Vall d'Hebron
Barcelona Campus Hospitalari

The challenge of
MDR & XDR
infections

CLINICAL CASE- CMV MULTIRESISTANT

Isabel Ruiz Camps
Infectious Diseases Department
Universitary Hospital Vall d'Hebron
Barcelona

Disclosures

- Research funding
  - GSK
- Honoraria
  - Astellas, Gilead, MSD, Pfizer, Janssen, BMS, Lilly, Bayer
- Advisory board
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- Consultancy
  - Gilead, Pfizer, Ferrer
- Shareholder
  - No disclosures

Clinical case

- 49 years old man
- MDS with blast excess tipe 2 (4/19)
- BMO: Fibrosis grade I. Normal cytogenetics. BM: NMP1 mutate, FLT3, IDH1, IDH2 negatives, JAK2 negative.
- 1L: idarrubicine+Citarabine PR:5% blasts,
- 2L:azacitidine (2 cicles)
- CD34+ selected alloHSCT Unrelated donor HLA 9/10 (29/08/2019) :TBI/Thiotepa/Ciflofosfamide/ATG
- CMV R+/D-

Prophylaxis

- Fluconazole: 200mg/24h vo (+1)
- Nebulized amphotericine B
- Aciclovir: 400mg/12h vo
- Inhaled pentamidine before HSCT and after TMP/SMX

Does our patient have risk factors for CMV infection?

- Yes, one of the highest-risk. It's a CD34+ selected allo-HSCT
- No. The donor serology is negative
- May be, but the CD34+ selected transplant has a low risk for CMV replication
- I don't know. It's not my field of expertize

Cytomegalovirus infection in hematologic malignancy settings other than the allogeneic transplant

Risk Group	Features
Very high	Allo-HSCT by cord blood donor Allo-HSCT by any source treated with high-dose steroids (ie, ≥1 mg/kg of prednisone) Allo-HSCT by any source treated with anti-T-cell agents T-cell depleted allo-HSCT CD34+-selected allo-HSCT
High	Allo-HSCT by any source before day 100
Intermediate[a]	Allo-HSCT after day 100, in absence of adjunctive risk factors (ie, high-dose steroids and anti-T-cell agents) CD34-selected ASCT ASCT patients treated with Alemtuzumab, Fludarabine, Cladribine, TBI, or high-dose steroids (ie, ≥1 mg/kg of prednisone) Nontransplant patients treated with Alemtuzumab or high-dose steroids (ie, ≥1 mg/kg of prednisone)
Low	Other ASCT patients Other nontransplant patients

F. Marchesi *Hematological Oncology*. 2017;1–11.

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Cytomegalovirus DNAemia and risk of mortality in allogeneic hematopoietic stem cell transplantation: Analysis from the Spanish Hematopoietic Transplantation and Cell Therapy Group

Am J Transplant. 2021;21:258–271.

The net impact of cytomegalovirus (CMV) DNAemia on overall mortality (OM) and nonrelapse mortality (NRM) following allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a matter of debate. This was a retrospective, multicenter, noninterventional study finally including 749 patients. CMV DNA monitoring was conducted by real-time polymerase chain reaction (PCR) assays. Clinical outcomes of interest were OM and NRM through day 365 after allo-HSCT. The cumulative incidence of CMV DNAemia in this cohort was 52.6%. A total of 306 out of 382 patients with CMV DNAemia received preemptive antiviral therapy (PET). PET use for CMV DNAemia, but not the occurrence of CMV DNAemia, taken as a qualitative variable, was associated with increased OM and NRM in univariate but not in adjusted models. A subcohort analysis including patients monitored by the COBAS Ampliprep/COBAS Taqman CMV Test showed that OM and NRM were comparable in patients in whom either low or high plasma CMV DNA threshold (<500 vs ≥500 IU/mL) was used for PET initiation. In conclusion, CMV DNAemia was not associated with increased OM and NRM in allo-HSCT recipients. The potential impact of PET use on mortality was not proven but merits further research.

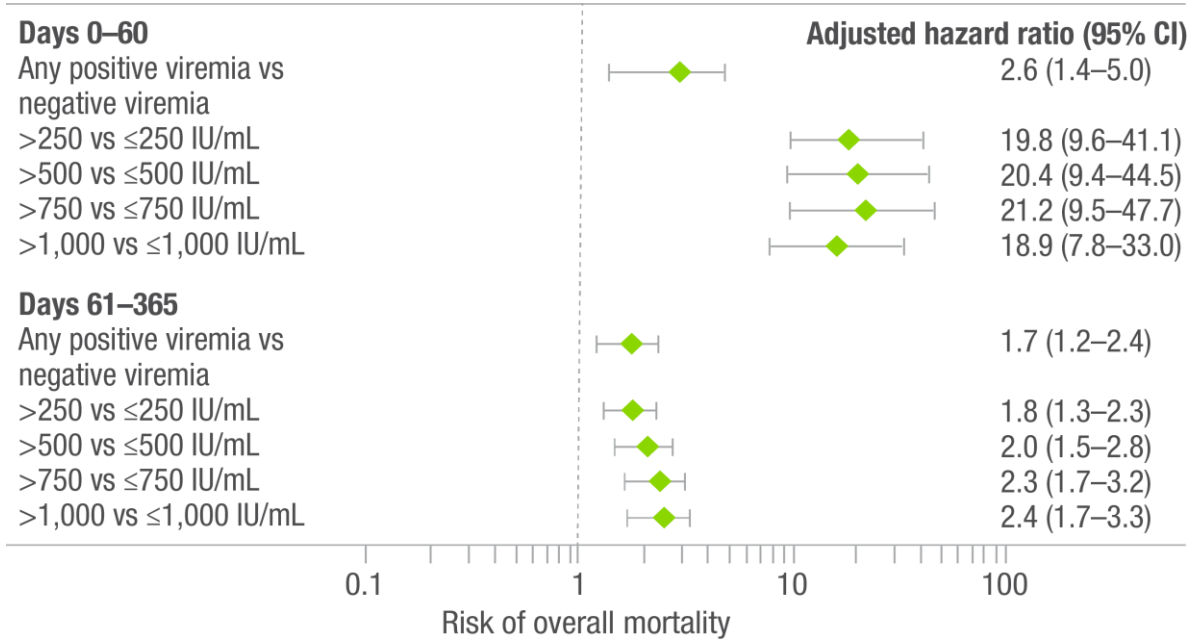
There is limited information on the impact of CMV DNAemia episodes developing prior to engraftment (pre-CMV DNAemia) on clinical outcomes following allogeneic hematopoietic stem cell transplantation (allo-HSCT). This issue was addressed in the current retrospective multicenter study including 878 patients. All participant centers used preemptive antiviral therapy strategies for prevention of CMV disease. CMV DNA load in blood was monitored by real-time PCR assays. A total of 144 patients (cumulative incidence 16.5%, 95% CI, 14%–19%) had an episode of pre-CMV DNAemia at a median of 10 days after allo-HSCT. Patients who developed pre-CMV DNAemia had a significantly higher ($P = < 0.001$) probability of recurrent episodes (50%) than those who experienced post-CMV DNAemia (32.9%); Nevertheless, the incidence of CMV disease was comparable ($P = 0.52$). Cumulative incidences of overall mortality (OM) and non-relapse mortality (NRM) at 1-year after allo-HSCT were 32% (95% CI, 29–35%) and 23% (95% CI 20–26%), respectively. The risk of OM and NRM in adjusted models appeared comparable in patients developing a single episode of CMV DNAemia, regardless of whether it occurred before or after engraftment, in patients with pre- and post-engraftment CMV DNAemia episodes or in those without CMV DNAemia.

Clinical outcomes of allogeneic hematopoietic stem cell transplant recipients developing Cytomegalovirus DNAemia prior to engraftment

Bone Marrow Transplant. 2021 Jun;56(6):1281-1290

Any Level of CMV Infection Is Associated With a 2.6 Times Greater Risk of Mortality

CMV viral loads as a time-dependent risk factor for overall mortality 1 year after HSCT (N=926)



Adapted from Green et al.

HSCT patients with any positive viremia had **2.6 times greater risk** of overall mortality than patients with no viremia up to **60 days** post-transplant.

Green ML et al. *Lancet Haematol.* 2016;3(3):e119–e127.

31/10/19	Negatiu		
08/11/19	Negatiu		
11/11/19	Negatiu		
14/11/19	Negatiu		2,78
19/11/19	Positiu	11751	4,07
21/11/19	Positiu	19501	4,29
25/11/19	Positiu	3023	3,48
28/11/19	Positiu	4523	3,66
04/12/19	Positiu	6787	3,83
10/12/19	Negatiu		
13/12/19	Positiu	2247	3,35
17/12/19	Negatiu		
18/12/19	Negatiu		
23/12/19	Negatiu		
27/12/19	Negatiu		
03/01/20	Positiu	13372	4,13
07/01/20	Positiu	227	2,36
10/01/20	Positiu	919	2,96
14/01/20	Positiu	875	2,94
21/01/20	Negatiu		
24/01/20	Negatiu		
27/01/20	Negatiu		
31/01/20	Negatiu		
05/02/20	Negatiu		
12/02/20	Negatiu		
17/02/20	Negatiu		
20/02/20	Positiu	386	2,59
24/02/20	Positiu	2002	3,3
27/02/20	Positiu	5338	3,73
03/03/20	Positiu	1128	3,05
10/03/20	Positiu	2132	3,33
16/03/20	Positiu	1904	3,28
24/03/20	Positiu	1101	3,04
31/03/20	Positiu	4513	4,65
07/04/20	Negatiu		
16/04/20	Negatiu		
22/05/20	Positiu	3636	3,56
22/06/20	Positiu	4294	3,63
13/07/20	Positiu	1901	3,28
10/08/20	Negatiu		1,85
14/09/20	Negatiu		

1- Valganciclovir 900 mg/12h

2 - Valganciclovir 900 mg/12h

3 - Valganciclovir 900 mg/12h

4 -Foscarnet 90mcg/kg/12h

15/10/20	Positiu	3148	3,5
19/10/20	Positiu	4890	3,69
26/10/20	Positiu	3475	3,54
29/10/20	Negatiu		
02/11/20	Negatiu		
04/11/20	Positiu	1480	3,17
06/11/20	Positiu	246	2,39
10/11/20	Positiu	665	2,82
20/11/20	Positiu	3657	3,56
23/11/20	Positiu	2640	3,42
26/11/20	Positiu	494	2,69
30/11/20	Positiu	1145	3,06
03/12/20	Positiu	979	2,99
07/12/20	Positiu	172	2,23
10/12/20	Positiu	366	2,56
14/12/20	Positiu	169	2,23
16/12/20	Negatiu		
21/12/20	Negatiu		
24/12/20	Negatiu		
28/12/20	Negatiu		
04/01/21	Negatiu	428	
14/01/21	Positiu	12050	4,08
18/01/21	Positiu	8298	3,92
21/01/21	Positiu	22143	4,35
26/01/21	Positiu	15399	4,19
01/02/21	Positiu	9363	3,97
08/02/21	Positiu	4020	3,6
15/02/21	Positiu	3907	3,59
22/02/21	Positiu	1001	3
08/03/21	Positiu	818	2,91
15/03/21	Negatiu		
29/03/21	Negatiu		

5 - Foscarnet 90mcg/kg/12h + EC ViroTCell (26/10) ???

6 – Foscarnet 90mcg/kg/12h + anti-CMV lymphocytes 26/11

7 – Foscarnet 90mcg/kg/12h

12/04/21	Positiu	692	2,84
11/05/21	Positiu	238	2,38
13/05/21	Positiu	2155	3,33
17/05/21	Positiu	2645	3,42
20/05/21	Positiu	13316	4,12
26/05/21	Positiu	3063	3,49
02/06/21	Positiu	45688	4,66
07/06/21	Positiu	151684	5,18
10/06/21	Positiu	83209	4,92
14/06/21	Positiu	3935	3,59
21/06/21	Positiu	405	2,61
23/06/21	Negatiu		
23/06/21	Negatiu		
25/06/21	Positiu	314	2,5
28/06/21	Negatiu		
05/07/21	Negatiu		
12/07/21	Positiu	393	2,59
19/07/21	Negatiu		
26/07/21	Negatiu		
02/08/21	Negatiu		
09/08/21	Negatiu		
18/08/21	Negatiu		
20/08/21	Negatiu		
01/09/21	Negatiu		
03/09/21	Positiu	1785	3,25
07/09/21	Positiu	707	2,85
14/09/21	Positiu	1352	3,13
21/09/21	Positiu	4641	3,67
28/09/21	Positiu	1465	3,17
05/10/21	Positiu	2509	3,4

8 - Valganciclovir 900 mg/12h-Foscarnet 90mcg/kg/12h*

9 – No treatment

Exitus 9/10/2021

Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials

Table 2. Summary of the Definitions of Refractory Cytomegalovirus Infection and Disease and Antiviral Drug Resistance for Use in Clinical Trials

Term	Definition
Refractory CMV infection	CMV viremia that increases[a] after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load[b] after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 wk of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs[c]

Abbreviation: CMV, cytomegalovirus.

[a]More than 1 $\log_{10}$ increase in CMV DNA levels in blood or serum and determined by $\log_{10}$ change from the peak viral load within the first week to the peak viral load at ≥2 weeks as measured in the same laboratory with the same assay.

[b]CMV viral load at the same level or higher than the peak viral load within 1 week but <1 $\log_{10}$ increase in CMV DNA titers done in the same laboratory and with the same assay.

[c]Known examples involve genes involved in antiviral drug anabolism (eg, UL97-mediated phosphorylation of ganciclovir), the antiviral drug target (eg, UL54, UL97, UL56/89/51), or compensation for antiviral inhibition of biological function (eg, UL27).

Chemaly RF. Clinical Infectious Diseases 2019;68(8):1420–6

Wich risk factors for CMV resistant infection does our patient present?

- Prolonged antiviral drug exposure
- Recurrent CMV infection
- Delayed immune reconstitution
- All of them

Risk factors for CMV resistance

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

El Clhaer F. Blood. 2016; 128(23): 2624–2636
Chemaly RF. CID Clinical Infectious Diseases 2019;68(8):1420–6

When a resistance study has to be done?

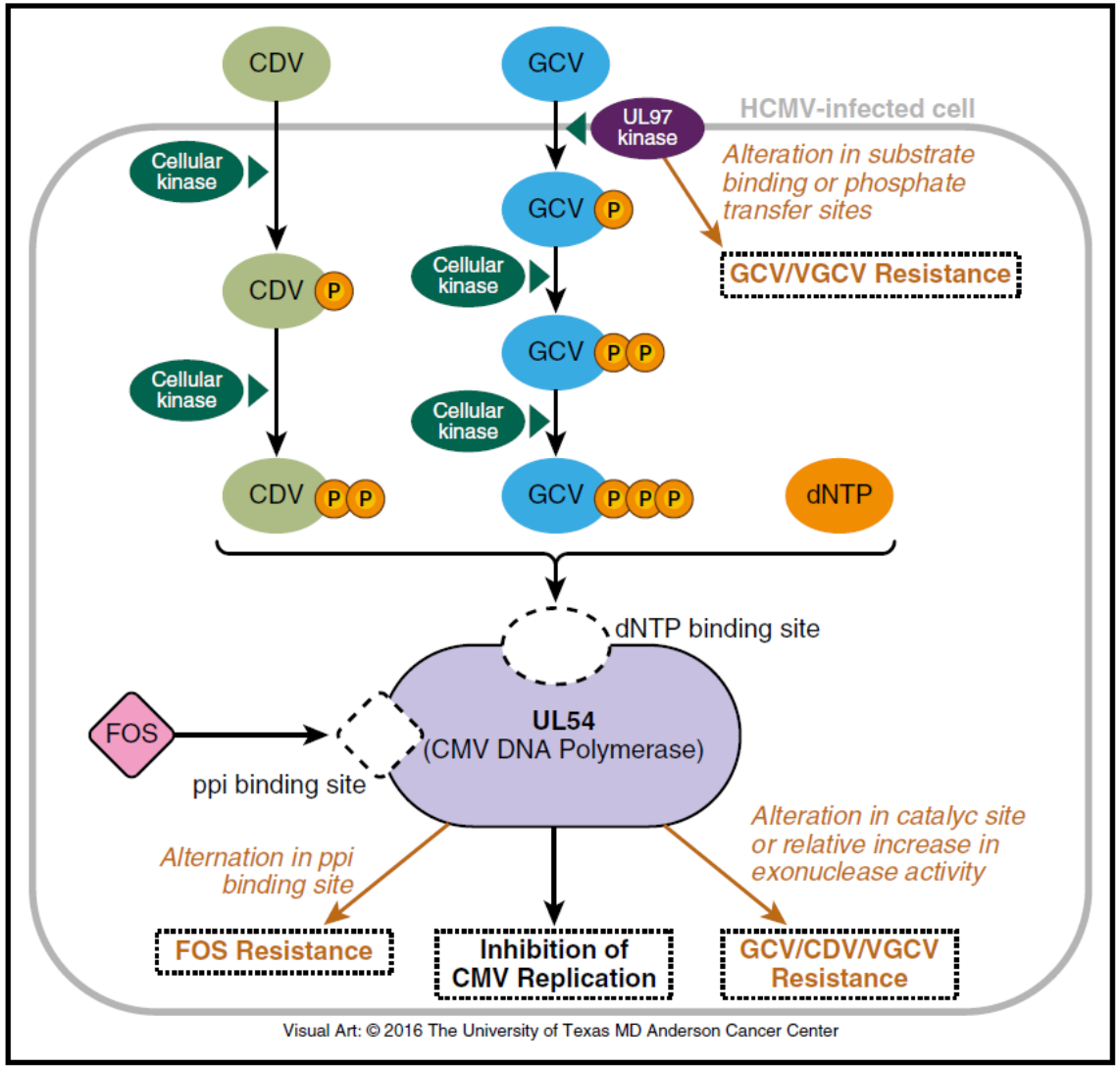
- If there is a viremia increase after 2w of treatment
- No consensus is available on when CMV antiviral resistance should be suspected and testing done
- If there is a relapse of CMV infection
- Never

CMV resistances.

Table 3. Cytomegalovirus Genes Associated With Novel or Commercially Available Antiviral Agents

CMV Gene	Role	Associated Drug Resistance
UL97	Kinase	Ganciclovir, valganciclovir, maribavir
UL54	Polymerase	Ganciclovir, valganciclovir, cidofovir, foscarnet, brincidofovir
UL27	Cell cycle regulation	Maribavir (low level)
UL51/UL56/UL89	Cleavage and packaging	Letermovir

- Mutation H520Q in pUL97: Ganciclovir resistance
- Mutation M844V and A987G in pUL54: Cidofovir and Foscarnet (Clinical implication?)
- Mutation A987Gin pUL54 : resistances to ganciclovir and cidofovir



El Chaer F. Blood. 2016; 128(23): 2624–2636

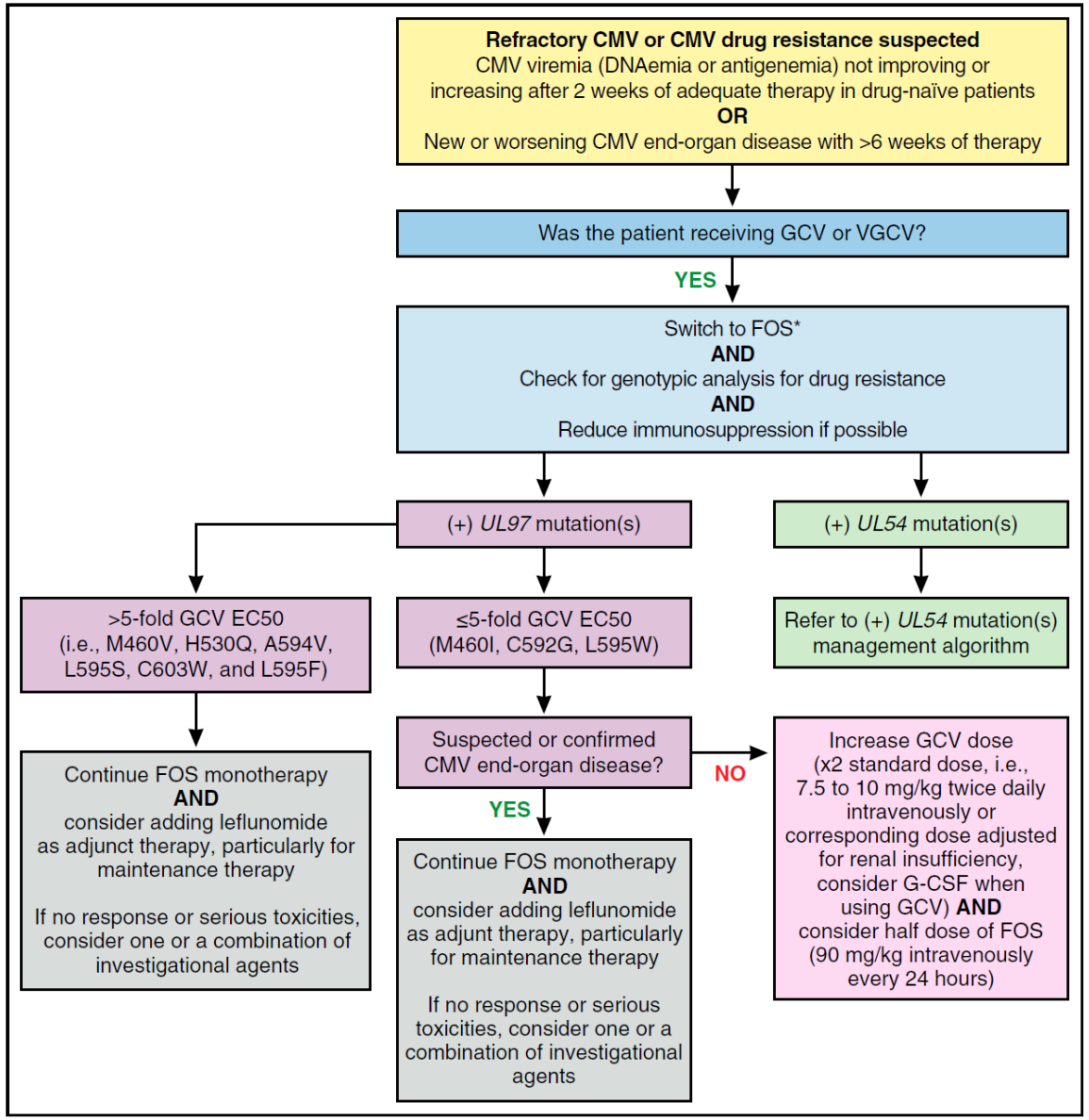


Figure 5. MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with *UL97* mutation(s). *While awaiting genotypic analysis results, maintaining GCV or VGCV and refraining from switching to FOS in low-risk patients (ie, HLA-identical HCT recipients without GVHD and/or without risk factors for CMV resistance) may be considered. EC50, concentration of a drug that gives half-maximal response; G-CSF, granulocyte colony-stimulating factor. Professional illustration by Patrick Lane, ScEYEnce Studios.

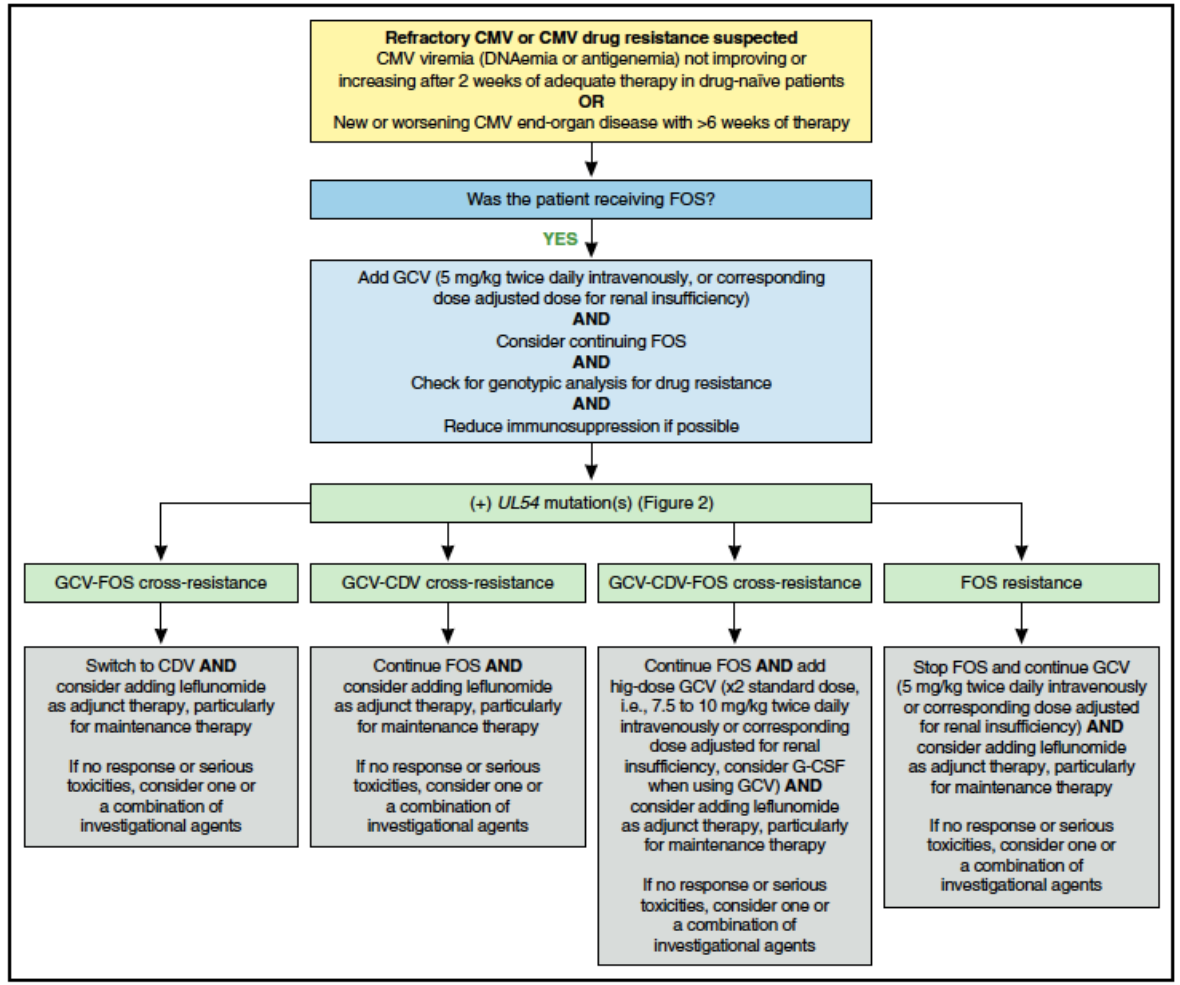


Figure 6. MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with *UL54* mutation(s). Professional illustration by Patrick Lane, ScEYEnce Studios.

El Chaer F. Blood. 2016; 128(23): 2624–2636

Treatment options

- **Maribavir**
  - competes with ATP for binding to pUL97. may not completely inhibit CMV replication, resulting in persistent low-level viremia
  - Phase 2: 68%of undetectable plasma CMV viral loads within 6 weeks; however, 68% AE during 25weeks and 25% recurrent CMV infection within 36weeks
  - Mutations T409M and H411Y in pUL97 resistance (ganciclovir could be used)

- **Brincidofovir**
  - Resistance to brincidofovir is expected to be similar to cidofovir after mutations in UL54
  - Less toxicity (GI more than cidofovir)
- **Letermovir**
  - it inhibits CMV DNA synthesis at a late step by targeting the pUL56 subunit of the terminase enzyme complex
  - in vitro letermovir resistance mutations in the codon range 231 to 369 of *UL56* have already been identified, suggesting a low genetic barrier to resistance
- **Cellular adoptive immunotherapy:**
  - restoring CMV-specific T-cell responses
  - cytotoxic T-lymphocyte (CTL) infusions : 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.

Blood. 2016; 128(23): 2624–2636/ Clinical Infectious Diseases 2019;68(8):1255–64/ Lancet Infect Dis. 2019 ;19(8):e260-e272

Is there any way to decrese CMV infection?

- Changing antiviral in each treatment
- Using letermovir as prophylaxis
- Administering antiviral as soon as possible
- There is no way

Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

Per Ljungman, Rafael de la Camara, Christine Robin, Roberto Crocchiolo, Hermann Einsele, Joshua A Hill, Petr Hubacek, David Navarro, Catherine Cordonnier, Katherine N Ward, on behalf of the 2017 European Conference on Infections in Leukaemia group*

	European Society of Clinical Microbiology and Infectious Diseases recommendation grading[4]	Study	Comment
Acidovir	CI	Prentice et al (1994)[92] Milano (2011)[93]	Less effective than valaciclovir
Valaciclovir	BI	Ljungman (2002)[94] Winston (2003)[95] Milano (2011)[93]	Used together with pre-emptive therapy
Ganciclovir	CI	Winston (1993)[96] Goodrich (1993)[97]	Used at engraftment
Valganciclovir	CIIh	Montesinos (2009)[98] Boeckh (2015)[99]	Cord blood HSCT used in Montesinos et al;[98] prophylaxis against late cytomegalovirus disease
Foscarnet	DIIu	Ordemann (2000)[100] Bregante (2000)[101]	NA
Letermovir	AI	Marty (2017)[102]	Only effective against cytomegalovirus

HSCT=haematopoietic stem cell transplantation. NA=not applicable.

Table: **Recommended drugs for antiviral prophylaxis after allogeneic HSCT**

Lancet Infect Dis. 2019 ;19(8):e260-e272.

Letermovir in CMV prophylaxis

- Pivotal study +100d: 122/ 325 patients (37.5%) vs. 103/170 (60.6%) clinically significant CMV (defined as CMV disease or CMV viremia leading to pre-emptive therapy). **CMV viremia** resulting in pre-emptive therapy occurred in 52 of 325 patients receiving **letermovir (16.0 percent**) and 68 of 170 patients receiving **placebo (40.0 percent).** [1]
- **All-cause mortality at week 24** following HCT was lower in Letermovir (**10.2 versus 15.9**), a difference that was statistically significant [1,2]
- All-cause mortality **at week 48 following HCT** was lower in letermovir recipients (**20.9 versus 25.5 percent**) [1,2]
- detection of CMV DNA in blood in letermovir prophylaxis may indicate abortive viral infection, rather than active viral replication[3]

1.- N Engl J Med. 2017;377(25):2433-44/ 2.- Clin Infect Dis. 2020;70(8):1525/3.-Am J Transplant. 2021;21(4):1622

Letermovir in CMV prophylaxis

- **EBMT 2022 (OS04-07):** Metanalysis (32 studies HSCT) CMV reactivation (CMVr), cs-CMVi, and CMVd:
  - were 19% vs 61%, 10% vs 58%, 1% vs 5% at day +100 (d100),
  - **and 27% vs 60%, 22% vs 64%, 2% vs 6% at D200**
  - letermovir was associated **with lower odds of all-cause mortality and non-relapse mortality at d200 post-HCT** without any significant heterogeneity.
  - Five studies reported recurrent and **resistant/refractory CMV infection** and five studies reported CMV-related hospitalization as an outcome with a trend toward **lower rates of the event in the letermovir arm** in comparison to the control arm.

220 participantes R+ HSCT that received LET 100 d randomized (14w) :

LET until 28w (~200 días) or PCB (100d of LET)

2,8% (LET) vs 18,9% (PCB), p <0,0005

Overall mortality: no differences

(w 14-28) : 2,1 % (LET) vs 1,4 % (PCB);

(w14-48): 8,3% (LET) vs 8,1% (PCB)

–

Refractory and Resistant Cytomegalovirus After Hematopoietic Cell Transplant in the Letermovir Primary Prophylaxis Era

Outcome	Primary Letermovir Prophylaxis: No (n = 414)	Primary Letermovir Prophylaxis: Yes (n = 123)	All Patients (n = 537)	*P* Value[a]
CS-CMVi, no. (%)	221 (53)	21 (17)	242 (45)	<.0001
Time from HCT to CS-CMVi, median (range), d	24 (1–1294)	15 (1–146)	23 (1–1294)	.16
CS-CMVi by day 100, no. (%)	218 (53)	19 (15)	237 (44)	<.0001
Late CS-CMVi (beyond day 100), no. (%)	3 (0.7)	2 (2)	5 (0.9)	.32
Peak CMV viral load, median (range), IU/mL	1485 (136–304 402)	756 (136–66 398)	1354 (136–304 402)	.047
Time from first detection of CMV in plasma to initiation of antiviral therapy, mean (range), d	16 (0–64)	22 (0–116)	17 (0–116)	.067
CMV end-organ disease, no. (%)	83 (20)	7 (6)	90 (17)	.0002
Gastrointestinal	13 (3)	0 (0)	13 (2)	.047
Lungs	51 (12)	4 (3)	55 (10)	.004
Retinitis	2 (0.5)	0 (0)	2 (0.4)	>.99
Bone marrow	25 (6)	1 (1)	26 (5)	.018
Other[b]	2 (0.5)	2 (2)	4 (1)	.23
R/R CMV, no. (%)	45 (11)	2 (2)	47 (9)	.001
Refractory	30 (7)	0 (0)	30 (6)	.002
Probable refractory	12 (3)	2 (2)	14 (3)	.75
Resistant	3 (1)	0 (0)	3 (1)	>.99
Time from HCT to R/R CMV, median (range), days	22 (1–44)	37 (15–59)	22 (1–59)	.48
All-cause mortality				
At day 100, no. (%)	51 (12)	9 (7)	60 (11)	.12
At week 24, no. (%)	81 (20)	19 (15)	100 (19)	.30
At week 48, no. (%)	129 (31)	35 (28)	164 (31)	.57
Time to all-cause mortality post-HCT, median (range), d	183 (1–1279)	179 (18–726)	181 (1–1279)	.85
CMV-related mortality, no. (%)	13 (3)	0 (0)	13 (2)	.047
Nonrelapse mortality				
At day 100, no. (%)	45 (11)	8 (7)	53 (10)	.15
At week 24, no. (%)	62 (15)	12 (10)	74 (14)	.14
At week 48, no. (%)	88 (21)	18 (15)	106 (20)	.11
Time to nonrelapse mortality post-HCT, median (range), days	174 (1–1279)	167 (18–565)	170 (1–1279)	.18

Abbreviations: CMV, cytomegalovirus; CS-CMVi, clinically significant cytomegalovirus infection; HCT, hematopoietic cell transplant; R/R, refractory or resistant.

[a]*P* values are from the test comparing patients with and without primary letermovir prophylaxis.

[b]Other sites of CMV end-organ disease include central nervous system and pericardium.

In conclusion, our cohort study showed that primary letermovir prophylaxis in allogeneic HCT recipients effectively prevents refractory or resistant CMV infections and decreases nonrelapse mortality at week 48. Our study also confirms the findings of prior studies with significant reductions in CS-CMVi, CMV disease, and peak CMV viral loads.

Cytomegalovirus in Haematological Tumours

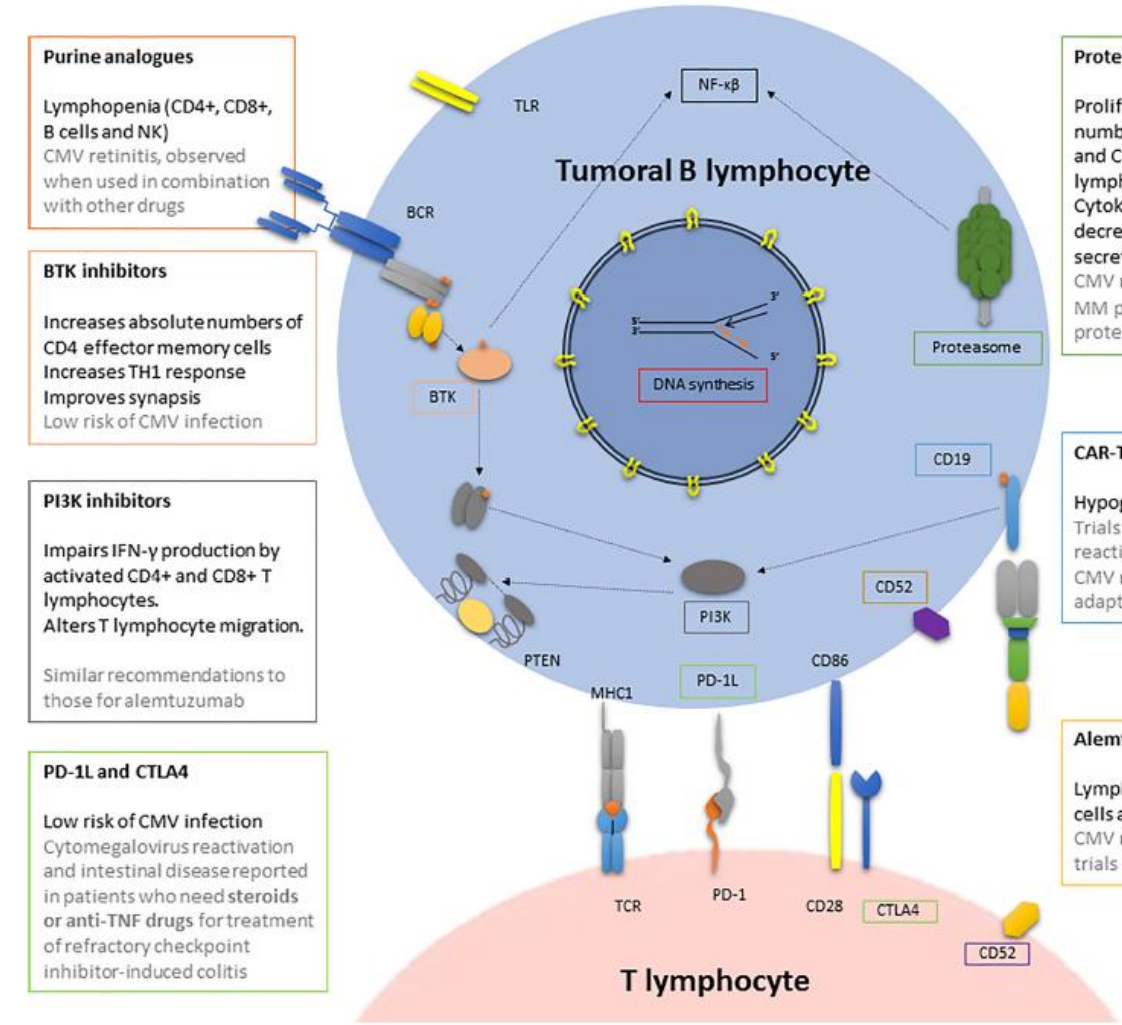


FIGURE 2 | CMV infection/reactivation in the context of antitumoral drugs used in haematological patients. BCR, B cell receptor; BTK, Bruton tyrosine kinase; CAR-T cells, chimeric antigen receptor T cell; CMV, cytomegalovirus; CTLA4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; NK, natural killer; PI3K, phosphatidyl inositol 3 kinase; PD, programmed death; PD-1L, programmed death-ligand 1; PTEN, phosphatase and tensin homologue; SCT, stem cell transplantation; TLR, toll-like receptor.

Take home messages

- CMV infection is frequent in alloTPH
- Some risk factors are related to CMV resistances
- Letermovir as prophylaxis decreases the incidence of resistant CMV

Personal Opinion