Journal of Microbiology, Immunology and Infection 55 (2022) 323—327

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Short Communication

Letermovir prophylaxis for cytomegalovirus reactivation in children who underwent hematopoietic stem cell transplantation: A single-institute experience in Taiwan

Chao-Neng Cheng [a], Sin-Syue Li [b], Yun-Hsuan Yeh [a], Ching-Fen Shen [a], Jiann-Shiuh Chen [a,*]

[a] *Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

Received 7 August 2021; received in revised form 24 November 2021; accepted 20 January 2022
Available online 23 February 2022

KEYWORDS
Children;
Cytomegalovirus;
Hematopoietic stem cell transplantation;
Letermovir;
Prophylaxis

Abstract From January 2019 to May 2021, 11 children underwent allogeneic stem cell transplantation at our institute. Four of them received letermovir for cytomegalovirus prophylaxis. Three children, none of whom received prophylaxis, experienced cytomegalovirus reactivation. Letermovir is a promising medication for use in cytomegalovirus prophylaxis in children. Further studies are warranted.

Introduction

Cytomegalovirus (CMV) infection is a severe complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Letermovir was approved for CMV prophylaxis in adult CMV-seropositive allo-HSCT patients on the basis of its favorable safety profile and substantial benefits to overall survival.[1—3] The letermovir treatment is the standard of care for CMV prophylaxis in CMV-seropositive adult patients undergoing unrelated or mismatched allo-HSCT in Taiwan.[4]

* Corresponding author. Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138, Sheng-Li Rd, Tainan, 70403, Taiwan. Fax: +886 6 2753083.
E-mail address: jian@mail.ncku.edu.tw (J.-S. Chen).

https://doi.org/10.1016/j.jmii.2022.01.002

However, insufficient data are available to justify proposing a recommendation for pediatric patients. Jaing et al. reported that the prevalence of CMV reactivation was high and occurred in 28.2% of pediatric CMV-seropositive allo-HSCT recipients.[5] The authors identified three independent risk factors for CMV infection. The strongest risk factor was a CMV-seronegative donor/seropositive recipient (D-/R+) serostatus, with an odds ratio (OR) of 11.07. The other risk factors were D+/R+ serostatus, grade 3–4 acute graft-versus-host disease (GvHD), unrelated or mismatched donors, with OR of 5.40, 6.02, and 4.24, respectively. In another study, patients with grade 2 acute GvHD receiving steroid therapy were also reported to be at high risk for CMV reactivation.[1] Only a few reports on the use of letermovir in children have been published.[6–10] Herein, we present our experience of off-label use of oral letermovir for primary CMV prophylaxis in pediatric allo-HSCT recipients.

Methods

We consecutively enrolled children who underwent allo-HSCT at our institute between January 2019 and May 2021. After letermovir became available for use in adult patients, we began offering off-label use of letermovir for CMV prophylaxis in children. We proposed a CMV risk prediction scale according to the results of Jaing's study.[5] We awarded two points for a D-/R + CMV serostatus because of the strongest risk factor. We awarded one point each for D+/R+ serostatus, an unrelated or mismatched donor, grade 3–4 acute GvHD, and grade 2 acute GvHD that led to the use of prednisolone (or its equivalent) at a dose of 1 mg/kg/day.[1] We categorized the patients into three groups according to their CMV risk: the low-risk group (score: 0–2), intermediate-risk group (score: 3), and high-risk group (score: 4). The patients' parents elected to have their children undergo letermovir treatment according to their own assessment of risk. After informed consent was obtained from the parents, we administered letermovir for primary CMV prophylaxis after allo-HSCT. The dosages of letermovir were 240 mg/day for the patients weighing less than 30 kg and 480 mg/kg for the patients weighing 30 kg or more. The patients who received concomitant cyclosporine (CsA) were administered half a dose of letermovir. We adjusted the patients' dosage of CsA to maintain a trough level of 100–150 ng/mL.

All the patients were routinely screened for CMV viral load twice weekly until 28 days posttransplant, weekly until 56 days posttransplant, biweekly until 100 days posttransplant, and at subsequent follow-ups during outpatient clinic visits. We defined CMV reactivation as a CMV viral load of more than 500 IU/mL.[4]

We reviewed the patients' baseline characteristics. Neutrophil engraftment was defined as the first day of three consecutive days when a patient's neutrophil count was more than 0.5×10^9/L, and platelet engraftment was defined as the first of three successive days when the platelet count was more than 20×10^9/L without platelet transfusion. We recorded the possible adverse events related to letermovir as defined by Marty et al. in their phase 3 clinical trial.[1]

We analyzed categorical variables with a chi-square test and continuous variables with a Mann–Whitney *U* test. We used the cumulative incidence and the Kaplan–Meier method with a log-rank test to analyze the time to CMV reactivation and the probability of being free of CMV. The study was self-funded.

Results

We included 11 children in the study. Four of the children received letermovir for CMV prophylaxis, and seven did not. All the patients in the letermovir group received concomitant CsA. Three patients received 240 mg of letermovir for 84 days, and one 9-year-old boy with a weight of 24 kg received 120 mg for 112 days. Two children with matched sibling donors received letermovir because their CMV serostatus was D-/R+ (CMV risk score 2). The transplant characteristics and adverse events of the letermovir and control groups are compared in Table 1.

The median numbers of infused CD34+ cells were similar between the groups (10.2×10^6/kg vs. 10.6×10^6/kg, $p > 0.999$), and no significant differences in time to neutrophil engraftment were observed between the groups. However, the median times to platelet engraftment were 17.5 days (range: 13–26) and 12 days (range: 10–60) in the letermovir group and control group, respectively ($p = 0.088$). Both groups had similar trough concentrations of CsA, but the median dosages of CsA were 1.5 mg/kg/day (range: 1–7.6) and 4.5 mg/kg/day (range: 2.4–9.4) in the letermovir group and control group, respectively ($p = 0.109$).

Five patients (45.5%) developed acute GvHD higher than grade 2, and four received steroid therapy. The median CMV risk scores were 2.5 (range: 2–3) and 3 points (range: 1–4) in the letermovir group and control group, respectively. Three patients (27.3%)—all of whom were in the control group—exhibited CMV reactivation (CMV viral load: 13,700; 2600; and 4,100, respectively). No breakthrough infection occurred in the letermovir group even after letermovir discontinuation.

Fig. 1 illustrates the cumulative incidence of CMV reactivation and the Kaplan–Meier curves of CMV-free probability in patients with different risk factors. The grade 2–4 acute GvHD (Fig. 1A) and steroid treatment (Fig. 1B) were significant risk factors for CMV reactivation ($p = 0.032$ and $p = 0.007$, respectively). CMV-free rates of 100%, 71%, and 50% were predicted for the low, intermediate, and high-risk groups, respectively, using the CMV risk prediction scale (Fig. 1E). The patients who received letermovir exhibited a lower cumulative incidence of CMV reactivation, but the difference was nonsignificant ($p = 0.149$; Fig. 1F).

To analyze adverse events, we recorded the incidence rates of 16 symptoms and signs for each group. The frequencies of adverse events were similar between the groups. The patients in the letermovir group experienced lower rates of vomiting within 30 days posttransplant and minor acute kidney injury after 30 days posttransplant ($p = 0.049$) than did those in the control group. One patient in the letermovir group developed liver function impairment within 30 days.

Table 1 Comparison (chi-square test) of transplant characteristics of and adverse events experienced by children in the letermovir prophylaxis group and control group.

Variables		Prophylaxis or not		*p*-value
		Letermovir group $n = 4$ (36%)	Control group $n = 7$ (64%)	
Age at diagnosis (years), median, range		16.1 (9.2～17.8)	13.9 (4.5～16.9)	$p = 0.315$
Male sex		3 (75%)	4 (57.1%)	$p = 0.572$
Cytomegalovirus (CMV) serostatus				$p = 0.308$
Donor positive/Recipient positive		0 (0%)	2 (28.6%)	
Donor positive/Recipient negative		0 (0%)	1 (14.3%)	
Donor negative/Recipient positive		4 (100%)	4 (57.1%)	
Underlying disease				$p = 0.856$
Acute lymphoid leukemia		2 (50%)	3 (42.9%)	
Acute Myeloid leukemia		1 (25%)	2 (28.6%)	
Severe aplastic anemia		1 (25%)	1 (14.3%)	
Hepatosplenic T-cell lymphoma		0 (0%)	1 (14.3%)	
HLA matching and donor type				$p = 0.116$
Matched sibling		2 (50%)	0 (0%)	
Matched unrelated [a]		1 (25%)	4 (57.1%)	
Mismatched unrelated[b]		1 (25%)	3 (42.9%)	
Conditioning regimen				$p = 0.347$
CY + TBI		1 (25%)	0 (0%)	
CY + TBI + ATG		1 (25%)	3 (42.9%)	
BuCy 2		1 (25%)	0 (0%)	
BuCy 2+ATG		0 (0%)	3 (42.9%)	
FluCy + ATG		1 (25%)	1 (14.3%)	
GvHD prophylaxis				$p = 0.326$
Cyclosporine + D1,3,6 Methotrexate[c]		3 (75%)	3 (42.9%)	
Cyclosporine + D1,3,6,11 Methotrexate		1 (25%)	4 (57.1%)	
CD34+ cell (x 106/kg), median, range		10.2 (4.3～13.6)	10.6 (5.8～14.4)	$p > 0.999$
Neutrophil engraftment (days), median, range		11.5 (10～12)	10 (9～14)	$p = 0.209$
Platelet engraftment (days), median, range		17.5 (13～26)	12 (10～60)	$p = 0.088$
Follow-up (days), median, range		325 (90～411)	492 (48～867)	$p = 0.527$
Steady Cyclosporine level (ng/mL), median, range		144.5 (103.3～180.9)	122.1 (98.4～202.7)	$p = 0.788$
Cyclosporine dose (mg/kg) at steady level, median, range		1.5 (1～7.6)	4.5 (2.4～9.4)	$p = 0.109$
Grade 2–4 GvHD		1 (25%)	4 (57.1%)	$p = 0.326$
GvHD with steroid therapy		0 (0%)	4 (57.1%)	$p = 0.071$
CMV risk score, median, range		2.5 (2～3)	3 (1～4)	$p = 0.234$
CMV reactivation		0 (0%)	3 (42.9%)	$p = 0.143$
Adverse event		Letermovir group $n = 4$	Control group $n = 7$	
Diarrhea	Before Day +30	2 (50%)	5 (71.4%)	$p = 0.498$
	After Day +30	1 (25%)	2 (28.6%)	$p = 0.903$
Constipation	Before Day +30	3 (75%)	4 (57.1%)	$p = 0.572$
	After Day +30	0 (0%)	3 (42.9%)	$p = 0.143$
Nausea	Before Day +30	3 (75%)	7 (100%)	$p = 0.186$
	After Day +30	2 (50%)	4 (57.1%)	$p = 0.827$
Vomiting	Before Day +30	2 (50%)	7 (100%)	$p = 0.049$*
	After Day +30	1 (25%)	4 (57.1%)	$p = 0.326$
Fever	Before Day +30	3 (75%)	6 (85.7%)	$p = 0.673$
	After Day +30	2 (50%)	5 (71.4%)	$p = 0.498$
Rash	Before Day +30	3 (75%)	6 (85.7%)	$p = 0.673$
	After Day +30	2 (50%)	6 (85.7%)	$p = 0.223$
Cough	Before Day +30	1 (25%)	3 (42.9%)	$p = 0.572$
	After Day +30	2 (50%)	4 (57.1%)	$p = 0.827$
Fatigue	Before Day +30	4 (100%)	7 (100%)	$p = 0.366$
	After Day +30	3 (75%)	6 (85.7%)	$p = 0.673$
Headache	Before Day +30	0 (0%)	2 (28.6%)	$p = 0.260$
	After Day +30	0 (%)	0 (0%)	$p = 0.366$

(*continued on next page*)

Table 1 (*continued*)

Variables		Prophylaxis or not		*p*-value
		Letermovir group $n = 4$ (36%)	Control group $n = 7$ (64%)	
Abdominal pain	Before Day +30	1 (25%)	6 (85.7%)	$p = 0.055$
	After Day +30	1 (25%)	4 (57.1%)	$p = 0.326$
Creatinine 33% elevation	Before Day +30	3 (75%)	6 (85.7%)	$p = 0.673$
	After Day +30	2 (50%)	7 (100%)	$p = 0.049$*
Peripheral edema	Before Day +30	0 (0%)	1 (14.3%)	$p = 0.450$
	After Day +30	0 (0%)	0 (0%)	$p = 0.366$
AST 5 × elevation	Before Day +30	1 (25%)	0 (0%)	$p = 0.186$
	After Day +30	0 (0%)	3 (42.9%)	$p = 0.143$
ALT 5 × elevation	Before Day +30	1 (25%)	0 (0%)	$p = 0.186$
	After Day +30	1 (25%)	4 (57.1%)	$p = 0.326$
Hypertension	Before Day +30	3 (75%)	7 (100%)	$p = 0.186$
	After Day +30	0 (0%)	1 (14.3%)	$p = 0.450$
Mucosal inflammation	Before Day +30	4 (100%)	7 (100%)	$p = 0.366$
	After Day +30	1 (25%)	4 (57.1%)	$p = 0.326$
Chronic GvHD		n = 3	n = 6	$p = 0.638$
No		1 (33.3%)	1 (16.7%)	
Limited		1 (33.3%)	4 (66.7%)	
Extensive		1 (33.3%)	1 (16.7%)	
Outcome				$p = 0.450$
Death from any cause		0 (0%)	1 (14.3%)	
Alive without disease		4 (100%)	6 (85.7%)	

[a] 10/10 matched in letermovir group ($n = 1$), two 10/10, one 8/8, and one 6/6 matched in the control group ($n = 4$).
[b] 9/10 matched in letermovir group ($n = 1$), one 7/8, and two 5/6 matched in the control group ($n = 3$).
[c] Day 11 methotrexate was omitted in case of severe mucositis.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ATG: antithymocyte globulin; BU: busulfan; CY: cyclophosphamide; Flu: fludarabine; GvHD: graft-versus-host disease; TBI: total-body irradiation.

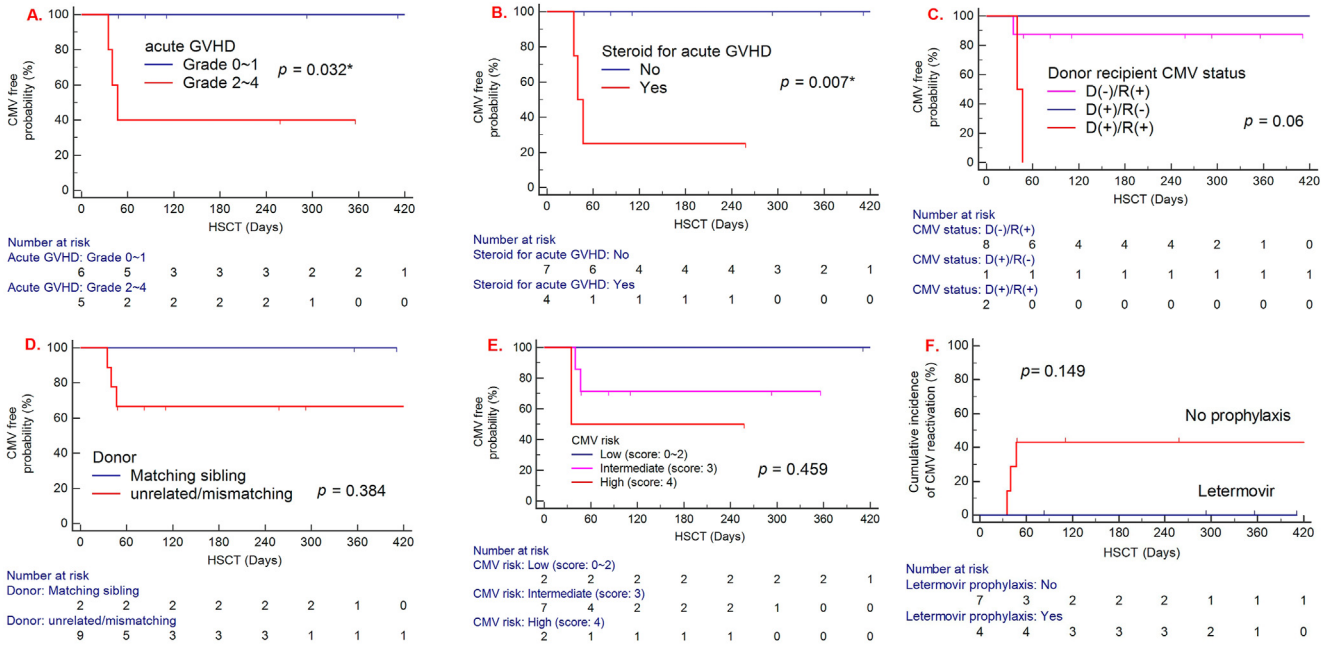

Figure 1. Kaplan–Meier curves of the time to cytomegalovirus reactivation and comparison with the log-rank test results for patients with different risk factors: (A) acute graft-versus-host disease (GvHD), (B) steroid treatment, (C) donor/recipient CMV serostatus, (D) donor type, and (E) CMV risk groups. (F) Cumulative incidence of CMV reactivation in patients with or without letermovir prophylaxis.

Discussion

In our study, four children received letermovir as primary prophylaxis. No breakthrough CMV reactivation occurred during the prophylactic period nor after discontinuation of letermovir. Only 10 cases of letermovir in pediatric patients have been reported (Table S1 in the Supplementary Appendix).[6—10] Our study revealed that letermovir as primary prophylaxis had promising efficacy and was tolerable in pediatric allo-HSCT. We found that CMV reactivation was associated with grade 2—4 acute GvHD and steroid therapy, consistent with other reports.[1,5] The proposed CMV risk prediction scale was used to predict CMV-free rates of 100%, 71%, and 50% for patients with scores of 0—2, 3, and 4, respectively. We suggest the use of letermovir in children with CMV risk scores of three points or more, especially children receiving steroid treatment for acute GvHD.

Marty et al. reported letermovir was not associated with myelotoxicity.[1,3] Our data indicated that neutrophil engraftment was comparable between the letermovir and control groups, but we identified a delay in platelet engraftment in the letermovir group ($p = 0.088$). CsA can interfere with the metabolism of letermovir and vice versa. In our study, patients in the letermovir group required less CsA than did those in the control group (1.5 mg/kg vs. 4.5 mg/kg, $p = 0.109$) to achieve the same concentrations. This might explain the occurrence of the minor acute kidney injury in the letermovir group after 30 days posttransplant ($p = 0.049$).

Regarding safety, the symptoms and signs exhibited by patients in both groups were similar, although patients in the letermovir group experienced less vomiting before 30 days posttransplant than did those in the control group. These symptoms may have been related to the patients' transplantation procedures and acute GvHD, rather than to letermovir. Strenger et al. observed rising liver parameters during letermovir treatment.[6] In our study, one patient experienced transient liver function impairment related to letermovir within 30 days posttransplant, which resolved spontaneously.

A major limitation of our study is the small sample size; achieving statistical significance in a study involving such few patients is challenging. Because no therapeutic drug monitoring for letermovir is available in Taiwan, we administered a dose of 120 mg/day to a patient who weighed less than 30 kg and was administered concomitant CsA, which was proposed by other studies.[6,8—10] No data on pharmacokinetics in children have been published to date; thus, dosages for young children must be selected with caution.

Our data suggest that letermovir is a promising option for use in CMV prophylaxis in pediatric allo-HSCT. However, we also determined that letermovir may delay platelet recovery, interfere with the metabolism of CsA, and cause transient liver function impairment. Further studies are required to determine the optimal dosage and explore the efficacy and safety of letermovir prophylaxis in pediatric allo-HSCT.

Declaration of competing interest

All authors declare no conflicts of interest.

References

1. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* 2017;**377**:2433—44.
2. Ljungman P, Schmitt M, Marty FM, Maertens J, Chemaly RF, Kartsonis NA, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis* 2020;**70**:1525—33.
3. Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. *Blood Adv* 2018;**2**:2159—75.
4. Jerry Teng CL, Wang PN, Chen YC, Ko BS. Cytomegalovirus management after allogeneic hematopoietic stem cell transplantation: a mini-review. *J Microbiol Immunol Infect* 2021;**54**:341—8.
5. Jaing TH, Chang TY, Chen SH, Wen YC, Yu TJ, Lee CF, et al. Factors associated with cytomegalovirus infection in children undergoing allogeneic hematopoietic stem-cell transplantation. *Medicine (Baltim)* 2019;**98**:e14172.
6. Strenger V, Sperl D, Kubesch K, Donnerer J, Schwinger W, Zach K, et al. Letermovir in paediatric HSCT recipients. *J Antimicrob Chemother* 2019;**74**:2820—1.
7. Kilgore JT, Becken B, Varga MG, Parikh S, Prasad V, Lugo D, et al. Use of letermovir for salvage therapy for resistant cytomegalovirus in a pediatric hematopoietic stem cell transplant recipient. *J Pediatric Infect Dis Soc* 2020;**9**:486—9.
8. Perez Marin M, Decosterd LA, Andre P, Buclin T, Mercier T, Murray K, et al. Compassionate use of letermovir in a 2-year-old immunocompromised child with resistant cytomegalovirus disease. *J Pediatric Infect Dis Soc* 2020;**9**:96—9.
9. Chiereghin A, Belotti T, Borgatti EC, Fraccascia N, Piccirilli G, Fois M, et al. Off-label use of letermovir as preemptive anti-cytomegalovirus therapy in a pediatric allogeneic peripheral blood stem cell transplant. *Infect Drug Resist* 2021;**14**:1185—90.
10. Styczynski J, Tridello G, Xhaard A, Medinger M, Mielke S, Taskinen M, et al. Use of letermovir in off-label indications: infectious diseases working party of European society of blood and marrow transplantation retrospective study. *Bone Marrow Transplant* 2021;**56**:1171—9.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.01.002.