Understanding Bone Marrow Transplant: Before, During, & After

Claudio Anasetti, MD
Professor of Oncology and Medicine
Chair, Blood and Marrow Transplant Dpt
Moffitt Cancer Center

What is the Bone Marrow?
- Central portion of bone
- Contains basic blood elements
- In adults, marrow is replaced by fat in long bones
- In hips, sternum, ribs and skull are rich of marrow

The production of blood
- Stem Cells
- Myeloid Progenitor
- Erythrocytes
- Thrombocytes
- Granulocytes, Monocytes
- T-Cell
- B-Cell

Why Stem Cell Transplantation?
- Replaces dysfunctional marrow
  - Aplastic anemia
  - PNH
  - Myelodysplastic Syndromes
- Chemotherapy
  - Where standard therapy is insufficient
  - Relapse risk is high
  - Lymphoma
  - Leukemias
  - Myeloma
- Immune therapy against resilient blasts

Types of Transplants
- Allogeneic (from another person)
  - Tissue Type Matched
    - Related
    - Unrelated
  - Tissue Type Mismatched
    - Related
    - Unrelated
    - Cord
- Syngenic – identical twin
- Autologous (from yourself)
Unrelated transplant outcome: improved survival after 2004

Survival for Severe Aplastic Anemia has improved over time

Allogeneic Transplant for PNH

Reduced Intensity Regimen – NIH data

Transplants for MDS have increased by 3.7-fold over 10 years

Improving survival after transplant for MDS
Explaining Trends...

Transplant outcomes have improved because of:
- Better matched donors
- Better regimens for GVHD prophylaxis and therapy
- Better therapy for infection

Transplant utilization has increased because of:
- Improved outcomes encouraging referrals
- Reduced intensity regimens allowing access to older pts
- Expansion of unrelated donor registries
- Medicare patients access to transplant

Timing of Transplant Consultation for Marrow Failure

- At diagnosis

Sibling Transplant outcome for SAA:
Second line therapy worse than first line therapy

Worse outcome with delayed unrelated transplant

Timely Referral Affects Survival

Early referral is the single most important step that can affect survival

Who should get a transplant?


Bacigalupo A et al. Haematologica 2010;95:976-982
**Severe Aplastic Anemia**

- **Marrow Function**
- **Thrombosis**
- **Response to Eculizumab**
- **Clonal Evolution**
- **Comorbidity**
- **Donor Type**

**Survival and Relapse after transplant for MDS**

By IPSS-R

- Overall survival
- IPSS-R risk
- Low risk
- Intermediate risk
- High risk
- Very high risk

Della Porta et al. Blood 2014;123:2333-2342

**Allogeneic SCT for MDS**

QA Life Expectancy Estimate (Years)

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Immediate Transplant</th>
<th>Transplant at Progression</th>
</tr>
</thead>
<tbody>
<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>Int-2</td>
<td>4.93</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
</tr>
</tbody>
</table>


**What does it mean for the MDS patient?**

If MDS is **low risk** (IPSS low or intermediate 1):
- wait and receive best supportive therapy,
  - consider transplant if risk increases

If MDS is **high risk** (IPSS intermediate 2 or high):
- proceed immediately to transplant

**Transplant vs. Best Care**

Intermediate-2 and High-Risk MDS - Age 50 to 75

BMT CTN Protocol #1102

MEDICARE pays for transplant in MDS
Transplantation Process

- Minimize sensitization
- Tissue typing
- Donor Search
- Evaluation
- Conditioning therapy
- Transplantation
- Engraftment
- Recovery

Donor Search

- We look for a genetic match
- Not your blood type!
- Human Leukocyte Antigens
- Typing blood or buccal swab
- Chance of match
  - 1 in 4 if sibling
  - 1 in 1,000 if unrelated

HLA inheritance

Father: a
Mother: c
Possible Offspring:
- d: 25%
- b: 25%
- c: 25%
- a: 25%

Probability of finding a HLA mismatched donor

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Unrelated Adult</th>
<th>Unrelated Cord</th>
<th>Related Haploidentical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>90%</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>75%</td>
<td>95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Black</td>
<td>70%</td>
<td>90%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

*Matching for HLA-A, -B, -C, -DRB1
**Matching for HLA-A, -B, -DRB1
**Total time to transplant**

<table>
<thead>
<tr>
<th></th>
<th>% at risk</th>
<th>Median days</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search to first donor</td>
<td>85%</td>
<td>20</td>
<td>[11-59]</td>
</tr>
<tr>
<td>First donor to back-up donor</td>
<td>34%</td>
<td>8</td>
<td>[3-85]</td>
</tr>
<tr>
<td>Donor to transplant</td>
<td>48%</td>
<td>81</td>
<td>[45-199]</td>
</tr>
</tbody>
</table>

**Pre-transplant Evaluation**

- Medical Assessment
  - Disease status, assess for Fanconi, Dyskeratosis, PNH, MDS...
  - Organ function
  - Infectious status
  - by transplant physician
    - psychologist
    - social worker
    - dentist
  - Education of the recipient and family

**Transplantation Procedure**

![Diagram of transplantation procedure]

- Stem Cells
- Conditioning Therapy
- Anti-rejection Drugs
- day 0

**Conditioning Therapy**

- Suppressive drugs to prevent rejection
- SAA – none additional
- MDS – chemotherapy

**Side effects:**
- Low blood counts
- Hair loss
- Mouth sores
- Vomiting
- Diarrhea

- Death: 0-2%

**Transplant Conditioning**

- Cyclophosphamide
- Fludarabine
- Total Body Irradiation
- Anti-thymocyte-globulin

**Sib transplant conditioning: ATGAM is marginally beneficial**

![Graph of transplant conditioning]

Sib transplant conditioning: Fludarabine is beneficial in SAA

Maury S et al. Haematologica 2009;94:1312-1315

Unrelated transplant conditioning: Fludarabine is beneficial in FA


Unrelated transplant conditioning: Low dose irradiation is beneficial

200 cGy Total Body Irradiation is well tolerated: outpatient, does not cause loss of hair, mouth sores, diarrhea.

Bacigalupo A et al. Haematologica 2010;95:976-982

About Regimen Intensity for MDS

More intense regimens are more effective in eradicating MDS, but are more toxic.

Regimens may need to be tuned to the disease risk, and the patient vulnerability.

There may not be an optimal regimen intensity for everyone.

Domains of vulnerability in the elderly: Assessing risk for treatment complications

Age
Comorbidity
Functional Status

Courtesy of Andy Artz, BBMT 2012

Mortality after Transplant: Effect of Co-Morbidity

The good news: Older age per se should not limit the indication for HCT. Physicians are learning to tune regimen intensity to the patient perceived tolerance.

The bad news: Comorbidity and functional performance are just beginning to be defined and validated, and thresholds for patient or regimen selection cannot be drawn.

Sources of Stem Cells
- Bone Marrow
- Peripheral Blood
- Umbilical Cord Blood

About patient vulnerabilities...

Bone Marrow Harvest
- 1-2 hour surgery
- Anesthesia required
- No growth factors

Blood Stem Cell Collection - Apheresis -
- Outpatient procedure
  - 4-6 hours
- Growth factors given
- No sedation
- Peripheral veins used

Stem Cell Transplant

Marrow vs. Blood Stem Cells
- Blood Stem cells are preferred for:
  - High Risk patients with a matched sibling donor
    because they improve survival
- Marrow Stem Cells are preferred for:
  - Everybody else
    because they cause less GVHD and improve quality of life
**Stem cell source:**
Better outcome with Bone Marrow compared to Blood Stem Cells


**Umbilical Cord Blood**
- Obtained from placenta remnants
- Typed and banked
- Less GVHD
- Stem Cell Dosage may be an issue

**Promising survival in 12 patients with SAA after unrelated cord blood transplantation**


**Questions**

- Issues in Transplants
  - Rejection
  - Graft Versus Host Disease
  - Infection
  - Organ damage
  - Late effects

- Issues in Transplants

  - Rejection <1-10%
  - Graft Versus Host Disease
  - Organ damage - chemotherapy
  - Infection
  - Late Effects

*Major impact of Fludarabine and low dose irradiation*
Issues in Transplants

- Rejection <1%
- Graft Versus Host Disease ~50%
- Organ damage - chemotherapy
- Infection
- Late Effects

Modest impact of tacrolimus and ATG, promising sirolimus and cyclophosphamide

Clinical manifestations

**Acute**

- Skin rash
- Nausea, vomiting
- Diarrhea
- Abdominal cramps
- Intestinal bleeding
- Hepatitis: AST, ALT elevation
- Cholestasis: GGT, AP, Bili elevation


Stage 1 GVHD of Skin

http://www.gsic.jp/cancer/cc_21/aml/sp/02.html

Acute GVHD mortality

<table>
<thead>
<tr>
<th>Overall Grade</th>
<th>%</th>
<th>Non-Relapse Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>I</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>II</td>
<td>60%</td>
<td>15%</td>
</tr>
<tr>
<td>III</td>
<td>15%</td>
<td>60%</td>
</tr>
<tr>
<td>IV</td>
<td>5%</td>
<td>95%</td>
</tr>
</tbody>
</table>

GVHD Complications

- Infections
  - From immunodeficiency
  - From glucocorticoid use
- Burn syndrome
- GI bleeding
- Liver failure
- Respiratory Failure

Immune suppressive Drugs

**Anti-rejection**

- Tacrolimus
- Cyclosporine
- Sirolimus
- Cyclophosphamide
- Methotrexate
- Mycophenolate
- Anti-Thymocyte Globulin
- Prednisone
GVHD prophylaxis: Improved outcome with Tacrolimus

Yagasaki et al, BBMT 2009, 15: 1603-1608

- Largely prevents acute and chronic GVHD, and mortality after mismatched related transplant.
- Currently tested in mismatched related phase III trial vs. cord blood.
- Currently tested in HLA-matched related or unrelated BMT vs. CD34-selection vs. CNI/MTX.
- Currently tested in HLA-mismatched unrelated in single arm study.
- Proposed by Ciurea et al, for PT/Cy testing in haplos vs. unrelated.

Post-Transplant Cyclophosphamide

1. Largely prevents acute and chronic GVHD, and mortality after mismatched related transplant.
2. Currently tested in mismatched related phase III trial vs. cord blood.
3. Currently tested in HLA-matched related or unrelated BMT vs. CD34-selection vs. CNI/MTX.
4. Currently tested in HLA-mismatched unrelated in single arm study.
5. Proposed by Ciurea et al, for PT/Cy testing in haplos vs. unrelated.

Is post-transplant cyclophosphamide a disruptive innovation?

“Generally, disruptive innovations were technologically straightforward, consisting of off-the-shelf components put together in a product architecture that was often simpler than prior approaches.”

Christensen, Clayton M. (1997), The innovator’s dilemma: when new technologies cause great firms to fail, Boston, Massachusetts, USA: Harvard Business School Press

Late effects

- Sterility
- Secondary cancers
- Coronary artery disease
- Chronic GVHD

Clinical manifestations

Chronic

- Skin
  - Dark or light spots
  - Hardening
- Mouth
  - White plaques
  - Thickening
  - Restriction of mouth opening
- Genitalia
  - Vaginal stenosis
- Gastro-Intestina
  - Esophageal stricture
- Lung
  - Chronic Asthma
- Joints
  - Stiffness or contractures

Summary (1)

- Transplant outcome has improved with less toxic but more immune suppressive conditioning with less rejection, and with better GVHD prevention.
Summary (2)
- Tissue matched sibling transplants should be considered for first line therapy in patients with SAA at diagnosis up to age 40 or 50 depending on comorbidities.

Summary (3)
- Transplants should be considered for second line therapy after immune suppression failure in patients over 50 years of age, or patients without a tissue matched sibling.

Summary (4)
- Transplants should be considered intermediate-2 and high risk for MDS.

Summary (5)
- Research continues in the area of GVHD prevention, immune reconstitution, and prevention of late effects.

Questions