Understanding BMT: Before, During, and After Transplant

(BMT 101)

Corey Cutler, MD MPH FRCP(C)
Associate Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, MA

Definitions
- Stem Cell Transplantation (aka BMT)
  - The transfer of Hematopoietic Stem Cells from Donor to Recipient
- What is a Stem Cell?
  - Stem cells are defined by two characteristics:
    - They can make copies of themselves, or self-renew
    - They can differentiate, or develop, into more specialized cells

Rationale for Transplantation
- Elimination AND Replacement of:
  - Diseased marrow
  - Poorly functioning marrow
  - Immune compromised marrow
  - Metabolically compromised marrow
- Protection against ultra-high doses of chemoradiotherapy
- Establish immunologic platform for immunotherapy

Types of Transplantation

Autologous
- High doses of chemotherapy and/or radiation
- Designed to kill tumor; overcome resistance with dose intensity
- Requires stem cell rescue
- Not really a transplant

Allogeneic
- 2 mechanisms to cure:
  - Immunologic: Donor vs. Host (Graft vs. Tumor)
  - Chemotherapy and/or radiation

Decision to use autologous/allogeneic marrow source is disease, stage and patient specific

Indications for Transplantation
- Autologous
  - Multiple Myeloma in remission
  - Prolongation of remission
  - Diffuse Large B Cell NHL in 2nd remission
  - Hodgkin Disease in remission
  - Mantle Cell NHL
  - Some Germ Cell Tumors
  - AML, in very rare circumstances

Curative Intent
Indications for Transplantation - Allogeneic

Stem Cell Transplant Decision Tree

Conditioning Regimen
- Determined by:
  - Primary tumor type
  - Stage of disease at transplantation
  - Graft vs. tumor effect in that disease
  - Performance status/comorbidity of recipient
- Large variety of regimens exist
- Differ in intensity and toxicity
  - Ablative is Hard; RIC is pretty easy
- We have “Recipes” for these regimens

What is Better? Myeloablative or RIC?
CIBMTR, Age >50, 1998–2006

Overall Survival by Treatment Arm
P=0.07 (18 month pointwise)
9.7% difference (95% CI: -0.9%, 20.3%) MAC vs. RIC
### Overall Survival by Disease Group

<table>
<thead>
<tr>
<th>Disease Group</th>
<th>Survival Probability</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>81.5%</td>
<td></td>
</tr>
<tr>
<td>RIC</td>
<td>85.2%</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>72%</td>
<td></td>
</tr>
</tbody>
</table>

- MAC: 34 months follow-up
- RIC: 35 months follow-up
- AML: 34 months follow-up

### Stem Cell Transplant Decision Tree

- **Type of Transplant**
  - Autologous
  - Allogeneic

- **Conditioning Intensity**
  - High (Myeloablative)
  - Reduced Intensity

- **Donor Type**
  - Self
  - Related
  - Unrelated

- **Degree of Match**
  - Perfect
  - Matched
  - Mismatched
  - Highly Mismatched

### Finding a Donor

- Goal is to MATCH donor-recipient pairs
  - Not a problem in Autologous transplantation
  - Identical Twins (Syngeneic Transplantation) not commonly found nor used

- Matching performed for HLA (Human Leukocyte Antigen) molecules, encoded by MHC complex (Major Histocompatibility Complex)

- Matching at non-HLA loci also important, but not done (yet).

### The HLA System

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- Matching at non-HLA loci also important, but not done (yet).

### Histocompatibility

- HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ

- Nearly Infinite Possible Combinations!!!
"Perfect" Match Rates in the Adult Donor Registry

"Perfect" and "Pretty Good" Match Rates in the Adult Donor Registry

Does the Degree of Match Matter?

Stem Cell Transplant Decision Tree

Stem Cell Source

Umbilical Cord Blood – A New Alternative

- Medical waste – Procured at the time of delivery
- Contains hematopoietic stem cells – Can be used for transplantation

- Immunologically “immature” – Can be used with less stringent matching
**“Perfect”, “Pretty Good” and UCB Match Rates in the Adult Donor Registry**

![Graph showing match rates](image)

*Courtesy Martin Mairns, NMDP Bioinformatics*

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**Haploidentical Transplantation**

![Diagram showing haploidentical transplantation process](image)

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**Preparing for Transplantation**

- **Pre-Transplant Testing**
  - Blood tests: Kidney, Liver function, Infectious disease
  - Functional tests: Heart, Lung
  - Psychosocial interviews
  - Financials

- **Pre-Transplant Teaching**
  - Restrictions / Safety
  - Nutrition
  - Medication

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**Preparing for Transplantation**

- **Consent Session**
  - Should be VERY thorough
  - At least an hour
  - Ask a lot of questions
  - Be prepared to be offered participation in Research studies

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**Other Things To Do Pre-Transplant**

- Go see a bunch of movies
- Go out to eat
- Gain some weight
- Have a party

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**Grand Overview of Transplantation**

![Diagram showing overview](image)
Transplantation Timeline

Admission
Line Placement
Chemotherapy, Radiation
Conditioning
Await Engraftment
Infection
Mucositis
Bad Complications
Transplantation
Discharge
Recovery
GVHD
Infection
GVHD Grade
GVHD Grade

Post-Transplantation

- A lot of ‘alone’ time
  - Designed to PROTECT you
- Frequent visits to the clinic (big social outing of the week)
- Lots of medications
- Complication time
- You won’t feel great. Yet.

GVHD - Background

- After disease relapse, GVHD is the most common cause of treatment failure after transplantation.
- 2 syndromes:
  - Acute GVHD
  - Chronic GVHD
    - Previously defined by temporal relationship to time of transplantation
    - Now defined by clinical features
    - Differences in pathobiology

GVHD

- Caused by the interaction between the transplanted immune system (Graft) and recipient tissues (Host)

Graft-vs.-Leukemia

Twins (N=70)
T Cell Depletion (N=401)
No GVHD (N=433)
Acute GVHD only (N=738)
Chronic GVHD only (N=127)
Both Acute and Chronic GVHD (N=485)

Double-Edged Sword

Horowitz et al, Blood 1990
Acute GVHD

Incidence:
- 35% after Related Donor Transplantation
- 50% after Unrelated Donor Transplantation

Despite prophylaxis
- Current Standard: Tacrolimus/Cyclosporine and Methotrexate

Risk Factors for Acute GVHD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Condition That ↑ Risk of Acute GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor-Recipient Factors</td>
<td></td>
</tr>
<tr>
<td>Major HLA Disparity (HLA Class I, II)</td>
<td>HLA Mismatched donor &gt; Matched Donor</td>
</tr>
<tr>
<td>Minor HLA Disparity (mHA)</td>
<td>Unrelated Donor &gt; Related Donor</td>
</tr>
<tr>
<td>Sex Matching</td>
<td>Malematch &gt; Match</td>
</tr>
<tr>
<td>Donor Parity</td>
<td>Multiparity &gt; Nullarity</td>
</tr>
<tr>
<td>Donor Age</td>
<td>Older donor &gt; Younger Donor</td>
</tr>
<tr>
<td>ABO type</td>
<td>ABO Mismatch &gt; ABO Match</td>
</tr>
<tr>
<td>Donor CMV Serostatus</td>
<td>CMV positive &gt; CMV Negative</td>
</tr>
<tr>
<td>Cytokine Gene Polymorphisms</td>
<td>Numerous Associated with Acute GVHD</td>
</tr>
<tr>
<td>Stem Cell/Graft Factors</td>
<td></td>
</tr>
<tr>
<td>Stem Cell Source</td>
<td>PBSC &gt; BM &gt; UCB</td>
</tr>
<tr>
<td>Graft composition</td>
<td>Higher CD34+ count &gt; Lower CD34+ cell count*</td>
</tr>
<tr>
<td></td>
<td>Higher T cell dose &gt; Lower T cell dose*</td>
</tr>
</tbody>
</table>

Transplantation Factors
- Conditioning Intensity
  - Myeloablative > Reduced-intensity Regimens

Acute GVHD

- Clinicopathologic syndrome
  - Skin
    - Erythematous rash → Bullae → Desquamation
  - Liver
    - Hyperbilirubinemia → Hepatic failure
  - Gut
    - Secretory diarrhea → Ileus

Infection

Post-Transplantation – Beyond 100 Days

- 2 Main issues
  - Middle Term Complications
  - Late Effects and Survivorship

Chronic GVHD - Background

- >50% of Related and Unrelated Recipients
  - Incidence increasing as early transplant outcomes improve

- Important cause of morbidity in the later post-transplant period
  - Most have more than 1 organ system involved

- Median 2-3 years of treatment

- Associated with Quality of Life and functional deficits
Chronic GVHD – Organ Involvement

Adapted from Lee et al., 2002

Treatment Strategy

- Local Symptoms → Local Rx
  - Early identification crucial
  - Supportive vs. Local immunosuppressive

  Biology of Blood and Marrow Transplantation, 2015
  • Can be accessed through ASBMT Website:
    http://www.asbmt.org/?page=GuidelineStatements

Post-Transplant Transitions

- You will experience a number of transitions post transplant
  - Gaining more independence and freedom - welcomed yet very stressful
  - Relationships with family/friends/loved ones-going through a time of adjustment
  - Financial pressures – Going/not going back to work

- Acknowledge the enormity of your experience
  - The reality of your diagnosis
  - The trauma inherent in transplant
  - The loss of who you were and the security you previously felt
  - Seek help if you are stuck

Treatment Strategy

- Systemic Symptoms / Multiple Local Sites → Systemic Rx
- Initial Rx:
  - Prednisone 1 mg/kg/day
  - Tacrolimus: 5-10 ng/ml or
  - Cyclosporine: 200-400 µg/L
- Complete Response Rate: 50-55%
- Median Time to Discontinue Immune Therapy: 1.6 – 2.2 years!!
- Multiple Clinical Trials available – You should participate!!!
  - www.clinicaltrials.gov
Psychosocial Effects of BMT

- BMT survivors generally experience a high global quality of life
- Some problems may be persistent
  - Low energy, sleep problems
- Emotional or psychological distress can be common
- Depression
  - Frequently observed
  - Exact prevalence rates unknown
  - Depression before and after transplant can affect morbidity and mortality
  - Treatment is important
  - Women more likely to have current depression (75% v 25%, p=0.07)
  - Women more likely to receive antidepressants (60% v 10%, p<0.01)
  - People with treated depression are similar to those without depression

Changing Emotions

- Recovery is a slow process
- Emotions some experience after transplant:
  - Frustration: Lack of energy to do what you once did
  - Anger: Why do I have GVHD? Why can’t I just feel normal?
  - Guilt: Being a burden to caregiver/family/loved ones
  - Mood Changes: “up and down”—caused by medications (steroids)
  - Depression/Anxiety

Quality of Life

- Fatigue: Patients give up being as they were
- Work: full-time, part-time, permanent disability
- Recreation: This can change too. Figure out what you CAN do.
- Relationships: Transplant can take a toll
- Chronic Graft vs. Host Disease

Cognitive Changes

- Clinical evaluation for neurologic dysfunction is warranted
  - Neuropsychological testing
  - Additional tests may be indicated
- What we know
  - Pre HSCT deficits are common
  - Post HSCT deficits are even more common
- Complication rates
  - Allogeneic (Unrelated > Related) >> Autologous
- Types of complications
  - Late CNS infections
  - Cerebrovascular complications
  - 20% will report impaired memory, attention span, verbal fluency

Sexuality after Transplant

- Important QoL issue
- Sexual dysfunction is a common, enduring consequence of systemic cancer treatment
- Changes in body image, decline in perceived attractiveness
- Infertility for both men and women
- Majority of survivors say they were not prepared for changes in sex life
  - Women: Ovarian failure→low estrogen levels and vaginal GVHD→stress, mucosal changes→pain, irritation and sensitivity
  - By 2 yrs, there is improvement compared to 6 months, but quantity and quality still not what it was even 5 yrs later
  - Men: Gonadal and cavernosal insufficiency→ED and lower libido
  - Rates of sexual activity improve by 1 year, but takes 2 years to see improvement in quality and quantity. At 5 years still lower function compared to no BMT group

Coping Strategies

- Recognize the impact has been physical, emotional, psychological and spiritual
- Go at your OWN pace, not an ‘expected’ pace
- Your situation, coping style may be different from others - that’s OK!
- Be open, be honest about your feelings and needs
- Try to process what you are experiencing with a loved one or a professional
- Ask what would be most helpful to me now?
  - Support group
  - One on one counseling
  - Reading
Taking care of yourself

• Take your medications
• Make your appointments
• Respect your altered immune function
• Mind your emotional well being
• Get enough sleep
• Pay attention, keep lists, make associations
• Consider cognitive rehabilitation services
• Keep your perspective
  – Do not over-generalize
  – Time heals all?
• Nutrition
• Exercise

Dietary Challenges after Transplant

• Weight gain or loss
• Appetite changes
  – Small, frequent meals
  – Avoid eating snacks too close to meal times
  – Choose nutrient dense foods
  – Fortify foods to boost calories
  – Try new recipes
• Lack of interest in food
• Taste alterations / Dry Mouth
  – Drink plenty of fluids, at least 8 cups per day
  – Moisten foods with gravies, sauces, or broth
  – Limit caffeine
  – Artificial saliva products
• Steroids, GVHD

Post-Transplant Diet

• Eat 5-10 servings fruits & veggies each day
  – 1 serving = 1/2 cup cut, cooked or sliced; 1 piece medium fruit; 1 cup leafy greens
• Re-shape your plate
  – 1/2 veggies, 1/4 protein, 1/4 whole grains
• Emphasize whole grains
  – Reduce risk for certain cancers, diabetes and heart disease
  – Keep weight off
  – Lower cholesterol levels
  – Promote digestive health
• Reduce consumption of saturated and trans-fats, increase monounsaturated and omega-3 Fats

Focus on Physical Activity

Physical Activity + Proper Diet = Healthy Weight

• Create an individualized fitness plan
  – Always talk with your doctor first
  – Schedule time for activity each day, remember every bit counts
  – Ensure intensity appropriate
  – Choose activities you enjoy
  – Find a workout “buddy”
• Incorporate key components
  – Cardiovascular exercise, strength, flexibility and relaxation

Returning to Work

• Up to 89% of BMT patients return to work or school within 5 years after treatment.
• Influences that impact the ability to return to work are:
  – Age
  – Gender
  – Education
  – Personal values
  – Perceived advantages of work
• Influences that impact the inability to return to work:
  – Physical demands
  – Job Lock
  – Employer accommodation
  – Fear of disclosure
  – Perceived discrimination
• Data suggests BONE MARROW recipients more likely to return to work than PBSC recipients (Lee, ASH 2015)

Employer Accommodation

Accommodation: Aiding an employee to perform their job by providing modifications.
“Reasonable” accommodations
  – Change in duties
  – Change in work hours
  – Flexible work hours
  – Periodic rest breaks
  – Allow employees to work from home
  – Modify dress code
Caregivers

- Acknowledge the long haul of BMT caregiving
  - Physical demands
  - Feelings of loss, anger, fatigue, resentment, hope
- Change has been difficult, you have HAD to adapt to the change-shift in roles
- Sometimes paddling in the same direction as your loved one is difficult
- Every relationship/family functions differently
- As a caregiver, must adapt to what works best for you
- Make time for yourself
- Rely upon others (transportation, child care, meals)
- Say NO to non-essential needs – Prioritize!

Survivorship in BMT

- 2 components:
  - Surviving Malignancy
  - Surviving Transplantation
- Different sets of risks and complications need to be considered

Medical Monitoring after BMT

Majhail et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation.
Biology of Blood and Marrow Transplantation, 2012

Antin JH. Long term care after hematopoietic-cell transplantation in adults.
New England Journal of Medicine, 2002

Medical Monitoring

<table>
<thead>
<tr>
<th>Organ</th>
<th>Risk</th>
<th>Outcome</th>
<th>What To Do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>Radiation, cGVHD</td>
<td>Dryness, Caries</td>
<td>Regular dental exams Monitor for oral cancers</td>
</tr>
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<td>Infection</td>
<td>cGVHD, Immune Suppression</td>
<td>Prophylaxis</td>
</tr>
</tbody>
</table>
Allogeneic BMT Survivorship Clinic

• Target population
  – Allogeneic recipients of high-dose myeloablative conditioning
  – Alive, without malignancy, 12 months after transplantation
  – May have evidence of chronic GVHD
  – Total treatment considered
    • Chemotherapy to treat malignancy
    • Focal radiotherapy to treat malignancy
    • High-dose chemotherapy for transplant prep
    • Total body irradiation for transplant prep

Allogeneic BMT Survivorship Clinic

• Multidisciplinary clinic
  – 1x/month, capture all patients (voluntary) for a one time consultative visit
• Goals of the clinic
  – Develop wellness plan to address the needs of this high risk group
  – Develop an individualized follow up plan to address the non-GVHD related risks of transplant survivors

Allogeneic BMT Survivorship Clinic

• Providers
  – BMT Specialists: MD and NP – Endocrine, cardiovascular, respiratory, bone, sexuality, cancer screening
  – Dermatology
  – Oral Medicine
  – Ophthalmology
  – Exercise Physiology
  – Nutrition
  – Psychosocial Counselor

• Patients will be followed annually by NP for their survivorship needs, outlined in the wellness plan

Treatment summary

➢ Diagnostic tests performed and results
➢ Tumor characteristics (e.g. site, stage, grade, markers)
➢ Dates of treatment initiation and completion
  ➢ Surgery, radiotherapy, chemotherapy, including agents used
➢ Treatment regimen, total dosage, clinical trials (if any), and toxicities experienced during treatment
➢ Psychosocial, nutritional, and other supportive services
➢ Contact information on treating institutions and providers
  ➢ Identification of a key coordinator of continuing care

More Resources in BMT

• National Marrow Donor Program
  – www.bethematch.org
  – Smartphone app (excellent)

• BMT InfoNet
  – www.bmtinfonet.org

• nbmtLink
  – www.nbmtlink.org

Questions?
Transplant for MDS and AA

Timing of HCT for MDS

When?
Not too early, but not too late
Probably no single formula to fit all patients

Markov Models useful since there is NO randomized data

Summary of Decision Models

Low Risk IPSS
Int-1 Risk IPSS
Int-2 Risk IPSS
High Risk IPSS

Donor Availability

Relative Risk (95% CI):
8/8 MUD vs. Sib: 1.12 (0.89-1.39)
7/8 MUD vs. Sib: 1.43 (1.08-1.91)
7/8 MUD vs. 8/8 MUD: 1.29 (1.00-1.65)

Saber et al, Blood 2013
McClune et al, J Clin Onc 2009
Sorror et al, J Clin Onc 2014
Donor Availability

[Graph showing donor availability with different types of donors and their probability over years.]

HSCT Outcomes - SAA

[Graph showing HSCT outcomes for SAA with different donor types and years.]

HCT for SAA

- This is an HCT EMERGENCY
- HLA type IMMEDIATELY
  - Serologic family typing available often in 1-2 business days
- Avoid Transfusion if possible
  - Permissive anemia
  - Permissive thrombocytopenia

[Graph showing box norman and transfusion with difference in outcome.]