Late effects, health status and quality of life after hemopoietic stem cell transplantation (HSCT)

André Tichelli
Chairman Late effects Working Party

The European Group for Blood and Marrow Transplantation
Survivorship after allogeneic HSCT

**Aim of HSCT**
- Cure from the primary disease
- Complete recovery of the health status
- Normal physical and psychological functioning
- Normal family and social integration
- Good subjective well being
Late morbidity and mortality in long term survivors


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Multifactorial etiology of post-transplantation late effects

Common diseases
Chemotherapy
GVHD
Physiologic aging
Immune reconstitution
TBI
Virus
Life track resetting
Life style

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Causes of death in long term survivors after allogeneic HSCT

- Relapse: 44%
- cGvHD: 18%
- Infection: 18%
- Secondary cancer: 8%
- Late pulmonary toxicity: 5%
- Late cardiac toxicity: 4%
- Other causes: 3%
Ocular complications

- Cataract formation
  - Irradiation
  - Single > fractionated dose
  - Dose rate?
  - Steroids
- Keratoconjunctivitis sicca
  - Part of the general sicca syndrome
  - Risk factors
    - Irradiation
    - Chronic GvHD
    - Infections

Tichelli et al. BMT. 1995. 17; 1105-1111
Bronchiolitis Obliterans (BO)

- Severe pulmonary manifestation
  - affecting the small airways
- Incidence rates: 2% - 14%
- Clinical presentation
  - Insidious
  - Dry cough, progressive dyspnea, wheezing, no fever
- Clinical diagnosis of BO
  - Expiratory flow <75% of predicted
  - High resolution CT
  - Absence of infection in the respiratory tract

Afessa B et al. Review. BMT. 2001; 28:425-434
High resolution CT in expiration

Mosaic pattern
- evidence of air trapping
- small airway thickening
Risk Factors for Bronchiolitis Obliterans

- Strong association with chronic GvHD
  - BO is considered a manifestation of pulmonary GvHD
  - Few cases of BO in autologous HSCT

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan based conditioning</td>
<td>2.24</td>
<td>1.4 - 3.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>Time from diagnosis (&gt;14 months)</td>
<td>1.93</td>
<td>1.2 – 3.1</td>
<td>0.0053</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>3.35</td>
<td>1.8 – 6.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Female donor into male recipient</td>
<td>1.78</td>
<td>1.1 – 2.8</td>
<td>0.0152</td>
</tr>
<tr>
<td>Acute GvHD Grade ≥II</td>
<td>2.12</td>
<td>1.3 – 3.4</td>
<td>0.0014</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>2.28</td>
<td>1.3 – 3.9</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

Filipovich A. et al. BBMT. 2005;11:945-955
Skeletal disorders

Osteopenia/osteoporosis
- Reduced bone mass and increased susceptibility of bone fractures
  - Low bone density (50%)
  - Osteopenia (30%)
  - Osteoporosis (10%)
- Risk factors
  - TBI for conditioning
  - Chronic GvHD
  - Steroids, CSA and tacrolimus
  - Prolonged inactivity
  - Estrogen deficiency

Avascular necrosis of bone
- Leading symptom: pain
- Most affected joint: hip
- Risk factors
  - Steroids and TBI
- Early detection by MRI

Late Avascular Necrosis in 1346 long-term survivors

S Bhatia, personal communication, 2008

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# Fertility and frequency of pregnancy following HSCT

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors</td>
<td>Pregnanacies n (%)</td>
</tr>
<tr>
<td>Total</td>
<td>7'615</td>
<td>113 (1.5%)</td>
</tr>
<tr>
<td>Allografts</td>
<td>3'695</td>
<td>74 (2%)</td>
</tr>
<tr>
<td>Autografts</td>
<td>3'920</td>
<td>39 (1%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3713</td>
<td>32 (0.9%)</td>
</tr>
<tr>
<td>SAA</td>
<td>385</td>
<td>47 (12.2%)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>323</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

Sperm recovery after HSCT

Late Cardiac and Cardiovascular Complications

Cardiac complications

- Cardiomyopathy
- Pericarditis
- Congestive heart failure

Cardiovascular complications

- Cerebrovascular
- Coronary artery disease
- Peripheral artery disease


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Late Cardiac Toxicity in Cancer Survivors

- Study on 1474 survivors of Hodgkin lymphoma
- < 41 years at diagnosis
- Median follow-up 19 years
- Standardized mortality ratio:
  - for myocardial infarction 3.6
  - congestive heart failure 4.9
- Risk factors
  - Mediastinal radiotherapy for coronary disease
  - Anthracycline for congestive heart disease

**Late Cardiovascular Events after HSCT**

<table>
<thead>
<tr>
<th></th>
<th>Allo HSCT</th>
<th>Auto HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>265</td>
<td>145</td>
</tr>
<tr>
<td>Median age at HSCT</td>
<td>27 years</td>
<td>44 years</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>9 years</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial events</td>
<td>18 (6.8%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Age at vascular event</td>
<td>48 (29-62)</td>
<td>54 (38-60)</td>
</tr>
<tr>
<td>Time interval</td>
<td>9 years</td>
<td>1.3 years</td>
</tr>
</tbody>
</table>

**Arterial events after allo HSCT**

Cumulative incidence

Cumulative Incidence of Arterial Event after H SCT adjusted for Age

RR: 2.2; 95%CI: 1.19-5.27; P=0.009)

## Cardiovascular Risk factors after allogeneic HSCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV event With N=20</th>
<th>CV event Without N=528</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>14 (70%)</td>
<td>59 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (25%)</td>
<td>26 (6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (58%)</td>
<td>65 (15%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI ≥ 25 mg/m2</td>
<td>10 (56%)</td>
<td>128 (33%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (41%)</td>
<td>49 (12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>12 (75%)</td>
<td>142 (44%)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Renal Complications after HSCT

• Chronic kidney disease after HSCT
  - Progressive loss of renal function
  - With sustained decrease of Glomerular Filtration Rate (GFR)
    • < 60mL/min/1.73m²

• In 266 survivors > 6 months after HSCT
  - 61 (23%) developed chronic kidney disease
  - after a median time of 2.6 years
  - most of the patients were asymptomatic
  - 6/61 had severe disease (GFR < 30 mL/min/1.73m²)
  - 2 needed dialysis after 2.8 and 9.8 years post HSCT

Calcineurin Inhibitors and Chronic Kidney Disease

- 1190 patients surviving 1 year after HSCT

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>1.00</td>
</tr>
<tr>
<td>CSA</td>
<td>1.9 (1.07-3.4)</td>
</tr>
<tr>
<td>CSA + Tacrolimus</td>
<td>4.6 (1.8-11.5)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>2.5 (1.1-5.6)</td>
</tr>
</tbody>
</table>

Secondary malignant neoplasm in long term survivors after HSCT

- MDS and Leukemia
- Solid tumors
- Post-transplant lympho-proliferative disorders

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Low incidence of secMDS/AML in node-positive breast cancer

• Case-control study in women with breast cancer 1973 - 1985
• Secondary MDS/AML/ total number 90 / 82’700
• Relative risk
  Regional radiotherapy 2.4
  Alkylating agent 10.0
  Combination chemotherapy and radiation 17.4
  Melphalan versus cyclophosphamid 31.3 vs 3.1


<table>
<thead>
<tr>
<th>Type &amp; number of studies</th>
<th>No of patients</th>
<th>sMDS/AML</th>
<th>Actuarial risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>conventional chemotherapy (6 studies)</td>
<td>25’096</td>
<td>86</td>
<td>1.1% (0.2-1.7)</td>
</tr>
<tr>
<td>Autologous HSCT (3 studies)</td>
<td>1’457</td>
<td>6</td>
<td>0.3% (0-1.6)</td>
</tr>
</tbody>
</table>
Lymphoma patients have a higher risk of secondary MDS/leukemia

- Cytogenetic anomalies
  - complex anomalies in 80%
  - 75% involving -5/5q-
  - 62% involving -7/7q-
- Risk factors
  - Pretransplant chemotherapy
    - alkylating agents
    - Fludarabine
  - TBI for conditioning
  - Older age

Cumulative probability
10% at 5 years
36% at 10 years

Long term cancer survivors are at risk for secondary solid tumors

- **Hodgkin disease**
  - 18.5 increased risk
- **Breast cancer**
- **Thyroid cancer**
- **Epithelial neoplasms**

- **Risk factors**
  - Involved irradiation field
  - Younger age

Bonadonna G. EJ Cancer 2005;41:745-751
Bhatia S. JCO. 2003;23:4386-4394.
Secondary malignancy after allogeneic HSCT

Update | Patients with secondary malignancy
---|---
1999 | 54/1117 patients
2007 | 134/959 patients


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Secondary Breast Cancer after allogeneic HSCT

Retrospective analysis
EBMT/Seattle

- 52 breast cancers among 3337 survivors
- Median age at transplant 32.9 years (3.7 – 59.2)
- Median time to breast cancer 12.5 years (5.7 – 24.8)
- Mortality
  BC 9/52 (17.3%)
  non BC 7.4%
- Standardized incidence ratio 1.4 (95% CI 1.1, 1.8)


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## Clinical performance and social activity

### Kamofsky score (n)  

<table>
<thead>
<tr>
<th>Kamofsky score</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100%</td>
<td>125</td>
<td>19%</td>
</tr>
<tr>
<td>90%</td>
<td>81</td>
<td>12%</td>
</tr>
<tr>
<td>80%</td>
<td>33</td>
<td>5%</td>
</tr>
<tr>
<td>≤70%</td>
<td>11</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Social activity (n)  

<table>
<thead>
<tr>
<th>Social activity</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>full time</td>
<td>510</td>
<td>89%</td>
</tr>
<tr>
<td>part-time</td>
<td>28</td>
<td>5%</td>
</tr>
<tr>
<td>not attending</td>
<td>32</td>
<td>6%</td>
</tr>
</tbody>
</table>
Other aspects of social integration after HSC T

- Marital state
  - Less often married as compared to sibling donors
- Employment and professional integration
  - Difficulties holding a job
- Insurance status
  - Difficulty in obtain health / life insurance
  - Depending on national regulatory
- Child adoption
  - Difficulties to obtain an adoption for long term cancer survivors
What is Quality of Life (QoL)?

- Subjective perception of
  - Social well being
  - Emotional well being
  - Health and physical well being

- Decreased Quality of Life
  - gap between patients’ expectation of health
  - and his experience of his health status
Sexual problems after HSCT

40% of women are not sexually Active at each time point

What do we need to learn from the long-term survivors

• Conditioning regimen
  ■ No longer the unique cause of late effects in long-term survivors
  ■ Reduced intensity conditioned patients will also experience late effects

• The well being of the patient depends on
  ■ Late events
  ■ General health status
  ■ Patient’s expectations and experiences
  ■ Biological and psychological life adaptation
What do we need to learn from the long-term survivors?

- Life-long observation of long-term survivors
  - Encourage patients to self-examination
  - Every decade will provide new aspects on health status

- General health maintenance
  - Long-term cancer survivors remain at risk of common diseases found in general population
  - Healthy life style recommendations