Prevention of Cytomegalovirus Disease in Allogeneic Stem Cell Transplant: Are We Being Tricked to Treat?

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Objectives:

1. Understand the process of hematopoietic stem cell transplant and the risk of infections
2. Describe the epidemiology and classification of cytomegalovirus (CMV)
3. Review the methods for prevention of CMV
4. Formulate an evidence based recommendation for prevention of CMV disease
Hematopoietic Stem Cell Transplant (HSCT)

I. Overview of HSCT
   a. HSCT involves the administration of autologous (recipient’s own) or allogeneic (donor derived) stem cells into a recipient\(^1,2\)
      i. Hematopoietic stem cells give rise to myeloid and lymphoid lineages of blood cells
      ii. HSCT is indicated for many oncologic and non-oncologic conditions
   b. U.S. Transplant Data from the Center for International Blood and Marrow Transplant Research state that approximately 21,766 transplants were performed in 2016\(^3\)
   c. HSCT was first conceived as a rescue for the reconstitution of blood cells after the induction of life threatening irradiation\(^2\)
      i. Adapting this theory of rescue, the first ever bone marrow transplant was performed in 1957 for acute leukemia patients after administration of supralethal chemotherapy\(^4\)
      ii. Major complications developed including graft failure, graft versus host disease (GVHD), and/or death
   d. In 1958 the discovery of Human Leukocyte Antigens (HLA) occurred and numerous studies have helped elucidate the role of these antigens in HSCT\(^5\)
      i. HLA class I (Region A,B,C) and class II antigens (Region DP, DQ, DR) can elicit an immune response by presentation to donor derived T-cells
      ii. HLA disparity between donor and recipient has been associated with graft failure, delayed immune reconstitution, GVHD, and mortality
   e. Transplant process overview

Figure 1. Chart depicting HSCT stages\(^6-9\)
i. Mobilization: involves the movement of stem cells from the bone marrow into the blood with the help of granulocyte-colony stimulating factors for allogeneic HSCT and plerixafor for autologous HSCT.

ii. Hematopoietic stem cell collection: the process of collecting stem cells from the donor or recipient.
   a) Bone marrow harvesting: consists of aspirating bone marrow from the posterior iliac crest in a donor.
   b) Cord blood harvesting: following birth, an umbilical cord vein is collected, punctured, and then drained into an anticoagulated sterile closed harvesting system.
   c) Peripheral blood stem cell collection: blood is run through an apheresis machine which separates stem cells from other blood parts which are then collected for storage for infusion into the recipient.

iii. Conditioning regimen: process of eradication or suppression of the host’s stem cells in order for donor stem cells to engraft adequately and eradicate underlying malignant disease (may include chemotherapy, monoclonal antibody therapy and radiation to the entire body).

iv. Pre-engraftment: period where patients are profoundly pancytopenic and are at highest risk for bleeding and infections.

v. Engraftment phase: the process of transplanted stem cells traveling to the bone marrow of the recipient and beginning production of platelets, red blood cells and white blood cells.

Table 1: Comparison of autologous versus allogeneic hematopoietic stem cell transplant

<table>
<thead>
<tr>
<th>Autologous Graft</th>
<th>Allogeneic Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell source is self</td>
<td>Stem cell source is non-self (foreign)</td>
</tr>
<tr>
<td>Moderate morbidity, low mortality</td>
<td>High morbidity, high mortality</td>
</tr>
<tr>
<td>No graft versus host disease</td>
<td>Improved outcomes in leukemia and diseases of the bone marrow</td>
</tr>
<tr>
<td>Low infection risk</td>
<td>Risk of GVHD</td>
</tr>
<tr>
<td></td>
<td>Increased risk of infection due to prolonged immunosuppression</td>
</tr>
</tbody>
</table>

II. Graft versus host disease
   a. A condition that may develop in allogeneic HSCT where the donated graft views the recipient’s tissue as foreign and attacks the recipient’s tissues.
   b. Patients may develop acute or chronic GVHD which can affect various systems of the body.
   c. About 35-50% of HSCT recipient will develop acute GVHD.
   d. Risk factors
      i. Stem cell source
      ii. Donor and recipient mismatch
      iii. Age of the patient and donor
      iv. Conditioning regimen intensity
      v. GVHD prophylaxis
   e. Management
      i. Classified based on grade and stage
      ii. Managed through immunosuppression
iii. Degree of immunosuppression depends on the conditioning regimen and the level of HLA match
iv. GVHD is typically managed with steroids, calcineurin inhibitors or mTOR inhibitors

III. Infection Risk of HSCT

   a. Depending on the intensity of the conditioning regimen, patients may experience a period of profound pancytopenia spanning days to weeks depending upon the donor source

   b. Neutrophil recovery varies but typically occurs:
      i. Two weeks with G-CSF mobilized peripheral blood stem cell grafts
      ii. Two weeks with bone marrow grafts
      iii. Four weeks with umbilical cord blood grafts

   c. For several months patients experience a prolonged period of lymphocyte recovery with some patients not recovering fully for several years
      i. Deficiency in lymphocytes is paramount to infection risk
      ii. Lymphocytes are vital for viral immunity

   d. T-cell recovery is prolonged with CD8+ cells recovering faster than CD4+ cells
      i. CD4+ counts may provide the most readily available and predictive marker of the restoration of immune competence following HSCT
      ii. CD4+ recovery is associated with diminished infectious risk and improved transplant outcomes

   e. Risk Factors:
      i. GVHD severity and degree of therapeutic immunosuppression
      ii. Age
      iii. Comorbidities
      iv. Pathogen exposure prior to transplant of recipient and donor
      v. Graft associated factors
         a) Peripheral blood stem cell grafts have a more rapid immune reconstitution
         b) Umbilical cord blood transplantation
         c) Transplantation of profoundly T cell-depleted grafts
d) Haploidentical grafts  

e) Stem cell dose is vital and levels of $3 \times 10^6$ or more are associated with an improved hematopoietic recovery

**Figure 3. Type of infection risk based on time post-transplant**

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**Cytomegalovirus (CMV)**

<table>
<thead>
<tr>
<th>Phase 1: Pre-engraftment</th>
<th>Phase 2: Post-engraftment</th>
<th>Phase 3: Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, barrier breakdown (mucositis, central venous access devices)</td>
<td>Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing, but restricted T cell repertoire</td>
<td>Impaired cellular and humoral immunity; B cell &amp; CD4 T cell numbers recover slowly and repertoire diversifies</td>
</tr>
</tbody>
</table>

**Bacterial**
- Gram negative bacilli
- Gram positive organisms
- Gastrointestinal streptococci species

**Viral**
- Herpes Simplex Virus
- Cytomegalovirus
- Varicella/Zoster virus

**Fungal**
- Aspergillus
- Candida species
- Pneumocystis

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I. **Epidemiology**

   a. Transmission occurs via direct contact with infected secretions  
   b. Infants may be infected in utero  
   c. Cytomegaloviruses are among the most prevalent viral infections worldwide  
      i. 60-70% of the U.S. population is CMV seropositive  
      ii. CMV seropositivity increases with age and correlates with socioeconomic level and race

II. **Microbiology**

   a. CMV is a icosapentahedral capsid member of the herpesviridae family  
   b. Classification: Beta herpesvirus, it has a long replicative cycle and restricted host range  
   c. Multiplication: transcription, genome replication and capsid assembly occur in the host cell nucleus

III. **Pathogenesis**

   a. CMV carries mRNAs in the virion particle into the host cell

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5 Ramirez
b. Cytomegalovirus replicates mainly in the salivary glands and kidneys and is shed in saliva and urine\(^\text{17}\)

c. The cleaving of viral DNA and packaging of viral genes into preformed capsids is mediated by CMV-terminase complex (UL51, UL56, UL89)\(^\text{18,19}\)

d. UL97 is a viral kinase responsible for phosphorylation of natural viral and cellular protein substrates\(^\text{20}\)

e. UL54 is a DNA polymerase responsible for DNA replication\(^\text{21}\)

f. CMV grows in human epithelial, endothelial, smooth muscle, neurologic and fibroblast cells\(^\text{22}\)

g. CMV can establish latency in T-cells and macrophages\(^\text{21}\)
   i. The latent viral genome may reactivate at any time, but typically occurs after immunosuppression, illness, or use of chemotherapeutic agents\(^\text{22}\)
   ii. CMV is highly cell associated and spreads throughout the body within infected lymphocytes\(^\text{21}\)

IV. Clinical Manifestation\(^\text{21}\)

a. Cytomegalovirus clinical syndromes\(^\text{21}\)
   i. Congenital CMV infection
   ii. CMV mononucleosis in healthy young adults
   iii. Life threatening disseminated disease in transplant recipients and human immunodeficiency virus (HIV) infected individuals

b. Early CMV occurs ≤100 days post-transplant\(^\text{9}\)

c. Late CMV occurs >100 days post-transplant\(^\text{9}\)

| CMV Pneumonia | Signs/symptoms: fever, cough, hypoxemia and diffuse radiographic opacities
|               | Associated with high mortality |
| CMV Gastrointestinal disease | Can develop in the upper and lower GI tract |
|               | Signs/symptoms of esophageal CMV: odynophagia, nausea, vomiting, weight loss, fever, diarrhea or abdominal pain |
|               | Signs/symptoms of CMV colitis: abdominal pain, persistent small-volume diarrhea, and rectal bleeding |
| CMV Hepatitis | Signs/symptoms: acute right upper quadrant pain with cholestatic profile |
| CMV CNS disease | Signs/symptoms: diffuse encephalitis, ventriculoencephalitis, cerebral mass lesions |
| CMV Retinitis | Signs/symptoms: inflammation of the retina of the eye |
|               | May lead to blindness |

V. Diagnostic Methods\(^\text{23}\)

a. Serology
   i. Detects CMV-specific antibodies (IgG and IgM)
   ii. Determines a patient’s risk for CMV infection after transplantation
   iii. CANNOT be used for the diagnosis of CMV infection or disease

b. Polymerase chain reaction (PCR)
   i. Most sensitive method for detecting CMV DNAemia
   ii. Relies on the amplification of quantitative measurement of CMV DNA
   iii. Maintains high specificity
   iv. Higher levels of DNA in blood are predictive of CMV disease in immunocompromised patients

c. pp65 antigenemia
i. CMV pp65 antigenemia in peripheral blood leukocytes is a rapid and semi-quantitative method of diagnosing CMV infection
ii. A positive pp65 assay is predictive for the development of invasive disease in transplant patients
d. Histopathology is the gold standard for diagnosis of CMV disease
e. Other testing options not routinely used: CMV RNA by nucleic acid, culture

**Figure 4. CMV classifications and definitions**

**VI. Diagnosis of CMV Disease**

a. Negative DNA in blood does not rule out disease
b. Positive DNA in blood does NOT equate to disease
c. Histopathology of tissue biopsy is gold standard
d. Risk Factors
   i. Age
   ii. Sex match of donor/recipient
   iii. Type of conditioning regimen
   iv. Use of high dose corticosteroids
   v. GVHD severity
   vi. Use of alemtuzumab or antithymocyte globulin
   vii. Immune recovery after HSCT
   viii. Graft factors such as umbilical cord, haploidentical, T-cell depleted, mismatched or unrelated
   ix. Serostatus of the donor and recipient studies suggest is MOST IMPORTANT

**Figure 5. Depicts the percentage risk of CMV recurrence based on donor/recipient serostatus**

**VII. CMV Specific Cytotoxic T lymphocytes (CTLs)**
a. Donor CMV seronegative: Does not have anti-CMV IgG there are NO CMV CTLs
b. Donor CMV seropositive: Donor immune system has CMV in a latent phase after CMV primary infection. This donor would have CMV CTLs, but there is also the risk of CMV infection being transferred to a CMV seronegative recipient

VIII. CMV Resistance

a. Development of drug resistance requires prolonged exposure to the antiviral drug and persistent reactivation in the presence of drug, which will ultimately lead to the selection of resistant strains
b. CMV strains have amino acid deletions or substitutions of the UL97 or UL54 regions or point mutations in the DNA polymerase

c. UL97 mutations are resistant to ganciclovir, but susceptible to foscarnet and cidofovir

d. UL54 mutations can be resistant to ganciclovir, foscarnet and cidofovir

e. CMV strains with both mutations are highly resistant to ganciclovir

CMV Prevention Approaches

I. Without any form of prevention, approximately 80% of CMV seropositive recipients are likely to reactivate CMV and 20%-35% will develop CMV disease after allogeneic HSCT

II. Primary Prophylaxis

a. Therapy used to prevent the development of CMV disease in a person who is at risk for, but has no prior history of the disease
b. Usually started at engraftment and continued until day 100 after transplant
c. Higher rates of late CMV disease have been seen with this strategy as recipients are unable to develop CMV-specific immune responses

III. Preemptive therapy

a. Viral load is monitored at frequent intervals (usually weekly) with pp65 antigenemia or PCR detection to identify infection before the onset of symptoms or tissue invasion
b. Supported by the observation that CMV can be detected 1-2 weeks prior to symptoms
c. No well-defined threshold for the initiation of anti-CMV therapy
d. Preemptive therapy does not aim to prevent viremia, but rather to prevent disease
   i. Green et al. conducted a single-center retrospective US study that showed any level of viremia is associated with an increased risk of mortality at one year after allogeneic transplant
   ii. Teira et al. showed that early CMV reactivation is associated with increased transplant-related mortality
   iii. Ljungman et al. state that some viral replication may be beneficial as it can stimulate immune responses and promote CMV-specific immune reconstitution leading to less CMV late disease (>3 months post-transplant)
Goodrich et al. showed ganciclovir prophylaxis significantly decreased disease. Failed to show a mortality benefit due to the large amount of neutropenia and bacterial associated infections.

Mond et al. applied the principals of preemptive therapy, showed that early treatment with ganciclovir in patients with positive surveillance cultures reduces the incidence of CMV disease and improves survival.

Boeckh et al. pp65 antigenemia to guide initiation of ganciclovir, showed the noninferiority of ganciclovir prophylaxis vs preemptive therapy.

Salzberger et al. reaffirmed the findings in previous ganciclovir prophylaxis study from 1993. Neutropenia determined an independent risk factor for mortality.

Ayala et al. valganciclovir shown to be as efficacious as ganciclovir in the prevention of CMV.

Vusirikala et al. valacyclovir prophylaxis showed no difference in CMV disease and survival compared to acyclovir.

Figure 6. Depicts the milestones of CMV prevention through the years.
Letermovir\textsuperscript{47-48} 

i. New agent approved in 2017 for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HSCT

ii. Novel mode of action that targets the UL56 subunit of the viral terminase complex specifically seen in CMV

iii. In-vitro data has shown the development of CMV resistance to letermovir

iv. Low to absent myelotoxic and nephrotoxic effects

**Clinical Question:** Is preemptive therapy an appropriate approach to prevention with the introduction of a new, less myelosuppressive CMV prophylaxis option?

**Literature Review**


**Purpose**

This study compared CMV antigenemia-guided ganciclovir treatment to prophylaxis with ganciclovir by assessing CMV disease, neutropenia and bacterial, fungal, viral infections.

**Study Design**

Randomized, double-blind, placebo controlled study conducted from 1992-1994 stratified by presence of acute GVHD

- Randomized to either placebo or ganciclovir 5mg/kg BID for 5 days then daily for 6 days/week until day 100 after transplantation
- If high-grade CMV antigenemia or CMV viremia was detected the study drug was stopped and an open label ganciclovir treatment was started

**Patient Population**

**Inclusion**

- CMV seropositive patients undergoing allogeneic marrow transplantation

**Exclusion**

- Serum creatinine of ≥ 2.5mg/L
- CMV disease, viremia or antigenemia
- Received any antiviral drug the preceding 7 days

**Endpoints**

**Primary Endpoint**

- CMV disease and neutropenia

**Secondary Endpoints**

- Monitored bacterial, fungal and viral infection rates
- Use of ganciclovir
- Hospitalization duration

**Statistics**

- Kaplan-meier method
- Log-rank test
- Cox proportional hazards models

**Results**

Baseline characteristics

- 226 patients randomized (antigenemia-ganciclovir n=114, ganciclovir n=112)
- No significant difference in age, sex, serostatus before transplant, underlying disease, disease stage, HLA donor matching, conditioning therapy, GVHD prophylaxis, GVHD grade
Subset analysis showed GVHD grade 3-4 were significantly more likely to develop CMV disease.
More late CMV disease developed with 16% in the ganciclovir prophylaxis and only 8% in the preemptive ganciclovir group.

**Authors**
- A trade-off exists for CMV-related morbidity versus antiviral drug toxicity
- More fatal fungal infections developed in the ganciclovir prophylaxis group
- Patients with higher grades of GVHD were more likely to progress to CMV disease
- Results showed no apparent difference in survival or CMV related mortality
- CMV antigenemia guided antiviral treatment prevents CMV disease

**Critique**

**Strengths**
- Trial design
- Reported degree of GVHD
- Reported anti-fungal prophylaxis
- Reported detection with PCR based methods

**Limitations**
- Did not start antigenemia ganciclovir in patients with low grade antigenemia
- Patients received acyclovir, famciclovir prophylaxis
- Single center
- Definitions for CMV disease

**Take away**
- Preemptive therapy is the preferred method of CMV disease prevention as it showed similar survival rates when compared to primary prophylaxis
- Preemptive therapy should especially be considered in patients with lower CMV viral load and CMV disease risk
- Preemptive therapy reduces the amount of exposure of anti-CMV agents

HSV= herpes simplex virus, ANC= absolute neutrophil count

**Purpose**  
This study compared PCR guided valganciclovir therapy against valganciclovir prophylaxis by assessing: CMV disease, non-viral infectious events, toxicity, mortality

**Study Design**  
Multicenter, double blind, placebo controlled, randomized clinical trial between 1999-2008, primary study period was until day 270 after HSCT  
- Valganciclovir 900mg daily or matching placebo for 6 months  
- Study drug was discontinued when CMV viral load was >1000 copies/mL or >5 times baseline value and preemptive treatment initiated  
- Viral load was monitored weekly  
- If ANC dropped < 1.0 X 10^9/L study drug was held and growth factors were started

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
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</table>
| - Allogeneic HSCT recipients ≥ 16 years who:  
  - If R+ and D-/D+, had one of the following:  
    - Previous CMV Infection  
    - GVHD that required immunosuppression  
    - Receipt of anti-CMV prophylaxis therapy  
  - If R-/D+, one of the following:  
    - CMV infection with appropriate treatment course pre-randomization  
    - Antiviral utilization prior to study entry permitted |  
- Neutropenia within one week of study enrollment  
- Renal insufficiency or inability to take oral medications  
- CMV disease within 6 weeks prior to randomization  
- Uncontrolled CMV load at time of evaluation  
- Prophylactic use of high dose acyclovir or valacyclovir  
- Imminent demise (<2 weeks)  
- HIV infection

**Endpoints**

**Primary Endpoint**
- Composite outcome consisting of CMV disease or invasive bacterial or fungal infection or death and assessment of neutropenic consequences

**Secondary Endpoint**
- Primary endpoint at day 640  
- Neutropenia  
- CMV lymphoproliferative response  
- Days alive outside of hospital  
- Treatment-emergent ganciclovir resistance  
- Immunosuppression discontinuation at day 270  

**Statistics**
- To demonstrate a 45% reduction of the primary endpoint, 92 patients per treatment arm were needed for 87% power  
- Cox regression models  
- Chi-square, Fisher’s exact or Wilcoxon rank-sum tests as appropriate  
- Interim analysis conducted after 50% of patients completed 90 days of study

**Results**

**Baseline Characteristics**
- N=184 (valganciclovir n=95, placebo n=89)
No significant difference seen in gender, age, type of transplant, donor relationship, disease status, conditioning intensity, CMV donor and recipient serostatus, HSV and VZV status, CD34 selections, refractory GVHD pre-randomization, neutropenia pre-randomization

*Day 270

Authors

Conclusion

- Valganciclovir prophylaxis did not improve the CMV disease-free and invasive infection free survival composite endpoint when compared to PCR-guided preemptive therapy
- Both strategies performed similarly with regard to most clinical outcomes

Critique

**Strengths**
- Multi-center
- Primary endpoint included invasive bacterial and fungal infections
- No use of acyclovir
- Measured CMV lymphoproliferative response

**Limitations**
- Some high risk patients not included
- Did not report use of other prophylactic antimicrobials

Take Away

- No difference in CMV disease or mortality
- Preemptive therapy is a highly effective CMV prevention method

HSV= herpes simplex virus, VZV= varicella zoster virus, ANC= absolute neutrophil count

| Purpose | Compared primary prophylaxis using the new anti-CMV agent, letermovir, placebo by assessing CMV infection, CMV disease, mortality |
| | • Letermovir 480mg daily or placebo |
| | • Patients were stratified into either high risk or low risk groups |
| | • High Risk for CMV reactivation defined as: |
| | o Significant HLA mismatching |
| | o Haploidentical donor or umbilical cord graft |
| | o Ex-vivo T-cell depleted grafts |
| | o Moderate to severe GVHD |
| | • If a certain threshold (PCR viral load of 1000 copies/ml for low risk or 500 copies/ml for high risk) was met, patients in either group were started on preemptive therapy with ganciclovir |

| Patient Population | Inclusion | Exclusion |
| Age ≥ 18 years undergoing allogeneic HSCT and were CMV seropositive | Age ≥ 18 years undergoing allogeneic HSCT and were CMV seropositive |
| Undetectable CMV before randomization | Undetectable CMV before randomization |
| Must enroll in trial by day 28 post-transplant | Must enroll in trial by day 28 post-transplant |
| | Young hepatic impairment |
| | CrCl < 10mL/min |
| | Current or recent receipt of antiviral agents with anti-CMV activity |

| Endpoints | Primary Endpoint |
| Proportion of patients with clinically significant CMV infection through week 24 after transplantation | Proportion of patients with clinically significant CMV infection through week 24 after transplantation |
| o Patients who for any reason discontinued the trial before week 24 or who had missing data at week 24 were defined as having a primary-endpoint |
| Secondary Endpoints |
| • Time to clinically significant CMV infection |
| • Safety endpoints |
| • Cumulative all-cause mortality |
| • GVHD |
| • Rates of infection |

| Statistics | Mantel-Haenszel method |
| Kaplan-Meier plots |

| Results | Baseline Characteristics |
| Patients were well balanced at baseline |
| 540 patients (letermovir n=325, placebo n=170) |
| Baseline characteristics included: age, gender, race, CMV seropositive donor, reason for HSCT, HLA matching and donor type, haploidentical related donor, stem cell source, myeloablative conditioning regimen, antithymocyte globulin use, alemtuzumab use, ex vivo T-cell depletion, immunosuppressant use, acute GVHD of grade ≥ 2 at randomization and risk of CMV disease (high or low risk) |
### Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Letermovir, n (%)</th>
<th>Placebo, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint*</td>
<td>122 (37.5)</td>
<td>103 (60.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMV disease*</td>
<td>5 (1.5)</td>
<td>3 (1.8)</td>
<td>0.4056</td>
</tr>
<tr>
<td>Preemptive therapy initiation</td>
<td>119 (36.6)</td>
<td>101 (59.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CMV infection week 14</td>
<td>25 (7.7)</td>
<td>67 (39.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMV disease week 14</td>
<td>1 (0.3)</td>
<td>2 (1.2)</td>
<td>0.2258</td>
</tr>
<tr>
<td>Mortality*</td>
<td>33 (10.2)</td>
<td>23 (15.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mortality week 48</td>
<td>68 (20.9)</td>
<td>43 (25.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Bacterial and fungal infections</td>
<td>78 (24)</td>
<td>37 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count &lt;500mm3</td>
<td>71 (19)</td>
<td>37 (19)</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine &gt;2.5mg/dL</td>
<td>8 (2)</td>
<td>6 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*at week 24

- Letermovir has a limited adverse effect profile it has not been associated with hematologic or renal toxicity
- One patient developed CMV resistance to letermovir with a UL56 mutation

### Authors

- Letermovir prophylaxis resulted in lower risk of CMV infection
- Letermovir has an overall safety profile similar to placebo

### Critique

#### Strengths

- Stratified patients based on risk for CMV infection
- Randomized controlled trial
- Developed thresholds for initiation of preemptive therapy in each risk category

#### Limitations

- Primary endpoint was CMV infection rather than CMV disease
- All patients received prophylaxis with acyclovir, valacyclovir or famciclovir with could provide anti-CMV activity

### Take Away

- A survival benefit was seen at week 24, but not seen at week 48
- There was no difference seen in CMV disease incidence
- Letermovir is well-tolerated
- Studies comparing letermovir against preemptive ganciclovir with CMV disease as the primary endpoint are needed

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**Table 3. Cost analysis of CMV therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letermovir prophylaxis*</td>
<td>$324</td>
<td>~$28,000</td>
</tr>
<tr>
<td>Valganciclovir prophylaxis*</td>
<td>$68</td>
<td>~$5,800</td>
</tr>
<tr>
<td>Valganciclovir preemptive †</td>
<td>$68</td>
<td>~$4,800</td>
</tr>
</tbody>
</table>

*assuming engraftment at day 14
†average duration 35 days
Summary

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preemptive Therapy</th>
<th>Letermovir Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to anti-CMV agents</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Drug toxicities</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Antiviral resistance</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Viremia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Development of CMV specific immunity</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Late CMV disease</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Conclusion

I. No difference in mortality or CMV disease in preemptive and primary prophylaxis approaches
II. Patients are at higher risk of bacterial and fungal infections with primary prophylaxis with ganciclovir
III. Higher rates of CMV resistance are seen with prolonged exposure of anti-CMV agents
IV. Letermovir for CMV
   a. Drastically more expensive than valganciclovir for primary prophylaxis
   b. A decrease in CMV infection existed, however, no benefit in CMV disease demonstrated
   c. Significant decrease in mortality at week 24 but none seen at week 48

Recommendations for Prevention of CMV

- Assess Patients Risk for CMV Disease
  - Yes
    - Recipient CMV seropositive?
      - Yes
        - Can consider primary prophylaxis with letermovir and continued viral monitoring
      - No
        - Preemptive therapy
  - No
    - Preemptive therapy

High Risk Criteria
- Stem cells from a CMV seronegative donor
- Mismatched donor/recipient
- Haploidentical donor
- Umbilical cord graft
- T-cell depleted graft
- GVHD of grade 2 or greater requiring steroids
References:


46. Valgaclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28(3):265-270.

47. Valgaclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;37(9):851-856.

48. Valgaclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;37(9):851-856.


*Black box warning*
### Anti-CMV Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Main Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir/Valacyclovir</td>
<td>• Not completely understood, thought to be phosphorylated by viral UL97</td>
<td>• Prophylaxis dosing: IV acyclovir 500mg/m² TID then Oral: 800mg QID</td>
<td>• Malaise</td>
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<td></td>
<td>• Valacyclovir 2gm PO TID- QID</td>
<td>• Renal toxicity (low risk)</td>
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<td>• Begin at engraftment and continue to day 100</td>
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<tr>
<td>Ganciclovir/ Valganciclovir</td>
<td>• Phosphorylated by the UL97 viral kinase to ganciclovir monophosphate. Inhibits viral replication by competing with deoxyguanosine triphosphate as a substrate for viral polymerase UL54</td>
<td>• Ganciclovir preemptive dosing: 5mg/kg IV BID for 14 days with maintenance of 5mg/kg daily for a further 7-14 days</td>
<td>• Pancytopenia</td>
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<td>• Valganciclovir is the valine ester of ganciclovir. Hydrolyzed to ganciclovir after oral absorption</td>
<td>• Valganciclovir preemptive dosing: 900mg PO BID continue for a minimum of 2 weeks</td>
<td>• Myelosuppression</td>
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<td>• Ganciclovir prophylaxis: 5mg/kg/day from engraftment to day 100 post-transplant</td>
<td>• Increased rate of infection</td>
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<td></td>
<td>• Valganciclovir prophylaxis: 900mg PO daily from engraftment to day 100 post-transplant</td>
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<tr>
<td>Foscarnet</td>
<td>• Does not require phosphorylation and is virustatic through inhibition of viral DNA polymerase</td>
<td>• Preemptive dosing: 60mg/kg BID for 7-14 days then 90mg/kg daily. Minimum total duration is 2 weeks</td>
<td>• Electrolyte abnormalities*</td>
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<td>• Prophylaxis dosing: 60mg/kg/day for seven days followed by 90-120mg/kg daily until day 100 after transplant</td>
<td>• Nephrotoxicity*</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>• Nucleotide analogue that does not require phosphorylation by viral UL97 kinase</td>
<td>• Preemptive dosing: 5mg/kg per week for a medium duration of 3 weeks</td>
<td>• Seizures*</td>
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<tr>
<td>Marabavir</td>
<td>• Directly inhibits protein kinase enzyme UL97</td>
<td>• Currently in phase 3 trials</td>
<td>• Taste disturbances</td>
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<tr>
<td>Brincidofovir</td>
<td>• Prodrug of cidofovir, designed to release cidofovir intracellularly allowing for higher intracellular and lower plasma concentrations of cidofovir</td>
<td>• Not on the market</td>
<td>• Diarrhea</td>
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<tr>
<td>Letermovir</td>
<td>• Targets the DNA terminase complex UL56 which is required for viral DNA processing and packaging</td>
<td>• Prophylaxis dosing: IV or PO 480mg once daily beginning between day 0-28 post HSCT for CMV seropositive recipients, continue through day 100 post-transplant</td>
<td>• Thrombocytopenia</td>
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<td>• Dose adjustment with concomitant cyclosporine therapy 240mg daily</td>
<td>• Peripheral edema</td>
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<td>• Headache</td>
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<td>• Nausea/vomiting</td>
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