Allogeneic Hematopoietic Stem Cell transplantation in MDS

Theo de Witte, on behalf of the International expert panel which developed recommendations of HSCT for patients with MDS, MDS subgroup of EBMT CMWP
Age and Vitality!
Introduction

• Allogeneic hematopoietic stem cell transplantation (HSCT) is an increasingly used, curative treatment option for patients with MDS

• **Lower intensity conditioning regimens** have extended the indication for HSCT to patients with increased comorbidities and reduced fitness/vitality

• Nontransplant treatment modalities for patients with MDS, including lenalidomide, hypomethylating agents (HMA) and investigational drugs, may influence the indication, timing, and preparation for HSCT

We will focus on the following issues:

- selection of appropriate patients
- timing of transplantation of patients treated with nontransplant interventions
- Post-transplant strategies
- presentation of our new interactive website EUMDS/MDS-RIGHT

This published review with the recommendations for MDS and CMML is the backbone of the current interactive recommendations

The recommendations for HSCT in MDS will distinguish:

- HSCT as standard practice

- HSCT as non-standard (investigational) practice in patients who have an expected poor outcome after HSCT due to patient-related (e.g. high co-morbidity index) or disease-related factors (e.g. refractory after cytoreductive therapy or TP53 mutations)

Conditioning intensity not discussed in detail, assuming general recommendations (reduced intensity in less fit patients)

Type of donors not discussed in detail: we distinguish as standard donors identical siblings or matched unrelated donors and other donors

Timing of HSCT in lower-risk MDS patients without poor-risk features
Factors playing a role to recommend and to time a HSCT for MDS patients

- **Patient characteristics**: fitness, co-morbidity and chronic transfusion dependency/transfusion density

- **Disease characteristics** which determine response to chemotherapy and hypomethylating agents: cytogenetic (molecular) characteristics

- **Disease characteristics** which determine risk of relapse after HSCT: cytogenetic (molecular) characteristics and disease stage

- The availability of a suitable donor: 100%?

- Expected response to proposed treatment before transplantation

- Response and disease status after given treatment prior to start HSCT

Allogeneic HSCT (16,000) in Europe (2015)

Passweg, JR BMT 2020 online: 13% increase in 2018 when compared to 2017 (2322 pts)

Passweg, JR BMT 2017 online; doi.1038/bmt.2017.34
Increase of number of transplants in older MDS/sAL patients

>50% unrelated donors

Kröger N. Blood 2012;119: 5632-5639
Survival following HSCT in MDS patients stratified according to their pretransplant IPSS or IPSS-R risk

IPSS-R better model to predict outcome after HSCT

Impact of poor risk cytogenetics: more important in patients with advanced MDS

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)
Lower-risk MDS recommendations for “standard” allogeneic HSCT

(Very) Low Risk
Intermediate Risk
IPSS-R

Poor performance
Nonfit®

No poor risk features**

Nontransplant strategies*

Failure*

Transplant strategies#

Good performance
Fit®

Poor risk features**

Available donor^

Transplant strategies#
Lower-risk MDS
According to IPSS-R: Low and Intermediate Risk

Fit patients: <3 co-morbidities and good performance status (Karnofsky >60)

No upper age limit, if patients are fit, without serious co-morbidity and good Karnofsky status

Nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN

Failure of nontransplant strategies: ESAs, lenalidomide and cytoreductive therapy, including HMA. Nontransplant interventions may include more than one line of nontransplant intervention, e.g. treatment with ESAs, followed by lenalidomide in patients with 5q-.

Poor risk features:

- (very) poor risk cytogenetic characteristics
- persistent blast increase (>50% increase from base line or with >15% BM blasts)
- life threatening cytopenias: neutrophil counts < 0.3 x 10^9/l; platelet counts < 30 x 10^9/l)
- high transfusion intensity ≥2 units/month for 6 months
- molecular testing is generally recommended, especially in case of absence of poor risk cytogenetic characteristics or persistent blast increase
HSCT for patients with refractory anemia with matched related and unrelated donors

When to transplant?

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

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survival HR (95% CI)</th>
<th>P-value</th>
<th>RFS HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIC vs. MAC</td>
<td>1.0 (0.6–1.6)</td>
<td>1.0</td>
<td>1.2 (0.8–1.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Disease duration &gt;12 months</td>
<td>1.4 (1.0–1.9)</td>
<td><strong>0.05</strong></td>
<td>1.3 (1.0–1.8)</td>
<td><strong>0.09</strong></td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.1 (1.0–1.3)</td>
<td>0.05</td>
<td>1.1 (1.0–1.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>PB vs. BM</td>
<td>1.3 (0.9–2.1)</td>
<td>0.2</td>
<td>1.2 (0.8–1.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Year transplant (per year)</td>
<td>0.95 (0.9–1.0)</td>
<td>0.05</td>
<td>1.0 (0.9–1.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>1.3 (0.9–1.9)</td>
<td>0.2</td>
<td>1.2 (0.8–1.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>IPSS – low</td>
<td>(1)</td>
<td>0.6</td>
<td>(1)</td>
<td>0.6</td>
</tr>
<tr>
<td>IPSS – intermediate-1</td>
<td>0.8 (0.5–1.4)</td>
<td>0.9</td>
<td>0.6 (0.6–1.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>IPSS – Intermediate-2</td>
<td>0.5 (0.1–2.1)</td>
<td>0.5</td>
<td>0.5 (0.1–2.0)</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Contribution of gene mutations in predicting survival after HSCT

Combination TP53 and complex karyotype dismal outcome after HSCT

These patients are recommended to be treated in investigational studies

R. Bejar, et al JCO 2014; 29: 504-15
TP53 mutations (19%) inferior outcome after HSCT

RAS mutations inferior outcome after RIC only
**Selection of patients for HSCT, including all selection criteria and <10% marrow blasts**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Donors</th>
<th>Conditioning</th>
<th>HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Standard donors: HLA-identical siblings (including one Class I [A/B] mismatch), Syngeneic donors, Matched unrelated donors 8/8 and 10/10</td>
<td>Myeloablative</td>
<td>Option 1: no cytoreduction before conditioning (click for details)</td>
</tr>
<tr>
<td>IPSS-R Risk</td>
<td>Very Low to Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Score</td>
<td>≥ 80</td>
<td>Reduced intensity</td>
<td>Option 2: no cytoreduction before conditioning (click for details)</td>
</tr>
<tr>
<td>HSCT-CI Score</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow Blasts</td>
<td>&lt; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast Increase &gt;50%</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic Risk</td>
<td>Very Good to Intermediate</td>
<td>Alternative donors: Mismatched related / unrelated donors, Cord blood</td>
<td>Myeloablative</td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>No</td>
<td>Reduced intensity</td>
<td>Option 2: no cytoreduction before conditioning (click for details)</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>&lt; 0.3 x 10^4/L</td>
<td></td>
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</tbody>
</table>

**Standard donors:** young donors are preferred in view of better results with younger donors, possibly related to reduced stem cell renewal at higher age and risk of clonal hematopoiesis at advanced age.

**Alternative donors, if no standard donors available:** second option
Selection of patients for standard HSCT
Using all selection criteria in fit patient

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<th>HSCT</th>
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<tr>
<td>IPSS-R Risk</td>
<td>Very Low to Intermediate, Standard donors: HLA-identical siblings (including one Class II A/B mismatch), Syngeneic donors, Matched unrelated donors 8/8 and 10/10</td>
<td>Myeloablative</td>
<td></td>
</tr>
<tr>
<td>Karnofsky Score</td>
<td>≥ 80</td>
<td>Reduced intensity</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Very Good to Intermediate, Alternative donors: Mismatched related / unrelated donors, Cord blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>≥ 0.3 x 10^9/L</td>
<td></td>
<td>Reduced intensity</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥ 30 x 10^9/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion intensity</td>
<td>&lt; 2 units/month</td>
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</tbody>
</table>

molecular testing should be seriously considered in all candidates for standard HSCT, but especially in case of absence of all nonmolecular poor risk factors

Standard: nontransplant strategies;

optionally: HSCT in investigational studies
Higher-risk MDS recommendations

(Very) Poor Risk
IPSS-R

Poor performance
Nonfit®
- Nontransplant strategies*

Good performance
Fit®
- No suitable donor
  - Nontransplant strategies*
- < 10% marrow blasts
  - Transplant strategies*
- ≥ 10% marrow blasts
  - Cytoreductive therapy
  - Transplant strategies*

Available donor^
Patients may receive cytoreductive therapy prior to the conditioning both for myeloablative and reduced intensity conditioning.

Two cytoreductive approaches possible: IC of HMA.

Selection of IC and HMA are based traditionally on age, co-morbidity. No prospective studies to support choice.
Cytoreductive therapy prior to conditioning

Intensive remission chemotherapy (IC)

- Remission induction regimens: including standard dose ara-c or higher dosage and anthracyclines
- Number of courses: 1 or 2

After remission-induction

- Consolidation therapy: no proof of value for additional consolidation courses
- HSCT recommended in:
  - CR1, CR2
  - Resistant to IC in investigational studies only

Hypomethylating agents (HMA)

- Number of courses: 4 to 6

After treatment

- HSCT recommended in:
  - CR1, PR or stable disease after 4 to 6 courses
  - Progressive disease or loss of response in investigational studies only
Prevention and treatment of relapse in a MDS patient with >15% marrow blasts by cytoreduction?

SCT not part of the protocol; survival measured from time of SCT. Interval between start treatment and SCT not provided

Prevention and treatment of relapse in a MDS patient with >15% marrow blasts

Post-transplant follow-up

Step 1
Monitoring of minimal residual disease (MRD) and/or mixed chimerism after transplantation

Step 2
In the event of increasing/persisting MRD or increasing autologous cells, prophylactic treatment with donor lymphocyte infusions (DLI) and/or HMA treatment (investigational)

Step 3
in the event of relapse, treatment with DLI or second HSCT (with cyto reduction in case of >15% marrow blasts) or other investigational approaches

Prevention and/or treatment of iron toxicity
Treatment options are limited:
- palliative care, including supportive care
- treatment with HMA or ICT
- cellular immunotherapy after withdrawal of IS: DLI, second HSCT or a combination approach. DLI
- combination of DLI and azacitidine
Treatment options for patients with relapse of MDS or MDS/MPN after AHCT

- MDS patients relapsing after allo-SCT: n=147
  - PSC-group: n=46/147 (31%)
  - CRT-group:
    - DMA: n=23 (16%)
    - ICT: n=16 (11%)
    - n=39/147 (27%)
  - IT-group:
    - DLI alone: n=24 (16%)
    - DLI + CRT: n=18 (12%)
    - 2nd allo-SCT alone: n=7 (5%)
    - 2nd allo-SCT + CRT/DLI: n=13 (9%)
    - n=62/147 (42%)

Treatment options for patients with relapse of MDS or MDS/MPN after HSCT

Immunotherapy (second HSCT or DLI) for treatment of 147 patients with MDS relapse after HSCT was associated with superior survival when compared with cytoreductive therapy (23 HMA; 16 ICT) or supportive care only.

Relapses within 6 months after HSCT and high tumor burden at relapse associated with poor survival.

Recommendation: to offer salvage immunotherapy to patients with relapsing MDS after HSCT and a low risk profile (relapse >6 months after HCT and low tumor burden).
Conclusions

• Identification of risk factors predicting relapse after HSCT: important

• Measurement of MRD at HSCT and after HSCT: prognostic for relapse, but contribution of various methods may change

• Prevention of relapse before HSCT: early HSCT may be relevant, especially when BM blast counts <5%; cytoreduction usually applied when BM blasts are >10%, but value remains unproven

• Pre-emptive interventions are recommended in patients without complete donor chimerism or declining donor chimerism; pDLI most promising approach

• Outcome relapse after HSCT generally with short median survival of 5 months. Cellular therapies best results until now.
Prevention and treatment of transfusion-related toxicity after HSCT in MDS

No accepted method to monitor iron overload in the transplant setting. In practice: ferritin levels are used despite some drawbacks, but LPI levels might be more relevant.

- **Treatment of iron overload prior to HSCT**
  No prospective studies, but expert panel recommended appropriate iron chelation prior to HSCT in MDS patients with a RBC transfusion history of >20 units, who are candidates for HSCT

- **Treatment of iron overload after HSCT**
  The expert panel recommended treatment of iron overload after HSCT in patients with a high transfusion burden, but the choice between phlebotomies and iron chelation remained open due to the lack of prospective studies. The treatment should start within 6 months after HSCT
HR for risk of NRM and RI increased in patients (n = 201) with a high transfusion-burden (HR of 1.89; P = 0.03 and HR 2.67; P = 0.03). HR for ferritin level and comorbidity not significantly increased.
Prospective observational EBMT study
Survival according to iron reduction therapy prior to HSCT

31 patients (14%) received iron chelation prior to HSCT with a median duration of 4 months
Median ferritin level at HSCT was 1598 ng/ml

LPI levels predict survival in patients with lower-risk MDS
Figure 4: Exploratory post-hoc overall survival analysis

(A) Kaplan-Meier estimates for overall survival by liver iron content at baseline and (B) by eLPI concentration before the initiation of cytotoxic conditioning. P values were calculated with the log-rank test. eLPI=enhanced labile plasma iron.
Phlebotomy was initiated in 61 recipients of allografts due to hematologic malignancies (median age 48 years) after a median of 18 months. Acute leukemia & MDS 61%, Chronic leukemia 24%, Others 15%

Phlebotomy is a convenient therapy of iron overload in survivors of HCT.
A negative iron balance and a rise in hemoglobin were observed in the majority of patients.

Phlebotomy was initiated in 61 recipients of allografts due to hematologic malignancies (median age 48 years) after a median of 18 months. Acute leukemia & MDS 61%, Chronic leukemia 24%, Others 15%

A prospective non-interventional study on the impact of transfusion burden and related iron toxicity on outcome of HSCT in MDS

<table>
<thead>
<tr>
<th>Start iron reduction treatment after HSCT</th>
<th>Iron reduction after HSCT</th>
<th>Landmark after HSCT (months)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0-6</td>
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<td>0-12</td>
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<td></td>
<td></td>
<td>12-2</td>
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<tr>
<td>Nr of patients</td>
<td>No</td>
<td>101</td>
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<td></td>
<td>Yes</td>
<td>12</td>
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<td>77</td>
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<td>51</td>
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<td></td>
<td></td>
<td>21</td>
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<tr>
<td>OS#</td>
<td>No</td>
<td>65% (54-75%)</td>
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<td></td>
<td>Yes</td>
<td>90% (71-100%)</td>
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<td>75% (65-86%)</td>
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<td>85% (79-98%)</td>
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<td>88% (73-100%)</td>
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<tr>
<td>RFS#</td>
<td>No</td>
<td>56 (46-67%)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>90% (71-100%)</td>
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<td></td>
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<td>0.04</td>
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<td>67% (55-79%)</td>
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<td>0.3</td>
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<td>81% (69-93%)</td>
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<td>88% (74-100%)</td>
</tr>
</tbody>
</table>

* Control group: patients with ferritin levels above 1000 ng/ml at start comparison

Relapse-free survival of patients alive and relapse-free at 6 months after transplantation, stratified in 2 groups according to iron reduction therapy given during the first 6 months after transplantation or not.
A prospective non-interventional study on the impact of transfusion burden and related iron toxicity on outcome of HSCT in MDS

Relapse-free survival of patients alive and relapse-free at 6 months after transplantation, stratified in 2 groups according to iron reduction therapy given during the first 6 months after transplantation or not.
Conclusions

• Selection of MDS patients for standard and investigational allogeneic stem cell transplantation requires intensive evaluation of patient- and disease-related factors

• Age is not the major determining selection criterium, if fitness/vitality and co-morbidities are evaluated carefully

• New effective nontransplant treatment modalities may lead to delay or reduction of allogeneic HSCT in MDS

• Molecular features are expected to increase the accuracy of selection of patients for allogeneic HSCT and may lead to better outcome after allogeneic HSCT
Conclusions

• The interactive website on recommendations for selecting and timing of allogeneic HSCT is expected to improve the implementation of high quality allogeneic HSCT in MDS

• Visit: https://mds-europe.eu

Acknowledgements:
• experts of the MDS HSCT Recommendations team
• Website team of EUMDS in York, UK: Dan Painter, Alex Smith, John Blaise