Allogeneic Stem Cell Transplantation in AML/MDS

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Department of Internal Medicine
Seoul National University Hospital
Allogeneic stem cell transplantation

Donor

Stem cell collection

Conditioning Chemotherapy RT

Patient

Infusion
Allogeneic HSCT

- Allogeneic stem cell
  - Restoration of conditioning-induced cytopenia
  - Exertion of an anti-tumor effect
  - GVHD
- Trade-off for allogeneic transplantation
  - Greater anti-leukemic effect but more toxic

- As a consolidation Tx
- As a salvage Tx.
Issues of Allogeneic HSCT in AML

- In what category of patients is allo-HSCT the treatment of choice?
  - Allo-HSCT in AML-CR1
    - Donor versus no-donor studies
    - Allo-HSCT after relapse
- What is the overall value of RIST?
  - Maintain anti-leukemic activity?
  - Generate reduced mortality?
- What is the current role of HSCT using alternative donors?
- Sources of stem cells
- Supportive cares
- Complications
Cytogenetic risk influences on outcomes of post-remission therapy

- Cytogenetics strongly predicts for outcomes of post-remission CT, allo-HSCT (EBMT, IBMTR)
- Allo-HSCT improves DFS in intermediate risk (MRC, EBMT), or poor risk patients (EORTC, SWOG)
## DFS by Cytogenetics

*Blood 2003, BJH 2002, ASH 2005*

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td></td>
</tr>
<tr>
<td><strong>EORTC (&gt;1000)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>49</td>
<td>45</td>
<td>1.16</td>
</tr>
<tr>
<td>Poor</td>
<td>43</td>
<td>18</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>MRC (&gt;1500)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>51</td>
<td>40</td>
<td>0.74</td>
</tr>
<tr>
<td>Poor</td>
<td>21</td>
<td>20</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>HOVON/SAKK (&gt;1000)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>0.76</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>0.65</td>
<td>S</td>
<td></td>
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</tbody>
</table>
## Meta-analysis for OS by donors versus no-donors

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths/Patients</th>
<th>O.R. &amp; 95% CI (Donor : No donor)</th>
<th>Odds Redn. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC</td>
<td>158/ 333</td>
<td>348/ 639</td>
<td></td>
</tr>
<tr>
<td>EORTC-GIMEMA</td>
<td>106/ 293</td>
<td>187/ 441</td>
<td></td>
</tr>
<tr>
<td>HOVON-SAKK</td>
<td>165/ 339</td>
<td>329/ 603</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>44/ 137</td>
<td>56/ 249</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>261/ 561</td>
<td>575/ 1045</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>74/ 125</td>
<td>159/ 232</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-35</td>
<td>167/ 445</td>
<td>381/ 786</td>
<td></td>
</tr>
<tr>
<td>35+</td>
<td>262/ 520</td>
<td>483/ 897</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>429/ 965</td>
<td>864/ 1683</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(44%)</td>
<td>(51%)</td>
<td></td>
</tr>
</tbody>
</table>

11% (5) reduction

P = .04

ASH 2005
Conventional allo-HSCT is the treatment of choice for younger patients with AML of intermediate or poor risk in CR1

- Therapy-related AML
- AML after MDS
## Indications of Allo-HSCT in AML

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; CR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable-risk</strong></td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td>No</td>
</tr>
<tr>
<td>CBF-AML</td>
<td>No</td>
</tr>
<tr>
<td><strong>Intermediate-risk</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Poor-risk</strong></td>
<td>Yes*</td>
</tr>
</tbody>
</table>

- If a matched family donor is not available, UBMT should be considered in younger patients.
Overall Survival Allo HCT Beyond CR1

Ref: Michallet M et al, BMT 2000 1157-1163
## OS of AML in 1st Relapse

Breems J CO 2005
HOVON-SAKK

<table>
<thead>
<tr>
<th>Variables</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at relapse</td>
<td>&lt; .00001</td>
</tr>
<tr>
<td>Relapse-free interval from first CR</td>
<td>&lt; .00001</td>
</tr>
<tr>
<td>Cytogenetics at diagnosis</td>
<td>&lt; .00001</td>
</tr>
<tr>
<td>Previous stem-cell transplantation</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group A: 1 – 6</th>
<th>Group B: 7 – 9</th>
<th>Group C: 10 - 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A 57</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Group B 165</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>Group C 445</td>
<td>56</td>
<td>20</td>
</tr>
</tbody>
</table>

![Graph showing overall survival with different groups and event counts](image)
### OS according to Salvage Tx. (CR2)

Breems J CO 2005
HOVON-SAKK

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>OS at 5 yrs from relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allo (n=109)</td>
</tr>
<tr>
<td>A</td>
<td>88%</td>
</tr>
<tr>
<td>B</td>
<td>48%</td>
</tr>
<tr>
<td>C</td>
<td>26%</td>
</tr>
</tbody>
</table>

p=0.008
## Indications of Allo-HSCT in AML

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>1st CR</th>
<th>&gt;1st CR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Induction Failure*</td>
</tr>
<tr>
<td>Favorable-risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td>No</td>
<td>(Yes)</td>
</tr>
<tr>
<td>CBF-AML</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor-risk</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

If a matched sibling donor is not available, then an alternative donor should be searched (MUD, UCB)
HCT for APL

- CR1: no role
- CR2 PCR positive, Induction failure: Allo
- CR2, PCR negative: Auto?
New Biomarker, Underdetermined Impacts on Decision of Allo-HSCT

NPM1, FLT3
Normal Cytogenetics AML
Dohner Blood 2006

Allo-HSCT
- Negative: MRC Blood 2005
- Positive: Blood 2006

KIT mutation
Inv(16) AML
Paschka JCO, 2006
Role of NST/RIST in Patients with AML/MDS
Nonmyeloablative and Reduced Intensity Regimens
Advantages of NST/RIST

- Two crucial functions of allogeneic stem cells
  - Restoration of conditioning-induced cytopenia
  - **Exertion of an anti-tumor effect**
- Reduced toxicity
- Reduced GVHD
  - Less tissue damage
  - Less cytokine storm
- Reduced infection
  - NST reduces neutropenia
  - Host immunity not ablated, although later may become donor derived.
Conditioning

- Traditional, conventional, myeloablative, ablative
- Reduced intensity conditioning (RIST), non-myeloablative (NST), mini-transplant, transplant-lite
Maximize conditioning

Minimize conditioning

**Allogeneic**

Stem cells

Lymphocytes

**Stem cells**

**Autologous**

**One-step procedure**

**Conventional myeloablative BMT**

Attempt to eradicate all tumor cells prior to BMT and use hematopoietic cells for rescue

**Two-step procedure**

**Non-myeloablative conditioning**

1. Donor stem cells for tolerance
2. Donor T & NK cells for GVL/GVT of otherwise abnormal host cells
Non-myeloablative hematopoietic cell transplant

Preparative regimen

Recipient

Donor

Mixed chimera

Complete chimera
Expectations for NST

- Expand to older and debilitated patients
- GVM effect would be more important than the intensity of conditioning
- Change the standard of care in allogeneic HSCT: ?
Limitations-NST

- Dose does matter
  - Reduced intensity of conditioning: Loss of control of malignant cells? (esp. in adv. disease)
- Some patients tolerate supralethal BMT well (young, no comorbidity – reducing intensity won’t improve their survival)
- GVM is inactive against some malignancies and advanced disease
ALLOTRANSPLANTS REGISTERED WITH THE IBMTR, 1998-2003

* Data incomplete
AGE OF ALLOTRANSPLANT RECIPIENTS REGISTERED WITH THE IBMTR, 1998-2003

- >70y: 62 Non-Myeloablative, 56 Traditional
- 60-69y: 872 Non-Myeloablative, 798 Traditional
- 50-59y: 1659 Non-Myeloablative, 4670 Traditional
- 40-49y: 964 Non-Myeloablative, 7484 Traditional
- 30-39y: 527 Non-Myeloablative, 6539 Traditional
- 20-29y: 282 Non-Myeloablative, 5441 Traditional
- <20y: 575 Non-Myeloablative, 11166 Traditional
EORTC
Survival in AML trials (age 60+)

Number of patients at risk:

- AML-11* (1990-94)
- AML-7 (1983-85)
- AML-9 (1986-90)
- AML-13** (1995-01)
Defining NST(RIST)

CIBMTR/NMDP

- \(<500\) cGy TBI, \(<9\)mg/kg busulfan, \(<140\)mg/m² melphalan
- Usually includes a purine analogue (fludarabine)
  
  Champlin Oncol 1999

- Reversible myelosuppression (within 28d) without stem cell support
- MC in a proportion of patients at 1ˢᵗ assessment
- Low rates of non-hematologic toxicity
Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors (Blood. 2004;104:1550-1558)

Razvan Diaconescu, Christopher R. Flowers, Barry Storer, Mohamed L. Sorror, Michael B. Maris,
Nonrelapse mortality

<table>
<thead>
<tr>
<th>Causes of death, n</th>
<th>Nonablative</th>
<th>Ablative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/GVHD</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>SDS</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>12</td>
<td>22</td>
<td>.04</td>
</tr>
<tr>
<td>Cumulative incidence, %</td>
<td>16</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

(Blood. 2004;104:1550-1558)
Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age


- 152 pts (AML, MDS, ALL, CML, CLL, NHL)
  - RIST
    - Fludarabine + iv BU : 71
  - Myeloablative CTX + TBI or BUCY: 81
- Acute GVHD: 28 vs. 27% (p=NS)
- NRM: 32 vs. 50% (p=0.01)
Comparisons of OS and PFS

2-year OS 39% vs. 29% (p=0.05)
2-year PFS 27% vs. 25%
NST for AML

- Hegenbart, Seattle JCO 2006
- N=122, Median age 58 yo
- Flu/TBI
- Gr III, IV AGVHD, 12%
- CGVHD (Ext.), 36%
- 2 yr NRM: 16%
- 2 yr OS: 48%
- 2 yr PFS 44%
NST for AML

- Hegenbart, Seattle J CO 2006
- URD, 1<sup>st</sup> CR compared to MRD
  - lower risk of relapse (16% vs. 50%, $P = 0.005$)
  - higher 2-year OS (63% vs. 44%, $P = 0.13$)
- Enhanced GVL
NST vs. Conventional HSCT (Myeloid)

- Scott, FHCRC Leukemia 2006
- N=150, tAML or MDS
- 2 Gy TBI or Flu/TBI (n=38)
- BUCY (n=112)
- Median age: 62 vs. 52 (p=S)
- 3 yr NRM: 41% vs. 34%, p=NS
- 3 yr RFS: 28% vs. 44%, p=NS
- 3 yr OS: 27% vs. 48%, p=NS
NST vs. Conventional HSCT (Myeloid)

- Scott, FHCRC
  Leukemia 2006
- BM blast < 5%
  - OS ($P = 0.84$)
  - RFS ($P = 0.93$)

![Graph showing relapse rate and percent progression for nonmyeloablative and myeloablative treatments.](image)
GVHD and NST

- Baron FHCRC JCO 2005
- Flu/TBI, n=322
- AGVHD
  - Increased risk of NRM
  - No impact on risk of relapse
- CGVHD (ext.)
  - Decreased risk of relapse ($P = 0.006$)
  - Improved RFS ($P = 0.003$) without an increased risk of NRM
## RIST (n=315) vs. Myeloablative HSCT (n=407), EBMT

Aoudjhane M et al Leukemia 2005

<table>
<thead>
<tr>
<th>RIC vs. MA</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRM</td>
<td>0.48</td>
<td>0.33 – 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse</td>
<td>1.78</td>
<td>1.3 – 2.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LFS</td>
<td>1.15</td>
<td>0.9 – 1.47</td>
<td>0.24</td>
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</table>
## RIST in AML CR1
### Donor vs. No-donor Analysis

Mohty leukemia 2005

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Donor (n=35)</th>
<th>No donor (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRM</td>
<td>34%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>12%</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DFS</td>
<td>54%</td>
<td>30%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
# Indications of Allo-HSCT in AML

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>1st CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable-risk</td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td>No</td>
</tr>
<tr>
<td>CBF-AML</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>Yes*</td>
</tr>
<tr>
<td>Poor-risk</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

• RIST may be the choice in old or debilitated patients.
Probability of Survival After Myeloablative Transplants for AML, 1996-2001 - by donor type and remission status
Cord Blood vs. Unrelated Marrow

- Rocha NEJ M 2004
- EBMT, Adults, n=682
- CB TPL: more adv. disease
- AGVHD: ↓
- TRM, RR, DFS: no difference
- A: OS  B: DFS
# Marrow vs. PBSC

Sibling Data, EBMT, IBMTR, Champlin Blood 2001

<table>
<thead>
<tr>
<th></th>
<th>Marrow (n=536)</th>
<th>PBSC (n=288)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to ANC &gt; 500</td>
<td>19D</td>
<td>14D</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to PLT &gt; 20K</td>
<td>25D</td>
<td>18D</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AGVHD</td>
<td>35%</td>
<td>40%</td>
<td>0.2</td>
</tr>
<tr>
<td>CGVHD</td>
<td>65%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>CGVHD (Ext.)</td>
<td>1</td>
<td>RR: 1.44</td>
<td>0.04</td>
</tr>
<tr>
<td>TRM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>28%</td>
<td>18%</td>
<td>0.25</td>
</tr>
<tr>
<td>CR2</td>
<td>30%</td>
<td>13%</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Effects of Stem Cell Source on DFS
Sibling Data, EBMT, IBMTR, Champlin Blood 2001

![Graph showing survival rates]

- PBSC, CR1 (N = 82)
- PBSC, CR2 (N = 28)
- BM vs PBSC, CR1 (P = 0.25)
- BM vs PBSC, CR2 (P = 0.003)
- BM, CR2 (N = 40)
- BM, CR1 (N = 181)
Hematological malignancy (n=60 vs. 74)
- MDS, AML, CML etc.
- BU/CY+TBI/CY vs. NST (Flu/TBI)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease (mild)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary disease (moderate/severe)</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (no end organ damage)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (end organ damage)</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease (moderate/severe)</td>
<td>2</td>
</tr>
<tr>
<td>Liver disease (moderate/severe)</td>
<td>3</td>
</tr>
<tr>
<td>Solid tumor (without metastasis)</td>
<td>2</td>
</tr>
<tr>
<td>Solid tumor (with metastasis)</td>
<td>6</td>
</tr>
<tr>
<td>Patient’s score</td>
<td>Total</td>
</tr>
</tbody>
</table>
Nonrelapse Mortality by CCI

(Blood. 2004;104:961-968)

67%

28%
2-yr OS by CCI

(A) Nonablative

- CCI score 0-2 (n=49)
- CCI score ≥3 (n=11)

(B) Ablative

- CCI score 0 (n=65)
- CCI score 1-2 (n=9)

(Blood. 2004;104:961-968)
Comparative outcomes of reduced intensity and myeloablative allogeneic hematopoietic stem cell transplantation in patients under 50 with hematologic malignancies


Abstract: We have conducted a direct comparison of the outcomes of reduced intensity and myeloablative conditioning in younger adults with hematological malignancies <50 yr. One hundred and five patients received transplants from HLA-matched donors, via either reduced intensity

Inho Kim\textsuperscript{a,1}, Sung Soo Yoon\textsuperscript{a,1}, Kyung-Hun Lee\textsuperscript{a}, Bhumsuk Keam\textsuperscript{a}, Tae Min Kim\textsuperscript{a}, Jin-Soo Kim\textsuperscript{a}, Hoon-Gu Kim\textsuperscript{a}, Myoung-Don Oh\textsuperscript{a}, Kyou-Sup Han\textsuperscript{b}, Myoung Hee Park\textsuperscript{b}, Seonyang Park\textsuperscript{a} and Byoung Kook Kim\textsuperscript{a}

Departments of \textsuperscript{a}Internal Medicine and \textsuperscript{b}Laboratory Medicine, Seoul National University, College of Medicine, Seoul, Korea
## Patient Characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>NST</th>
<th>Conventional</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>35</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td><strong>Median age (range)</strong></td>
<td>36(21-50)</td>
<td>33(17-50)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Time to TPL, mo (range)</strong></td>
<td>13(3-142)</td>
<td>8(2-151)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Prior TPL, no. (%)</strong></td>
<td>6(17)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Diagnosis, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>11(31)</td>
<td>25(36)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>7(20)</td>
<td>20(29)</td>
<td></td>
</tr>
<tr>
<td>ABL</td>
<td>3(9)</td>
<td>3(4)</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>7(20)</td>
<td>3(4)</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>5(14)</td>
<td>5(7)</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>1(3)</td>
<td>14(20)</td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td>1(3)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
## Comparison of CCI scores

<table>
<thead>
<tr>
<th>CCI score</th>
<th>Nonablative (n=35, %)</th>
<th>Ablative (n=70, %)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16 (46)</td>
<td>59 (84)</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>17 (49)</td>
<td>11 (16)</td>
<td></td>
</tr>
<tr>
<td>3 or higher</td>
<td>2 (6)</td>
<td>0</td>
<td>0.034</td>
</tr>
</tbody>
</table>
NRM by CCI scores

The graph shows the cumulative probability of NRM (non-cardiac mortality) by CCI (Charlson Comorbidity Index) scores. The solid line represents CCI=0, and the dotted line represents CCI\geq 1. The probability increases over days, with a notable difference between the two groups, indicated by the p-value of 0.04.
MDS

- **Consequences**
  - Progressive decline in blood cell counts
  - Transformation into leukemia

- **Prognosis**
  - Blasts in BM
  - Number of cell lines involved
  - Cytopenia
  - Chromosome abnormalities
  - FAB, WHO, IPSS
How to Treat MDS?

- Supportive care
- Altering natural history without curing the disease
- Curing the disease: Allo-HSCT

Deeg ASH 2005
Incidence of MDS and AML
MDS, Transplantation

- Role for induction chemotherapy
- Optimal timing for respective disease status
- Conditioning intensity
- Source of stem cells
- Alternative donors
Outcomes of Allo HSCT improved in the past decade (EBMT)

De Witte BJH 2000

![Graph showing improvement in EFS over time with different HR values for different time periods.](image-url)
Age impacts on the outcomes of Allo-HSCT (EBMT)

MDS, HLA-id.sib transplanted > 1995, standard conditioning, Good Risk

EFS

Age classes

- ≤ 30 yrs (N=71)
- > 50 yrs (N=61)
- 31-50 yrs (N=188)

p=0.04

MONTHS

De Witte ASH 2004
### Outcome (%) at 3 yrs

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Relapse</th>
<th>NRM</th>
<th>RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Int-1</td>
<td>6</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>Int-2</td>
<td>29</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>High</td>
<td>42</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>
Cytogenetics impacts on the outcomes of Allo-HSCT (EBMT)

De Witte ASH 2004

Event-free Survival (n=523)

Cytogenetics
Good (238)
Intermediate (154)
Poor (131)

p=0.016
Role of Induction Chemotherapy

Yakoub-Agha J CO 2000

- t-MDS, t-AML (n=70)
- Induction CT (n=33)
Role of Induction Chemotherapy

Scott BBMT 2005

n=125 (RAEB, RAEB in T)
Role of Induction Chemotherapy

- Lower blasts: superior outcomes
- Role of intensive induction CT
  - Pre-transplant chemotherapy may select for “treatment sensitive” patients.
- Role of hypomethylating agents
When to perform Allo-HSCT?

<table>
<thead>
<tr>
<th>IPSS</th>
<th>By time of TPL</th>
<th>Early 2 yrs Prog.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.9</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>3.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Net benefit or loss of overall life expectancy

![Graph showing gain/loss of discounted life expectancy over years of delay.](image-url)
Low/Int-1 Risk IPSS

- Delayed transplantation (before leukemic transformation) maximizes OS (Culter Blood 2004)
- Usually low intensity approach, except:
  - Younger age (good performance status + clinical indication)
  - Progression
    - Aggravation of cytopenia
    - Increase of % marrow blasts
    - New chromosomal abnormality
IPSS Risk:

- Low risk IPSS patients OS is similar to matched donors, except:
  - Disease progression:
    - Progression
    - Aggravation of cytopenia
    - Increase of % marrow blasts
    - New chromosomal abnormality

- Intermediate-1 (Int-1) and Intermediate-2 (Int-2) risk IPSS patients OS is lower than matched donors, except:
  - Disease progression:
    - Progression
    - Aggravation of cytopenia
    - Increase of % marrow blasts
    - New chromosomal abnormality
Int-2/High risk IPSS

- Transplantation at diagnosis maximizes OS (Culter Blood 2004)
- Curative approach
  - Allogeneic HSCT
  - Except
    - Age > 50 (60, 70) years
    - Poor performance