Late effects and long-term survivorship after HSCT

What are late effects?
Why is it of importance?
How to proceed in daily routine?
59-year old male survivor
22 years after allogeneic HSCT

- Chronic myeloid leukemia in chronic phase
  - Allogeneic HSCT at 37-years of age
    - conditioning with TBI, cyclophosphamide and etoposide
    - Persisting complete molecular remission since 1991

- Long-term follow-up
  - 2 years, cataract, surgical repair
  - 3 years, infertility and gonadal insufficiency (remarried)
  - 6 years, osteopenia (osteodensitometry)
  - Over the years, cardiovascular risk factors
    - Overweight (BMI 27kg/m2)
    - Dyslipidemia, arterial hypertension
    - No physical activity,
  - 18 years, basal cell carcinoma, complete excision
  - 20 years, cardiovascular complications
    - Myocardial infarction
Last annual control (3 months ago)

- Physically in good condition

- Subjective complains
  - Sicca syndrome
    - Xerophthalmia
    - Skin dryness
  - Fatigue, depression, loss of concentration
  - Works 50%; needs 50% social support; financial problems
  - Divorced, remarried, three children (conceived before HSCT)
What is the problem?
The definitive aim of the HSCT

- Cure from the primary disease
- Complete recovery of the health status
Estimated 30% lower life expectancy than that of the US population, regardless of current age.

Projected reduction in life expectancy in patients surviving > 5 years after HSCT.
## What does affect long-term survivorship after HSCT?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Aspect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course of the primary disease</td>
<td>➡️ Late relapse of the primary disease</td>
</tr>
<tr>
<td>Late complications</td>
<td>➡️ Malignant and non-malignant</td>
</tr>
<tr>
<td>Chronic health condition</td>
<td>➡️ Burden of active late complications</td>
</tr>
<tr>
<td>Quality of life</td>
<td>➡️ The way that the life is perceived</td>
</tr>
<tr>
<td>Social integration</td>
<td>➡️ Family, partnership, school, job, financial aspects, assurances</td>
</tr>
</tbody>
</table>
Main players and confounders for late complications

- **Age at HSCT**
- **Primary disease**
- **Pretransplant treatment**
- **Conditioning regimen**
- **GVHD**
- **Comorbidity**
- **Familial predisposition**
- **Life style after HSCT**
- **Premature ageing**
Late complications after HSCT

**Malignant complications**
- Secondary MDS/AML after autologous HSCT
- Donor type leukemia
- Solid tumors
- Post-transplant lymphoproliferative disorders (PTLD)

**Non-malignant complications**
- Endocrine dysfunction
- Skeletal disorders
- Ocular problems, skin, mucosa
- Respiratory tract problems
- Liver complication
- Chronic kidney disorder
- Neurological complications
- Cardiac and vascular complications
- Others.....

Secondary malignancy after allogeneic HSCT

<table>
<thead>
<tr>
<th>Update</th>
<th>Patients with secondary malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>54/1117 patients</td>
</tr>
<tr>
<td>2008</td>
<td>134/959 patients</td>
</tr>
</tbody>
</table>

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

Heilmeier B. BMT. Abstract 2010
## Risk factors of secondary cancers after HSCT

>28’000 allo transplants; 189 tumors

<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</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Younger age at radiation (&lt;30)</td>
<td>Thyroid</td>
</tr>
<tr>
<td></td>
<td>Increasing with longer follow-up</td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone and connective tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Chronic GVHD</td>
<td>Oral cavity</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No relation with TBI and with time since follow-up</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Cirrhosis, HCV infection</td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>T-cell depletion</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

Also recipients of allogeneic HSCT using Bu-Cy conditioning are at risk for secondary solid tumors

4,318 recipients of first allogeneic HCT for AML in first CR or CML in first CP

In total 66 solid tumors

Estimated Cumulative Incidence

<table>
<thead>
<tr>
<th></th>
<th>AML</th>
<th>CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>@ 10-years</td>
<td>1.2% (95% CI, 1-2%)</td>
<td>2.4% (95% CI, 2-3%)</td>
</tr>
</tbody>
</table>

However, the type of solid cancers can be different

<table>
<thead>
<tr>
<th>Risk-factor</th>
<th>No. of Events</th>
<th>Relative risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trachea, bronchus and lung</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>1</td>
<td>1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>35-50 years</td>
<td>5</td>
<td>5.0 (0.6-43.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>4</td>
<td>17.4 (1.9-159.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking prior to HCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>13.3 (1.6-108.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>3.8 (0.2-61.7)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Lip, tongue and mouth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>12.4 (1.6-96.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Majhail NS. et al. Blood. 2011; 117: 316-322*
Reduced use of TBI changes the pattern of late effects

- In a cohort of 620 patients transplanted between 1997-2007
- 8 patients presented steroid-induced cataract

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


“Asymptomatic” late effects with significant effects on long-term survivorship

without TBI n = 81

- 41 (51%)
- 15 (18%)
- 9 (11%)
- 16 (20%)

with TBI n = 145

- 123 (85%)
- 11 (8%)
- 3 (2%)
- 3 (2.1%)
- 5 (3%)

p<0.0001

Accelerated bone mineral loss and micro-architectural deterioration

- Allo > auto HSCT
- Allo-HSCT with GVHD at higher risk for bone loss

Osteoprotegrin (OPG) ➔ osteoblast progenitors ➔ osteoclastic production

Chemo-radiotherapy
Gonadal failure
GVHD
↓ FGF2, ↓ IGF1

Glucocorticoids
Cytokines
UPTH
↓ Sex hormones

Cytokines (TNFα, INFγ, IL1)
Glucocorticoids
1,25OH-vit D
UPTH

Diabetes, Hypertension and CV Events in 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>Allo</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>Auto</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>Sibling</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

Risk factors for late vascular complications after allogeneic HSCT

- 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
Cardiovascular events after HSCT: Premature vascular aging?

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

Burden of morbidity with active late complications even beyond 10 years post HSCT

- No difference between autologous and allogeneic HSCT
- Significant higher among allo HSCT survivors with active chronic GVHD
- Nearly all patients maintained some medical contact
- Only 27% returned to transplantation centers

**Chronic health conditions in HSCT recipients with chronic GVHD**

- Diabetes
- Coronary artery disease
- Stroke
- Ocular complications resulting in significant visual impairment
- Osteonecrosis that necessitated joint replacement

Sun, C.-L. et al. BBMT 2013;19:1073-1080
Will we observe late effects after RIC?

Late effects due to toxicity of conditioning will be reduced
- Cataract
- Endocrine dysfunction
- Infertility
- Radiation associated cancers

Late effects due to GVHD/IS will not be reduced
- Avascular osteonecrosis
- Squamous cell carcinoma
- Chronic kidney disease

But new confounders
- Older age
- More comorbidity
- New drugs (Fludarabine)

Cumulative incidence of chronic kidney disease after allogeneic HSCT

The question with RIC is not so much more or less, but which type of late effects

Al-Hazzouri A. et al. BBMT. 2008;14: 658-663
Why does it matter to know about late complications?

- Not simply an enumeration of bad events

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

Majhail NS. et al. BBMT. 2012; 18: 348-371
Majhail NS. et al. BMT. 2012; 47: 337-341
Late effects as a direct consequence of the transplant procedure

- **TBI / Conditioning**
- **GVHD**

**Intervention**
- Change in the conditioning
- Pretransplant intervention (sperm cryopreservation)
- Early treatment

**Primary late effects**
- Cataract formation
- Infertility
- Secondary malignancy

TBI / Conditioning

Primary late effects
- Endocrine dysfunctions

Primary late effects
- Endothelial lesions

Secondary late effects
- Metabolic syndrome

Tertiary late effects
- Cardiovascular complications

GVHD

Immunosuppressive treatment

Intervention
Treatment of the modifiable risk factors
- Healthy heart lifestyle
- Cardiovascular risk factors

Centers’ attitude in respect of cardiovascular risk factors after HSCT

- For long, cardiovascular risk factors have been underestimated and undertreated

- Argument evoked
  
  "CV risk-factors will disappear when immunosuppression is stopped"

- Since 2-3 years attitude in centers seem to improve

![Bar chart showing number of persons with CV risk factors](image)
Long-term follow-up (LTFU) transplant clinic setup

**Why a transplant survivorship program**
- Specialized follow-up care
- Increasing expectations
- Less disease oriented
- More on screening, prevention and counseling

**Main barriers for a LTFU transplant clinic**
- lack of time, space, resources
- not enough support from the head of the transplant program
- deficits of knowledge
- not covered by health care insurance
- not perceived as a need
  - immediate complications and survival has priority
- **Distance to the transplant center**


Eshelm-Kent J Cancer Surviv. 2011; 5; 345-357
Models of long-term follow-up (LTFU) clinic

- **Transplantation Center**
  - Outpatient clinic: LTFU patients integrated

- **Independent specialized LTFU clinic**

- **Specialized LTFU clinic integrated within the transplant center**
  - Satellite LTFU clinic
    - Same program
    - Trained platform
    - Skype for counseling

- **Community-based care**

Multidisciplinary team for a long-term follow-up transplant clinic

Core Team
- Specialized physicians
- Specialized nurses
- Supportive structures
- Social worker
- Psychologist
- Nutritionist
- Physical specialist

Consultative services
- Pulmonology
- Infectious diseases
- Ophthalmology
- Neurology
- Endocrinology
- Dermatology
- Dental medicine
- Gynecology
- Fertility counseling
- Cardiology
- Nephrology

Coordination team
- Data manager

Head of HSCT clinic

Lead of LTFU clinic
Organization of the long-term follow-up visit

**Survivorship care plan**
- Patient's history and treatment summary
  - Exposure / radiation
- Co-morbidity
- Transplantation information
  - Type of HSCT
  - Conditioning
  - GVHD
- Risk profile for late complications
- Late complications
  - present
  - possible

**Preparation**
- Review of all documents
- Organization of the visit according risk profile
- Team meeting (who does what)

**Follow-up visit**
- Medical consultation
- Specialized investigations
- Consultative services
- Psychosocial assessment
- Counseling and answering special questions

**Post-clinic follow-up**
- Assemble and summarize all information
- Multidisciplinary discussion of the problems
- Recommendation plan for the next period

Back to our patient: Individualized risk profile
What we do during our follow-up control

- CML
- TBI
- Pretransplant treatment
- GVHD and IS
- No comorbidity
- Young age at HSCT
- Familial predisposition?
- Life style after HSCT
- Premature ageing
Take home messages

- Late effects and their consequences are of major issue
- With change in the transplant procedure, late effects and long-term survivorship will continue to evolve
- Life-long controls, counseling and prevention/treatment in a transplantation center are mandatory
- A model of long-term follow-up clinic should be available
- The “annual” follow-up control have to be planed
- We have to continue research on long-term survivorship “life-long”!
Thank you for your attention
Neglected long-term effects after HSCT

**Genital chronic GVHD in men**
- Single center cross-sectional analysis of 155 male patients
- Genital skin changes in 31/155 (20%)
- 21 (13%) with inflammatory genital skin changes (genital GVHD)
- Significant higher coincidence of oral, ocular, cutaneous chronic GVHD
- Erectile dysfunction was significantly more frequent

**Increased death rate due to suicide and accident after HSCT**
- Suicides (versus general population)
  - Standard mortality ratio 2.12
  - and absolute excess risk 10.91
- Accidents (versus general population)
  - Standard mortality ratio 2.12
  - and absolute excess risk 10.91
- Relapse associated with more suicide and accidents after autologous HSCT
- GVHD associated with more suicide after allogeneic HSCT

Mueller SM et al. BBMT  Online 2013 (article in Press)
Late congestive heart failure mainly as the consequence of pretransplant treatments

**Congestive heart failure**

- Dose dependent cardiotoxicity of anthracycline
  - 26% in non-HSCT population with doses ≥ 550mg/m²

- Risk factors after autologous HSCT
  - Pretransplant exposure of anthracycline (≥ 250mg/m²)
  - Post-transplant cardiovascular risk factors in patients with pre-HSCT anthracycline therapy

- Genetic susceptibility to anthracycline-related cardiac failure after HSCT

*Armenian S et al. Blood. 2011;118:6023-6029*
*Armenia S et al. BJH, Online 2013*