEFORE**

**AFTER**