Stem cell Transplantation for Primary Myelofibrosis or post ET/PV Myelofibrosis
Where do we stand?

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Department of Stem cell Transplantation
University Hospital Hamburg/Germany
### Regression of fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 2</th>
<th>Grade 1</th>
<th>Grade 0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior SCT</strong></td>
<td>49%</td>
<td>51%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 30</strong></td>
<td>18%</td>
<td>35%</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 100</strong></td>
<td>0</td>
<td>25%</td>
<td>41%</td>
<td>34%</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 180</strong></td>
<td>5% (relapse)</td>
<td>10% (n=1:relapse)</td>
<td>45%</td>
<td>40%</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 360</strong></td>
<td>0</td>
<td>0</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Allogeneic SCT for Myelofibrosis

- Allogeneic SCT is currently the only curative treatment for myelofibrosis resulting in:
  - regression of bone marrow fibrosis
  - induction of molecular remission
  - normalisation of spleen size
  - resolution of constitutional symptoms
  - normal blood count

- *Due to the inherent complications of allogeneic stem cell transplantation, such as treatment related mortality, several issues remain to be solved*
Allogeneic SCT for Myelofibrosis

- Intensity of the conditioning regimen?
- Timing of transplantation?
- Role of splenectomy before transplantation?
- Upper age limit?
- Relapse strategies?
- Future of transplant in PMF?

Myeloablative conditioning

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Med. age</th>
<th>NRM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballen et al., 2010 (CIBMRT)</td>
<td>n = 134 (sibling) n = 23 (other related) n = 72 (MUD)</td>
<td>45 yrs 40 yrs 47 yrs</td>
<td>22% (day 100) 27% (day 100) 42% (day 100)</td>
<td>39% (5 yrs) 31% (5 yrs)</td>
</tr>
<tr>
<td>Guardiola et al., 1999 (EBMT/GITMO/SFGM/FHCRC)</td>
<td>n = 55</td>
<td>42 yrs</td>
<td>27% (1 y)</td>
<td>47% (5 yrs)</td>
</tr>
<tr>
<td>Deeg et al., 2003 (FHCRC)</td>
<td>n = 56</td>
<td>43 yrs</td>
<td>32% (3 y)</td>
<td>58% (3 yrs)</td>
</tr>
<tr>
<td>Kerbauy et al., 2007 (FHCRC)</td>
<td>n = 95</td>
<td>49 yrs</td>
<td>34% (5 yrs)</td>
<td>61% (7 yrs)</td>
</tr>
</tbody>
</table>
# Reduced conditioning

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median age</th>
<th>NRM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rondelli et al. 2005</td>
<td>21</td>
<td>54 yrs</td>
<td>10% (1 yr)</td>
<td>85% (2.5 yrs)</td>
</tr>
<tr>
<td>Kröger et al. 2005</td>
<td>21</td>
<td>53 yrs</td>
<td>16% (1 yr)</td>
<td>84% (3 yrs)</td>
</tr>
<tr>
<td>Bacigalupo et al. 2010</td>
<td>46</td>
<td>51 yrs</td>
<td>24% (5 yrs)</td>
<td>45% (5 yrs)</td>
</tr>
<tr>
<td>Kröger et al. EBMT 2009</td>
<td>103</td>
<td>55 yrs</td>
<td>17% (1 yr)</td>
<td>67% (5 yrs)</td>
</tr>
</tbody>
</table>

# Comparison: RIC vs myeloablative

<table>
<thead>
<tr>
<th>Study</th>
<th>RIC n</th>
<th>MAC n</th>
<th>Median age</th>
<th>TRM</th>
<th>Relapse</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al. 2009</td>
<td>23</td>
<td>23</td>
<td>54 yrs</td>
<td>23% (1 yr)</td>
<td>14% (9%)</td>
<td>68% (3 yrs)</td>
</tr>
<tr>
<td>Stewart et al. 2010 (BSBMT)</td>
<td>27</td>
<td>24</td>
<td>54 yrs</td>
<td>21% (day 100)</td>
<td>46% (15%)</td>
<td>31% (44%)</td>
</tr>
<tr>
<td>Robin et al. 2010 (SFGM-TC)</td>
<td>46</td>
<td>101</td>
<td>56 yrs</td>
<td>HR 1</td>
<td>n.d.</td>
<td>HR 1</td>
</tr>
<tr>
<td>Patriarca et al. 2008 (GITMO)</td>
<td>48</td>
<td>52</td>
<td>n.d.</td>
<td>HR 0.93</td>
<td>n.d.</td>
<td>HR 0.78</td>
</tr>
</tbody>
</table>
Allogeneic SCT for Myelofibrosis

- Intensity of the conditioning regimen?
- Timing of transplantation?
- Role of splenectomy before transplantation?
- Age limit?
- Relapse strategies?
- Future of transplant in PMF?

Treatment decision for PMF

Allografting

treatment related mortality alternative options potential cure

Balance according:
1. performance status/ comorbidity
2. life expectancy (e.g. IPSS)
Primary myelofibrosis (n=1054): IPSS score

**Risk factors**
1. Age ≥ 65 years
2. Constitutional symptoms
3. Circulating blasts ≥ 1%
4. Hb ≤ 10 g/dl
5. WBC ≥ 25 x 10⁹/l

<table>
<thead>
<tr>
<th>Risk status</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low+Inter-1</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Inter-2</td>
<td>0.8 (0.3-2.37)</td>
<td>0.7</td>
</tr>
<tr>
<td>High</td>
<td>2.7 (1.18-6.60)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Low rik (0) med. OS 135 months
Intermediate 1 (1) med. OS 95 months
Intermediate 2 (2) med. OS 48 months
High (≥ 3) med. Os 27 months

Cervantes et al., Blood 2009, Passamonti et al Blood 2010
Risk model according dynamic IPSS

### OS by DIPSS category (Seattle data: n = 170)

Scott B L et al., Blood 2012;119:2657-2664
TRM by DIPSS category (Seattle data: n = 170)

Scott B L et al. Blood 2012;119:2657-2664

Allogeneic SCT for Myelofibrosis

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Long Term Complications of MPDs

Surgical Therapy of Splenomegaly

Role of splenectomy for allogeneic SCT in PMF

<table>
<thead>
<tr>
<th>Author</th>
<th>Engraftment</th>
<th>TRM</th>
<th>relapse</th>
<th>survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robin et al. 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Guardiola et al. 1999</td>
<td></td>
<td></td>
<td></td>
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<td>Kröger et al. 2009</td>
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<tr>
<td>Patriarca et al. 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kerbauy et al. 2007</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Li et al. 2001</td>
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Risk factor for outcome after allogeneic SCT

<table>
<thead>
<tr>
<th>Age</th>
<th>Donor</th>
<th>Disease-stat.</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kröger et al. EBMT</td>
<td>&gt; 55 yrs</td>
<td>Mismatched UD</td>
<td>Lille high</td>
</tr>
<tr>
<td>Robin et al. SFGM</td>
<td>-</td>
<td>Unrelated (mismatch)</td>
<td>Lille high, sAML Male without splenectomy</td>
</tr>
<tr>
<td>Guardiola et al.</td>
<td>&gt; 45 yrs</td>
<td></td>
<td>Hb &lt; 10 g/L and grade III fibrosis</td>
</tr>
<tr>
<td>Deeg et al.</td>
<td>increasing age</td>
<td>Lille high</td>
<td>Abnorm. cytogenetic marrow fibrosis</td>
</tr>
<tr>
<td>Bacigalupo et al.</td>
<td>Unrelated donor</td>
<td></td>
<td>&gt; 20 transfusions spleen size &gt; 20 cm</td>
</tr>
<tr>
<td>Alchalby et al.</td>
<td>advanced age</td>
<td>Mismatch UD</td>
<td>Lille high JAK2 wildtype</td>
</tr>
<tr>
<td>Kerbauy et al.</td>
<td>advanced age</td>
<td></td>
<td>Low platelet, comorbidity score ↑, no Bu-target</td>
</tr>
</tbody>
</table>
Allograft in Myelofibrosis in EBMT

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft</td>
<td>153</td>
<td>467</td>
</tr>
<tr>
<td>RIC</td>
<td>76 (50%)</td>
<td>302 (~ 65%)</td>
</tr>
<tr>
<td>&gt; 50 yrs</td>
<td>86 (56%)</td>
<td>353 (~ 75%)</td>
</tr>
</tbody>
</table>

unpublished EBMT data

Allogeneic haematopoietic cell transplantation for myelofibrosis in 30 patients 60–78 yrs

Samuelson et al., BJH 2011
Allogeneic SCT in elderly PMF patient (German experience)

- n = 42
- median age: 64 yrs (60-73)
- Donor:
  - MUD n = 32
  - Related n = 10
- IPSS:
  - intermediate 1 n = 4
  - intermediate 2 n = 8
  - high n = 30
- Conditioning regimen: Busulfan 10 mg/kg/ fludarabine

Allogeneic SCT in elderly PMF pts (median age 64 y) (MRD n= 10 and MUD n= 32)

![Graph showing survival probability](attachment:image)
Allogeneic SCT for Myelofibrosis

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Relapse (according Lille score) EBMT trial

[Graph showing cumulative incidence of relapse with Lille score levels and numbers at risk]
Patients with relapsed myelofibrosis after initial allo-SCT (n = 30)

Donor lymphocyte infusions (n = 26)
- CR (n = 10, 39%)
- Non-responding (n = 16)
  - GvHD - acute 23%
  - chronic 27%
  - TRM 0%

2nd allo-SCT from an alternative donor as 1st line (n = 4) and 2nd line option (n = 13)
- GvHD - acute 35%
- chronic 35%
- TRM 12%

CR (n = 14, 82%)
No CR response (n = 3)

Overall survival for relapsed patients after DLI and/or second allo SCT (n=30)

2-year OS 68% (95% CI: 48% - 88%)
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Allogeneic SCT for Myelofibrosis

- Future of transplant in PMF...

- *Reducing mortality of the transplant procedure*

- *Reducing the risk of relapse*
Allogeneic SCT for Myelofibrosis

• Reducing mortality of the transplant procedure
  1) optimise donor selection: TRM 10% -13% if donor fully HLA matched
  2.) improve performance status before Tx

JAK Inhibitors and allo SCT

Potential effects of JAK2 inhibitors which may be useful in combination with allo SCT

1.) Reduction of constitutional symptoms

2.) Reduction of spleen size
Allogeneic SCT for Myelofibrosis

- Future of transplant in PMF...
- Reducing mortality of the transplant procedure
- Reducing the risk of relapse

JAK2 clearance post allogeneic SCT

JAK2 V617F real time PCR with nearly 100% specificity and sensitivity of 1 in 10,000 (0.01%) \( (Kröger \textit{et al.}, \textit{Blood} 2007) \)

JAK2 mutation was measured every 2-3 months after allogeneic SCT from peripheral blood

Follow up data available from 63 patients
- 45 cleared JAK2V617F (med 96 d post ASCT)
- 18 remained positive

JAK2V617F clearance was associated with a reduced time-dependent cumulative incidence of relapse \( Alchalby \textit{et al.}, \textit{Blood} 2010 \)
Clearance of JAK2 mutation level after allogeneic SCT (6 months)

Donor T-cell infusion in a patient with molecular residual disease after stem cell transplantation

Kröger et al., Blood 2007
Donor lymphocyte infusions for MRD or relapse after allo SCT for Myelofibrosis

<table>
<thead>
<tr>
<th></th>
<th>Molecular response</th>
<th>Acute GvHD II/IV</th>
<th>Median number of DLIs to achieve CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage DLI (n=9)</td>
<td>44 % CR</td>
<td>22 %</td>
<td>2</td>
</tr>
<tr>
<td>Pre-emptive DLI (n=7)</td>
<td>100 % CR</td>
<td>0 %</td>
<td>1</td>
</tr>
</tbody>
</table>

Kröger et al., Blood 2009a

Conclusion

- Allogeneic stem cell transplantation offers curative perspective even in elderly patients with myelofibrosis
- Decision for transplantation should based on life expectancy (IPSS), and performance status (biological age instead of chronological age), suitable donor (HLA fully matched)
- Treatment related mortality is lower after reduced intensity conditioning than after standard conditioning, but prospective studies are lacking
- There are no valid arguments to perform splenectomy prior transplantation
- Monitoring of molecular marker (JAK2, MPL) allows detection of MRD and guide adoptive immunotherapy
- Improvement of performance status and spleen size reduction prior to transplantation with JAK2 inhibitors will be investigated in prospective studies
Decision making for transplantation

IPSS low: no transplant, no JAK2 inhibitor

IPSS intermediate I: general: no transplant (individual exception possible: e.g. < 50 y)

IPSS intermediate II: 1) consider transplant (<65 y) if splenomegaly or and constitutional symptoms consider JAK2 inhibitor prior transplantation

IPSS high: 1) consider transplant (<70 y) if splenomegaly or constitutional symp JAK2 inhibitor pre-Tx

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