Bone Marrow Transplant in MDS

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What is Bone Marrow?

- Marrow is the soft tissue inside bones that produces blood forming cells that mature into red blood cells, white cells and platelets (factory)
  - **Red Blood cells** – carry oxygen through our body
  - **White Blood cells** – help fight infection
  - **Platelets** – help control bleeding
What is a Bone Marrow Transplant (BMT)?

- Healthy marrow and blood cells are required to survive.
- Disease’s such as MDS can affect the marrow’s ability to function properly, a transplant can offer a potential cure.
- A bone marrow transplant replaces unhealthy blood forming cells (aka stem cells) with healthy cells.
- Two types of transplant: **Autologous** and **Allogeneic**

**Autologous transplant** - Uses your own cells which are collected and stored for your transplant.

**Allogeneic transplant** - Uses cells donated by a family member, unrelated donor or umbilical cord blood unit.
Indications for Hematopoietic Stem Cell Transplants in the United States, 2010

Number of Transplants

- Allogeneic (Total N=8,860)
- Autogeneic (Total N=9,026)

Conditions:
- Multiple Myeloma
- NHL
- AML
- ALL
- MDS/MPD
- HD
- CML
- Aplastic Anemia
- Other Leuk
- Non-Malignant Disease
- Other Cancer
Sources of Stem Cells for Transplant

Bone Marrow  Peripheral Blood  Cord Blood
How Allogeneic transplant works

1. Collection
   - Stem cells are collected from patient’s bone marrow or peripheral blood

2. Processing
   - Bone marrow or blood is processed in the laboratory to isolate, concentrate, and prepare stem cells for storage

3. Cryopreservation
   - Stem cells are preserved by freezing at extremely low temperatures in protective solutions in order to keep cells alive until patient is ready for transportation

4. Chemotherapy
   - Patients are treated with chemotherapy and/or radiation therapy to destroy unwanted cancer cells and develop bone marrow failure

5. Infusion
   - Stem cells are reinfused into patient’s bone
Transplant Process (5 Steps)

1. Conditioning (1-7 days). Chemotherapy or radiation to suppress the patient’s immune system from rejecting the donor’s stem cells and to eliminate the residual tumor cells.

2. Stem cell infusion (hours)

3. Neutropenic phase (10-20 days)

4. Engraftment phase (2-3 weeks)

5. Post-engraftment period
Which MDS patients should be considered for transplant?

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
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<tr>
<td></td>
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<tr>
<td>Bone marrow blasts</td>
<td>&lt; 5%</td>
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<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias†</td>
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</table>

<table>
<thead>
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<th>Risk</th>
<th>Low</th>
<th>0.5</th>
<th>1.0</th>
<th>High</th>
<th>1.5</th>
<th>2.0</th>
<th>≥ 2.5</th>
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</thead>
<tbody>
<tr>
<td>Median survival, yr</td>
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<td>3.5</td>
<td></td>
<td></td>
<td>1.2</td>
<td></td>
<td>0.4</td>
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</table>

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.

†Hb < 10 g/dL; ANC < 1800/μL; platelets < 100,000/μL.
IPSS: Distribution of Risk Groups in MDS

- Int-1: 38%
- Int-2: 22%
- Low: 33%
- High: 7%

Revised International Prognostic Scoring System (R-IPSS)
Transplant for High Risk MDS Patients

1. Allogeneic hematopoietic stem cell transplant is the only curative approach for MDS patients, however it is associated with high risk of severe and life threatening complications

2. To be considered for transplant a patient should meet following criteria:
   a) To be in relatively good health (transplants typically done for patients younger than age 70, however no definitive age limits exists)
   b) Do not have acute severe illness (poorly controlled infections, etc.)
   c) Preferably have well HLA matched donor
   d) Do not to have rapidly progressing and poorly controlled MDS
   e) Have a reliable and dedicated caregiver
Efficacy of BMT for MDS

- Survival benefit in Intermediate-2 and High risk patients
  - 20-30% progression free survival (PFS) at 5 years in older patients
  - 30-40% PFS in Center for International Blood and Marrow and Transplant Research (CIBMTR)
- Quality of life improved with transplant in high risk patients
Potential Risks of BMT for MDS

- Allogeneic transplant is one of the higher risk procedures in medicine
- Higher IPSS increases relapse risk and transplant related mortality (TRM)
- Average age 60s → increases comorbidities/TRM
Causes of Death after HLA Match Sibling Transplants done in 2011-2012

- Primary Disease: 48%
- GVHD: 16%
- Infection: 13%
- Organ Failure: 18%
- Second Malignancy: 4%
- Other: 1%
Graft vs Host Disease (GVHD)

- Only happen with allogeneic transplant
- Condition occurs when donor stem cells that make up new immune system see host body (tissues and organs) as foreign and attack it

**Acute GVHD**
- Skin rash, GI and Liver
- Generally occurs within 100 days of transplant
- Prevention: CSA or tacrolimus
- Treatment: Steroids, Mycophenolate, ATGAM
- Risk Factors
  - MSD > MUD > Mismatched related or unrelated
  - Parous female for male
  - Older > Younger

**Chronic GVHD**
- Resembles autoimmune disorders
- Protean manifestations
- Major cause of long-term morbidity and late mortality
- Treatment: Steroids are first line so infection major cause of death
- In vast majority > Resolves so no life-long immunosuppression
Other Risks

Deaths during cytopenia (low counts)
- Uncommon
- Less than 5%

Failure to engraft
- Rejection, also uncommon and approx. equal to 5%

Organ failure
- Heart, liver and lungs
What Mutations in MDS Predict a Poor Outcome After Transplant?

- Tumor samples from 87 pts were sequenced prior to transplant to look at what mutations predicted a poor outcome after transplant

- TP53 mutation (21%), DNMT3A (18%), TET2 (13%)
- Pt’s who carried these mutations represented 64% of deaths in this study
- Three year overall survival in patients without these mutations was 59% vs 19% for those with these mutations

1520 patient samples with MDS enrolled from CIBMTR database

TP53 mutations were present in 19% of pts and were associated with shorter survival and a shorter time to relapse than absence of TP53 mutations

Adverse effect of TP53 was similar in patients who received reduced intensity conditioning (RIC) vs myeloablative conditioning regimens

Presence of JAK2 mutations was associated with shorter survival than absence of JAK2

Among pts>40yrs who did not have TP53, RAS was associated with shorter survival

The effect of RAS on relapse only evident in RIC regimens

Lindsley RC, et al. NEJM 2017
Thank You!

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Christopher R. Cogle, MD
Nosha Farhadfar, MD
John Hiemenz, MD
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Jan S. Moreb, MD
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