MAYO CLINIC

C[MV] You Later: Letermovir for Prevention of Cytomegalovirus Infection

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Pharmacy Grand Rounds
June 9, 2020

Objectives

- Explain the difference between pre-emptive and prophylaxis strategies for cytomegalovirus infection prevention
- Select patients that may benefit from letermovir prophylaxis based on existing literature
- Identify areas of investigational use of letermovir

Patient Case

MR is a 47 year old female with a history of acute myeloid leukemia who is day +10 from allogeneic hematopoietic stem cell transplant (HSCT)

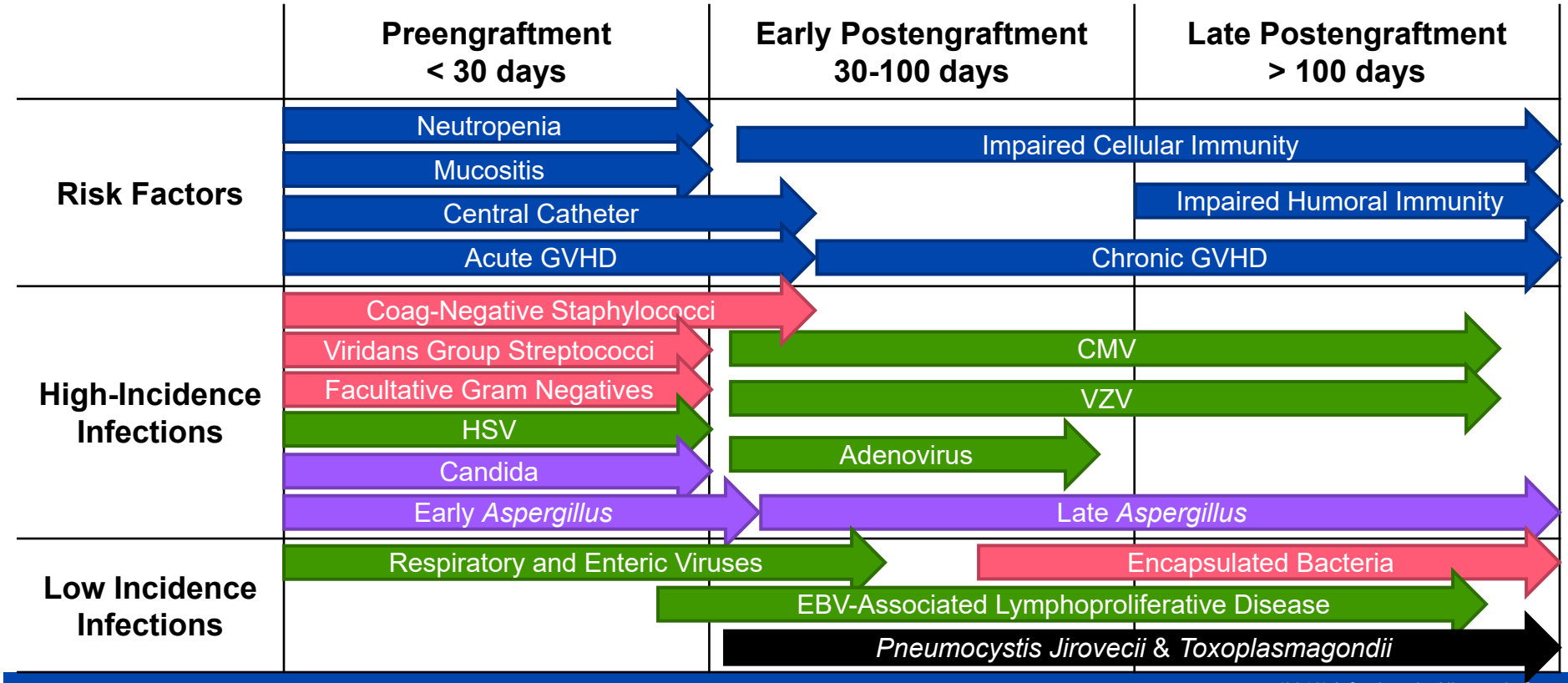
- Bone marrow from haploidentical donor
- Conditioning regimen: Fludarabine, Melphalan, TBI
  - Myeloablative regimen
- CMV seropositive recipient, seronegative donor
- No known drug allergies

<u>Post-Transplant Immunosuppression</u>

- Cyclophosphamide
- Tacrolimus
- Mycophenolate

TBI = total body irradiation

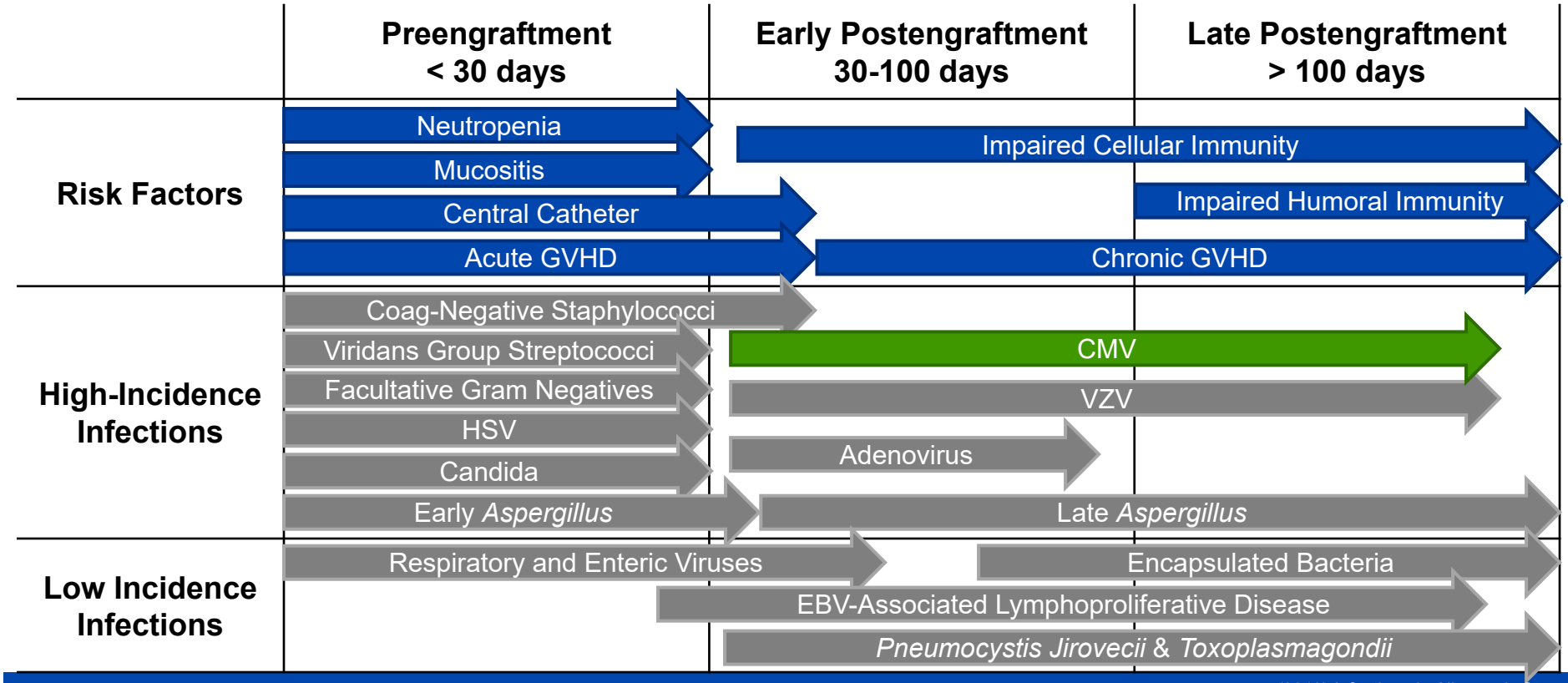
Opportunistic Infections



GVHD = graft versus host disease
HSV = herpes simplex virus
CMV = cytomegalovirus
VZV = varicella-zoster virus
EBV = Epstein-Barr virus

(2019) Infections in Allogeneic Stem Cell Transplantation. In: Safdar A. (eds) Principles and Practice of Transplant Infectious Diseases

Opportunistic Infections



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Patient Case

Post-Transplant Infectious Complications

- Bacterial infections: Gram positive and negative
- Fungal infections: Candida, Aspergillus, PJP
- Viral infections: HSV, CMV, VZV

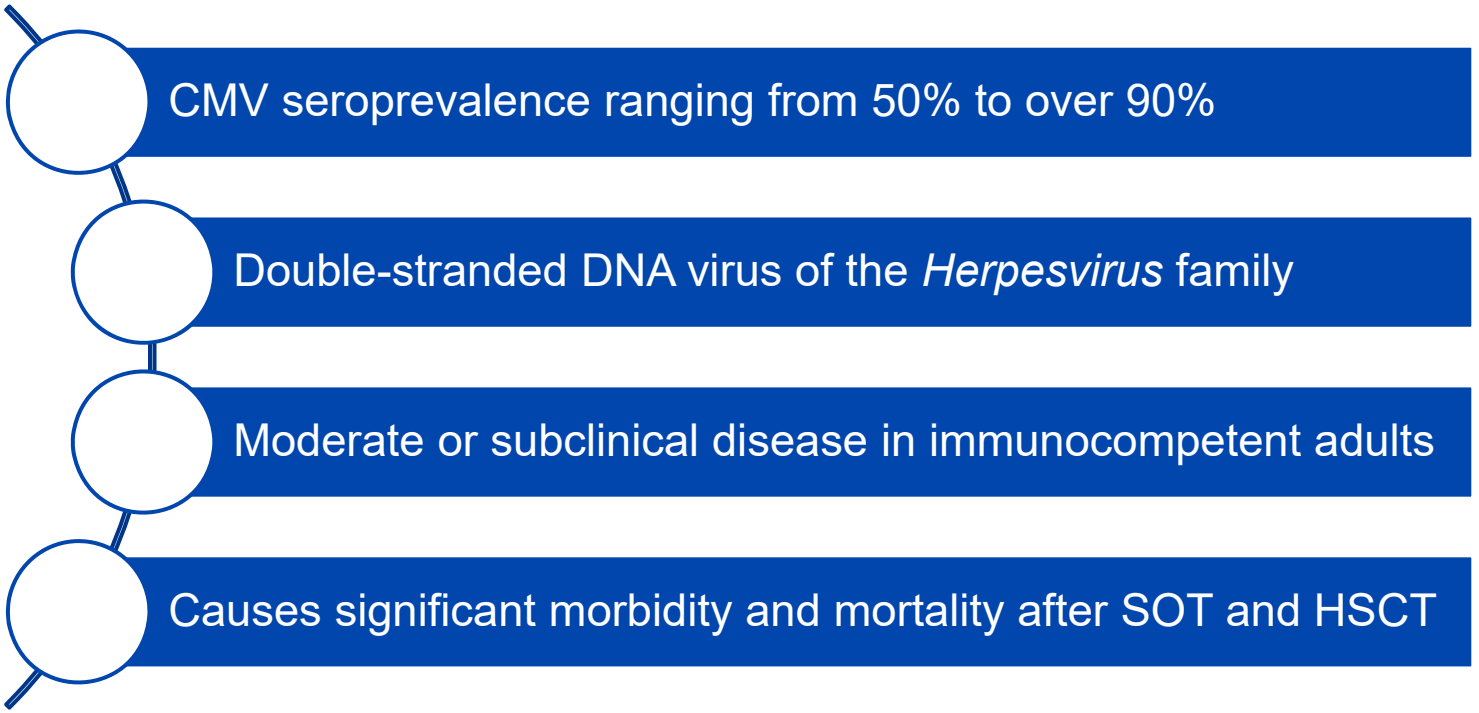
Recommended Antimicrobials

- Penicillin VK
- Levofloxacin
- Posaconazole
- Acyclovir
- Post-engraftment: sulfamethoxazole-trimethoprim

Should we provide CMV prophylaxis?

PJP = Pneumocystis jirovecii pneumonia
HSV = herpes simplex virus
CMV = cytomegalovirus
VZV = varicella-zoster virus

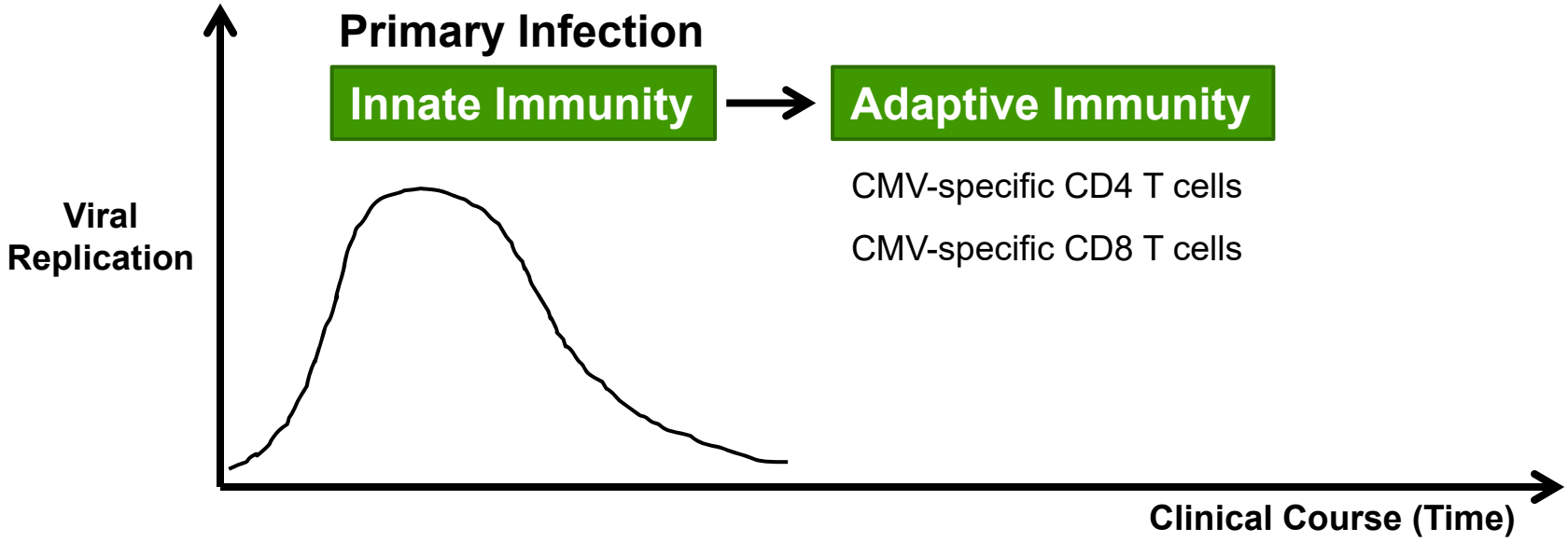
Cytomegalovirus



CMV = cytomegalovirus
SOT = solid organ transplant
HSCT = hematopoietic stem cell transplant

Blood. 2018;2(16):2159-75..
Viruses. 2020;12(21).

Cytomegalovirus: Clinical Course



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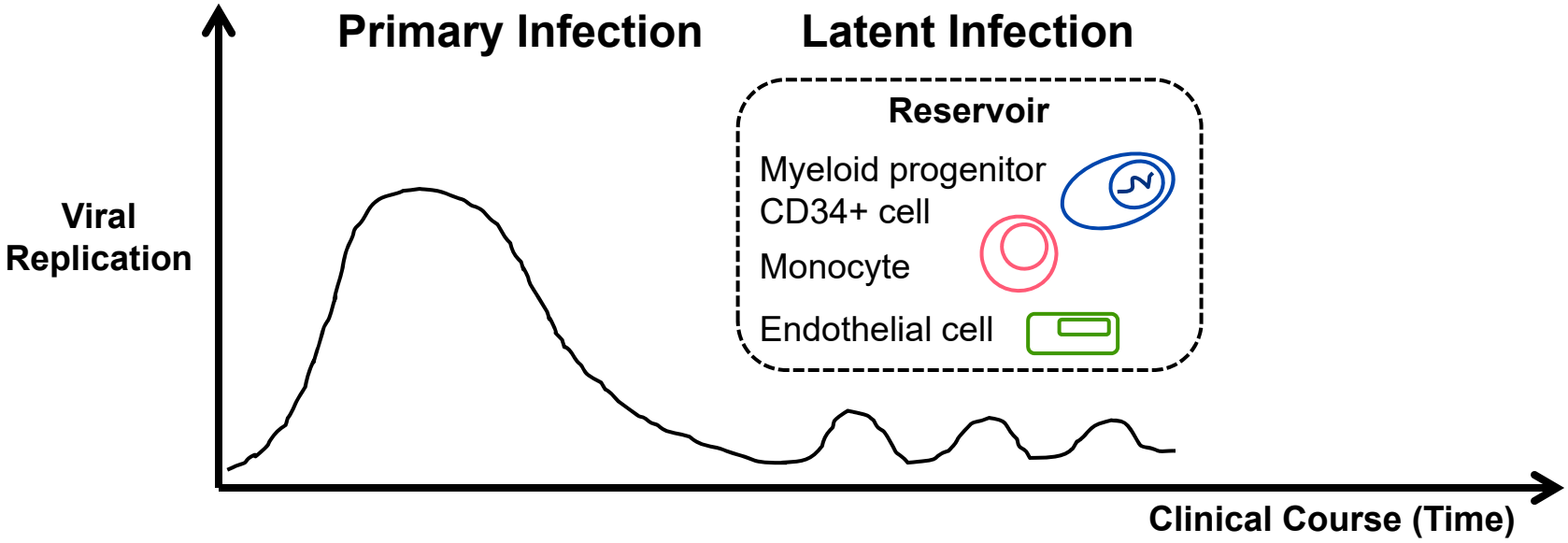
Int J Mol Sci. 2019;20:2666.

Cytomegalovirus: Clinical Course



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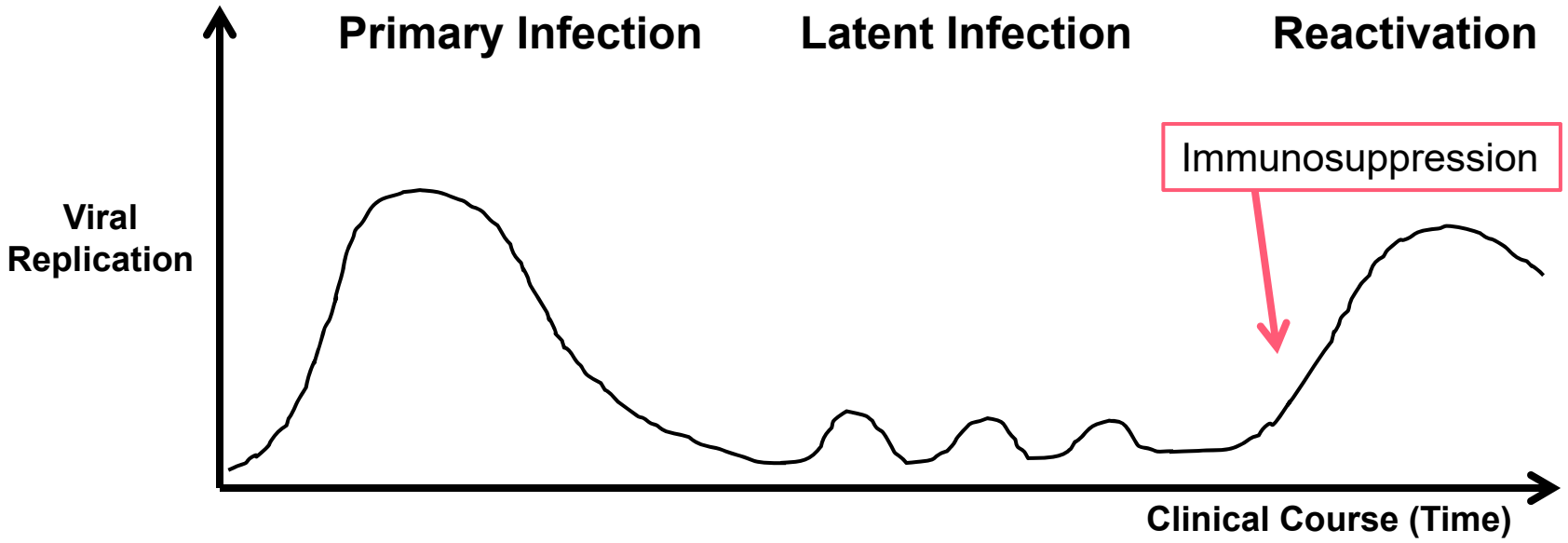


Int J Mol Sci. 2019;20:2666.

Cytomegalovirus in Immunocompromised Hosts

CMV Infection

- Detection of CMV DNA in a blood sample

CMV Disease

- Presence of signs and symptoms compatible with CMV end-organ involvement
- Detection of CMV in the involved specimen

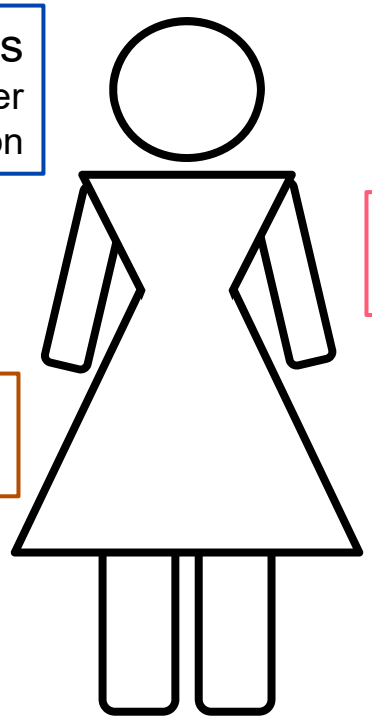
Hematol Oncol Clin North Am. 2011;25(1):151-69.

Cytomegalovirus Disease in HSCT

Retinitis
Uncommon after transplantation

Pneumonia
Mortality > 50%

Gastrointestinal Tract
May overlap with GVHD

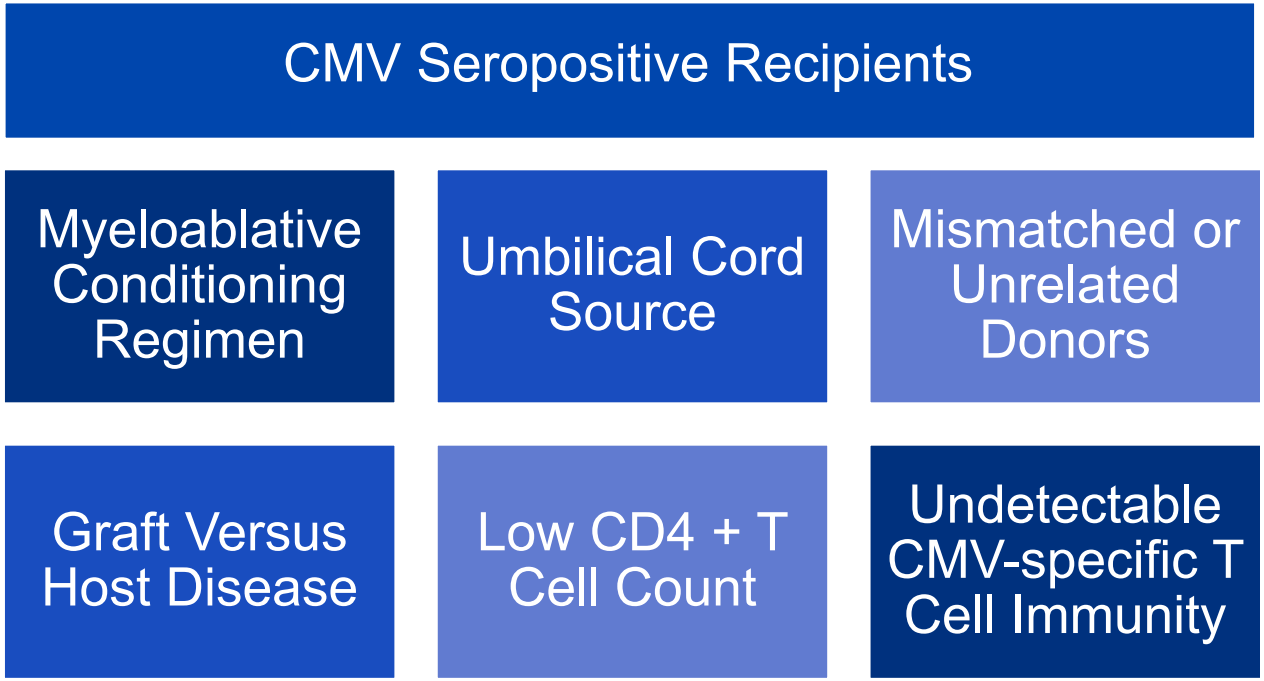


Rarer Manifestations:
Hepatitis
Encephalitis

HSCT = hematopoietic stem cell transplant
GVHD = graft versus host disease

Hematol Oncol Clin North Am. 2011;25(1):151-69.

Risk Factors for CMV in Allogeneic HSCT



HSCT = hematopoietic stem cell transplant
CMV = cytomegalovirus

Drugs. 2018;78:1085-103.

Association with Non-Relapse Mortality

Center for International Blood and Marrow Transplant Research (CIBMTR) Database

Inclusion: Patients with AML, ALL, MDS, or CML who received first allogeneic HSCT between 2003 and 2010.

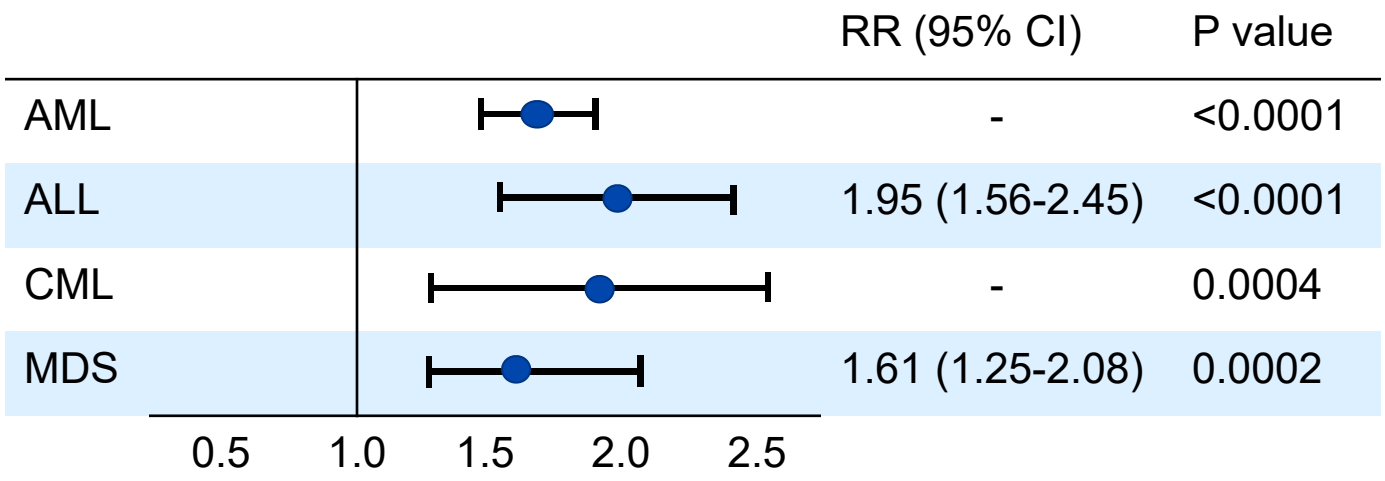
Objective

Analyze the impact of CMV reactivation on hematologic disease relapse and non-relapse mortality.

AML = acute myeloid leukemia
ALL = acute lymphoblastic leukemia
MDS = myelodysplastic syndrome
CML = chronic myeloid leukemia
HSCT = hematopoietic stem cell transplant

Blood. 2016;127(20):2427-38.

CMV Reactivation and Non-Relapse Mortality



CMV reactivation is associated with an increase in non-relapse mortality following allogeneic HSCT.

AML = acute myeloid leukemia
ALL = acute lymphoblastic leukemia
MDS = myelodysplastic syndrome
CML = chronic myeloid leukemia
CMV = cytomegalovirus
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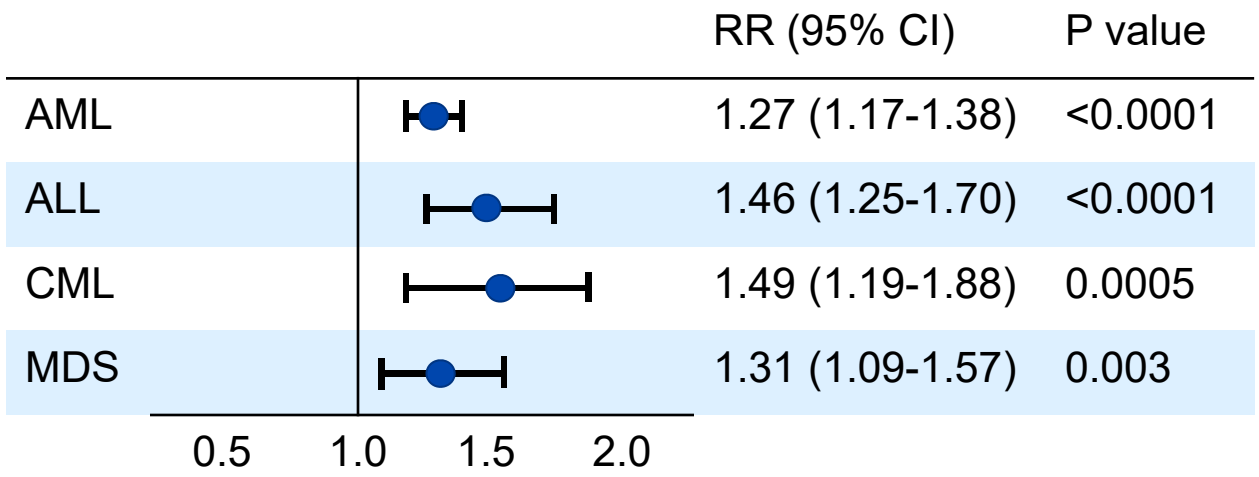
Blood. 2016;127(20):2427-38.

CMV Reactivation and Overall Survival



CMV reactivation is associated with a decrease in overall survival following allogeneic HSCT.

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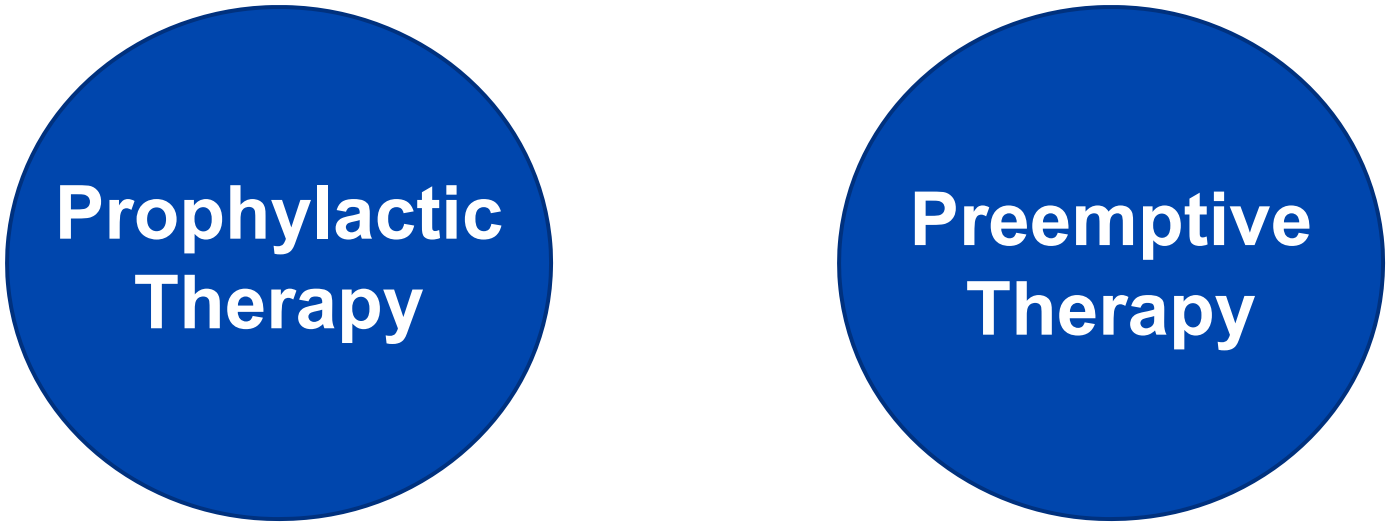
Preventative Strategies in HSCT



HSCT = hematopoietic stem cell transplant

Preventative Strategies in HSCT

Provide antiviral therapy for a pre-specified duration post-transplant.

Pros

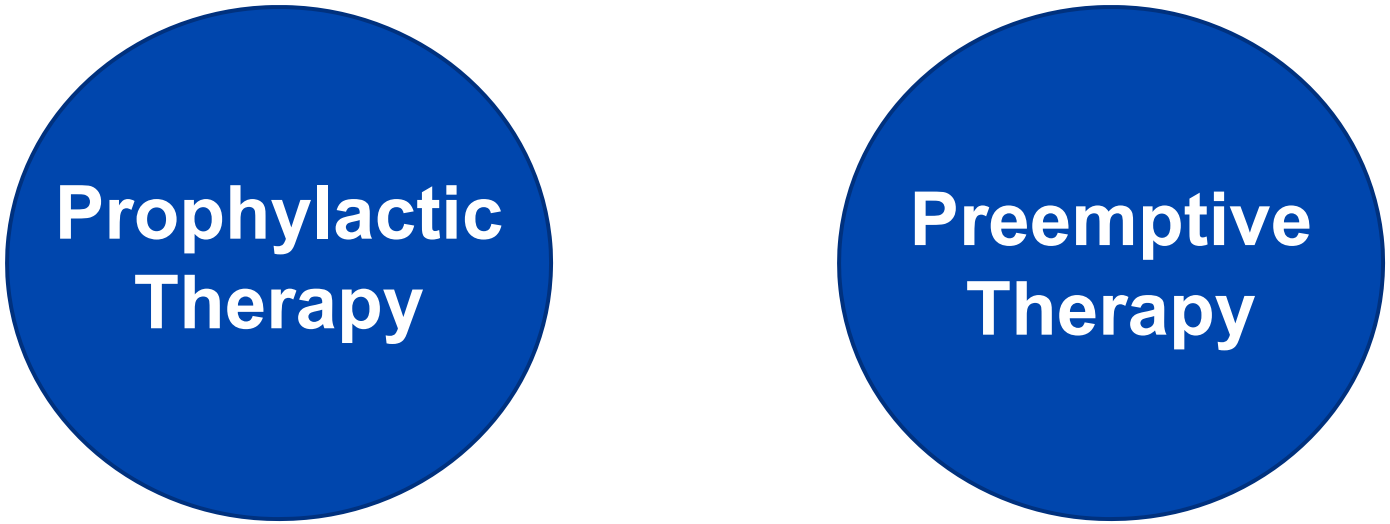
- Reduction in CMV infection and disease

Cons

- Adverse drug events
- High cost
- Use of antivirals in patients who may not develop CMV infection
- Risk of viral resistance

JID. 2020:221(Suppl 1):S23-31.

Preventative Strategies in HSCT



HSCT = hematopoietic stem cell transplant

Preventative Strategies in HSCT

Monitor for asymptomatic CMV replication, and provide antivirals only upon detection of CMV viremia.

Pros
- Reduction in mortality
- Limited toxicity
- Acceleration of immune constitution

Cons
- Lab costs
- Possibility for loss to follow up
- Possibility for rapid doubling time of CMV viral loads in some patients

Preemptive Therapy

HSCT = hematopoietic stem cell transplant
CMV = cytomegalovirus

JID. 2020:221(Suppl 1):S23-31.

Antivirals for Prophylaxis and Preemptive Treatment

Ganciclovir and Valganciclovir

- Greatest evidence for prevention and treatment of CMV
- Toxicities limit use following HSCT

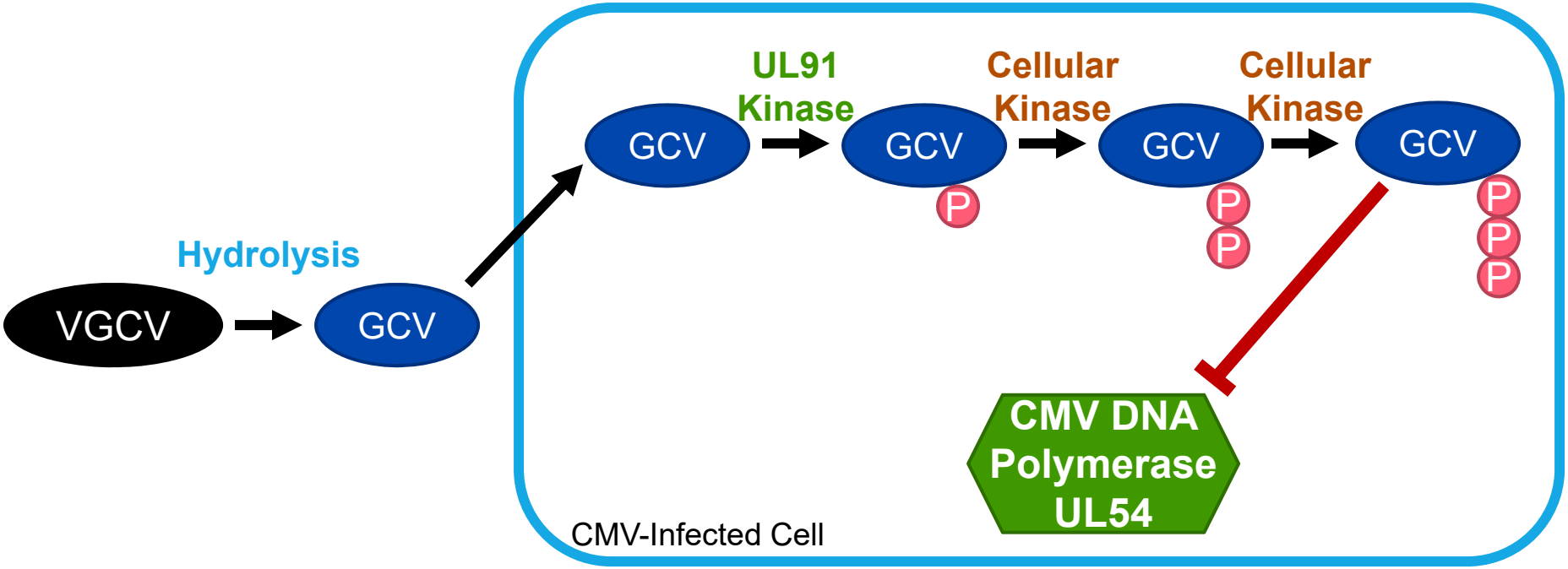
Acyclovir and Valacyclovir

- Some evidence to support use for CMV prophylaxis following HSCT
- Not routinely utilized due to poor efficacy against CMV

Letermovir

- Approved only for CMV prophylaxis in allogeneic HSCT

Ganciclovir and Valganciclovir



VGCV = valgancyclovir
GCV = ganciclovir
CMV = cytomegalovirus

Drugs. 2018;78:1085-103.

Ganciclovir and Valganciclovir

	Prophylaxis	Preemptive Treatment	Side Effects
Ganciclovir	5 mg/kg IV daily	Induction: 5 mg/kg IV every 12 hours Maintenance: 5 mg/kg IV every 24 hours	Myelosuppression Rash, pruritus, diarrhea, nausea, vomiting, increased serum creatinine and liver enzymes, and neurotoxicity Renal dose adjustments required for CrCl < 60-70
Valganciclovir	900 mg PO daily	Induction: 900 mg PO every 12 hours Maintenance: 900 mg every 24 hours	

Drugs. 2018;78:1085-103.

Patient Case

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- Bone marrow from haploidentical donor
- Conditioning regimen: Fludarabine, Melphalan, TBI
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- CMV seropositive recipient, seronegative donor
- No known drug allergies

<u>Post-Transplant Immunosuppression</u>

- Cyclophosphamide
- Tacrolimus
- Mycophenolate

Should we provide CMV prophylaxis?

TBI = total body irradiation
CMV = cytomegalovirus

Learning Question #1

What strategy would you recommend for prevention of CMV in our patient?

A. Prophylaxis with valganciclovir because our patient is at high risk for CMV

B. Prophylaxis with letermovir because our patient is at high risk for CMV

C. Preemptive therapy with initiation of antiviral therapy only if our patient displays signs or symptoms of CMV

D. Preemptive therapy with initiation of antiviral therapy if our patient has a detectable CMV DNA viral load

CMV = cytomegalovirus

Learning Question #1

What strategy would you recommend for prevention of CMV in our patient?

A. Prophylaxis with valganciclovir because our patient is at high risk for CMV

B. **Prophylaxis with letermovir because our patient is at high risk for CMV**

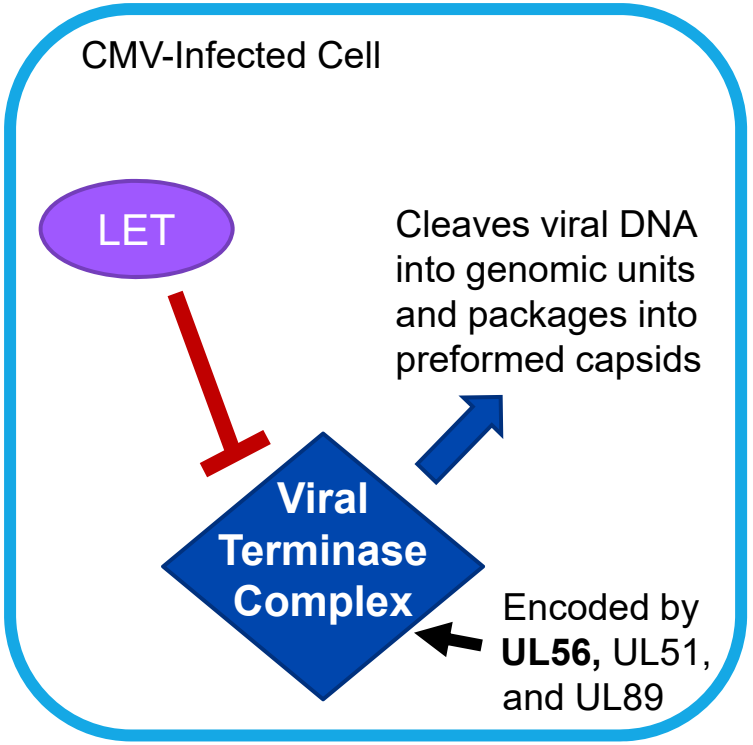
C. Preemptive therapy with initiation of antiviral therapy only if our patient displays signs or symptoms of CMV

D. **Preemptive therapy with initiation of antiviral therapy if our patient has a detectable CMV DNA viral load**

CMV = cytomegalovirus

Letermovir

FDA Approved in 2017	
Indication	CMV prophylaxis in CMV-seropositive HSCT recipients
Prophylaxis	480 mg PO or IV once daily
Treatment	Not recommended
Side Effects	Uncommonly nausea, vomiting, headache
Spectrum	Limited to CMV. No HSV or VZV coverage.



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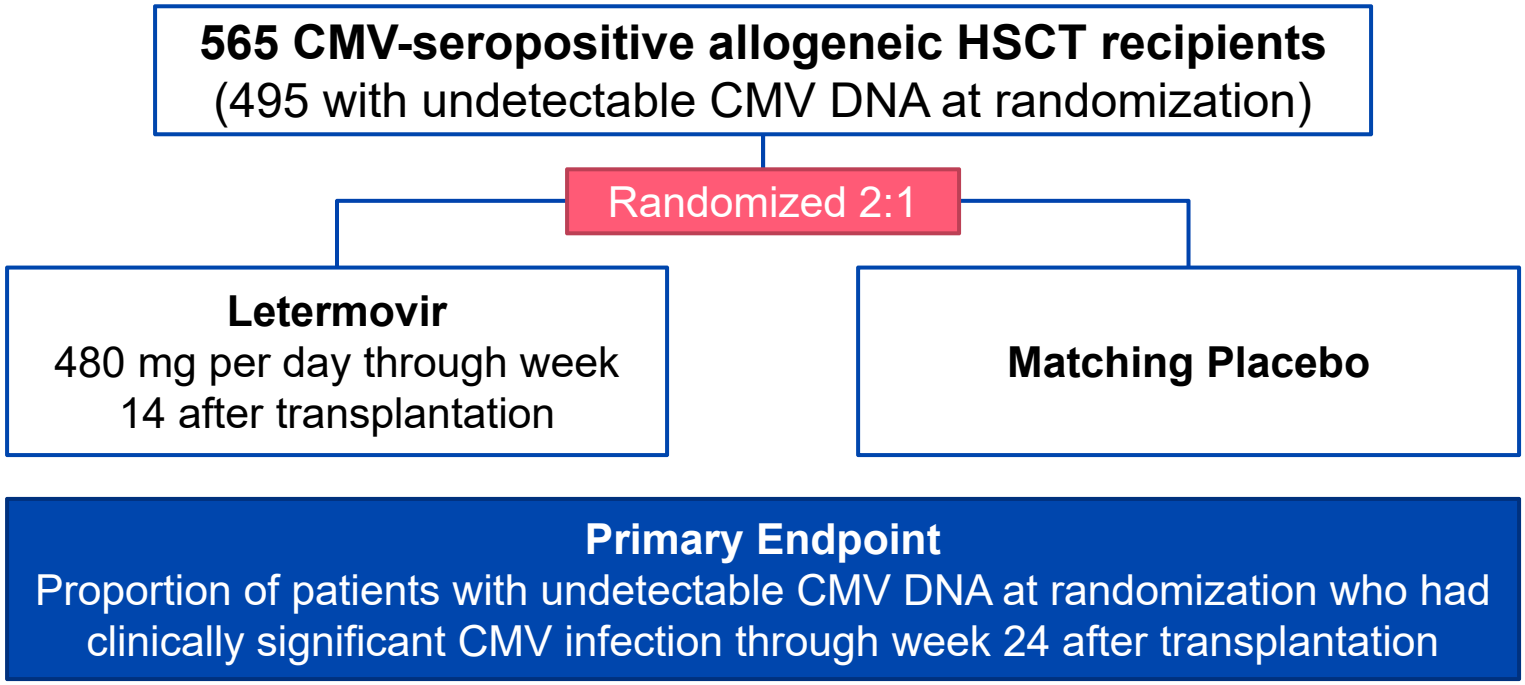
HSCT = hematopoietic stem cell transplant
HSV = herpes simplex virus
VZV = varicella-zoster virus
LET = letermovir

Infect Drug Resist. 2019;12:1481-91.
Drugs. 2018;78:1085-103.

Letermovir Phase III Trial



CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

N Engl J Med. 2017;377(25):2433-44.

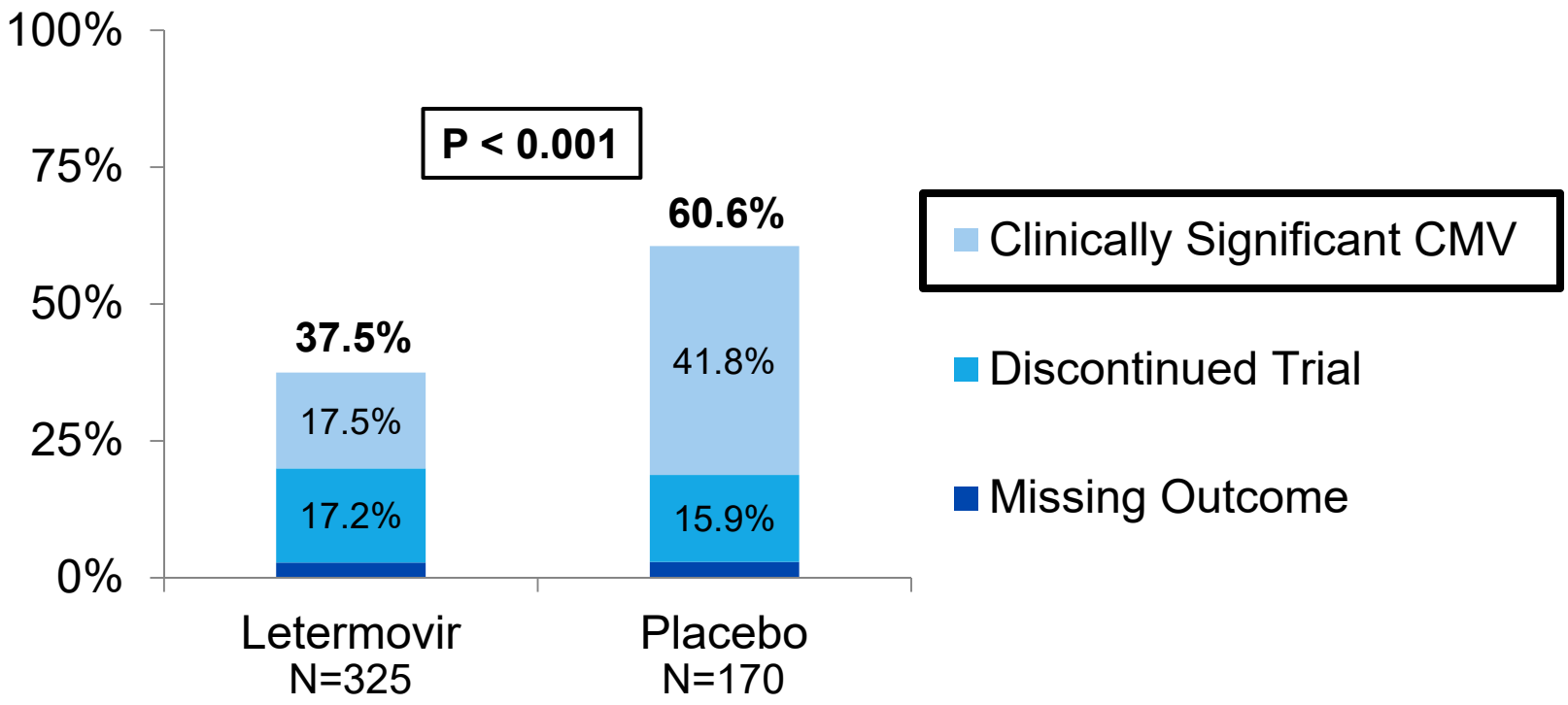
Baseline Characteristics

Characteristic	Letermovir (n=373)	Placebo (n=192)
Age (y), median (range)	53 (18-75)	54 (19-78)
Male sex, n (%)	211 (56.6)	116 (60.4)
CMV-seropositive donor, n (%)	230 (61.7)	114 (59.4)
High risk of CMV disease, n (%)	121 (32.4)	54 (28.1)

CMV = cytomegalovirus

N Engl J Med. 2017;377(25):2433-44.

Primary Endpoint: Clinically Significant CMV at Week 24



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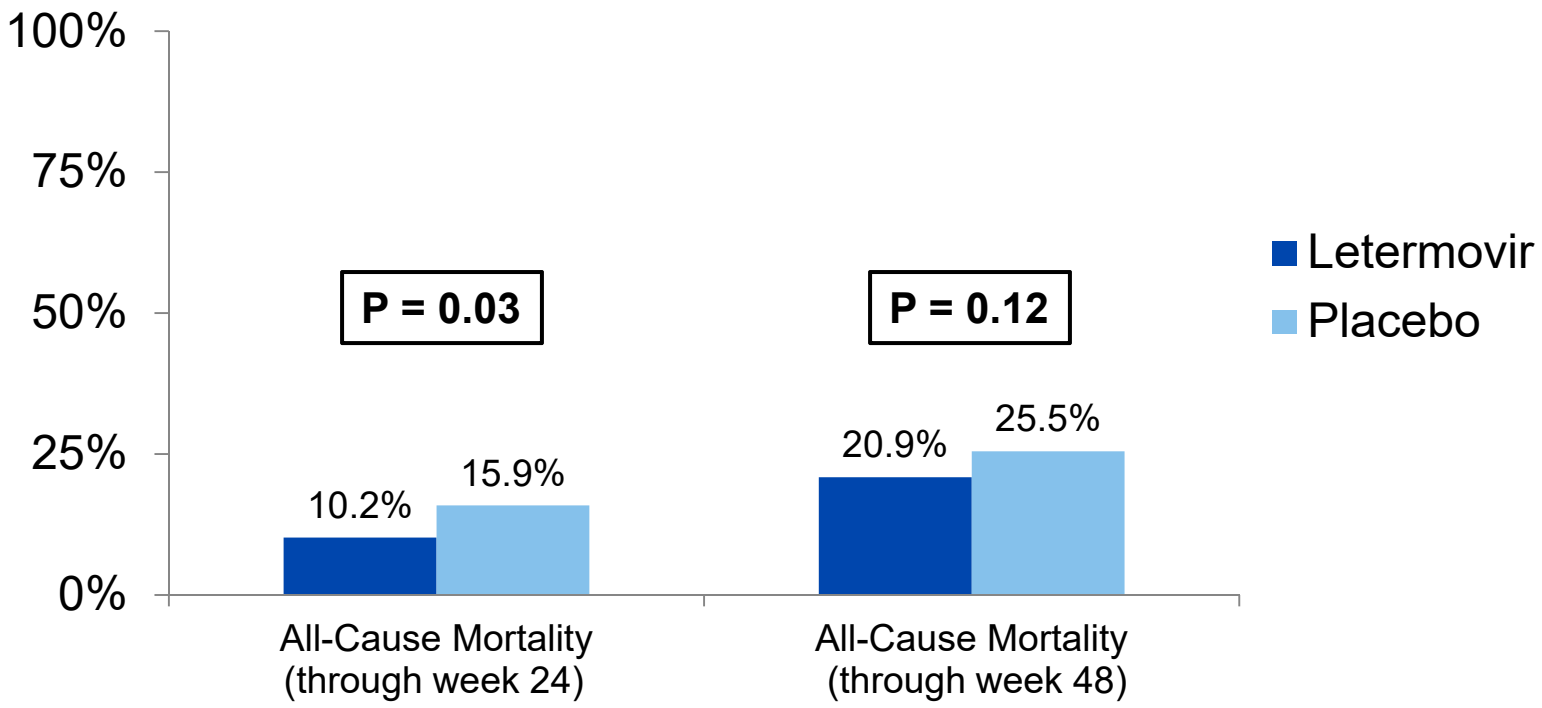
N Engl J Med. 2017;377(25):2433-44.

Exploratory Endpoints: All-Cause Mortality



N Engl J Med. 2017;377(25):2433-44.

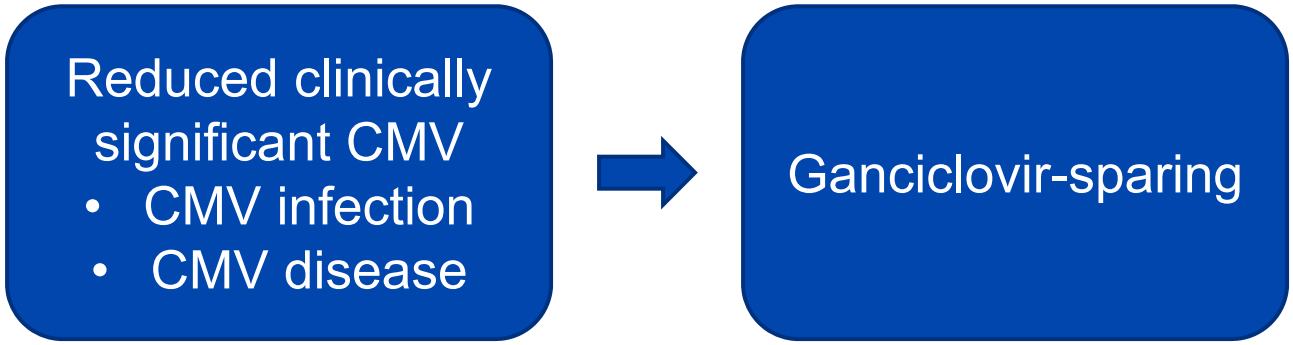
Safety Outcomes

Adverse Events, n (%)	Letermovir (n=373)	Placebo (n=192)	Difference (95% CI)	P Value
Vomiting	69 (18.5)	26 (13.5)	5.0 (−1.7 to 11.0)	0.17
Peripheral edema	54 (14.5)	18 (9.4)	5.1 (−0.8 to 10.4)	0.11
Dyspnea	30 (8.0)	6 (3.1)	-	-
Myalgia	19 (5.1)	3 (1.6)	-	-
Atrial fibrillation	17 (4.6)	2 (1.0)	-	-
ALT ≥ 5 x ULN	13 (3.5)	3 (1.6)	-	-

ALT = alanine aminotransferase
ULN = upper limit of normal

N Engl J Med. 2017;377(25):2433-44.

Clinical Application



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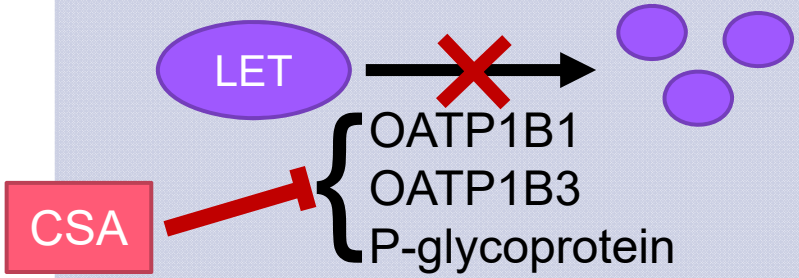
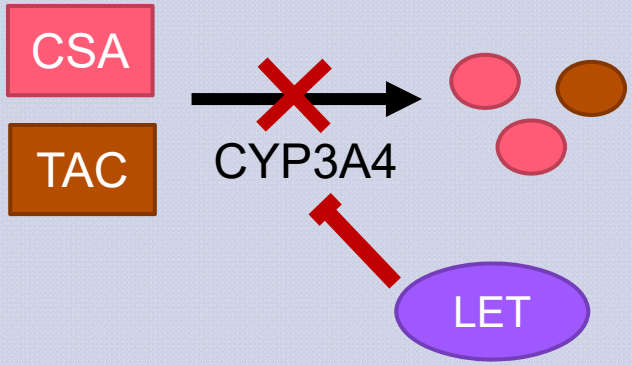
Drug Interactions: Letermovir and Calcineurin Inhibitors

Cyclosporine (CSA)



Phase III trial utilized a reduced dose of 240 mg daily in patients receiving concomitant cyclosporine

CSA & Tacrolimus (TAC)



Are empiric dose adjustments necessary?

CSA = cyclosporine
TAC = tacrolimus
LET = letermovir

Bone Marrow Transplant. 2020. https://doi.org/10.1038/s41409-020-0785-9

Drug Interactions: Letermovir and Calcineurin Inhibitors

Single-center, retrospective study including 46 patients who were CMV seropositive and received letermovir following allogeneic HSCT

Tacrolimus (n=36)
Letermovir 480 mg daily

Cyclosporine (n=10)
Letermovir 240 mg daily

Primary Endpoint
Percent change in concentration to dose (C/D) ratio over the 7-day period after initiation of letermovir.

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CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

Bone Marrow Transplant. 2020. https://doi.org/10.1038/s41409-020-0785-9

Drug Interactions: Letermovir and Calcineurin Inhibitors

Outcome	Tacrolimus (n=36)	Cyclosporine (n=10)
Number of dose changes over 7 days, average (range)	2 (0-5)	3.8 (1-6)
From baseline to 4 days post-letermovir, mean percent change in C/D ratio	+22.9%	+15.9%
From 4 to 7 days post-letermovir, mean percent change in C/D ratio	-8.5%	-10.0%
Cumulative incidence of day 100 grade II-IV GVHD, % (95% CI)	62 (43-76)	50 (16-77)

MAYO CLINIC

C/D = concentration to dose
GVHD = graft versus host disease

Bone Marrow Transplant. 2020. https://doi.org/10.1038/s41409-020-0785-9

Drug Interactions: Letermovir and Calcineurin Inhibitors

Increase in concentration to dose ratios were marginal and compensated by appropriate dosage adjustments.

Empiric dose reduction in calcineurin inhibitors is not recommended.

Drug Interactions: Letermovir and Azole Antifungals

Pharmacokinetic study conducted in health subjects

Posaconazole

Substrate of P-glycoprotein and glucuronosyltransferase

- Inhibited by letermovir

Geometric mean ratio (95% CI) for POS+letermovir/POS

AUC: 0.98 (0.83, 1.17)

Cmax: 1.11 (0.95, 1.29)

Voriconazole

Substrate of CYP2C9 and CYP2C19

- Induced by letermovir

Geometric mean ratio (95% CI) for VOR+letermovir/VOR

AUC: 0.56 (0.51, 0.62)

Cmax: 0.61 (0.53, 0.71)

AUC = area under the curve
Cmax = maximum concentration

POS = posaconazole
VOR = voriconazole

J Clin Pharmacol. 2018;58(7):897-904.

Drug Interactions: Letermovir and Azole Antifungals

Empiric dose changes not recommended.

Consider obtaining antifungal levels one week after letermovir initiation, especially if using voriconazole.

Mayo Clinic Post-HSCT Standard Operating Procedure

High-Risk Allogeneic HSCT Recipients
(Haploidentical, Cord blood, and Mismatch)

Positive Donor and/or Recipient
- CMV prophylaxis
  - Letermovir 480 mg daily starting D0 to D28 and continued through D100
- Monitor CMV PCR weekly

Negative Donor and Recipient
- No CMV prophylaxis
- Monitor CMV PCR weekly

Low-Risk Allogeneic HSCT Recipients
- No CMV prophylaxis
- Monitor CMV PCR weekly

MAYO CLINIC

HSCT = hematopoietic stem cell transplant
CMV = cytomegalovirus
PCR = polymerase chain reaction

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<u>Post-Transplant Immunosuppression</u>

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Should we provide CMV prophylaxis?

Letermovir 480 mg daily

TBI = total body irradiation
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Learning Question #2

Which patient would benefit most from letermovir prophylaxis?

A. Autologous HSCT recipient, CMV-seropositive recipient
B. Allogeneic cord blood SCT recipient, CMV-seronegative donor and recipient
C. Allogeneic HSCT recipient, mismatched unrelated donor, CMV-seropositive recipient, CMV-seronegative donor
D. Allogeneic HSCT recipient, matched related donor, CMV-seronegative recipient, CMV-seropositive donor

HSCT = hematopoietic stem cell transplant
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Learning Question #2

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HSCT = hematopoietic stem cell transplant
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Objectives

- Explain the difference between pre-emptive and prophylaxis strategies for cytomegalovirus infection prevention
- Select patients that may benefit from letermovir prophylaxis based on existing literature
- Identify areas of investigational use of letermovir

Future Potential Applications of Letermovir

- Resistant or refractory CMV
- Secondary prophylaxis of CMV infection and disease
- Prevention and treatment of CMV in solid organ transplant and other at risk populations

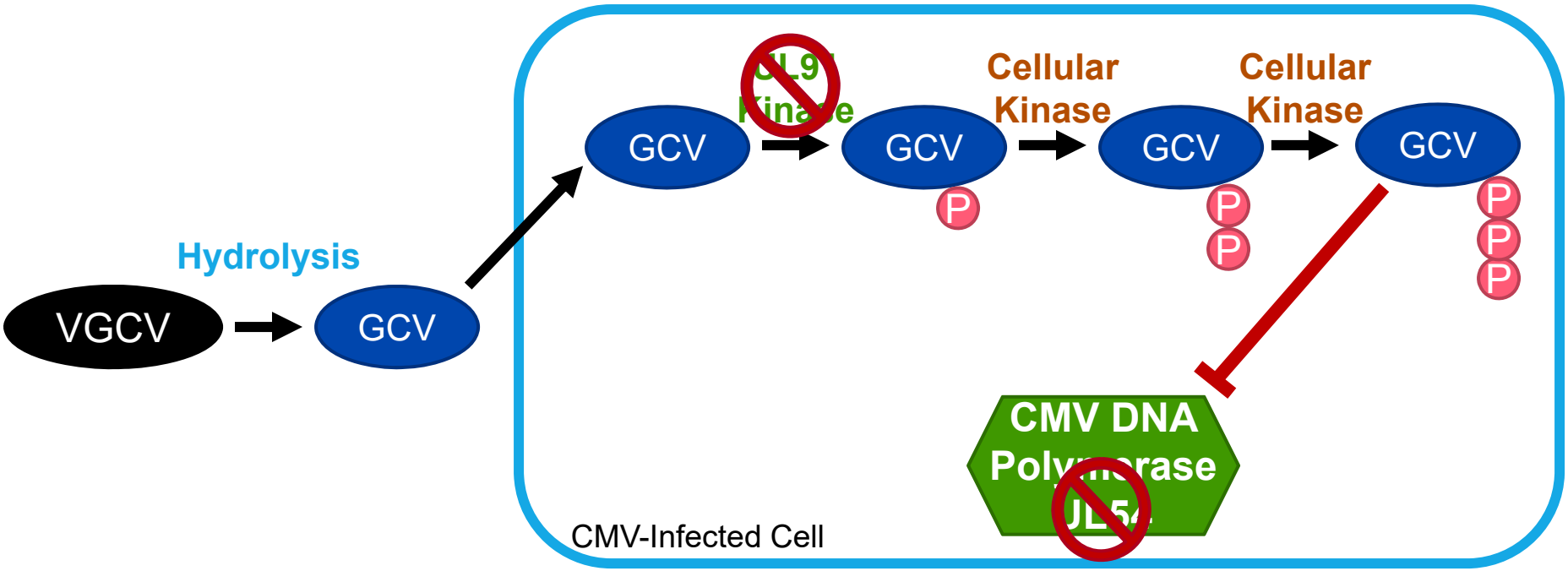
CMV = cytomegalovirus

Future Potential Applications of Letermovir

Resistant or refractory CMV

CMV = cytomegalovirus

CMV Resistance to Ganciclovir and Valganciclovir



VGCV = valgancyclovir
GCV = ganciclovir
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Drugs. 2018;78:1085-103.

CMV Resistance to Ganciclovir and Valganciclovir

Rates of Resistant and Refractory CMV

- Rates of resistant CMV in HSCT recipients range from 1.7-14.5%
- Rates of refractory CMV in HSCT recipients range from 29-39%
- Associated outcomes are usually poor

Risk Factors for Resistance

- Prolonged antiviral treatment
- Poor host immune response to CMV
- Reduced drug delivery

MAYO CLINIC

CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

Curr Opin Infect Dis. 2019;32:565-74.

Letermovir for CMV Salvage Therapy

Age, Sex	Tx	Diagnosis	Prior Therapy	Resistance	Outcome
68, M	Lung	Asymptomatic viremia	PPX: Valganciclovir TX: Ganciclovir, Foscarnet	Unable to amplify	6 weeks to achieve < 200 IU/mL
51, M	Lung	Viral syndrome	PPX: Valganciclovir TX: Ganciclovir, Foscarnet	Negative	Increase in viral load by ~2-log
59, M	Lung	Asymptomatic viremia	PPX: Valganciclovir TX: Ganciclovir, **Foscarnet**	UL97	3 weeks to achieve < 200 IU/mL
30, F	Lung	Asymptomatic viremia	PPX: Valganciclovir TX: **Ganciclovir**, Foscarnet	Negative	4 weeks to achieve < 200 IU/mL
70, M	Allo HSCT	CMV colitis & pneumonitis	PPX: None TX: Ganciclovir, **Foscarnet**	UL97, UL54	2-log reduction in viremia

Bolded medications were continued in combination therapy with letermovir for treatment of resistant/refractory CMV.

MAYO CLINIC

CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

Transplantation. 2020;104(2):404-9.

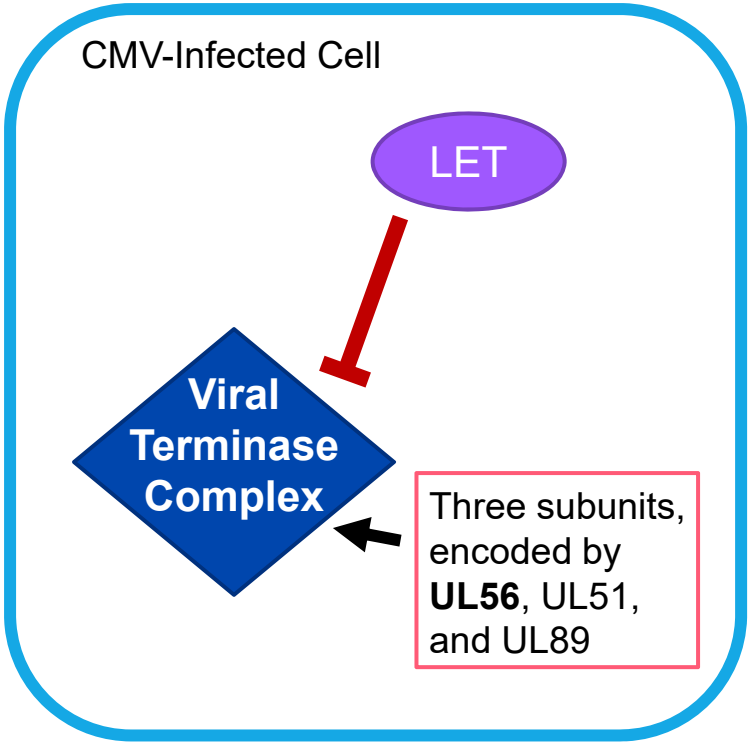
Resistant and Refractory CMV: Ongoing Trials

Study	Design	n	Intervention	Status	Completion
NCT03728426	Single Group Phase II	32	Letermovir for refractory or resistant CMV with concurrent organ dysfunction	Recruiting	Jul 2021

CMV = cytomegalovirus

CMV Resistance to Letermovir

- In vitro selection studies have suggested a low genetic barrier to development of letermovir resistance
- One patient in the letermovir prophylaxis trial who developed a breakthrough CMV infection due to a mutation in UL56



CMV = cytomegalovirus
LET = letermovir

JID. 2020:221:1036-8.
JID. 2020;221:1117-26.
Curr Opin Infect Dis. 2019;32:565-74.

Patient Case

MR is a 47 year old female with a history of acute myeloid leukemia who is day +56 from allogeneic hematopoietic stem cell transplant

CMV Prevention Strategy: Letermovir prophylaxis

New Hospital Admission:
Patient admitted with abdominal pain and fever.
CMV DNA 9430 IU/mL
CMV colitis suspected

Failure of treatment-dose ganciclovir with mutations in UL54 and UL97 identified.

CMV = cytomegalovirus

Learning Question #3

Which of the following is true regarding use of letermovir in this patient for resistant CMV?

A. Letermovir has demonstrated efficacy against resistant CMV in recent randomized clinical trials

B. Use of letermovir prophylaxis may predispose this patient to develop letermovir-resistant CMV

C. Letermovir should not be combined with other antiviral agents for resistant CMV

D. Letermovir would not be effective in this patient because of the UL54 mutation

CMV = cytomegalovirus

Learning Question #3

Which of the following is true regarding use of letermovir in this patient for resistant CMV?

A. Letermovir has demonstrated efficacy against resistant CMV in recent randomized clinical trials

B. **Use of letermovir prophylaxis may predispose this patient to develop letermovir-resistant CMV**

C. Letermovir should not be combined with other antiviral agents for resistant CMV

D. Letermovir would not be effective in this patient because of the UL54 mutation

CMV = cytomegalovirus

Future Potential Applications of Letermovir

Resistant or refractory CMV

CMV = cytomegalovirus

Future Potential Applications of Letermovir

- Resistant or refractory CMV
- Secondary prophylaxis of CMV infection and disease

CMV = cytomegalovirus

Secondary Prophylaxis of CMV Following HSCT

Population

- 80 CMV-seropositive adult patients who had ≥ 1 episode of CMV infection (n=66) or disease (n=14) following HSCT

Intervention

- Letermovir for secondary prophylaxis of CMV

Outcome

- Four patients (5.5%) developed breakthrough CMV infections or diseases
- Three of these patients had documented CMV UL56 mutation

Possible Clinical Role

- Bridge between treatment for CMV and CMV-specific immune reconstitution

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CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

Biol Blood Marrow Transplant. 2020:978984.

Secondary Prophylaxis of CMV: Ongoing Trials

Study	Design	n	Intervention	Status	Completion
NCT04017962	Single Group Phase II	86	Letermovir for prevention of recurrent CMV infection post-HSCT	Recruiting	Jul 2021

CMV = cytomegalovirus
HSCT = hematopoietic stem cell transplant

Future Potential Applications of Letermovir

- Resistant or refractory CMV
- Secondary prophylaxis of CMV infection and disease

CMV = cytomegalovirus

Future Potential Applications of Letermovir

- Resistant or refractory CMV
- Secondary prophylaxis of CMV infection and disease
- Prevention and treatment of CMV in solid organ transplant and other at risk populations

CMV = cytomegalovirus

Letermovir in Thoracic Organ Recipients

Population

- 8 heart or lung transplant patients

Intervention

- Letermovir for prophylaxis of CMV

Outcome

- Three (37.5%) developed CMV infection during prophylaxis
- No major side effects reported

Possible Clinical Role

- Well tolerated, but a higher rate of development of CMV infection

Letermovir in Other Patient Groups: Ongoing Trials

Study	Design	n	Intervention	Status	Completion
NCT03443869	Randomized Phase III	600	Letermovir **vs** valganciclovir to prevent CMV post-kidney transplant	Recruiting	Sep 2021
NCT04312841	Single Group Phase II	30	Letermovir for CMV prophylaxis in patients with hematological malignancies treated with alemtuzumab	Not yet recruiting	Dec 2022

CMV = cytomegalovirus

Future Potential Applications of Letermovir

- Resistant or refractory CMV
- Secondary prophylaxis of CMV infection and disease
- Prevention and treatment of CMV in solid organ transplant and other at risk populations

CMV = cytomegalovirus

Summary

- A preemptive strategy is typically favored in HSCT recipients
  - Avoid myelosuppressive effects of antiviral medications
- Letermovir may be used for CMV prophylaxis in allogeneic HSCT recipients
  - We reserve use for high-risk patients
- Future uses for letermovir may include resistant or refractory CMV, secondary prophylaxis for recurrent CMV, and prophylaxis or treatment in solid organ transplant or other at-risk groups

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Discussion & Questions

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