Disclosure

- Jenna Bender has no actual or potential conflicts of interest to report
- Off-label use of medication will be discussed in this presentation

Objectives - Pharmacist

1. Understand the pathophysiology of graft-versus-host disease (GvHD) and hepatic veno-occlusive disease (VOD)
2. Recognize the clinical and laboratory presentation of GvHD and VOD
3. Identify prevention measures against complications of pediatric HSCT
4. Develop recommendations for the management of pediatric HSCT complications
5. Discuss the adverse effects of medication used for the management of GvHD and VOD
Objectives - Technician

1. Understand the pathophysiology of GvHD and VOD
2. Describe the management of pediatric HSCT complications
3. Recognize the medications used in the management of GvHD and VOD

Immune System Overview

Hematopoietic Stem-Cell Transplant

- Transplantation of hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord
  - Hematopoietic stem-cell transplant (HSCT) vs bone marrow transplant (BMT)

- Types of HSCT
  - Autologous – from self
  - Allogeneic – from donor
  - Syngeneic – from twin
Pediatric HSCT

- 1959 – First stem cell transplant
- 1960s – First pediatric stem cell transplant
- Children are transplanted less frequently than adults
  - 37% of 71,108 allogeneic transplants and 16% of 60,190 autologous transplants between 1964 to 2000


HSCT Indications

- Varying indications between adult and pediatric patients
  - Allogeneic
    - AML or ALL with failed induction
    - ALL with relapse within 36 months
    - AML or ALL with high risk features
  - Autologous
    - High risk neuroblastoma
    - Some brain tumors (medulloblastoma)
    - Relapsed HL or germ cell tumors

Allogeneic Transplant Indications

- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic myeloid leukemia
- Myelodysplastic syndromes
- Myeloproliferative disorders
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Fanconi's anemia
- Thalassemia major
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Inborn errors of metabolism

Autologous Transplant Indications

- Multiple myeloma
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Acute myeloid leukemia
- Chronic myeloid leukemia
- Myelodysplastic syndromes
- Myeloproliferative disorders
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Chronic lymphocytic leukemia
- Multiple myeloma
- Juvenile chronic myeloid leukemia
- Aplastic anemia
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Inborn errors of metabolism

HSCT Process: Autologous
HSCT Process: Allogeneic

Donor selection (allogeneic)
- HLA matching
- Matched sibling
- Matched unrelated
- Cord blood transplant
- Haploidentical

Conditioning or preparative regimen
Transplant
Recovery

This diagram reflects a general overview of the transplant process.

HSCT Complications

- 40% of all patients undergoing allogeneic HSCT die of complications related to transplant
- Mucositis
- Pain
- Nutrition
- Emesis
- Infection
- GVHD
- VOD
- Psychosocial and educational needs

GRAFT-VERSUS-HOST DISEASE
GvHD Basics

• T cell mediated reaction of the donor’s immune system (graft) to the recipient’s tissues (host)

• Types
  – Acute: within the first 100 days after transplant
  – Chronic: after the first 100 days of transplant

• Incidence
  – Acute: 20-80% of allogeneic transplant recipients
  – Chronic: 25% of transplants


GvHD Risk Factors

• Degree of HLA disparity

• Source of graft

• Donor and recipient gender mismatch

• Older age of recipient and donor

• Intensity of preparative regimen

• Immunosuppressive regimen

Jacobsohn DA. Bone Marrow Transplantation. 2008;41:215-221.


GvHD Pathophysiology

• Phase I
  – Preparative regimen induced tissue damage

• Phase II
  – Donor T cells become primed and activated

• Phase III
  – Target tissue damage induced directly by cytotoxic T cells and indirectly by inflammatory cytokines

Acute GvHD Prophylaxis

- Immunosuppression
  - No clear guidelines or consensus
  - Center-specific and based on protocol, preparative regimen, toxicity profile
- Balance risks of GvHD with benefits of graft-versus-tumor effects


Table 3
Approaches to post-HSCT GVHD prophylaxis and treatment in children

<table>
<thead>
<tr>
<th>GVHD prophylaxis agents and mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
</tr>
<tr>
<td>MMF</td>
</tr>
<tr>
<td>Alemtuzumab</td>
</tr>
</tbody>
</table>

HLA-identical donor  Matched unrelated donor  Unrelated cord blood

GVHD prophylaxis combinations (pediatric studies)

| Cyclosporine for 6 months, consider low-dose 1 mg/kg/day IV |
| Cyclosporine/methotrexate |
| Cyclosporine/prednisone |
| Tacrolimus/methotrexate |
| Cyclosporine/methotrexate/ATG |
| Tacrolimus/MMF |
| Cyclosporine/methotrexate/alemtuzumab |

Tacrolimus

- Binds FKBP-12 and complexes with calcineurin-dependent proteins to inhibit calcineurin phosphatase activity, which inhibits T-cell activation

- Variable
- 0.02-0.03 mg/kg/day as a continuous infusion

- IV, PO
- Conversion is 1:3 or 1:4, given twice daily

- Nephrotoxicity, transplant associated thrombotic microangiopathy, hypertension, tremor, headache, hypomagnesemia

- Trough goal: 5-15 ng/mL, variable
- Drug interactions, brand (Prograf®) versus generic, toxicity

Adverse effects

- Monitoring
Cyclosporine

**Mechanism**
- Inhibits the production and release of interleukin II and inhibits interleukin II-induced activation of resting T cells

**Dosing**
- Variable
- 1.5-2 mg/kg/dose IV every 12 hours

**Formulations**
- IV, PO
- Conversion is 1:3

**Adverse effects**
- Hypertension, nephrotoxicity, nausea, gingival hyperplasia, tremor

**Monitoring**
- Trough goal 100-300 ng/mL, variable
- Drug interactions, toxicity, formulation (Gengraf®, Neoral®, SandIMMUNE®)

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Mycophenolate mofetil

**Mechanism**
- Inhibits inosine monophosphate dehydrogenase (IMPDH), which inhibits de novo guanosine nucleotide synthesis. This results in inhibition of T and B cell proliferation.

**Dosing**
- 15 mg/kg IV every 8 hours, variable

**Formulations**
- IV, PO
- Conversion is 1:1

**Adverse effects**
- Nausea, vomiting, diarrhea, edema, neutropenia, hypertension, body aches, hyperkalemia

**Monitoring**
- Drug interactions, toxicity, formulations (Cellcept® versus Myfortic®)

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Immunosuppression Review

- Important to balance immunosuppression infection risks with benefits of graft-versus tumor effects
- Dosing and target drug levels vary based on center, time after transplant, protocol, and type of preparative regimen
- Important to monitor for infection, toxicity, drug interactions, formulation changes
Patient Case

• AB is a 12 yo male diagnosed with AML secondary to JMML. He is currently d-5 and starting his preparative regimen (fludarabine d-5 to d-3, TBI d-2 to d-1).
  – Donor information: 50 year old female, CMV+, 10/10 matched unrelated, peripheral collection
  – GvHD prophylaxis: mycophenolate and tacrolimus

• What risk factors does AB have for aGvHD?

Acute GvHD Presentation

• Most commonly affected systems: skin (80%), gastrointestinal tract (50%), and liver (50%)

  • Skin
    – Erythematous, maculopapular rash on face, ear, palms, soles, upper trunk
  • Liver
    – Increased bilirubin, usually asymptomatic
  • Gastrointestinal
    – Diarrhea, cramping, abdominal pain, ileus, nausea, vomiting, anorexia, dyspepsia

Acute GvHD Staging and Grading

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of organ involvement</th>
<th>Grade</th>
<th>Extent of organ involvement</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No GvHD rash</td>
<td>I</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% BSA</td>
<td>II</td>
<td>Stage 3 or Stage 1</td>
<td>Stage 1</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25-50% BSA</td>
<td>III</td>
<td>Stages 2-3 or Stages 2-4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular rash &gt;50% BSA</td>
<td>IV</td>
<td>Stage 4 or Stage 4</td>
<td></td>
</tr>
</tbody>
</table>

*Table adapted from Jacobsohn DA. Bone Marrow Transplantation. 2008;41:215-221.*

Acute GvHD Treatment

- **Grade I (mild)**
  - Topical steroids and observation

- **Grade II-IV (moderate to severe), 35-80% of cases**
  - Continue immunosuppression
  - First line: systemic steroids
    - ~50% will respond
    - Inadequate response to systemic steroids is associated with poorer prognosis and there is no clear guidance on second line therapies

*Jacobsohn DA. Bone Marrow Transplantation. 2008;41:215-221.*
Acute GvHD Treatment: First Line

- Systemic steroids (methylprednisolone)
  - **Mechanism**
    - Lympholytic and decreases the inflammatory cytokine cascade
  - **Dosing**
    - 2 mg/kg/day divided twice daily (or prednisone equivalent)
  - **Formulations**
    - IV, PO
  - **Adverse effects**
    - Hyperglycemia, weight gain, adrenal suppression, osteoporosis
  - **Monitoring**
    - Minimize complications of high-dose glucocorticoid therapy, taper by 10% every 4 days based on response

Acute GvHD Treatment: Second Line

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Humanized monoclonal TNF-α antibody</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Binds CSF2, resulting in B and T cells apoptosis</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Binds TNF-α and also depletes regulatory T cells</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>Rabbit or equine antibodies against human T cells</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Humanized monoclonal IL-2 receptor antagonist</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Adenosine deaminase inhibitor that leads to T cell apoptosis</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>Immunosuppressive cells from unrelated donor that may also aid in tissue repair</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>Ex vivo apoptosis of donor lymphocytes by UV irradiation</td>
</tr>
</tbody>
</table>

Patient Case

- AB’s post-HSCT was uncomplicated. He engrafted on d+28 and discharged on d+35. He is now d+44 and presents to clinic with diarrhea and a diffuse erythematous, maculopapular, pruritic rash on his head, neck, back, and upper chest.
- **What would you recommend?**
  - a) Send home with topical hydrocortisone 1% to affected areas
  - b) Admit for observation
  - c) Admit for treatment and start methylprednisolone
  - d) Send home with oral prednisone
HEPATIC VENO-OCCULSIVE DISEASE

Hepatic VOD

- Clinical syndrome characterized by jaundice with painful hepatomegaly, hyperbilirubinemia, and unexplained weight gain
  - Previously known as sinusoidal obstruction syndrome (SOS)
- Incidence
  - Review of 135 cases, mean incidence 13.7%
- Severity ranging from mild to severe with multi-organ failure (MOF)
  - Overall survival ~60%, mortality up to 90% in severe cases with MOF

VOD Pathophysiology

- Complex and not fully understood
  - Starts with injury to the sinusoidal epithelial cells and to hepatic venules
  - Damage leads to impairment of blood flow and generation of microthrombi
  - Results in obstruction of sinusoidal blood flow and hepatic necrosis
- Hypercoagulable state
  - Decreased: protein C, protein S, factor VII, and factor X
  - Increased: plasminogen activator inhibitor
VOD Risk Factors

<table>
<thead>
<tr>
<th>Pre-transplantation</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Cytoreductive treatment in conditioning regimen</td>
</tr>
<tr>
<td>AST increase</td>
<td>Busulfan and cyclophosphamide</td>
</tr>
<tr>
<td>Number of day of fever before transplant</td>
<td>TBI and cyclophosphamide</td>
</tr>
<tr>
<td>Number of days of broad antibiotics</td>
<td>GVHD prophylaxis</td>
</tr>
<tr>
<td>Amphotericin B, vancomycin, and/or acyclovir</td>
<td>Second transplant</td>
</tr>
<tr>
<td>Respiratory test alterations</td>
<td></td>
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<tr>
<td>Pre-existing liver disease</td>
<td></td>
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<tr>
<td>Source of graft</td>
<td></td>
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<tr>
<td>Poor baseline performance status</td>
<td></td>
</tr>
<tr>
<td>Patient age</td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
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</tbody>
</table>

VOD Presentation

**Signs**
- Unexplained weight gain (>5%)
- Refractory thrombocytopenia (<20,000/microliter)
- Abnormal liver function tests
- Hypoalbuminemia

**Symptoms**
- Jaundice
- Painful hepatomegaly
- Fluid retention with ascites
- Certain features are associated with increased mortality
  - Weight gain >9%, pleural effusion, unrelated donor or haploidentical transplant
  - Matched sibling donor and autologous, admission to PICU, rapid rise in bilirubin and higher peak bilirubin, moderate to severe hepatic or skin GVHD
VOD Diagnosis

- Liver biopsy is necessary to confirm

<table>
<thead>
<tr>
<th>Baltimore Criteria</th>
<th>Seattle Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires total bilirubin ≥ 2 mg/dL, with 2 of the following:</td>
<td>Requires 2 of the following:</td>
</tr>
<tr>
<td>- Painful hepatomegaly</td>
<td>- Total bilirubin &gt; 2 mg/dL</td>
</tr>
<tr>
<td>- Weight gain &gt; 5% from baseline</td>
<td>- Hepatomegaly or RUQ pain of liver origin</td>
</tr>
<tr>
<td>- Ascites</td>
<td>- &gt; 2% weight gain</td>
</tr>
</tbody>
</table>


VOD Prevention

- Prevention is key due to minimal effective treatments

**Likely benefit**
- Ursodiol
- Defibrotide

**Conflicting evidence**
- Low dose heparin

**Unlikely benefit**
- Pentoxifylline
- Antithrombin III
- Prostaglandin E1


Ursodiol

**Mechanism**
- Inducing a down-regulation of inflammatory mediators such as TNF-α, binds bile salts

**Dosing**
- 20–30 mg/kg/day divided twice daily
- Initiate the day prior to starting preparative regimen and continue for 3 months after transplant

**Formulations**
- PO

**Adverse effects**
- Nausea, diarrhea, headache, increased serum creatinine

Lexi-Comp Online™, Lexi-Drugs Online™. Hudson (OH): Lexi-Comp, Inc.; Available at: http://www-uptodate-com.proxy.lib.uiowa.edu/
Patient Case

- CD is a 15 yo male with recurrent Hodgkin’s Lymphoma s/p HSCT. He is currently d-6 and will be starting his preparative regimen (BCNU d-6, etoposide and cytarabine d-5 to d-2, melphalan d-1). On d0 he will receive a second autologous transplant.

- What do you recommend for prophylaxis?

VOD Treatment

- Supportive therapies:
  - Avoidance of hepatotoxins, nephrotoxins
  - Appropriate nutrition
  - Sodium intake restriction (<1 mEq/kg/d)
  - Diuretics for fluid retention
  - Platelet transfusions, ventilation, hemodialysis if needed
  - Correction of coagulopathy
  - Paracentesis for ascites in the case of respiratory distress
  - Pain control

- Defibrotide

Defibrotide (Defitelio®)

- FDA approval 3/30/2016
  - Treatment of adult and pediatric patients with hepatic VOD, with renal or pulmonary dysfunction following HSCT

- Mechanism:
  - Protects endothelial cells from damage caused by chemotherapy, TNF-α, serum starvation, and perfusion

- Dosing:
  - 6.25 mg/kg IV every 6 hours infused over 2 hours for at least 21 and up to 60 days
  - Adjustments for hypersensitivity, bleeding, invasive procedures

- Adverse effects:
  - Hemorrhage, hypersensitivity

- Cost:
  - ~$8,250 for 10 single-use vial pack (200 mg/2.5mL)

**Objectives and Outcomes**
- To demonstrate the efficacy of defibrotide 25 mg/kg/day in patients with hepatic VOD with MOF
  - Primary: difference in survival at day +100 post-HSCT
  - Secondary: difference in CR rate by day +100 and survival at day +180 post-HSCT, comparison of adverse effects

**Study Design**
- Historically controlled, multi-center, open-label, phase 3 study
  - Treatment: defibrotide 6.25 mg/kg infused over 2 hours every 6 hours for a minimum of 21 days

**Population**
- Adult and pediatric patients with severe hepatic VOD and multi-organ failure (MOF) as defined by the Baltimore diagnostic criteria
  - Treatment: 102 patients ages 0-72 years
  - Age < 16 years: 43.1% treatment, 43.8% control

**Primary Outcome**
38.2% defibrotide versus 25% control with an estimated between-group difference in survival of 23% (P=0.0109)

**Secondary Outcomes**
- CR by day +100: 25.5% defibrotide versus 12.5% control (P=0.0160)
- Survival at day +180: 32.4% defibrotide versus 25% control (P=0.0669)
- Median duration of treatment: 21.5 days
- Discontinuation for toxicity: 10.7%
- Fatal hemorrhagic event: 14.7% versus 6.3%

**Conclusion**
Defibrotide use in patients with hepatic VOD and advanced MOF post-HSCT was associated with a clinically meaningful improvement in survival and in rate of CR by day +100, compared with historical controls.

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**Patient Case**
- CD is now d+10 and having complaints of abdominal pain. He is found to have hepatomegaly and his laboratory values are significant for an increase in total bilirubin from 0.8 mg/dL to 5.0 mg/dL. His weight is also up 5.9 kg from 70 kg and the team suspects hepatic VOD.

- What would you recommend?
Summary

• Prevention of acute GvHD and hepatic VOD are critical due to limited effective treatment options

• Acute GvHD
  – Prevention: immunosuppression and risk factor management
  – Treatment: steroids (topical for Grade I, skin; systemic for Grade II-IV)
  – Limited evidence for second line therapies

• Hepatic VOD
  – Prevention: ursodiol and risk factor management
  – Treatment: defibrotide recently approved March 30, 2016!

• Monitoring for signs/symptoms, drug interactions, efficacy, toxicity, and infection is essential

QUESTIONS?

Management of Pediatric Hematopoietic Stem-Cell Transplant Complications

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May 3, 2016