Iron overload as a potential risk factor in the setting of allogeneic HSCT

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Therapeutic options in MDS: European perspective

Stratification according to IPSS-R

- Lower-risk
  - LEN (del 5q)
  - Iron chelation
  - ESA

- Higher-risk
  - HMA
  - Intensive CT/allo-Tx

CT, chemotherapy; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; IPSS-R, Revised International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndromes; Tx, transplantation

The main indications for allogeneic HSCT in Europe are myeloid malignancies

2015 European Society for Blood and Marrow Transplant activity survey report

AID, autoimmune disease; ALL, acute lymphoblastic anemia; AML, acute myeloid leukemia; BMF, bone marrow failure; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, Hodgkin’s disease; HSCT, hematopoietic stem cell transplantation; IDM, inherited disorders of metabolism; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin’s lymphoma; PCD, plasma cell disorder; PID, primary immunodeficiency

AML 39% (early AML 21%, advanced AML 12%, transformed AML 6%)

ALL 16%

MDS/MPN 12%

CML 2%

PDC 7.1%

NHL 4%

HD 3%

CLL 2%

Solid tumors 0.2%

Thal/sickle 3%

BMF 5%

PID 3%

IMD 0.8%

AID 0.1%

Others 1%

Others 1%

AID 0.1%

PID 3%

Thal/sickle 3%

BMF 5%

Solid tumors 0.2%

PDC 7.1%

NHL 4%

HD 3%

CLL 2%

ALL 16%

MDS/MPN 12%

AML 39%

(early AML 21%, advanced AML 12%, transformed AML 6%)

Passweg JR et al. Bone Marrow Transplant 2017;doi:10.1038/bmt.2017.34
Variables to consider for HSCT

- Disease-specific therapy
- Conditioning
- Graft
- Pre-emptive therapy
- Maintenance
- GvHD prophylaxis

GvHD, graft versus host disease
Major risk factors associated with allogeneic HSCT

1. GvHD
2. Infections
3. Relapse
Is iron a culprit or bystander?
Variables we (potentially) could change

1. GvHD
2. Infections
3. Relapse
NTBI levels increase shortly after the start of conditioning and correlate with transferrin saturation

N=10

ONSET OF CONDITIONING REGIMEN

Mean transferrin saturation ± SD (%)

Time to HSCT (days)

NTBI (μmol/L)

Transferrin saturation (%)

NTBI, non-transferrin-bound iron; SD, standard deviation

Chelation therapy can induce negative iron balance post-HSCT

![Graph showing the change in serum ferritin and transferrin saturation over time with deferasirox treatment.](image-url)

- **X-axis:** Time of chelation therapy with deferasirox (weeks)
- **Y-axis 1:** Serum ferritin (ng/mL)
- **Y-axis 2:** Transferrin saturation (%)
Effects of iron overload on HSCT outcomes (1)

N=102

**LIVER INJURY***

- **<1000 ng/mL**: 54%
- **≥1000 ng/mL**: 84%

**INVASIVE FUNGAL DISEASE**

- **<1000 ng/mL**: 0%
- **≥1000 ng/mL**: 13%

*Liver function test values (ALT, AST, GGT or ALP) > upper limit of normal
ALP, alkaline phosphatase; ALT, alanine aminotransferase;
AST, aspartate aminotransferase; GGP, gamma-glutamyl transferase

P<0.05

Effects of iron overload on HSCT outcomes (2)

N=190

BLOODSTREAM INFECTIONS/DEATH

<table>
<thead>
<tr>
<th>Serum ferritin levels</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 ng/mL</td>
<td>44%</td>
</tr>
<tr>
<td>≥1000 ng/mL</td>
<td>60%</td>
</tr>
</tbody>
</table>

\[ P=0.004 \]

ACUTE GvHD GRADE 2–4/DEATH

<table>
<thead>
<tr>
<th>Serum ferritin levels</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 ng/mL</td>
<td>43%</td>
</tr>
<tr>
<td>≥1000 ng/mL</td>
<td>63%</td>
</tr>
</tbody>
</table>

\[ P=0.009 \]
Is pre-transplant serum ferritin level a marker of comorbidity?
Is iron a culprit or bystander?

N=172 de novo MDS patients (median age, 51 years)

Iron overload may contribute to poor transplantation success by adding to overall comorbidities
Can liver iron concentration by MRI predict outcomes?

N=88 (n=64 AML; n=24 MDS)

Patients with pre-transplant LIC >7 mg Fe/g dw have increased risk of NRM and reduced probability of OS

dw, dry weight; LIC, liver iron concentration; OS, overall survival
Is iron overload prior to HSCT associated with higher mortality after HSCT?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MDS/AML only</th>
<th>Serum ferritin</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armand et al. 2007</td>
<td>247</td>
<td>+</td>
<td>survival↓, mortality↑</td>
<td></td>
</tr>
<tr>
<td>Platzbecker et al. 2008</td>
<td>172</td>
<td>+</td>
<td>survival↓, mortality↑</td>
<td></td>
</tr>
<tr>
<td>Mahindra et al. 2009</td>
<td>222</td>
<td></td>
<td></td>
<td>survival↓, mortality↑</td>
</tr>
<tr>
<td>Alessandrino et al. 2010</td>
<td>357</td>
<td>+</td>
<td>survival↓, mortality↑</td>
<td></td>
</tr>
<tr>
<td>Lim et al. 2010</td>
<td>99</td>
<td>+</td>
<td>survival↓</td>
<td></td>
</tr>
<tr>
<td>Busca et al. 2010</td>
<td>102</td>
<td></td>
<td></td>
<td>invasive mycosis↑</td>
</tr>
<tr>
<td>Wermke et al. 2012</td>
<td>88</td>
<td>+</td>
<td>–</td>
<td>mortality ↑</td>
</tr>
<tr>
<td>Armand et al. 2012</td>
<td>48</td>
<td>+</td>
<td>survival↓, mortality↑</td>
<td>–</td>
</tr>
<tr>
<td>Trottier et al. 2013</td>
<td>88</td>
<td></td>
<td>survival↓, mortality↑</td>
<td>–</td>
</tr>
</tbody>
</table>
The jury is still out on whether pre-HSCT iron overload influences outcomes

This prospective cohort study, using MRI to measure iron load, found no association between pre-transplant iron and HSCT outcomes.
### Patient demographics and transplant characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No iron overload</th>
<th>Iron overload</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>52 (19–70)</td>
<td>52 (20–69)</td>
<td>0.85</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>23 (82)</td>
<td>37 (62)</td>
<td>0.05</td>
</tr>
<tr>
<td>HCT comorbidity index, n (%)</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (61)</td>
<td>30 (50)</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>3 (11)</td>
<td>14 (23)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>5 (18)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 (10)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ALL</td>
<td>1 (4)</td>
<td>9 (15)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>3 (11)</td>
<td>24 (40)</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>4 (14)</td>
<td>11 (18)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7 (25)</td>
<td>12 (20)</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>7 (25)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (21)</td>
<td>3 (5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No iron overload</th>
<th>Iron overload</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High disease risk, n (%)</td>
<td>21 (75)</td>
<td>24 (40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Myeloablative</td>
<td>5 (18)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>Reduced intensity</td>
<td>23 (82)</td>
<td>45 (75)</td>
<td></td>
</tr>
<tr>
<td>Graft source, n (%)</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Marrow</td>
<td>5 (18)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>PBSC</td>
<td>14 (50)</td>
<td>22 (37)</td>
<td></td>
</tr>
<tr>
<td>UCB</td>
<td>9 (32)</td>
<td>33 (55)</td>
<td></td>
</tr>
<tr>
<td>Donor type, n (%)</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Matched sibling</td>
<td>14 (50)</td>
<td>20 (33)</td>
<td></td>
</tr>
<tr>
<td>Matched unrelated</td>
<td>5 (18)</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>Mismatched unrelated</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Single UCB</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Double UCB</td>
<td>9 (32)</td>
<td>32 (53)</td>
<td></td>
</tr>
</tbody>
</table>

**Single institution, heterogeneous patient population**

HCT, hematopoietic cell transplantation; PBSC, peripheral blood stem cell; UCB, umbilical cord blood
Iron overload (LIC >7 mg Fe/g dw) is a prognostic factor for mortality after RIC Tx

Meta-analysis of four trials using MRI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall cohort (N=276)</th>
<th>RIC cohort†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>OS</td>
<td>1.4 (0.9–2.3)</td>
<td>1.5 (0.8–2.7)</td>
</tr>
<tr>
<td>NRM</td>
<td>1.7 (0.9–3.3)</td>
<td>2.2 (1.1–4.6)</td>
</tr>
<tr>
<td>P</td>
<td>0.2</td>
<td>0.026</td>
</tr>
</tbody>
</table>

†N, not reported, but noted as almost two-thirds of patients
RIC, reduced intensity conditioning

ALLogeneic Iron in VEStigators observational trial

- MDS/AML prior to allo-SCT
- At risk of SIO

Days
-30 0 7 14 21 100 360
Cond.
Pre-SCT  SCT  Post-SCT

MRI

LPI/Hepcidin
Transl. research

LPI, labile plasma iron;
SCT, stem cell transplantation; SIO, systemic iron overload

Wermke M et al. Blood 2015;126:abst 386; oral presentation at ASH 2015; NCT01746147
ALLIVE study: Elevated LPI prior to conditioning and after transplantation were strongly predictive of adverse outcomes.
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ELEVATED LPI PREDICTS NRM

Day +14 after allo-SCT

- **eLPI ≤0.4 n=61**
- **eLPI >0.4 n=42**

Cumulative incidence NRM

Days

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRM</td>
<td>0</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

P=0.025
Conclusions

- Iron overload pre-HSCT as a prognostic factor of OS remains controversial
- Presence of free iron species, such as elevated LPI, at the time of HSCT appears to be a prognostic factor for NRM
- Chelation therapy may have a role in scavenging LPI prior to and during HSCT
- Studies are ongoing to further understand the role of chelation therapy in the HSCT setting (eg ALLIVE 2)
## Collaborators

M Wermke, G Ehninger, M Bornhäuser (Dresden)
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G Bug (Frankfurt/M.)
N Kröger (Hamburg)
A Giagounidis, U Germing (Düsseldorf)
WK Hofmann, S Klein (Mannheim)
D Haase (Göttingen)
G Mufti (London)
L Ades, P Fenaux (Paris)

## Groups

Dresden team
German MDS Study Group (DMDS)
Groupe Francophone Des Myelodysplasies (GFM)
German Cooperative Transplant Group (GCTSG)
Study Alliance Leukemia (SAL)
European MDS study coordinating office (EMSCO)
European Leukemia Net (ELN)
Novartis