Bone Marrow Transplantation in Myelodysplastic Syndromes

An overview for the Myelodysplasia Support Group of Ottawa
Objectives

• Provide brief review of marrow failure
• Re-emphasize the importance of predictions
• Explain the process of marrow transplantation
• Review the outcomes of transplantation
• Provide an idea of how we balance risk and benefit to come to decisions of whether to do it and if so when.
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blood cell lineage

1. clones itself to make more PHPCs
2. differentiates itself to form other blood cell precursors

B-lymphocytes
T-lymphocytes

common lymphoid progenitor

pluripotential hematopoietic precursor cell

basophilic erythroblast
myeloblast / monoblast
eosinophilic myelocyte

orthochromatric erythroblast
granulocyte / monocyte progenitor

reticulocyte

megakaryocyte

red blood cells
platelets
eosinophils
basophils
neutrophils
monocytes
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<table>
<thead>
<tr>
<th>IPSS Score</th>
<th>Risk grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>Intermediate-1 Risk</td>
</tr>
<tr>
<td>1.5 – 2.0</td>
<td>Intermediate-2 Risk</td>
</tr>
<tr>
<td>≥ 2.5</td>
<td>High risk</td>
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</table>
Higher-risk IPSS groups have high mortality
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BMT Course Outline

Donor Search, Eval

Salvage Rx

High dose Chemo/XRT

Day 0

Gut, Lung, Liver toxicity

Infections

Acute GVHD

PMN

Lymphs

Red Cells

Platelets

Anti-microbials

Anti-rejection drugs

Likely not cured

Disease + 1st Rx

Cured

Marrow Stem Cells

Auto

Allo

-100

BMT

-10

+30

+100
Enterococci (VR E),
E. Coli, Pseudomonas

Aspergillus,
Candida, Fusarium

Staph. (MRSA),
Strep.

CMV,
PIV3, H1NI, RSV
ERYTHRODERMA – At least 80% of the body is red and scaly; may be mistaken for drug reaction or cutaneous T-cell lymphoma
Morphea-like sclerosis – Typical site of superficial or morphea-like sclerosis in addition to dyspigmentation. The white areas (pigment loss) are sclerotic but can be moved over the clavicle.
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Indications for Allogeneic Hematopoietic Stem Cell Transplantation, 2005 – Worldwide

- Unrelated donor (Total N=7,670)
- Related donor (Total N=10,770)
NMDP Transplant Recipients by Diagnosis – Selected Malignancies

The graph shows the number of transplant recipients by diagnosis and year from 2001 to 2007. The diagnoses include AML, ALL, MDS, NHL, and CML. The y-axis represents the number of recipients, ranging from 0 to 1400. The x-axis represents the years from 2001 to 2007.
Survival of Aplastic Anemia patients after AlloBMT
ALLOGENEIC BMT VERSUS AUTOLOGOUS SCT AND CHEMOTHERAPY IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES AND SECONDARY ACUTE MYELOID LEUKEMIA.

N=341, median age 51, 319 int-2 and higher

- OS 4-year = 28%
  - Of those in CR (194)
    - Relapse incidence was 41% versus 64% in the no donor group (P=0.008),
    - OS 4-year donor vs. no donor = 54 vs. 41% (n=135)
    - Median survival of those in CR = 1.3 years
    - Relapse = 60%
    - NRM = 11%
from CR without relapse
donor no-donor < 55 y.o.

all patients and from CR
Targeted Bu/Cy for MDS

*Sib or Unrelated Transplants*
Targeted Bu/Cy for MDS
Sib or Unrelated Transplants

Years after transplantation
Similar survival after sib or unrelated donors for MDS or AML with IV Flu/BU
EFS for MDS or AML after IV Fludarabine/Busulfan

![Event-free Probability vs Time (weeks)]

- In remission, PB.blast=0
- Active Disease, PB.blast=0
- Active Disease, PB.blast>0

$P < .0001$
HSCT in MDS

- In the right population appears superior to medical management
- Only study dealing with timing favors waiting until IPSS int-2 and high
- Induction chemotherapy prior to HSCT unresolved
- Higher rate of relapse post RICT
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Factors Most Consistently Shown to Have Significant and Clinically Meaningful Importance for Survival

Patient-related:
- Age (younger is better)
- Performance status (good is better)

Graft-related
- HLA-match (well-matched is better)
- Cell-dose for cord blood, BM (more is better)

Disease-related
- Disease/subtype
- Disease status/duration (early disease, short duration better)
# Prognosis Determined by Sum of Risks for Adverse Events

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>GVHD</th>
<th>Infection</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease</td>
<td>• Age</td>
<td>◆ Donor type and match</td>
<td>◆ Age</td>
</tr>
<tr>
<td>• Disease status</td>
<td>• Donor type and match</td>
<td>◆ Graft type</td>
<td>◆ Performance status</td>
</tr>
<tr>
<td>• Disease duration</td>
<td>• Donor-recipient sex-match</td>
<td>◆ Disease</td>
<td>◆ Conditioning regimen</td>
</tr>
<tr>
<td>• Disease markers, e.g. cytogenetics</td>
<td></td>
<td>◆ Disease status and duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>◆ GVHD</td>
<td></td>
</tr>
</tbody>
</table>

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*The Ottawa Hospital*
Objectives/Conclusions

• marrow failure in its many forms is common.
• if we can predict the future we can alter it.
• the process of marrow transplantation remains complex.
• the outcomes of transplantation are ever better and remains the only curative therapy for MDS.
• If the prognosis is not so good and the conditions are right then yes to a BMT, but when remains an issue of wisdom and personal values.
Causes of Death after Unrelated Donor Transplantations Done in 2001-2006:

~1/3 Recurrent Malignancy
~1/3 GVHD and Infection
~1/3 Other Transplant-related toxicities
Sibling Transplants for AML, Age >50 Years, 1998–2006
By Disease Status and Conditioning Regimen

Probability of Survival, %

Years

Intensity

Early, myeloablative (N=660)
Intermediate, myeloablative (N=206)
Early, reduced-intensity conditioning (N=544)
Intermediate, reduced-intensity conditioning (N=77)

P = 0.3745.

By Disease Status

Probability of Survival, %

Years

Early (N=4,346)
Intermediate (N=1,124)
Advanced (N=1,628)

$P < .0001$. 
Causes of Death after Transplantations Done in 2001-2006

**HLA-identical Sibling**
- Relapse (41%)
- Infection (17%)
- Other (16%)
- GVHD (13%)
- Organ toxicity (10%)
- IPn (3%)

**Unrelated Donor**
- Relapse (34%)
- Infection (20%)
- Other (16%)
- GVHD (14%)
- Organ toxicity (10%)
- IPn (6%)