Late effects after hematopoietic stem cell transplantation (HSCT)

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Special thanks to
- Alicia Rovó
- Gérard Socié
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 and 20 years, basal cell carcinoma, complete excision
- 24 years, myocardial infarction
Physically in good condition

Subjective complains
- Sicca syndrome
  - Xerophthalmia
  - Skin dryness
  - Genital dryness
- Fatigue, depression, loss of concentration
- Works 50%; needs 50% social support; financial problems

Subjectively the patient considers to have a good to excellent quality of life
At the end of this presentation you should know

- what are late effects after HSCT
- why long-term surveillance is of importance
- what we can do to prevent and to treat late effects
This patient is most probably cured from his CML.
- He has developed a number of late complications.
- He is satisfied with his life.
- He wants to have a normal life.

**Aim of the HSCT**

- Cure of the primary disease (leukemia).
- Complete recovery of the health status and quality of life.
### What does affect long-term survivorship after HSCT?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact</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**
- **Conditioning regimen**
- **Pretransplant treatment**
- **GVHD**
- **Comorbidity**
- **Distance to the HSCT center**
- **Communication (language)**
- **Familial predisposition**
- **Premature ageing**
- **Life style after HSCT**
Late complications after HSCT

**Malignant complications**
- Late relapse
- 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.....

Ocular complications after HSCT

Subjective complains
- Blurred vision
- Light sensitivity
- Dry eyes
- Ocular pain

Kerato-conjunctivitis Sicca
- Risk factors
  - Chronic GVHD
  - TBI

Cataract
- Risk factors
  - TBI (total dose, fractionation)
  - Cortico-steroids

What are the consequences of this knowledge?

**Kerato-conjunctivitis sicca**

- **Significance**
  - Prevent lesions of the cornea
  - Maintenance of visual acuity

- **Treatment**
  - Local treatment
    - Artificial tears
  - Immunosuppressive substances
  - Systemic treatment of the GVHD
  - Treatment of super-infection

**Cataract**

- **Significance**
  - Increased risk of accidents?

- **Prevention**
  - Adapt conditioning
  - Reduction/shortening treatment with steroids

- **Treatment**
  - Operation
  - Optimal timing of the operation
Infertility, an asymptomatic late effect, becoming an issue when wish of a child

Risk factors of infertility in males
- TBI
- Older age at HSCT (>30 years)
- Shorter time since HSCT (< 9 years)
- Pretransplant radio/chemotherapy
- Chronic GVHD

Seminal fluid analysis
- red, azoospermia
- blue, normal sperm content
- green, reduced sperm content

with TBI n = 145

without TBI n = 81
### Pregnancy and paternity after HSCT

<table>
<thead>
<tr>
<th></th>
<th>Female patients</th>
<th>Male patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>patients</td>
<td>pregnancies</td>
<td>Number (%)</td>
<td>patients</td>
</tr>
<tr>
<td>All</td>
<td>7'615</td>
<td>113</td>
<td>1.5%</td>
<td>10'467</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>3'695</td>
<td>74</td>
<td>2%</td>
<td>5’124</td>
</tr>
<tr>
<td>Autologous</td>
<td>3’920</td>
<td>39</td>
<td>1%</td>
<td>5’343</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3713</td>
<td>32</td>
<td>0.9%</td>
<td>5152</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>385</td>
<td>47</td>
<td>12.2%</td>
<td>605</td>
</tr>
<tr>
<td>Myeloma</td>
<td>323</td>
<td>1</td>
<td>0.3%</td>
<td>485</td>
</tr>
</tbody>
</table>

Infertility, symptomatology, sexuality, and wish of having a child

- Infertility does not produce symptoms
  - symptoms are due to gonadal failure

- Infertility may produce enormous psychological stress for patient and partner
  - No association with sexuality

- High probability of infertility
  - does not exclude unwanted pregnancy
  - does not prevent sexually transmitted diseases

- Pregnancy/fatherhood rate and desire of having a child
  - Personality
  - Family situation before HSCT
  - Age at HSCT
  - Health status
  - ...
What are the consequences of this knowledge?

**Before HSCT**
- Discussion and counseling
  - Risk of infertility
  - Possibility for assisted fertility
  - Adoption
- Cryoconservation
  - Sperm
  - Embryos
  - Oocytes
- Conditioning?

**After HSCT**
- Control of hormonal situation
  - Hormonal substitution
- Referral to appropriate specialists for assisted conception
- Counseling on
  - contraception
  - prevention of sexually transmitted diseases
Osteopenia and osteoporosis

- Reduced bone density
- Increased risk for bone fractures
- No symptoms as long as no fractures

**Risk factors**

- TBI
- Chronic GVHD
- Steroids, Cyclosporine
- Gonadal deficiency
- Prolonged physical inactivity
- Smoking and excess of alcohol
- Underweight
- Age
- Familial risk
- Vitamin D deficiency

**Osteodensitometry**

(Bone density- Z-Score)

What are the consequences of this knowledge?

- Screening
  - Osteodensitometry
  - Vitamin D, Calcium

- Prevention
  - Hormonal substitution
  - Reduce steroids

- Treatment
  - Calcium / Vitamin D
  - Bisphophonates

What can the patient do?

- Regular physical activity
- Stop smoking
- No excess of alcohol
- Moderate light exhibition
Conventional cardiovascular risk factors are increased after HSCT

Cardiovascular risk factors
- Increased compared to general population
- 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><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basline</td>
<td>22.3</td>
<td>11.4</td>
<td>0.01</td>
</tr>
<tr>
<td>10 years</td>
<td>28.7</td>
<td>40.3</td>
<td></td>
</tr>
</tbody>
</table>

| **Diabetes**    |           |           | <0.01   |
| Basline         | 8.3       | 5.3       |         |
| 10 years        | 15.9      | 20.9      |         |

| **Dyslipidemia**|           |           | <0.01   |
| Basline         | 22.8      | 12.5      |         |
| 10 years        | 43.3      | 45.0      |         |
Increased risk of cardiovascular complications

Potential risk reduction by control of CV risk factors and healthy life style

**Control of CV risk factors**
- Coronary arterial disease (black)
- Cardiomyopathy (red)
- Cerebrovascular insult (blue)

**Healthy life style**
- Arterial hypertension (red)
- Dyslipidemia (blue)
- Diabetes (green)
What are the consequences of this knowledge?

Control of the cardiovascular risk factors

- Annual controls
- Treatment of arterial hypertension
- Treatment of dyslipidemia
- Control of diabetes

What can the patient do?

- Healthy life style
  - Healthy diet
  - No / stop smoking
  - Regular physical activity
- Compliance of the treatment of CV risk factors

➤ It is better to prevent cardiovascular complications than to treat them
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>


Heilmeyer B. BMT. Abstract 2010
## Risk factors of secondary solid 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>Skin</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>
<tr>
<td></td>
<td>Buslfan and cigarette smoking</td>
<td>Lung cancer*</td>
</tr>
</tbody>
</table>


What are the consequences of this knowledge?

- Early recognition
  - Regular controls
- Counseling
- Systematic examination according to the patient’s risk profile
  - Breast (TBI)
  - Oral cavity and skin (GVHD)
  - Thyroid gland (TBI)
  - Lung (Busulfan/cigarettes)
- Early therapeutic intervention

What can the patient do?

- Self-control
  - Skin, breast
  - Regular controls by specialists
- Stop smoking
- Annual controls

Majhail NS. et al. BMT. 2012; 47: 337-341
Quality of life
Subjective perception of well-being

- The most frequent subjective complaints in long-term survivors after allogeneic HSCT
  - Fatigue, Depression
  - Ocular problems and generalized sicca syndrome
  - Muscular and skeletal complaints
  - Problem to concentrate, forgetfulness

- Less frequently mentioned, but not less important
  - Problems in sexuality
  - Financial problems
Fatigue is one of the most difficult complains to approach.

Physical activity can improve fatigue (in early phase)

**Treatable factors**

- pain
- Depression, fear
- Sleep disorders
- Anemia
- Nutritional and hormonal factors
- Social integration
- Comorbidity
Posttraumatic growth and benefit-finding

- Greater meaning of life
- Positive experience of life after HSCT
- Increased personal strengths
- Enhanced interpersonal relationships
- Patients think about life
- How they treat other people
- How careful they are
- Thankful to be alive

Most of the patient would restart the HSCT
Take home messages

A clever person solves the problem, a wise person avoids it

- Late effects are a reality, but not a fatality
  - Examples, secondary malignancies and cardiovascular complications

- The occurrence of late effects and well-being simultaneously is not a contradiction

- Life-long controls in a specialized center are mandatory
  - Regular and systematic screening allows prevention and early treatment of late complications
  - Counseling of healthy life style is part of the yearly controls

- Long-term survivorship however includes also
  - Training and education of health care providers
  - Convince the health authorities of the need of life-long control
  - Continuous research on long-term survivorship
Thank you very much for your attention