Viral Infections in the Immune Compromised Host

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Declaration of Disclosure

• In the past 12 months, I have had the following financial relationships with the manufacturer of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity:
  – Alios – Research Grant for RSV study
  – All monies go directly to my university and not to me

• I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation
Stem Cell Transplant Recipients
Immune Risks for Infection

• Neutropenia (early)
  – Bacterial infections
  – Fungal infections

• Impaired cellular and humoral immunity (late)
  – Bacterial infections
  – Fungal infections
  – Viral infections
Stem Cell Transplant Recipients
Pulmonary Complications

• Bacterial pathogens
  – *Pseudomonas aeruginosa*
  – Streptococci
  – Legionella
  – *Staphylococcus aureus*
  – Aspiration events with severe mucositis (early after BMT)
  – Encapsulated sinopulmonary pathogens (late after BMT)

• Filamentous fungi
  – Early and late
  – *Aspergillus fumigatus*
Stem Cell Transplant Recipients Pulmonary Complications

- Respiratory virus infection follows seasonal epidemiology
  - Increased risk for lower tract involvement
  - Influenza, RSV, Parainfluenza 3, human metapneumovirus
  - Adenovirus: reactivation and acute infection

- Herpesviruses
  - CMV with prolonged impairment of cellular immunity
  - HSV classically described with prior airway manipulation
Stem Cell Transplant Recipients
Early Non-Infectious Lung Injury

• Diffuse alveolar hemorrhage
  – Bleeding in alveolar space
  – Heterogeneous etiology
    • Vasculitis, drug-induced injury, cancer chemotherapy, thrombocytopenia

• Idiopathic pneumonia syndrome
  – Within first 120 days of HSCT
  – Risks: conventional ablative conditions, acute GVHD (inflammatory pathogenesis?)
Stem Cell Transplant Recipients
Late Pulmonary Syndromes

• Infectious
  – CMV disease
  – Respiratory virus infections
  – *Pneumocystis jirovecii* (previously called *Pneumocystis carinii*)

• Non-infectious
  – Bronchiolitis obliterans organizing pneumonia
Stem Cell Transplant Recipients
Cytomegalovirus Infection

• Primary infection occurs in seronegative patients (R-) from positive graft (D+) or blood products
• Reactivation occurs in seropositive patients (R+)
  – Reactivation alone causes cytokine storm, GVHD, disease
  – Risk for disease dependent on immunity
  – Highest risk group for viral disease is D-/R+
Stem Cell Transplant Recipients
Cytomegalovirus Disease

- Pneumonitis
  - Indolent cough
  - Fever
  - Shortness of breath
  - Interstitial infiltrates

- Gastrointestinal disease
  - Esophagitis
  - Colitis
  - Hepatitis (rare)

- Central nervous system disease
  - Encephalitis
  - Retinitis (less frequent)
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Period</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Marty et al.</td>
<td>Lancet ID</td>
<td>2011</td>
<td>227</td>
<td>Early</td>
<td>4.8%</td>
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<tr>
<td>Marty et al.</td>
<td>NEJM</td>
<td>2013</td>
<td>59</td>
<td>Early</td>
<td>3.0%</td>
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<tr>
<td>Chemaly et al.</td>
<td>NEJM</td>
<td>2014</td>
<td>33</td>
<td>Early</td>
<td>0%</td>
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<tr>
<td>Boeckh et al.</td>
<td>Ann Int Med</td>
<td>2014</td>
<td>89</td>
<td>Late</td>
<td>2.0%</td>
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</table>
CMV PCR-based Risk Adapted Strategy

Immuno-suppression

CMV doubling time

Risk Groups

High

Short

Low

Long

Cord blood

Allograft
- High-dose steroids
- T cell depletion
- Anti-T cell antibodies
- CD34 selection

Allograft
- Low dose steroids
- No T cell depletion or anti T cell antibodies

Allograft
- after day 100

Boeckh & Ljungman Blood 2009
Stem Cell Transplant Recipients
Cytomegalovirus Disease

- Treatment concepts
  - Preemptive therapy with ganciclovir based upon PCR
    - Different than prophylaxis
    - Novel drugs under investigation
  - Induction therapy then maintenance
  - Resistance to ganciclovir is rare
    - Different than in solid organ transplant patients
    - Most failures are due to steroids, T cell depletion
Maximum CMV Viral Load Before Day 100 And Mortality after Day 100

Cumulative Incidence of Overall Mortality by 1 Year

Cumulative Incidence of Non-relapse Mortality by 1 Year

Overall Mortality
- Any positive- 150 IU/ml: $1.27 (0.8-2.0)$
- 150-1000 IU/ml: $1.55 (1.0-2.4)$
- >1000 IU/ml: $2.04 (1.2-3.4)$

Non-relapse Mortality
- Any positive- 150 IU/ml: $1.06 (0.6-1.9)$
- 150-1000 IU/ml: $1.16 (0.7-2.1)$
- >1000 IU/ml: $2.05 (1.1-3.9)$

Green ML et al., Lancet Haematology, 2016
Maribavir: High Dose Phase II Results

Maribavir Versus Valganciclovir for Preemptive Treatment of Cytomegalovirus (CMV) Viremia: A Randomized, Dose-Ranging, Phase 2 Study Among Hematopoietic Stem Cell Transplant (SCT) and Solid Organ Transplant (SOT) Recipients

Maertens J ID Week, New Orleans, LA, USA, 26–30 October 2016
## Maribavir: High Dose Phase II Results

<table>
<thead>
<tr>
<th>Responders (treatment effect estimate), n (%)</th>
<th>MBV dose</th>
<th>All MBV doses, n=120</th>
<th>VGC</th>
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<tbody>
<tr>
<td></td>
<td>400 mg BID, n=40</td>
<td>800 mg BID, n=40</td>
<td>1200 mg BID, n=40</td>
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<tr>
<td><strong>Week 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26/39 (67); 50, 81</td>
<td>23/40 (58); 41, 73</td>
<td>23/38 (61); 43, 76</td>
</tr>
<tr>
<td>OR</td>
<td>1.42; 95% CI 0.62, 3.24</td>
<td>1.52; 95% CI 0.52, 4.30</td>
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<tr>
<td><strong>Week 6</strong></td>
<td>31/39 (79); 64, 91</td>
<td>33/40 (83); 67, 93</td>
<td>28/38 (74); 57, 87</td>
</tr>
<tr>
<td>OR</td>
<td>1.22; 95% CI 0.91, 1.64</td>
<td>1.12; 95% CI 0.77, 1.61</td>
<td></td>
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</tbody>
</table>

- Most TEAEs were mild to moderate in severity.
- Gastrointestinal AEs: MBV (20–23%) versus VGC (10–15%)
- Taste changes: MBV (40%) versus VGC (3%), no apparent dose effect
- Neutropenia (ANC <1000/mm3): MBV (5%) versus VGC (18%)
Maribavir: High Dose Phase II Results
Maribavir: Phase III Studies

A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir

400 mg BID

Clinicaltrials.gov NCT02931539

Status: now enrolling at UAB

A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients

400 mg BID

Clinicaltrials.gov NCT02927067

Status: now enrolling at UAB
Letermovir

- Non nucleoside
- CMV terminase inhibitor
- CMV-specific
- Oral administration

Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation

Roy F. Chemaly, M.D., Andrew J. Ullmann, M.D., Susanne Stoelben, M.D., Marie Paule Richard, M.D., Martin Bornhäuser, M.D., Christoph Groth, M.D., Hermann Einsele, M.D., Margarida Silverman, M.D., Kathleen M. Mullane, M.D., Janice Brown, M.D., Horst Nowak, Ph.D., Katrin Kölling, M.Sc., Hans P. Stobernack, D.V.M., Peter Lischka, Ph.D., Holger Zimmermann, Ph.D., Helga Rübsamen-Schaeff, Ph.D., Richard E. Champlin, M.D., and Gerhard Ehringer, M.D., for the AIC246 Study Team

The NEW ENGLAND JOURNAL of MEDICINE

MAY 8, 2014  VOL. 370  NO. 19
Letermovir

Marty F et al. ASBMT/CIBMTR Tandem Meeting, Orlando, FL, USA, 2017
Brincidofovir

- Nucleotide analog
- Converted intracellularly to Cidofovir
- Long intracellular $T_{1/2}$

- DNA polymerase inhibitor (broad spectrum)

CMX001 to Prevent Cytomegalovirus Disease in Hematopoietic-Cell Transplantation

Francisco M. Marty, M.D., Drew J. Winston, M.D., Scott D. Rowley, M.D., Estil Vance, M.D., Genovefa A. Papanicolaou, M.D., Kathleen M. Mullane, D.O., Thomas M. Brundage, M.S., Alice T. Robertson, Ph.D., Susan Godkin, R.Ph., Hervé Momméja-Marin, M.D., and Michael Boechk, M.D., for the CMX001-201 Clinical Study Group*

![Graph showing probability of CMV DNAemia > 1000 copies/mL or CMV disease over days after transplantation with different treatment groups: Placebo, 40 mg qW, 200 mg qW, 100 mg qW, 100 mg BIW, 200 mg BIW.](image)
Brincidofovir: Phase III Study

Marty et al. ASBMT/CIBMTR Tandem Meeting, Honolulu, HI, USA, 2016
Brincidofovir: Phase III Study Subset Analysis

Days Post Transplant
Marty et al. ASBMT/CIBMTR Tandem Meeting, Honolulu, HI, USA, 2016
<table>
<thead>
<tr>
<th>Organ Stage</th>
<th>Skin (N=303)</th>
<th>Liver (N=303)</th>
<th>Gut (N=303)</th>
<th>Skin (N=149)</th>
<th>Liver (N=149)</th>
<th>Gut (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>49 (16.2%)</td>
<td>9 (3.0%)</td>
<td>88 (29.0%)</td>
<td>24 (16.1%)</td>
<td>1 (0.7%)</td>
<td>28 (18.8%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>42 (13.9%)</td>
<td>14 (4.6%)</td>
<td>40 (13.2%)</td>
<td>18 (12.1%)</td>
<td>0</td>
<td>7 (4.7%)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>22 (7.3%)</td>
<td>7 (2.3%)</td>
<td>33 (10.9%)</td>
<td>8 (5.4%)</td>
<td>3 (2.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0</td>
<td>6 (2.0%)</td>
<td>13 (4.3%)</td>
<td>3 (2.0%)</td>
<td>3 (2.0%)</td>
<td>3 (2.0%)</td>
</tr>
</tbody>
</table>

Eight-fold higher use of corticosteroids in the brincidofovir arm

Median cumulative prednisone-equivalent of 26 mg/kg vs. 3 mg/kg through week 14

Marty et al. ASBMTCIBMTR Tandem Meeting, Honolulu, HI, USA, 2016
Stem Cell Transplant Recipients
Pneumocystis Pneumonia

- Common late after BMT
  - Steroid receipt, T cell depletion
- Prophylaxis 6 months with chronic GVHD
  - Trimethoprim/sulfamethoxazole
  - Dapsone, atovaquone, aerosolized pentamidine less effective, and other infections can occur
- Late diagnoses with less sensitive bronchoalveolar lavage direct fluorescent antibody
Stem Cell Transplant Recipients
Toxoplasmosis

- Clusters of disease (some early) reported in BMT patients
  - T-cell depleted BMT
  - Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease, with preemptive therapy
- Pneumonia, encephalitis, fever
Stem Cell Transplant Recipients
Bronchiolitis Obliterans

- Chronic GVHD of lung
  - Allore cognition of lung antigens
- Circumferential fibrosis of terminal airways
- Ultimately leads to airflow obstruction
Stem Cell Transplant Recipients

Graft vs. Host Disease (GVHD)

- **Acute (early after HSCT)**
  - Fever
  - Rash
  - GI: hepatic, colon

- **Chronic (late after HSCT)**
  - Skin changes (lichen planus, scleroderma)
  - Hepatic (cholestatic)
  - Ocular (keratoconjunctivitis)
  - GI (oral, dysphagia)
  - Pulmonary syndromes
Stem Cell Transplant Recipients
Causes of GI Disease in BMT

- **Hepatitis**
  - GVHD
  - Herpesviruses (CMV, VZV)
  - Hepatitis B virus
    - Increased viral replication and liver damage
    - Hepatitis not common during neutropenia

- **Colitis**
  - GVHD
  - CMV
  - *Clostridium difficile*
  - Norovirus (chronic diarrhea mimicking GVHD)
  - Adenovirus
Stem Cell Transplant Recipients

Adenovirus Following BMT

• More common in children, high risk BMT
  – Severe GVHD and steroids

• Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis

• No controlled treatment studies
  – Taper immunosuppression
  – Cidofovir most active in vitro
    • Brincidofovir failed in open label study in late stage adenoviral disease, compared with historical controls
  – Ribavirin not effective in larger studies
Stem Cell Transplant Recipients
Causes of Hemorrhagic Cystitis

- Conditioning-related (early)
  - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)
Stem Cell Transplant Recipients
Causes of Neurologic Syndromes

• Infection
  – Herpesviruses: HSV, CMV, HHV-6
  – West Nile Virus
  – Pulmonary-CNS lesions
    • Invasive fungal infections
    • Nocardia
    • Toxoplasmosis

• Drugs: carbapenems, cefepime, posterior reversible encephalopathy syndrome (PRES)
Stem Cell Transplant Recipients
HHV-6 Following BMT

- HHV-6 seropositivity > 95% after 2 yoa
  - Early reactivation common after BMT (38-60%)
  - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis
  - Nonspecific presentation (confusion, memory loss, EEG/MRI: temporal)
  - Unrelated donor or umbilical cord blood SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- Treat with ganciclovir, foscarnet, cidofovir
Stem Cell Transplant Recipients
Posterior Reversible Encephalopathy

• Usually early after HSCT (within first 3 months)
• Calcineurin inhibitors
  – Cyclosporin
  – Tacrolimus
• Seizures, visual changes, mental status changes
Stem Cell Transplant Recipients

Zoster

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
  - Classic: abdominal pain, transaminitis late
  - Can occur without skin lesions
- VZV seropositive
- Severe GVHD
- Acyclovir prophylaxis effective long-term
Stem Cell Transplant Recipients
Summary

- Fundamentals of risk
  - Early: mucositis, neutropenia
  - Late: GVHD
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: alveolar hemorrhages, idiopathic pulmonary syndrome (IPS)
  - Late pulmonary syndromes
    - CMV, respiratory viruses, invasive fungal infection
    - Non-infectious: bronchiolitis obliterans organizing pneumonia (BOOP)
Stem Cell Transplant Recipients
Summary

• Syndromes
  – Hemorrhagic cystitis
    • BK
    • Non-infectious: conditioning
  – Diarrhea – colitis – hepatitis
    • Herpesviruses
    • Non-infectious: GVHD
  – Neurologic syndromes
    • Herpesviruses (including HHV-6), West Nile Virus, toxoplasmosis
    • Non-infectious: posterior reversible encephalopathy syndrome (PRES), antibiotics
Summary of New Antivirals for CMV

- **Maribavir** (high dose) (Shire)
  - Phase III study in refractory/resistant infection underway
  - Phase III study of preemptive therapy underway

- **Letermovir** (Merck)
  - Phase III completed, results forthcoming

- **Brincidofovir** (Chimerix)
  - Failed Phase III
  - IV formulation in development
Bacterial Infections in Neutropenic Patients

- ARDS, rash, mucositis $\rightarrow$ viridans Streptococci
- Sepsis with $\beta$-lactams $\rightarrow$ Stenotrophomonas, ESBL
- Sepsis with carbepenems $\rightarrow$ Klebsiella pneumoniae carbapenemase (KPC)
- Lung and skin lesions $\rightarrow$ Pseudomonas aeruginosa, fungi
- Skin lesions, gram + $\rightarrow$ Corynebacterium jeikeium
- Mucositis (upper and lower tract) $\rightarrow$ Fusobacterium spp., Clostridium spp., Stomatococcus mucilaginous
Fungal Infections in Neutropenic Patients

• Not receiving antifungal prophylaxis
  – *Candida albicans*, *Candida tropicalis*
  – Mucositis, colonization, neutropenia
  – Acquired through GI tract or catheter

• Receiving azole prophylaxis
  – *Candida glabrata*, *Candida krusei*
  – *Candida parapsilosis* (catheter, IV infusates)

• Mold infections
  – *Aspergillus fumigatus* most common
  – Risk increases with duration of neutropenia or prior neutropenic episodes
Pulmonary Fungal Infections in Neutropenic Patients

• *Aspergillus* species most common

• Nodular, tracheobronchial abnormalities (sometimes with “halo”) that enlarge before necrotizing

• Differential diagnosis
  – *Fusarium*, *Scedosporium*, others
  – Mucormycoses
Skin Lesions in Neutropenic Patients

- Candidiasis
  - Small, tender papules
- Herpes simplex virus
  - Vesicular
- Aspergillus
  - Ulcerative, necrotic
- Other filamentous fungi (*Fusarium, Pseudallescheria boydii*)
  - Multiple, erythematous, different stages
- *Pseudomonas aeruginosa*
  - Ecthyma gangrenosum
Fusarium in Neutropenic Patients

• Invasive pulmonary disease with skin lesions
• Locally invasive infections in neutropenic patients
  – Keratitis
  – Onychomycosis
Enterocolitis (Typhlitis) in Neutropenic Patients

- Necrotizing inflammation with transmural infection of damaged bowel wall
- Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
- Can be accompanied by bacteremia
- Medical and (less often) surgical management
Hepatosplenic Candidiasis in Neutropenic Patients

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alkaline phosphatase), fever, leg/flank pain
- Differential diagnosis: other fungi, bacteria, lymphoma
- *Candida albicans* most common