Metabolic syndrome and cardiovascular late effects after HSCT

André Tichelli
Aim of hematopoietic stem cell transplantation (HSCT)

- Cure of the disease
- Complete recovery of the health condition and quality of life

In the year 2020 there will be worldwide one million long-term survivors after HSCT.

Long-term survivors
- In the year 2020 there will be worldwide one million of long-term survivors after HSCT

Passweg JR et al. BMT 2015. EBMT Report : HCT in Europe 2013

Savani B. Blood and Marrow Transplantation: Long-term managment; Chapter one
Late mortality and morbidity in long term survivors after allo HSCT

Late effects
- Malignant
- Non-malignant
- Quality of life

53-year old male survivor
24 years after allogeneic HSCT for CML, in persistent CR

Immunosuppression

- allo-HSCT / TBI Cyclophosphamide
- Arterial hypertension
- Dyslipidemia / obesity
- Type 2 Diabetes

Non-smoker; no regular physical activity

Full-time working as a carpenter
What are the questions

- Are the cardiovascular diseases (CVD) related with HSCT?
  - myocardial infarction
  - cerebrovascular insult
  - peripheral arterial disease

- If yes, are they the direct consequence of HSCT and its preparative regimen?
What is the problem?

Causes of death in long-term survivors alive ≥5 years after HSCT

Syrjala KL et al. JCO. 2012;30:3746-3751
Cardiac morbidity and mortality after HSCT compared to a general population

Cumulative incidence of cardiovascular events in long-term HSCT survivors

Allo-HSCT compared to auto-HSCT have in increased risk of cardiovascular events

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

Cardiovascular events after allo-HSCT occur earlier in life

Cardiovascular diseases after HSCT

- have a higher incidence than in a general population
- are more frequent in allogeneic transplantation
- appear earlier in life
- have a long delay for appearance
Why do cardiovascular diseases (CVD) appear earlier and more frequently after allo-HSCT?

Vascular endothelial lesions

Atherosclerosis is an inflammatory process
Conventional cardiovascular risk factors are increased after allogeneic HSCT

<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>Baseline at 10 years</td>
<td>22.3</td>
<td>11.4</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>28.7</td>
<td>40.3</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline at 10 years</td>
<td>8.3</td>
<td>5.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>15.9</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline at 10 years</td>
<td>22.8</td>
<td>12.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>43.3</td>
<td>45.0</td>
<td></td>
</tr>
</tbody>
</table>
Cumulating risk factors increases the risk for CVD

<table>
<thead>
<tr>
<th>Cumulative incidence at 15 years</th>
<th>Without risk factor</th>
<th>With risk factor</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>2%</td>
<td>17%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3%</td>
<td>10%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2%</td>
<td>12%</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI &gt; 25 mg/m²</td>
<td>3%</td>
<td>7%</td>
<td>0.05</td>
</tr>
<tr>
<td>Persisting smoking</td>
<td>3%</td>
<td>15%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>2%</td>
<td>7%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Risk score ≥50%: cumulating ≥ 50% of the risk factors
Cardiovascular diseases

Cardiovascular risk factors

Atherosclerosis

Inflammatory process

allo-HSCT
Does radiation play a role?
Vascular late effects in non transplanted Hodgkin patients

Cumulative incidence of myocardial infarction
- Retrospective study on 1474 long-term Hodgkin survivors
- Age groups at diagnosis
  - ≤ 20 years
  - 21-40 years
- Median follow-up 19 years
- Mediastinal irradiation most important risk factor

Local radiation and TBI as risk factors for CVD

- TBI exposure was associated with an increased risk for diabetes, and dyslipidemia (Barker, Blood 2007; Armenian, Blood; 2012)
- Radiation exposure to the abdomen may contribute to insulin resistance / and or metabolic syndrome by pancreatic and gonadal injury (?) (Teinturier C, Lancet, 1995)
- Metabolic syndrome and growth hormone deficiency in subjects treated with cranial irradiation for ALL (Gurney, Am Cancer Soc 2006)

- Direct endothelial injury by radiation (Barker, Int J Radiat Biol; 2009; Soucy, Radiat Environ Biophys; 2010)

Extensive carotid atherosclerosis in a 50-year old patient with neck irradiation for sarcoma (Lenihan D and Cardinale D; JCO, 2012)
Predictors for cardiovascular (CV) events after HSCT

**Nested case control Study**
- 63 patients with CV events
  - Coronary heart disease, n=44
  - Cerebrovascular events, n=19
- 186 matched controls without CV events (HSCT patients)

**Multivariate Analysis**
- 9.2-fold increase of risk after pre-transplant radiation therapy
- 5.2-fold increase of risk when several CV risk factors appear after HSCT
- No difference between auto and allo HSCT

Cardiovascular events after autologous and allogeneic HSCT
- City of Hope study (Armenian BBMT 2010)
  - 66% of the patients were patients treated with auto HSCT for lymphoma or Hodgkin disease (mediastinal irradiation)
- Basel study (Tichelli Blood 2007)
  - Most autologous HSCT without local irradiation

**Mediastinal radiation, not autologous HSCT is related with cardiovascular events**

Armenian S et al. BBMT. 2010;16:1138-1144
Cardiovascular diseases

Radiation (chest; cranial) TBI

Endothelial lesions

Atherosclerosis inflammatory process

allo-HSCT

Risk factor
Pathophysiologic mechanism
Terminal event
Why is are cardiovascular risk factors increased after allogeneic HSCT?

- Hormonal deficiency
  - Hypogonadism
  - Growth hormone deficiency
  - Hypothyroidism
- Insulin resistance

Insulin sensitivity according to type of treatment

Why is are cardiovascular risk factors increased after allogeneic HSCT?

- Hormonal deficiency
  - Hypogonadism
  - Growth hormone deficiency
  - Hypothyroidism
- Insulin resistance


Taskinen et al. J pediatr hematol Oncol. 2007;29:529-534
Body composition - sarcopenia - insulin resistance after HSCT

**Obesity after HSCT**

- Obesity defined by BMI is not a real problem after allogeneic HSCT
- Sarcopenia - abdominal adiposity
  - Changes of the body composition with ± normal body weight
  - Loss of muscle mass
  - Increase of visceral fat

*Myocyte insulin receptors are more efficient than adipose tissue insulin receptors*

Barker KS. Review. BMT. 2012;47;619-625
# Metabolic syndrome and ATP III criteria

**Constellation of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and arterial hypertension**

<table>
<thead>
<tr>
<th>Criteria (≥ 3 criteria)</th>
<th>Adults</th>
<th>Adolescents (12-19 years)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride level</td>
<td>≥ 1.7 mmol/l</td>
<td>≥ 1.25 mmol/l</td>
<td>or treatment</td>
</tr>
<tr>
<td>HDL- level</td>
<td>≤ 1.05 mmol/l (♂)</td>
<td>≤ 1.05 mmol/l (♀)</td>
<td>≤ 1.25 mmol/l (♀)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 5.6 mmol/l</td>
<td>&gt; 5.6 mmol/l</td>
<td>or proven diabetes</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/85</td>
<td>≥ 90th percentile</td>
<td>or treatment</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>&gt;102 cm (♂)</td>
<td>&gt;88 cm (♀)</td>
<td>≥ 90th percentile</td>
</tr>
</tbody>
</table>

Barker KS. Review. BMT. 2012;47;619-625
Increased risk of metabolic syndrome after allo-HSCT

**Children and Adolescents**
- Insulin resistance after HSCT
  - 52% children with hyperinsulinemia after HSCT
  - 0% in the control group
- Patients conditioned with TBI have more insulin resistance
- Prevalence of metabolic syndrome > 30%

**Adults**
- Metabolic syndrome
  - 34% of long-term HSCT survivors
  - 15% in the control population
- Most frequent anomaly in patients with metabolic syndrome after HSCT
  - High triglyceride levels
  - Low HDL-Cholesterol level

**Open questions**
- Insulin resistance the primary mechanism for increased CV risk factors?
- What is the role of body composition??

*Annaloro C et al. BMT.2008;41:797-804*
Insuline resistance and abdominal adiposity in three categories of non-obese subjects after HSCT

Factors associated with metabolic risk
- TBI
- Time from HSCT

<table>
<thead>
<tr>
<th></th>
<th>% of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose intolerance Diabetes mellitus</td>
<td>80</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>40</td>
</tr>
<tr>
<td>Controls</td>
<td>20</td>
</tr>
</tbody>
</table>

Waist/height ratio

Cardiovascular diseases

- Radiosensitive TBI
  - Radiation (chest; cranial)
  - TBI

- Hormonal deficiency / Insuline resistance

- Cardiovascular risk factors
  - Metabolic syndrome

- Atherosclerosis
  - Inflammatory process

- Endothelial lesions

- allo-HSCT

Risk factor
Pathophysiologic mechanism
Terminal event
Endothelial injury in chronic GVHD


Vascular endothelial cells (blue)
T-lymphocytes (red)
Activated cytotoxic T-cells (green)
Vascular endothelial form of GVHD

- Early endothelial injury syndromes
  - Transplant-associated microangiopathy
  - Sinusoidal obstruction syndrome (VOD)
  - Diffuse alveolar hemorrhage
  - Engraftment syndrome

- Closely related with GVHD
  - More likely to occur after allo-HSCT
  - More often in unrelated HSCT

Pretransplant angioptetin, a hormone mediating endothelial vulnerability
GVHD and cardiovascular risk factors

Cardiovascular diseases

- Cardiovascular risk factors
  - Metabolic syndrome
- Atherosclerosis inflammatory process

- Endothelial lesions

- Radiation (chest; cranial)
  - TBI

- allo-HSCT

- Immunosuppressive drugs
  - GVHD

- Hormonal deficiency / Insuline resistance

- Accelerating factor
- Risk factor
- Pathophysiologic mechanism
- Terminal event
How can we intervene?

Intervention on modifiable risk factors

- Radiation (chest; cranial) TBI
- allo-HSCT
- Hormonal deficiency / Insulin resistance
- Cardiovascular risk factors Metabolic syndrome
- GVHD Immunosuppressive drugs
- Endothelial lesions
- Atherosclerosis Inflammatory process

Cardiovascular diseases

Risk factor
Pathophysiologic mechanism
Terminal event

Accelerating factor
Potential risk reduction of cardiovascular complications by effective control of CV risk factors

Coronary heart disease
Cardiomyopathy
Stroke

Chow EJ. et al. JCO. 2014;32:191-198
Potential risk reduction of cardiovascular risk factors by adherence to lifestyle recommendation

Attributable Risk (%)

- Obesity
- Current smoking
- Unhealthy diet
- Physical inactivity

Chow EJ. et al. JCO. 2014;32:191-198

Arterial hypertension
Dyslipidemia
Diabetes
Screening of patients at risk for cardiovascular risk factors

**Whom to screen (patients at risk)?**
- Allogeneic HSCT
- Autologous HSCT with radiation exposure

**When to screen**
- Pre-transplant
- Post-transplant
  - start at one year
  - even if patient still on immunosuppression/steroids
- Yearly controls

**What to screen?**
- Blood pressure assessment
  - Self-assessment
  - 24-hour blood pressure monitoring
- Lipid profile
  - Triglycerides, HDL-Cholesterol
- Screen for glucose intolerance
  - Fasting glucose
  - HbA1c
- Body weight and body composition
  - BMI
  - Waist circumference
- Patients life style
  - Cigarette exposure/smoking
  - Physical activity
  - Nutritional habits
  - Compliance
Prevention of cardiovascular events after HSCT: Intervention on modifiable factors

**Treatment of cardiovascular risk factors**

- Start early, do not wait until immunosuppression is stopped
- Decision to treat as for high risk patients (HSCT is per se a risk factor)
- Statins belong to the drug of choice for dyslipidemia, event in case of high triglyceride levels
- Consider side effects of statins and interference with cyclosporine

**Counseling of patients**

- Healthy heart life style
  - Healthy diet
  - No smoking, no passive smoke exposure
  - Regular physical activity
  - Healthy body weight and body composition
- Adherence to treatment and healthy life style recommendations
Reasons for poor adherence to treatment of cardiovascular risk factors and lifestyle recommendations

The main reason for non-adherence to treatment and lifestyle recommendation

- Cardiovascular risk factors are asymptomatic
- Lifelong nature of the disease

Other factors

- Demographic factors (age, education, gender)
- Patient’s understanding and perception of the disease/treatment
- Healthcare provider’s mode of delivering recommendations
- Relationship between patients and healthcare professionals
- Awareness of costs and benefits
- Complexity of the regimen
Take home messages

- Late effects after HSCT, including cardiovascular diseases (CVD) are a reality but not a fatality
- Cardiovascular diseases are the consequences of a long, asymptomatic atherosclerotic process
- Cardiovascular risk factors, radiation and GVHD are involved in the atherosclerotic process
- Regular screening and early intervention of modifiable factors may reduce the risk of late cardiovascular diseases
- The survivor is part of the actors - consider compliance/adherence
Thank you for your attention