Complications of Hematopoietic Stem Cell Transplantation Requiring Intensive Care

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Disclosures

- Clinical Trial Grant Support
  - Spectral Diagnostics (Septic shock trial)
  - Bayer HealthCare (Aerosolized amikacin for Gram-neg pneumonia in ventilated pts)
  - Asahi-Kasei (Thrombomodulin sepsis trial)
- Advisory Board
  - Theravance Biopharma
  - Bayer HealthCare

Indications for Hematopoietic Cell Transplant in the US, 2014

Annual Number of HCT Recipients in the US by Transplant Type
Allogeneic vs Autologous Stem Cell Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Autologous</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Donor readily available</td>
<td>Immunotherapy (GvL-GvTumor) on top of cytoreductive Rx</td>
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<tr>
<td></td>
<td>No GvHD</td>
<td>No tumor cell transplantation</td>
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<tr>
<td><strong>Disadvantages</strong></td>
<td>No GvL-GvTumor</td>
<td>Matching process</td>
</tr>
<tr>
<td></td>
<td>Graft potentially contaminated</td>
<td>aGvHD-cGvHD</td>
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<td></td>
<td>Late toxicity</td>
<td>Late toxicity</td>
</tr>
<tr>
<td><strong>RESULT</strong></td>
<td>LOWER TRM INCREASED RR</td>
<td>RESULT: HIGHER TRM DECREASED RR</td>
</tr>
</tbody>
</table>

Stem Cell Sources
- Bone marrow
- Peripheral blood (most common)
  - More rapid hematologic reconstitution
  - More GVHD
- Cord blood
  - Less GVHD but slow hematologic and immunologic reconstitution

Types of Conditioning Regimen
- Myeloablative: classical form
  - Prolonged period of pancytopenia
- Nonmyeloablative (“mini”) or reduced intensity
  - Less early post-transplant morbidity
  - Allows older patients to receive HSCT (CLL, MM, HL)
  - 20% of all allogeneic HSCTs

Allogeneic HCT Recipients in the US, by Donor Type

Types of Conditioning Regimen
- Myeloablative: classical form
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  - 20% of all allogeneic HSCTs
Causes of BMT Morbidity and Mortality

Early
- Mucositis
- Infection due to neutropenia
- Hemorrhagic Cystitis
- Cardiomyopathy
- Sinusoidal obstruction disease
- Graft rejection
- Graft-Versus-Host Disease
- Opportunistic infection
- EBV-PTLD
- Disease Recurrence
- Endocrine: growth, infertility, Cataracts, caries
- Secondary Malignancies

Late

Timeline of Noninfectious Complications

Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation

Improvements in HSCT

- Reduced intensity conditioning
- Better antimicrobial prophylaxis
- Pre-emptive therapy of CMV infections
- Improved antifungal therapy
- Improvements in intensive care
- Early use of noninvasive ventilation
- Early goal-directed therapy for septic shock
- Better patient selection
- Improved recognition of clinical deterioration & earlier ICU admission
- Use of palliative care for pts with a slim chance of recovery

Regimen Toxicity

- Regimen intensity
  - Myeloablative
  - Reduced intensity
  - Non-myeloablative

- Common Toxicities
  - Side effects of radiation and chemotherapy
  - Organ Toxicity
    - Mucositis
    - Bone marrow
    - Lung
    - Heart
    - Kidney
    - Liver
    - Nervous system

Organ Toxicity and Supportive Care

- Marrow toxicity
  - Neutropenia: factor support
  - Anemia: transfusional support
  - Thrombocytopenia: transfusional support

- Mucositis
  - Incidence and severity associated with regimen intensity & patient characteristics
  - Associated with pain & compromised nutritional intake
  - Management: Palifermin, oral care, pain control, TPN

- Nutritional Support

Pulmonary Complications after HSCT

- Engraftment syndrome
- Diffuse alveolar hemorrhage
- Idiopathic pneumonia syndrome
- Bronchiolitis obliterans

Engraftment Syndrome

- Seen primarily in autologous HSCT (7-10%)
- Develops 7-12 days post HSCT, around time of neutrophil recovery
- Associated with increased capillary leak
- Clinical presentation: dyspnea, fever and erythematous maculo-papular rash
- Chest imaging: bilateral ground-glass opacities, hilar or peri-bronchial consolidation
- Treatment: short course methylprednisolone 1mg/kg q12h
**Diffuse Alveolar Hemorrhage (DAH)**

- Incidence 2%-14% but with high mortality (>75%)
- Associated with infection, diffuse alveolar damage
- Clinical presentation: dyspnea, tachypnea, and hypoxia; hemoptysis is rare
- Chest imaging: patchy or diffuse opacities with air bronchograms
- Diagnosis: BAL - progressively hemorrhagic returns
- Treatment: moderate-high dose steroids + transfusion support, aminocaproic acid or recombinant human factor VII (refractory cases)


**Diffuse Alveolar Hemorrhage**

*Am J Roentgenol 1991;157(3):461-4*

**Idiopathic Pneumonia Syndrome**

- Evidence of diffuse lung injury after allogeneic transplant for which an infectious etiology is not identified.
- Incidence rate: 4-12%; median time of onset between 20 and 120 days after HSCT.
- Risk factors: old age, transplant for malignancy other than leukemia, pretransplant chemotherapy, TBI, GVHD, and (+) donor CMV serology.
- Diagnosis of exclusion.
- Treatment: high-dose steroids; etanercept (anti-TNF)
- Overall mortality: 50-90%, higher in pts requiring mechanical ventilation.

*Alissa B. Peters SG. Curr Opin Oncol 2008;20:227-33*

**Bronchiolitis Obliterans**

- Late (> 100 days) noninfectious complication after allo-HSCT
- More common after PBSCT, conventional myeloablative conditioning, & with busulfan-based prep regimens
- Risk factors: chronic GVHD, older age, airflow obstruction before transplant, & respiratory viral infections in 1st 100 days.
- Dry cough, dyspnea, wheezing, sinusitis
- Areas of hypoattenuation interspersed with ground-glass appearance on CT (“mosaic”)
- Treatment: high-dose steroids; reinstitution or augmentation of immunosuppressive agents; macrolides, inhaled steroids and montelukast

Cardiac Toxicity

- Pre-existing cardiac condition (coronary artery disease, prior regimen-related toxicity, disease-related – e.g. amyloidosis)
- Cardiomyopathy
  - Pre-existing
  - Related to specific drugs (e.g. cyclophosphamide)
- Arrhythmias
  - Pre-existing
  - Related to specific drugs (QTc prolongation)
  - Electrolyte abnormalities
- Hypertension
  - Calcineurin inhibitors

Acute Renal Toxicity

- Most common causes:
  - Acute tubular necrosis (ATN)
  - Drugs: calcineurin inhibitors, amphotericin B, aminoglycosides
  - Sinusoidal obstructive syndrome (SOS)
- Less common:
  - Tumor lysis syndrome
  - Thrombotic microangiopathy
  - Hemolysis due to ABO incompatibility
- Often multifactorial

Hepatic Sinusoidal Obstruction Syndrome (SOS) or VOD

- Triad:
  - Hepatomegaly with RUQ pain
  - Third spacing fluid retention, often including ascites
  - Jaundice (total bilirubin > 2.0 with cholestatic picture)
- Ancillary features:
  - Weight gain (>10%)
  - Increased platelet transfusion requirements
  - Coagulopathy
- Incidence:
  - Estimates vary from ~10-50%, per clinical criteria used.
  - Fatality high

SOS – Pathophysiology

- Damage to the endothelial lining of hepatic sinusoids
- Intrahepatic thrombosis and hemostasis
- Centrilobular hemorrhagic necrosis – this distinguishes lesion from (alcoholic) cirrhosis that involves portal triad
  - Portal vein obstruction
  - Liver failure with coagulopathy
  - Hepatorenal syndrome with hyperaldosterone state

SOS – Risk Factors and Diagnosis

• Risk Factors:
  – Preexisting liver conditions: Hepatitis (viral, drug-induced), Cirrhosis
  – Prior therapy: Second transplant, significant therapy prior
  – Conditioning regimen: Ablative regimens (high-doses of radiation therapy, use of busulfan), sirolimus in patients undergoing ablative transplants

• Diagnosis:
  – Clinical suspicion
  – Ultrasound: ascites, abnormal portal vein waveform, reversal of flow in the portal vein, increased hepatic artery resistance index.
  – Liver biopsy

SOS - Treatment

• Prevention:
  – Low-dose heparin
  – Ursodeoxycholic acid (Ursodiol)
  – Defibrotide (in high-risk children)

• Treatment:
  – Supportive care (euvolemia, avoid hepatotoxins, pain control, paracentesis)
  – Defibrotide: 20%-30% response rate
    • 6.25 mg/kg IV q 6h x 21 days
  – No role for TPA/heparin, antithrombin

Neurological Complications

• Infections
• Chemotherapy toxicity: fludarabine
• Calcineurin inhibitors (CNI) toxicity

Posterior reversible encephalopathy syndrome (PRES)

Richardson PG, et al. BBMT 2010;16:1005-17
Mosekilde et al. BMT 2007; 39:653-4
Graft-versus-Host Disease

- 30-70% of allogeneic HSCT develop GVHD.
- Acute
  - < 100 days (usually 30-40)
  - Skin, liver, GI tract
  - T cell and cytokine mediated
- Chronic
  - 100 days
  - “autoimmune like” syndrome
  - B cell mediated
- Overlap Syndrome

GVHD Risk Factors

- Degree of HLA-mismatch
- # T cells in graft
- Age of recipient (and donor)
- Gender
- Parity of donor
- Intensity of conditioning regimen
- CMV and other co-infections
- Source of stem cells

Acute GVHD: Clinical Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin (extent of rash)</th>
<th>Liver (Bilirubin)</th>
<th>LGI tract (Volume diarrhea/day)</th>
<th>UGI tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% BSA</td>
<td>2.1 – 3 mg/dL</td>
<td>501 – 1000 mL</td>
<td>Persistent nausea, vomiting, or anorexia</td>
</tr>
<tr>
<td>2</td>
<td>25-50% BSA</td>
<td>3.1 – 6 mg/dL</td>
<td>1001 – 1500 mL</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;50% BSA</td>
<td>6.1 – 15 mg/dL</td>
<td>&gt;1500 mL</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythodema with bullae and/or desquamation</td>
<td>&gt;15 mg/dL</td>
<td>Severe abdominal pain and/or clinical ileus, with or w/o hematochezia</td>
<td></td>
</tr>
</tbody>
</table>


**Therapy of Acute GVHD**

- Skin-directed: topical steroids
- Grade II or higher:
  - 1st line: Methylprednisolone 2 mg/kg/day IV
  - 2nd line: Mycophenolate mofetil, etanercept, pentostatin, sirolimus, ATG, OKT3 and anti-CD3 antibodies and other monoclonal antibodies
  - Mesenchymal stem cells (promising)
- Poor long-term survival with steroid-resistant GVHD

**Drug Toxicity – GVHD “drugs”**

- CNI (cyclosporine, tacrolimus):
  - Renal dysfunction, electrolyte abnormalities (K, Mg).
  - Hypertension
  - Neurological side effects: tremor (common), seizures (rare), ataxia, cortical blindness (rare), peripheral neuropathy.
  - Other: liver toxicity, hyperglycemia, hirsutism, hemolytic anemia (rare), AHUS (rare).
- Sirolimus (mTOR inhibitor)
  - Hypertriglyceridemia, hypercholesterolemia
  - Myelosuppression (mild).
  - Other: AHUS (rare), SOS (in combination with busulfan).
- Mycophenolate mofetil (MMF)
  - Myelosuppression
  - GI symptoms: nausea, anorexia and diarrhea

**Infectious Complications**

- Leading cause of death after allogeneic HSCT
- Major factors for infection:
  - Neutropenia and qualitative defects in phagocytosis
  - Humoral immune deficiency
  - Cellular immune deficiency or dysfunction
  - Impaired mucosal integrity
Bacterial Infections

• Risk factors:
  – Neutropenia, mucocutaneous damage, indwelling catheter
  – Common infections:
    – Aerobic gram-positive and gram-negative bacteria
    – Clostridium-difficile
    – Important to know local antibiotic-resistance patterns

Viral Infections

• Herpes Simplex Virus (HSV)
  – Reactivation (only seropositive patients at risk)
  – Prophylaxis with acyclovir
• Respiratory viruses
  – Seasonal fluctuation
  – Common pathogens: Respiratory syncitial virus (RSV), parainfluenza, rhinovirus, influenza A and B, metapneumovirus
  – Can be fatal
  – Infection control, droplet precautions, hand washing (!)
• Cytomegalovirus (CMV)
• Human Herpes Virus 6 (HHV6)
• Epstein-Barr Virus
• Adenovirus
• BK Virus (hemorrhagic cystitis)

CMV

• Historical data:
  – 70 – 80% risk of reactivation in CMV seropositive allo-HCT recipients
  – 1/3 of patients with reactivation developed CMV disease (pneumonitis, hepatitis, colitis)
  – Interstitial pneumonia was a major cause of death in the first 3 months; 50% due to CMV
• Risk factors:
  – CMV seropositive patient
  – Allogeneic HCT
  – T cell depletion (in vitro/in vivo)
  – Cord blood recipient
  – GVHD (due to added immune suppression)
Agents to Treat CMV

- **Ganciclovir**: 5 mg/kg q 12h induction therapy for 7-14 days then 5 mg/kg daily for maintenance therapy
  - Valganciclovir: 900 mg PO twice daily x 21 days during induction then single daily dosing
  - Toxicity: Bone marrow suppression (leukopenia)
- **Foscarnet**: 90 mg/kg q 12 hours for 2 weeks, then 120 mg/kg daily for ≥2 weeks
  - Toxicity: Renal failure
- **Cidofovir**: for CMV retinitis; 5 mg/kg IV once weekly for 2 weeks then 5 mg/kg IV once q 2 weeks as maintenance (with probenecid)
  - Toxicity: Renal failure

**HHV-6 Infection**

- Reactivation occurs in 30%-50% after allogeneic HSCT
- Often manifests as HHV-6 viremia and typically occurs 2-4 weeks after transplant
- Detection of HHV-6 DNA in plasma or serum correlates well with viremia and seroconversion
- Presentation
  - Encephalitis (confusion, short-term memory loss and/or anterograde amnesia with or without seizures)
  - HHV-6 DNA is usually detected in CSF
  - MRI: hyperintensities in medial temporal lobes
  - Others: delirium, bone marrow suppression, pneumonitis
- **Treatment**:
  - Foscarnet or Ganciclovir

**When to start preemptive therapy?**

<table>
<thead>
<tr>
<th>Immuno- suppression</th>
<th>CMV doubling time</th>
<th>Risk Groups</th>
<th>CMV Plasma DNA Level to Start PET at HICRC**</th>
<th>CMV Whole Blood DNA Level to Start PET at Karolinke Institute**</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Short</td>
<td>Any level 1</td>
<td>Any level 1</td>
<td>Any level 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cord blood</td>
<td>1000 copies</td>
<td>1000 copies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft</td>
<td>&gt; 100 copies/mL</td>
<td>&gt; 1000 copies/mL</td>
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<tr>
<td></td>
<td></td>
<td>- Low dose steroids*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anti-HLA antibodies*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- CD4&lt;500 cells*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft</td>
<td>&gt; 500 copies/mL</td>
<td>&gt; 1000 copies/mL</td>
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<tr>
<td></td>
<td></td>
<td>- after day 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Any level 1</td>
<td>Any level 1</td>
<td>Any level 1</td>
</tr>
</tbody>
</table>


1. Average or normal weekly or twice weekly (highest only); last of albumin ≥50 expander
2. HIA: human leukocyte antigen
3. Calculated in terms of 500 copies/mL of DNA

Boeckh M, Blood 2009;113:5711-19
Adenovirus

- Incidence: reactivation is common, but disease is rare (< 2%)
- Risk factors: similar to CMV (immune suppression), more common in children
- Clinical presentation:
  - Pneumonitis
  - Nephritis
  - Hemorrhagic enteritis
  - Hemorrhagic cystitis
  - Disseminated disease with multiorgan failure
- Treatment
  - Cidofovir

Fungal Infections

- Candida
  - Risk factors: severe neutropenia, broad-spectrum antibiotics, mucocutaneous damage, colonization
- Molds (Aspergillus, Fusarium, Zygomycetes)
  - Risk factors: allogeneic HCT, delayed engraftment, prior history, GvHD
  - Standard antifungal prophylaxis recommended

NCCN Guidelines for Prevention of IFI

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prophylaxis</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Autologous HCT</td>
<td></td>
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</tr>
<tr>
<td>With mucositis</td>
<td>Fluconazole (Category 1)</td>
<td>Until engraftment</td>
</tr>
<tr>
<td>Without mucositis</td>
<td>Micafungin (Category 1)</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic</td>
<td>Fluconazole (Category 1)</td>
<td>&gt; 75 days</td>
</tr>
<tr>
<td></td>
<td>Micafungin (Category 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole (Category 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole (Category 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B products (Cat 2B)</td>
<td></td>
</tr>
<tr>
<td>Severe GVHD</td>
<td>Posaconazole (Category 1)</td>
<td>Until resolution of significant GVHD</td>
</tr>
<tr>
<td></td>
<td>Voriconazole (Category 2B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echinocandin (Category 2B)</td>
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</tr>
<tr>
<td></td>
<td>Amphotericin B products (Cat 2B)</td>
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Adapted from NCCN Guidelines Version 1. 2012

Invasive Pulmonary Aspergillosis

- Clinical presentation: dyspnea, chest pain and hemoptysis
- Chest imaging: patchy bronchopneumonia or multiple nodular lesions; CT may show peripheral wedge-shaped infarcts or “halo or air-crescent sign”
- Biomarkers: Galactomannan, BD-glucan
- Treatment: Voriconazole, Isavuconazole (also useful for Mucor)
CT Findings in IPA

Pneumocystis Jiroveci Pneumonia

- Prophylaxis is standard
  - Until completion of immune suppression
  - At least until CD4 >200
- Trimethoprim/sulfamethoxazole (Bactrim) – also provides prophylaxis against toxoplasma, S. pneumoniae and other community-acquired pneumonia
- Aerosolized pentamidine
- Dapsone
- Atovaquone - also provides prophylaxis against toxoplasma

Toxoplasmosis

- Highly virulent infection
- Nearly 100% fatal
- Sepsis-like syndrome
- High fever
- Typically 30 – 120 days after HCT
- More closely linked to host than donor serostatus
- PCR monitoring available
- Standard prophylaxis with Bactrim or atovaquone

ICU Management

- Common indications for ICU admission of the BMT patient
  - Sepsis
  - SOS
  - Respiratory failure due to DAH, infection, volume overload
  - Acute kidney injury, cardiovascular and neurological issues
- Multidisciplinary management
  - ICU team, BMT, ID, Renal
- Mortality remains high (< 20% for ventilated pts at 6 mo)
- Risk factors for mortality:
  - Mechanical ventilation
  - Hemodynamic instability/shock requiring vasopressors
  - GVHD, hepatic failure
  - “Standard factors”: high APACHE II score, high lactate

Naeem N et al, BMT 2006; 37:119-133;
ICU Outcomes of Allogeneic HSCT after Reduced Intensity Conditioning

• N=102, French ICU
• Short-term outcomes encouraging
  – ICU mortality: 39.2%; Hospital: 59.8%
• Poor outcome variables:
  – Use of invasive mechanical ventilation
  – High SAPS II score
  – Longer time between diagnosis of malignancy and HSCT

Mokart D, J Crit Care 2015;30:1107-13

• N=161, MSKCC ICU
• ICU mortality: 64.6%; Hospital: 46%
• 5-yr survival: 20%
• Poor ICU outcome variables:
  – Use of invasive mechanical ventilation
  – Vasopressors
  – Hemodialysis

June 27, 2016:1-9

Summary

• Early complications after HSCT are related to:
  – Conditioning regimen
  – Patient’s co-morbidities
  – Underlying disease
• Improvements in treatment-related mortality result from:
  – Better donor selection (improvement in HLA-typing)
  – Patient selection
  – Advances in conditioning regimens
  – Improvements in supportive care
Thank You

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