Bone Marrow Transplantation- Risks and Benefits

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Topics of Discussion

• Why do we do Bone Marrow Transplants
• Pre-transplant- The Workup and the Process
• Peri-Transplant- The inpatient
• Post-Transplant- the first 100 days
• Long term follow up and Survivorship
• Questions
History of Bone Marrow Transplantation

- World War 2 era- high doses of radiation lead to marrow failure and death, with little understanding of radiobiological mechanisms.
- 1949- shielding the spleen of a mouse during otherwise lethal irradiation permitted survival.
- 1951- stem cells from shielded hematopoietic tissue (spleen) entered the circulating blood and subsequently repopulated the irradiated BM*
- Murine and canine models developed for transplant
  - Helped develop the basis of histocompatibility, secondary disease (now known as graft versus host disease), graft rejection, hematopoietic chimerism

• 1957: marrow safely infused intravenously

• 1958: reports of successful identical twin transplants (Cooperstown, NY)

• 1968: First successful non-twin (allogeneic) transplant - sibling donor (Minnesota)

• 1973: first successful unrelated donor transplant - young boy with SCID received multiple marrow transplants from a donor identified as a match through a blood bank in Denmark.

• 1979- The first successful unrelated donor transplant for a patient with leukemia (Seattle)

• 1990: first successful cord blood transplant

• 1996: first non-ablative transplant
Types of Stem Cell Transplant

**Autologous**
- "self transplant" - stem cells are from self
- High dose chemotherapy with stem cell rescue
- No GVHD, no immunosupression meds
- Faster recovery
- Myeloma, Lymphoma, Testicular cancer
- Safer

**Allogeneic**
- Stem cells from a matched donor
- High dose chemotherapy and immune Graft versus tumor effect
- Risk of GVHD, rejection
- Need immunosupression medications
- Takes longer for immune system to recover
- Leukemia, MDS/MPN, refractory Lymphomas
- Higher risk of mortality from transplant
Timeline

**Figure 1- Timeline of Allogeneic Stem Cell Transplantation**

- **Indication for allo-sct**
- **Donor search and workup**
- **Conditioning, stem cell infusion, GVHD prophylaxis**
- **Engraftment**
- **Post-transplant care**
  - Vaccinations
  - Chronic GVHD monitoring
  - Survivorship

- **Is patient fit to undergo asct?**
  - Organ testing, HCT-CI to assess comorbidities

- **Assess disease status**

- **Supportive care**
  - (transfusion, antibiotics, fluids, nutrition)

- **Acute GVHD monitoring/treatment**
Indication for Allo-HCT

• Acute Myeloid Leukemia
• High Risk MDS, MPN (risk of becoming leukemia)
• CML (treatment resistant or intolerant)
• Severe Aplastic Anemia
• High risk CLL
• Lymphoma (refractory or relapse; failed auto-hct)
Allogeneic SCT

- Donor
  - Related (sibling, haploidentical donor)
  - Unrelated (NMDP, cord blood)

- Graft source
  - Bone marrow (harvest in OR)
  - Peripheral blood (mobilized with g-csf and collected through peripheral line)
  - Umbilical Cord Blood
Matching a donor

HLA Match

- 6 main HLA loci – A, B, C, DP, DQ, DR on each set of chromosome – total 12
- 5 of 6 (total 10) are important (A, B, C, DR, DQ)
  - 10/10 = full match
  - 8 or 9/10 = mismatch
  - 5/10 = half match (haplo)
- More mismatch - more risk of Allo-hct toxicities (GVHD, rejection, mortality)
Inheritance of HLA

- Mother and Father each inherits two haplotypes from their parents.
- Then passes one of two haplotype to each child.
- Siblings have 25% chance of being donor.
- Parents, children can be haploidentical (half) donor.
## Choosing a donor

<table>
<thead>
<tr>
<th>Matched sibling</th>
<th>Matched unrelated</th>
<th>Haploidentical</th>
<th>Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% chance of identifying</td>
<td>Better chance of locating donor if pt caucasian than minoties</td>
<td>Easier to ID donor since related</td>
<td>Locate donor through cord bank Need 2 cords</td>
</tr>
<tr>
<td>Ideal donor</td>
<td>Similar to MSD, but sibling preferred</td>
<td>Less GVHD, higher risk of relapse</td>
<td>Less GVHD, more risk of infection/ prolong immune deficiency</td>
</tr>
<tr>
<td>Donor availability</td>
<td>Donor availability-difficult</td>
<td>Donor availability</td>
<td>Donor availability-difficult</td>
</tr>
</tbody>
</table>
### Odds of Finding a Match Based on Ethnic Background

<table>
<thead>
<tr>
<th>Ethnic Background</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black or African American</td>
<td>23%</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>41%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>46%</td>
</tr>
<tr>
<td>American Indian and Alaska Native</td>
<td>57%</td>
</tr>
<tr>
<td>White</td>
<td>77%</td>
</tr>
</tbody>
</table>

To donate: visit bethematch.org
Workup

Disease workup

• Imaging (CT/ PET/ MRI)
• Bone marrow biopsy

Patient workup

• Performance status
• Comorbidities/ medical history
• Cardiac (2d echo, EKG)
• Pulmonary (PFTs)
• Hepatic (LFTs)
• Infection (IDMs)
Assessing comorbidities

• The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) most widely and accepted pre-transplant comorbidity prognostication tool used today.

• Comprised of 17 specific comorbid assessments

• Validated in both autologous and allogeneic stem cell transplantation

• Higher scores (HCT-CT greater than or equal to 3) predictive of inferior survival and increased death from transplant
Timeline

Figure 1- Timeline of Allogeneic Stem Cell Transplantation
Factors when considering stem cell transplant (and what type...)

• Disease
  • State of disease
  • Chemosensitivity/ Risk of relapse
  • Donor selection
  • GVHD risk

• Patient
  • Age
  • Organ function/ comorbidities
  • Psychosocial assessments
  • Functional status
  • Donor availability
  • Caregiver availability

• From this we determine optimal
  • Donor
  • Conditioning regimen
  • GVHD prophylaxis
The formula for transplant

- **Disease state**
  - How much/deep remission is enough?

- **Donor**
  - Auto v allo
  - sibling v matched unrelated
  - Mismatch
  - Haploidentical
  - Cord

- **Stem cell source**
  - Peripheral blood vs bone marrow

- **Conditioning/ intensity**
  - Myeloablative vs reduce intensity

- **GVHD prevention**
Conditioning intensity

- Higher intensity: more toxic, higher risk of GVHD
- Lower intensity: less toxic, higher risk of relapse
Hospitalization

- Conditioning chemotherapy (5-6 days)
- Stem cell infusion (day 0)
- Start immunosupression
- Engraftment (typically 15-25 days following transplant)
The immediate post transplant

- Highest risk of mortality is through day +100
- Risk linked to distance from transplant center
- Transfusion support
- Drug monitoring
- Antibiotics (if indicated)
- Monitoring for GVHD
- Monitoring for infection (Bacterial, Viral, Fungal)
Graft versus host disease

• When white blood cells of the donor's immune system (in the graft) recognize the recipient as foreign.

• These donor cells (T cells) then attack the recipient's body's cells, which leads to GvHD

• Two types of GVHD
  • Acute (Up to day +100)
  • Chronic (After day +100)
<table>
<thead>
<tr>
<th>Signs of Acute GVHD</th>
<th>Signs of Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td><strong>Skin and nails</strong></td>
</tr>
<tr>
<td>• Very faint to severe sunburn-like rashes</td>
<td>• Skin texture changes (thickening)</td>
</tr>
<tr>
<td>• Blisters</td>
<td>• Nail changes</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>• Rash</td>
</tr>
<tr>
<td>• Nausea that doesn’t go away</td>
<td>• Unusual hair loss or thinning</td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td>• Itchy skin</td>
</tr>
<tr>
<td>• Vomiting (throwing up)</td>
<td><strong>Joints and muscles</strong></td>
</tr>
<tr>
<td>• Feeling full after eating very little</td>
<td>• Arthritis-like symptoms (pain and stiffness)</td>
</tr>
<tr>
<td></td>
<td>• Muscle pain, cramps or weakness</td>
</tr>
<tr>
<td><strong>Intestines</strong></td>
<td><strong>Eyes</strong></td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Dry eyes</td>
</tr>
<tr>
<td>• Belly pain that does not go away</td>
<td>• Irritation that doesn’t go away</td>
</tr>
<tr>
<td>• Feeling bloated, or full of gas</td>
<td>• Blurred vision</td>
</tr>
<tr>
<td>• Blood in your stool</td>
<td>• Teary eyes</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td><strong>Mouth</strong></td>
</tr>
<tr>
<td>• Jaundice (your skin or eyes look yellow)</td>
<td>• Trouble opening your mouth</td>
</tr>
<tr>
<td>• Dark (tea-colored) urine</td>
<td>• Sores</td>
</tr>
<tr>
<td>• Pain in the upper part of your belly</td>
<td>• Irritation that doesn’t go away</td>
</tr>
<tr>
<td>• Swelling in your legs or belly</td>
<td>• Chapped lips</td>
</tr>
<tr>
<td></td>
<td>• Pain</td>
</tr>
<tr>
<td></td>
<td><strong>Lungs</strong></td>
</tr>
<tr>
<td></td>
<td>• Cough that doesn’t go away</td>
</tr>
<tr>
<td></td>
<td>• Shortness of breath</td>
</tr>
<tr>
<td></td>
<td>• Trouble breathing</td>
</tr>
<tr>
<td></td>
<td><strong>Digestive system</strong></td>
</tr>
<tr>
<td></td>
<td>• Nausea or vomiting (throwing up)</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Stomach pain or cramping</td>
</tr>
<tr>
<td></td>
<td><strong>Genitals</strong></td>
</tr>
<tr>
<td></td>
<td>• Irritation or dryness</td>
</tr>
<tr>
<td></td>
<td>• Rash</td>
</tr>
<tr>
<td></td>
<td>• Painful intercourse</td>
</tr>
</tbody>
</table>
After 100 days

• Get to go home!
• Taper immune suppression if no GVHD
• Check disease status/ disease monitoring
  • Maintenance therapy?
• Vaccinations
• Survivorship
# Late Effects

<table>
<thead>
<tr>
<th>Complication</th>
<th>Screening tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary malignancy</td>
<td>Age-appropriate screening, including mammogram, colonoscopy, Pap smear, routine skin examinations; avoid prolong sun exposure</td>
</tr>
<tr>
<td>Sexual dysfunction/infertility</td>
<td>Regular assessments, FSH/LH testing, counseling</td>
</tr>
<tr>
<td>Endocrine (hypothyroidism, hypogonadism)</td>
<td>Thyroid function testing, FSH/LH</td>
</tr>
<tr>
<td>Cardiovascular (CHF, CAD, hyperlipidemia)</td>
<td>Assessment of cumulative anthracycline dose and chest radiation. EKG, 2-D echo, fasting lipid profile, early management of cardiac risk factors such as diabetes, hypertension</td>
</tr>
<tr>
<td>Skeletal-osteoporosis, avascular necrosis</td>
<td>DEXA scans, MRI-earlier screening with prolonged steroid use. Vitamin D levels and supplementation. Bisphosphonate therapy (experimental)</td>
</tr>
<tr>
<td>Psychologic (depression, anxiety, fatigue)</td>
<td>Routine psychologic evaluation of patient assessments of family and caregivers. Refer to support networks</td>
</tr>
</tbody>
</table>
Quality of life

Psychological/ emotional functioning
Anxiety, stress, depression...

Social functioning
Personal relations, interactions with the community...

Physical functioning
Activities of daily living, symptoms, signs...

Cognitive functioning
Mental agility, concentration...

Work functioning
Satisfaction with life, work capacity...

Perceived well-being and health
Acceptance of health, personal satisfaction

Sexual functioning
Sexual response and satisfaction
Long-term Survival after HCT
It takes a village

Social worker
Psychiatrist & addiction counselor
Dietitian
Pharmacist
Dermatologist
Nurse
Transplant physician
RN transplant coordinator
Physician
Advanced practitioner
Specialist in infectious diseases

You are not alone!