Oncologic Emergencies During Stem Cell Transplant

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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

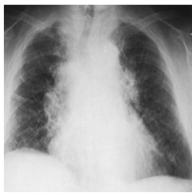
High dose chemotherapy toxicity/ Immunotherapy toxicity

- Alveolar Hemorrhage
- Cardiomyopathy; Dysrhythmias
- Hemorrhagic cystitis
- Hypersensitivity
- Seizures/ tremors
- Veno-occlusive disease (hepatic and pulmonary)
- Posterior reversible encephalopathy syndrome (PRES)

TBI toxicity

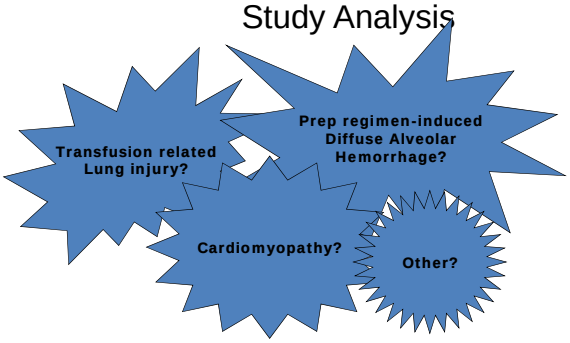
- Pneumonitis/ Acute lung injury/ Diffuse alveolar hemorrhage
- Veno-occlusive disease (hepatic and pulmonary)

Case Scenario



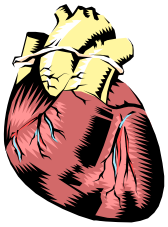
- BT is a 49 year old woman with Chronic myelogenous leukemia (CML) who is receiving Cyclophosphamide and etoposide as a preparative regimen for an allogeneic HSCT from her 6/6 matched sister.
- On the sixth day after beginning the prep regimen, she spikes her first fever and has the beginning of mucositis.
- 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.

Acute Complication- Case Study Analysis



Cardiomyopathy in HCST

- Rare complication of high dose cyclophosphamide (> 50 mg/M^2), TBI or agents with overlapping cardiotoxicity
- Occurs between 5th and 16th days after start of therapy
- Suspected pathophysiology is micorovascular hemorrhage
- Minor disease presents as murmur, gallop, fluid intolerance
- Severe disease presents as severe heart failure and/or cardiac tamponade



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 (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

Tumor Lysis Syndrome Management

Prevention

- Monitoring- medications, blood products, blood study monitoring
- Hydration- 150-300 mL/ hr***
- Alkylinization (controversial)
- Limiting dietary/ electrolyte intake
- Decrease uric acid- Allopurinol, Rasburicase
- Phosphate binders

Acute Management

- Renal failure < 1% 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

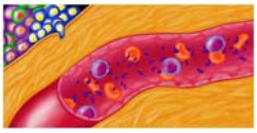
Infusional Reactions

- Hypersensitivity reactions
  - High risk: previous allergies, younger age, specific products
- Tumor lysis reaction
- Stem cell infusions
  - Bradycardia

Severity	Signs/ Symptoms	Management
Mild/ Moderate	Hives, itching, flushing, anxiety	Stop infusion Assess for serious signs/ symptoms Redose acetominophen and diphenhydramine Consider rapid acting corticosteroids (e.g. hydrocortisone 125 mg)
Severe	Dyspnea, hypotension, abdominal/ back pain	Epinephrine 0.3-0.5 mg 1:1000 IM or SC All of interventions for mild/ moderate reaction Consider albuterol metered dose inhaler Consider histamine 1 blockers (e.g. ranitidine)

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

Case Study

- DR is a 59 year old with multiple myeloma who is treated with a 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%

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 anti-microbials, percutaneous T-tube, cholecystectomy

Case Study… *revisted*

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- Diagnostic tests???

Hypertension

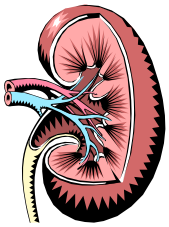
- Etiologies
  - Pre-existing disease
  - Volume overload
  - Renal dysfunction
  - Calcineurin inhibitor immunosuppressives (cyclosporine, tacrolimus)
- Defining Clinical Significance
  - Pre-hypertension- > 129/79
  - Essential HTN definition- > 139/89
- Management strategies
  - Diuretics
  - Calcium 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

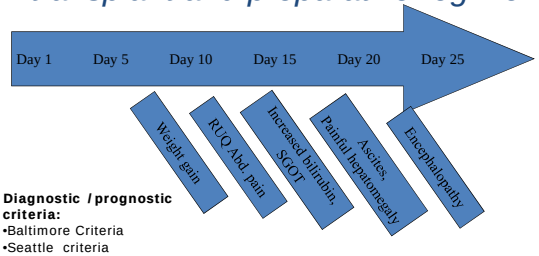
- Fibrotic deposits with obstruction of hepatic venules
- Decreased flow and venous congestion
- Back up of venous portal blood into IVC
- Portal hypertension
- Venous congestion
- Late central lobular destruction

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



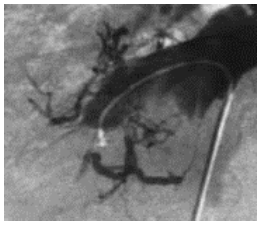
Diagnostic / prognostic criteria:

- Baltimore Criteria
- Seattle criteria

Bilirubin Levels

Total Bilirubin	< 1.5 mg/dl	Liver, spleen, bone marrow, Hgb breakdown	Increased all- jaundice, morphine, androgens, antibiotics
Direct = conjugated	0- 0.3 mg/dl	Excreted via intestine	Obstruction or hepatic disease
Indirect = un-conjugated	0.1-1 mg/dl	"free" circulating bilirubin	Hemolysis

Diagnosis of Sinusoidal Syndrome



- Presence of Risk factors
- Suspicious clinical symptomatology
- Hyperbilirubinemia
- Increased SGOT
- Increased alkaline phosphatase
- Hepatic doppler/ duplex ultrasound
- 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, PAI-1)
  - Ursodeoxycholic acid
  - Glutathione
- Treatment
  - High-dose methylprednisilone
  - Fluid restrictions
  - Consider diuretics- aldactone 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

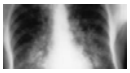
- GL is a 24 year old with refractory acute myelogenous leukemia who has been transplanted with a 6/6 matched unrelated donor.
- The donor is CMV + and the patient is CMV negative, so prophylactic ganciclovir is being administered post transplant.
- On day 14 post transplant the patient develops sudden 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, cytosine arabinoside), 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
- **Managemen**t- corticosteroids, noninvasive ventilation/mechanical ventilation, sedation/ paralysis



Source of x-ray: http://www.merck.com/mmpe/sec05/ch059/ch059a.html

Engraftment syndrome, Cytokine Release Syndrome

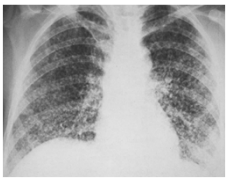
- **Risk factors-** HLA unrelated, mismatched allogeneic transplant, non-T-cell depleted marrows, early engraftment, cytokine sensitivity
- Peaks between days 12-21 (depending upon transplant regimen), resolves when neutrophils return
- **Key findings-** respiratory distress, fever, elevated transaminases, 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

	Risks	Timing	S & S
Prep regimen toxicity	+ + +	+ + +	+ + +
TRALI (transfusion-related acute lung injury)	+ + +	-	+ + +
Infection	+ + +	+ + +	+ + +
Engraftment	+ + +	+	+ +
DAL (Diffuse alveolar hemorrhage)	+	+	+ +
BOOP (Bronchiolitis obliterans organizing pneumonia)	+ + +	-	+

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!!