Long-term outcome after HSCT

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Special thanks to
Alicia Rovó
Gérard Socié
What is the problem?

- What is different in respect of
  - long-term outcome compared to immunosuppressive therapy
  - long-term outcome compared to HSCT of malignant diseases

- Long-term outcome, late effects and life after HSCT in aplastic anemia

- Why have we to know long-term events after HSCT?
Consequences of the type of treatment of SAA on long-term outcome and late events

**Successful immunosuppressive therapy**
- Reconstitution of peripheral blood counts
- Disease is not cured
- Risk of clonal evolution
- High risk of relapse

**Successful HSCT**
- Disease is cured
- Secondary leukemia is a rare event
- PNH clone is no longer present
- Late relapse is rare
- Treatment-related complications may occur (late events)
What is the difference of long-term outcome between SAA and malignant disorders

**Long-term outcome in malignant disorders**
- Age of the patient
- Pre-transplant treatment
- Conditioning regimen
- Need of GVHL effect

**Long-term outcome in aplastic anemia**
- Younger age at HSCT
  - Age-limit <40 years for first-line treatment still standard
- No previous chemotherapy or radiotherapy
- Conditioning regimen
- No need of GVHL effect
Characteristics of patients receiving allogeneic HSCT through 2003 surviving ≥2 years (CIBMTR)

<table>
<thead>
<tr>
<th></th>
<th>AML</th>
<th>MDS</th>
<th>Lymphoma</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>4’017</td>
<td>930</td>
<td>619</td>
<td>2’171</td>
</tr>
<tr>
<td>Median age</td>
<td>28 y</td>
<td>34 y</td>
<td>34 y</td>
<td>18 y</td>
</tr>
<tr>
<td>% of patients ≥40 years</td>
<td>24%</td>
<td>36%</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Use of TBI</td>
<td>60%</td>
<td>48%</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>Matched sibling donor</td>
<td>75%</td>
<td>52%</td>
<td>80%</td>
<td>81%</td>
</tr>
</tbody>
</table>
Excellent survival of 2-year survivors, but still a higher mortality rate than expected.

Patients with myelo-ablative allogeneic HSCT surviving ≥2 years in remission.

Wingard J. et al. JCO 2011.29:2230-2239
Causes of death of patients surviving $\geq 2$ years in remission - comparison between AML and SAA

- Late relapse is the leading cause of death in HSCT for malignant diseases
- GVHD, infections without GVHD and organ failure are the main causes of death in HSCT for SAA
- Deaths due to second cancers is of increasing importance in HSCT for both types of diseases
Relative rates of mortality are higher compared with a general population

- in HSCT of any disease
- Even in patients surviving more than 10 years

Wingard J. et al. JCO 2011.29:2230-2239
The definitive aim of the HSCT

- Cure from the primary disease
- Complete recovery of the health status
What does affect long-term survivorship after HSCT?

<table>
<thead>
<tr>
<th>Course of the primary disease</th>
<th>Late relapse of the primary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late effects</td>
<td>Malignant</td>
</tr>
<tr>
<td></td>
<td>Non-malignant</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>Infections</td>
</tr>
<tr>
<td></td>
<td>Immune reconstitution</td>
</tr>
<tr>
<td></td>
<td>Treatment related complications</td>
</tr>
<tr>
<td>Chronic health condition</td>
<td>Burden of active late complications</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Subjective perception</td>
</tr>
<tr>
<td>Social integration</td>
<td>Family</td>
</tr>
<tr>
<td></td>
<td>Partnership</td>
</tr>
<tr>
<td></td>
<td>School, job</td>
</tr>
<tr>
<td></td>
<td>Financial aspects, insurances</td>
</tr>
</tbody>
</table>
Main players and confounders responsible for late effects

- Age at HSCT
- Primary disease
- Conditioning regimen
- Communication (language)
- GVHD
- Pretransplant treatment
- Life style after HSCT
- Familiar predisposition
- Comorbidity
- Distance from transplant center
- Premature ageing
Prevalence of late effects in SAA patients transplanted 1995-2006 (CIBMTR)

- Increasing number of late effects with longer follow-up
- Unrelated HSCT more late effects than related HSCT
  - GVHD and its treatment more relevant in unrelated HSCT?
What are the most relevant late effects in SAA treated with HSCT?

- Study from the Late Effects Working Committee of the CIBMTR
- HSCT between 1995-2006, Median age 20 years (1-65 years)
- 1818 patients with acquired aplastic anemia
- No direct information on previous treatment (Immunosuppression ?)

<table>
<thead>
<tr>
<th></th>
<th>HLA matched sibling</th>
<th>Unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1176 (68%)</td>
<td>542 (32%)</td>
</tr>
<tr>
<td>Interval to HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &lt;6 months</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>- &gt;12 months</td>
<td>22%</td>
<td>57%</td>
</tr>
<tr>
<td>HLA matched</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI</td>
<td>4%</td>
<td>69%</td>
</tr>
<tr>
<td>TLI</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>cGvHD at 5 years</td>
<td>17%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Wingard J. et al. JCO 2011.29:2230-2239
### 5-year cumulative incidence rates of select late effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Related donors (%)</th>
<th>Unrelated donors % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataracts</td>
<td>1.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Gonadal insufficiency/infertility</td>
<td>3.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>1.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Growth disturbance</td>
<td>0.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>0.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Wingard J. et al. JCO 2011;29:2230-2239
Increased risk of late effects in this cohort of very young patients

- Cumulative incidence is increased for a number of late effects
  - Despite no direct comparison with a general population
- More increased for unrelated donor transplant compared with matched related HSCT
- Differences probably due to
  - Conditioning regimen (TBI)
  - More chronic GVHD and therefore more immunosuppressive treatment
- No conclusion for solid tumors
  - Too short follow-up time (5 year CI)
In 212 SAA patients
- Median age 18 year (1-42)
- TBI 15 patients
- Relative risk of cataract

Main risk factors of cataracts
- TBI
- Dose, fractionation and dose rate
- Steroids

Treatment of GvHD and not GVHD is responsible for the excess of cataract formation

Infertility, “asymptomatic” late effect with significant effects on long-term survivorship

Seminal fluid analysis

- Red, azoospermia
- Blue, normal sperm content
- Green, decreased sperm content

Risk factors for male infertility

- Radiation (TBI)
- Older age
- Short follow-up
- Chronic GVHD

Normal gonadal function in children after HSCT conditioned with Cy ± ATG

SAA patients 137
Median age at HSCT 11 years (0.8-18)
Median follow-up since HSCT: 22 years (1-38)
Conditioning Cy±ATG / TBI (12 Gy) 100 / 10

<table>
<thead>
<tr>
<th></th>
<th>Female patient</th>
<th>Male patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-pubertal</td>
<td>Post-pubertal</td>
</tr>
<tr>
<td>No patients</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Evaluable by virtue of age</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Normal menses</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Normal development</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal gonadotropin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Early menopause</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low testosterone</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

# Pregnancies and fatherhood in patients transplanted during childhood

Median age at first pregnancy (women): 24 years (12-32)

Age of 2 women who received TBI conditioning
- 3 years and 13 years at HSCT

Born babies normal except one
- congenital aortic stenosis

Born babies born from transplanted father
- 2 with congenital abnormalities: hip dysplasia and cleft lip

<table>
<thead>
<tr>
<th>Preparative regimen</th>
<th>Cy</th>
<th>TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Evaluable pregnancies</td>
<td>73</td>
<td>59</td>
</tr>
<tr>
<td>Live births n (%)</td>
<td>58 (82%)</td>
<td>47 (80%)</td>
</tr>
<tr>
<td>Abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spontaneous</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>- Stillbirth</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>- Elective</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>- Tubal pregnancy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Birth defects</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Influence of conditioning and GVHD on pregnancy / fatherhood in SAA

Patients with malignant diseases
- Prevalence of pregnancy/fatherhood after TBI conditioning - < 1%

Patients with SAA (median age 18 years at HSCT)
- At 20 years post-transplant, probability to become pregnant /father
  - Pregnant: 47%
    - GVHD 26%; no GVHD 61%
  - Father: 50%
    - GVHD 29%; no GVHD 62%

Outcome of pregnancy (any type of conditioning)
- Increased risk of abortion and preterm delivery
- Low birth weight baby
- No increased risk of congenital malformation

Avascular osteonecrosis - chronic GVHD or immunosuppression used to tread GVHD?

Retrospective study on 1346 long-term patients

- Risk factors for allogeneic HSCT
- Presence of chronic GVHD
- Exposure to immunosuppression
- Increased risk with exposure to ≥ 3 drugs


Cumulative incidence of avascular necrosis after HSCT
Multicenter retrospective study

Société Française de Greffe de Moelle

4588 patients recorded in the registry between 1973-1993

77 patients avascular necrosis

Cumulative incidence at 5 years 4.3%

445 patients with SAA

### Multivariate logistic regression

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGVHD</td>
<td>3.52</td>
<td>2.20-6.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aGVHD</td>
<td>3.73</td>
<td>1.64-7.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥16 years</td>
<td>581</td>
<td>2.23-14.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Diagnosis AA</td>
<td>3.90</td>
<td>2.01-7.59</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Higher risk for aseptic necrosis in aplastic anemia:**

- half of the patients were given immunosuppressive treatment before HSCT

Socié G. et al. BJH. 1997;97:865-870
Other non-malignant late events in children

- **Thyroid dysfunction**
  - Common after TBI conditioning
  - In 137 AA patients prevalence 12%
  - In non irradiation AA patients 8.4%

- **Growth in patients transplanted during childhood**
  - Basically normal height growth

- **Bone density**
  - Patients without cGVHD, normal bone density in 76%
  - Patients with cGVHD 1/17 had normal bone density

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Secondary malignancy after allogeneic HSCT

Update | Patients with secondary malignancy
---|---
1999 | 54/1117 patients
2008 | 134/959 patients

Secondary solid tumor increase with longer follow-up time since HSCT

Heilmeier B. BMT. Abstract 2010
Malignant tumors occurring after HSCT in aplastic anemia

- 9 tumors in 748 patients
  - 7 solid tumors (5 head and neck cancers)
  - 2 acute leukemia
- Relative risk of cancer 6.67 compared to general population
- 10-year cumulative incidence of cancer 3.1%

Socié G. et al. NEJM. 1993:329:1152-1157
# Secondary cancers after HSCT in a cohort of 28’874 allogeneic transplant recipients

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk factor</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous cell carcinoma</td>
<td>Radiation&lt;br&gt;Younger age at radiation (&lt;30)&lt;br&gt;Increasing with longer follow-up</td>
<td>Breast cancer&lt;br&gt;Thyroid&lt;br&gt;Brain&lt;br&gt;Bone and connective tissue&lt;br&gt;Melanoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Chronic GVHD&lt;br&gt;Male sex&lt;br&gt;No relation with TBI and with time since follow-up&lt;br&gt;Limited field irradiation in SAA - increased risk of SSC of oral cavity</td>
<td>Oral cavity&lt;br&gt;SCC of the Skin</td>
</tr>
</tbody>
</table>

Risk for SAA only marginally lower (RR, 0.83; 95%CI 0.37-1.13)

Malignancies after HSCT for acquired aplastic anemia and Fanconi anemia

- Retrospective analysis
  - Fred Hutchinson Cancer RC
  - Hôpital St Louis

- 700 patients
  - Fanconi Anemia: 79
  - Acquired aplastic anemia: 621

- 23 malignancies
  - 18 solid tumors
    - SCC (17)
    - mucoepidermoid ca (1)
  - 5 others
    - posttransplant LPD (3)
    - ALL (2)

- Standardized incidence ratio (SIR)
  - All patients 9.9
  - Fanconi anemia 167

**Acquired aplastic anemia patients**

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine/cGVHD</td>
<td>7.5</td>
<td>1.8-30.2</td>
<td>0.043</td>
</tr>
<tr>
<td>Irradiation</td>
<td>3.9</td>
<td>1.0-15.0</td>
<td>0.42</td>
</tr>
<tr>
<td>age</td>
<td>1.1</td>
<td>1.0-1.12</td>
<td>0.525</td>
</tr>
</tbody>
</table>

Head and neck squamous cell cancers in Fanconi anemia (FA)

**Annual hazard rates by age**

- SLH (Hôpital St. Louis): transplanted Fanconi anemia
- NAS (North American Survey): non-transplanted Fanconi anemia

- Fanconi anemia have a high baseline risk of squamous cell cancers
- Hazard increased by age of the patients
- HSCT may increase this risk
  - Chronic GVHD
  - Radiation therapy

Cardiovascular events after HSCT

RR: 2.2; 95%CI: 1.19-5.27; P=0.009
Conventional cardiovascular risk factors increase the risk of cardiovascular disease after HSCT

Cardiovascular risk factors
- Higher compared to general population
- Older age and obesity
- Mainly in allogeneic HSCT

History of acute GVHD
- Risk of hypertension, diabetes, dyslipidemia

TBI
- Risk of diabetes, dyslipidemia

<table>
<thead>
<tr>
<th>Factor</th>
<th>auto HSCT</th>
<th>Allo HSCT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Basline</td>
<td>22.3</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>28.7</td>
<td>40.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Basline</td>
<td>8.3</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>15.9</td>
<td>20.9</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td>22.8</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43.3</td>
<td>45.0</td>
</tr>
</tbody>
</table>
Why does it matter to know about late complications?

- Early detection
- Prevention
- Treatment
- Change in the transplant procedure

Not simply an enumeration of bad events

Majhail NS. et al. BBMT. 2012; 18: 348-371
Majhail NS. et al. BMT. 2012; 47: 337-341
Take home messages

- Late effects and their consequences are of major issue
  - it is a reality but not a fatality

- Continuously changes in the transplant procedure
  - late effects will continue to evolve - but with delay

- In aplastic anemia long-term morbidity and mortality is strongly related with GVHD and its treatment

- The non-malignant late effects in patients not conditioned with radiation is low, particularly in children

- Secondary solid tumors are great concern

- There are still open questions (cardiovascular problems and cardiovascular risk factors)
Thank you for your attention