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

André Tichelli
Chairman Late effects Working Party
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

Multifactorial etiology of post-transplantation late effects

- Common diseases
- Life track resetting
- Chemotherapy
- TBI
- Virus
- GVHD
- Immune reconstitution
- Physiologic aging
- 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%
What is late effects after HSCT?

Any complication with consequences on the long term

- BOS
- Thyroid dysfunction
- Secondary cancers
What does long-term survivorship after HSCT include?

- Non-malignant late effects
- Malignant late effects
- Health status and social integration
- Quality of Life and sexuality
- Chronic Graft versus Host disease and immune reconstitution
Non-malignant late effects
Late Infections and GvHD

- P. carinii, (T. gondii)
- Aspergillus
- Candida
- (Aspergillus)
- staphylococcus
- streptococcus
- Gram neg.
- S. pneumonia
- H. influenza
- CMV
- HSV
- VZV
- steroids
- APLASIA
- GVH acute
- GVH chronic
- 0 1 2 3 4 5 6 7 8 9 10 11 12

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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

6% at 10 years

Unrelated donor HCT (15% at 10 years)

Allogeneic related HCT (6% at 10 years)

Autologous HCT 4% at 10 years

S Bhatia, personal communication, 2008
### Fertility and frequency of pregnancy following HSCT

<table>
<thead>
<tr>
<th></th>
<th>Female Survivors</th>
<th>Female Pregnancies n (%)</th>
<th>Male Survivors</th>
<th>Male Pregnancies n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7,615</td>
<td>113 (1.5%)</td>
<td>10,467</td>
<td>119 (1.1%)</td>
</tr>
<tr>
<td>Allografts</td>
<td>3,695</td>
<td>74 (2%)</td>
<td>5,124</td>
<td>93 (1.8%)</td>
</tr>
<tr>
<td>Autografts</td>
<td>3,920</td>
<td>39 (1%)</td>
<td>5,343</td>
<td>26 (0.5%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3,713</td>
<td>32 (0.9%)</td>
<td>5,152</td>
<td>59 (1.4%)</td>
</tr>
<tr>
<td>SAA</td>
<td>385</td>
<td>47 (12.2%)</td>
<td>605</td>
<td>32 (5.3%)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>323</td>
<td>1 (0.3%)</td>
<td>485</td>
<td>2 (0.4%)</td>
</tr>
</tbody>
</table>

Retrospective EBMT Study

- Two step design
  - First step
    - Questionnaire to each center
    - Patients with pregnancy/fatherhood post transplant (y/n)
    - Do the center wish to participate
  - Second step
    - Questionnaire to the participating center
    - Specific questions
Sperm recovery after HSCT

- 62 invited to participate
- 5 had vasectomy before HSCT
- 18 declined

Seminal fluid analysis
LEWP Study 18

• Two step design

• First step
  – Questionnaire to each center
  – Patients with seminal fluid analysis post transplant (y/n)
  – Do the center wish to participate

• Second step
  – Questionnaire to the participating center
  – Specific questions
Late Cardiac and Cardiovascular Complications

**Cardiac complications**
- Cardiomyopathy
- Pericarditis
- Congestive heart failure

**Cardiovascular complications**
- Cerebrovascular
- Coronary artery disease
- Peripheral artery disease

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 since HSCT</td>
<td>9 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Arterial events</td>
<td>18 (6.8%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Age at vascular event (y)</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>


The European Group for Blood and Marrow Transplantation
Cumulative Incidence of Arterial Event after HSCT adjusted for Age

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

Risk factors for late vascular complications

- **Arterial Hypertension**
  - RR: 3.64; CI 1.41-9.44

- **Diabetes**
  - RR: 9.62; CI 3.32-27.84

- **Dyslipidemia**
  - RR: 5.44; CI 2.02-14.62

- **BMI**
  - RR: 1.91; CI 0.74-4.95

- **Gender**
  - RR: 0.39; CI 0.14-1.09
Diabetes, Hypertension and CV Events in 1089 long-term HSCT-Survivors

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

Adjusted for age, age at transplant, and sex

## Comparison patients with/without arterial event after allogeneic HSCT

<table>
<thead>
<tr>
<th></th>
<th>with</th>
<th>without</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20 (3.6%)</td>
<td>528</td>
<td></td>
</tr>
<tr>
<td>Gender (male / female)</td>
<td>13 / 7</td>
<td>299/229</td>
<td>n.s.</td>
</tr>
<tr>
<td>Median age at transplant</td>
<td>44 (29-59)</td>
<td>26 (0.5-58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age at last follow-up</td>
<td>54 (41-70)</td>
<td>36 (3-72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time interval (years)</td>
<td>9.6 (1-16)</td>
<td>10 (2-15)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acute GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>2 (10%)</td>
<td>156 (32%)</td>
<td>0.039</td>
</tr>
<tr>
<td>- Grade 1-2</td>
<td>17 (85%)</td>
<td>289 (58%)</td>
<td></td>
</tr>
<tr>
<td>- Grade 3-4</td>
<td>1 (5%)</td>
<td>48 (10%)</td>
<td></td>
</tr>
<tr>
<td>Chronic GvHD</td>
<td>10 (50%)</td>
<td>353 (67%)</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Cardiovascular Risk factors after allogeneic HSCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV event with</th>
<th>CV event without</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>
LEWP Study on cardiovascular events

• Two step design

• First step
  – Questionnaire to each center
  – Patients with seminal fluid analysis post transplant (y/n)
  – Do the center wish to participate

• Second step
  – Questionnaire to the participating center
  – Specific questions

• MedA Data for data analysis form EBMT center
• Database for Analysis principal investigator of the LEWP
Renal Complications after HSCT

- Chronic kidney disease after HSCT
  - Progressive loss of renal function
  - With sustained decrease of Glomerular Filtration Rate (GFR)
    - < 60mL/min/1.73m$^2$

- 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/1.73m$^2$)
  - 2 needed dialysis after 2.8 and 9.8 years post HSCT

Risk Factors of Chronic Kidney Disease after HSCT

- Older age at HSCT
- Female gender
- Hypertension after HSCT
- Low pretransplant GFR
- Acute and chronic GvHD
- Effect of TBI controversial
  - Radiation provokes sclerosis of arterioles and capillaries
  - Secondary fibrosis of tubules and glomeruli

Cyclosporine Nephropathy
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>

Nonmalignant late effects are heterogeneous in nature & 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
- Cardiac and cardiovascular complications
  - Cardiovascular risk factors
- Chronic kidney disorder

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

Malignant late effect
Secondary malignant neoplasm in long term survivors after HSCT

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


The risk of secMDS/AML increases with increasing doses

- Review from 19 randomized trials in early breast cancer
- Epirubicin cyclophosphamide containing regimen
- Number of women
  - total number 7'110
  - sMDS/AML 28

Joint study on late effects after HSCT for autoimmune disorders

- Retrospective joint study of Autoimmune Diseases WP, Lymphoma WP and LEWP

- Aim of the study
  - Secondary cancers and MDS/AML after HSCT for autoimmune disorders, compared to “matched” lymphoma patients

- Databases
  - Data base from AIDWP
  - Merged to data base from LWP

- Based on MedA Data
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. EJCancer 2005;41:745-751
Bhatia S. JCO. 2003;23:4386-4394.
Secondary malignancy after allogeneic HSCT

Update

1999

54/1117 patients

2007

134/959 patients

First LEWP Study – Update 10 years after

- Cross sectional EULEP/EBMT study on late effects
  - Questionnaire 1990
  - Patients transplanted before 1985 and survived > 5 years
  - 43 EBMT centers
  - 1117

- Update in 2005
  - Secondary cancers Databases
  - Same patient cohort
  - 959
## Standardized incidence ratio (SIR) for specific types of sec. cancers

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Observed</th>
<th>O / E</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All solid cancers</td>
<td>161</td>
<td>2.2</td>
<td>1.9-2.6</td>
</tr>
<tr>
<td>Buccal cavity</td>
<td>28</td>
<td>7.4</td>
<td>4.9-10.7</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>6.4</td>
<td>2.6-13.2</td>
</tr>
<tr>
<td>Brain</td>
<td>18</td>
<td>6.0</td>
<td>3.6-9.5</td>
</tr>
<tr>
<td>Thyroid</td>
<td>16</td>
<td>5.9</td>
<td>3.4-9.6</td>
</tr>
<tr>
<td>Bone</td>
<td>7</td>
<td>10.0</td>
<td>4.0-20.6</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>7</td>
<td>6.6</td>
<td>2.6-13.6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>21</td>
<td>4.1</td>
<td>2.5-6.3</td>
</tr>
</tbody>
</table>
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)

Probability of Secondary Breast Cancer after allogeneic HSCT

$p = 0.06$

TBI

no TBI
Joint study on breast cancer after HSCT

• Retrospective joint study of LEWP EBMT and Fred Hutchinson Cancer Research Center, Seattle

• Aim of the study
  – Cumulative Incidence and risk factors after allogeneic HSCT

• Databases
  – Questionnaire to EBMT centers to ask for breast cancer
  – MedA data for the whole patients cohort of all participating centers provided by EBMT London Office
  – Number of patients from the EBMT 2369; 289 breast cancers
  – 82 reporting EBMT centers

• Data analysis in Seattle
Follow-up Joint study on breast cancer after HSCT

• Retrospective joint study of LEWP EBMT and Fred Hutchinson Cancer Research Center, Seattle

• Aim of the study
  – Cumulative Incidence and risk factors after allogeneic HSCT

• Databases
  – Case control study
  – 1 patient : 2 matched controls
  – Matches for centre, age at HSCT, TBI, year of HSCT
  – 80% centers filled out the patients’ questionnaire
  – So far only 4 centre replied

• Data analysis in Seattle
Health status and social integration
Clinical performance and social activity

<table>
<thead>
<tr>
<th>Karnofsky score (n)</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>

<table>
<thead>
<tr>
<th>Social activity (n)</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>

First LEWP Study

• Cross sectional EULEP/EBMT study on late effects
  – Questionnaire 1990
  – Patients transplanted before 1985 and survived > 5 years
  – 43 EBMT centers
  – 789
Other aspects of social integration after HSCT

• 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
Quality of life and sexuality
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
Interrelationship between expectations and experiences

- posttransplant infection
- early relapse
- chronic GvHD
Quality of life in an individual person

• Perception of Quality of Life varies
  ■ between individuals with similar health status
  ■ changes over time for an individual person

• Recipients with different expectations will report different quality of life
Fatigue is the most often reported complaint in the long-term

1. Extreme and persistent tiredness or exhaustion that is not proportional to recent activities
2. Decreased ability of perform usual physical and mental activities
3. No improvement of fatigue after sleep and rest

**Contributing (treatable) factors**
- Pain
- Emotional distress, anxiety and depression
- Sleep disturbance
- Anemia
- Nutrition, hormonal factors
- Activity level
- Comorbidity
Sexual problems after HSCT

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

Common cancer-related sexual problems in men

- Erectile dysfunction
- Loss of desire for sex
  - 45% had low desire in past 6 months
- Difficulty reaching orgasm
  - 17% tried to reach orgasm but could not
- Diminished orgasmic pleasure
  - 28% found their orgasms weak and unsatisfying
- Pain during intercourse
  - GvHD
Common cancer-related sexual problems in women

- Low sexual desire
- Genital dryness and pain during sexual activity
- Feeling unattractive
- Orgasm problems tend to be secondary to above issues
Experience of coping

- Perception of benefit following HSCT
- New life, new priorities in life
- Impression of living more intensely
- Enhanced spirituality
- Thankful feelings to life
- Most long term survivors would do it again
Benefits from late effects

- alopecia totalis with 28-years
- CML with 40 years
- HSCT from HLA-identical sibling donor
  - uncomplicated transplant
  - immunosuppression with CSA and steroids
60 days after HSCT
Chronic Graft versus Host disease and immune reconstitution
cGVHD and late infections - major cause of non-relapse morbidity & mortality

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<tbody>
<tr>
<td>Patients at risk</td>
<td>6691 at 2 years</td>
<td>798 at 5 years</td>
<td>854 at 2 years</td>
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<td>Total deaths</td>
<td>679 (10%)</td>
<td>55 (7%)</td>
<td>251 (29%)</td>
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<td>- Relapse</td>
<td>304 (46%)</td>
<td>21 (38%)</td>
<td>140 (56%)</td>
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<tr>
<td>- Chronic GVHD</td>
<td>204 (31%)</td>
<td>11 (20%)</td>
<td>-</td>
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<tr>
<td>- Infection without GvHD</td>
<td>39 (6%)</td>
<td>9 (16%)</td>
<td>-</td>
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<tr>
<td>- Sec. cancer</td>
<td>40 (6%)</td>
<td>8 (15%)</td>
<td>62 (25%)</td>
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<tr>
<td>- Organ dysfunction</td>
<td>40 (6%)</td>
<td>3 (5.5%)</td>
<td>46 (18%)</td>
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<tr>
<td>- Other</td>
<td>52</td>
<td>3 (5.5%)</td>
<td>3 (1%)</td>
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Immunity in patients surviving 20-30 years after allogeneic HSCT

- 72 patients
- 16 donors

- Rare infections
  - 0.07 infection per patient-year
- Biologic parameters
  - Normal lymphocyte subpopulations, Ig

Thymic output (TREC’s)

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