CMV TREATMENT AND THE DILEMMA OF RESISTANCE

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AMMI Canada Merck
Integrated Symposium
May 4, 2017

DISCLOSURES

Educational grant money
• UBC-Pfizer
• UBC-Sunovion

Advisory board
• Merck
• Pendopharm

Speaker fees
• Astellas
• Merck
OBJECTIVES

Review the current approaches to treatment of CMV disease for SOT and HSCT patients.

Discuss treatment challenges associated with patients with CMV resistance.

CASE

45M s/p allogeneic HSCT for AML
• 10/10 matched VUD, CMV D-/R-

Post-transplant
• Recurrent infections → antibiotics + IVIG
• Developed cGVHD including BOS (O₂ dependent)

Accepted for lung transplant
• Serology: CMV D+/R+
QUESTION 1: WHAT IS THIS PATIENT’S RISK FOR CMV POST-LUNG TRANSPLANT?

1. High risk because he is a lung transplant recipient
2. Intermediate risk because of the previous HSCT
3. High risk because he is CMV seronegative (D+/R-)
4. Intermediate risk because he is CMV seropositive (D+/R+)

CMV RISK FACTORS

<table>
<thead>
<tr>
<th>Risk of CMV</th>
<th>SOT Serostatus</th>
<th>HST Serostatus</th>
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</thead>
<tbody>
<tr>
<td>High (30-80%)</td>
<td>D+/R-</td>
<td>D+/R+, D-/R+</td>
</tr>
<tr>
<td>Intermediate (5-30%)</td>
<td>D+/R+ &gt; D-/R+</td>
<td>D+/R-</td>
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<tr>
<td>Low (&lt;5%)</td>
<td>D-/R-</td>
<td>D-/R-</td>
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Lung or intestinal transplant
Haploidentical or UCBT
T-cell-depleted graft
IS/Chemo regimen
  - ATG, alemtuzumab, fludarabine
Leukopenia, lymphopenia
aGVHD
Graft rejection

Panagou et al. TID. 2016.
POST-TRANSPLANT MANAGEMENT STRATEGIES

1. Prevention – leukoreduced blood for CMV -/-
2. Pre-emptive therapy
   - Check virus, treat if positive
3. Prophylaxis
   - VGCV

Hybrid?

GUIDELINE RECOMMENDATIONS

SOT
- Universal prophylaxis favoured for D+/R-
- Duration 3-12 months
- Either strategy for R+

HSCT
- Pre-emptive therapy currently favoured
- Drug toxicity limits prophylaxis
- Screen weekly from day 10 to 100

Adapted from Razonable et al. AJT 2013
CASE

Receives 6 months of VGCV + monthly IVIG

Two months later, clinic follow-up
• c/o intermittent non-bloody diarrhea & abdominal cramping
• CMV PCR 20,000 IU/mL
• WBC 3.9 (1.5), AST/ALT N, Cr 75
• Stool studies negative

QUESTION 2: THIS PATIENT HAS

1. Asymptomatic DNAemia
2. CMV tissue invasive disease (GI)
3. Diagnosis depends on endoscopy + CMV PCR of tissue
4. Diagnosis depends on endoscopy + histopathology
**COMPLICATIONS**

**Direct Effects**

CMV Viral Syndrome
- T>38°C, malaise, leukopenia, atypical lymphocytes, thrombocytopenia, elevated ALT/AST
  - PLUS
- CMV detected in blood
  **ONLY FOR SOT**

Tissue Invasive Disease
- GI – colitis, hepatitis
- Pneumonia
- Retinitis...
  **CAN BE PROVEN OR PROBABLE**

**Indirect Effects**

Bacterial, viral or fungal infections
- PTLD
- Cardiovascular events
- New-onset DM
- Immunosenescence
- Acute and chronic rejection
- Mortality

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**DIAGNOSIS**

**Cannot use CMV IgG**

Diagnostic tests of choice
- PCR of plasma
- Biopsy of affected organ(s)
  - Histopathology + immunostaining/in situ hybridization

**CMV pneumonia**
- BAL PCR may be disease vs. shedding = possible CMV

**CMV GI disease**
- Disease may still occur with negative blood PCR
  - Tissue PCR alone may be disease vs. shedding = possible CMV

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QUESTION 3: I WOULD START

1. Ganciclovir 5 mg/kg IV BID
2. Valganciclovir 900 mg PO BID
3. Ganciclovir 5 mg/kg IV BID + CMV IgG
4. Valganciclovir 900 mg PO BID + CMV IgG

TREATMENT OPTIONS

(Val)ganciclovir
- Available
- Main toxicities: myelosuppression

Foscarnet
- Special Access Program
- Main toxicities: Electrolyte disturbance, renal failure

Cidofovir
- Special Access Program
- Main toxicities: Renal failure, uveitis
326 patients randomized

PO VGCV vs. IV GCV

“Non-life threatening”

Predominantly:
- Kidney Tx recipients
- CMV syndrome > colitis

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**TREATMENT**

First line therapy
- VGCV (900 mg every 12 hours) or IV GCV (5 mg/kg every 12 hours)

In SOT, VGCV is preferred except
- Life-threatening disease
- Poor oral drug bioavailability
- Medication non-adherence

In HSCT, cohort data suggests VGCV can be used safely for pre-emptive treatment
- Noninferiority RCT terminated for low accrual
- GCV still has best evidence

CMV IGG (CYTOGAM) OR IVIG

Ljungman et al. CID, 1992.a

Reduced Mortality of Cytomegalovirus Pneumonia After Hematopoietic Cell Transplantation Due to Antiviral Therapy and Changes in Transplantation Practices

Examined patients at FHCRC from 1986-2011

Diagnosis per standard criteria

421 recipients
- 30% 6 mo. survival
- 296 deaths
  - 63% from CMV
- Antivirals reduced mortality
  HR 1.9 (95% CI 1.2–3.2)
- No improvement in mortality with Ig
CASE

CMV VL

- Week 1 CMV 20,000
- Treatment initiated 3 days after blood drawn
- Week 2 CMV 78,000
- Week 3 CMV 40,500
- Week 4 CMV 18,000
- ...

QUESTION 4: I AM CONCERNED ABOUT DRUG RESISTANCE

1. True
2. False
Rising pp65 antigenemia during preemptive anticytomegalovirus therapy after allogeneic hematopoietic stem cell transplantation: risk factors, correlation with DNA load, and outcomes

W. Garrett Nichols, Lawrence Corey, Ted Gooley, W. Lawrence Drew, Richard Miner, Meei-Li Huang, Chris Davis, and Michael Boeckh
BLOOD, 15 FEBRUARY 2001 • VOLUME 97, NUMBER 4

119 allogeneic HSCT patients
- 1995-1997 at FHCRC

45% had a rise in antigenemia after Rx started
- Correlated with CMV VL
  - 39% 2x & 28% ≥5x
  - 43% within 1 week → 47% → 6% → 4% after 4+ weeks
- 15 patients had susceptibility testing
  - 20/21 isolates GCV sensitive
- RF for rise: corticosteroids
  - OR 4.0 if 1-2 mg/kg
  - OR 10.1 if ≥2 mg/kg

Of 47 patients with rising values
- 15 re-induced, 32 maintenance
  - If re-induced, next value was lower & no CMV disease
  - If not re-induced
    - 4 patients developed CMV disease on treatment
    - 3/4 patients died of CMV disease
  - At the time, only 1 week “induction Rx” used
    - Suggestion was to increase antiviral dose
TREATMENT

Weekly PCR during therapy for monitoring
• Half life ~3-4 days → no benefit increased testing

Continue until 2 negative assays one week apart (min. 2 weeks)

Viral load kinetics
1. Predict outcome
   • ≥1-log drop at day 7 = lower risk of recurrence (8.7 vs. 34.5%)
2. Do not predict for drug resistance early on
   • Reflect immune response


TREATMENT TIPS

1. Consider IS reduction (esp. if severe dz)
2. Account for delay in therapy initiation when assessing response
   • Median doubling times for SOT
     • 1.54 days for D+/R-
     • 2.67 days for D+/R+
3. Induction and maintenance dosing are likely no longer relevant → treatment dose or prophylaxis
4. Do not dose reduce for leukopenia
5. Careful dosing if AKI/CKD

Atabani et al. AJT 2012.
CASE

Viral load slowly fell to <526 IU/mL
- No negative values
- Patient continued on valganciclovir

Low level DNAemia for 9+ months
- Small decline in renal function CrCl 58 ml/min
- Dose reduced to 450 mg po BID

CMV PCR <526 → 6,200

CASE

No symptoms, laboratory work unchanged

Patient admitted for high dose GCV
- 10 mg/kg IV BID

CMV PCR
- Week 1 CMV 6,200
  - Treatment initiated 1 day after blood drawn
- Week 2 CMV 21,800
- Week 3 CMV 18,100
- Week 4 CMV 22,000
QUESTION 5: I AM CONCERNED ABOUT DRUG RESISTANCE

1. True
2. False

DRUG RESISTANT VIRUS?

Unchanged/rising viral loads after >2 weeks of full dose therapy

- Prolonged antiviral drug therapy
- High levels of DNAemia at treatment initiation
- No prior CMV immunity (D+/R-)
  - High immunosuppression (e.g. lung tx, T-cell depleted, UCBT)
- Persistent DNAemia

**CASE**

**Blood sent to National Lab for resistance testing**

- Positive UL97 mutation (L595S)
- Unable to amplify UL54 region
QUESTION 6: AT THIS POINT, I WOULD

1. Keep going with high-dose GVC
2. Change to foscarnet
3. Change to cidofovir
4. Phone a colleague and ask for advice
UL97 GENOTYPES

<table>
<thead>
<tr>
<th>Fold change in EC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>5-15x</th>
<th>2-5x</th>
<th>&lt;2x</th>
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<tbody>
<tr>
<td><strong>Most common</strong></td>
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<td></td>
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<tr>
<td><strong>Less common</strong></td>
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Only able to use high-dose GVC if <5x change in EC<sub>50</sub>
~90% of the time, occur before UL54 mutations


CASE

Patient changed to foscarnet
CMV declined to <526 x 6 weeks
  * Finally 2 negative values
  * Immediately after d/c, positive again
  * Remained stable <526 IU/mL off treatment

Two months later, decline in spirometry
  * BAL negative
  * Team suspects rejection
  * Pulse steroids initiated
  * CMV rises to 13,100
  * Patient admitted for foscarnet
CASE

On foscarnet
• Week 2 CMV 35,200 → UL54 typing requested
• Week 3 CMV PCR 13,200
• Week 4 CMV PCR 21,000
• Week 5 CMV PCR 9,400

UL54 typing returns
• Positive for Q578H

QUESTION 7: AT THIS POINT, I WOULD

1. Continue on with foscarnet.
2. Change to cidofovir
3. Look for alternative agents (activated T-cells, maribavir)
4. Phone a colleague and ask for advice
UL54 GENE MAP

Structure Domain 1

Amino Terminal 1 (94-295)

Exonuclease
(296-554)

Amino Terminal 2
(555-600)

Palm1 696
Finger 765
Palm2 825
Thumb 981 (982-1226)

Codon

Conserved region Exol IV/Exoll Exoll/deltaC II VI III I VII V

Mutations affecting drug susceptibility in clinical isolates

Q578H

Susceptibility Phenotype GCVr CDVr FOSr FOSrGCVr CDVr GCVrCDVr


GENOTYPIC VS. PHENOTYPIC

Phenotypic plaque reduction assay (PRA)

- Gold standard
- Slow (4-6 weeks) & labour-intensive

Genotypic analysis

- Quick
- Falsely negative if subpopulation <20-30%
- Difficult to interpret due to natural polymorphisms

Q578H

- NML report: “published reports… contentious with regards to sensitivity to ganciclovir and cidofovir”

NOVEL THERAPIES

Drugs
- Brincidofovir
- Maribavir
- Letermovir

Immunotherapies
- Activated CMV-specific T-cells
- Vaccines (prevention)

BRINCIDOFOVIR

Similar MOA to cidofovir
- Higher cellular concentrations ➔ less nephrotoxicity
- Cross-resistance

Failed phase 3 clinical trial for CMV prophylaxis post-HSCT (SUPPRESS trial)
- Many subsequent planned trials have been withdrawn

Few case reports in resistant/refractory CMV infections
- Failed if UL54 mutation present for CDV-R

MARIBAVIR

Inhibits UL97 kinase & viral DNA synthesis
- No cross-resistance
- Antagonistic with GCV/VGCV

Success in case series of GCV-resistant CMV infections
- May not completely inhibit DNAemia

Failed phase 3 clinical trial for CMV prophylaxis post-HSCT
- Suboptimal dosage? Wrong endpoint?

Two trials in Canada starting
- RCT of VGCV vs. maribavir in HSCT
- Phase 3 multicenter trial for refractory/resistant CMV infections in transplant patients


LETTERMOVIR

Inhibits UL56 (CMV terminase complex)
- Converts concatemeric progeny DNA \(\rightarrow\) small genomes for packaging
- No cross-resistance

Single case reports of success in refractory/resistant CMV infections
- PCR may be slow to decline because does not inhibit synthesis

Letermovir resistance mutations already detected
- Low genetic barrier to resistance?

Success in phase 3 clinical trial for CMV prophylaxis post-HSCT (NCT02137772)
- New standard of care?

ACTIVATED T-CELLS

Attractive for multiple viral infections, including CMV

Significant logistical issues
- E.g. availability, cost, time delay to generate cells, research protocol
- Donor-derived vs. third party

Best evidence in HSCT population
- Donor may be easily available

More difficult in SOT because of IS
- CNIs prevent activation of cytokine genes in T cells → lack of efficacy


QUESTIONS?
REFERENCES


