Refractory and Resistant CMV Infections in Hematopoietic Cell Transplant Recipients in the Letermovir Primary Prophylaxis Era

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Introduction

- CMV – Most common infection after allo-HCT with considerable morbidity and mortality
- Letermovir – Novel anti CMV agent, inhibitor of viral terminase complex
- Reduction in incidence of clinically significant CMV infection (CS-CMVi) with primary letermovir prophylaxis in phase 2 and phase 3 clinical trials [1]
- Refractory CMV infections
  - Worsening/lack of response of viremia or disease to antiviral agents [2]
  - Represents 19-29% of CMV infections in HCT recipients [3]
- Resistant CMV infections
  - Presence of a genetic mutation conferring antiviral resistance (e.g. UL97, UL54) [2]
  - Represents 1.7-14.5% of CMV infections in HCT recipients [3]
- Primary study objective – Explore the effect of primary letermovir prophylaxis on the occurrence of refractory or resistant CMV infections

Methods

- Design – Single center retrospective study of all consecutive CMV-seropositive allo-HCT recipients at MD Anderson Cancer Center from March 2016 through October 2018
- Patients divided into two groups, based on whether they received letermovir for primary CMV prophylaxis or not.
- Letermovir administered as 480 mg IV/PO daily (240 mg if with cyclosporine) from D+5 through D+100. All patients have at least weekly CMV PCR monitoring.
- Primary outcome - Development of refractory or resistant CMV infection after HCT
- Secondary outcomes
  - CS-CMVi
  - CMV end organ disease
  - CMV-related mortality
  - All cause mortality at D100, week 24, week 48
  - Non-relapse mortality at D100, week 24, week 48
  - Need for anti-CMV therapy and side effects

Results

Table 1 – Patient Characteristics

Characteristics	Primary Letermovir Prophylaxis No (n= 414) N (%)	Primary Letermovir Prophylaxis Yes (n= 123) N (%)	All patients (n = 537) N (%)
Age (years), median (range)	54 (6-78)	57 (18-93)	55 (6-93)
Gender, male	215 (52)	64 (52)	279 (52)
Underlying disease			
AML	187 (45)	52 (42)	239 (45)
ALL	59 (14)	16 (13)	75 (14)
MDS	57 (14)	14 (11)	71 (13)
MF	33 (8)	10 (8)	43 (8)
Others	78 (19)	31 (25)	109 (20)
Type of conditioning regimen			
Myeloablative/reduced-intensity	401 (97)	116 (94)	517 (96)
Non-myeloablative	13 (3)	7 (6)	20 (4)
Type of transplant			
MRD	128 (31)	37 (30)	165 (31)
MUD/MMUD	190 (46)	58 (47)	248 (46)
Haploidentical	74 (18)	24 (20)	98 (18)
Cord	22 (5)	4 (3)	26 (5)
Source of stem cell			
Marrow *	141 (34)	27 (22)	168 (31)
Peripheral *	251 (61)	92 (75)	343 (64)
Single cord	1 (0.2)	0 (0)	1 (0.2)
Double cord	21 (5)	4 (3)	25 (5)
Donor CMV seropositivity *	211/407 (52)	79/122 (65)	290/529 (55)
ATG *	134 (32)	19 (15)	153 (28)
Post-Cy *	158 (38)	78 (63)	236 (44)
Any GVHD	212 (51)	65 (53)	277 (52)
Skin GVHD *	136/212 (64)	31/65 (48)	167/277 (60)
Gastrointestinal GVHD	130/212 (61)	40/65 (62)	170/277 (61)
Liver GVHD *	9/212 (4)	7/65 (11)	16/277 (6)
Ocular GVHD	8/212 (4)	2/65 (3)	10/277 (4)

* Denotes a statistically significant difference between patients with and without primary letermovir prophylaxis ($p < 0.05$)

Table 2 – Clinical Outcomes by Primary Prophylaxis

Outcomes	Primary Letermovir Prophylaxis No (n= 414) N (%)	Primary Letermovir Prophylaxis Yes (n= 123) N (%)	All Patients (n = 537) N (%)	p-value
CS-CMVi	221 (53)	21 (17)	242 (45)	< .0001
CMV end organ disease	83 (20)	7 (6)	90 (17)	0.0002
Gastrointestinal	13 (3)	0 (0)	13 (2)	0.047
Lung	51 (12)	4 (3)	55 (10)	0.004
R/R CMV	45 (11)	2* (2)	47 (9)	0.001
Refractory	30 (7)	0 (0)	30 (6)	0.002
Probable refractory	12 (3)	2 (2)	14 (3)	0.75
Resistant	3 (1)	0 (0)	3 (1)	> .99
Mortality				
All-cause mortality at day 100	51 (12)	9 (7)	60 (11)	0.12
All-cause mortality at week 24	81 (20)	19 (15)	100 (19)	0.30
All-cause mortality at week 48	129 (31)	35 (28)	164 (31)	0.57
CMV-related mortality	13 (3)	0 (0)	13 (2)	0.047
Non-relapse mortality at day 100	45 (11)	8 (7)	53 (10)	0.15
Non-relapse mortality at week 24	62 (15)	12 (10)	74 (14)	0.14
Non-relapse mortality at week 48	88 (21)	18 (15)	106 (20)	0.11

* One patient was checked for letermovir resistance at UL56 and no mutations were identified

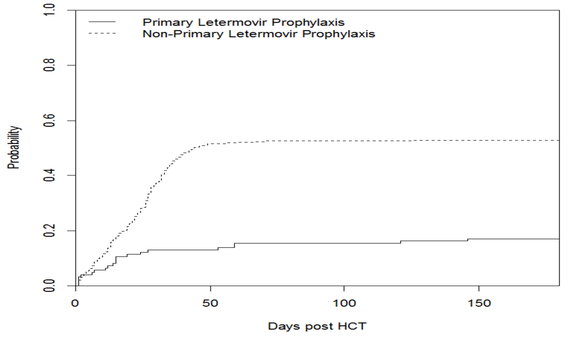
Table 3 – Primary Letermovir Prophylaxis as an Outcome Predictor

Outcomes	Adjusted HR	95% CI	p-value
CS-CMVi	0.26	0.16 – 0.41	< 0.0001
CMV end organ disease	0.23	0.10 – 0.52	< 0.001
Refractory or resistant CMV	0.15	0.04 – 0.58	0.006
Non-relapse mortality at 48 weeks	0.55	0.32 – 0.93	0.025

Table 4 – Outcomes of Patients with CS-CMVi

Outcomes	Primary Letermovir Prophylaxis No (n= 221) N (%)	Primary Letermovir Prophylaxis Yes (n= 21) N (%)	All Patients (n = 242) N (%)	p-value
Number of CS-CMVi episodes				0.23
One episode	201 (91)	21 (100)	222 (92)	
Two episodes	20 (9)	0 (0)	20 (8)	
Anti-CMV therapy				
Ganciclovir	100 (45)	7 (33)	107 (44)	0.29
Valganciclovir	106 (48)	11 (52)	117 (48)	0.70
Foscarnet	153 (69)	9 (43)	162 (67)	0.014
Major side effects during antiviral therapy	165 (75)	15 (71)	180 (74)	0.75
Myelosuppression	137 (62)	13 (62)	150 (62)	0.99
Nephrotoxicity	98 (44)	4 (19)	102 (42)	0.025
Hepatotoxicity	33 (15)	0 (0)	33 (14)	0.088

Figure 1 – Cumulative Incidence of CS-CMVi ($p < 0.0001$)



Supplementary materials can be accessed by scanning this QR code

Figure 2 – Kaplan-Meier Non-Relapse Mortality Curves ($p = 0.10$)

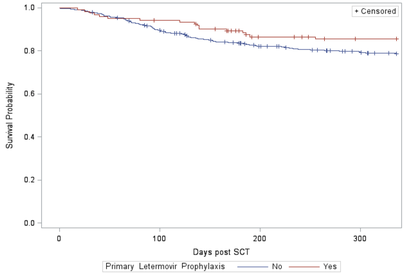
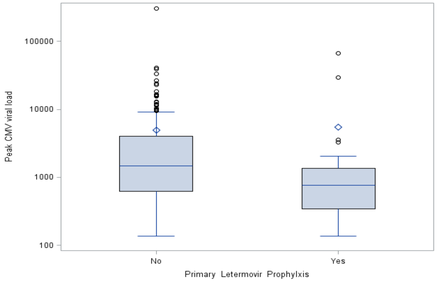


Figure 3 – Box Plots of Peak CMV Viral Load ($p = 0.047$)



Conclusion

- Primary letermovir prophylaxis in allogeneic HCT recipients is associated with a reduction in:
  - Refractory or resistant CMV
  - CS-CMVi
  - CMV end organ disease
  - CMV-related mortality
  - Non-relapse mortality at week 48
  - Peak CMV viral load
  - Need for foscarnet therapy and resultant nephrotoxicity

References

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2. Chemaly, R.F., *et al.* Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials. *Clin Infect Dis* **68**, 1420-1426 (2019).
3. Khawaja, F., Batista, M.V., El Haddad, L. & Chemaly, R.F. Resistant or refractory cytomegalovirus infections after hematopoietic cell transplantation: diagnosis and management. *Curr Opin Infect Dis* **32**, 565-574 (2019).