Cytomegalovirus infection in hematopoietic cell transplantation recipients

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Risk Factor For CMV Infection

Day 0-29

- CMV seropositive recipient
- Advance age
- Type of transplant(MUD-Haplo-CBT)
- Conditioning regimen(Fludarabine-Anti thymocyte globulin-Alemtuzumab-TBI)

Day 30- 100

- Prior RF+
- GVHD
- Delay of T cell recovery

Day >100

- Steroids use- GVHD
- Delay of T cell recovery
- Non myeloablative conditioning
- CMV reactivation before day 100

ECIL7:Lancet Infect Dis:2019

Impact of positive serology

Risk of post-transplant CMV infection

R-/D-	1%-3%	Low risk
R-/D+	10%-30%	
R+/D+/-	30%-70%	High risk

CMV-seropositive recipients still have a lower rate of survival than CMV-seronegative recipients.

ECIL7:Lancet Infect Dis:2019

INTRODUCTION

Direct effects

- CMV syndrome and tissue-invasive organ disease, such as gastrointestinal

Indirect effects

- Graft failure
- Graft-versus-host disease (GVHD)
- Accelerated atherosclerosis
- Secondary bacterial and fungal infections.

BLOOD, 8 DECEMBER 2016 x VOLUME 128, NUMBER 23

What to Prevent

Until 2018

Development of infection

Development of CMV disease

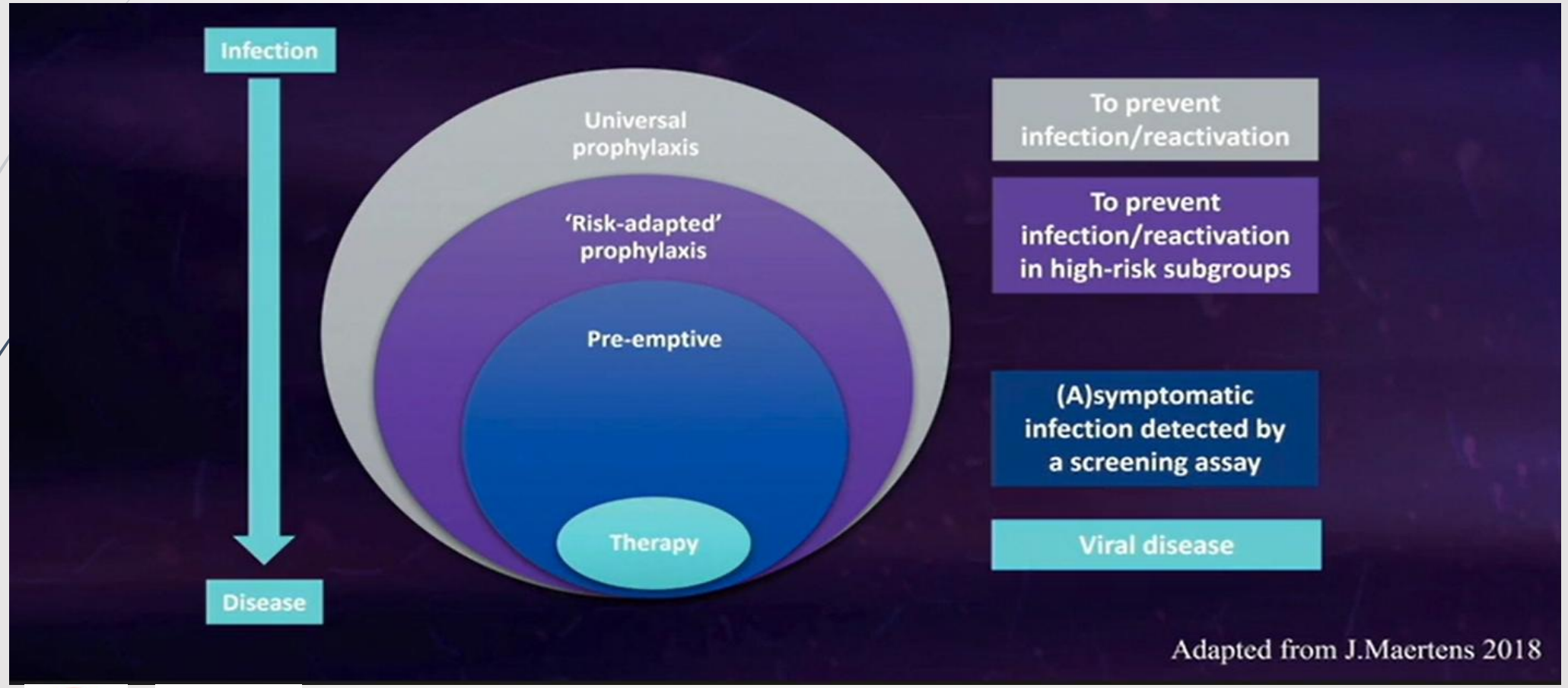
Reason

For many **years, CMV disease was considered the first cause of TRM** in HSCT

Strategies

1-Pre-emptive
2-Prophylaxis

Current strategies to prevent or treat CMV reactivation



What to Prevent

- The risk of CMV complications refer to the incidence of CMV disease and NOT to the rate of CMV infection.

(With the available antiviral)

The strategy of choice : PET

Guidelines for CMV management in HSCT

But things are changing!

ECIL7:Lancet Infect Dis:2019

PET

- **Until 2018 ,the strategy of choice was PET , base on 4 principles:**

1- PET as effective as universal prophylaxis in the prevention of CMV disease.

2-High level viremia cleared by PET does not impair survival

3-Low level viremia can be cleared by the immune system of the host without antiviral therapy and without the negative impact on patient survival.

4- The available anti-CMV agents are too toxic for prophylaxis.

British Journal of Haematology, guideline 2017

Current strategies to prevent or treat CMV reactivation

- **Preemptive** antiviral therapy is based on surveillance by quantitative polymerase chain reaction (PCR) assays, which allows the initiation of preemptive therapy above a certain detection threshold, depending on the risk of CMV disease in a specific patient.

- With this strategy, the risk of early-onset CMV disease (before 100 days posttransplant) is ,3%, but patients continue to be at risk for late-onset CMV disease and CMV-related complications

CMV Prevention

- CMV viral load monitoring should continue

for 6-12 months

with chronic GVHD

OR

prolonged T-cell immunodeficiency

British Journal of Haematology, guideline 2017

CMV Diagnosis

- The most commonly used methods
  - CMV pp65 Ag
  - CMV PCR(quantitative)

E.J. Ariza-Heredia et al. Cancer Letters 2014

CMV pp65 Ag

- Relatively easy to perform
- Not expensive , rapid
- Lack of standardization
- Need for an adequate neutrophil count (>1000/ml)
- Often rises during the first week of therapy for CMV infection

E.J. Ariza-Heredia et al. Cancer Letters 2014
Kedia et al., J Stem Cell Res Ther 2013

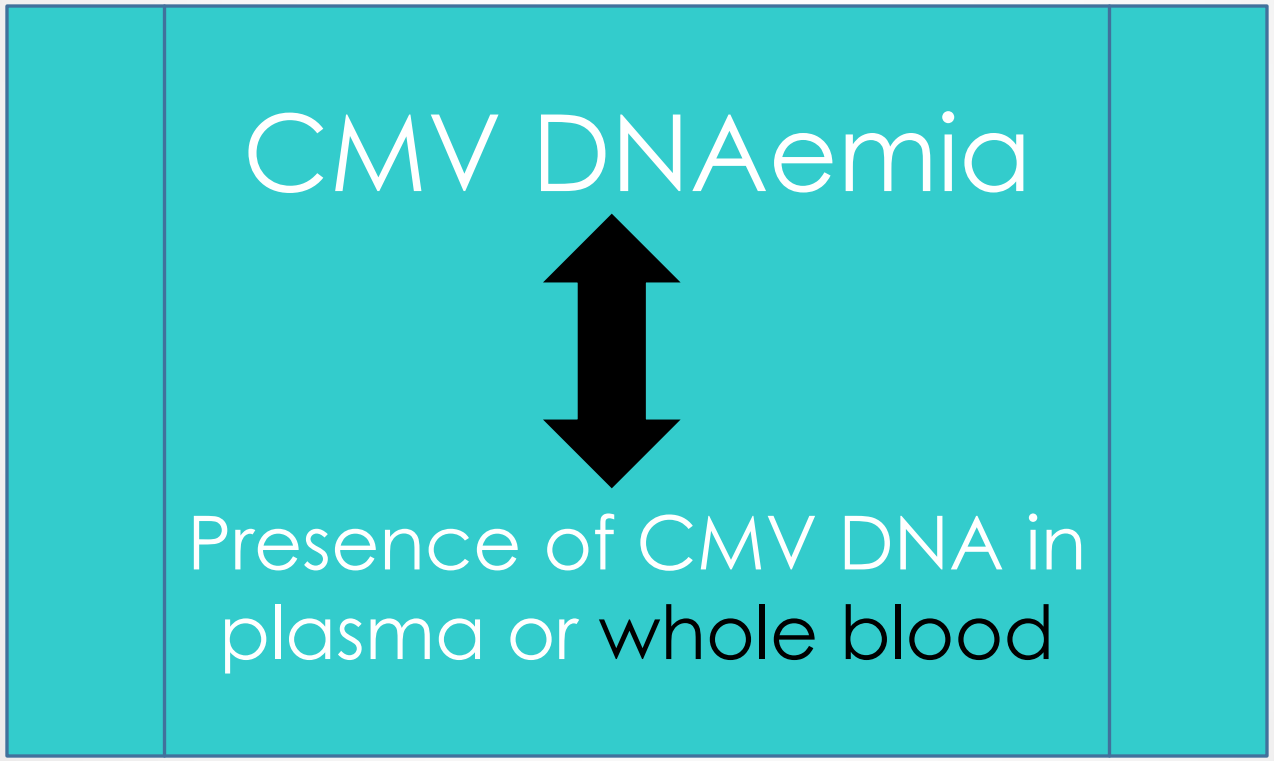
CMV pp65 Ag

- **>2/400,000** leukocytes in 2 consecutive tests
- **>5/400,000** leukocytes in a single test

- 1/200,000 leukocytes

PLoS ONE 2012
Bone Marrow Transplant 2013

Quantitative CMV PCR



Enrico Maffini et al. Expert Review of Hematology 2019

Quantitative CMV PCR

- Results of CMV PCR assays
  may vary depending on the specimen type
  (plasma versus whole blood)

Only one of these specimen types should be used in serial viral load testing

E.J. Ariza-Heredia et al. Cancer Letters 2014

CMV Prevention

- Each transplant center should have a risk-adapted policy detailing threshold values for treatment of CMV infection, taking into account patient factors and local PCR methodology

>100 c/ml
>500 c/ml
>1000 c/ml
250 c/ml
≥600 c/m

Time after HSCT	Unmodified autologous <1mg/kg steroids	D-/R- Allograft, unmodified autologous>=1 mg/kg steroids or R- autologous with CD34 selection	R+ or D+/R- allograft receiving <1mg/kg steroids and no T cell depletion	R+ or D+/ R- allograft receiving >=1 mg/kg steroids and/or T cell depletion or cord blood or R + autologous with CD34 selection
Pre-transplant	N/A	>5antigen-positive cell per slide	>=500 copy/ml	>=100 copies/ml
Conditioning until day 100	>5antigen-positive cell per slide	Any positive anti genemia	>=500 copy/ml or rising DNA level(>5 baseline whitin one month)	>=100 copies/ml
>day 100	N/A	Any positive anti genemia	>=1000 copy/ml or rising DNA level(>5 baseline whitin one month)	>=1000 copy/ml or rising DNA level(>5 baseline whitin one month)

<table>
<tr><th>Antiviral</th><th>Prophylaxis</th><th>Dose, Induction</th><th>Dose, Maintenance</th><th>Adverse Effects</th></tr>
<tr><td>Valganciclovir (Valcyte®)</td><td>Yes</td><td>900 mg BID</td><td>900 mg QD</td><td rowspan="2">• GI (N/V/D)
• Hematologic (leukopenia, neutropenia, thrombocytopenia)</td></tr>
<tr><td>Ganciclovir (Cytovene®)</td><td>Yes</td><td>5 mg/kg BID</td><td>5 mg/kg QD</td></tr>
<tr><td>Foscarnet (Foscavir®)</td><td>Not recommended</td><td colspan="2"><table>
<tr><th>mL/min/kg</th><th>Induction for CMV (dose in mg/kg)</th><th>Maintenance for CMV (dose in mg/kg)</th></tr>
<tr><td>>1.4</td><td>90 mg q12h</td><td>90-120 mg q24h</td></tr>
<tr><td>>1-1.4</td><td>70 mg q12h</td><td>70-90 mg q24h</td></tr>
<tr><td>>0.8-1</td><td>50 mg q12h</td><td>50-65 mg q24h</td></tr>
<tr><td>>0.6-0.8</td><td>80 mg q24h</td><td>80-105 mg q48h</td></tr>
<tr><td>>0.5-0.6</td><td>60 mg q24h</td><td>60-80 mg q48h</td></tr>
<tr><td>≥0.4-0.5</td><td>50 mg q24h</td><td>50-65 mg q48h</td></tr>
<tr><td><0.4/iHD</td><td>Not recommended</td><td>Not recommended</td></tr>
</table></td><td>• GI (N/V/D)
• Hematologic (anemia, pancytopenia)
• Metabolic (hypo-P, Ca, K, Mg)
• Renal (ARF, SCr inc)</td></tr>
<tr><td>Cidofovir (Vistide®)</td><td>Not recommended</td><td colspan="2">5 mg/kg once weekly x 2 weeks
5 mg/kg every other week

PO probenecid:
2 g 2hrs pre-dose, 1 g 2hrs & 8hrs post-dose</td><td>• Hematologic (anemia, neutropenia)
• Metabolic (metabolic acidosis)
• Renal (ARF, SCr inc, proteinuria)
• Neurologic (HA, asthenia)</td></tr>
</table>

Valganciclovir, Ganciclovir, Foscarnet, Cidofovir (Lexi-Drugs). Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.

CMV Prevention

- Pre-emptive therapy should be discontinued in case of CMV-DNAemia clearance after two consecutive negative tests performed at least 3-4 days apart.
- According to the ECIL 7 Guidelines and other studies a duration of therapy for at least 2 weeks, aiming for at least one negative cytomegalovirus test, is recommended

Enrico Maffini et al. Expert Review of Hematology 2019
Per Ljungman et al. Lancet Infect Dis 2019

Current strategies to prevent or treat CMV reactivation

- **Anti-CMV prophylaxis**

Several studies demonstrated that CMV reactivation posttransplant was associated with an increased risk for overall and all-cause mortality, independent of the use of preemptive therapy

In the 1980s and 1990s, anti-CMV prophylaxis with high-dose acyclovir or valacyclovir was studied and shown to have some effect on CMV reactivation; however, it is not widely used because its efficacy in preventing CMV disease is limited.

Anti-CMV prophylaxis

- For decades, highly effective agents to control CMV infection have been limited to drugs with significant toxicity (ie, ganciclovir, foscarnet, and cidofovir). Ganciclovir is associated with hematotoxicity and thus, an increased incidence of secondary bacterial and fungal infections

- IV foscarnet is associated with electrolyte disturbances and severe nephrotoxicity, and cidofovir is associated with nephrotoxicity, hematotoxicity, and ocular toxicity

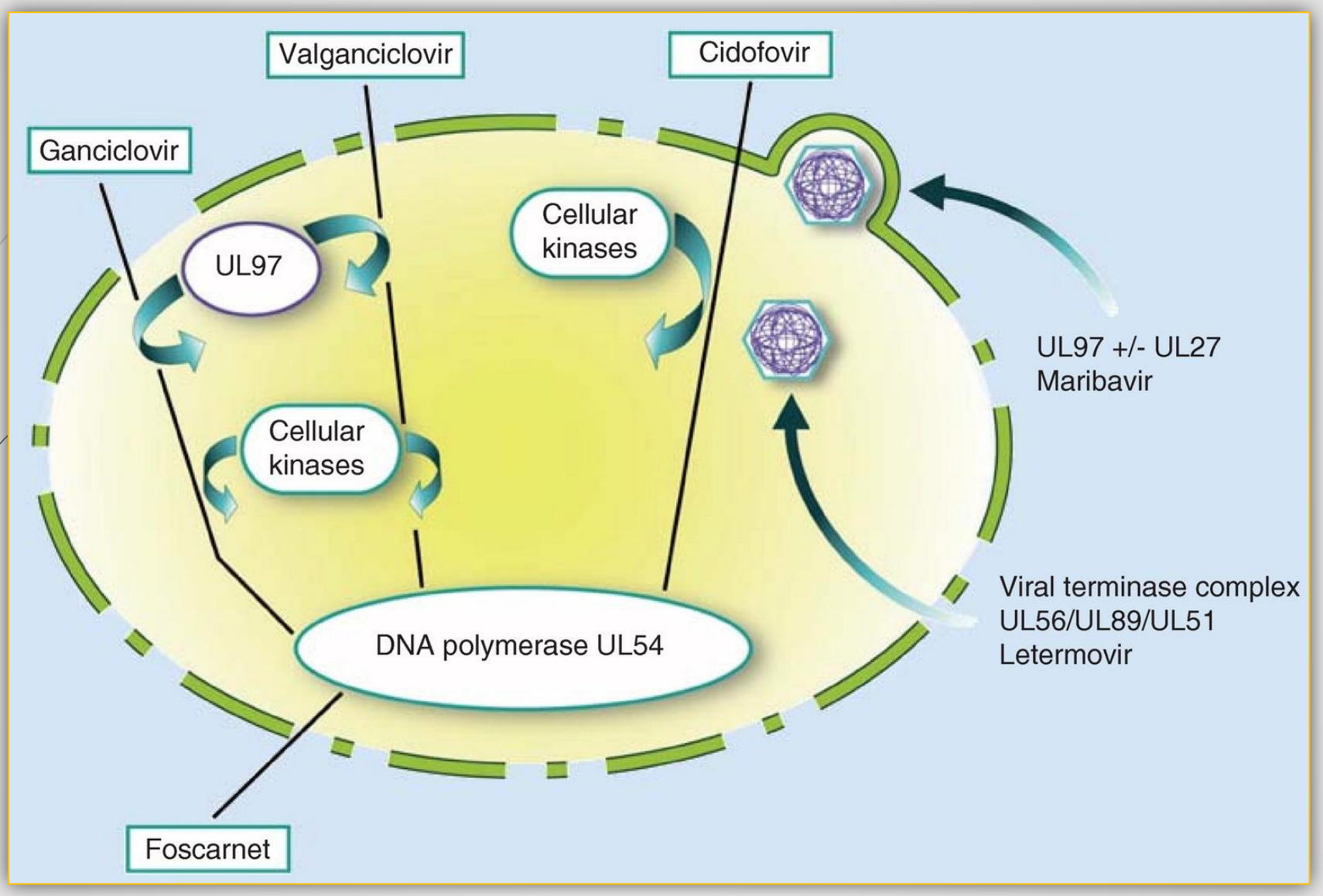
Anti-CMV prophylaxis

- The results from relatively small uncontrolled trials provide support for prophylaxis with valganciclovir or foscarnet only in very high-risk patients
- Valganciclovir prophylaxis was not shown to provide improved protection from CMV disease compared with PCR-guided preemptive therapy for the prevention of late-onset CMV disease.
- Thus, until recently, most centers have not used antiviral prophylaxis; instead, they have relied on preemptive therapy as the management strategy. This has changed recently with the introduction of letermovir

Letermovir (Prevymis™)

- FDA Approval, 2017: CMV prophylaxis, allo-HSCT CMV R+ patients
  - IV/PO: 480mg (240mg when co-administered with cyclosporine) PO QD beginning between Day 0-28 post-transplantation through Day 100
- MOA: viral terminase inhibitor
  - Inhibits replication by targeting the CMV DNA terminase complex (pUL51, pUL56, pUL89)
  - **Antiviral spectrum: CMV, NO HSV or VZV**
- No renal or hepatic dosage adjustments
- Drug interactions: substrate of CYP3A4 & CYP2D6, inhibits CYP3A4
  - Cyclosporine: bi-directional
  - Azoles: reduces voriconazole levels
- Adverse effects: GI (N/V/D), headache, peripheral edema, thrombocytopenia (grade 4: 27%)
- Cost/day: ~$284

Letermovir (Prevymis) [Package Insert]. Merck. Whitehouse Station, NJ. 2021.
Letermovir (Lexi-Drugs). Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.



Van Hecke, et al. *Future Microbiology*. 2019;14(3):175–184

Development of Resistant/Refractory CMV Infection

- **Refractory CMV <u>infection</u>:**
  - **Proven/Definite:** CMV DNAemia or antigenemia increases (*ie, >1 log_{10} increase in CMV DNA blood levels between peak viral load within 1st week and the peak viral load at 2+ wk*) after at least 2 wk of appropriately dosed antiviral therapy
    - **Probable:** Viral load persistence (*at the same level or higher than the peak viral load within 1 wk but <1 log_{10} increase in CMV DNA titers*) after at least 2 wk of appropriately dosed antiviral therapy
- **Refractory CMV <u>disease</u>:**
  - **Proven/Definite**: Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy
    - **Probable:** Lack of improvement in clinical signs and symptoms after at least 2 wk of appropriately dosed antiviral therapy
- **Resistance:** Presence of viral genetic alteration that confer reduced susceptibility to one or more antiviral drugs

Razonable R. *Clinical Transplantation*. 2019;33:e13512

Table 2. Risk factors for CMV resistance in HCT recipients

Host factors
Prolonged antiviral CMV drug exposure (>3 mo)
Previous antiviral CMV drug exposure
Recurrent CMV infection
Inadequate antiviral CMV drug absorption and bioavailability
Inadequate antiviral CMV oral prodrug conversion
Variation in antiviral CMV drug clearance
Subtherapeutic antiviral CMV drug level
Poor compliance
T-cell depletion
Haploidentical, allogeneic, and cord blood HCT
Delayed immune reconstitution
CMV-seropositive recipient
Treatment with antithymocyte antibodies
Active GVHD
Young age
Congenital immunodeficiency syndromes
Viral factors
CMV viral load rise while receiving treatment (after >2 wk with adequate dosing)
Failure of CMV viral load to fall despite appropriate treatment
Rise in CMV viral load after decline while receiving appropriate therapy
Intermittent low-level CMV viremia
High CMV viral loads

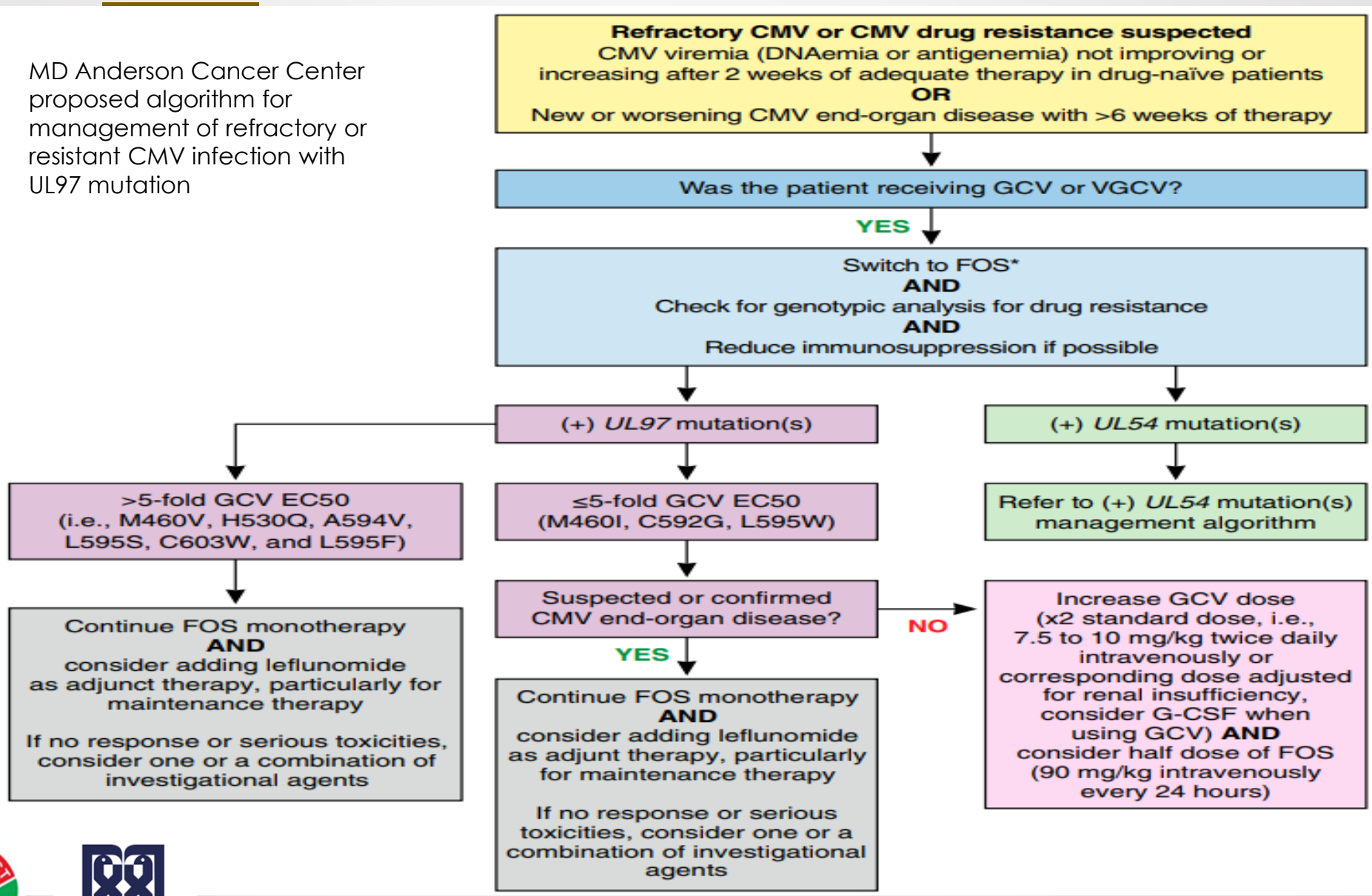
Treatment and Prophylaxis of Resistant/ Refractory CMV Infection

- For asymptomatic or mildly **symptomatic disease, or with low-level** DNAemia, guidelines recommend the use of **high dose GCV** (from 7.5 to 10 mg/kg every 12 h in normal renal function) .
- For **severe, life-threatening, or sight-threatening disease**, international guidelines recommend the use of **foscarnet .**
- An updated clinical decision support tool, developed by several of the guidelines authors, also recommends **maribavir**, although not with retinitis or encephalitis due to poor drug penetration, where **foscarnet** would be preferred .

Camille Nelson Kotton New Insights on CMV Management in Solid Organ Transplant Patients: Prevention, Treatment, and Management of Resistant/Refractory Disease, Infect Dis Ther,October 31, 2022

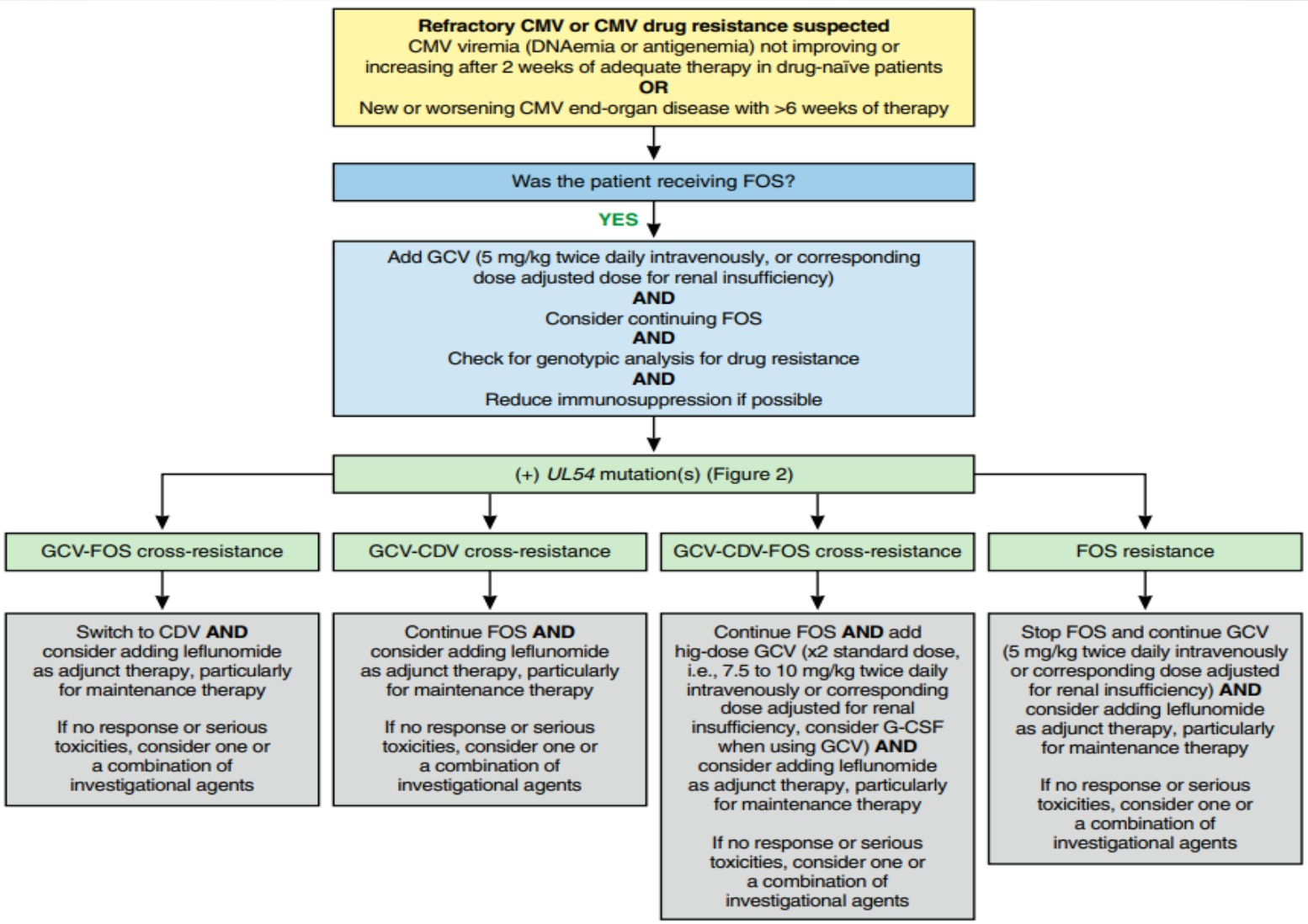
UL97

MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with UL97 mutation



El Chaer, et al. *Blood*. 2016;128(23):2624-2636

UL54



El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Maribavir (Livtencity™)

- FDA Approval, 2021: adults and pediatric patients (≥12yo & ≥35kg) with post-transplant CMV infection/disease refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet
  - PO: 400mg PO BID
- MOA: competitively inhibits the protein kinase activity of human CMV enzyme pUL97, resulting in inhibition of the phosphorylation of proteins
  - **Antiviral spectrum: CMV, NO HSV or VZV**
- No renal or hepatic dosage adjustments
- Drug interactions: substrate of CYP3A4 & CYP1A2
  - Carbamazepine, phenytoin, phenobarbital, primidone
- Adverse effects: GI (N/V/D), hematologic (decreased Hgb, PLTs)
- Cost/day: ~$1,068

- **Warning**: virologic failure/relapse post-treatment (usually occurs within 4-8 weeks after maribavir discontinuation)

Maribavir(Livetencity) [Package Insert]. Takeda. Lexington, MA. 2021.
Maribavir Lexi-Drugs). Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.

Brincidofovir

- Brincidofovir is the oral lipid conjugate of cidofovir.
- It is more potent and less nephrotoxic and achieves higher serum concentrations than cidofovir.
- brincidofovir (administered weekly) is associated with increased gastrointestinal toxicities (mainly diarrhea) compared with cidofovir.
- Resistance to brincidofovir is expected to be similar to cidofovir after mutations in UL54, although in vitro novel resistance mutations have been identified as well.
- Brincidofovir can be used for ganciclovir-resistant CMV infection, unless resistance is acquired through a UL54 mutation

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

CMV-specific CTLs

- cellular adoptive immunotherapy has been used to treat CMV infections that are unresponsive to antiviral therapy, with promising results.
- When treating resistant CMV infections, cytotoxic T-lymphocyte (CTL) infusions when available as adjunct therapy, particularly if multidrug resistance is identified.
- Multiple infusions maybe needed, especially if the initial response is suboptimal or rebound of CMV viremia occurs.
- major adverse events, such as graft failure and transplantation-associated microangiopathy, have been reported in a very small number of patients undergoing donor-derived CTL infusions.

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Other therapies

- **Leflunomide**, inhibits protein kinase activity and may interfere with CMV virion assembly.
- Because leflunomide showed in vitro activity against wild-type and ganciclovir-resistant CMV, it has been used to treat multidrug-resistant or refractory CMV infections, with variable results.
- Leflunomide recommend as adjunct therapy in addition to other anti-CMV drugs or other strategies.
- Higher doses and monitoring of teriflunomide (active metabolite) levels in the serum may be necessary to keep drug levels above 40 mg/mL.
- Moreover, close monitoring of patients for leflunomide side effects, which may include elevated liver enzymes, impaired bone marrow function, and potential severe life-threatening toxicities.

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Other therapies

- **Artesunate**, an antimalarial agent, has shown in vitro activity against ganciclovir-resistant CMV.
- Artesunate interferes with the host cell kinase signaling system required for CMV replication.
- The clinical efficacy of artesunate remains questionable, because only a few cases were reported, with variable success.
- Artesunate is generally well-tolerated; however, transient neurologic abnormalities and neutropenia have been observed in patients treated for malaria.

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Other therapies

- **The mammalian target of rapamycin drugs sirolimus and everolimus** may reduce the incidence of CMV infections in HCT recipients.
- The mechanism of action of these drugs against CMV is still unclear; however, it is thought that these drugs have an indirect effect by inhibiting host cell proliferation and signaling pathways.
- Whether switching to a mammalian target of rapamycin drugs inhibitor could be beneficial for management of resistant CMV infection still need to be determined in future trials.

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Other therapies

- **CSJ148**, a combination of 2 newly discovered monoclonal antibodies against CMV, binds and inhibits the CMV viral glycoprotein B (gB) and gH/gL/UL128/UL130/UL131, a pentameric complex essential for CMV infectivity.
- CSJ148 showed 100- to 1000-fold more potency than CMV hyperimmunoglobulin at inhibiting CMV replication.
- In the firstin-human study, CSJ148 was safe and well tolerated by healthy volunteers.
- Interestingly, no resistance was seen when CMV was cultured in the presence of the compound .

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Other therapies

- The use of **CMV intravenous immunoglobulins** as adjunct therapy for CMV end-organ disease, particularly for CMV pneumonitis, in HCT recipients remains at best controversial.
- To date, available data on the utility of adding CMV intravenous immunoglobulins for the treatment of resistant CMV infection in this patient population are lacking.

El Chaer, et al. *Blood*. 2016;128(23):2624-2636

Prophylaxis of Resistant/ Refractory CMV Infection

- Prophylaxis after treatment of R/R CMV infection can be challenging, especially if there is multidrug resistance.
- Maribavir is rarely available and not approved for prophylaxis, VGCV is usually ineffective, and foscarnet is often considered impractical and too toxic.
- In general, **preserving letermovir for prophylaxis** after treatment of R/R CMV, rather than using it for treatment, given the lower barrier to developing resistance with letermovir treatment. Other options that may be effective, depending on prior exposures and resistance mutations, include **CMV immunoglobulin and cidofovir every 2 weeks**.

Camille Nelson Kotton New Insights on CMV Management in Solid Organ Transplant Patients: Prevention, Treatment, and Management of Resistant/Refractory Disease, Infect Dis Ther,October 31, 2022

Take Home Message

- There are two ways to prevent CMV among allograft recipients: Preemptive antiviral therapy is based on surveillance by quantitative polymerase chain reaction (PCR) assays and prevention of viral replication.

- For decades, highly effective agents to control CMV infection have been limited to drugs with significant toxicity (ie, ganciclovir, foscarnet, and cidofovir). Thus, until recently, most centers have not used antiviral prophylaxis; instead, they have relied on preemptive therapy as the management strategy. This has changed recently with the introduction of letermovir.

Take Home Message

- Depending on the genotyping results, multiple strategies can be adopted to treat resistant CMV infections, albeit no randomized clinical trials exist so far, after reducing immunosuppression (if possible): ganciclovir dose escalation, ganciclovir and foscarnet combination, and adjunct therapy such as CMV-specific cytotoxic T-lymphocyte infusions.

- Novel therapies such as maribavir, brincidofovir, and letermovir should be further studied for treatment of resistant CMV.