Oncologic Emergencies During Stem Cell Transplant

Brenda K. Shelton M.S., R.N., CCRN, AOCN
Critical Care Clinical Nurse Specialist
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
sheltbr@jhmi.edu

Objectives

• Describe pre-transplant risk factors that predispose HSCT patients to oncologic emergencies.
• Identify current evidenced-based management for transplant related oncologic emergencies.

Why are HSCT Patients at Risk?

• High dose therapy and associated toxicities
• Previous therapy toxicities
• Introduction of foreign antigens (allogeneic hematopoietic stem cells)
• Severity and length of aplasia, multiple blood products
• Characteristics of their underlying disease
• Highest risk: matched unrelated donor, heavily pre-treated, prior problems with marrow recovery, comorbid health conditions

Methods to Classify

• Type of Transplant
  — Allogeneic vs Autologous
  — Marrow vs Peripheral stem cell
  — Myeloablative vs Non-myeloablative
• Chronologic
  — Preparative regimen
  — During stem cell infusion
  — Aplasia/Immunosuppressive-related
  — Late after transplant
• Organ systems
  — Hematologic/Immunologic
  — Cardiopulmonary
  — Gastrointestinal/ Hepatic

Related to Preparatory Regimen

<table>
<thead>
<tr>
<th>High dose chemotherapy toxicity/Immunotherapy toxicity</th>
<th>TBI toxicity</th>
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<tbody>
<tr>
<td>• Alveolar Hemorrhage</td>
<td>• Pneumonitis/ Acute lung injury/ Diffuse alveolar hemorrhage</td>
</tr>
<tr>
<td>• Cardiomyopathy; Dysrhythmias</td>
<td>• Veno-occlusive disease (hepatic and pulmonary)</td>
</tr>
<tr>
<td>• Hemorrhagic cystitis</td>
<td></td>
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<tr>
<td>• Hypersensitivity</td>
<td></td>
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<tr>
<td>• Seizures/ tremors</td>
<td></td>
</tr>
<tr>
<td>• Veno-occlusive disease (hepatic and pulmonary)</td>
<td></td>
</tr>
<tr>
<td>• Posterior reversible encephalopathy syndrome (PRES)</td>
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Case Scenario

• BT is a 49 year old woman with Chronic myelogenous leukemia (CML) who is receiving Cyclophosphamide and etoposide as a preparative regimen for an allogeneic HSCT from her 6/6 matched sister.
• On the sixth day after beginning the prep regimen, she spikes her first fever and has the beginning of mucositis.
• She complains of profound fatigue and does not want to get out of bed to shower.
• On the same day, she develops dyspnea and crackles after a blood transfusion.
Seizures in HSCT
- Unlike other cancer-related seizures, these are usually generalized.
- Often multifactorial
- Contributory causes- busulfan, TBI, anti-viral medications, glucose and electrolyte disturbances, altered hepatic clearance, thrombocytopenia or other coagulation abnormalities
- Management
  - Thorough medical history
  - Busulfan dosing according to blood levels
  - Limiting TBI in high risk patients
  - Prophylactic anti-convulsants

Tumor Lysis Syndrome Management
**Prevention**
- Monitoring: medications, blood products, blood study monitoring
- Hydration: 150-300 mL/hr***
- Alkalinization (controversial)
- Limiting dietary/ electrolyte intake
- Decrease uric acid- Allopurinol, Rasburicase
- Phosphate binders

**Acute Management**
- Renal failure < 2% all tumor lysis, 30% survival
- Hemodialysis removes uric acid, BUN, creatinine more efficiently; limited time per day risky in TLS
- Continuous dialysis removes phosphate better than hemodialysis
- Usual plan: When uric acid or electrolytes rise and unresponsive to fluid and diuretics:
  - Single hemodialysis treatment
  - Followed by continuous dialysis throughout high risk period

Cardiomyopathy in HCST
- Rare complication of high dose cyclophosphamide (>50 mg/M²), TBI or agents with overlapping cardiotoxicity
- Occurs between 5th and 16th days after start of therapy
- Suspected pathophysiology is microvascular hemorrhage
- Minor disease presents as murmur, gallop, fluid intolerance
- Severe disease presents as severe heart failure and/or cardiac tamponade

Tumor Lysis Syndrome (TLS) after Preparative Regimen
- Metabolic abnormality caused by rapid collection of metabolic waste generated by cell lysis.
- Higher risk: renal dysfunction, hypovolemia
- Often asymptomatic until clinically significant laboratory abnormalities
- Common manifestations:
  - Hyperkalemia
  - Hyperuricemia
  - Hyperphosphatemia
  - Hypocalcemia
  - Acidosis
- Onset 6 hr - 48 hr, up to 5 days
- Duration 5-10 days
- Prognosis-5-8% mortality no renal failure, 30% with renal failure.
- Patients with active malignancy- High LDH, Abdominal disease, Presenting with lethargy
- Chemo/radiosensitive tumors or associated with differentiating agents such as Rituximab
- Common malignancies in transplant setting
  - High grade lymphoma
  - Multiple myeloma

Infusional Reactions
<table>
<thead>
<tr>
<th>Severity</th>
<th>Signs/ Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal/Mild</td>
<td>Hives, itching, flushing, anxiety</td>
<td>Stop infusion</td>
</tr>
<tr>
<td>Moderate</td>
<td>High rectal temperature, dyspnea, tender abdomen</td>
<td>Assess for serious signs/ symptoms, Resuscitate if needed, administer diphenhydramine.</td>
</tr>
<tr>
<td>Severe</td>
<td>Dyspnea, hypertension, abdominal/back pain</td>
<td>Epinephrine 0.3-0.5 mg 1:1000 IM or SC, All of interventions for mild/moderate reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider albuterol metered dose inhaler, Consider histamine 1 blockers (e.g. ranitidine)</td>
</tr>
</tbody>
</table>
Complications Related to Aplasia

- Marrow suppression (cytopenia) requiring blood product support
  - Neutropenia
  - Thrombocytopenia
  - Anemia
- Infections/sepsis
  - Organisms: bacterial, fungal, opportunistic, viral
  - Locations: pneumonitis, gastrointestinal
- Engraftment syndrome
- Coagulopathies
  - Bleeding tendency
  - Clotting tendency

Typhlitis

- Also known as: neutropenic enterocolitis, necrotizing enterocolitis
- Enteric bacteria in the large bowel
- Cecum and appendix: high risk due to low blood supply, tortuous physiology and incompetent ileocecal valve
- Iatrogenic destruction of mucosa in bowel lumen
- Translocation of bacteria across gut wall into bloodstream
- Risk factors
  - Prolonged neutropenia
  - Intact appendix
  - Live gram negative bacteria in the gut
  - Certain chemotherapy agents: Cytarabine (ara-C), Paclitaxel
  - Pre-existing bowel vascular abnormalities (known CAD/ atherosclerotic vascular disease)

Clinical Findings of Typhlitis

- Signs/symptoms
  - Right sided abdominal pain
  - Fever
  - Confusion
  - Hypotension/hypovolemia
  - Diarrhea, mucousy stools
- Diagnosis
  - Screening abdominal flat plate and right lateral x-ray
  - Abdominal CT scan with contrast
  - Exploratory surgery
- Prevention
  - Growth factors
  - Oral antibiotics with prolonged neutropenia
- Emergency management
  - Fluids: 2000-5000 mL
  - Broad spectrum antibiotics with gram negative coverage
  - Consider emergency bowel resection
- Acute management
  - NPO
  - Nasogastric decompression

Acalculous Cholecystitis

- Risk factors: previous cholecystitis, NPO, no gut decontamination, parenteral alimentation, shock episode, systemic infection
- Can occur any time post-transplant, but is most common in period of aplasia
- Key findings: fever and RUQ pain, may even progress to symptoms of septic shock
- Prognosis good with early intervention
- Key management: prophylactic and therapeutic antimicrobials, percutaneous T-tube, cholecystectomy

Case Study

- DR is a 59 year old with multiple myeloma who is treated with an allogeneic transplant.
- The patient has a personal history of GERD.
- Twelve days after transplant, the patient continues with aplasia, and develops a new high spiking fever.
- DR complains of diffuse abdominal pain and is guarding the right upper abdomen.
- VS: T: 39.2, HR: 122/min, R: 32/min, BP: 96/48, pulse ox-91%

Case Study... revised

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- Diagnostic tests???
Hypertension

- Etiologies
  - Pre-existing disease
  - Volume overload
  - Renal dysfunction
  - Calcineurin inhibitor immunosuppressives (cyclosporine, tacrolimus)
- Defining Clinical Significance
  - Pre-hypertension: > 129/79
- Management strategies
  - Diuretics
  - Calcium channel blockers
  - Magnesium repletion

Complications R/T Engraftment

- Renal insufficiency
- Veno-occlusive disease
- Engraftment syndrome

Differential Diagnosis of Renal Dysfunction

- Present in 11-16% of BMT patients
- Risk factors for increased prevalence: pre-existing renal dysfunction, amphotericin
- Treatment toxicities
- Engraftment syndrome
- Hemolytic uremic syndrome (HUS)
- Sepsis
- Hepatorenal syndrome

Hemolytic Uremic Syndrome (HUS)

- Risk factors: specific chemotherapy agents (e.g. mitomycin, nitrogen mustard), autoimmune disease prior to transplant, allogeneic transplant, HLA mismatched transplant, GVHD
- Peaks 30-60 days post transplant, but may persist for months
- Key findings: jaundice, oliguria, increased bilirubin and creatinine, coagulopathy
- Key management: supportive care with blood product transfusions, dialysis, corticosteroids

Sinusoid Obstruction Syndrome

**Hepatic Veno-occlusive Disease (VOD) of the Liver**

**Pathophysiology**

- Fibrotic deposits with obstruction of hepatic venules
- Decreased flow and venous congestion
- Back up of venous portal blood into IVC
- Portal hypertension
- Venous congestion
- Late central lobular destruction

**Risk factors**

- Prior alkylating agents, gemtuzumab
- Previous radiation therapy
- TBI regimen
- Sirolimus GVHD prophylaxis
- History of hepatitis, prior fungal infection, iron overload
- Older age

Clinical Presentation of Sinusoid Syndrome:

*Time-line varies with type of transplant and preparative regimen*

**Diagnostic/prognostic criteria:**
- Baltimore Criteria
- Seattle criteria

Clinical Flowchart:

- Transplantation
- Immunosuppression
- GVHD prophylaxis
- Hematoopoietic growth factors
- Hematopoietic growth factors
- Engraftment syndrome

**Complications**

- Renal insufficiency
- Veno-occlusive disease
- Engraftment syndrome
### Bilirubin Levels

<table>
<thead>
<tr>
<th>Total Bilirubin</th>
<th>&lt; 1.5 mg/dl</th>
<th>Liver, spleen, bone marrow, Hgb breakdown</th>
<th>Increased all- jaundice, morphine, androgens, antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct = conjugated</td>
<td>0- 0.3 mg/dl</td>
<td>Excreted via intestine</td>
<td>Obstruction or hepatic disease</td>
</tr>
<tr>
<td>Indirect = unconjugated</td>
<td>0.1-1 mg/dl</td>
<td>“free” circulating bilirubin</td>
<td>Hemolysis</td>
</tr>
</tbody>
</table>

### Diagnosis of Sinusoidal Syndrome

- Presence of Risk factors
- Suspicious clinical symptomatology
- Hyperbilirubinemia
- Increased SGOT
- Increased alkaline phosphatase
- Hepatic doppler/ duplex ultrasonound
- Transjugular hepatic biopsy
- Late / severe
  - Transaminase elevations
  - Thrombocytopenia
  - Altered coagulation profile

### Management of Sinusoidal Syndrome

- **Prevention**
  - Monitoring busulfan dose
  - Avoidance of TBI for high risk patients
  - Anti-platelet / anti-coagulant administration during preparative regimen (heparin, enoxaparin, warfarin, defibrotide, PTA-1)
  - Ureodeoxyxilic acid
  - Glutathione

- **Treatment**
  - High-dose methylprednisolone
  - Fluid restrictions
  - Consider diuretics- alactone or low dose loop diuretics
  - Ventilatory support as needed
  - Avoidance of other risk factors for increased bilirubin- reduce protein in diet, administer blood cautiously
  - Rule out other etiologies
  - Portacaval shunt
  - Potential new agents- defibrotide*
  - novoseven

### Case Scenario

GL is a 24 year old with refractory acute myelogenous leukemia who has been transplanted with a 6/6 matched unrelated donor.

- The donor is CMV + and the patient is CMV negative, so prophylactic ganciclovir is being administered post transplant.
- On day 14 post transplant the patient develops sudden onset of respiratory distress and frothy hemoptysis.
- Chest x-ray shows bilateral patchy infiltrates
- CT scan shows diffuse alveolar hemorrhage.
- Corticosteroids, and mechanical ventilation with sedation are implemented.

### Transfusion-related Acute Lung Injury (TRALI)

- **Within 6-24 hours of a transfusion.**
- Incidence 1 in 5000 transfusions
- Related to antigenic reaction, more common with FFP.
- Risk factors- history of reactions, frequent transfusions or transplant, multiparous women, prolonged banked blood recent viral illness of donor.
- Clinical presentation- fever, dyspnea, crackles, hypotension
- Diagnosis by exclusion
- Prognosis- 6-9% mortality, most have complete recovery within 48-72 hours

### Diffuse Alveolar Hemorrhage (DAH)

- **Microvascular inflammation (vasculitis)** with small vessel hemorrhage.
- **Risk factors**- lung toxins [e.g. smoke inhalation], high dose chemotherapy [methotrexate, cyclophosphamide, cytoxin ara-binoside], infection [esp viral]
- **Clinical findings**- sudden onset respiratory distress and hypoxemia, decreased compliance
- **Diagnosis**- echocardiogram to R/O cardiac etiology, chest x-ray bilateral infiltrates, bronchoscopy identifies persistent bleeding after multiple lavages, hemosiderin on lavage stain
- **Management**- corticosteroids, noninvasive ventilation/mechanical ventilation, sedation/ paralysis

**Engraftment syndrome, Cytokine Release Syndrome**

- **Risk factors:** HLA unrelated, mismatched allogeneic transplant, non-T-cell depleted marrows, early engraftment, cytokine sensitivity
- **Peaks** between days 12-21 (depending upon transplant regimen), resolves when neutrophils return
- **Key findings**- respiratory distress, fever, elevated transaminases, elevated creatinine, GI bleeding
- **Prognosis** yet undetermined due to the few cases documented and difficulties differentiating from sepsis
- **Key management**- supportive care, postulated that continuous veno-venous hemofiltration removes toxic cytokines

**Case Scenario**

- **HJ** is a 62 year old man with large cell lymphoma who is being treated with a non-myeloablative transplant.
- He has a past history of smoking
- Fifteen days after transplant, he calls the clinic, reporting new onset fever, rash, and dyspnea.
- Upon exam, there are bilateral crackles, and hypoxemia (O2 sat 86% on room air).
- **VS:** T- 38.0, HR- 110/min, R- 26/min, BP- 98/50

**Respiratory Distress in the HSCT Patient**

- **Characteristics of respiratory symptoms**
  - Continuous vs. intermittent
  - Activity intolerance
  - Hypoxic vs. hypercarbic
  - Associated symptoms- cough, fever, breath sounds
- **Temporal relationship to:**
  - Preparative regimen
  - Transplant
  - Engraftment
  - Blood transfusions

**Respiratory Distress: Critical Thinking**

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<thead>
<tr>
<th></th>
<th>Risks</th>
<th>Timing</th>
<th>S &amp; S</th>
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<tbody>
<tr>
<td>Prep regimen toxicity</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>TRALI (transfusion-related acute lung injury)</td>
<td>++++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Infection</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Engraftment</td>
<td>++++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>DAL (Diffuse alveolar hemorrhage)</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>BOOP (Bronchiolitis obliterans organizing pneumonia)</td>
<td>++++</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Respiratory Distress HSCT**

- **Diagnosis**
  - Physical examination/ Arterial saturation
  - Radiology- Chest radiograph, Chest CT
  - Serum viral titers
  - Pulmonary function tests
  - Invasive- Bronchoscopy, Open lung biopsy
- **Management**
  - Evaluate anti-microbial coverage- consider covering anaerobes (e.g. H. influenzae), fungi, viruses
  - Debate risk: benefit ratio for use of corticosteroids
  - Consider anti-cytokine therapies: NSAIDS, Novaseven, CVVH (continuous dialysis)
  - Supportive care: mechanical ventilation

**Keeping the Patient OUT of the ICU**

- Implement prophylactic monitoring, advanced assessment for patients at risk.
- Recognize signs/ symptoms of disease escalation.
- Conservative implementation of interventions with frequent reassessment.
- Expect and plan for the worst so you can be pleasantly surprised when it does not occur.
- Consult intensivists/ critical care resources early.
Critical Thinking…and Excellent Assessment Skills…
*The mainstay of expert nursing practice*

Thanks!!