Stem cell transplantation for myelodysplastic syndromes: where do we stand?

Theo de Witte, on behalf of:
Transplant team RUNMC, Netherlands
MDS Subcommittee CLWP, EBMT
EORTC Leukemia Group

The median age of a MDS patient: >70 years

Aul & Gattermann
1992
Düsseldorf

Median age
72 years
84% >60

Fig 1. Age distribution of MDS and AML patients.
**Therapeutic approaches in MDS/sAML**

- **Supportive therapy**: majority of patients
- **Nonintensive therapy**: improvement of cytopenias
- **Intensive antileukemic treatment**: chemotherapy and/or transplantation

**Stem cell transplantation in MDS**

- MDS is potentially curable by HSCT
- Allogeneic HSCT is preferred choice of HSCT for MDS
- However, allogeneic HSCT is only suitable for < 5% of MDS patients who have
  - unfavourable cytogenetics
  - adequate performance status, low co-morbidity score
  - appropriately matched donor
- HSCT is poorly tolerated in older patients
  - increased transplantation-related morbidity and mortality due to increased co-morbidity
  - non-myeloablative HSCT may be better tolerated

Options to improve outcome of HSCT in MDS?

- Proper evaluation of patient: co-morbidity, performance status, motivation/vitality, iron load
- Induction chemotherapy or hypomethylation therapy
- Conditioning
  - myeloablative vs reduced intensity conditioning (RIC)
- Post-transplantation strategies
  - Consider young unrelated donors
  - iron-reductive treatment (iron chelation therapy or phlebotomies)
  - donor lymphocyte infusion
  - maintenance therapy: hypomethylating agents, others
  - vaccination and immunotherapy

IPSS

International MDS Risk Classification

A. Survival

- Low 207 pts
- Int-1 314 pts
- Int-2 170 pts
- High 56 pts

B. AML Evolution

- Low 235 pts
- Int-1 295 pts
- Int-2 171 pts
- High 58 pts

Greenberg et al., Blood, 89: 2079, 1997
Eligibility of MDS patients for HSCT

- **IPSS Int-2- and High-risk MDS**
  - allo-SCT is first choice, unless clear comorbidity or refractory disease
- **IPSS Int-1 MDS**
  - consider allo-HSCT seriously, especially in case of young age, adverse cytogenetic characteristics, life-threatening cytopenias, or signs of progression (blasts and/or marrow failure)
- **IPSS Low-risk MDS**
  - consider allo-HSCT in case of prognostic adverse factors, including high transfusion need not responding to erythropoietin and/or lenalidomide

Transfusion dependency/anemia and co-morbidity are two new prognostic factors to be considered during the selection process

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**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>ET1V6</td>
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<tr>
<td>CBL</td>
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<td>IDH2</td>
</tr>
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<td>NPM1</td>
</tr>
<tr>
<td>IDH1</td>
</tr>
<tr>
<td>KRAS</td>
</tr>
<tr>
<td>GNAS</td>
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<tr>
<td>IDH1</td>
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<td>ETV6</td>
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<td>GNAS</td>
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<tr>
<td>PTEN</td>
</tr>
<tr>
<td>CDKN2A</td>
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</tbody>
</table>

Adapted from: Ljungman P, et al. Bone Marrow Transplantation 2010; 219-34.

R. Bejar et al, NEJM, 2011
MDS transplantation activity in Europe reported to EBMT

The number of HSCT in MDS patients is increasing, especially RIC HSCT

Factors influencing post-HSCT outcomes

- **Disease-related**
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- **Related to transplantation procedure**
  - conditioning intensity
  - donor age, type
- **Patient-related**
  - age
  - comorbidity index
  - transfusion burden
  - iron overload
Survival by IPSS risk in patients who did or did not undergo transplantation

Survival (%)

No transplantation

Transplantation

Overall survival (%)

IPSS = International Prognostic Scoring System.

Prognostic pre-transplant factors in MDS primarily treated by allogeneic hematopoietic stem cell transplantation

CLWP of the EBMT: Eline Cremers, et al

Who classification

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA/RARS/5q-</td>
<td>72 (36%)</td>
</tr>
<tr>
<td>RCMD</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>39 (20%)</td>
</tr>
<tr>
<td>sAML</td>
<td>41 (20%)</td>
</tr>
</tbody>
</table>

Prognostic factors influencing post-HSCT outcomes

- Disease-related
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- Related to transplantation procedure
  - conditioning intensity
  - donor age, type
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  - age
  - comorbidity index
  - transfusion burden
  - iron overload

Impact of Karyotype in patients with MDS
Francesco Onida and Ronald Brand
Impact of Karyotype in patients with MDS
Francesco Onida and Ronald Brand

### OS at 5y (*)
- **RA/RARS**
  - Cytogenetics
    - Good/Intermediate: 44%, HR(#): 0.9, 95% c.i.: 0.5-1.8, p: 0.9
    - Poor: 32%, HR(#): 1.1, 95% c.i.: 0.6-2.0, p: 0.81

### RFS at 5y (*)
- **RA/RARS**
  - Cytogenetics
    - Good/Intermediate: 49%, HR(#): 1.4, 95% c.i.: 0.9-2.1, p: 0.1
    - Poor: 55%, HR(#): 1.5, 95% c.i.: 1.0-2.2, p: 0.03

### Prognostic factors influencing post-HSCT outcomes
- **Disease-related**
  - Disease stage
  - Cytogenetics
  - Response to (chemo-)therapy
- ** Related to transplantation procedure**
  - Conditioning intensity
  - Donor age, type
- **Patient-related**
  - Age
  - Comorbidity index
  - Transfusion burden
  - Iron overload
Correlation between age and HCT-CI

Older candidates for HSCT are more likely to have comorbidities.


Comorbidity and disease status-based risk stratification

Overall survival decreases with increasing HCT-CI score and disease risk of MDS patients.

Prognostic factors influencing post-HSCT outcomes

- **Disease-related**
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- **Related to transplantation procedure**
  - conditioning intensity
  - donor age, type
- **Patient-related**
  - age
  - comorbidity index
  - transfusion burden
  - iron overload

Pathophysiology of iron overload in MDS

- Ineffective erythropoiesis
- RBC transfusions
- Myelosuppressive therapy
- Iron utilization
- Decreased erythropoiesis
- Increased transferrin saturation
- Elevated NTBI and LPI
- Ferritin
- Ferroportin
- Ferritin-mediated export
- Duodenal absorption
- Macrophage iron
- Hepcidin

LPI = labile plasma iron; NTBI = non-transferrin-bound iron; SCT = stem cell transplantation

NTBI during allogeneic HSCT

C = onset of conditioning regimen.


Impact of serum ferritin level prior to HSCT on OS and NRM post-HSCT (n = 129)


Overall survival by serum ferritin level prior to HSCT

Non-relapse mortality by serum ferritin level prior to HSCT
Prognostic pre-transplant factors in MDS primarily treated by allogeneic hematopoietic stem cell transplantation

CLWP of the EBMT: Eline Cremers, et al

Cox models

<table>
<thead>
<tr>
<th>Hazard ratios (p-values)</th>
<th>Overall Survival</th>
<th>Non-relapse mortality</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/RARS</td>
<td>1.00 (.02)</td>
<td>1.00 (.05)</td>
<td>1.00 (.009)</td>
</tr>
<tr>
<td>RCMD</td>
<td>2.81 (.004)</td>
<td>2.51 (.02)</td>
<td>3.20 (.19)</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>1.14 (.68)</td>
<td>0.73 (.41)</td>
<td>6.67 (.001)</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>1.78 (.05)</td>
<td>1.50 (.21)</td>
<td>2.68 (.13)</td>
</tr>
<tr>
<td>sAML</td>
<td>1.89 (.03)</td>
<td>1.38 (.31)</td>
<td>6.27 (.002)</td>
</tr>
<tr>
<td>RBC transfusion*</td>
<td>2.04 (.004)</td>
<td>1.88 (.03)</td>
<td>2.66 (.03)</td>
</tr>
<tr>
<td>Iron load**</td>
<td>1.51 (.23)</td>
<td>1.43 (.36)</td>
<td>1.84 (.38)</td>
</tr>
<tr>
<td>Comorbidity ***</td>
<td>1.50 (.11)</td>
<td>1.79 (.05)</td>
<td>0.90 (.81)</td>
</tr>
</tbody>
</table>

*<20 RBC units versus ≥20 RBC units; ** very high versus all others; *** yes versus no
Iron chelation prior to HSCT improves survival

ICT = iron chelation therapy;
SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of HSCT;
SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of HSCT, without ICT;
IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before HSCT.


Prognostic factors influencing post-HSCT outcomes

- Disease-related
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- Related to transplantation procedure
  - conditioning intensity
  - donor age, type
- Patient-related
  - age
  - comorbidity index
  - transfusion burden
  - iron overload
The Role of Reduced-Intensity Regimens in High-risk Myelodysplasia

- Main cause of treatment failure: related to toxicity of conditioning regimen, graft-versus-host disease, infections, immune suppression
- Reduction of the intensity of the conditioning regimen may reduce the nonrelapse mortality

**Conditioning Regimens**

- 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)

Intensity

Toxicity

*TBI at ≥12 Gy; †2 Gy

HJ Deeg
GVL reduced in RIC regimens?

Impact of intensity of conditioning on outcome of MDS after allo-HSCT

### Allogeneic HSCT for MDS patients ≥ 50 years old: multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>4-Year outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Relapse rate</td>
<td>1.42 (0.99–2.04)</td>
<td>0.42</td>
</tr>
<tr>
<td>RIC</td>
<td>Relapse rate</td>
<td>1.44 (1.13–1.84)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Advanced disease stage at HSCT</td>
<td>Relapse rate</td>
<td>1.51 (1.18–1.93)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-matched, unrelated</td>
<td>Relapse rate</td>
<td>1.08 (0.68–1.70)</td>
<td>0.75 (NS)</td>
</tr>
<tr>
<td>HLA-mismatched, unrelated</td>
<td>Relapse rate</td>
<td>0.99 (0.62–1.59)</td>
<td>0.98 (NS)</td>
</tr>
<tr>
<td>Reduced intensity conditioning (RIC)</td>
<td>NRM</td>
<td>0.79 (0.65–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Advanced disease stage at HSCT</td>
<td>NRM</td>
<td>1.43 (1.13–1.79)</td>
<td>0.01</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-matched, unrelated</td>
<td>NRM</td>
<td>1.57 (1.10–2.24)</td>
<td>0.01</td>
</tr>
<tr>
<td>HLA-mismatched, unrelated</td>
<td>NRM</td>
<td>1.31 (0.91–1.87)</td>
<td>0.14 (NS)</td>
</tr>
<tr>
<td>Advanced disease stage at HSCT</td>
<td>OS</td>
<td>1.55 (1.32–1.83)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

NS = not significant; OS = overall survival


**Disease stage at transplantation was the most important factor influencing outcome in this analysis**

### RFS Probability by Conditioning Intensity

**coordinator Rodrigo Martino**

- Conventional (n=566)
- Hyperintensive (n=80)
- Intermediate RIC (n=98)
- Micro intensity (n=29)

\[ p=0.007 \]

Conditioning Intensity
Prospective trial of EBMT MDS Subcommittee on intensity of conditioning on outcome of MDS/sAML after allo-SCT

coordinator: Nicolaus Kröger

**Randomisation**

**ARM A**
- Busulfan 12.8 mg/kg i.v. (or Busulfan, 16 mg/kg p.o.)
- Cyclophosphamide, 120 mg/kg

**ARM B**
- Busulfan 6.4 mg/kg i.v. (or Busulfan, 8 mg/kg p.o.)
- Fludarabine, 5 x 30 mg/m²

**Prognostic factors influencing post-HSCT outcomes**

- **Disease-related**
  - disease stage
  - cytogenetics
  - response to (chemo-)therapy
- **Related to transplantation procedure**
  - conditioning intensity
  - donor age, type
- **Patient-related**
  - age
  - comorbidity index
  - transfusion burden
  - iron overload
MDS, MUD, and standard conditioning
Improvement in time

Cox model evaluated for good risk and age: 31–50 years

EFS

![](image1)

EFS = event-free survival; HR = hazard ratio;
MDS = myelodysplastic syndromes; MUD = matched, unrelated donor.

P < 0.01

MDS, MUD, and standard conditioning
Improvement in time

TRM

![](image2)

Personal communication. EBMT registry.
Donor selection for stem cell transplantation in elderly patients with advanced MDS

**Younger MUD or older HLA-identical sibling?**

**Inclusion criteria:**
- Pts age > 50 yrs
- Advanced MDS: RAEB, RAEB-t, CMML or sAML
- HLA-identical sibling or matched unrelated donor

Donor selection for 871 patients
Median age: 57 years (range 50 – 73)

- HLA-identical sibling donor 706
- Matched unrelated donor 168
- RIC 481
- Standard conditioning 387
- Med. age of sibling donor 56 years (35-81)
- Med. age of MUD 34 years (19-64)  p < 0.001
Allogeneic SCT in CR-1 after intensive chemotherapy in patients with bad prognosis MDS treated results in better outcome in the intermediate/high-risk cytogenetic group


EORTC, GIMEMA, SAK, HOVON, Nordic MDS groups

T de Witte et al: Haematologica
06961 Criant

ICE (1-2x) → 341 → 194 CR

59 donor

IDIA 175

135 no donor

Donor Allo-SCT

No donor mobilize stem cells

H-D Ara-C 38 (27)

APSCT 33 (21)

Survival from CR impact of presence of donor

Age <= 55 yrs

p=0.23
Survival from CR impact of presence of donor
Cytogenetic good risk group

Survival from CR impact of presence of donor
Cytogenetic interm/high-risk risk group
Survival by salvage treatment in 5-azacitidine treated patients

HCT

Th. Prébet et al. JCO 2011;29:3322

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
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<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>6/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>0.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2**</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5**</td>
</tr>
</tbody>
</table>

Overall Survival (%)

Time Since AZA Failure (days)

However,.......... Sustained remissions were achieved only in patients who had not progressed an 5-azacitidine
Post-HCT Vidaza and overall survival (AML and MDS)

De Lima et al, Cancer, 2010

Impact of pretransplant variables

- Disease-related
  - disease stage: high
  - cytogenetics: certain subgroups
  - prior (chemo-)therapy: only in high-risk likely to respond to chemotherapy
- Related to transplantation procedure
  - conditioning intensity: uncertain
  - donor age: only very young donors
  - donor type: no impact if properly matched
- Patient-related
  - age: low impact if corrected by co-morbidity
  - comorbidity index: high
  - transfusion burden: high
  - iron overload: related to transfusion burden

De Lima et al, Cancer, 2010