Late complications after hematopoietic stem cell transplant in adult patients

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Allogeneic HSCT activity in Europe

Synopsis
Plan of this overview

Why an educational talk on LE?
Non malignant Complications (selected)
Secondary malignancies
Quality of life issues

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Late complications after hematopoietic stem cell transplant in adult patients

Why an educational talk on LE?

1. Increasing numbers of transplants

Transplant activity in Europe

Bone Marrow Transplantation (2011) 46, 174–191
Why an educational talk on LE?  

2. Improved results

Table 1. Characteristics of Transplant Recipients According to Time Period.*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>37.4</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.6–67.8</td>
<td>0.4–78.9</td>
<td></td>
</tr>
</tbody>
</table>

Why an educational talk on LE?

3. But still faced with increased late mortality!

Mortality ratios
cohort of 7,984 long term survivors
4. And some morbidity in long term! For some patients
Risk factors

- Chemotherapy
- TBI
- Virus
- GVHD
- Immunosuppressive therapy
- Immunodeficiency

Non malignant LE

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Nonmalignant late effects are heterogeneous in nature and intensity

- Endocrine dysfunction
  - Thyroid function
  - Gonadal, fertility
  - Growth and development
- Skeletal disorders
- Ocular problems
- Respiratory tract problems
  - Restrictive lung disease
  - Obstructive lung disease
- Salivary function and dental problems
- Liver complication
- Vascular complication


Any organ or tissue can be the target of late effects after allogeneic stem cell transplantation
Hypo-, hyperthyroidism

- Incidence thyroid dysfunction
  - Biological in 40%
  - Clinical in 5%-25%
- Median time for appearance
  - Median time 5 years
- Irradiation, the main risk factor
  - Single dose (50%)
  - Fractionated (15%)
  - BuCy (11%)
  - Younger age

Irradiation of the thyroid gland region is associated with increased risk of hypothyroidism.


Hiroyuki Ishiguro et al. JClinEndocrinolMetab. 2004; 89:5981-5986
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**
- Incidence rates 5-15%
- Leading symptom: pain
- Most affected joint: hip
- Risk factors
  - Steroids and TBI
- Early detection by MRI

Increasingly recognized

Osteonecrosis

Allo-HSCT: unrelated

Allo-HSCT: related

Auto-HSCT

Obstructive lung Diseases

Savani B. et al. BBMT. 2006; 12:1261-1269

Non malignant LE

Changing incidences

### New complications on the very long term

#### Cardio-vascular LE

**Autologous HCT**  
*n=854*

<table>
<thead>
<tr>
<th>Category</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at HSCT</td>
<td>36 (0.6-69)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>7.6 (2.0-20.5)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>251</td>
</tr>
<tr>
<td>Primary disease</td>
<td>140 (56%)</td>
</tr>
<tr>
<td>cGvHD</td>
<td>-</td>
</tr>
<tr>
<td>Infection without GVHD</td>
<td>0</td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Treatment related deaths</td>
<td>108 (43%)</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>62 (25%)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>35 (13.5%)</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

**Allogeneic HCT**  
*n=1479*

<table>
<thead>
<tr>
<th>Category</th>
<th>Allogeneic HCT</th>
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</thead>
<tbody>
<tr>
<td>Median age at HSCT</td>
<td>26 (0.2-71)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>9.5 (2-28.4)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>240</td>
</tr>
<tr>
<td>Primary disease</td>
<td>70 (29%)</td>
</tr>
<tr>
<td>cGvHD</td>
<td>53 (22%)</td>
</tr>
<tr>
<td>Infection without GVHD</td>
<td>27 (11%)</td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>23</td>
</tr>
<tr>
<td>Treatment related deaths</td>
<td>61 (25%)</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

Cardiovascular LE

Complications types

- Myocarditis
- Pericarditis
- Congestive heart failure
- Coronary disease

Dose of anthracycline in pediatric cancer survivors

![Graph showing risk of cardiac failure over time since anthracycline administration.](image)
Cardiovascular LE

- Prospective
- 119 children
- Left ventricular function (US)

Résults
- > cumulative incidence
- < ventricular function
  - TBI+ anthracyclines 26%
  - No TBI, no anthracyclines: 2%
- At 5 years 13% of kids had asymptomatic decreased functioning

Uderzo C. et al. BMT. 2007; 39:667-675
## Cardio-vascular LE

### Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Allogeneic HSCT (n=265)</th>
<th>Autologous HSCT (n=145)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>145 (55%)</td>
<td>87 (60%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Median age at HSCT</td>
<td>27 (2-60)</td>
<td>44.5 (2-69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age at last follow-up</td>
<td>39 (6-66)</td>
<td>49 (3-72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median follow-up since HSCT</td>
<td>9 (2-24)</td>
<td>5 (2-16)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Cardiovascular risk factors before HSCT

## Cardiovascular LE

### Non malignant LE

<table>
<thead>
<tr>
<th></th>
<th>Allo HSCT</th>
<th>Auto HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial events</td>
<td>18 (6.8%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Territories involved</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Age at HSCT</td>
<td>39 (19-59)</td>
<td>50 (36-59)</td>
</tr>
<tr>
<td>Age at vascular event</td>
<td>48 (29-62)</td>
<td>54 (38-60)</td>
</tr>
<tr>
<td>Time interval to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (2-21)</td>
<td>1.3 (0.7-4)</td>
</tr>
</tbody>
</table>

![Cumulative incidence graph](image)
Cardiovascular LE

## Cardiovascular LE

### Non-malignant LE

#### Allogeneic HSCT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Allogeneic HSCT</th>
<th>Autologous HSCT</th>
<th>Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.6 (1.8-7.3)</td>
<td>2.0 (0.8-4.2)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.1 (1.4-3.0)</td>
<td>0.9 (0.6-1.4)</td>
<td>1</td>
</tr>
<tr>
<td>Arterial Disease</td>
<td>1.2 (0.3-4.0)</td>
<td>0.4 (0.1-1.5)</td>
<td>1</td>
</tr>
<tr>
<td>MI</td>
<td>1.2 (0.2-6.0)</td>
<td>0.4 (0.1-1.5)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.5 (0.4-30.6)</td>
<td>2.6 (0.3-26.8)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Adjusted for age, age at transplant, and sex*

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Non malignant LE

International Recommended Screening 2012

Majhail et al, for the EBMT/CIBMTR/ASBMT.
Biol Blood Marrow Transplant. 2012
Blone Marrow Transplant 2012
High priority!

Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer

Second malignancies


- N=1036; allogeneic SCT, survivor > 5 years
- Incidence SC 3.5% at 10y, 12.8% at 15y, 3.8 X general population

2008 Update


- N=28874 Allogeneic SCT
- SC x 2 (O/E = 2.1)
- 3-X in patients followed more than 15 years.

**Graph:** Cumulative Incidence

- Cumulative Incidence
- Upper Confidence Limit
- Lower Confidence Limit

**Source:** Rizzo, J. D. et al. Blood 2009;113:1175-1183
Second malignancies

- SC 4318 patients Bu-Cy: AML CR1 & CML CP1.
- Incidence at 10 years: 1.2% AML & 2.4% CML
- O/E = 1.4

Not only TBI!
Second malignancies

Cancers in very long term survivors

⇒ **EBMT/Seattle**
- 52 Breast cancers / 3337 survivors: incidence = 4.7% at 20 years.
- Age at transplant:
  - 32.9 years (3.7–59.2)
- **Interval SCT/cancer : 12.5 years**
- **O/E: 1.4** (95%CI, 1.1,1.8)
Second malignancies

Thyroid Cancer

Age +++: RR, 24.61 age 0 - 10 y. & 4.80 11 - 20 years

Cohen A et al. JCO 2007;25:2449-2454
immediate survival and early relapse

Organ complications

reproductive status and pregnancy outcome

Health status after transplant

performance and social activity

Quality of life

fatigue syndrome

Resetting life track


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Quality of life

• **QOL is a subjective perception** of
  – social
  – emotional
  – physical well being

• **Gap** between patients' expectation of health and his experience of it

• **perception of QOL varies**
  – between individuals
  – changes over time

• **In the same clinical condition**
  – patients with different expectations will report different quality of life
Fatigue appears as one of the most common and distressing symptoms reported

cross-sectional studies 50-75% have moderate to severe fatigue ≥3 years after HSCT

longitudinal study (43 and 62 months post transplant) – no significant changes

at 10 years after transplant, fatigue still the second most problematic concern
Sexual dysfunction is one of the most prevalent and persistent long-term problem after allogeneic SCT

immediate survival and early relapse

Organ complications

reproductive status and pregnancy outcome

Health status after transplant

performance and social activity

Quality of life

fatigue syndrome

Resetting life track


counseling

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