Challenging Case: Hemorrhagic Cystitis

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Disclosures

• I have no relevant conflicts of interest to disclose.
• This presentation contains discussion of published and/or investigational uses that are not indicated by the FDA. Please refer to the official prescribing information for each product for discussion of approved indication, contraindications and warnings.

Learning Objectives

• Identify risk factors associated with hemorrhagic cystitis (HC) after hematopoietic stem cell transplant (HCT)
• Summarize therapeutic options for treating HC after HCT
Patient Introduction

- Mrs. K: 61 year old female
- Oncologic history
  - Severe aplastic anemia: Received eltrombopag + immunosuppressive therapy
  - High-grade MDS: Received decitabine x 4 cycles
  - Nonmyeloablative haploidentical peripheral blood HCT 4/2015
  - Conditioning: fludarabine, cyclophosphamide, TBI
- Transferred for blood in the urine in 9/2015

Hemorrhagic Cystitis

- Occurs in up to 70% of HCT recipients
- Associated with significant morbidity and prolonged hospitalization

<table>
<thead>
<tr>
<th>Grade</th>
<th>Microscopic</th>
<th>Macroscopic</th>
<th>Gross</th>
<th>Massive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hematuria</td>
<td>hematuria</td>
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<tr>
<td>2</td>
<td>hematuria</td>
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<td>3</td>
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<td>4</td>
<td>hematuria</td>
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<td>5</td>
<td>hematuria</td>
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Signs & Symptoms

- Dysuria
- Urinary frequency
- Urinary urgency
- Suprapubic pain
- Hematuria

Possible Complications

- Severe bladder pain
- Significant blood loss
- Prolonged hospital stay
- Renal failure
- Bladder rupture

Diagnosis

- Symptoms of cystitis
- Grade ≥ 2 hematuria
- BK viruria > 7 log10 copies/mL
Risk Factors for HC

<table>
<thead>
<tr>
<th>Donors</th>
<th>Conditioning regimen</th>
<th>Immune suppression</th>
<th>Infections</th>
<th>Risk of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic</td>
<td>Unrelated donors</td>
<td>Myeloablative</td>
<td>BKV in urine or serum</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Cord</td>
<td>Blood</td>
<td>conditioning</td>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td>Haploidentical</td>
<td></td>
<td></td>
<td>HHV-6</td>
<td></td>
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</table>

Factors associated with increased immunosuppression or immune dysfunction are associated with higher rates of HC.

Causes of HC in HCT Population

Early HC
- 24-72 hours after HCT
- Often drug-induced: Cyclophosphamide

Late HC
- > 2 weeks after HCT
- Viral infections: BK virus (BKV), Adenovirus, Cytomegalovirus (CMV)
- Fungal or bacterial infections
- GVHD
- Malignancy

BK Virus (BKV)
- Non-encapsulated DNA polyomavirus
- >80% seropositivity in adults
- Transmission in childhood
- Reactivation of latent virus in the kidneys or urothelium may occur during immunosuppression
- HC is a well-recognized complication of BKV infection in HCT recipients
BKV-Induced Disease

- Asymptomatic BKV viruria – 50-80% of allogeneic HCT patients
- BKV-hemorrhagic cystitis (BKV-HC) – reported incidence 7-54% of alloHCT patients
  - Ranges from asymptomatic hematuria and self-limited illness to a more severe disease process requiring clinical interventions
  - As early as 10 days post-HCT, but typically 2-8 weeks post-HCT
  - Associated with increased transplantation costs and poorer OS
- Ureteral stenosis
- Interstitial nephritis/nephropathy

Knowledge Check

What is the most common cause of late-onset HC after HCT?

A. Radiation
B. GVHD
C. BKV
D. Cyclophosphamide

Prevention

- Conventional methods:
  - Mesna
  - Hydration
- Questionable benefits:
  - Continuous bladder irrigation
  - Fluoroquinolones

Initial Treatment

- Aggressive IV hydration
- Forced diuresis
- Pain control
- Continuous bladder irrigation

Refractory Treatment

- Antivirals?
- Intravenous immune globulin (IVIG)?
- Intravesical agents to locally control bleeding?
- Cystectomy
- Virus specific T-cells

- Inpatient management for severe symptoms or macrohematuria with clots
- Cystoscopy for clot removal
- Platelet or blood transfusions to control/prevent bleeding
Back to Mrs. K

HC treatment:
• Bladder cauterization (prior to transfer)
• IVIG
• Intravesicular aminocaproic acid
• Intravesicular carboprost
• Conjugated estrogen
• Phenazopyridine and oxybutynin for bladder spasms

BKV-Directed Antiviral Therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Response Rate</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir</td>
<td>Standard dose: 3-5 mg/kg/dose with probenecid</td>
<td>Clinical response: 74%</td>
<td>Nephrotoxicity&lt;br&gt;May be mitigated by low-dose or intravesical administration&lt;br&gt;Avoid other nephrotoxic medications</td>
</tr>
<tr>
<td></td>
<td>Low-dose: ≤ 1.5 mg/kg/dose without probenecid</td>
<td>Clinical response: 83%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravesical: 5 mg/kg/dose without probenecid</td>
<td>Clinical response: 43%</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Example: 100 mg PO daily x 3 days, then 20 mg daily</td>
<td>Complete response: 64%&lt;br&gt;Partial response: 26%</td>
<td>Gastrointestinal toxicity, myelosuppression</td>
</tr>
</tbody>
</table>

Treatments for Refractory HC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Response Rate</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravesical Alum</td>
<td>Stimulates vasoconstriction, decreases capillary permeability and causes sclerosis of exposed capillary endothelium</td>
<td>60% in review of 40 patients with refractory HC</td>
<td>Bladder spasms, transient delirium, UTI, asymptomatic increase in blood aluminum</td>
</tr>
<tr>
<td>Silver Nitrate</td>
<td>Cauterizing agent. Produces nitric acid when combined with water</td>
<td>No response in review of 9 patients with refractory HC</td>
<td>None noted</td>
</tr>
<tr>
<td>Formalin</td>
<td>Capillary occlusion and protein fixation at the level of the urothelium</td>
<td>75% response in review of 8 patients with refractory HC</td>
<td>Bladder contracture, reduced bladder capacity, hydronephrosis, acute kidney injury, and urinary tract fistula</td>
</tr>
<tr>
<td>Hyperbaric Oxygen</td>
<td>Promotes tissue healing and angiogenesis through steep oxygen gradient</td>
<td>Various case reports and series, n=20</td>
<td>Complete clinical response: 80%</td>
</tr>
</tbody>
</table>
**Additional Treatments for Refractory HC**

- Intravesical aminocaproic acid
- Prostaglandins
- IVG
- Estrogens
- Fibrin glue application
- Cystectomy

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**T-Cell Adoptive Immunotherapy**

1. Transfer of ex vivo isolated or generated virus-specific T cells from autologous or allogeneic sources

2. Natural stimulation and isolation of VSTs

3. Antigen presentation to T cells

4. T cell expansion

5. Surface expression of virus-specific construct

6. Transduction of T cells

7. Production of TCR or CAR Constructs

8. Cytotoxic activity analyzed

9. Antigen presentation to APCs incubated with viral peptide mix

10. Transduction of T cells

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**Virus Specific T-cells (VSTs)**

**Stem-cell donor-derived**

- Board implementation limited by:
  - Cost and complexity of individualized product manufacturing
  - Time needed to manufacturing (not immediately available for urgent cases)
  - Donor must be seropositive for virus of interest

**Third-party**

- “Off the shelf”
- Manufactured from third-party donors to recognize one or more viruses
- Partially HLA-matched
**Off-the-Shelf VSTs after AlloHCT**

- Bank of VSTs that recognized EBV, AdV, CMV, BKV, and HHV-6
- 38 patients received VSTs
- BKV specific results
  - 16 patients, 14 with BKV HC
  - 13/14 BKV HC patients with CR of gross hematuria by week 6 post infusion
  - One patient able to proceed to 2nd HCT due to resolved hematuria
- AdV specific results
  - 7 patients: 4 CRs, 1 PR, 2 nonresponses
  - One patient with AdV-associated pneumonitis and HC with a PR

**Knowledge Check**

Which of the following treatments for refractory HC or BKV-HC is **least** likely to provide clinical benefit:

A. Intravesical silver nitrate  
B. Cidofovir  
C. Virus-Specific T-cells  
D. Leflunomide

**Summary**

- HC occurs in up to 70% of patients after alloHCT, most commonly caused by BKV.
- While supportive measures are often sufficient, patients with refractory HC may require BKV-directed antiviral therapy or one of a number of different intravesical or systemic treatments. Data supporting any of these treatment modalities is not robust.
- While more data is needed, VSTs provide a promising cellular therapy for BKV-HC.
References

