Transplant Complications - including VOD

Grzegorz W. Basak
Complications and Quality of Life Working Party, EBMT, Secretary
Dept. of Hematology, Oncology and Internal Diseases, the Medical University of Warsaw, Poland
Commonly used end-points of transplant studies may hide part of the truth

Transplant complications largely affect the OS, but also strongly impact the life of survivors.

Investigations and attempts to decrease the incidence and severity of complications is an obligation of every transplant physician
Causes of transplant complications

Before HSCT

Conditioning-dependent

GvHD and treatment-dependent

Patient (age, sex)

Comorbidities

Conditioning

-5 -4 -3 -2 -1 0

Donor characteristics

GvHD and immune suppression

HSC source
Transplant complications

<table>
<thead>
<tr>
<th>Pre-engraftment Days 0 - 30</th>
<th>Early post-transplantation Days 31 - 100</th>
<th>Late post-transplantation Beyond Day 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>Acute GVHD</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td></td>
<td>Hepatic VOD</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td></td>
<td>Neutropenic colitis</td>
<td></td>
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<tr>
<td></td>
<td>Hemorrhagic cystitis</td>
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<tr>
<td></td>
<td>Engraftment syndrome</td>
<td>LIP</td>
</tr>
<tr>
<td></td>
<td>DAH</td>
<td>OB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of PTLD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of MDS/leukemia</td>
</tr>
</tbody>
</table>
Natural history of transplant complications

Early complications

Late complications

- Delayed events
- Late events
- Very late events

0 3 months 2 years 10 years
# Early transplant complications

- Direct toxicity of chemo/radiotherapy
- "Endothelial syndromes"
- Acute graft versus host disease
- HSC graft failure
- Side effects of drugs used for immune suppression and antimicrobials
Early transplant complications – direct toxicity of conditioning regimen

- Nausea, vomiting, diarrhoea
- Mucositis
- Pain
- Hemorrhagic cystitis
Mucositis
Early transplant complications – direct toxicity of conditioning regimen

**Causes**
- Chemo/radiotherapy
- Methotrexate
- Xerostomy
- Infections
- Acute GvHD

**Symptoms**
- Mucositis
- Pain
- Diarrhoea
- Abdominal discomfort
- Electrolyte disturbances
Mucositis – grading systems:

<table>
<thead>
<tr>
<th>Table 3: Scales Used to Assess OM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
</tr>
<tr>
<td>WHO</td>
</tr>
<tr>
<td>RTOG</td>
</tr>
<tr>
<td>NCI CTC</td>
</tr>
<tr>
<td>OMAS Ulceration/erythema</td>
</tr>
</tbody>
</table>

OM: oral mucositis; WHO: World Health Organization; RTOG: Radiation Therapy Oncology Group; ±: with or without; NCI CTC: National Cancer Institute Common Toxicity Criteria; NA: not applicable.

Source: References 8-10, 12.

Can’t eat
Can’t drink
Mucositis – treatment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route/Dose/Frequency</th>
<th>MOA</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palifermin</td>
<td>IV: 60 mcg/kg/day for three consecutive days before and after myelotoxic therapy; total of 6 doses</td>
<td>Recombinant KGF; binds to KGF receptor, resulting in proliferation, differentiation, and migration of epithelial cells in tongue, buccal mucosa, esophagus, and salivary glands</td>
<td>Rash, edema, fever, taste alteration, hypertension</td>
</tr>
<tr>
<td>Amifostine</td>
<td>IV: 200 mg/m²/day over three min, 15-30 min before RT</td>
<td>Its active metabolite binds to and detoxifies reactive metabolites of cisplatin; also scavenges free radicals generated in tissues</td>
<td>Hypotension, NV</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Oral rinse; 15 mL undiluted solution as gargle or rinse 3-4 times/day</td>
<td>Local anesthetic, anti-inflammatory</td>
<td>Local numbness, burning/tingling sensation, NV</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Oral: 10 mL (1 g/10 mL suspension); swish and spit/swallow 4 times/day</td>
<td>Forms complex by binding with positively charged proteins in exudates, forming a viscous, pastelike, adhesive substance; this selectively forms a protective coating that acts locally to protect gastric lining against peptic acid, pepsin, and bile salts</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

OM: oral mucositis; MOA: mechanism of action; KGF: keratinocyte growth factor; min: minute; RT: radiotherapy; NV: nausea and vomiting.
Source: Reference 14.
Early transplant complications – direct toxicity of conditioning regimen:

**Hemorrhagic cystitis**
Early transplant complications – direct toxicity of conditioning regimen:

Hemorrhagic cystitis

Conditioning CTX-TBI → "0" → Mucositis → Infections → Aplasia → GvHD prophylaxis

Engraftment → Acute GvHD

SCT

Early onset: <72h from treatment
Caused by: Cyclophosphamide, busulfan, etoposide or TBI

Late onset: > 2 weeks after alloSCT
Multifactorial
Viral infections: polyomavirus BK or JC, or: adenovirus type 11 or CMV
Early transplant complications – direct toxicity of conditioning regimen:

Hemorrhagic cystitis

Grading

• grade 0 = none;
• grade I = microscopic hematuria with urinary symptoms;
• grade II = macroscopic hematuria;
• grade III = macroscopic hematuria with clots; and
• grade IV = macroscopic hematuria with intervention for clot evacuation and/or urinary retention
Early transplant complications – direct toxicity of conditioning regimen: Hemorrhagic cystitis

**Prophylaxis**

- Hydration
- Mesna (for cyclophosphamide)
- Early detection, viral tests, ciprofloxacin

**Treatment**

- Hydration
- Platelet transfusion
- Bladder irrigation
- Invasive urological procedures
- Late: antivirals (cidofovir, ganciclovir), ciprofloxacin
Early transplant complications – endothelial syndromes

- Venoocclusive disease (VOD/SOS)
- Capillary leak syndrome
- Transplant-associated microangiopathy (TAM)
- Engraftment syndrome
- Idiopathic pneumonia
- Diffuse alveolar hemorrhage
Early transplant complications – endothelial syndromes

Common pathogenesis of the vascular endothelial syndromes developed early after HSCT.
CLS, capillary leak syndrome; CNI, calcineurin inhibitors; DAH, diffuse alveolar haemorrhage; ES, engraftment syndrome; IPS, idiopathic pneumonia syndrome; LPS, lipopolysaccharide; TAM, transplant-associated microangiopathy; VOD, veno-occlusive disease.
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)
Liver provides detoxication systems to the body
Some of them are used to detoxify the chemotherapeutic drugs but also, accidentally, to produce toxic metabolites of chemotherapeutic agents.
Example:

**Non-toxic** metabolite of cyclophosphamide

**Toxic** metabolite of cyclophosphamide

Cyclophosphamide
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

- Sinusoids are surrounded by zone 3 of hepatic acinus
- So, there accumulate toxic metabolites of e.g. cyclophosphamide, which is further increased by impaired detoxication mechanisms
- The endothelium of hepatic sinusoids is affected
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)
Current understanding of Tx related VOD

Conditioning regimen
chemo/DXT

Endothelial cell and hepatocellular damage
Direct and cytokine mediated e.g. TNFa, IL1b, IL-6, etc.

↑ INFLAMMATION and release of TF/reduced TF inhibitor + increased ICAM-1 etc. Attached monocytes and neutrophils release further cytokines

↑ COAGULATION triggered by TF

↓ FIBRINOLYSIS by release of PAI-1 + ↓ tPA

Fibrin deposition
Hepatic venous outflow obstruction

VOD
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

- Clinical consequences (symptoms):
  - HEPATOMEGALY
  - FLUID RETENTION
  - HYPERBILIRUBINEMIA

Usually develops within 21 days from HSCT
## Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

### Diagnostic Criteria

<table>
<thead>
<tr>
<th>Before the day +21</th>
<th>Seattle*</th>
<th>Baltimore**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice (bilirubin &gt;2 mg/dl)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>&gt;2%*, &gt;5%** increase in body weight caused by fluid retention</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ascites</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Clinical criteria</strong></td>
<td><strong>2</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

- Up to 30 per cent may develop VOD with no (Seattle criteria) or too late hyperbilirubinaemia
- Close to 30 percent of the cases occur after day +21 and about ten per cent after day +30
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

Severity of VOD

- **Mild**
  - no apparent adverse effects of liver disease
  - no need for medications for diuresis or hepatic pain
  - completely reversible signs, symptoms and laboratory abnormalities

- **Moderate**
  - adverse effects from liver disease
  - requirement of sodium restriction and diuretics
  - requirement of medication for pain from hepatomegaly
  - complete resolution of all signs of liver damage

- **Severe**
  - adverse effects from liver disease
  - signs, symptoms and laboratory values do not resolve before day +100
  - ± multiorgan failure (MOF)
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

Outcome of VOD

• Depends largely on the severity grade (which again is defined by the outcome.....)

• Severe VOD is a serious disorder, usually with poor outcome

• Patients often have other concomitant complications

Figure 2. Kaplan-Meier survival curve for retrospective historical controls with severe VOD (MOF) (n = 38).

Coppel et al 2010
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)
Risk factors

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Transplant-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• MUD vs MRD vs autoSCT</td>
</tr>
<tr>
<td>• Sex</td>
<td>• PBSCT vs BM</td>
</tr>
<tr>
<td>• Comorbidities</td>
<td>• CONDITIONING</td>
</tr>
<tr>
<td>• Disease stage</td>
<td>• Second transplant</td>
</tr>
<tr>
<td>• Earlier liver disorders</td>
<td>• Hepatotoxicity of drugs</td>
</tr>
<tr>
<td>• Previous liver irradiation</td>
<td></td>
</tr>
<tr>
<td>• Previous fungal infections</td>
<td></td>
</tr>
<tr>
<td>• General status</td>
<td></td>
</tr>
<tr>
<td>• CMV</td>
<td></td>
</tr>
</tbody>
</table>
Prophylaxis:

- Delay HSCT in case of hepatitis
- TBI: decrease the dose, fractionate the dose
- Avoid cyclophosphamide and oral busulfan (Bu)
- Cy/Bu: adjust the dose of Bu or use Bu iv.
- Avoid hepatotoxic drugs
- Consider RIC-SCT
- **Use ursodeoxycholic acid for prophylaxis**
Venoocclusive Disease (VOD)/Sinusoid Obstruction Syndrome (SOS)

TREATMENT

• Symptomatic:
  - Decrease intake of salt and water
  - Maintain the intravascular volume and renal perfusion (albumins, plasma, transfusions)

• Specific:
  - Diuretics
  - PGE-1; heparin (?)
  - rt-PA (efficient in <30% patients)
  - Defibrotide …
Venoocclusive Disease (VOD)/
Sinusoid Obstruction Syndrome (SOS)

Defibrotide (Defitelio)

- Sodium salt of a mixture of single-stranded polydeoxyribonucleotides
- Prepared by controlled depolymerisation of deoxyribonucleic acid (DNA) obtained from porcine intestinal mucosa
- Intravenous administration
- Registered in Europe for the treatment of severe VOD (SOS)
Transplant-associated microangiopathy (TAM)

Hemolytic anemia with schistocytes

Thrombocytopenia
Diagnostic criteria (International Working Group)

- All of them must be fulfilled:
  - >4% schistiiocytes in blood smear
  - *De novo* or prolonged thrombocytopenia
  - Rapid increase in LDH
  - Decrease in hemoglobin concentration or increased demand for RBC transfusion
  - Decreased haptoglobin concentration

Ruutu et al. Haematologica 2007
Transplant-associated microangiopathy (TAM)

- **INCIDENCE:**
  - Auto-SCT: <4%
  - Allo-SCT: up to 15%

- **RISK FACTORS**
  - Calcineurin inhibitors (CsA, tacrolimus) or sirolimus
  - MUD or mMUD
  - GvHD, CMV or fungal infection

- **Prophylaxis**
  - 2-3 x/week: LDH activity, creatinine

- **Treatment**
  - Stop taking calcineurin inhibitors, take steroids or MMF instead
  - Anti-TNF (etanercept, infliximab), defibrotide, rituximab, daklizumab
Acute graft versus host disease (GvHD)

• Attack of donor’s immune cells towards the recipient of hematopoietic stem cell product;
• Donor’s lymphocytes attack mainly 3 important organs:
  - SKIN
  - LIVER
  - GI TRACT
  - RASH
  - JAUNDICE
  - VOMITING, DIARRHOEA
## Acute graft versus host disease (GvHD)

### SKIN

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SKIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&lt;25% body surface area</td>
</tr>
<tr>
<td>++</td>
<td>25-50% body surface area</td>
</tr>
<tr>
<td>+++</td>
<td>Generalized erythroderma</td>
</tr>
<tr>
<td>++++</td>
<td>Generalized erythroderma with bullae formation and desquamation</td>
</tr>
</tbody>
</table>
Acute graft versus host disease (GvHD)

**GUT**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Gut/diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt;500 ml</td>
</tr>
<tr>
<td>++</td>
<td>&gt;1000 ml</td>
</tr>
<tr>
<td>+++</td>
<td>&gt;1500 ml</td>
</tr>
<tr>
<td>++++</td>
<td>Severe abdominal pain with or without ileus</td>
</tr>
</tbody>
</table>
Acute graft versus host disease (GvHD)

**LIVER**

<table>
<thead>
<tr>
<th>Stage</th>
<th>LIVER/BILLIRUBIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>34-50 umol/l</td>
</tr>
<tr>
<td>++</td>
<td>51-102 umol/l</td>
</tr>
<tr>
<td>+++</td>
<td>103-255 umol/l</td>
</tr>
<tr>
<td>++++</td>
<td>&gt;255 umol/l</td>
</tr>
</tbody>
</table>
## Grading of acute GvHD (Glucksberg scale)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Organ stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>skin: + to ++</td>
</tr>
</tbody>
</table>
| II    | skin: + to +++  
Gut and/or liver: +  
Mild decrease in performance |
| III   | Skin: ++ to +++  
Gut and/or liver: ++ to +++  
Marked decrease in performance |
| IV    | Skin: ++ to ++++  
Gut and/or liver: ++ to +++  
Extreme decrease in performance |
Risk factors of aGvHD development

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HLA mismatch</td>
<td>1. Age</td>
</tr>
<tr>
<td>2. Gender mismatch</td>
<td>2. Conditioning</td>
</tr>
<tr>
<td>3. Alloimmunisation (pregnancy, transfusions)</td>
<td>3. GvHD prophylaxis</td>
</tr>
<tr>
<td>4. Stem cell source (PBSC&gt;BM&gt;CB)</td>
<td></td>
</tr>
</tbody>
</table>
Standards:

• For myeloablative conditioning:
  - Cyclosporine A – at least for 6 months
  - Methotrexate: infusions on day +1, +3, +6 and +11

• For RIC:
  - Cyclosporine A – at least for 6 months
  - Mofetil mycophenolate (MMF) for 1-3 months

Acute GvHD: Prophylaxis
Acute GvHD treatment

**aGvHD**

- **Grade I**
  - Optimize the dose of CsA and topical treatments (e.g. steroids)

- **Grade II**
  - Initiate **methylprednisolone**: 1 mg/kg po./IV.
  - Optimize the dose of CsA and topical treatments (e.g. steroids)

- **Grade III**
  - Initiate **methylprednisolone**: 2 mg/kg po./IV.
  - Optimize the dose of CsA and topical treatments (e.g. steroids)
Acute GvHD treatment

Acute GvHD – 3-4°

1-line
- Optimize the dose of CsA
- Methylprednizolone: 2 mg/kg
- Skin: topical steroids
  Diarrhoea: Budesonide

When lack of response after 7 days or progression after 5 days

Alternatively: clinical trial

2-line
- Extracorporeal photopheresis
- Anti-IL-2R
- anti-TNF
- MTOR inhibitors
- MMF

3-line
- Methotrexate
- Pentostatin
- Mesenchymal stem cells
- Alemtuzumab
Engraftment failure

• Usually, engraftment is observed after 2-3 weeks from PBSCT, 3-4 weeks after BMT and 4-6 weeks after UCBT

• Engraftment failure (in case of PBSCT and BMT) is defined as lack of any signs of neutrophil or platelet regeneration 28 days after HSCT

• Is a consequence of too low number of transplanted HSCs, their low viability, BM stroma dysfunction etc.

• **Treatment**: transplantation of additional portion of stem cell product from the same donor, without conditioning
Inability to establish long-term hematopoiesis of donor’s origin, because of immune attack of recipient’s lymphocytes towards donor’s hematopoietic stem cells. Occurs as a result of sensitization of recipient to antigens of donor’s stem cell product, usually long before transplantation (e.g. by blood transfusions, pregnancies etc.). May be hyperacute: there is no regeneration of hematopoiesis (exactly like in engraftment failure). But may have delayed onset, especially after RIC conditioning.

Treatment: ASAP transplantation of PBSCs from another donor after strongly immunosuppressive conditioning.
Natural history of transplant complications

Early complications

- Delayed events
- Late events
- Very late events

Organ involved
- Lungs
- Kidneys
- Cardiovascular system
- Secondary cancers

Major risk factor
- Chronic GvHD
- Calcineurin inhibitors
- Cardiovascular risk factors
- TBI

Late complications may affect any organ or tissue.
Relapse is the main cause of mortality, even long-term after alloSCT, but it’s frequency decreases with time

Main reasons of death in long-term (> 5 y.) survivors of alloHSCT

- Relapse: 44%
- cGvHD: 18%
- Infection: 8%
- Secondary cancer: 5%
- Late pulmonary toxicity: 4%
- Late cardiac toxicity: 3%
- Other causes: 18%

Secondary cancers after alloSCT

- 3-30 x increase in incidence compared with remaining population;
- None of cancers is characteristic for this group of patients

Incidence of secondary cancers increases in time after alloSCT, especially after long-term follow up
Chronic GvHD

Acute GVHD:
Red skin rash, GI symptoms, liver

Chronic GVHD
Skin, eyes, mouth, gastrointestinal, liver, musculoskeletal, lung, genitourinary

NIH
Mild
Moderate
Severe

3-48%
13-82%

Day 0 50 100 180 1 y 2 y 3 y 5 y
Inflammation Injury Repair Healing or Damage

Pavletic S Z, and Fowler D H Hematology 2012;2012:251-264
Differences between acute and chronic GvHD

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of diagnosis</th>
<th>Acute GvHD symptoms</th>
<th>Chronic GvHD symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute</td>
<td>≤100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, refractory or late onset acute GvHD</td>
<td>&gt;100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlapp syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Chronic GvHD (cGvHD)

• The most serious long-term complication of alloSCT;
  – Resembles different autoimmune disorders
  – 30-70% of long-term survivors
  – Main reason of non-relapse mortality (NRM) >2 years after HSCT
  – 90% cases diagnosed within 1 year
  – Median time of treatment: 1-3 years

• Both cGvHD and its treatment increase rate of other complications;
### cGvHD

- **Frequency of involvement of organs and tissues**

- **Skin**: 80%
- **Oral**: 75%
- **Liver**: 75%
- **Infections**: 60%
- **Eyes**: 48%
- **Muscles and fascia**: 10%
- **Intestinal**: 12%
- **Cachexia**: 18%
- **Lungs**: 10%
- **Esophagus**: 5%
- **Contractions**: 5%
cGvHD

- Lichen sclerosus
- Scleroderma-like
- Conjunctivitis
- Corneal scarring
Signs and symptoms of cGvHD (according to NIH consensus)

• **Diagnostic signs and symptoms**
  – manifestations that establish the presence of chronic GVHD without the need for further testing or evidence of other organ involvement.

• **Distinctive signs and symptoms** of chronic GVHD
  – manifestations that are not ordinarily found in acute GVHD but are not considered sufficient to establish an unequivocal diagnosis of chronic GVHD without further testing or additional organ involvement.

• **Other features** of chronic GVHD
  – rare, controversial, or nonspecific features of chronic GVHD that cannot be used to establish the diagnosis of chronic GVHD.

• **Common signs and symptoms** of chronic GVHD
  – manifestations found in both chronic and acute GVHD
Criteria of cGvHD diagnosis (NIH)

1. Distinction from acute GVHD.

2. Presence of at least:
   - 1 diagnostic clinical sign of chronic GVHD or
   - presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests.

3. Exclusion of other possible diagnoses.
<table>
<thead>
<tr>
<th>Organ or Site</th>
<th>Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)</th>
<th>Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)</th>
<th>Other Features*</th>
<th>Common (Seen with Both Acute and Chronic GVHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Poikiloderma</td>
<td>Depigmentation</td>
<td></td>
<td>Sweat impairment</td>
</tr>
<tr>
<td></td>
<td>Lichen planus-like features</td>
<td></td>
<td>Ichthyosis</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Sclerotic features</td>
<td></td>
<td>Keratosis pilaris</td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Morphea-like features</td>
<td></td>
<td>Hypopigmentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen sclerosus-like features</td>
<td></td>
<td>Hyperpigmentation</td>
<td></td>
</tr>
<tr>
<td>Nails</td>
<td></td>
<td>Dystrophy</td>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Longitudinal ridging, splitting, or brittle features</td>
<td></td>
<td>Maculopapular rash</td>
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<tr>
<td></td>
<td></td>
<td>Onycholysis</td>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pterygium unguis</td>
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<tr>
<td></td>
<td></td>
<td>Nail loss (usually symmetric; affects most nails)†</td>
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</tr>
<tr>
<td>Scalp and body hair</td>
<td></td>
<td>New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy)</td>
<td></td>
<td>Thinning scalp hair, typically patchy, coarse,</td>
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<tr>
<td></td>
<td></td>
<td>Scaling, papulosquamous lesions</td>
<td></td>
<td>or dull (not explained by endocrine or other</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>causes)</td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen-type features</td>
<td>Xerostomia</td>
<td></td>
<td>Gingivitis</td>
</tr>
<tr>
<td></td>
<td>Hyperkeratotic plaques</td>
<td>Mucocele</td>
<td></td>
<td>Mucositis</td>
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<tr>
<td></td>
<td>Restriction of mouth opening from sclerosis</td>
<td>Mucosal atrophy</td>
<td></td>
<td>Erythema</td>
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<tr>
<td></td>
<td></td>
<td>Pseudomembranes†</td>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulcers†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ or Site</td>
<td>Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)</td>
<td>Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)</td>
<td>Other Features*</td>
<td></td>
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<td>----------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Poikiloderma</td>
<td>Depigmentation</td>
<td>Sweat impairment, Ichthyosis, Keratosis pilaris, Hypopigmentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen planus-like features</td>
<td></td>
<td>Erythema, Maculopapular rash, Pruritus</td>
<td></td>
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<tr>
<td></td>
<td>Sclerotic features</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Morphea-like features</td>
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<tr>
<td></td>
<td>Lichen sclerosus-like features</td>
<td></td>
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<tr>
<td>Nails</td>
<td>Dystrophy</td>
<td>Longitudinal ridging, splitting, or brittle features</td>
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<tr>
<td></td>
<td></td>
<td>Onycholysis</td>
<td></td>
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<td></td>
<td></td>
<td>Pterygium unguis</td>
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<td></td>
<td></td>
<td>Nail loss (usually symmetric; affects most nails)†</td>
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<tr>
<td>Scalp and body hair</td>
<td>New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy)</td>
<td>Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)</td>
<td>Premature gray hair</td>
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<tr>
<td></td>
<td>Scaling, papulosquamous lesions</td>
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<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen-type features</td>
<td>Xerostomia</td>
<td>Gingivitis</td>
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<td>Mucosae</td>
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<td></td>
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</tr>
<tr>
<td>Organ or Site</td>
<td>Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)</td>
<td>Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)</td>
<td>Other Features*</td>
<td>Common (Seen with Both Acute and Chronic GVHD)</td>
</tr>
<tr>
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<td>---------------------------------------------</td>
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<tr>
<td>Hematopoietic and immune</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<td></td>
<td></td>
<td></td>
<td>Eosinophilia</td>
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<td></td>
<td></td>
<td></td>
<td>Lymphopenia</td>
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<td></td>
<td></td>
<td></td>
<td>Hypo- or hypergammaglobulinemia</td>
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<td></td>
<td>Autoantibodies (AIHA and ITP)</td>
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<td></td>
<td></td>
<td></td>
<td>Pericardial or pleural effusions</td>
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<td></td>
<td></td>
<td></td>
<td>Ascites</td>
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<td></td>
<td></td>
<td></td>
<td>Peripheral neuropathy</td>
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<td></td>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
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<td></td>
<td></td>
<td></td>
<td>Myasthenia gravis</td>
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<td></td>
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<td></td>
<td>Cardiac conduction abnormality or cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>
Bronchiolitis obliterans syndrome (BOS): frequency 5-15%
- fibrosis
- dyspnoea, cough, especially on exertion
- CT: bronchiectases, "air trapping" (increased aeration of small areas within the lung seen at the end of expiration)

Bronchiolitis obliterans organizing pneumonia, BOOP/COP (cryptogenic organizing pneumonia)
- dyspnoea, cough, fever
- CT: patchy „milk glass” lesions and nodules
Global scoring system of cGvHD (NIH)

A clinical **scoring system** (0-3) is provided for evaluation of the involvement of individual organs and sites.

**Mild chronic GVHD:**
- involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites).

**Moderate chronic GVHD:**
1. at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or
2. 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites).
3. A lung score of 1 will also be considered moderate chronic GVHD.

**Severe chronic GVHD:**
- indicates **major disability** caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.
Global scoring system of cGvHD has prognostic significance
Seattle Classification of Chronic GVHD (unconfirmed significance but widely used in practice)

- **Limited**
  - Localized skin and/or hepatic dysfunction due to cGVHD

- **Extensive**
  - Generalized skin involvement
  - Localized skin involvement and/or hepatic dysfunction plus liver histology or cirrhosis or involvement of eye or minor salivary glands or oral mucosa or any other target organ
### Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Recomm.</th>
<th>Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td>A</td>
<td>I</td>
<td>Most important drug in cGVHD, monotherapy in mild cGVH, otherwise combined with CNI</td>
</tr>
<tr>
<td>Cyclosporin / (Tacrolimus) + Steroid</td>
<td>C-1</td>
<td>II</td>
<td>Steroid-sparing effect</td>
</tr>
<tr>
<td>MMF + Steroid</td>
<td>C-1</td>
<td>III-1</td>
<td>Increased risk for viral infections</td>
</tr>
<tr>
<td>MMF + Steroid + CNI</td>
<td>D</td>
<td>II</td>
<td>No improved efficacy compared to CNI + steroids alone</td>
</tr>
<tr>
<td>Therapy</td>
<td>Rec.</td>
<td>Evid.</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Steroid</td>
<td>B</td>
<td>III-1</td>
<td>Serious side effects</td>
</tr>
<tr>
<td>Photopheresis</td>
<td>C-1</td>
<td>II</td>
<td>Steroid-sparing, excellent safety profile</td>
</tr>
<tr>
<td>mTOR – Inhib.</td>
<td>C-1</td>
<td>III-1</td>
<td>↑ TAM with CNI</td>
</tr>
<tr>
<td>Cyclosporin / FK506</td>
<td>C-1</td>
<td>III-1</td>
<td>Spare steroids</td>
</tr>
<tr>
<td>MMF</td>
<td>C-1</td>
<td>III-1</td>
<td>↑ viral infections, GI toxicity</td>
</tr>
<tr>
<td>Imatinib</td>
<td>C-2</td>
<td>III-1</td>
<td>Best in sclerodermoid GvHD and BO</td>
</tr>
<tr>
<td>Rituximab</td>
<td>C-2</td>
<td>II</td>
<td>Effective in autoAB mediated diseases</td>
</tr>
<tr>
<td>Total nodal Rx</td>
<td>C-2</td>
<td>III-2</td>
<td>Best in fasciitis and mucocutaneous cGvHD</td>
</tr>
</tbody>
</table>
Cardiovascular late complications

Patients, who survived alloSCT have elevated risk of developing diabetes, hypertension, lipid disorders and metabolic syndrome

### Risk of cardiovascular event after alloSCT correlates with risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV event</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with</td>
<td>without</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (70%)</td>
<td>59 (13%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (25%)</td>
<td>26 (6%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (58%)</td>
<td>65 (15%)</td>
</tr>
<tr>
<td>BMI ≥ 25 mg/m2</td>
<td>10 (56%)</td>
<td>128 (33%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (41%)</td>
<td>49 (12%)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>12 (75%)</td>
<td>142 (44%)</td>
</tr>
</tbody>
</table>

Gonadal toxicity

- **Women:** HSCT affects fertility directly and impairs hormonal balance causing hypergonadotrophic hypogonadism (high FSH, LH);

- **Men:** Leidig cells usually survive and testosterone secretion is spared
  - Azoospermia rate:
    - almost 100% after TBI,
    - 50% after BuCy
    - 10% after Cy.
  - After years, spermatogenesis may recover, even after TBI
The pattern of early and late complications is changing

- Less TBI used;
- More frequently RIC conditioning;
- More unrelated donors;
- More haploidentical transplants
- More frequently transplantation in the elderly;
- Better prevention and treatment of infectious complications;
Complications after alloSCT

• AlloSCT frequently means trading one disease for the other;
• We must be responsible for our patients who we encourage to go into transplant;
• Posttransplant care is multidisciplinary and the number of problems (and possibly studies) is unlimited…