Prophylaxis vs. Preemptive Treatment of Cytomegalovirus

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Agenda

- Burden of CMV Disease in Post-Transplant Patients (HSCT and SOT)
- Assessing CMV Disease Risk
- Appropriate Pharmacotherapy Regimen for Post-Transplant Patients
- In-development Agents to Treat/Prevent CMV Infection
Learning Objectives

- Characterize the burden of CMV infection in the post transplant setting
- Interpret diagnostic testing to better categorize CMV risk in post transplant patient
- Summarize the rationale for preemptive treatment and universal prophylaxis against CMV in the post treatment setting
- Discuss recent advances in the management of CMV infection
Background

- CMV is a prototypic –B- herpesvirus that infects humans causing life-long persistent infection.
- CMV is a leading cause of morbidity and mortality in transplant recipients despite advances in preventative strategies.
- CMV disease is influenced by age, geography, culture, and social economic status.
- Among individuals with a competent immune system, CMV will result in symptomatic disease.
Background

- 50-80% of the US population over the age of 40 is estimated to be infected with CMV.
- *Immunosuppressed* patients who receive transplants:
  - CMV disease can occur from *re-activation* of latent infection or from newly acquired infections.
- CMV is the most common opportunistic infection among transplant recipients.
Background

- CMV is associated with > than 280,000 direct medical cost among patients with HSCT & SOT and prolonged hospital stay.
- Most children in developing countries become infected early in life compared to developed countries as many 50-80 % of the population are infected by adulthood most frequently during childhood and adolescence.
Why such a concern

- Since 1990 the yearly number of organ transplants in the US has **nearly doubled**, according to the Virginia-based *United Network for Organ Sharing*

- The number of stem cell transplant from donors have increased **4-fold** according to preliminary data from the Center for Blood Marrow Transplant Research & Medical College of Wisconsin.

- With the number to transplants increasing so too does the treat from virus that lives in the body of most people.
Dormant Danger

- CMV usually lies dormant and is kept in check by the immune system.
- When the immune system is suppressed as in transplant recipients who receive drugs with these effects the virus can reactivate.
- “More types of patients are receiving transplants” ~ Roy Chemaly, Virologist at MD Anderson in Houston, Texas
  - ex. (Elderly and patients at high risk for Leukemia)
Modes of Transmission

- **Oral** transmission - early age
- **Sexual** transmission – adulthood
- **Mother to child** transmission – non-leukocyte–depleted blood products through placenta
- **Orthotopic liver transplant recipients**
Burden of Disease

- Great cost and increased length of stay has been noted in the first year post transplantation.
  - Bacteremia ($p = .0001$)
  - CMV disease ($p = .0007$)
  - Abdominal re-exploration excluding re-transplantation ($p = .0070$)
  - Recipient age $< 16$ ($p = 0.0352$), which includes the number of blood products or FFP administered during transplant
What factors contribute to increased burden of disease

- CMV primarily causes infection due to ongoing viral replication in the absence of symptoms, which can be seen after transplantation.

- CMV disease has been associated with the following:
  - Acute /Chronic Allograft rejection
  - HCV reoccurrence
  - Opportunistic Infections
  - Decreased survival
Who will most likely be affected?

- 18-29% of Liver Transplant recipients will develop CMV disease, particularly those who are elderly or patients at high risk of Leukemia.
What is currently being done to prevent CMV Disease in LTR

- Acyclovir, ganciclovir (GCV) valganciclovir (VGCV), and CMV immunoglobulin
- Only CMV immunoglobulin and oral ganciclovir have been approved by the FDA for anti-CMV prophylaxis in LTR
- In clinical trials, oral GCV and VGCV were equally effective in preventing both CMV disease and infection
Valgancyclovir

- VGCV in *one clinical trail* CMD was higher among LTR who received VGCV prophylaxis in a meta analysis looking at presumptive strategies in preventing CMD after liver transplantation.
- This lead to a *black box warning* for VGCV in LTR
Pathway of CMV

Cytomegalovirus

Vehiculization

Allograft Transplantation

Non-leucyte-depleted product

Placenta Mother

Child

Primary CMV (Immunocompetent host)

Mild

Asymptomatic

Latent Persistent Infection

cd14

Peripheral Bld Monocytes

In the Bone Marrow

cd33 & cd34

Myeloid Precursor Cells
Infiltration of CMV

These cells CD14, CD33, & CD34 of several organ & mucosal sites & diffuse cell types including:

- Macrophages
- Epithelial
- Endothelial

- Lungs
- Salivary Glands
- Kidneys
How CMV is Dispersed

Thus affecting the incompetence of the immune system to clear the infection

From these sites the virus is shed intermittently

Cytomegalovirus → Immune Invasion Gene

Expressed

Lytic → Latent

Infective Cycle
which allows the virus to escape from innate natural killer cells
What Triggers Reactivation of CMV

- Stress conditions and severe inflammatory mediators are known to trigger reactivation
- Why is there a Risk?
  - SOT + Allogenic Stem Cell Transplants
- Presentation
  - CMV presents as a Viral Syndrome
    - Fever, Malaise
    - Leukopenia
    - Tissue Invasive Disease
      - (GI or Pneumonia)
CMV Negative Recipients

CMV (N) – patient

- Allograft seropositive (D) (15-25% Transplant population)

CMV/ seropositive SOT (R)

- Treated w/T-cell depleting agent
  - Azemtazumab
  - Anti-thymocyte globulin or undergoing antirejection therapies greater risk for CMV including transplants of lung, pancreas, intestine
Effects of CMV

- CMV – linked with allograft rejection & graft loss
- Acute and chronic CVHD are at increased risk. Bacterial, Fungal superinfections and overall mortality
So what has been done?

Strategies to prevent occurrences of CMV End Organ Disease in the Transplant settings

- **Universal Prophylaxis**
  - Antiviral Therapy Early on Following Transplantation
  - Recommended for SOT at patients are highest risk for CMV end organ disease

- **Pre-Emptive Antiviral Therapy**
  - Antiviral prescribed to patients with active CMV replication
  - Intermediate to low risk managed with pre-emptive antiviral therapy

In contrast, Universal prophylaxis is not commonly used toin Allo-SCT because of potential hematologic toxicity
Results

- The incidence of CMV end organ disease developing early after transplantation has decreased dramatically in recent years, by both strategies equally effective SOT irrespective of the type of allograft.
- Late onset CMV disease (defined as CMV onset >100 days after transplant ALLo-SCT patient after cessation of antiviral prophylaxis in SOT recipients)
Results continued

- 25 to 30% D+ R-SOT recipients develop late onset disease within one year after transplant after completion of prophylaxis
- 15% of CMV seropositive Allo-SCT had active CMV infection or CMV end organ disease
Controversy

- Meta analysis of these two methods have yielded conflicting results for the prevention of CMV syndrome/diseases, rejection, graft loss, death and opportunistic infections.
- It is probable that that CMD and its outcomes may be different in liver and other SOT recipients.
- Prophylaxis can result in neutropenia and leukopenia.
Conclusion

- A review and post hoc sensitivities and analysis of good quality studies suggest that PE more effective than prophylactic strategy.
- Due to limited number of studies and limited number of outcomes reported, they were unable to compare the relative effects of both strategies on ACR (acute cellular rejection), GL (Graft Loss) and all-cause mortality.
Future Studies Needed

Large multi-center, adequately powered low risk of bias trail comparing these two strategies head to head would be useful for further evaluation of the significant issue that CMV represents in the liver transplant population.
Universal Prophylaxis

- Universal prophylaxis has been historically considered to be more effective than preemptive antiviral therapy. Strategies for CMV–related in SOT recipients
- Universal prophylaxis leads to overtreatment drug related toxicity is associated with increased incidence late onset disease.
Baseline and Post Transplant Parameters

What are the baseline and post transplant parameters for CMV End organ disease, but SOT & Allo-SCT?

- Presence or absence CMV IgG – best marker for addressing the risk of CMV end organ disease – SOT – R

- Universal prophylaxis (R- / D+) or a pre-emptive antiviral therapy strategy (most R+)
What test should be ordered

- 30 to 40% of seronegative R of seropositive allograft never develop active CMV infection.
- CMV-specific T-cell response include
  1. Flow cytometry
  2. Enzyme–linked immunosorbent spot assay
  3. Quantiferon CMV test - FDA cleared
- All need further standardization and validation before they can be implemented in routine clinical practice
Drawbacks

Use of antiviral for prevention or treatment of CMV viremia or CMV disease has two major drawbacks: toxicity and inevitable, the selection of resistant strains!
Assessment of Pre-treatment CMV Specific Cells

- Genotypic Analysis of transplant recipients determines the risk of active CMV infection and invasive disease.
- Implementation of molecular methods for viralogic monitoring of active CMV infection
- Assessment of CMV DNA levels in blood major breakthrough in CMV Infection
- Predetermine antiviral prophylaxis regimen's prescribes to high risk SOT patients
Cytomegalovirus
Recent Advances in Cytomegalovirus

- Perspectives on therapy for CMV infection in the setting hematopoietic stem cell transplantation (HSCT)
- Phase 3 trials of new novel agents which will shift our current standards therapeutic strategies
- The role of Natural Killer cells
Treatment as we know it now

- Treatment of CMV disease after HSCT consist of ganciclovir induction dose for 2 to 3 weeks, followed by maintenance dose, until signs and symptoms have resolved
- Cytopenias – foscarinet is an alternative concerned for renal failure and electrolyte abnormalities
- Valganciclovir
- Drug resistant CMV is rare, but should be suspected in patients with poor clinical outcomes
New Treatment for CMV

- **Chimerix** developed *Brincidofovir* - Broad spectrum DNA polymerase inhibitor. It’s a lipid-conjugated nucleotide analogue of cidofovir that has high oral bioavailability and long half life that allows twice a week dosing
  - Activity against a wide range of DNA Virus
  - CMV, Adenovirus and Herpes Simplex, Papillomavirus and Variola virus
- Two phase 3 trails
  - Prevent CMV in stim cell transplant patients
  - Treatment adenovirus infections
  - Side effect – some GI discomfort diarrhea, no bone marrow suppression, doesn’t effect WBC’s
New Treatment for CMV

- **GlaxoSmithKline** developed **Maribavir**
- **UL97 protein Kinase Inhibitor** – oral drug
- Combats CMV in individuals who had developed full-blown AIDS.
  - As AIDS improved or virtually non existent, ViroPharma licensed maribavir 2003 beyond HIV, failed to meet efficacy endpoints in phase 3 trails with liver and stim cell transplant patients.
Maribavir

- Specific activity against CMV
- Phase2 dose –ranging study HSCT recipitants showed that CMV disease or infection was reduced at all three dose levels, but the lowest dose of 100mg BID failed to prevent CMV disease.
- Has in vitro activity against ganclovir or cidofovir – resistant CMV, and some preclinical benefits at higher doses.
- Currently 2 ongoing trails examing higher doses of maribavir for the treatment of refractory or resistant CMV
New treatment in CMV

- Merk licensed from Wuppertal Germany based AiCuris released Letermovir, currently in phase 2 of development.
- CMV replicates by creating long strings of DNA containing multiple complete genome attached to the tail.
- If successful will be the first in new class of drugs that prevent CMV chopping its long DNA strand into individual genome unit.
- Phase 3 trails with stem cell transplant patients
Letermovir

- CMV terminates inhibitor highly selective anti-CMV agent
- Orally or intravenously and is highly active against wild type and multi-drug resistant CMV
- Phase 2 dose-escalation study of CMV-seropositive HLA matched HSCT recipients showed a reduction of prophylaxis failure, 240mg of Letermovir compared to placebo
- Drug well tolerated few SE
Leflunomide

- Drug approved by the Food and drug Administration for the treatment of arthritis with activity against several viruses, including CMV, BK virus.
- It’s been used in salvage therapy for CMV with mixed results
- No studies in efficacy and toxicity either as mono – or combination therapy has been performed.
Artesunate

- Antimalarial drug with broad activity against in vitro Herpes virus, hepatitis virus, HIV due to its ability to downregulate NF-kB or Sp1 pathway
- Antidotal reports in patients with complicated CMV infection
- No systemic evaluation of the efficacy and toxicity of artesunate for CMV treatment has been performed
Advances in T cell therapy

Adoptive transfer of donor-derived CMV reactive T-cells will hasten reconstitution of protective pathogens – specific immunity, potentially reducing the infective burden and associated treatment cost.
Biological Role of Natural Killer Cells

- Have a role in mediating resistance to viral infections like CMV. Some CMV viral particles can directly inhibit NK by pirating MCH-like domains thus inhibiting their response.
- NK cells have been demonstrated to mediate direct anti-tumor and antiviral immunity
- NK cells kill by perforin/granzyme which results in direct lysis of the cell.
Race for Vaccine

- Vaccine development is needed for long term solution.
- CMV vaccine has been a priority since 1999.
- Several companies are currently working on development including GSK, Merck, Pfizer and Sanofi, most of their early clinical trials have failed.
- TranVAX, a vaccine composed of DNA plasmid that encode CMV antigen, has made it to the phase 3 trial stage, developed by Astella Pharma.
- Currently phase 2 Kidney transplant and phase 3 in stem cell transplant.
Conclusion

- CMV is a ubiquitous pathogen which has been and will be around for years to come.
- As long as we have a need for SOT and LT in immunocompetent host the pathogens like CMV can be treated and prevented with new antiviral agents which will have the potential to shorten disease burden, decrease bone marrow toxicity and lessen organ rejection, sepsis and length of hospital stay.
Questions?
Comments?
References

Thank you!