CMV Disease in Transplant Recipients: Clinical Cases and Expert Opinion
Clinical Case 1: CMV in Hematopoietic Stem Cell Transplantation

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Disclosure of Conflicts of Interest

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Dr. Michael J. Boeckh has an affiliation with ViroPharma Incorporated, Roche, Novartis, and AlphaVax (Consulting Fees); ViroPharma Incorporated, Roche, and Vical Inc. (Contracted Research); and Baxter (Other).
Clinical Case

- 58-year-old woman, 9 months after NM PBSCT for ALL in 1st remission
- Pretransplant serostatus: VZV+, CMV R+/D+, HSV-
- Early posttransplant complications
  - 2 episodes of CMV reactivation (+ one pre-Tx)
  - Acute GvHD
  - RSV URI
- Now severe GI GVHD, diagnosed 4 weeks ago
  - 1 mg/kg steroids, FK506 and B & B
- Admitted with respiratory failure requiring intubation
Clinical Case (continued)

- CMV reactivation 7 weeks prior to admission: plasma PCR 1100 treated with valganciclovir, initially with 900 mg twice daily, switched to 450 mg/day after 1 week, switched back to low-dose acyclovir prophylaxis 2 days prior to admission
- Lab: Creatinine 0.2, bilirubin 23.4, AST 390
- PCP prophylaxis: atovaquone 1500 mg/d, acyclovir 800 mg BID, fluconazole 400 mg, penicillin 750 mg twice daily
- Other medications: prednisone 2 mg/kg, B & B, FK506
Clinical Case (continued)

Question 1: Differential Diagnosis

A. Viral pneumonia (CMV, respiratory viruses)
B. Fungal pneumonia (PCP, Aspergillus)
C. Bacterial pneumonia
D. BOOP
E. All of the above
Clinical Case (continued)

Question 2: Initial Management

The patient was started on broad spectrum antibiotics (imipenem, vancomycin, gentamicin, levofloxacin). Which additional agents would you start empirically?

A. High-dose TMP-SMX, ganciclovir (induction) therapy
B. High-dose TMP-SMX, ganciclovir (induction) therapy, aerosolized ribavirin
C. High-dose TMP-SMX, ganciclovir (induction) therapy, voriconazole
D. All 4 drugs
E. No additional empiric therapy – wait until BAL results are available
Clinical Case (continued)
Additional Information

- IT aspirate: GPC, GPR, GNR (mixed flora), yeast
- BAL:
  - Gram’s stain: GPC, GNR
  - Viral DFA; negative for ADV, RSV, FLU, PIV, HMPV
  - PCP DFA: negative
  - CMV shell vial: pending
  - Respiratory virus multiplex PCR (12 viruses): pending
    - Aspergillus GM: positive
    - Aspergillus PCR: pending
    - Legionella DFA: negative
- CMV PCR (plasma): 2 million copies/mL
Clinical Case (continued)

Question 3: Further Treatment

How would you adjust treatment?

A. Switch to foscarnet
B. Add foscarnet
C. Add voriconazole
D. Add both foscarnet and voriconazole
E. No change
Clinical Case (continued)

Internal Working Diagnoses

• Presumed CMV pneumonia
  – Drug resistance possible (to probable)
  – Treatment: ganciclovir + foscarnet

• Probable pulmonary aspergillosis
  – Treatment: voriconazole

• Bacterial pneumonia
  – Treatment: imipenem, levofloxacin
Utility of *Aspergillus* Galactomannan Detection in BAL Samples

<table>
<thead>
<tr>
<th></th>
<th># pt</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>160</td>
<td>47</td>
<td>93</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>BAL</td>
<td></td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
</tbody>
</table>

Ganciclovir Resistance against CMV
Prevalence 2008

SOT  >>>>  HCT
Ganciclovir Resistance against CMV
Prevalence 2008

SOT >>>> HCT

However . . .
CMV Drug Resistance

- Prolonged drug administration (pre- and/or posttransplant)
- Low antiviral drug levels
- Low immune status
  - Drug induced
  - T-cell depletion (e.g., haploidentical donor transplants)
  - Cord blood transplantation
- Resistance
- Subclinical CMV load
CMV Drug Resistance
High-Risk Situation

- Ganciclovir-experienced patient (prophylaxis, preemptive therapy, pretransplant use), especially with low doses
- Increase of viral load > 2 weeks
- High-risk transplant setting
  - Lung, K-P transplant (D+/R-)
  - HSCT (severe TCD or immunosuppression, e.g., haplo Tx)
CMV Drug Resistance
Low-Risk Situation

- Ganciclovir-naïve patient
- Increase of viral load during the first 2–3 weeks of therapy
- Low-risk setting (R+, kidney Tx, liver Tx, heart Tx, HCT)

**Diagram:**
- **Viral Load** vs. **Months after Transplant**
- Ganciclovir administration and subsequent decline in viral load.
# Viral Load Increases

## Example: Early Response to Ganciclovir in HCT

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>( \uparrow \text{Ag} &gt; 2x ) adj OR</th>
<th>95% CI</th>
<th>( \uparrow \text{Ag} &gt; 5x ) adj OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-TBI containing</td>
<td>1.0 *</td>
<td></td>
<td>1.0 *</td>
<td></td>
</tr>
<tr>
<td>TBI-containing</td>
<td>2.6 1.0–6.8</td>
<td></td>
<td>1.8 0.9–4.2</td>
<td></td>
</tr>
<tr>
<td>Steroid use at 1st Ag +ve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0 *</td>
<td></td>
<td>1.0 *</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 mg/kg</td>
<td>5.0 1.0–24.5</td>
<td></td>
<td>4.3 0.4–51.3</td>
<td></td>
</tr>
<tr>
<td>1–2 mg/kg</td>
<td>4.3 1.2–5.3</td>
<td></td>
<td>14.3 1.8–110.7</td>
<td></td>
</tr>
<tr>
<td>≥ 2 mg/kg</td>
<td>10.5 3.1–35.8</td>
<td></td>
<td>28.6 3.6–229.7</td>
<td></td>
</tr>
</tbody>
</table>

\( P < 0.05 \)

## Efficacy of Ganciclovir

<table>
<thead>
<tr>
<th>Route/Dose</th>
<th>Wild-Type</th>
<th>Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>91.5%</td>
<td>62%</td>
</tr>
<tr>
<td>5 mg/kg bid</td>
<td>91.5%</td>
<td>62%</td>
</tr>
<tr>
<td>Oral</td>
<td>46.5%</td>
<td>35%</td>
</tr>
<tr>
<td>1 g tid</td>
<td>46.5%</td>
<td>35%</td>
</tr>
</tbody>
</table>

CMV Drug Resistance
Mutation Map for the UL97 Gene

CMV Drug Resistance
Mutation Map for the DNA Polymerase Gene

CMV Drug Resistance Diagnosis

- Increases of viral load as surrogate marker for resistance
  - Drug-naïve subjects, early during treatment, low-risk setting (R+):
    • Drug resistance unlikely
    • Increases most likely due to the underlying immunosuppression
  - After significant exposure (especially low-dose), high-risk setting
    • More likely
    • True viral load increase: > 0.5 \( \log_{10} \) (> 3x baseline)

- Testing: direct genotypic testing if resistance is suspected
  - UL97 gene: CMV, maribavir
  - UL 54 gene: foscarnet, cidofovir, ganciclovir (high level)
CMV Drug Resistance
Management Strategies

• Switch to alternative drug
  – Ganciclovir \(\rightarrow\) Foscarnet
  \(\rightarrow\) Cidofovir (some cross-resistance)
  \(\rightarrow\) Maribavir
  – Foscarnet \(\rightarrow\) Ganciclovir
  \(\rightarrow\) Cidofovir
  \(\rightarrow\) Maribavir

• Reduce immunosuppression (if possible)
CMV Drug Resistance
Management Strategies

• In refractory situations (viral load increases, clinical deterioration):
  – Reduce immunosuppression if feasible
  – Consider dose increase if possible\(^1\)
  – Consider combination therapy
    • Continue ganciclovir in addition to foscarnet\(^2\)
    • Foscarnet + maribavir (no clinical data)
    • Cidofovir + maribavir (no clinical data)
    • NOT: ganciclovir + maribavir\(^3\)

CMV Drug Resistance
Management Strategies

• In refractory situations – continued:
  – Consider alternative agents (alone or in combination)
    CASE REPORTS ONLY – NO CONSISTENT EVIDENCE
    • Leflunomide¹,²
    • Artesunate³,⁴
  – Consider alternative immunosuppressive agents
    • Sirolimus⁵

Panel Discussion
Clinical Case 2: CMV in Hematopoietic Stem Cell Transplantation

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Director, Blood and Bone Marrow Transplant Program
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Disclosure of Conflicts of Interest

John R. Wingard, MD

Dr. John R. Wingard has an affiliation with Merck & Co., Inc., and Pfizer Inc. (Consulting Fees); and Astellas, Merck & Co., Inc., and Pfizer Inc. (Fees for Non-CME Services Received Directly from a Commercial Interest or their agents, e.g., speakers’ bureaus).
Clinical Case

- 47-year-old man underwent a matched unrelated donor HCT 5 months ago for acute myelogenous leukemia after cyclophosphamide + total body irradiation
- Tacrolimus + methotrexate given as GvHD prophylaxis
- Engrafted on day 20
- Valacyclovir and trimethoprim-sulfamethoxazole prophylaxis given
Clinical Case (continued)

- Developed cutaneous and gastrointestinal GvHD on day 38
- Prednisone given at a dose of 2 mg/kg/d
- GvHD improved
- Prednisone tapered weekly by 0.5 mg/kg/d (and discontinued on day 70)
Clinical Case (continued)

- Weekly CMV assessed by quantitative PCR
- CMV PCR + on day 54
- Valganciclovir given for 2 wks
- CMV PCR negative and valganciclovir stopped
Clinical Case (continued)

- Day 100 no active infections or GvHD
- Tacrolimus on slow taper
- Patient discharged to local community with monthly follow-up
- On day 120, pt developed rash and dry mouth
Clinical Case (continued)

- Skin biopsy showed lichenoid chronic GvHD
- Prednisone started at 1 mg/kg/d with gradual taper to alternate-day schedule
Clinical Case (continued)

- Day 140, pt developed low-grade fever, dry cough, dyspnea on exertion
- Scattered rales noted
- Chest radiograph performed
Question 1

This is unlikely to be CMV pneumonia because most CMV pneumonias occur before day 100.

A. True
B. False
Shifts in CMV infections

- Historically, CMV pneumonia usually occurred before day 100
- Rising rate of late-onset disease
- Resistance
- New oral agents
  - Valganciclovir
  - Maribavir
Late CMV Disease in HCT
Incidence Variability

- Incidence 3%–17%
- Incidence is variable in different series; reasons include:
  - Risk groups
  - Denominator (day of transplantation vs 3 months)
  - Different stem cell sources?
  - Duration of follow-up
  - Work-up variable
Differential Diagnosis

- Non-infectious
  - Idiopathic pneumonitis
  - Bronchiolitis obliterans with organizing pneumonia
- Infectious
  - PCP
  - CMV
  - Respiratory virus
  - Adenovirus
  - *Legionella*
Diagnostic Evaluation

- Plasma CMV PCR +
- Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy
- CMV demonstrated
- Ganciclovir initiated
Question 2

Risk factors for late CMV pneumonia are:

A. Acute GvHD
B. Early CMV infection
C. Ganciclovir prophylaxis
D. All of the above
E. All patients are equally at risk
Current Issues for CMV Therapy: Should I Worry About Late Disease?

- **Risk factors:**
  - Early CMV or low CD4
  - GvHD

- **Graphs:**
  - Distribution of CMV disease before day 100 and after day 100.
  - Probability of late CMV disease.
  - Probability of late CMV disease associated with pp65 antigenemia < day 95 + CD4 < 50/mm².
  - Probability of late CMV disease associated with Any GvHD before day 95 (n=119).
  - Probability of late CMV disease associated with No GvHD before day 95 (n=27).

- **Statistics:**
  - P=0.02
  - P=0.03
  - P=.03

- **Figures:**
  - CMV disease before day 100 and after day 100.
  - Probability of late CMV disease.
  - Probability of late CMV disease associated with pp65 antigenemia < day 95 + CD4 < 50/mm².
  - Probability of late CMV disease associated with Any GvHD before day 95.
  - Probability of late CMV disease associated with No GvHD before day 95.

- **References:**
<table>
<thead>
<tr>
<th>CMV Disease</th>
<th>Prophylaxis</th>
<th>Preemptive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to day 100</td>
<td>2.7%</td>
<td>14.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Beyond day 100</td>
<td>13.4%</td>
<td>6.1%</td>
<td>—</td>
</tr>
<tr>
<td>Total before day 400</td>
<td>16.1%</td>
<td>20.2%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Prevention of Late CMV Disease
Who is at Risk? Current Data

• Continued surveillance of high-risk patients
  – Allogeneic transplantation
  – CMV recipient seropositive or D+/R−
    • CMV infection < day 100 or
    • Ganciclovir/valganciclovir/FSC prophylaxis (mainly in R+)
      plus
      • GvHD
      • High-dose steroids for other reasons
      • T-cell depletion
      • DLI
Late CMV Prevention
CIBMTR Survey

• Prophylaxis or preemptive therapy in HIGH RISK recipients after day 100
  (i.e., recipients with CMV infection before day 100, steroid or ATG use, GvHD, or low CD4 counts) ?

  YES (122 centers, 70%)
  NO (52 centers, 30%)

• Among centers with after day 100 strategies:
  – Most (79%) used virologic surveillance/preemptive therapy
  – 12% used symptomatic surveillance based on clinical signs
  – 3.3% used prophylaxis with high-dose VACV
  – 1.6% (2 centers) used prophylaxis with oral VGCV

Prevention of Late CMV Disease
Current Strategies

Diagnostic Test
(e.g., PCR > 1000 copies/mL)

Ganciclovir/Foscarnet

0 100 days 200 days

• Duration of monitoring: until 6–12 mo after HCT
  – Detectable CMV-specific T-cell function
  – No or minimal systemic immunosuppression
    • No or minimal systemic steroids
    • No anti–T-cell agents
    • No DLI
  – Surveillance assays negative on several determinations
Prevention of Late CMV Infection and Disease

Issues

• Logistics and cost of testing
  – Availability: CMV vs hematologic/chemistry testing
  – Cost
  – Adherence

• Direct vs indirect effects
  – Prophylaxis may reduce both

• Available agents
  – Valganciclovir: ASBMT 2008 abstract
  – Valacyclovir: no studies
  – Cidofovir: no studies
  – In the future: maribavir?
Panel Discussion
Clinical Case 3: CMV in Solid Organ Transplantation

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Disclosure of Conflicts of Interest

Raymund R. Razonable, MD

Dr. Raymund R. Razonable has an affiliation with Roche (*Contracted Research*).
Clinical Case

- 55-year-old Caucasian woman from Las Vegas
- PMHx: astrocytoma, seizures, dyslipidemia, diabetes, idiopathic pulmonary fibrosis
- 10-05-2005: Right single-lung transplant
- Induction with muromunab-CD3 (OKT3)
- Maintenance therapy: cyclosporine, azathioprine, and prednisone
- CMV D+/R--; EBV R+
- Uncomplicated early posttransplant course
Prevention of CMV After SOT

• **Prophylaxis**
  - Universal or targeted
  - Reduces direct and indirect effects of CMV
  - Risk of late-onset CMV disease after prophylaxis

• **Preemptive therapy**
  - Antiviral drug initiated based on virologic markers
  - Minimizes drug exposure (lower risk of drug toxicity and resistance)
  - May not eliminate the indirect effects of CMV
  - Some episodes may escape detection

SOT=solid organ transplantation.
## Preemptive Therapy: Meta-Analyses

<table>
<thead>
<tr>
<th>Study Author</th>
<th>CMV Disease Relative Risk (95% CI)</th>
<th>All-Cause Mortality Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodson et al.</td>
<td>0.29 (0.11–0.80)</td>
<td>1.23 (0.35–4.30)</td>
</tr>
<tr>
<td>Kalil et al.</td>
<td>0.28 (0.11–0.69)</td>
<td>0.94 (0.32–2.76)</td>
</tr>
<tr>
<td>Small et al.</td>
<td>0.30 (0.15–0.60)</td>
<td>0.94 (0.43–2.07)</td>
</tr>
</tbody>
</table>

Hodson et al., Curr Opin Organ Transplant. 2007;12:610-617.
**Oral GCV vs VGCV Prophylaxis in CMV D+/R- Non-Lung SOT Patients**

<table>
<thead>
<tr>
<th>CMV Disease by 6 Months</th>
<th>Valganciclovir 900 mg QD until D+100 (n=239)</th>
<th>Ganciclovir 1 g TID until D+100 (n=125)</th>
<th>Total (n=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint committee</td>
<td>12.1%</td>
<td>15.2%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Protocol definition</td>
<td>11.3% (27)</td>
<td>12.8%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Investigator-treated disease</td>
<td>23.0%</td>
<td>21.6%</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

GCV = ganciclovir; VGCV = valganciclovir.
## Antiviral Prophylaxis: Meta-Analyses

<table>
<thead>
<tr>
<th>Study Author</th>
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<th>All-Cause Mortality Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodson et al.</td>
<td>0.42 (0.34–0.52)</td>
<td>0.63 (0.43–0.92)</td>
</tr>
<tr>
<td>Kalil et al.</td>
<td>0.20 (0.13–0.31)</td>
<td>0.62 (0.40–0.96)</td>
</tr>
<tr>
<td>Small et al.</td>
<td>0.34 (0.24–0.48)</td>
<td>0.99 (0.68–1.43)</td>
</tr>
</tbody>
</table>
Clinical Case (continued)

- Valganciclovir 900 mg PO BID × 1 year
- 10-05-2006: End of valganciclovir prophylaxis
- 11-21-2006: URI symptoms, low-grade fever, malaise, weakness, cough, shortness of breath, and runny nose
  - Local physician: Amoxicillin-clavulanic acid and increase prednisone → no response
Clinical Case (continued)

- 11-27-2006: Levofloxacin 500 mg PO BID
- 12-04-2006: High-grade fever (104°F)
  - Local hospital admission
  - Chest x-ray: Left-sided pneumonia
  - Blood and sputum culture – negative
  - Linezolid, moxifloxacin, cefepime, oseltamivir
  - TMP-SMX/itraconazole prophylaxis
- 12-06-2006: Transferred to transplant center
Clinical Case (continued)

- Physical examination: O₂ requirement by nasal cannula, afebrile, ill-looking, crackles in left lung, with scant crackles in the right base, mild right upper quadrant tenderness
- Initial laboratory examination: WBC 5.2, hemoglobin 8.6, platelet 99, AST 124, LDH 577
- Chest radiographic studies
Clinical Case (continued)

- 12-07-2008: CMV PCR 224,500 copies/mL blood
- 12-07-2008: Bronchoscopy, TBBx, and BAL-ICH
  - Shell vial culture: cytomegalovirus
  - Histology: acute CMV pneumonitis
Late-Onset Primary CMV Disease in D+/R- SOT Patients

- VGCV 900 mg QD
- GCV 1000 mg TID

Late-Onset CMV Disease

• CMV syndrome 60%
  – Fever with myelosuppression

• Invasive CMV disease 40%
  – Hepatitis
  – Pneumonia
  – Gastrointestinal disease (90%)
  – Retinitis
  – Encephalitis
  – Others

### Risk Factors for Late CMV Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV D+/R−</td>
<td>11.00</td>
</tr>
<tr>
<td>Allograft rejection</td>
<td>6.60</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.19</td>
</tr>
<tr>
<td>Blood group A</td>
<td>2.36</td>
</tr>
<tr>
<td>Low creatinine clearance</td>
<td>4.28</td>
</tr>
<tr>
<td>Mycophenolate mofetil use at end of prophylaxis</td>
<td>1.99</td>
</tr>
<tr>
<td>Prednisone use at end of prophylaxis</td>
<td>2.70</td>
</tr>
</tbody>
</table>

Treatment of CMV Disease After SOT

- IV ganciclovir is the preferred drug for treating CMV disease in SOT recipients
- Duration individualized (at least 2–4 weeks)
  - Guided by molecular methods
  - Challenge: compartmentalized CMV diseases
- Reduction in immunosuppression
- Valganciclovir for treatment of CMV disease
Clinical Case (continued)

IV Ganciclovir + CMV Ig

Valganciclovir 900 BID

Valganciclovir 900 QD

Viral load copies/mL


Time

Ig=immunoglobulin.
Valganciclovir Treatment of CMV Disease in SOT Recipients

Clinical Case (continued)

- Resolution of CMV pneumonia
- Persistent bilateral leg weakness (possible CMV polyradiculopathy)
- Valganciclovir secondary prophylaxis
- Persistently CMV IgG-seronegative at 1 year later (IgM-seropositive)
Question 1

What is the optimal duration of antiviral prophylaxis after solid organ transplantation?

A. 1 month
B. 3 months
C. 6 months
D. 12 months
E. Indefinite duration
Question 2

Which of the following statements is TRUE?

A. Preemptive therapy is the preferred approach for the prevention of primary CMV disease.

B. Treatment for CMV disease after SOT is for a fixed duration of 3 weeks.

C. Antiviral prophylaxis is complicated by the occurrence of late-onset CMV disease.

D. Valganciclovir is a proven effective oral option for treatment of all cases of CMV disease after SOT.
Panel Discussion
Clinical Case 4: CMV in Solid Organ Transplantation

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Disclosure of Conflicts of Interest

Ajit P. Limaye, MD

Dr. Ajit P. Limaye has an affiliation with Roche (Consulting Fees, Contracted Research) and ViroPharma Incorporated (Contracted Research).
# Clinical Case

45-year-old man receives a cadaveric kidney/pancreas transplant  
CMV serostatus: Donor+, Recipient−  
Immunosuppression: ATG, tacrolimus, MMF, prednisone  
CMV prevention: oral GCV × 3 months

<table>
<thead>
<tr>
<th>Time Post-Txp</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo post-txp</td>
<td>Allograft rejection, methylpred pulse × 3</td>
</tr>
<tr>
<td>4.5 mo post-txp</td>
<td>CMV pneumonia, IV GCV + IVIG × 3 wk then oral GCV × 3 mo (as secondary prophylaxis)</td>
</tr>
<tr>
<td>9 mo post-txp</td>
<td>CMV syndrome, pp65 Ag &gt;100 but culture negative. IV GCV, but slow clinical response and increasing viral load.</td>
</tr>
</tbody>
</table>
## Clinical Case (continued)

<table>
<thead>
<tr>
<th>Time (mo post-txp)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.5</td>
<td>Progressive SOB, pulmonary infiltrates and rising pp65 Ag despite IV GCV. Lung biopsy ==&gt; CMV pneumonia IV FSC + GCV and CMVIG, reduced immunosuppression. Nephrotoxicity and electrolyte abn.</td>
</tr>
<tr>
<td>10</td>
<td>Patient dies of respiratory failure Autopsy = CMV pneumonia (no other pathogens)</td>
</tr>
<tr>
<td>10.5</td>
<td>Genotype = UL97 mutation Phenotype = pending</td>
</tr>
</tbody>
</table>
Issues

1. Incidence
2. Risk Factors and Pathogenesis
3. Diagnosis
4. Treatment
Question 1

Which of the following is considered the most important risk factor for development of ganciclovir-resistant CMV in SOT recipients?

A. Female gender
B. Recipient CMV seropositive status (R+)
C. Liver vs other organ-type transplant
D. Donor positive, recipient negative CMV serostatus
E. Use of cyclosporine
Question 2

Which of the following statements regarding ganciclovir resistance in CMV is CORRECT?

A. Mutations in UL97 are the most common mechanism
B. Resistant strains are not capable of causing tissue-invasive disease
C. Assessment of IC$_{50}$ (phenotypic testing) is the preferred diagnostic method
D. Mutations in UL97 confer cross-resistance to foscarnet and cidofovir
## Antiviral-Resistant CMV: Incidence (Abdominal Organs)

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Overall Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Kidney</td>
<td>&lt;1%–3%</td>
</tr>
<tr>
<td>Kidney/pancreas or pancreas</td>
<td>1%–13%</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

## Antiviral-Resistant CMV: Incidence (Thoracic Organs)

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Overall Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>&lt;1%–5%</td>
</tr>
<tr>
<td>Lung</td>
<td>5%–16%</td>
</tr>
</tbody>
</table>

Ganciclovir-Resistant CMV in SOT Recipients: Risk Factors

- CMV D+R− serostatus
- High CMV viral load
  (==> subclinical reactivation)
- Highly potent immunosuppression
  (antilymphocyte antibodies)
- Prolonged (suboptimal) ganciclovir exposure
  (?oral ganciclovir)
Ganciclovir-Resistant CMV: Laboratory Diagnosis

**Phenotypic Methods**
- Plaque reduction assay
- DNA hybridization

**Genotypic Methods**
- UL97 and UL54 mutation analysis*
  (sequencing, RE digestion)

*Detection of CMV mutations directly from clinical samples.
## CMV UL97 Phosphotransferase Mutation Map

![CMV UL97 Phosphotransferase Mutation Map](image)

### Codon

<table>
<thead>
<tr>
<th>1</th>
<th>Nuclear localization signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>337</td>
<td></td>
</tr>
<tr>
<td>GTK</td>
<td></td>
</tr>
</tbody>
</table>

### Mutation Map

**GW1263-R**

- **460**
- **520**
- **590-607**

**Strain Variation**

(Lurain NS, AACTG CMV Labs)

### Mutations conferring GCV resistance in marker transfer studies

<table>
<thead>
<tr>
<th>≥ 4-fold resistance</th>
<th>&lt;4-fold resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>M460V</td>
<td>A591V</td>
</tr>
<tr>
<td>M460I</td>
<td>C592G</td>
</tr>
<tr>
<td>H520Q</td>
<td>A594T</td>
</tr>
<tr>
<td>A594V</td>
<td>E596G</td>
</tr>
<tr>
<td>L595S</td>
<td>del600</td>
</tr>
<tr>
<td>L595F</td>
<td>C607F</td>
</tr>
<tr>
<td>K599T</td>
<td></td>
</tr>
<tr>
<td>C603W</td>
<td></td>
</tr>
<tr>
<td>C607Y</td>
<td></td>
</tr>
<tr>
<td>del595</td>
<td></td>
</tr>
<tr>
<td>del590-3/591-4</td>
<td></td>
</tr>
<tr>
<td>del595-603</td>
<td></td>
</tr>
<tr>
<td>del591-607</td>
<td></td>
</tr>
</tbody>
</table>

### Most common UL97 mutations detected in GCV-resistant CMV

<table>
<thead>
<tr>
<th>All resistant isolates (n=79)</th>
<th>Oral GCV recipients (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A594V (29%)</td>
<td>C592G (37%)</td>
</tr>
<tr>
<td>L595S (23%)</td>
<td>A594V (26%)</td>
</tr>
<tr>
<td>M460V (14%)</td>
<td>M460I (22%)</td>
</tr>
<tr>
<td>C592G (13%)</td>
<td>A594T (15%)</td>
</tr>
<tr>
<td>M460I (9%)</td>
<td>(Portland, OR data)</td>
</tr>
<tr>
<td>del595 (5%)</td>
<td>(Roche 1654 study)</td>
</tr>
</tbody>
</table>

Ganciclovir-Resistant CMV: Mechanism(s)

UL97 mutations

- Point mutation(s) or deletion(s)
- Lead to decreased levels of ganciclovir triphosphate in CMV-infected cells
- Mutations at 3 specific codons (460 [22%], 594 [21%), 595 [25%]) account for the majority of clinical ganciclovir-resistant isolates (~70%)
- Do not generally confer cross-resistance to either cidofovir or foscarnet

Ganciclovir-Resistant CMV: Treatment

Current antiviral options
- High-dose ganciclovir\textsuperscript{1,2}
- Foscarnet
- Cidofovir
- Ganciclovir + foscarnet\textsuperscript{3,4}

Other interventions
- Reduction in immunosuppression
- CMV-IG\textsuperscript{5}

Ganciclovir-Resistant CMV: Treatment

Potential future considerations

• Leflunomide/FK 778\textsuperscript{6}
• Maribavir\textsuperscript{7}
• Lipid ester cidofovir conjugates\textsuperscript{8}
• Artesunate\textsuperscript{9}

Clinical Approach to Suspected Resistant CMV

Clinical and/or virologic failure
• No clinical improvement at 2 wks
• No reduction in viral load at 2 wks

Prolonged antiviral drug exposure

YES

> 2 risk factors for resistance
(D+R-, potent IS, K/P or lung tx)

YES
Drug resistance possible/probable
Genotypic testing, reduce IS, addition of foscarnet
+/- CMV Ig

NO
Drug resistance unlikely (possible)

Non–life-threatening CMV
Genotypic testing, reduce IS, higher doses of GCV,
+/- CMV Ig

Life-threatening CMV
Genotypic testing, reduce IS
Addition of foscarnet
+/- CMV Ig

NO
(Drug resistance unlikely)
Host factors
Drug dosing
Panel Discussion
Question-and-Answer Session