Late Effects after allogeneic stem cell transplantation

Annual BHS Meeting
Nurses Session

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“After allogeneic stem cell transplantation, half of the patients dies, and the other half wished they would have died, because their life is hell…”
“Life after transplant is a different challenge than treatment. Paving the road to your new normal has its emotional ups and downs. However, if you lean on your support system and listen to your doctors, your road will be much smoother.”
— Matt, transplant recipient (with wife Cori)
Overview

Allogeneic SCT

Late effects after allogeneic SCT

- General
- cGVHD
- Infectious complications
- Pulmonary complications
- Endocrinologic complications – metabolic syndrome
- Cardiovascular complications
- Renal complications
- Malignancies

Quality of life

What can we do? (screening guidelines)

Case
Allogeneic SCT: principle

1. Immunosuppress recipient to prevent graft rejection
2. Reduce number of tumour cells
3. Reduce number of recipient haematopoietic cells
Allogeneic SCT: principle

1 Conditioning

2 Stem cell transplantation

3 Cytopenias

4 Immune reconstitution
Allogeneic SCT: principle

- T cells recognize target cells

- TCR
- HLA
- Antigen/peptide
- Target cell
Allogeneic SCT: principle

- **RBC/WBC/TROG**
- **Host**
  - Extrathymic sites
- **Allograft**
  - Haematopoietic precursor
  - Bone marrow
  - T-cell precursor
- **T cells**
  - Non-alloreactive T cells
  - Alloreactive T cells
  - Residual host T cells
- **Thymus**
  - Naive T cells
  - Homeostatic T-cell clonal expansion
  - Alloreactive T-cell clonal expansion
- **Graft versus host disease**
- **GVT**
- **IS**

*T-cell immunity and homeostasis*
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Late effects after SCT: time of appearance

Figure 1. Time of appearance of the different late effects after hematopoietic stem cell transplantation. In some cases the late effects can appear earlier, however, the awareness of the complication becomes relevant later for the long-term survivor. For many long-term survivors, the performance score, QoL and social integration improves with longer follow-up.

QoL: Quality of life.
Late effects after SCT: complex interplay

Pulsipher et al, BBMT, 2012
Late effects after SCT: causes

- **TBI/conditioning**
  - Primary late effects
    - Cataract formation
    - Endocrine dysfunction
    - Secondary malignancy

- **GVHD**
  - Primary late effects
    - Sicca syndrome of the oral cavity
  - Secondary late effect
    - Dental caries

- **Immunosuppressive treatment**
  - Secondary late effect
    - Metabolic syndrome
  - Tertiary late effect
    - Cardiovascular complications
Late effects after SCT: incidence

Khera et al, JCO, 2011
Late effects after SCT: incidence

Cumulative incidence (%)

Grade 1–5

Grade 3–5

Time after HSCT (years)
Late effects after SCT: late mortality causes

Fig. 1. All-cause mortality in a cohort of 1,479 long-term survivors after allogeneic HSCT. From Bhatia et al. [1].
Late effects after SCT: late mortality causes

**A** Autologous HSCT (n = 854)
- US female
- US male
- Female
- Male
- SMR = 13

**B** Allogenic HSCT (n = 1601)
- US female
- US male
- Female
- Male
- SMR = 9.9

**Cause of death:**
- Primary disease: 56% (A), 44% (B)
- SMNs: 25% (A), 18% (B)
- Cardiac complications: 2% (A), 9% (B)
- Pulmonary complications: 2% (A), 5% (B)
Late effects after SCT: Children ≠ small adults

- Children are a heterogeneous group: different developmental stages (infant, toddler, pre-adolescent, young adult) → different sensitivities to therapies → different complications
  - Infants/toddlers: neurocognitive damage after RT
  - Adolescents: joint/bone issues after corticoid therapy
- Influence on growth, neurocognitive and gonadal development, …
- Children have decades before them if the transplant is successful
- Self-report symptoms = challenge
- International consensus conferences on late affects after pediatric SCT
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cGVHD: pathogenesis
**cGVHD: pathogenesis**

- Conditioning
- *aGVHD*
- Infections
- Age

**DAMAGE**

- Auto-ABs
- Stimulation fibroblasts
- Auto-immunity

↓ Negative selection
↓ Treg development

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cGVHD: impact on relapse

![Graph showing the impact of cGVHD on relapse probability.](image)

Weiden et al, NEJM, 1981
cGVHD: impact on DFS

Weiden et al, NEJM, 1981

Elk nadeel hep z’n voordeel...
cGVHD: clinical manifestations

- Dry eyes
- Oral lesions
- Nail dystrophy
- Skin sclerosis
- Deep sclerosis

- Bronchiolitis obliterans
- Loss of bila ducts
- Fascitis
- Skin ulcers

Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability

Spectrum of manifestations in cGVHD
cGVHD: clinical manifestations
cGVHD: clinical manifestations
cGVHD: treatment

- Corticosteroids
- PUVA / UVB
- Immunosuppressives: CNI (cyclosporin, tacrolimus, rapamune, MMF, …)
- ECP
- Rituximab (anti-CD20)
- Imuran
- Glivec
- …
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Infectious complications

- People remain very vulnerable for infections
- Takes at least 2 years to recover immune system post allo SCT, depending on age: never complete recovery
- In case of cGVHD, prolonged treatment with IS: ↑↑ risk
- Bacterial, fungal, viral infections
- Important morbidity and mortality!
- Preventive drugs: Acyclovir, eusaprim, AB
- Vaccinations
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Pulmonary complications: What, incidence, risk factors, diagnosis

▶ Bronchiolitis obliterans (BO)
  ▶ = non-specific inflammatory injury affecting small airways → peribronchial fibrosis → restrictive changes
  ▶ SS: dry cough, wheezing, progressive dyspnoea
  ▶ Incidence: 8%, onset 1 year after transplant or later
  ▶ RF: cGVHD, PBSC, MTX (IS), older age at SCT of recipient/donor, busulfan, history of respiratory infectious, low Ig
  ▶ Diagnosis
    ▶ PFT: FEV1/FVC < 0,7, FEV1< 75%
    ▶ HRCT: insp/exp: mosaic, air trapping, small airway thickening or bronciolectasies
Pulmonary complications: What, incidence, risk factors, diagnosis

- Bronchiolitis obliterans with organizing pneumonia (BOOP)
  - = inflammation of bronchioles, alveolar ducts, alveoli
  - SS: sudden onset, dry cough, dyspnoea, fever
  - Incidence: <2%, onset within first 12 months
  - RF: aGVHD, cGVHD

Diagnosis
  - PFT: restrictive pattern
  - HRCT: peripheral patchy consolidation, ground glass opacities
  - Biopsy = definite diagnosis
Pulmonary complications: What, incidence, risk factors, diagnosis

- **IPS (idiopathic pneumonitis syndrome)**
  - = interstitial pneumonia of unknown origin (non-infectious)
  - SS: cough, dyspnoe, increasing with physical activity
  - Incidence: 3-4%, onset <4 m or several years post SCT, mortality very high (80-90%)
  - RF: cGVHD/sclerodermia, TBI, pre SCT chemo, older age

- **Diagnosis**
  - PFT: restrictive
  - HRCT: bilateral diffuse parenchymal interstitial/alveolar infiltrates: >> central with bilateral/symmetric distribution, ground glass apacities
Pulmonary complications: Screening

- **Screening / prevention**
  - PFT /6m 1st year, then yearly, in case of cGVHD
  - In case of chronic dry cough, dyspnoea: diagnostic tests (PFT, HRCT, biopsies)
  - No smoking!
  - Vaccinations (pneumococcal, influenza)
  - PFT/RX thorax: screening
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Overview

- Allogeneic SCT
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  - Endocrinologic complications
    - Thyroid dysfunction
    - Osteoporosis/osteopenia
    - Growth impairment
    - Gonadal dysfunction
    - Metabolic syndrome
Endocrinologic complications: thyroid dysfunction

**What:**
- Compensated hypothyroidism: ↑TSH, nl T4
- Overt hypothyroidism: ↑TSH, ↓T4

**Incidence:**
- Compensated hypothyroidism: 25-30%, usually within 2 years
- Overt hypothyroidism: after 2,7 years

**Risk factors:** TBI, RT on thyroid, younger age at SCT, post SCT R/ of GVHD
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    - Metabolic syndrome
Endocrinologic complications: osteopenia/osteoporosis

- **What:** ↓ bone density → ↑ risk of fractures

- **Incidence:**
  - Osteopenia (BMD -1 to -2.5): 50% (until 4-6 years post SCT)
  - Osteoporosis (BMD <-2.5): 20% at 2 years post SCT
  - Non-traumatic fractures: 10% within 3 years post SCT

- **Risk factors:** corticosteroid use (GVHD), GH deficiency (children), hypogonadism, ++ physical activity, low Ca diet

- **Screening/Prevention:**
  - Bone density measurement: at 1 year: if nl → no follow-up unless new RF; if abnormal: yearly FU
  - Ca/vitD in case of prolonged corticosteroid therapy

- **Treatment:** Ca/vitD/bisphosphonates
Overview

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    - Growth impairment
    - Gonadal dysfunction
    - Metabolic syndrome
Endocrinologic complications: growth impairment

- **What**: growth below growing curve (children)
- **Incidence**: 20-85%
- **Risk factors**:
  - TBI, cranial RT → damage to hypothalamic/pituitary axis = central
  - Bone/cartilage lesions, damage to epiphysal growth plates
  - Modifying factors: genetic, nutritional, hormonal, corticosteroid
- **Screening/Prevention**: growth curve evaluation (6m), GH measurement
- **Treatment**: GH replacement R/ (↑ risk of secondary malignancies?)
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    - Osteoporosis/osteopenia
    - Growth impairment
    - Gonadal dysfunction
    - Metabolic syndrome
Endocrinologic complications: gonadal dysfunction

- **What:**
  - Pubertal disturbances
  - Testicular function: Sertoli cells (spermatogenesis) more sensitive than Leydig cells (testosteron)
  - Ovaries: more vulnerable to RT/CT

- **Incidence:**
  - Male: <25y at SCT and no cGVHD: chance to recover some degree of spermatogenesis
  - Female: prepubertal at SCT: 50% have puberty / menarche at nl age; ≥12y: 100% ovarian failure
  - Infertility: 36-fold higher risk not to report conception than control
Endocrinologic complications: gonadal dysfunction

**Risk factors:**
- RT → damage to hypothalamic-pituitary axis
- Chemotherapy (esp high dose Bu) → damage to gonads
- Older age at SCT (>25-30 years), female, GVHD

**Screening/Prevention:**
- Screening for effects on libido/impotence/fertility; delayed puberty (children); hormone levels (LH, FSH, estradiol, testosterone, GH) in blood
- Fertility preservation options preSCT!

**Treatment:**
- Male: testosterone replacement
- Female: hormone replacement (prevention osteoporosis)
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    - Thyroid dysfunction
    - Osteoporosis/osteopenia
    - Growth impairment
    - Gonadal dysfunction
    - Infertility, sexuality
    - Metabolic syndrome
Endocrinologic complications: metabolic syndrome

- **What**: collection of symptoms

  - Metabolic syndrome (Syndrome X)
    - Central obesity
    - High blood pressure
    - High triglycerides
    - Low HDL-cholesterol
    - Insulin resistance

- **Risk for cardiovascular diseases**
- **Diabetes mellitus type II**
Endocrinologic complications: metabolic syndrome

» **Incidence:** 34-49%

» **Risk factors:**
  - Hypothalamus-pituitary axis disturbed → hypogonadism
  - chemoR/ - RT → direct impact on vascular endothelium
  - IS (cyclosporin, tacrolimus, sirolimus, corticosteroids) → dyslipidemia, glucose intolerance, arterial hypertension
  - TBI → ↑TG, ↓HDL, ↑glucose

» **Screening/Prevention:** follow-up weight, BP, blood levels for glucose/lipids
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Cardiovascular complications

What:
- Cardiomyopathy
- Chronic heart failure
- Valvular dysfunction
- Arrhythmia
- Pericarditis
Cardiovascular complications

- Endothelial damage
- Hormonal deficiencies
- Hypomagnesimia

- AHT
- Insuline resistance
- Dyslipidemias

- Genetic factors
- Heart unhealthy lifestyle
- Pretransplant injuries (local RT, chemo)

What: pathogenesis

Rovo and Tichelli, Seminars Hematol, 2012
Cardiovascular complications

- Incidence: high!, after allo SCT: 2.5-4-fold ↑ risk of death due to CV causes compared to general population

_Rovo and Tichelli, Seminars Hematol, 2012_
Cardiovascular complications

**Risk factors:**
- Pre-existing general CV risk factors (diabetes, smoking, AHT, family history, hyperlipidemia)
- PreSCT exposure: Anthracyclins, mediastinal RT
- Conditioning
- Post SCT: GVHD, treatment

**Screening/Prevention:**
- Lifestyle counseling
- Screen for risk factors (blood pressure, lipids, glucose intolerance), and treat them if abnormal
- Esp risk groups: monitor for early onset heart problems (US heart, cycling test)
- In case of SS: send to cardiologist!!
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Renal complications: chronic kidney disease

- **What:** persistent ↑ serum creatinin (GFR <60 ml/’) for ≥ 3m
- **Incidence:** 4.4% at 5y post SCT (3.8% auto, 4.5% MRD, 10% MUD); per 5 year increment: risk ↑ with 33%

![Graph showing cumulative incidence of renal complications](image-url)
Renal complications: chronic kidney disease

- **Risk factors:** CNI, other nephrotoxic medications

- **Screening/Prevention:**
  - Regular testing of creat/urea/electrolytes and urinalysis
  - Regular blood pressure measurement
  - Avoid nephrotoxic drugs (e.g., NSAIDs, certain Abs)
  - Early treatment of UT infections
  - Stop CNI – replace by less nephrotoxic IS if very serious
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Malignancies

- **What:**
  - T-MDS, t-AML
  - Lymphoma, PTLD, late occurring lymphoma
  - Solid non-hematological tumors: skin cancer (BCC, SCC), breast cancer, thyroid cancer, colon ca, prostate ca…

- **Incidence:** risk x4-11 compared to general population

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A. Tichelli et al, Exp Reviews Hematol, 2009
Malignancies

**Incidence:**

- **Solid tumors**
- **MDS/AML**
Malignancies:

Risk factors:
- Age at SCT, preSCT chemo/RT, TBI (conditioning), infections with oncogenic viruses (EBV/hepB/C), prolonged IS postSCT (GVHD), GVHD (local), allo>auto

Screening/Prevention:
- Annual complete blood count (until 10y)
- PE: skin (RT), lymphadenopathies
- Females: Gynaecologist Breast exam (6m), annual mammogram/MRI
- Colon (risk groups): colonoscopy 1x/5y, starting at 35y of age or 10y post SCT
Other

- Visual impairment: >> cataract, cGVHD
- Iron overload
- Avascular necrosis

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# Impact of late effects on quality of life

## Relationship of Quality-of-Life Measures With Late Effects in 544 Survivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Prior/Contemporaneous Late Effects</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 182)</td>
<td>1 (n = 152)</td>
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<tr>
<td></td>
<td>No.</td>
<td>%</td>
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<td>Karnofsky score</td>
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<td>Mean</td>
<td>88.4</td>
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<tr>
<td>SD</td>
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<tr>
<td>Work limitations</td>
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<tr>
<td>No limit</td>
<td>70</td>
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<tr>
<td>Limited a little</td>
<td>59</td>
<td>34</td>
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<tr>
<td>Limited a lot</td>
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<td>15</td>
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<tr>
<td>Limited completely</td>
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<td>Current work status</td>
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<tr>
<td>Full-time</td>
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<td>39</td>
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<tr>
<td>Work/student</td>
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<tr>
<td>Part-time work/student</td>
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<td>Work at home</td>
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<td>Retired</td>
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<tr>
<td>Other</td>
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<td>PCS-12</td>
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<tr>
<td>&gt; 50</td>
<td>83</td>
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<td>&lt; 40</td>
<td>61</td>
<td>35</td>
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<tr>
<td>MCS-12</td>
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<tr>
<td>&gt; 50</td>
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<tr>
<td>40-50</td>
<td>26</td>
<td>15</td>
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<tr>
<td>&lt; 40</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

- Abbreviations: MCS, mental component score; PCS, physical component score; SD, standard deviation.

Khera et al, JCO, 2011
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What can we do?

1. Screening guidelines
   Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation.
   
   N. Majhail et al, BMT, 2012

2. Questionnaire

3. Create group of specialists (multidisciplinary)

4. Counselling for healthy life style

5. Involve patients in their FU care!
### Screening guidelines

**Recommended Screening/Prevention**

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Frequency</th>
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<tbody>
<tr>
<td><strong>Immunology</strong></td>
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<td>Encapsulated organism prophylaxis</td>
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<td>FCP prophylaxis</td>
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<td>CMV testing</td>
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<td>Vaccinations</td>
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<td><strong>Ocular</strong></td>
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<td>Ocular clinical symptom evaluation</td>
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<td>Ocular fundus exam</td>
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<tr>
<td><strong>Oral complications</strong></td>
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<tr>
<td>Clinical assessment</td>
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<tr>
<td>Dental assessment</td>
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<tr>
<td><strong>Respiratory</strong></td>
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<td>Clinical pulmonary assessment</td>
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<td>Smoking tobacco avoidance</td>
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<td>Pulmonary function testing</td>
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<td>Chest radiography</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<td>Cardiac and vascular risk-factor assessment</td>
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<tr>
<td><strong>Liver</strong></td>
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<td>Liver function testing</td>
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<tr>
<td>Serum ferritin testing</td>
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<td><strong>Kidney</strong></td>
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<td>Blood pressure screening</td>
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<td>Urea/creatinine screening</td>
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<tr>
<td><strong>Muscle and connective tissue</strong></td>
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<tr>
<td>Evaluation for muscle weakness</td>
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<tr>
<td>Physical activity counseling</td>
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<tr>
<td><strong>Skeletal</strong></td>
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<tr>
<td>Bone density testing (adult women, all allogeneic transplant recipients and patients at high risk for bone loss)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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<tr>
<td><strong>Nervous system</strong></td>
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<td>Neurologic clinical evaluation</td>
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<tr>
<td>Evaluate for cognitive development</td>
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<tr>
<td><strong>Endocrine</strong></td>
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<td>Thyroid function testing</td>
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<td>Growth velocity in children</td>
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</tr>
<tr>
<td>Gonadal function assessment (prepubertal men and women)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gonadal function assessment (postpubertal women)</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Gonadal function assessment (postpubertal men)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Mucocutaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin self-exam and sun exposure counseling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gynecologic exam in women</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td><strong>Second cancers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second cancer vigilance counseling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Screening for second cancers</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial/QOL clinical assessment</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sexual function assessment</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1 = recommended for all transplant recipients  
2 = recommended for any patient with ongoing chronic GVHD or immunosuppression  
+ = reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms  

N. Majhail et al, BMT, 2012
Screening guidelines

www.BeTheMatch.org/Patient
www.marrow.org/mdguidelines
Questionnaire

1. Activiteitsniveau

Duid aan welk van onderstaande beschrijvingen het best aansluit bij uw activiteitsniveau:

☐ Ik ben in staat om zonder beperking alle normale activiteiten uit te voeren.
☐ Ik ben beperkt in zware lichamelijke activiteiten, maar kan mezelf verplaatsen en ik ben in staat om lichte arbeid uit te voeren.
☐ Ik kan voor mezelf zorgen, maar ben niet in staat tot enig werk gedurende meer dan 50% van de dag.
☐ Ik ben slechts tot beperkte zelfverzorging in staat, ik verblijf meer dan 50% van de dag in bed of op een stoel.
☐ Ik ben volledig hulpbehoevend, ik verblijf de hele dag in bed of op een stoel.

2. Huid en nagels

2.1. Is er een deel van uw huid dat gespannen of opgezet aanvoelt? Duid de plaats aan op de figuur.

☐ Nooit ☐ Zelden ☐ Soms ☐ Vaak ☐ Altijd

2.2. Is er een deel van uw huid verdikt? Duid de plaats aan op de figuur.

☐ Nooit ☐ Zelden ☐ Soms ☐ Vaak ☐ Altijd

2.3. Is er een deel van uw huid dat rood of geirriteerd is? Duid de plaats aan op de figuur.

☐ Nooit ☐ Zelden ☐ Soms ☐ Vaak ☐ Altijd
There is progress!

![Graph showing survival probability over years after transplantation with two curves representing different time periods: 1993-1997 and 2003-2007.]
Overview

- Allogeneic SCT
- Late effects after allogeneic SCT
  - General
  - cGVHD
  - Infectious complications
  - Pulmonary complications
  - Endocrinologic complications – metabolic syndrome
  - Cardiovascular complications
  - Renal complications
  - Malignancies
- Quality of life
- What can we do? (screening guidelines)
- Case
Case

- Vrouw, ° 1974
- Medical history: none
- Symptoms:
  - Since a few weeks: aphtous ulcers in the mouth
  - Since 2 weeks: sinusitis, R/ antibiotics
  - Vaginal candidiasis
Case

WT1-overexpressie

% blasten

IVA1
SCT
DLI

Case
Case

- Severe acute GVHD of skin, liver and stomach: R/ corticosteroids → good response
- While tapering (slowly) corticosteroids: chronic GVHD of skin, eyes, stomach, vagina: R/ increase corticosteroids (+local corticosteroids while tapering) and start rapammune
- Frequent infections (pneumonia, sinusitis, upper airway tract infections)
- Impact on QOL, self-image, relationship
- 2013: cGVHD controlled, corticosteroids tapered to 2 mg /3 days, rapammune continued
- General condition is very good, no infections, enjoying life with her husband and two sons…
The End

If you’re going through hell, keep going.

Winston Churchill
Heaven on earth!