Recommendations of allogeneic transplantation for patients with MDS

Theo de Witte, on behalf of an International expert panel preparing recommendations of alloHSCT for patients with MDS
I have no relevant financial relationships to disclose.
• Allogeneic SCT is an increasingly used, curative treatment option for patients with MDS

• **Reduced-intensity conditioning regimens** have extended the indication for SCT to patients with older age, comorbidities and less fit groups

• New treatment modalities for patients with MDS, including lenalidomide and hypomethylating agents (HMA) may influence the timing, indication and preparation for allogeneic SCT
This presentation will give an overview of current recommendations for allogeneic SCT with the focus on issues which have not yielded consensus amongst the members of the expert panel and recommendations for allogeneic HSCT in low and intermediate risk MDS.

The recommendations will address issues:
- selection of appropriate patients
- timing of transplantation
- management of patients before and after SCT
Allogeneic SCT is preferred curative choice for patients with MDS, but ...

- Allogeneic SCT is only suitable for the minority of MDS patients who have
  - Unfavourable forms of MDS
  - Adequate performance status, low co-morbidity score
  - Appropriately matched donor

- Allogeneic SCT is poorly tolerated in older, unfit patients
  - Increased transplantation-related morbidity and mortality due to increased co-morbidity
  - Non-myeloablative HSCT may be better tolerated, but it is difficult to prove a higher efficacy compared to standard regimens
Which factors play a role to recommend MDS patients a transplant and when?

- **Patient-related factors:**
  - age, frailty, co-morbidity and transfusion burden/iron toxicity
- **Disease-related factors which determine response to chemotherapy and hypomethylating agents:**
  - cytogenetic (molecular) characteristics and disease stage
- **Disease-related factors which determine risk of relapse after alloSCT:**
  - cytogenetic (molecular) characteristics and disease stage
- **The availability of a sibling donor (age donor) or a matched related donor (young donors!)
- **The choice of the intensity of the conditioning regimen
- **Expected response to proposed treatment before transplantation**
Increase of Number of transplants in elderly MDS/sAL patients

- 2001: n = 737, >50% = 47%, >55% = 22%, >60% = 10%, >65% = 2%
- 2005: n = 1140, >50% = 52%, >55% = 32%, >60% = 18%, >65% = 6%
- 2010: n = 1636, >50% = 100%, >55% = 64%, >60% = 50%, >65% = 33%

Kröger N. Blood 2012;119: 5632-5639
Survival benefit in higher risk MDS patients older than 60 years compared to control group

A

Overall Survival (probability)

Time (months)

P < .001

Lower risk

C

Overall Survival (probability)

Time (months)

P < .001

Higher risk

Koreth J, et al JCO 2013; 31: 2662-70
Increased use of unrelated donors in MDS/sAL patients

Adjusted probability of overall survival in 701 adult MDS patients by donor source

8/8 HLA-A, -B, -C, -DRB1

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
MDS > 50years and allo SCT

MDS > 50 years and allogeneic SCT

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ age</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.538</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Donor type/donor age</strong></td>
<td></td>
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<tr>
<td>Related</td>
<td>1</td>
<td></td>
<td>0.060 (global)</td>
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<tr>
<td>Unrelated &lt;30 years</td>
<td>0.65</td>
<td>0.45–0.95</td>
<td>0.026</td>
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<tr>
<td>Unrelated ≥30 years</td>
<td>1.07</td>
<td>0.81–1.41</td>
<td>0.622</td>
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<tr>
<td><strong>Stem cell source</strong></td>
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<tr>
<td>Peripheral blood</td>
<td>1</td>
<td>1.05–1.67</td>
<td>0.020</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1.32</td>
<td></td>
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<tr>
<td><strong>Cytogenetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
<td>0.007 (global)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.43</td>
<td>1.13–1.80</td>
<td>0.003</td>
</tr>
<tr>
<td>Missing</td>
<td>1.37</td>
<td>1.05–1.79</td>
<td>0.022</td>
</tr>
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<td></td>
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<tr>
<td><strong>Disease status at ASCT</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CR</td>
<td>1</td>
<td></td>
<td>&lt;0.001 (global)</td>
</tr>
<tr>
<td>Non CR</td>
<td>1.73</td>
<td>1.40–2.13</td>
<td>&lt;0.001</td>
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<tr>
<td>Missing</td>
<td>1.56</td>
<td>1.02–2.40</td>
<td>0.040</td>
</tr>
</tbody>
</table>
“Standard” eligibility criteria of MDS patients for HSCT based on IPSS (1997)

- **IPSS Int-2- and High-risk MDS**
  - Allogeneic SCT is first choice, unless clear co-morbidity or refractory disease!

- **IPSS Int-1 MDS**
  - Consider allogeneic SCT 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 allogeneic SCT in case of prognostic adverse factors, including high transfusion need not responding to erythropoietin and/or lenalidomide

- **IPSS-R will be the basis of the new SCT guidelines in MDS**
More than 50% of intermediate risk-1 patients move to (very) low risk groups around 10% to (very) high risk groups.
IPSS-revised: prognostic risk groups

OS by IPSS-R

<table>
<thead>
<tr>
<th></th>
<th>Very low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, years</td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>AML 25%, years</td>
<td>NR</td>
<td>10.8</td>
<td>3.2</td>
<td>1.4</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Survival following allogeneic HSCT in MDS patients stratified according to their pretransplant IPSS or IPSS-R risk

Low risk MDS: Recommendations from the ELN

Not symptomatic cytopenia
- watchful-waiting

Symptomatic anemia
- MDS del(5q)
- High-quality RBC transfusion and iron chelation therapy
- sEPO >500 mU/mL and RBC transfusion >=2 U/month
- Lenalidomide
- sEPO <500 mU/mL and/or RBC transfusion <2 U/month
- rHuEPO + G-CSF

sEPO <500 mU/mL and/or RBC transfusion <2 U/month
- rHuEPO + G-CSF

Age <60 years, BM blasts <5%, normal cytogenetics, <2 years RBC transfusion, hypocellular bone marrow

Immunosuppressive therapy with ATG

*IPPS-R: low + very low risk

Intermediate risk MDS: Recommendations from the ELN

Intermediate-1 IPSS risk

- **<5% BM blasts, no poor risk cytogenetics, not symptomatic cytopenia**
  - Watchful-waiting

- **Symptomatic anemia**
  - MDS del(5q)
  - RBC transfusion and iron chelation therapy
  - sEPO <500 mU/mL and/or RBC transfusion <2 U/month
  - rHuEPO + G-CSF

- **sEPO >500 mU/mL and RBC transfusion >=2 U/month**
  - Lenalidomide within clinical trial

- **sEPO <500 mU/mL and/or RBC transfusion <2 U/month**
  - rHuEPO + G-CSF

- **Age up to 65-70, poor risk cytogenetics or persistent blast increase**
  - Immunosuppressive therapy with ATG

- **Age <60 years, BM blasts <5%, normal cytogenetics, <2 years RBC transfusion, (hypocellular bone marrow ± HLA-DR15)**
  - rHuEPO + G-CSF

- **Available stem cell donor**
  - Allo-SCT

*IPPS-R: intermediate risk*
Allogeneic HSCT for patients with refractory anemia with matched related and unrelated donors

When to transplant?

Delay of HSCT is associated with inferior survival
Allogeneic HSCT for patients with refractory anemia with matched related and unrelated donors

- Disease duration of >12 months is associated with inferior survival
- AlloSCT should be preferentially performed early after diagnosis after careful analysis of prognostic variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survival</th>
<th>RFS</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>RIC vs. MAC</td>
<td>1.0 (0.6–1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Disease duration &gt;12 months</td>
<td>1.4 (1.0–1.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.1 (1.0–1.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>PB vs. BM</td>
<td>1.3 (0.9–2.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Year transplant (per year)</td>
<td>0.95 (0.9–1.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>1.3 (0.9–1.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>IPSS - low</td>
<td>(1)</td>
<td>0.6</td>
</tr>
<tr>
<td>IPSS - intermediate-1</td>
<td>0.8 (0.5–1.4)</td>
<td></td>
</tr>
<tr>
<td>IPSS - Intermediate-2</td>
<td>0.5 (0.1–2.1)</td>
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</table>
The impact of poor risk cytogenetics is more important in patients with advanced disease.

- **Alive after relapse**
- **Dead after relapse**
- **Nonrelapse death**

**Hazard Ratio’s**

- **RA/RARS**: 0.9 (0.5 to 1.8)
- **RAEB/CML**: 1.4 (0.9 to 2.1)
- **RAEBt**: 2.5 (1.6 to 3.7)

Mutations in candidate genes and survival

A

- 0 driver mutations identified (n=116)
- 1 driver mutations identified (n=138)
- 2 driver mutations identified (n=167)
- 3 driver mutations identified (n=111)
- 4-5 driver mutations identified (n=50)
- ≥6 driver mutations identified (n=13)

Leukemia-free survival vs. time (months)
P < 0.0001

(19%)

E. Papaemmanuel et al, Blood 2013; 122::3616-27
Contribution of gene mutations in predicting survival

E. Papaemmanuel et al, Blood 2013; 122::3616-27
Combination TP53 and complex karyotype dismal outcome after allogeneic SCT.

These patients are recommended to be treated in investigational studies only.
Diagnosis and treatment of MDS in adults: recommendations from the ELN


*IPPS-R: high + very high risk

Intermediate-2 or High IPSS risk

- >65-70 yrs or poor performance status
  - Supportive care
  - <75 yrs
    - Hypomethylating agents

- <65-70 yrs Good performance status
  - No suitable stem cell donor
    - poor risk cytogenetics
      - Hypomethylating agents
    - >10% BM blasts No poor risk cytogenetics
      - AML-like CT
    - <10% BM blasts
      - Available stem cell donor
        - >10% BM blasts
          - Allo-SCT
        - Allo-SCT

<70 yrs or poor performance status

- Supportive care
- <75 yrs
  - Hypomethylating agents
  - AML-like CT
  - Allo-SCT
Which factors play a role in decision to give cytoreduction prior to HSCT?

- It takes 2 to 6 months before a suitable donor can be identified.
- Does the disease allow delay of treatment? Bridging meaningful in certain subgroups?
- Chance of required response to ICT or HMA?
- What is the chance of reaching the transplant procedure (selection!)?
- Reduction of relapse risk after allogeneic SCT if CR (ICT) or response (HMA)?
- Prevention of disease-related complications
Approach of patients who have received ICT or HMA before considering alloHSCT or as “bridging”

• Many high-risk MDS patients receive ICT or HMA before considering alloHSCT as part of a bridging strategy
• The optimal time point of starting transplant conditioning is unclear both after ICT and after HMA
• Patients in CR1 after ICT do better than patients with failure after ICT, but the optimal number of consolidation courses is unknown
• The optimal timing of alloHSCT in patients responding to HMA is unknown: at time of partial or complete response? Additional courses: positive contribution?

Answer: some (personal) recommendations at the end (not based on published data)
Matched related donors and standard conditioning

<table>
<thead>
<tr>
<th>Approach</th>
<th>Status</th>
<th>Nr of patients</th>
<th>3-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct alloHSCT</td>
<td>RAEB(t)/sAML</td>
<td>111</td>
<td>31</td>
</tr>
<tr>
<td>Prior Remission-induction therapy</td>
<td>CR-1</td>
<td>230</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>No CR-1</td>
<td>440</td>
<td>32</td>
</tr>
</tbody>
</table>

Survival in 3 cytogenetic risk groups (IPSS)

Conclusion: cytogenetic poor risk patients also after HSCT poor prognosis
Survival by 5-group cytogenetic classification: IPSS-R

Survival analysis showing different groups:
- Very Good (n=13)
- Good (n=440)
- Intermediate (n=175)
- Poor (n=148)
- Very Poor (n=97)

Years after Transplant

Probability of RFS

Conclusion: in this group of 903 patients with complete cytogenetic information to calculate IPSS-R cytogenetic risk groups patients in CR are not doing better compared to “untreated” patients.
Post-transplantation outcome of higher risk MDS patients stratified according to whether or not induction chemotherapy was received before AHSCT

- 209/457 received AML like chemotherapy
- No detailed data of both groups; control arm: HMA?
- In patients who received AML-like chemotherapy, the achievement of CR before AHSCT was associated with prolonged survival and reduced incidence of relapse (27% vs 39% in patients with CR compared with unresponsive patients).
- Survival after transplantation was similar between patients who achieved CR after cytoreductive treatment and untreated patients.
- In a multivariable analysis, a significant effect of disease status at transplantation (CR vs no response) on survival was observed (HR, 0.6; \( P = .007 \)).
06961 Criant

ICE (1-2x) 341→194 CR: 57%

IDIA 175

59 donor

Donor Allo-SCT

No donor mobilize stem cells 135 no donor

H-D Ara-C 38 (27)

APSCT 33 (21)

EORTC LG

Survival from CR impact of presence of donor
Cytogenetic good risk group

\[ p = 0.95 \]
Survival from CR impact of presence of donor
Cytogenetic interm/high-risk risk group <55 years

CR rate in this group: around 50%

Comparison on intention-to-treat

p=0.04
Impact of Azacitidine Before Allogeneic HSCT for MDS: GFM an GMTC

HR = 1.27, 95% CI (0.78-2.34)

P = 0.69
Survival by salvage treatment in 5-azacitidine treated patients

Th. Prébet et al. JCO 2011;29:3322
Survival (A), EFS (B), relapse (C), and NRM (D) according to the prior-to-transplantation treatment.

Damaj G et al. JCO 2012;30:4533-4540.
163 consecutive patients (2005-2009)
  • 98 ICT alone
  • 48 AZA alone
  • 17 AZA-IC

Excluded: 74 patients treated with BSC

Median age: 57 years; not different in 3 groups

Multivariate analysis: no statistical differences between the AZA and the ICT groups in terms of OS, EFS, relapse, and NRM

More progression to aggressive disease in ICT group: 51% vs 15% in AZA group (p <0.001). This variable has not been included in the multivariate analysis because nonsignificant in univariate analysis!
Regression analyses of HSCT Outcome on 35 patients treated with Aza versus 33 patients treated with chemotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
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<tr>
<td>Univariate</td>
<td>0.68 (0.35-1.30)</td>
<td>.24</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.87 (0.44-1.69)</td>
<td>.68</td>
</tr>
<tr>
<td>NRM</td>
<td>1.06 (0.45-2.54)</td>
<td>.88</td>
</tr>
<tr>
<td>Relapse Risk</td>
<td>0.43 (0.15-1.20)</td>
<td>.10</td>
</tr>
</tbody>
</table>
Risk score for response to Azacytidine

Scoring system based on 4 prognostic factors:
1 point was attributed to:
• ECOG PS 2
• Presence of circulating blasts
• RBC TD 4 RBC units/8 weeks
1 and 2 points to intermediate- and poor-risk cytogenetics, resp.

Three risk categories in 269 patients:
low (score 0), intermediate (score 1-3), and high (score 4-5).

Median OS in 3 groups:
• not reached in the low-risk (n 30)
• 15.0 months in the intermediate-risk (n 191)
• 6.1 months in the high-risk (n 48)
Conclusions

- No randomized clinical trials available to address the issue of treatment strategy prior to allogeneic SCT: many high-risk patients start cytoreductive treatment before considering allogeneic SCT

- Both the expected the response rates to the pre-transplant strategies and relapse risk and NRM after SCT play a role

- Fit patients younger 60-65 years with >10% marrow blasts and without high risk cytogenetic abnormalities might be considered for ICT (1 or 2 courses: not more): role of consolidation courses unclear, but likely not associated with beneficial effect (antileukemic effect < toxicity)

- Patients with high risk cytogenetic abnormalities should be treated in investigational protocols if not candidates for ICT
Approach of patients who have received ICT or HMA before considering alloHSCT or as “bridging”

Unfit patients up to the age of 75 years might be considered for HMA pretreatment: number of courses unclear; benefit unproven

Expert opinions: patients in CR after 4 courses of HMA should continue HMA. Opinion TdW: might be reasonable for patients with low Aza score

Patients with stable disease after 6 courses are recommended for allogeneic SCT

Patients with relapse/progression after 6 courses are candidates for allogeneic SCT

Bridging (treatment with HMA during donor search) is widely applied, but evidence of benefit is not supported by clinical data
• Start immediately after diagnosis MDS explaining the role of allogeneic SCT in the treatment of high risk MDS

• Initiate family HLA typing as soon as patient has agreed

• Start donor search as soon as the lack of a family donor is clear

• In the mean time consider cytoreduction only in case of rapid progression of marrow blasts and circulating blasts