Updates in the Treatment and Prophylaxis of CMV Reactivation in Allogeneic Stem Cell Transplantation

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Disclosures

- Nothing to disclose

Objectives

- By the end of the presentation, attendees should be able to:
  - Describe the prophylactic and pre-emptive treatment strategies for CMV reactivation in HSCT, including current recommendations for standard treatment guidelines
  - Recall different pharmacologic agents with anti-CMV activity, including the recently FDA-approved letermovir, such as: dosing, route, frequency, adverse effects, and other pertinent warnings
  - Review and analyze the published literature regarding letermovir in primary prophylaxis against CMV reactivation in seropositive allogeneic stem cell transplant patients
  - Evaluate letermovir's current role and future areas for research in the treatment and prophylactic modalities for CMV reactivation in this patient population

Cytomegalovirus (CMV)

Centers for Disease Control and Prevention. (2018).

- Member of the herpesvirus family
- One in three children are infected by age five
- Over half of adults are infected by age 40
- Transmitted by contact with bodily fluids
  - High concentrations in urine, saliva in small children

Cytomegalovirus (CMV) Infection

Centers for Disease Control and Prevention. (2018).

- Initial infection – mononucleosis-like reaction
- Virus remains latent in leukocytes, may occasionally reactivate
- Disease from reactivation rare in immunocompetent hosts
- Populations at high risk for complications from CMV infection
  - Infants infected in utero (congenital CMV infection)
  - Very low birth weight and premature infants
  - People with compromised immune systems

CMV in Stem Cell Transplant

Boeckh, et al. *Blood* 2009;113(23):5711-19.
Chaer, et al. *Blood* 2016;128(23):2624-36.

- Leading viral cause of morbidity and mortality in HSCT patients
- Direct effects on organ systems
  - Gastroenteritis
  - Retinitis
  - Pneumonia
  - Hepatitis
  - Encephalitis
- Indirect effects
  - Increased risk for graft failure
  - Increased acute/chronic GVHD
  - Secondary bacterial/fungal infections

CMV in Stem Cell Transplant

- Important factors to consider before HSCT
  - CMV status of patient/donor
  - Level of immunosuppression before HSCT
  - Conditioning/immunosuppression regimen

Strategies against CMV in HSCT

- Prophylaxis
- Pre-emptive

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Prophylaxis against CMV in HSCT

- Administering antiviral prophylaxis to **ALL** HSCT recipients
  - Ganciclovir IV from engraftment to day 100
  - Optional – brief prophylactic course during pre-transplant conditioning

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Prophylaxis against CMV in HSCT

- Pros
  - Lower incidence of CMV reactivation
- Cons
  - Excessive exposure to toxic anti-CMV pharmacological agents resulting in adverse effects
  - Treatment of patients who would never develop CMV reactivation

Pre-emptive Treatment of CMV

- pp65 antigenemia testing
  - Less sensitivity, particularly in leukopenic patients
- Quantitative CMV DNA testing by PCR
  - High sensitivity for low-level CMV reactivation
  - CMV reactivation by PCR testing can pre-date symptomatic infection by several weeks
  - Wide variability of viral load values among different assays
- Add anti-CMV agent when patient's CMV quantitative levels rise to institution-specific cutoffs

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Pre-emptive Treatment of CMV

- Pros
  - Avoid unnecessary exposure to toxic anti-CMV pharmacological agents
- Cons
  - Requires weekly lab testing to detect pre-symptomatic reactivation
  - Variability of assays, interpretation of results
  - Still results in having to use toxic agents if CMV reactivates

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Pharmacologic Agents with Anti-CMV Activity

- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Letermovir

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Tomblyn M, et al. *Biol Blood Marrow Transplant* 2009;15:1143-1238.
Vuorinkala M, et al. *Bone Marrow Transplant* 2001:28:265-70.

Acyclovir/Valacyclovir

- Historically not associated with anti-CMV activity
- Small retrospective study using high-dose valacyclovir (1g TID) showed significant reduction in CMV reactivation

Cytovene® [package insert].

Ganciclovir

- Mechanism
  - Nucleoside analogue of 2'-deoxyguanosine
  - Competitively inhibits DNA replication of herpes viruses
  - Virostatic agent
- Dosing
  - Induction: 5mg/kg/dose IV every 12 hours for 7 to 14 days
  - Maintenance: 5mg/kg/dose IV once daily
    - Duration dependent on duration and degree of immunosuppression

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Cytovene® [package insert].

Ganciclovir

- Warnings/Clinical pearls
  - Myelosuppression
    - Do not administer if ANC <500 and/or platelets <25
    - May require growth factor support
  - Teratogenicity
  - Dose adjustments for renal impairment

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Milano F, et al. Blood. 2011 Nov;118(20):5689-96.
Boeckh M, et al. *Blood* 1996;88(10):4063.
Goodrich JM, et al. N Engl J Med. 1991;325(23):1601.
Boeckh, et al. *Blood* 2009;113(23):5711-19.

Ganciclovir

- Prophylaxis
  - Several randomized trials showed reduced CMV reactivation
  - Did not correlate with survival advantage
- Pre-emptive
  - Multiple randomized trials have shown reduced CMV reactivation with improved overall survival

Valcyte® [package insert].

Valganciclovir

- Oral prodrug of ganciclovir
  - Rapid conversion to ganciclovir in the body
  - 10x bioavailability of ganciclovir (70% vs. 7%)
- Dosing
  - Induction (off-label) – 900mg by mouth twice daily for 7 to 14 days
  - Maintenance (off-label) – 900mg by mouth once daily for 7 to 14 days or until indicator test is negative

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Valcyte® [package insert].

Valganciclovir

- Warnings/Clinical pearls
  - Myelosuppression
    - Do not administer if ANC <500 and/or platelets <25
  - Teratogenicity
  - Dose adjustments for renal impairment
  - Cost - $65 per 450mg tablet = $260/day of induction

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Ayala E, et al. Bone Marrow Transplant. 2006;37:851-856.
Einsele H, et al. Blood. 2006;107:3002-08.

Valganciclovir

- Although not FDA-approved for CMV prophylaxis/treatment in HSCT, several studies have shown efficacy similar to that of ganciclovir
- Concerns with absorption in gut GVHD
  - Not shown in PK studies
- Cost

Foscavir® [package insert].

Foscarnet

- Mechanism
  - Pyrophosphate analogue that inhibits several viral-specific RNA and DNA polymerases
  - Virostatic agent
- Dosing (off-label)
  - Induction: 60mg/kg IV every 12 hours for 7 to 14 days
  - Maintenance: 90mg/kg IV once daily until indicator test is negative – minimum 2 weeks

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Foscavir® [package insert].

Foscarnet

- Warnings/clinical pearls
  - Renal dosing/toxicity
    - Requires IV fluid bolus pre- and post-infusion
    - Dose adjustments ambiguous with HSCT dosing schema
    - Based on mL/min/kg
  - Electrolyte abnormalities
    - Low K, Mg, Ca, Phos
    - Risk for seizures
  - QT prolongation

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Reusser P, et al. Blood. 2002;99:1159-1164.
Morretti S, et al. Bone Marrow Transplant. 1998;22:175-180.

Foscarnet

- Pre-emptive
  - Multiple studies have shown foscarnet is equally efficacious for CMV reactivation to ganciclovir
  - No synergy seen when combining foscarnet with ganciclovir

Vistide® [package insert].

Cidofovir

- Mechanism
  - Selective inhibition of viral DNA synthesis by incorporation into growing viral DNA chain
- Dosing (off-label)
  - Induction: 5mg/kg/dose IV with concomitant probenecid once weekly for 2 consecutive weeks
  - Maintenance: 5mg/kg/dose with concomitant probenecid once every 2 weeks

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Vistide® [package insert].

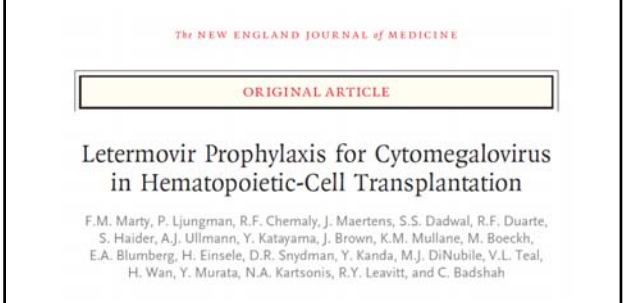
Cidofovir

- Warnings/Clinical pearls
  - Must use concomitant probenecid
    - 2 grams 3 hours prior to cidofovir infusion, 1 gram 2 hours after completion, and 1 gram 8 hours after completion
    - Nausea/vomiting related to probenecid
  - Renal toxicity
    - Can result in dialysis and/or contributing to death in as few as 1 to 2 doses
    - Must receive a 1L saline bolus over 1-2 hours before dose
    - Use is contraindicated if SCr >1.5mg/dL, CrCl ≤55mL/min, or urine protein ≥100mg/dL (≥2+ proteinuria)

Ljungman P, et al. Blood. 2001;97(2):388.

Cidofovir

- Pre-emptive
  - Fewer randomized studies are available for cidofovir in pre-emptive setting
  - Retrospective studies show efficacy in first- and second-line pre-emptive setting
    - High rate of discontinuation due to toxicity


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

F.M. Marty, P. Ljungman, R.F. Chemaly, J. Maertens, S.S. Dadwal, R.F. Duarte, S. Haider, A.J. Ullmann, Y. Katayama, J. Brown, K.M. Mullane, M. Boeckh, E.A. Blumberg, H. Einsele, D.R. Snydman, Y. Kanda, M.J. DiNubile, V.L. Teal, H. Wan, Y. Murata, N.A. Kartsonis, R.Y. Leavitt, and C. Badshah

Marty FM, et al. *New Engl J Med* 2017;377(25):2433-44.

Letermovir

- FDA approved in 2017 for prophylaxis against CMV infection in adult seropositive recipients of HSCT
- Approval based on a Phase 3, randomized, double-blind, placebo-controlled multinational trial
- Primary end-point: proportion of patients who had clinically significant CMV infection through week 24 after transplantation
- Patients following through week 48 after transplantation
- Intent-to-treat analysis

Marty FM, et al. *New Engl J Med* 2017;377(25):2433-44.

Letermovir

- Results – primary endpoint
  - Week 24 - 122 of 325 patients (37.5%) in letermovir group vs. 103 of 170 patients (60.6%) in placebo group had clinically significant CMV infection ($p < 0.001$)

Marty FM, et al. *New Engl J Med* 2017;377(25):2433-44.

Letermovir

- Results – secondary endpoints
  - Week 14 – 62 of 325 patients (19.1%) in letermovir groups vs. 85 of 170 patients (50.0%) in placebo group had clinically significant CMV infection ($p < 0.001$)
  - All cause mortality
    - Week 24 - 10.2% vs. 15.9% ($p = 0.03$)
    - Week 48 - 20.9% vs. 25.5% ($p = 0.12$)
  - Adverse events
    - No statistically significant difference in adverse effects between the groups
    - Vomiting (18.5% vs. 13.5%), edema (14.5% vs. 9.4%), dyspnea (8.0% vs. 3.1%), myalgia (5.1% vs. 1.6%), atrial fibrillation/flutter (4.6% vs. 1.0%), and ALT 5x ULN (3.5% vs. 1.6%) were biggest differences
      - Further analysis did not show a relationship with letermovir exposure and atrial arrhythmias

Prevymis® [package insert].

Letermovir

- Dosing – 480mg orally/IV once daily
  - Starting between day 0 and day 28 post-transplant
  - Dose reduce to 240mg with concomitant cyclosporine
- Renal dose adjustments
  - None for CrCl >10mL/min
  - Insufficient data for use in patients with CrCl <10mL/min
  - Accumulation of intravenous vehicle, hydroxypropyl betadex, in patients with CrCl <50mL/min
- Hepatic dose adjustments
  - None for Child-Pugh Class A or B
  - Not recommended for Child-Pugh Class C

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Prevymis® [package insert].

Letermovir

- Drug interactions
  - Substrate of CYP2D6 (minor), CYP3A4 (minor)
  - Moderate inhibitor of CYP3A4
  - Substrate/inhibitor of OATP1B1/3 transporters
  - Substrate of P-glycoprotein
  - Cyclosporine associated with a 2-4 fold increase in overall letermovir exposure
    - Decrease letermovir dose to 240mg daily with concomitant cyclosporine
    - No dose reduction needed with concomitant tacrolimus

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Prevymis® [package insert].

Letermovir

- Warnings/Clinical pearls
  - Not active against other herpesviruses besides CMV
    - Patients will require additional HSV/VZ prophylaxis
  - Mutations in UL56 may infer resistance to letermovir
    - Cross resistance does not occur in patients with resistance to CMV DNA polymerase inhibitors
  - Cost - $234 per tablet; $23,400 for 100 days of treatment

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Future Directions

- Additional questions for letermovir
  - Treatment of CMV reactivation
  - Secondary prophylaxis against CMV reactivation
  - Optimal time for initiation
  - Pharmacoeconomic data

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Marty FM, et al. *Biol Blood Marrow Transplant* 2016;22:523.
Marty FM, et al. *Lancet Infect Dis* 2011;11:284-92.

Future Directions

- Investigational Agents
  - Maribavir
  - Brincidofovir

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Conclusion

- CMV infection is associated with increased morbidity/mortality in HSCT patients
- Two modalities exist (prophylaxis, pre-emptive treatment) for preventing symptomatic CMV infection
- Most agents with anti-CMV activity are associated with significant toxicity
- Letermovir, recently FDA approved, offers a new option for prophylaxis in these patients
- While outcomes are promising, further investigation into the pharmacoeconomic impact of this treatment is warranted

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Questions?

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