Transplantation for MDS: Where do we stand?

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Outline

• Relevance of MDS classification
• Transplant-specific questions
  – Conditioning intensity
  – Comorbid conditions
  – Relapse
  – GVHD
• Molecular outlook
### WHO Classification of MDS 2008

<table>
<thead>
<tr>
<th>Entity</th>
<th>Dysplasia</th>
<th>Blasts PB</th>
<th>Blasts BM</th>
<th>Ringsidero-blasts</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with isolated 5q-deletion</td>
<td>mostly DysE</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>&lt;15%</td>
<td>sole 5q-deletion</td>
</tr>
<tr>
<td>RA, RN, RT, RCUD</td>
<td>DysE, DysG, DysM</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>&lt;15%</td>
<td>various</td>
</tr>
<tr>
<td>RARS</td>
<td>mostly DysE</td>
<td>0%</td>
<td>&lt;5%</td>
<td>≥15%</td>
<td>various</td>
</tr>
<tr>
<td>RCMD</td>
<td>2-3 lineages</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>&lt;15%/≥15%</td>
<td>various</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>1-3 lineages</td>
<td>&lt;5%</td>
<td>5-9%</td>
<td>&lt;15%/≥15%</td>
<td>various</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>1-3 lineages</td>
<td>5-19% Auer rods</td>
<td>10-19% Auer rods</td>
<td>&lt;15%/≥15%</td>
<td>various</td>
</tr>
<tr>
<td>MDS-U</td>
<td>1-3 lineages</td>
<td>≤1%</td>
<td>&lt;5%</td>
<td>&lt;15%</td>
<td>various</td>
</tr>
</tbody>
</table>

### WHO Classification and Survival

![Survival Graph](image)

Malcovati et al, JCO 2005
**WHO Classification and Transplant Outcome**

*E.P. Alessandrino et al, Blood 112, 2008*

**WPSS: Clinical Outcomes**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>Survival</th>
<th>AML Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
<td>11.3 yr</td>
<td>7% @ 10 yr</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>5.3</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>3.7</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>Very High</td>
<td>5-6</td>
<td>0.7</td>
<td>50% @ 8 mo</td>
</tr>
</tbody>
</table>

RA, RARS, 5q- = 0  
RCMD/RS = 1  
RAEB-1 = 2  
RAEB-2 = 3

No Tx = 0  
Reg. Tx = 1  
Cyto good = 0  
intermed. = 1  
Poor = 2

*L. Malcovati et al, JCO, 2005*
WPSS Classification and Transplant Outcome

Effect of marrow fibrosis on survival and AML progression of MDS

Della Porta et al., J Clin Oncol 2008
Three Major Problems post-HCT

<table>
<thead>
<tr>
<th>Post HCT Complication</th>
<th>Risk by IPSS or WPSS Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Low”</td>
</tr>
<tr>
<td>Toxicity (RRT)</td>
<td>+</td>
</tr>
<tr>
<td>GVHD (+ associated complications)</td>
<td>++</td>
</tr>
<tr>
<td>Relapse</td>
<td>(+)</td>
</tr>
</tbody>
</table>

How to tackle them?

- **Toxicity**
  - Conditioning regimens; spread the components (pre, peri, post)

- **GVHD**
  - Reduce conditioning toxicity; T cell depletion in vivo or in vitro; novel post-HCT agents; consider the GVL effect

- **Relapse**
  - Pre-HCT therapy; modify GVHD; post-HCT therapy
Conditioning

Conditioning Regimens

**Required Contribution of Allogeneic GVT Effect**

- BU+CY+TBI*
- BU+TBI*
- CY + TBI*
- FLU + AraC
- BU + CY (± ATG)
- CY + BU
- BU + Melphalan
- FLU + Melphalan
- FLU + Treosulfan
- FLU + BU (3.2-16)
- tbi† + FLU (90-250)

**Toxicity**

- 12 Gy; *TBI at ≥12 Gy; HJ Deeg

**Intensity**

- tbi†

HJ Deeg
Flu/Treo Treatment Scheme

- TREO 14 g/m²/day
- FLU 30 mg/m²/day
- HCT
- Methotrexate 10 mg/m²/dose
- Tacrolimus BID

Flu + Treosulfan Conditioning (N=60)

Transplant related mortality

N = 60
Related and Unrelated donors
MDS or AML

E. Nemecek et al., BBMT, 2011
Flu + Treo: Comorbidity, Karyotype and TRM

Patients with HCT-CI ≥3

Non-relapse mortality

Years after transplant

High risk (n=17)

Standard or intermediate risk (n=11)

K. Guthrie, H.J. Deeg, unpubl.

Flu + Treosulfan Conditioning: Impact of Cytogenetics

Event-free survival

Years after transplant

Standard or intermediate risk

High risk

RFS

E. Nemecek et al. BBMT, 2011
Flu/Treo/TBI Treatment Scheme

- TREO 14 g/m²/day
- FLU 30 mg/m²/day
- TBI 2 Gy
- HCT
- Methotrexate 10 mg/m²/dose
- Tacrolimus BID

Days: -6, -5, -4, -3, -2, -1, 0, +1, +3, +6, +11, +56, +180

Relapse and NRM

- Flu/Treo/2 Gy TBI
- N=46
- Relapse Mortality 9% at 1 yr
- NRM 7% at 1 yr

Gyurkocza, Deeg et al
Cytogenetics and Transplantation
### 5-Group Cytogenetic Classification

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Cytogenetic Abnormality</th>
<th>Survival (ms)</th>
<th>Median (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Double</td>
<td>Complex</td>
</tr>
<tr>
<td>Very good</td>
<td>del(11q) -Y</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Good</td>
<td>normal del(5q) del(12p) del(20q) incl.del(5q)</td>
<td>---</td>
<td>48.6 (44.6-54.3)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, i(17q), +19, any other</td>
<td>---</td>
<td>26.0 (22.1-31.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3)(q21;q26), -7 incl. -7 del(7q)</td>
<td>3 abnl.</td>
<td>15.8 (12.0-18.0)</td>
</tr>
<tr>
<td>Very poor</td>
<td>---</td>
<td>---</td>
<td>≥4 abnl.</td>
</tr>
</tbody>
</table>

J. Schanz et al, JCO, 2011

### Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1,007</td>
</tr>
<tr>
<td>Patient age (ys), range (median)</td>
<td>1-75 (45)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>588 (58%)/419 (42%)</td>
</tr>
<tr>
<td>De novo MDS</td>
<td>771 (77%)</td>
</tr>
<tr>
<td>Secondary MDS</td>
<td>236 (23%)</td>
</tr>
<tr>
<td>FAB/WHO classification</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>377 (37.4%)</td>
</tr>
<tr>
<td>RCMD</td>
<td>82 (8.1%)</td>
</tr>
<tr>
<td>MDS-U</td>
<td>25 (2.5%)</td>
</tr>
<tr>
<td>RARS</td>
<td>15 (1.5%)</td>
</tr>
<tr>
<td>RAEB</td>
<td>304 (30.2%)</td>
</tr>
<tr>
<td>RAEB-Ti/AML</td>
<td>204 (20.3%)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
</tr>
<tr>
<td>5-group</td>
<td></td>
</tr>
<tr>
<td>- very good</td>
<td>13 (1.3%)</td>
</tr>
<tr>
<td>- good</td>
<td>440 (43.7%)</td>
</tr>
<tr>
<td>- intermediate</td>
<td>175 (17.4%)</td>
</tr>
<tr>
<td>- poor</td>
<td>148 (14.7%)</td>
</tr>
<tr>
<td>- very poor</td>
<td>97 (9.8%)</td>
</tr>
<tr>
<td>- data incomplete</td>
<td>134 (13.3%)</td>
</tr>
</tbody>
</table>

Deeg et al., manuscript submitted
Impact of Karyotype on Post-transplant Relapse

5-Group

IPSS

A

B

C

Monosomal Karyotype (MK) and Post-transplant Relapse

Deeg et al., unpublished
Survival by 5-group Cytogenetic Classification

Deeg et al., unpublished

Survival by Conditioning Regimen

Deeg et al., unpublished
Relapse and RFS with *de novo* and secondary MDS by cytogenetic risk

Survival According to Conditioning Intensity

The older patient
Risk model for non-HCT patients:

![Graph showing survival probability over time with annotations for IPSS, Age ≥ 65, and Comorbidity increases.]

K. Naqvi et al. JCO 2011

Low Intensity Conditioning: Outcome by Age (Various Diagnoses)

![Graphs showing NRM and Survival by age groups (60-64, 65-69, ≥70) with statistical significance annotations.]

M. Sorror et al, JAMA, 2011
5-AZA versus HCT: Overall Survival and RFS (60 - 70 vs)

OS

RFS

U.Platzbecker et al, unpublished

GVHD
PBPC vs. Marrow

A  PB 50%
   BM 39%

B  PB 57%
   BM 36%

P=0.15


Chronic GvHD

No ATG, PBPC
No ATG, BM.
ATG < 4.5 PBPC
ATG 6.0 PBPC
ATG 4.5 PBPC
Special considerations

HLA-Haploidenticel HCT

A

B

Cumulative incidence (%)

Survival (%)

Non-relapse mortality

Overall survival

Relapse

Event-free survival

Days after transplantation

Days after transplantation

L.Luznik, P.O’Donnell et al
Survival by salvage treatment in azacitidine treated patients

Th. Prébet et al. JCO 2011;29:3322-3327

Current CTN Trial 0901

MDS/AML < 5% blasts Age 18-65 yrs

Enrollment / Randomization

RIC Regimens
Flu/Bu
Flu/Mel

High Intensity Regimens
Bu/Flu
Bu/Cy
Cy/TBI

Primary Endpoint: 18-months Overall Survival
And the molecular era?

Mutations in candidate genes and survival

<table>
<thead>
<tr>
<th>Candidate Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
</tr>
<tr>
<td>ASXL1</td>
</tr>
<tr>
<td>RUNX1</td>
</tr>
<tr>
<td>TP53</td>
</tr>
<tr>
<td>EZH2</td>
</tr>
<tr>
<td>NRAS</td>
</tr>
<tr>
<td>JAK2</td>
</tr>
<tr>
<td>ETV6</td>
</tr>
<tr>
<td>CBL</td>
</tr>
<tr>
<td>IDH2</td>
</tr>
<tr>
<td>NPM1</td>
</tr>
<tr>
<td>IDH1</td>
</tr>
<tr>
<td>KRAS</td>
</tr>
<tr>
<td>GNAS</td>
</tr>
<tr>
<td>PTPN11</td>
</tr>
<tr>
<td>BRAF</td>
</tr>
<tr>
<td>PTEN</td>
</tr>
<tr>
<td>CDKN2A</td>
</tr>
</tbody>
</table>

R. Bejar et al, NEJM, 2011
RNA Splicing

Graubert, et al., Nat Genetics, 2011

Wahl, et al, Cell, 2009

Visconte, et al, Leukemia, 2011

U2AF35  = U2AF1
U2AF65  = U2AF2
SF3b155 = SF3B1

Survival in patients with low or intermediate-1 IPSS risk stratified by SF3B1 mutation status.

Summary

• HCT offers curative therapy for MDS
• Results with HLA matched related and unrelated donors are comparable
• Older patients can be transplanted successfully, but all reports to date show selection bias
• Need new strategies to overcome high risk cytogenetics
• Molecular data must be incorporated into classification and treatment decisions

Thank you to all contributors and, of course, our patients