Iron overload in MDS

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MDS transplantation activity in Europe reported to EBMT

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

EBMT = European Group for Blood and Marrow Transplantation.
# Changes in MDS transplantation activity in Europe reported to EBMT

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of allografts</td>
<td>786</td>
<td>1,028</td>
<td>1,259</td>
<td>1,560</td>
<td>1,117</td>
</tr>
<tr>
<td>RIC</td>
<td>259</td>
<td>483</td>
<td>589</td>
<td>787</td>
<td>626</td>
</tr>
<tr>
<td>Related donors</td>
<td>460</td>
<td>558</td>
<td>591</td>
<td>647</td>
<td>421</td>
</tr>
<tr>
<td>Unrelated donors</td>
<td>318</td>
<td>459</td>
<td><strong>653</strong></td>
<td>902</td>
<td>683</td>
</tr>
<tr>
<td>Age ≥ 50 years</td>
<td>383</td>
<td><strong>589</strong></td>
<td>753</td>
<td>928</td>
<td>733</td>
</tr>
</tbody>
</table>

*The frequency of HSCT in MDS patients is increasing with time, especially in patients ≥ 50 years of age*

EBMT CLWP registry. Personal communication.
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 EPO and/or lenalidomide

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

EPO = erythropoietin.

Adapted from: Ljungman P, et al. Bone Marrow Transplantation 2010; 219-34.
Survival by IPSS risk in patients who did or did not undergo transplantation

IPSS = International Prognostic Scoring System.
Correlation between age and HCT-CI

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>100</td>
</tr>
<tr>
<td>40–49</td>
<td>80</td>
</tr>
<tr>
<td>50–59</td>
<td>60</td>
</tr>
<tr>
<td>&gt; 59</td>
<td>40</td>
</tr>
</tbody>
</table>

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

Pathophysiology of iron overload in MDS

Ineffective erythropoiesis

Hepcidin

Duodenal absorption

↑ Ferroportin

↑ Ferroportin-mediated export

RBC transfusions

Macrophage iron

Increased transferrin saturation

Elevated NTBI and LPI

Infection

↑ ↑ ↑ ↑ ↑

SCT mortality

Leukaemic transformation

Myocardial iron

Myelosuppressive therapy

Decreased erythropoiesis

Iron utilization

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

NTBI during allogeneic HSCT

C = onset of conditioning regimen.

NTBI during allogeneic HSCT (cont.)

- NTBI peaks around day 4 of the conditioning regimen and is detectable for around 2 weeks
- NTBI increases generation of hydroxyl radicals by
- Hydroxyl radicals can cause tissue damage by oxidative damage to proteins and lipid peroxidation

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

The impact of serum ferritin remained unchanged when the model was adjusted for albumin level.

Overall survival by serum ferritin level prior to HSCT

Non-relapse mortality by serum ferritin level prior to HSCT

Impact of pre-SCT iron overload on risk of blood stream infections

- Result of compromised immunity due to conditioning regimens, cytopenias, and the use of immunosuppressive agents\(^1\)

- Pre-SCT serum ferritin $\geq 1,000$ µg/L is associated with a significant increase in the incidence of blood stream infections\(^1,2\)
  - iron overload in HSCT is associated with increased the risk for aspergillosis and *Staphylococcus epidermidis*\(^1,3–7\)

Impact of pre-SCT iron overload on risk of hepatic VOD

- VOD is associated with high morbidity and mortality\textsuperscript{1–6}
- VOD is a result of endothelial and hepatocyte damage\textsuperscript{1}
  - due to conditioning regimen
  - due to chemotherapy and elevated LPI after conditioning
- Pre-HSCT serum ferritin > 1,000 µg/L is a risk factor for the subsequent development of VOD\textsuperscript{7–9}

The European Group for Blood and Marrow Transplantation

The effect of transfusions and iron toxicity on non-relapse mortality in patients with untreated adult MDS treated with myeloablative alloSCT

a retrospective study of the MDS subcommittee of the Chronic Leukaemia Working Party of the EBMT

Cox model for overall survival in untreated adult MDS patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>p value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS at tx*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/RARS</td>
<td>69</td>
<td>0.018</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>RAEB</td>
<td>107</td>
<td>0.011</td>
<td>1.8</td>
<td>1.1–2.9</td>
</tr>
<tr>
<td>RAEB-t/sAML</td>
<td>37</td>
<td>0.012</td>
<td>2.1</td>
<td>1.2–3.6</td>
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<tr>
<td>RBC pretx†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–20</td>
<td>86</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>44</td>
<td>0.029</td>
<td>1.7</td>
<td>1.1–2.7</td>
</tr>
<tr>
<td>Serum ferritin levels†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1,500 ng/mL</td>
<td>51</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥ 1,500 ng/mL</td>
<td>19</td>
<td>0.113</td>
<td>1.8</td>
<td>0.9–3.9</td>
</tr>
<tr>
<td>Composite iron score†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate/high</td>
<td>53</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>34</td>
<td>0.05</td>
<td>1.8</td>
<td>1.0–3.4</td>
</tr>
</tbody>
</table>

*Adjusted for donor, t-cell depletion, interval diagnosis-tx, age.
†Adjusted for donor, t-cell depletion, interval diagnosis-tx, age, MDS classification at tx.
A Non-Interventional Prospective Study to Evaluate the effect of transfusions and Iron toxicity in patients with myelodysplastic syndrome (MDS) treated with allogeneic stem cell transplantation (SCT)

Inclusion of patients Jan-2010 to Dec-2011
Options to improve outcome of HSCT in MDS

- Induction chemotherapy or hypomethylation therapy
  - possible delay of induction and use of iron chelation therapy
- Conditioning
  - myeloablative vs reduced intensity conditioning (RIC)
  - management of iron overload
- Post-transplantation strategies
  - iron-reductive treatment (iron chelation therapy or phlebotomies)
  - donor lymphocyte infusion
  - maintenance therapy
  - vaccination and immunotherapy
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.

Phlebotomy post-HSCT

- Patients surviving ≥ 4 years from SCT
  - to limit to patients with transfusional iron overload, excluding
    - hepatitis B/C, alcohol, hepatotoxic or immunosuppressive treatment, GVH, VOD/SOS, bleeding, inflammatory/neoplastic condition
  - 38 of 65 patients (58%) had serum ferritin above the normal range
  - MRI was abnormal in 31 of 32 patients
  - 29 of 38 patients accepted phlebotomy
    - AST/ALT normalized in 10 of 16 patients
    - serum ferritin normalized in 24 of 28 patients
  - conclusion: transfusional iron overload remains long-term following SCT and at least moderately impacts organ function

AST/ALT = aspartate transaminase/alanine transaminase; GVH = graft-versus-host; VOD/SOS = veno-occlusive disease/sinusoidal syndrome.
Planned prospective study to compare iron chelation with phlebotomy after allogeneic SCT for MDS (cont.)

- Conditioning and SCT
- Day -14
- Day 0
- Day 30
- Month 6
- Month 18
- Screen inclusion
- Randomization
- No ICT/No phlebotomy (Control)
- Phlebotomy
- Deferasirox
- Assessments for Core study end-points
- Assessments for Extension study end-points
- No ICT / No Phlebotomy (Control)
Iron chelation in MDS

The role of iron chelators to prevent the adverse effects of toxic iron should be addressed in clinical studies.

Present guidelines: indications iron chelation in MDS:

- Serum ferritin $>1,000 \, \mu g/l$
- Transfusion dependency: $>4\, \text{units/2 months}$
- Prognosis $>2\, \text{years}$ (lower risk MDS only?)
- Candidates allogeneic SCT
Case presentation

● Patient characteristics
  – 58-year-old female patient
  – 73 kg, 1.57 m

● Anaemia since April 2006
  – transfusion dependent: 2 units every 3 weeks

● Bone marrow in May 2006
  – Ring-sideroblastic anaemia with thrombocytosis (600 x 10^9/L): RARS-T
  – Normal cytogenetics; JAK2 mutation negative
Case presentation (cont.)

- October 2006: referral to RUNMC
  - serum ferritin 673 µg/L; transferrine saturation 81%
  - EPO level 482 mU/mL
- May 2007: 20 units of blood
  - serum ferritin 1,560 µg/L
- HLA-identical donor available (brother)

EPO = erythropoietin; HLA = human leucocyte antigen; RUNMC = Radboud University Medical Centre Nijmegen.
**Case presentation (cont.)**

**Serum ferritin (µg/L)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct-06</td>
<td>0</td>
</tr>
<tr>
<td>Jan-07</td>
<td>200</td>
</tr>
<tr>
<td>Apr-07</td>
<td>400</td>
</tr>
<tr>
<td>Jul-07</td>
<td>600</td>
</tr>
<tr>
<td>Oct-07</td>
<td>800</td>
</tr>
<tr>
<td>Jan-08</td>
<td>1,000</td>
</tr>
<tr>
<td>Apr-08</td>
<td>1,200</td>
</tr>
<tr>
<td>Jul-08</td>
<td>1,400</td>
</tr>
<tr>
<td>Oct-08</td>
<td>1,600</td>
</tr>
<tr>
<td>Nov-08</td>
<td>1,800</td>
</tr>
<tr>
<td>Dec-08</td>
<td>2,000</td>
</tr>
</tbody>
</table>

**Trisomy 8 in 60% of the metaphases; leucocytosis**

**Deferasirox (mg/µg/day)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec-08</td>
<td>5 → 20</td>
</tr>
<tr>
<td>Jan-08</td>
<td>15</td>
</tr>
<tr>
<td>Apr-08</td>
<td>25</td>
</tr>
<tr>
<td>Jul-08</td>
<td>10</td>
</tr>
<tr>
<td>Oct-08</td>
<td>0</td>
</tr>
</tbody>
</table>

**Hydroxyurea discontinued due to severe cryptogenic pneumonitis**

**De Novo translocation t(10;16)(q23;p13)**

**Start hydroxyurea due to progression**

**Started prednisone (1 mg/kg/day) for treatment of the pneumonitis**

**Allogeneic SCT (standard intensive conditioning with ex vivo T-cell depletion)**

**Transfusion requirement**

<table>
<thead>
<tr>
<th>Date</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct-06</td>
<td>2 pRBC per 3 weeks</td>
</tr>
<tr>
<td>Jan-07</td>
<td>2 pRBC per 2 weeks</td>
</tr>
</tbody>
</table>
Case presentation (cont.)

- After allogeneic SCT
  - 14 units of blood
  - 9 thrombocyte transfusions
  - last transfusion: 4 weeks after SCT
- February 2009
  - complete donor chimera
- April 2009
  - stopped ciclosporin immunosuppression
  - patient developed chronic renal function impairment (30 mL/min) owing to the renal toxicity of the ciclosporin treatment
  - serum ferritin 1,351 µg/L
Case presentation (cont.)

- June 2009: prophylactic donor lymphocyte infusion: non-severe chronic skin GVHD (no systemic treatment required)
- August 2009: right hip replacement
- December 2009: serum ferritin 846 µg/L
- March 2011: serum ferritin 613 µg/L; Hb 8.3 mmol/L; WBC 6.2 x 10^9/L; thrombocytes 150 x 10^9/L

WBC = white blood count.
Case summary

- 60-year-old female patient with a 3-year history of MDS, type RCMD
- After 2 years, progression with high transfusion need (10 units per month), cytogenetic abnormalities, leucocytosis, persisting thrombocytosis
- Proactive iron chelation allowed an uneventful allogeneic SCT (with standard conditioning) apart from coxarthrosis owing to corticosteroid therapy prior to SCT
- Following the allogeneic SCT, the patient remained transfusion independent for more than two years with no significant complication except a severe VZV-infection

RCMD = refractory cytopenia with multilineage dysplasia.