Activity Description

Target Audience

Long-term success of transplant recipients requires an interdisciplinary approach that includes all healthcare providers involved in the management of these patients to prevent and treat CMV viremia. Therefore, this continuing medical education activity will target ID clinicians involved in the care of transplant recipients. These include ID physicians and pharmacists, nurses, microbiologists and allied healthcare providers.

Learning Objectives

Those attending the program will be able at its conclusion to:

- Recognize the burden of CMV and identify risk factors for CMV infection and disease
- Evaluate the benefits and risks of antiviral prophylaxis versus pre-emptive approaches in the prevention of CMV
- Assess the utility of advanced diagnostic monitoring tools to guide medical decision-making for patients with or at risk of CMV
- Describe the mechanisms of CMV resistance and assess the potential role of newer and emerging antiviral agents in overcoming resistance

Faculty

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University Health Network
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Toronto, ON

Recognizing the Burden of CMV and Risk Factors for Infection

Atul Humar, MD, FRCP(C)
Director, Multi Organ Transplant Program
R. Fraser Elliott Chair in Transplantation
University Health Network
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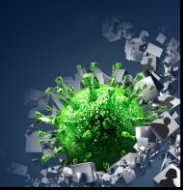
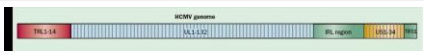
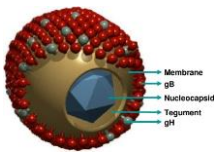


Cytomegalovirus (CMV) Composition



- Genetic composition
  - 2 unique regions of DNA (U_L and U_S), flanking terminal repeat regions (TR), and internal repeat region (IR)
  - Encodes ≥168 unique functional genes (exact number unknown)
  - Gene expression occurs in a temporal cascade (IE, early, and late)



IE, immediate early

Crough T, Khanna R. *Clin Micro Rev*. 2009;22:76-98.
Gandhi MK, Khanna R. *Lancet Infect Dis*. 2004;4:725-38.

Effects of CMV Infection Post-Transplant

Direct Effects

CMV Viral Syndrome [SOT]
- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities

Tissue Invasive Disease [SOT/HSCT]
- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

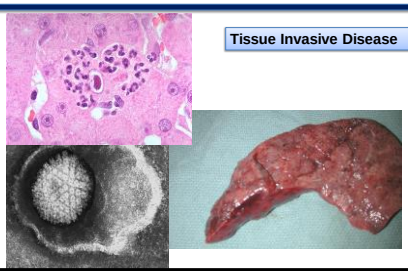
Indirect Effects

SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant

The Burden of CMV

- Despite widespread use of preventive measures, CMV infection (viremia) and disease (symptoms) continues to be common in certain settings
- There has been:
  - Decrease in incidence of symptomatic disease
  - More commonly asymptomatic or mildly symptomatic viremia
  - Fewer cases of severe tissue invasive disease

However CMV Can Still Cause Life-Threatening Disease



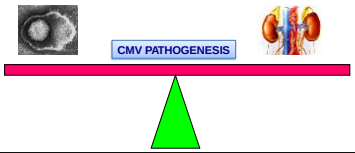
Audience Question

Which of these patients is at highest risk of CMV disease?

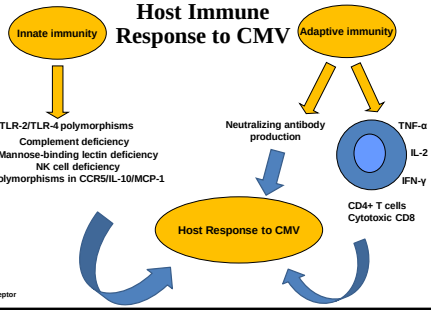
1. D-/R+ HSCT recipient with acute graft-versus-host-disease
2. D+/R- lung transplant recipient
3. D+/R+ kidney transplant with steroid-resistant rejection treated with thymoglobulin
4. All of the above are at high risk

Factors Influencing the Burden of CMV

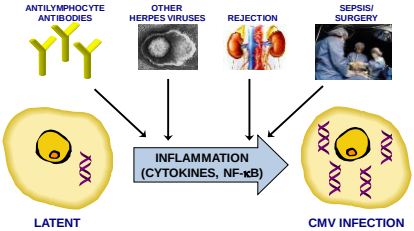
- **Viral factors**
  - Replication dynamics
  - Immune evasion
  - Viral heterogeneity
  - Viral co-infections
- **Host factors**
  - CD4+, CD8+ T cell
  - NK cell, B cell
  - Exogenous immunosuppression
  - D/R immune status



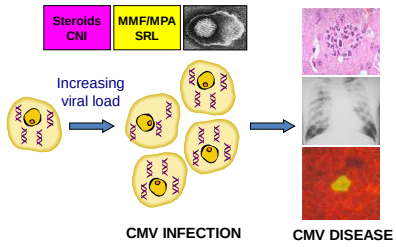
Host Immune Response to CMV



Reactivation of CMV



CMV Infection to CMV Disease



CNI, calcineurin inhibitors; MPA, mycophenolic acid; MMF, mycophenolate mofetil; SRL, sirolimus.

Risk Profile for CMV in SOT

Risk Category	Donor (D) / Recipient (R) Serologic Status (+/-)
High	D+/R-
Intermediate*	D+/R+, D-/R+
Low	D-/R-

- Anti-lymphocyte globulin induction/therapy– major risk factor
- Lung, small bowel, VCA–highest risk; pancreas, heart–intermediate risk; kidney, liver–lower risk but depends on immunosuppression

*D+/R+ generally at higher risk than D-/R+
D-/R-, leuko-depleted blood products or seronegative

VCA, vascular composite allotransplantation
Razonable RR, et al. *Am J Transplant.* 2013;13:93-106.
Kotton CN, et al. *Transplantation.* 2013;96:333-60.

Risk of CMV in HSCT

- Serostatus (in the US, ~60% population is CMV+)
  - D+/R-: 30% develop primary CMV
  - R+: 80% will have some degree of reactivation (although disease has been significantly reduced due to monitoring and preemptive therapy)
- High-dose steroids
- T cell depletion
- Acute and chronic GVHD
- Mismatched or unrelated donor
- Cord blood transplant (donors CMV negative)
- Alemtuzumab

Ljungman P, et al. *Hematol Oncol Clin North Am.* 2011;25:151-69.

CMV PREVENTION: Prophylaxis

- Prophylaxis
  - Antiviral therapy from the time of transplant to all patients or a subgroup of patients
  - E.g. 3–6 months of antiviral prophylaxis in all D+/R- transplant patients
  - Prophylaxis very successful in multiple clinical trials for CMV prevention

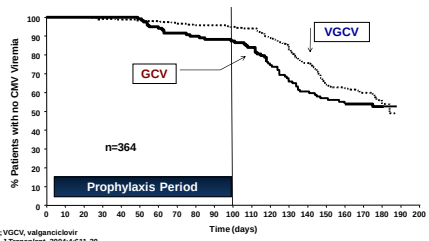
Kotton CN, et al. *Transplantation.* 2013;96:333-60.

What are the Major Problems with Prophylaxis?

1. Drug toxicity – makes use of (val)ganciclovir as prophylaxis early post-HSCT unattractive
2. After discontinuation of prophylaxis – viremia and disease often develops
   - "Late-onset CMV disease"
     - May present with atypical symptoms (no fever – malaise, fatigue); diagnosis can be missed

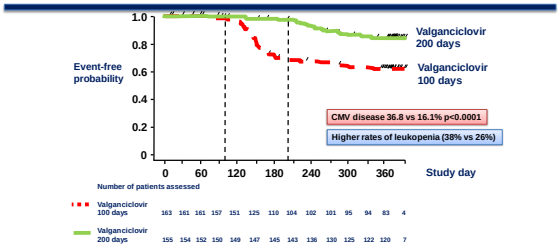
Kotton CN, et al. *Transplantation.* 2013;96:333-60.

Viremia Common After Prophylaxis



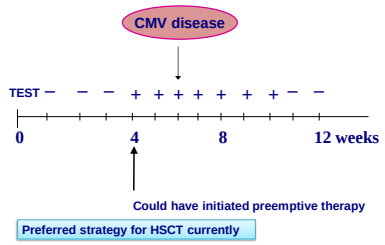
GCV, ganciclovir; VGCV, valganciclovir
Paya C, et al. *Am J Transplant.* 2004;4:611-20.

Extended Prophylaxis: Kidney Transplant Study

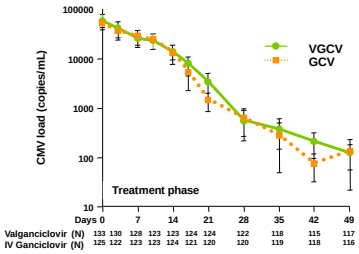


Humar A, et al. *Am J Transplant*. 2010;90:1427-31.

CMV Prevention: Preemptive Therapy

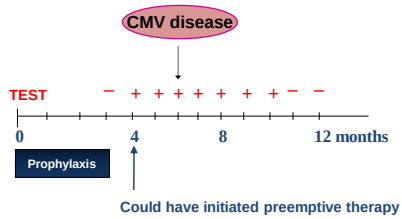


Can Either Oral or IV be Used for Preemptive Therapy?

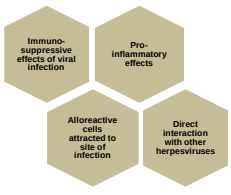


Asberg A, et al. *Am J Transplant*. 2007;7:2106-2113.

Hybrid Strategy: Preemptive After Prophylaxis



The Burden of CMV: Indirect Effects



- Graft rejection; graft dysfunction
- Opportunistic infections: bacterial, fungal superinfection
- Decreased graft and patient survival
- Herpesvirus interactions: EBV/PTLD

EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disease.

Role of Diagnostics in Monitoring CMV Infection and Treatment Response

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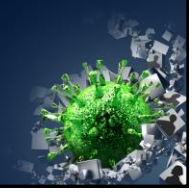
Seattle, WA

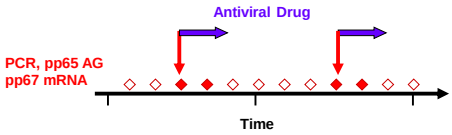


Outline

- CMV viral load
  - Blood
    - Start of preemptive therapy
    - Monitoring treatment responses
  - BAL
    - Pulmonary shedding versus pneumonia

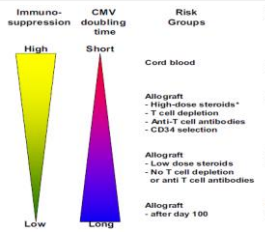
BAL, bronchoalveolar lavage

Preemptive Therapy



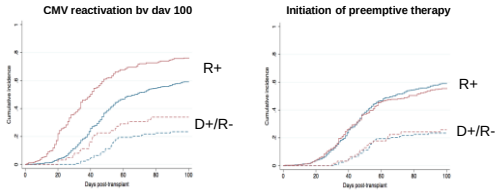
	RCT
Ganciclovir	+
Foscarnet	+
Cidofovir	not tested
Valganciclovir	+

Preemptive Therapy PCR-based Risk-adapted Strategy



Boeckh M, Ljungman P. *Blood*. 2009;113:5711-9.

PCR-based Risk-adapted Strategy



Green ML, et al. *Biol Blood Marrow Transplant*. 2012;18:1687-99.

Viral Load Increases on Preemptive Therapy

- Up to 2 weeks <u>not</u> unusual
- Occurs with severe immunosuppression
- Antiviral resistance unusual

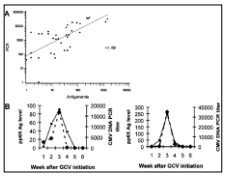


Table 2. Risk factors for increasing pp65 antigenemia among 119 recipients of allogeneic HSCT

	↑ Ag > 2× baseline			↑ Ag > 5× baseline		
	OR	95% CI	P	OR	95% CI	P
Multivariate analysis‡						
Conditioning						
Non-TBI-containing	1.0*					
TBI-containing	2.6	1.0-6.8	.04			
Steroid use at 1st Ag + wk						
None	1.0*			1.0*		
< 1 mg/kg	5.0	1.0-24.5	.05	4.3	0.6-31.3	.25
1-2 mg/kg	4.0	1.0-16.0	.06	14.3	1.7-120.2	.01
≥2 mg/kg	10.1	2.6-40.2	.001	28.6	3.6-229.7	.002

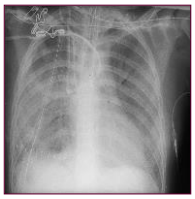
Nichols WG, et al. *Blood*. 2001;97:867-74.

CMV Disease

Preemptive Era – Placebo Group in Randomized Trials

Author	Journal	Year	N	Period	Incidence
Marty et al.	*Lancet ID*	2011	227	Early	2.4%
Marty et al.	*NEJM*	2014	59	Early	3.0%
Chemaly et al.	*NEJM*	2014	33	Early	0%
Boeckh et al.	*Ann Int Med*	2014	89	Late	2.0%
Marty et al.	ASBMT	2016	149	Early	3.4%
Marty et al.	ASBMT	2017	170	Early	1.2%

CMV Pneumonia in HSCT Recipients



Diagnosis of CMV Pneumonia

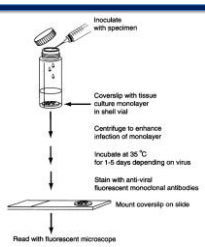
Before 1988: Lung Biopsy

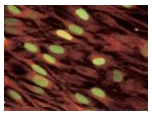
Images: Cancer Research UK / Wikimedia Commons and http://www.olympus-europa.com/; Shelhamer et al. *Ann Intern Med*. 1996;124(6):585-599

BAL and quantitative PCR?

Crawford SW, et al. *Ann Intern Med*. 1988;108:180-5.

Shell Vial Cultures





Revello MG, Gerna G. *Clin Microbiol Rev*. 2002;15:680-715.

Shelhammer. *Ann Int Med*. 1996.

Issues

Detection ≠ Disease

- **PCR is highly sensitive – good NPV but poor PPV**
- **Asymptomatic shedding**
- **Pulmonary hemorrhage**
- **Distribution of viral load in the lung**
  - **Radiographic presentation**
- **Need for appropriate controls**

Cut-off value to distinguish pulmonary shedding from CMV pneumonia?

NPV, negative predictive value; PPV, positive predictive value

Case

- 57-year-old male, 112 days after HLA mismatched unrelated donor PBSC transplant for AML
- CMV R+/D-, HSV+, VZV+
- Engraftment: day 14
- Acute GI GVHD, grade 3; current steroid dose: 0.6 mg/kg
- Two courses of ganciclovir/valganciclovir during the first 100 days, now presenting with shortness of breath, cough and bilateral interstitial infiltrates
- BAL results
  - CMV: shell vial cultures toxic; PCR: 910 IU/mL
  - Respiratory virus PCR panel negative
  - All other stains, *Aspergillus* GM and PCR, panfungal PCR, and cultures are negative
- Plasma CMV DNA PCR: 660 IU/mL

HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; AML, acute myeloid leukemia; HSV, herpes simplex virus; VZV, varicella zoster virus; GM, galactomannan.

Audience Question

How do you interpret this result and what action do you take?

1. CMV pneumonia – treat with antivirals and IVIG/CMV-Ig
2. CMV pneumonia – treat with antivirals only
3. CMV pulmonary shedding – treat with short-term antivirals
4. No treatment

Pulmonary Shedding of CMV

Figure 1. Kaplan–Meier Product-Limit Estimates of the Probability of CMV Pneumonia in Recipients of Bone Marrow Transplants. There were significant differences in the probability of CMV pneumonia between groups 1 and 2 ($P = 0.0013$) and between groups 2 and 3 ($P<0.0001$), on the basis of the log-rank test.

Schmidt GM, et al. *N Engl J Med*. 1991;324:1005-11.

Study Methods

Cases: CMV pneumonia (N=132)

- BAL done 1988–2014
- SV, culture (+/- DFA, cytology) attempted
- Positive by at least one

Controls (N=139)

- SV and culture negative for CMV
- Asymptomatic HSCT recipients (N=21), normal chest x-ray around day 40
- Idiopathic pneumonia syndrome (IPS; no known pathogens) (N=18)
- Bacterial, fungal or viral (non-CMV) pneumonia (N=100)

Test by quantitative PCR

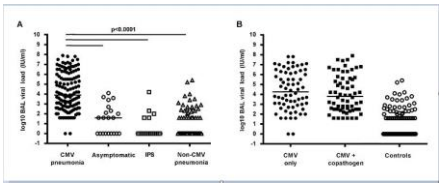
- Archived BAL
- Results in IU/mL (1 copy/mL = 1.2 IU/mL), plotted as $\log_{10}$ (IU/mL)

SV, shell vial; DFA, direct fluorescent antibody

Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

Quantitative CMV Load in BAL Fluid

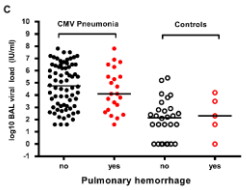
Higher Viral Load in CMV Pneumonia Patients



Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

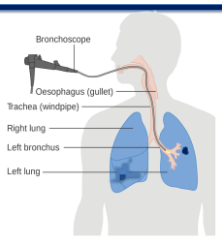
BAL CMV Load

No Impact of Pulmonary Hemorrhage



Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

Impact of Radiographic Presentation?



Images: Cancer Research UK

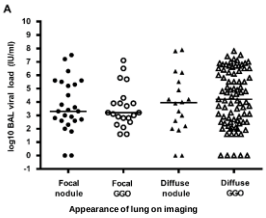
Does viral load differ based on radiology?

Radiologic score
1 = Focal nodule
2 = Focal GGO
3 = Diffuse nodule
4 = Diffuse GGO

GGO, ground glass opacity

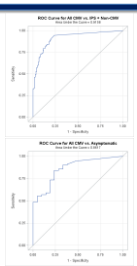
BAL CMV Load by Lung Imaging

No Difference in Viral Load



Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

ROC Curve: CMV Viral Load IU/mL



All CMV cases (N=132)
and controls (N=118)
(Asymptomatic patients excluded)

AUC = 0.9158

Optimal cut-off point
99.7 IU/mL
Sensitivity = 90.2%; Specificity = 80.5%

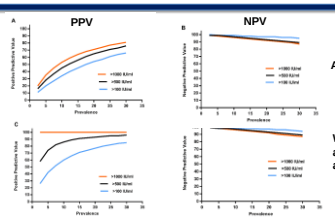
All CMV cases (N=132)
and Asymptomatic controls (N=21)

AUC = 0.8617

Optimal cut-off point
203.3 IU/mL
Sensitivity = 84.1%; Specificity = 76.2%

ROC, receiver operating characteristic; AUC, area under the curve.
Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

Which Threshold is Most Predictive for CMV Pneumonia?



All Patients

Without antiviral agents at time of BAL

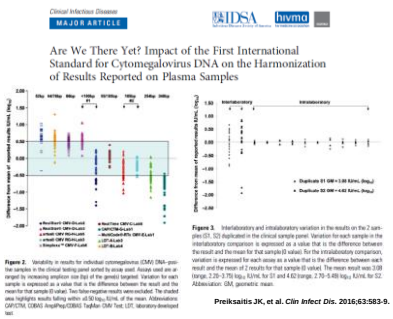
Prevalence of CMV pneumonia among patients who undergo bronchoscopy

Boeckh M, et al. *J Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jix048.

Case - Interpretation

How do you interpret this result and what action do you take?

1. CMV pneumonia – treat with antivirals and IVIG/CMV-Ig
2. CMV pneumonia – treat with antivirals only
   Erard V, et al. *Clin Infect Dis*. 2015;61:31-9.
3. CMV pulmonary shedding – treat with short-term antivirals
4. No treatment



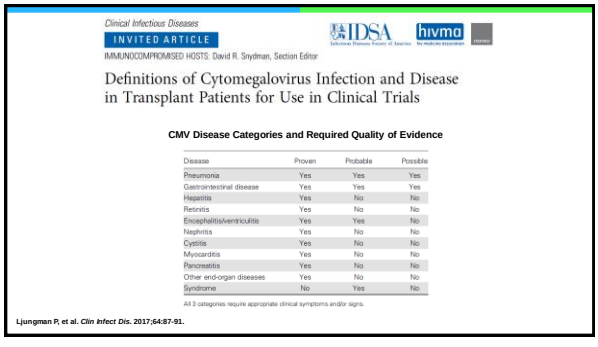
Clinical Infectious Disease
MAJOR ARTICLE

IDSA hivma

Are We There Yet? Impact of the First International Standard for Cytomegalovirus DNA on the Harmonization of Results Reported on Plasma Samples

Figure 2. Figure 3.

Preiksaitis JK, et al. *Clin Infect Dis*. 2016;63:583-9.



Clinical Infectious Diseases
INVITED ARTICLE

IDSA hivma

IMMUNOCOMPROMISED HOSTS: David R. Snydman, Section Editor

Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials

CMV Disease Categories and Required Quality of Evidence

Disease	Proven	Probable	Possible
Pneumonia	Yes	Yes	Yes
Gastrointestinal disease	Yes	Yes	Yes
Hepatitis	Yes	No	No
Retinitis	Yes	No	No
Encephalitis/ventriculitis	Yes	Yes	No
Nephritis	Yes	No	No
Cystitis	Yes	No	No
Myocarditis	Yes	No	No
Pancreatitis	Yes	No	No
Other end-organ diseases	Yes	No	No
Syndrome	No	Yes	No

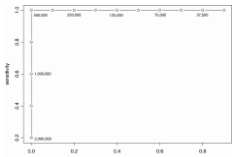
All 3 categories require appropriate clinical symptoms and/or signs.

Ljungman P, et al. *Clin Infect Dis*. 2017;64:87-91.

Clinical Utility of Cytomegalovirus Viral Load in Bronchoalveolar Lavage in Lung Transplant Recipients

Roy F. Chemaly, Belinda Yen-Lieberman, Jeffrey Chapman, Amy Reilly, B. Nebiyou Bekele, Steven M. Gordon, Gary W. Procop, Nabin Shrestha, Carlos M. Isada, Malcolm DeCamp and Robin K. Avery

American Journal of Transplantation. 2005;5:544–548.



Threshold: 500,000 copies/mL

Take-Home Points

- CMV DNA-based preemptive therapy is effective in preventing CMV disease
- Increased viral load during the first two weeks of preemptive therapy is usually not due to drug resistance in drug-naïve patients
- Quantitative DNA PCR of BAL fluid can differentiate between CMV pneumonia and asymptomatic shedding in HSCT recipients
- Pulmonary hemorrhage and copathogens, even with distinct radiographic presentation, did not seem to alter viral load
- Possible cut-off recommendations:
  - 500 IU/mL might provide improved PPV with acceptable NPV
  - Lower levels in highest risk patients
- Shell vial testing may be helpful to assess patients with viral load <500 IU/mL
- Threshold may differ between the HSCT and lung transplant setting

Utilizing Immune Monitoring Assays to Predict CMV Disease – SOT Focus

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Director, Multi Organ Transplant Program
R. Fraser Elliott Chair in Transplantation
University Health Network
Director, University of Toronto Transplant Institute
Toronto, ON




Case

- 48-year-old man post DD liver transplant for HCV-related cirrhosis
- CMV D+/R-
- About to finish 3 months of antiviral prophylaxis

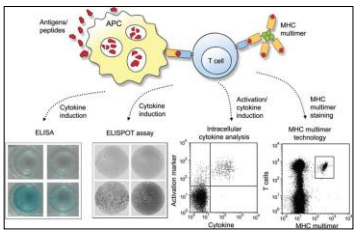
DD, deceased donor

Audience Question

What are the potential options to prevent late-onset CMV disease?

1. Do nothing and accept risk of late-onset CMV
2. Extend prophylaxis to 6 months
3. Check CMV PCR every week (hybrid strategy)
4. Check whether his T cells produce interferon-γ in response to CMV

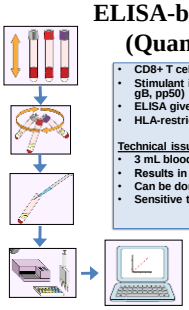
Specific CMI Assays: Characterizing CMV-specific T Cells



Assays based on measurement of IFN-γ production by cells stimulated with CMV peptides, whole proteins, or CMV whole virus

CMI, cell-mediated immunity
Sester M, et al. *LaboratoriumsMedizin.* 2008;32:121-30.

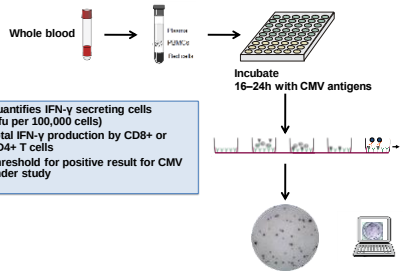
ELISA-based Detection of IFN-γ (Quantiferon-CMV Assay)



- CD8+ T cell assay
- Stimulant is a mixture of 23 peptides (pp65, IE1/2, gB, pp50)
- ELISA gives IFN-γ value (IU/mL) – validated cut-off
- HLA-restricted so some HLA types not covered

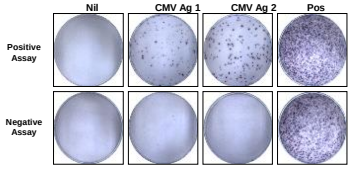
Technical issues:
- 3 mL blood
- Results in 1–2 days
- Can be done at any center
- Sensitive to lymphopenia

ELISPOT

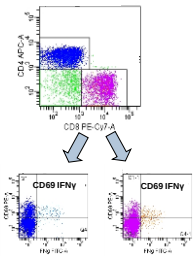


- Quantifies IFN-γ secreting cells (sfu per 100,000 cells)
- Total IFN-γ production by CD8+ or CD4+ T cells
- Threshold for positive result for CMV under study

ELISPOT (T-SPOT®.*CMV* or T-Track® CMV)



Cytokine Flow Cytometry



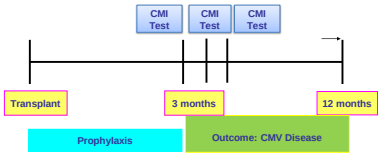
- Provides highest resolution data for cytokines expressed by CD4+ and CD8+ T cells
- Primarily a research tool for CMV in many labs
- Limited by number of fluorochromes for each antibody
- No standardization

Summary of Clinical Studies of CMV Cell-mediated Immunity

- Numerous observational studies of CMI that have clinical endpoints (CMV disease or viremia)
  - Include studies that have used ELISA, ELISPOT, or cytokine flow cytometry
- Majority of studies:
  - Measures IFN-γ release or enumerate IFN-γ+ T cells
  - Relatively small numbers
  - Heterogeneous population (mix of D+/R- and R+; various transplant types)
- Limited pediatric data

Kotton CN, et al. *Transplantation*. 2013;96:333-60.

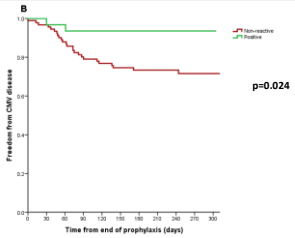
End of Prophylaxis CMI (D+/R- only)



n=127 D+/R- patients [Canada, US, Europe]

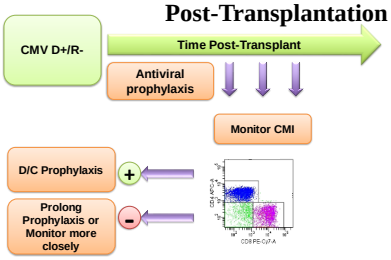
Manuel O, et al. *Clin Infect Dis*. 2013;56:817-24.

Incidence of CMV Disease Based on CMI Assay Result



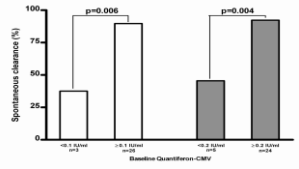
Manuel O, et al. *Clin Infect Dis*. 2013;56:817-24.

Utilization of CMI Assays Post-Transplantation



Utility of CMI in Another Clinical Scenario: Low-level Viremia

- 37 SOT patients enrolled at the time they had low-level CMV viremia (~1000 copies/mL)
- 78% spontaneously cleared whereas 22% progressed to require antivirals



Lisboa LF, et al. *Transplantation.* 2012;93:195-200.

Potential Post-transplant Clinical Scenarios for CMI Use

Clinical Scenario	Potential clinical management
CMV D+/R- on primary prophylaxis	For negative assay, ongoing prophylaxis or frequent monitoring. For positive assay, no further prophylaxis or monitoring.
CMV R+ with other risk factors (e.g., lung transplant, ATG induction)	
Post-therapy for acute rejection	
Recent completion of therapy for CMV disease (Prediction of relapse)	
Recent completion of therapy for CMV viremia (Prediction of relapse)	
Low-level viremia	For negative assay, start therapy. For positive assay, continue to monitor.

ATG, anti-thymocyte globulin

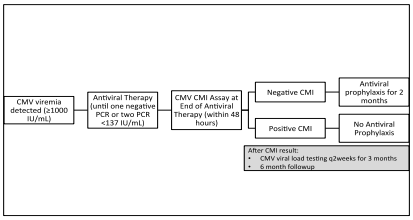
Egli A, et al. *Clin Infect Dis.* 2012;55:1678-89.

ARE THERE ANY INTERVENTIONAL STUDIES IN SOT?

SEVERAL ARE ONGOING!

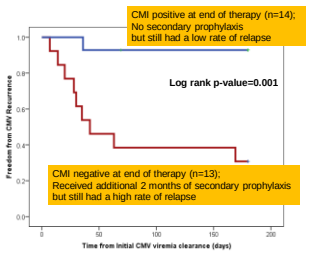
An Interventional Study Using Cell Mediated Immunity to Personalize Therapy for Cytomegalovirus Infection after Transplantation

Authors: Deepali Kumar, Muhtashim Mian, Lianne Singer, Atul Humar



Kumar D, et al. *Am J Transplant.* 2017;[Epub ahead of print].
Available at: http://onlinelibrary.wiley.com/doi/10.1111/ajt.14347/epdf.

CMV Recurrence After Initial Viral Load Clearance



Kumar D, et al. *Am J Transplant.* 2017;[Epub ahead of print]. Available at: http://onlinelibrary.wiley.com/doi/10.1111/ajt.14347/epdf.

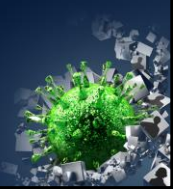
Why CMI Assays are not yet in Routine Clinical Practice?

More interventional clinical studies are necessary!

- Several observational studies now show a link between T cell immunity and CMV viremia
- Studies in which a CMI assay is used in real time to make clinical decisions are ongoing:
  - Stopping prophylaxis early
  - Initiating antiviral treatment for low-level viremia
  - Withholding secondary prophylaxis from patients who finish CMV therapy and are CMI positive

Utilizing Immune Monitoring Assays to Predict CMV Disease – HSCT Focus

Roy F. Chemaly, MD, MPH, FIDSA, FACP
Professor of Medicine
Director, Infection Control Section
Director of Clinical Virology
Department of ID/IC/EH
UT MD Anderson Cancer Center
Houston, TX



How to Increase Specificity of Preemptive Therapy Approach?

- Combine monitoring of viral load with monitoring of CMV-specific T cell immunity
- This strategy allows withholding preemptive therapy in patients with low-to-moderate levels of CMV DNA, in presence of CMV-specific T cell responses
- However, protective T cell immunity thresholds need to be determined

Utility of the Enzyme-Linked Immunospot Interferon-γ–Release Assay to Predict the Risk of CMV Infection in HCT Recipients

- Observational prospective study in 63 CMV-recipient positive HCT recipients
  - Low risk: MRD
  - High risk: MUD, haploidentical, CBT, GVHD, prednisone >1 mg/kg
- Blood draws at specific time points from transplantation:
  HSCT—30—60—100 days
- The primary objective: To assess the ability of an ELISPOT assay (T-SPOT.*CMV)* to predict CMV reactivation and/or disease in HCT recipients during the high-risk period

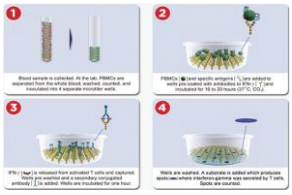
MRD, match-related donor; MUD, match-unrelated donor; CBT, cord blood transplantation
Nesher L, et al. *J Infect Dis.* 2016;213(11):1701-1707.

ELISPOT (T-SPOT®.*CMV*) Technology

Density gradient isolation of mononuclear cells

Quantitation of cells and adjustment of concentration

Incubation with specific antigens on ELISPOT microtiter plate



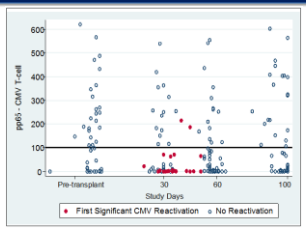
T-SPOT is a registered trademark of Oxford Immunotec Ltd.
Oxford Immunotec Ltd. T-SPOT.CMV Package Insert PI-CMV-IVD-UK-V1. Abingdon, UK. 2015.

Clinical Characteristics and Outcomes at Day 100

	Total	CMV reactivation	No CMV reactivation
Number	63	23	40
Age (in years)	56 (21 – 73)	57 (21 – 69)	56 (24 – 73)
Sex			
Male	37 (59)	14 (61)	23 (58)
Female	26 (41)	9 (39)	17 (43)
Race			
White	49 (78)	17 (74)	32 (80)
African American	6 (10)	3 (13)	3 (8)
Hispanic	7 (11)	2 (9)	5 (13)
Asian	1 (2)	1 (4)	0
Type of Cancer			
Acute Leukemia	38 (60)	11 (48)	27 (68)
Chronic Leukemia	8 (13)	3 (13)	5 (13)
Myelodysplastic Syndrome	17 (27)	9 (39)	8 (20)
Type of Transplant			
Match Related Donor	23 (37)	5 (22)	18 (45)
Match Unrelated Donor	35 (56)	15 (65)	20 (50)
Cord	5 (8)	3 (13)	2 (1)
Corticosteroid use	19 (31)	5 (22)	14 (36)
GVHD	12 (19)	4 (17)	8 (20)
HCT donor status			
CMV +	41 (65)	13 (57)	28 (70)
CMV -	22 (35)	10 (43)	12 (30)
Outcomes			
All-cause mortality	8 (13)	4 (17)	4 (10)

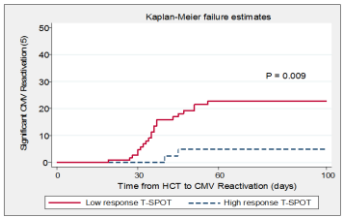
Nesher L, et al. *J Infect Dis.* 2016;213:1701-1707.

Scatterplot for CMV Reactivation vs Number of Spots, Over Different Time Points



Nesher L, et al. *J Infect Dis*. 2016;213:1701-1707.

Probability of CMV Reactivation Stratified by High and Low Assay Response



Nesher L, et al. *J Infect Dis*. 2016;213:1701-1707.

After the Proof of Concept

REACT Study

Multicenter, prospective, observational study

First patient enrolled June 2015; LPLV April 2017

244 CMV seropositive (R+) candidates for allogeneic HCT were included in this analysis

T-SPOT.*CMV* (ELISPOT) assay was used to assess the production of IFN-γ following ex-vivo stimulation with CMV-specific antigens (IE1 and pp65)

Serial blood draws (T-SPOT.*CMV* and CMV PCR) were done as follows:

Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Definition of Events

CMV Event: The first episode of significant CMV reactivation, defined as the detection of CMV in blood via the antigenemia assay or the CMV PCR assay, after which anti-CMV therapy was initiated by the treating physician in accordance with institutional guidelines.

CMV Disease: The first episode of CMV disease, consisting of "end-organ disease" as defined by Per Ljungman *et al**.

*Ljungman P, et al. *Clin Infect Dis*. 2017;64:87-91.

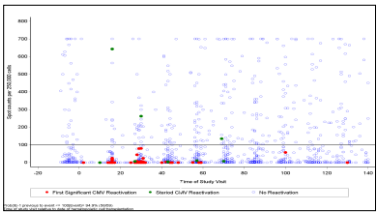
Results

Clinical Characteristics of 244 HCT Recipients

Characteristics		CMV Reactivation (n=59)	No CMV Reactivation (n=185)
Sex		No (%)	No (%)
	Male	29 (49)	108 (58)
	Female	30 (51)	77 (42)
Race			
	White	40 (68)	138 (74)
	African American	3 (5)	13 (7)
	Asian	7 (11)	9 (5)
	Unknown/Other	9 (15)	25 (14)
Type of Transplant			
	Match Related Donor	15 (25)	76 (41)
	Match Unrelated Donor	31 (53)	79 (43)
	Cord Blood	3 (5)	1 (1)
	Haploidentical	9 (15)	27 (14)
	Unknown	1 (2)	2 (1)
HCT donor status			
	CMV +	33 (56)	99 (54)
	CMV -	24 (41)	72 (39)
	Unknown	1 (2)	12 (7)

Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Scatterplot of IE1 Responses and Probability of CMV Events



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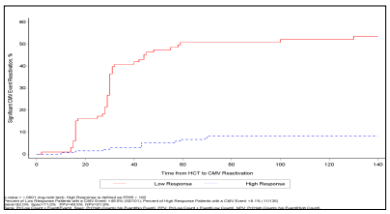
KM Plot – Time from HCT to CMV Event pp65 count >100 (high response)/≤100 (low response)



Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Cox Model for CMV Events Using Maximum pp65 as a Covariate, Retaining only Covariates with a *p*-value <0.15 via Stepwise Selection

- Endpoint:
  - Time to CMV Event
- The set of predictor variables were:
  - Maximum pp65 count >100
  - Recipient's age
  - GVHD (Yes/No)
  - Transplant Type (4 categories: Cord Blood, Haploidentical, Matched or Mismatched unrelated donor, Unknown)
  - Receipt of systemic corticosteroids (Y/N)
  - Donor CMV sero-status (Positive/Negative)
  - Time to engraftment

Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Likelihood of CMV events

Analysis of Maximum Likelihood Estimates				
Parameter	p-value	Hazard Ratio	95% CI	
Max pp65 count >100	<.0001	0.091	0.042	0.196
Steroid Use	0.0038	6.124	1.796	20.877

Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Summary

- **IE1 spot counts ≥100 was a significant predictor of protection against CMV reactivation**
- **Trend towards lower mortality in patients with pp65 spot count ≥100**
- **After adjusting for different risk factors, pp65 spot count ≥100 was significantly associated with protection against CMV reactivation while the use of systemic steroids was significantly associated with CMV reactivation**

Chemaly R, et al. A Prospective Observational Study to Evaluate a Cytomegalovirus (CMV)-Specific Enzyme-Linked Immunospot (Elispot) Assay in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients: The REACT Study. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/9026. 2017.

Future Directions:
CMV Immune Monitoring– Are We There Yet?

Clinical Scenarios	Potential Clinical Management
As part of preemptive strategy	Result may help guide frequency of viral load monitoring and thresholds for initiating antiviral therapy
Post-therapy for GVHD	For negative assay, viral load monitoring; For positive assay, no further intervention
Recent completion of therapy for CMV disease or viremia (Prediction of recurrence of viremia)	For negative assay, consider secondary prophylaxis, close monitoring; For positive assay, no further therapy
Risk stratification in patients pre-transplant	For positive assay, assume true positive CMV status

Prevention of CMV: Latest Approaches in Prophylaxis and Pre-emptive Strategies

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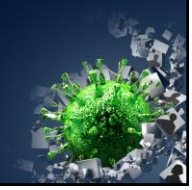
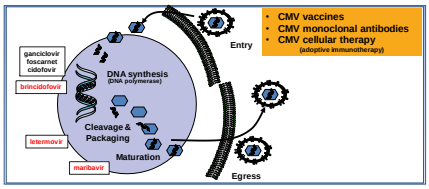
Professor of Medicine
Director, Infection Control Section
Director of Clinical Virology
Department of ID/IC/EH
UT MD Anderson Cancer Center
Houston, TX

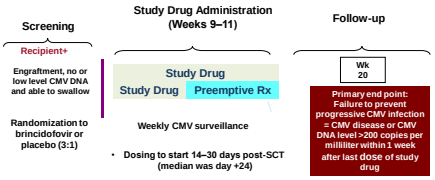


New Anti-CMV Approaches in Development



Courtesy Karl S. Peggs

CMV Prophylaxis in HCT Recipients
Brincidofovir Phase II Study Design (n=230)



Marty FM, et al. *N Engl J Med.* 2013;369:1227-36.

Brincidofovir Phase II: Efficacy Data

Primary Efficacy Endpoint in the Brincidofovir Groups as Compared with Placebo			
Study Group	Patients with CMV events* no./total no. (%)	Absolute Risk Difference Percentage points (95% CI)	P Value
Placebo	22/59 (37)	-	-
CMX001			
40 mg weekly	13/25 (52)	15 (-8 to 38)	0.23
100 mg weekly	6/27 (22)	-15 (-35 to 5)	0.22
200 mg weekly	12/39 (31)	-6 (-26 to 13)	0.53
200 mg twice weekly	7/30 (23)	-14 (-34 to 6)	0.24
100 mg twice weekly	5/50 (10)	-27 (-42 to -12)	0.002

*The primary efficacy endpoint was a CMV event, defined as CMV disease or a level of CMV DNA greater than 200 copies per milliliter at the end of treatment assessment.

Marty FM, et al. *N Engl J Med.* 2013;369:1227-36.

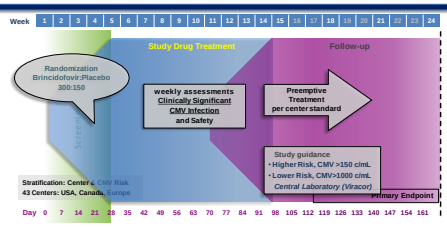
Brincidofovir Phase II: Toxicity Data

Serious Adverse Events (in ≥5% of patients in ITT population) %			
Study Group	Acute GvHD %	Diarrhea %	Pneumonia %
Placebo	7	2	0
CMX001			
40 mg weekly	4	0	0
100 mg weekly	7	DOSE LIMITING TOXICITY	7
200 mg weekly	15	↓	0
200 mg twice weekly	40	33	3
100 mg twice weekly	30	10	8

No evidence of increased myelosuppression or nephrotoxicity!

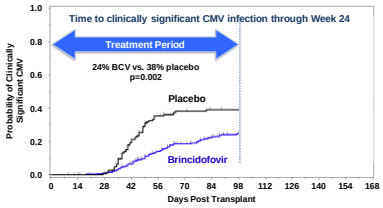
Marty FM, et al. *N Engl J Med.* 2013;369:1227-36.

Brincidofovir vs Placebo in HCT Recipients Phase III



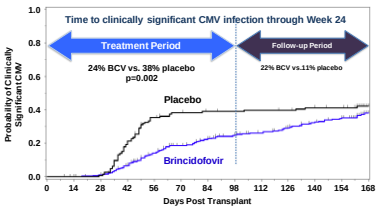
Marty FM, et al. Presented at the 2016 BMT Tandem Meetings, February 18-22, 2016; Honolulu, HI.

Brincidofovir vs Placebo in HCT Recipients Phase III



Marty FM, et al. Presented at the 2016 BMT Tandem Meetings, February 18-22, 2016; Honolulu, HI.

Brincidofovir vs Placebo in HCT Recipients Phase III



Marty FM, et al. Presented at the 2016 BMT Tandem Meetings, February 18-22, 2016; Honolulu, HI.

First Significant Observation

GVHD events on BCV were predominantly the gut, not skin, suggesting the diagnosis was driven by diarrhea

N (%)	Brincidofovir (n=303)			Placebo (n=149)		
GVHD Stage	Skin	Liver	Gut	Skin	Liver	Gut
Stage 1	49 (16.2)	3 (1.0)	88 (29.0)	24 (16.1)	1 (0.7)	28 (18.8)
Stage 2	42 (13.9)	14 (4.6)	40 (13.2)	18 (12.1)	0	7 (4.7)
Stage 3	22 (7.3)	7 (2.3)	33 (10.9)	8 (5.4)	3 (2.0)	2 (1.3)
Stage 4	0	6 (2.0)	13 (4.3)	0	3 (2.0)	3 (2.0)

The median cumulative exposure to corticosteroids was 8-fold higher in subjects in the BCV arm than those on placebo

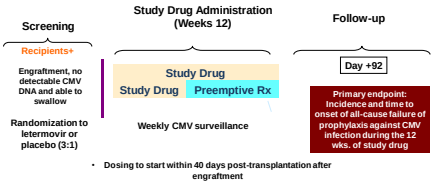
Marty FM, et al. Presented at the 2016 BMT Tandem Meetings, February 18-22, 2016; Honolulu, HI.

What's Next for Brincidofovir? Intravenous Formulation

- Bypassing the gut appears to avoid local irritation and decrease incidence of diarrhea
- Preliminary data from 28-day preclinical study show that IV BCV has a significantly lower risk of GI effects
  - Maintained body weight during dosing
  - No evidence of injury in preliminary review of the GI tract

Courtesy of Chimerix

CMV Prophylaxis in HCT Recipients Letermovir Phase II Study Design (n=131)



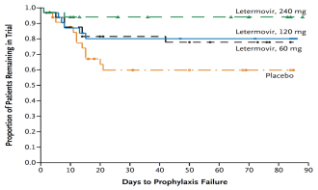
Chemaly RF, et al. *N Engl J Med.* 2014;370:1781-9.

Letermovir Phase II Dose Escalation Efficacy Data

Incidence of failure of prophylaxis against CMV infection				
Study Group	Letermovir 60 mg	Letermovir 120 mg	Letermovir 240 mg	Placebo
Modified intention-to-treat excluding patients with CMV replication at screening or day 1 detectable by central lab				
All-cause failure %	48	21	12	61
Virologic failure %	17	8	0	29
Letermovir vs. placebo (odds ratio)	0.60	0.17	0.16	-
Letermovir vs. placebo (P value)	0.43	0.005	0.003	-

Chemaly RF, et al. *N Engl J Med.* 2014;370:1781-9.

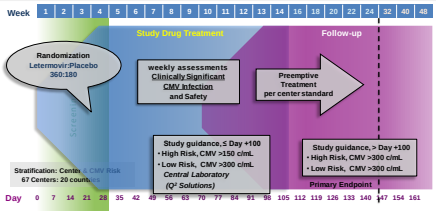
Letermovir Phase II Dose Escalation Efficacy Data



Letermovir was well tolerated overall with an AE profile similar to placebo

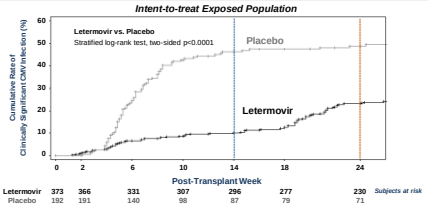
Chemaly RF, et al. *N Engl J Med.* 2014;370:1781-9.

Letermovir vs Placebo in HSCT Recipients Phase III



Marty FM, et al. Presented at 2017 BMT Tandem Meetings, February 22-26, 2017; Orlando, FL.
Ljungman P, et al. Presented at the 43rd European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, March 25-29, 2017. Marseille, France.

Letermovir vs Placebo in HSCT Recipients Phase III



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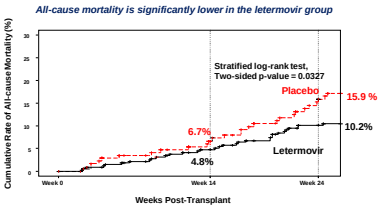


Ljungman P, et al. Presented at the 43rd European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, March 25-29, 2017. Marseille, France.

Letermovir: Safety

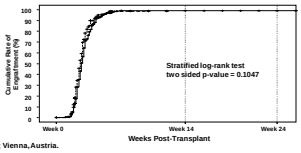
Safety Outcome During Treatment Phase, %	Letermovir (n = 373)	Placebo (n = 192)
Any AE	97.9	100
Drug-related AE	16.9	12.0
Serious AE	44.2	46.9
▪ Infection	20.6	18.8
▪ GVHD	9.9	10.4
▪ Relapse of AML	4.0	4.7
▪ Acute kidney injury	1.3	4.7
▪ Diarrhea	0.5	2.6
▪ Atrial arrhythmia	0.5	0
Discontinuation due to AE	19.3	51.0
▪ CMV treatment	6.2	39.1
▪ Other	13.1	12.0

GVHD was the most common AE of any severity (39% in both groups)
- Diarrhea, nausea, fever, and rash also occurred in >20% of pts in both groups with similar frequency

Marty FM, et al. Presented at 2017 BMT Tandem Meetings, February 22-26, 2017; Orlando, FL. Abstract LBA2.

Hematological Analyses

- No evidence of bone marrow suppression
  - Hematological lab parameters similar between letermovir and placebo
  - >60% of subjects had not engrafted at baseline:
    - Incidence of engraftment similar between letermovir (95%) and placebo (91%)
    - Median time to engraftment similar between letermovir (19 days) and placebo (18 days)



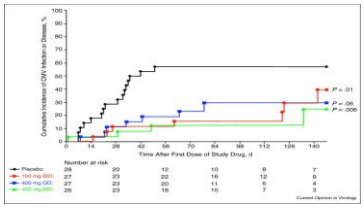
Chemaly RF, et al. Presented at 2017 ECCMID Meeting, April 22-25, 2017; Vienna, Austria.

CMV Prophylaxis in HSCT Recipients Maribavir Phase II Data

	Placebo	Maribavir	P value
Use of preemptive therapy based on CMV pp65 Ag or DNAemia			
100 mg bid (N=28)	57%	15%	0.001
400 mg qd (N=28)	57%	30%	0.051
400 mg bid (N=27)	57%	15%	0.001
CMV disease (day 100)			
100 mg bid (N=28)	11%	0%	0.089
400 mg qd (N=28)	11%	0%	0.084
400 mg bid (N=27)	11%	0%	0.091

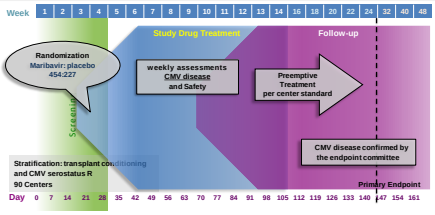
Winston DJ, et al. *Blood*. 2008;111:5403-10.

Maribavir Phase II: Efficacy Data



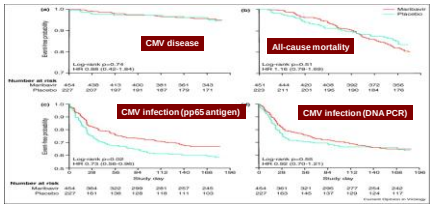
Winston DJ, et al. *Blood*. 2008;111:5403-10.

Maribavir vs Placebo in HSCT Recipients Phase III



Marty FM, et al. *Lancet Infect Dis*. 2011;11:284-94.

Maribavir vs Placebo in HSCT Recipients Phase III



Marty FM, et al. *Lancet Infect Dis*. 2011;11:284-94.

Maribavir vs Placebo in HSCT Recipients Phase III

AEs Reported in ≥10% of Patients (ITT, Safety Population)

	Placebo (n=223)	Maribavir (n=451)
Patients with ≥1 adverse event	213 (96%)	440 (98%)
Adverse events		
Acute graft-versus-host disease	74 (33%)	164 (36%)
Diarrhea	42 (19%)	93 (21%)
Fatigue	22 (10%)	73 (16%)
Pyrexia	39 (17%)	72 (16%)
Nausea	35 (16%)	71 (16%)
Dysgeusia	13 (6%)	66 (15%)
Anemia	17 (8%)	63 (14%)
Rash	30 (13%)	60 (13%)
Peripheral edema	28 (13%)	58 (13%)
Vomiting	31 (14%)	52 (12%)
Renal failure	20 (9%)	46 (10%)
Headache	21 (9%)	44 (10%)
Hypertension	13 (6%)	43 (10%)
Weight decrease	29 (13%)	41 (9%)

Marty FM, et al. *Lancet Infect Dis*. 2011;11:284-94.

Conclusions

- Ganciclovir and valganciclovir remain first-line agents for prophylaxis/preemptive treatment of CMV reactivation, but are associated with side effects (especially myelosuppression and renal toxicity)
- Novel anti-viral agents with different MOA have the potential to render prophylactic therapy more feasible, though it remains to be determined whether prophylaxis will impact transplant outcomes associated with CMV seropositivity

Mechanisms of CMV Resistance and Emerging Tools to Overcome It

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Member, Vaccine and Infectious Disease & Clinical Research Divisions
Head, Infectious Disease Sciences Program
Fred Hutchinson Cancer Research Center
Professor of Medicine, Division of Allergy and Infectious Diseases, Department of Medicine
University of Washington
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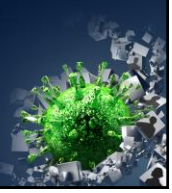
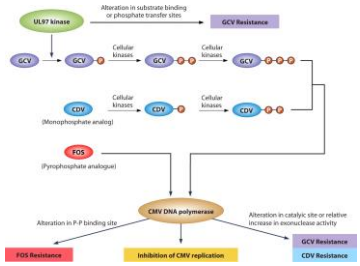
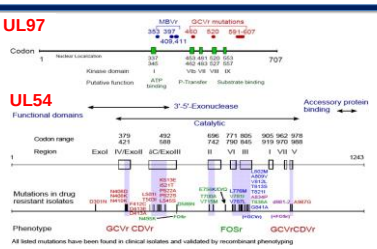


Antiviral Targets of Approved CMV Drugs: DNA Polymerase



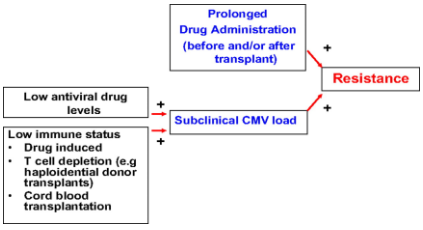
Lurain NS, Chou S. *Clin Microbiol Rev*. 2010;23:689-712.

Genotypic Basis of CMV Resistance



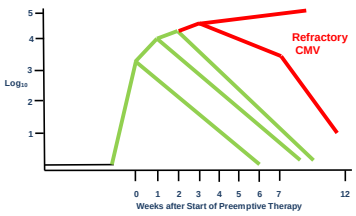
Lurain NS, Chou S. *Clin Microbiol Rev*. 2010;23:689-712.

Resistant CMV: Not Everyone is at Risk



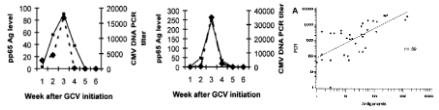
Boeckh M, et al, *Blood*. 2009;113:5711-9.

Viral Load Patterns with Preemptive Therapy



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, Mees-Li Huang, Chris Davis, and Michael Boeckh



Nichols WG, et al. *Blood.* 2001;97:867-74.

Who is at Risk for Increasing Viral Load?

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, Mees-Li Huang, Chris Davis, and Michael Boeckh

Table 2. Risk factors for increasing pp65 antigenemia among 119 recipients of allogeneic HSCT

	↑ Ag > 2× baseline			↑ Ag > 5× baseline		
	OR	95% CI	*P*	OR	95% CI	*P*
Multivariate analysis‡						
Conditioning						
Non–TBI-containing	1.0*					
TBI-containing	2.6	1.0-6.8	.04			
Steroid use at 3rd Ag + wk						
None	1.0*			1.0*		
<1 mg/kg	5.0	1.0-24.5	.05	4.3	0.4-51.3	.25
1-2 mg/kg	4.0	1.0-16.8	.06	14.3	1.7-120.2	.01
>2 mg/kg	10.1	2.6-40.2	.001	28.6	3.6-229.7	.002

Nichols WG, et al. *Blood.* 2001;97:867-74.

Factors Associated with GCV-resistant CMV

	Cases (n=37)	Controls (n=109)	p
Male	28 (75.7)	63 (57.8)	0.052
Induction Immunosuppression[a]			
Yes	31 (86.1)	81 (86.2)	
No	5 (13.9)	13 (13.8)	0.99
Induction Immunosuppression Type			
Anti-lymphocyte antibody	17 (54.8)	38 (46.9)	
IL-2 receptor antagonist	14 (45.2)	43 (53.1)	0.45
Median days to CMV diagnosis post-transplant (IQR)	196 (147-300)	143 (112-230)	0.059
Median ganciclovir exposure prior to CMV diagnosis, days (IQR)[b]	153 (121-208)	91 (41-108)	<0.001
Rejection within 3 mo prior to CMV diagnosis	8 (21.6)	26 (23.9)	0.78

[a]Received antiviral and immune suppression therapy
[b]Exposure of ganciclovir (oral or intravenous) and/or valganciclovir prior to diagnosis of either ganciclovir-sensitive or ganciclovir-resistant CMV as applicable

Fisher CE, et al. *Clin Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cix259

Ganciclovir/Valganciclovir Exposure Prior to Drug-resistant CMV

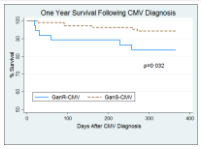
Days of ganciclovir/valganciclovir received prior to development of ganciclovir-resistant CMV in patients by type of organ transplanted		
Organ transplanted	Days of ganciclovir/ valganciclovir received, median (range)	P value
All organs (n=37)	153 (30–284)	
Lung (n=17)	121 (30–269)	p=0.02
Non-lung (n=20)	160 (90–284)	

Fisher CE, et al. *Clin Infect Dis*. 2017;[Epub ahead of print]. Available at: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cix259

Outcomes Associated with GCV-resistant CMV

Outcome, n (%)	Cases (n=37)	Controls (n=109)	P value
Days to clearance of viremia, median (IQR)	113 (50-394)	53 (32-149)	0.006
≥20% decrease in eGFR by 3 months after CMV diagnosis	15 (41.7)	21 (19.4)	0.008
Well days[a] in the 3 mo after CMV diagnosis, mean (SE)	72.7 (4.8)	81.0 (1.7)	0.039
Rejection within 1 year following CMV diagnosis			
All organs	15 (40.5)	38 (34.9)	0.54
Kidney	4 (66.7)	2 (10.5)	0.005
Mortality:			
Three months	4 (10.8)	1 (0.92)	0.004[b]
Twelve months	6 (16.2)	6 (5.5)	0.032

[a]Alive and nonhospitalized
[b]Fisher exact test



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Case

- 51-year-old male with history of AML, s/p unrelated allogeneic myeloablative PBSCT
- Serostatus: CMV D+/R+, HSV+, VZV+
- Post-transplant complications
  - Acute GVHD (skin, GI)
  - Organizing pneumonia 12 months after HSCT
- Recurrent CMV reactivation episodes
  - Day 38: 8 weeks of ganciclovir
  - Day 117: increasing levels (max 2500 IU/mL) on ganciclovir, UL97 positive for A594V
  - Switch to foscarnet
  - Seizure due to electrolyte abnormalities
  - Continued foscarnet with close monitoring resulting in viral load decline to 0
  - One additional episode treated successfully with valganciclovir

AML, acute myeloid leukemia; PBSCT, peripheral blood stem cell transplantation; HSV, herpes simplex virus; VSV, varicella zoster virus

Case - continued

- **Now (22 mo after HSCT) he presents again with increasing viral load on maintenance VGCV**
  Current episode:
  - **1100 IU/mL: 900 mg VGCV twice daily**
  - **Initial response (below level of detection), switch to maintenance: 900 mg/day**
  - **UL97 mutation still present: A594V**
  - **Now 650 IU/mL**
- **Other relevant information**
  - **Creatinine clearance: 67 mg/min/m²**
  - **WBC: 4100 per mm³, ANC: 1400 per mm³**
  - **Electrolytes within normal limits**
  - **Weight: 94 kg (BMI: 34 kg/m²)**
- **Physical exam: unremarkable**
- **Social history**
  - **Lives in a small town**
- **Presently no line access**

VGCV, valganciclovir; ANC, absolute neutrophil count

Audience Question

What would you do next?

1. Continue current dose of valganciclovir
2. Double the dose of valganciclovir (re-induction)
3. Place a line and start IV ganciclovir
4. Place a line and start foscarnet

Question: What would you do next?

1. **Continue current dose of valganciclovir – increase indicates lack of effectiveness (low levels, fixed dosing, high weight)**
2. **Double the dose of valganciclovir (re-induction) – viral load was still relatively low**
3. **Place a line and start IV ganciclovir - logistically difficult**
4. **Place a line and start foscarnet – logistical issues, prior toxicity**

Case - continued

After one week, viral load increased further to 1800 IU/mL on valganciclovir 900 mg twice daily

Audience Question

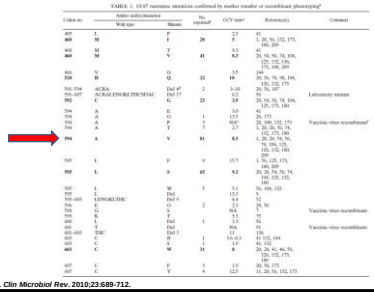
What would you do next?

1. Increase the dose of valganciclovir to 1350 mg twice daily, provide G-CSF as needed
2. Keep current dose of valganciclovir and add leflunomide
3. Place a line/access and start IV ganciclovir at 7.5 mg/kg plus preemptive G-CSF
4. Place a line/access and start foscarnet

Question: What would you do next?

1. **Increase the dose of valganciclovir to 1350 mg twice daily, provide G-CSF as needed – theoretically an option but no data or experience with this dose**
2. **Keep current dose of valganciclovir and add leflunomide – limited data, concern that it would be less effective and potentially toxic (remote outpatient setting)**
3. **Place a line/access and start IV ganciclovir at 7.5 mg/kg plus preemptive G-CSF**
4. **Place a line/access and start foscarnet – due to prior experience there was great reluctance to do this**

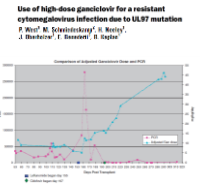
UL97 Mutations and Level of Resistance



Lurain NS, Chou S. *Clin Microbiol Rev*. 2010;23:689-712.

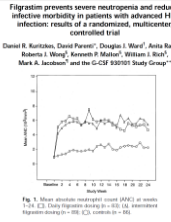
High-Dose Ganciclovir

- **Emerging experience**
  - **Adjusted max dose >40 mg/kg/day**
- **7.5–10 mg/kg twice daily**
  - **Adjusted for renal function**
  - **Testing drug levels**
    - **Issue: availability**
- **Valganciclovir**
  - **Fixed dose**
  - **Issue drug levels – weight**
  - **No clinical data on higher doses**
- **Toxicity**
  - **G-CSF: preemptive vs. salvage**
  - **HIV experience**
  - **Fred Hutch experience**

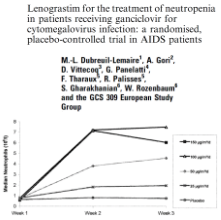


West P, et al. *Transplant Infect Dis*. 2008;10:129-32.

Preemptive G-CSF



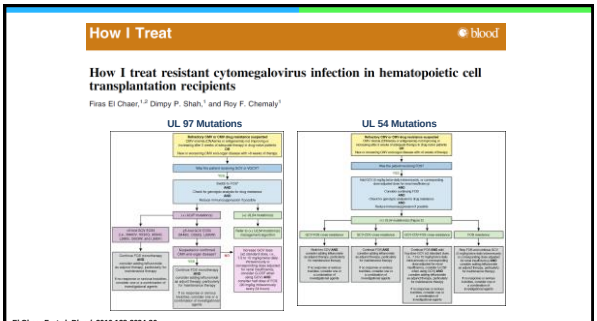
Kuritzkes DR, et al. *AIDS*. 1998;12:65-74.



Dubreuil-Lemaire M-L, et al. *Eur J Haematol*. 2000;65:337-43.

Intervention

- **Existing drugs**
- **New therapeutics**
  - **Maribavir**
  - **Letermovir**
  - **Brincidofovir**
  - **T cell therapies**
  - **Monoclonal antibodies**



El Chaer F, et al. *Blood*. 2016;128:2624-36.

Maribavir

- Potent member of a new class of drugs, the benzimidazole ribosides
- Inhibits the CMV UL97 kinase by competitively inhibiting the binding of ATP to the kinase ATP-binding site
- Active against wild-type and ganciclovir-resistant CMV strains
- 3- to 20-fold more potent than ganciclovir and cidofovir, and at least 100-fold more potent than foscarnet[1,2]

1. Biron KK, et al. *Antimicrob Agents Chemother*. 2002;46:2365-72.
2. Drew WL, et al. *J Clin Virol*. 2006;37:124-7.

Past Studies with Maribavir

Phase 3 trials for CMV prevention

- Maribavir *prophylactically* administered at 100 mg BID for up to 12 weeks post-HCT
- Failed to reduce the incidence of CMV disease within 6 months (Study 1263-300)

Two Phase 2 studies were conducted to assess the safety, tolerability, and anti-CMV activity of maribavir for treatment of CMV infections:

- In transplant recipients with resistant/refractory CMV infection or disease and with wild-type CMV infections without disease
- 3 dose strengths: 400, 800, or 1200 mg BID
- Both studies demonstrated favorable anti-CMV activity, the drug was well-tolerated, and there were no safety concerns at all doses evaluated

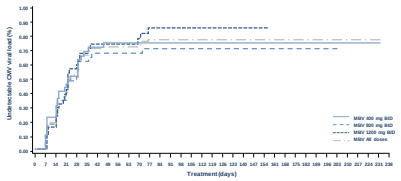
Maribavir: High Dose Phase II Results

- **Most TEAEs were mild–moderate in severity.**
- **Gastrointestinal AEs: MBV (20–23%) versus VGC (10–15%)**
- **Dysgeusia: MBV (40%) versus VGC (3%), no apparent dose effect**
- **Neutropenia (ANC <1000/mm³): MBV (5%) versus VGC (18%)**

Responders (treatment effect estimate), n (%); 95% CI	MBV dose			All MBV doses, N=120	VGC
	400 mg BID N=40	800 mg BID N=40	1200 mg BID N=40		
Week 3	26/39 (67); 50, 81	23/40 (58); 41, 73	23/38 (61); 43, 76	72/117 (62); 52, 70	22/39 (56); 40, 72
				OR 1.42; 95% CI 0.62, 3.24; P=0.41	
Week 6	31/39 (79); 64, 91	33/40 (83); 67, 93	28/38 (74); 57, 87	92/117 (79); 70, 86	26/39 (67); 50, 81
				OR 2.12; 95% CI 0.91, 4.96; P=0.08	

Maertens J, et al. Presented at IDWeek 2016, New Orleans, LA, USA, October 26-30, 2016.

Maribavir: High Dose Phase II Results



Papanicolaou G, et al. Presented at 2017 BMT Tandem Meeting, Orlando, FL, February 22-26, 2017.

Maribavir Phase III

A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir
Clinicaltrials.gov NCT02931539
Status: enrolling

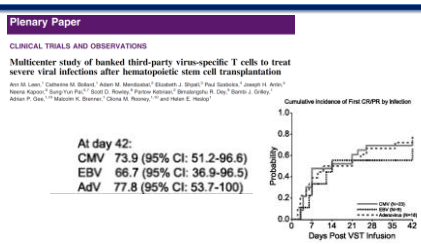
A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients
Clinicaltrials.gov NCT02931539
Status: enrolling

Potential Role of Other Emerging Antivirals

- **Letermovir**
  - **Highly specific against CMV**
  - **Phase III for prophylaxis completed**
  - **Limited data on treatment**
- **Brincidofovir**
  - **Broad-spectrum activity, including CMV and ADV**
  - **Phase III completed – GI toxicity**
  - **Development continues for ADV**
  - **IV preparation being developed**

ADV, adenovirus

Cellular Therapy


Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation

Cumulative Incidence of First CR/PR by Infection

At day 42:
CMV 73.9 (95% CI: 51.2-96.6)
EBV 66.7 (95% CI: 36.9-96.5)
AdV 77.8 (95% CI: 53.7-100)

Probability

Days Post VST Infusion

CR/PR, complete/partial response; EBV, Epstein-Barr virus; AdV, adenovirus; VST, virus-specific T cells.
Leen AM, et al. *Blood.* 2013;121:5113-23.

CMV Resistance: Take-Home Points

- UL97 can occur after prolonged ganciclovir exposure
- The level of susceptibility of different mutations matters
- Fixed-dose regimens may not work in all treatment situations
  - Weight
  - Renal function close to the adjustment threshold
  - Testing of ganciclovir levels – limited data, availability
- High-dose ganciclovir may overcome low- and intermediate-level resistance
- Preemptive G-CSF may be an option to delay the development of neutropenia
- New drugs and immunotherapies are presently being evaluated in clinical trials

Learning by Sharing: Q and A