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ORIGINAL RESEARCH

Efficacy and Safety of Letermovir for Cytomegalovirus Prophylaxis Following Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients

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Purpose: Cytomegalovirus (CMV) infection represents a severe complication following hematopoietic cell transplantation (HCT), resulting in high mortality. The prevention of CMV reactivation is crucial for enhancing patient prognosis post-HCT. Letermovir prophylaxis has effectively reduced the incidence of clinically significant CMV infection (csCMVi) in adult HCT recipients. However, clinical data in pediatric patients remain limited.

Patients and methods: We included 106 children who underwent HCT at our hospital between March 2019 and July 2024. The patients were grouped based on whether or not they received letermovir prophylaxis. By analyzing their general characteristics and laboratory findings, exploring the risk factors of csCMVi, and assessing the efficacy and safety of letermovir in pediatric patients.

Results: Among the 106 patients, all patients were at high risk for CMV reactivation. Forty-four received letermovir prophylaxis, while 62 did not. CsCMVi occurred in 45 patients, with a significantly lower incidence in the letermovir group compared to the control group (5 [11.3%] vs 40 [64.5%], $p < 0.001$). Umbilical cord blood (UCB) was used in 7 patients (15.9%) in the letermovir group and in 1 patient in the control group ($p < 0.05$). There was no statistically significant difference in all-cause mortality between the two groups. Grade II–IV GvHD and the use of letermovir were associated with csCMVi, with letermovir identified as the only independent preventive factor for csCMVi during the first 100 days post-HCT, especially in patients with 4–5 risk factors of csCMVi. In patients with aplastic anemia, the incidence of csCMVi was notably lower in those who received letermovir prophylaxis. No patients in the study withdrew from treatment due to adverse reactions.

Conclusion: Letermovir is both effective and safe for CMV prophylaxis in pediatric patients following HCT, especially in patients with more risk factors of csCMVi. Grade II–IV GvHD increases the risk of csCMVi, while letermovir prophylaxis reduces the risk.

Keywords: letermovir, pediatric, cytomegalovirus prophylaxis, hematopoietic cell transplant

Introduction

CMV infection is one of the major complications following hematopoietic cell transplantation (HCT),[1] often accompanied by graft-versus-host disease (GvHD), which can lead to graft failure and result in high morbidity and mortality rates.[2,3] Patients, particularly pediatric patients, are immunocompromised after HCT, significantly increasing their vulnerability to infections and other complications. This immunocompromised state arises due to the conditioning regimens used prior to transplantation, which often involve myeloablative therapies that deplete the patient's immune

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cells.[4] Consequently, meticulous monitoring and management are essential for these children to prevent infections, particularly during the early post-transplant stage when their immune system is in the process of recovery.[5]

Risk factors for clinically significant CMV infection (csCMVi) after HCT are pre-transplant CMV seropositivity,[6] the type of transplantation[7] (such as haploidentical or umbilical cord blood), HLA-mismatched unrelated donor (mMUD) and the occurrence of acute GvHD.[8] In recent years, clinicians have implemented a preemptive approach to prevent CMV-related diseases upon the detection of CMV in blood through various methodologies.[9] The preemptive therapy has successfully reduced the incidence of csCMVi and other CMV-related diseases.[10] However, early CMV reactivation remains correlates with unfavorable prognostic outcomes. Evidence supported the use of valganciclovir for prophylaxis, yet it poses a risk of myelosuppression, making its application challenging.[11] Consequently, there is an urgent need to identify an effective and safe agent for CMV prophylaxis following HCT.[12]

Unlike ganciclovir or foscarnet, letermovir specifically targets the viral terminase complex of CMV, effectively eliminating the virus while reducing marrow suppression.[13] Letermovir was approved by the US Food and Drug Administration and by the European Medicines Agency for prophylaxis of csCMVi in patients posttransplant in 2017[13] and 2018,[14] respectively. Several retrospective and prospective studies have shown that letermovir significantly decreased both CMV infection rates and overall mortality, including non-relapse mortality.[2,12,15–17] However there is limited evidence on the efficacy and safety of letermovir for CMV prophylaxis in children following HCT.[18,19] To address this gap, we conducted a retrospective analysis comparing the clinical characteristics of pediatric patients who received letermovir for CMV prophylaxis with those who did not, seeking to provide additional insights into the safety and efficacy of letermovir in this specific population.

Method

Study Population

A total of 106 pediatric patients who underwent allo-HSCT from related or unrelated donors at the Department of Pediatric Hematology and Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, between May 2019 and July 2024 were enrolled in this study. Inclusion criteria included (1) patients under 18 years of age (2) Available follow-up data for more than 100 days or until death. Patients were excluded if they had CMV disease or CMV loads ≥400 copies/mL in plasma before HCT or if their medical records were incomplete. Patients at high risk for CMV reactivation were identified by meeting one or more criteria, including having a related donor with at least one mismatch in any of the three specified HLA gene loci (HLA-A, B, or DR); an unrelated donor with at least one mismatch in any of the four HLA gene loci (HLA-A, B, C, and DRB1); a haploidentical donor; the utilization of umbilical cord blood as the stem-cell source; the administration of ex vivo T cell-depleted grafts; the use of Pt-cy or the occurrence of graft-versus-host disease (GVHD) of grade 2 or higher.[13]

The requirement for informed consent was waived because of the retrospective nature of this study. The study was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology. We ensured that the data was anonymized and maintained with confidentiality. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki. Study data on patients, diagnosis, examination, and treatment were extracted from the electronic hospital record system.

CMV Management

Quantitative polymerase chain reaction (qPCR) was employed to assess CMV-DNA concentrations in the plasma of all patients. Measurements were performed biweekly until day 60 and then at least once a week until day 168 (24 weeks). Patients classified as high-risk for CMV infection were monitored for longer periods and at more frequent intervals, depending on their clinical condition.

Oral letermovir (Merck Sharp & Dohme B.V.) prophylaxis once daily was started from day 5 after allo-HSCT to day 100, and patients transplanted after December 2022 received primary letermovir prophylaxis within 30 days after HCT. Dose was calculated based on weight and varied from 20mg/d to 480mg/d according to the literature.[20] Dose adjustments were made in the presence of concomitant cyclosporine due to pharmacological interactions. Additionally, all patients

received oral acyclovir (200 mg twice daily) from day 1 post-transplant to prevent herpesvirus infections. Preemptive therapy with ganciclovir or a phosphonate was initiated when CMV DNA levels exceeded 400 copies/mL, and was discontinued after two consecutive negative CMV-DNA results.

Definitions of CMV Infection

The diagnosis of cytomegalovirus (CMV) disease is based on clinical symptoms of specific diseases and the detection of CMV in diseased tissues through virus culture, immunohistochemistry, or DNA hybridization techniques. CMV viremia is defined as the detection of the virus in plasma, serum, or whole blood.[21,22] Meanwhile, csCMVi was defined as initiating anti-CMV preemptive therapy or diagnosing CMV end-organ disease.

Statistical Analysis

SPSS 26.0 software (IBM) was used for statistical analysis. GraphPad Prism 8.0 (GraphPad Software) was used to prepare the figures. Continuous variables are expressed as the means ± standard deviations (SDs), whereas categorical variables are described as counts and percentages. Pearson's chi-square test or Fisher's exact test and two-tailed t tests were used to analyze categorical and continuous variables, respectively. Cumulative incidence curves were constructed within a competing risks framework, where death was treated as a competing event, to estimate the cumulative incidences of csCMVi. These incidences were subsequently compared using Gray's test. Statistical significance was set at $P < 0.05$.

Result

Study Population

A total of 106 hematological pediatric patients underwent HSCT were enrolled between March 2019 and July 2024 (Figure 1). Forty-four received letermovir prophylaxis during the first 100 days posttransplant and 62 did not. Patient characteristics were listed in Table 1. The median age at HCT was 7.3 ± 3.7 years. Forty-seven (44.3%) patients received HCT for malignant diseases. The median day of starting letermovir was 5 days (range, 3–29) and duration of letermovir administration was 95 days (range, 71–97). The graft source of 98 pediatric patients were peripheral blood (PB) or PB plus bone marrow (BM), and 8 patients were umbilical cord blood (UCB). Using UCB is one of the risk factors of csCMVi, and the proportion in letermovir group was much higher than that in control group (7 [15.9%] vs 1 [1.6%], p = 0.018), which emphasized the important role of letermovir in reducing the incidence of csCMVi. Based on the risk factors of CMV reactivation mentioned before, we calculated the number of risk factors of every patient. The proportion of risk factors for

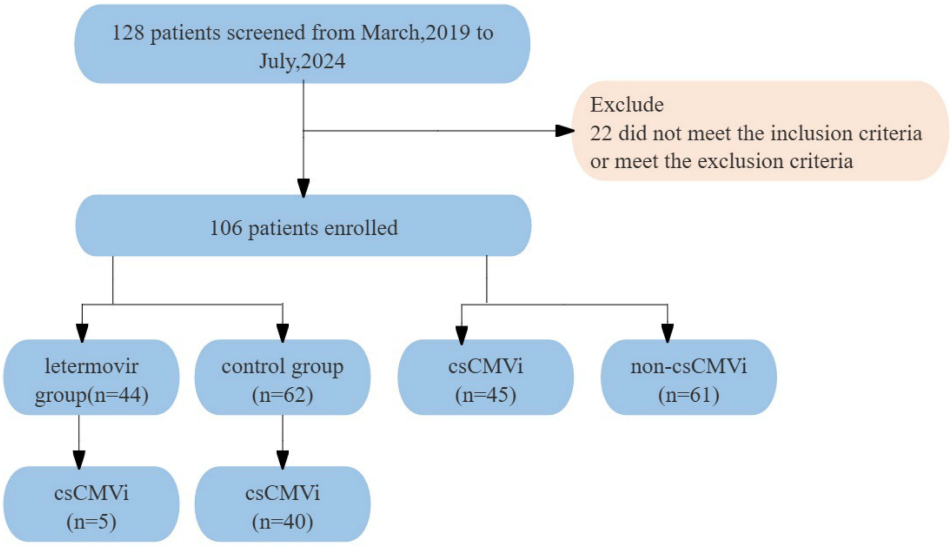

Figure 1 Patients flow chart.

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Table 1 Patients Characteristics

Variables	Control (n=62)	Letermovir (n=44)	*P*
Age, x±SD	7.31±3.54	7.11±3.86	0.774
Gender, n(%)			0.206
Male	40 (64.5)	23 (52.3)	
Female	22 (35.5)	21 (47.7)	
Diagnosis, n(%)			0.319
Malignant	30 (48.4)	17 (38.6)	
Non-malignant	32 (51.6)	27 (61.4)	
Stem cell source, n(%)			0.018*
PB/PB+BM	61 (98.4)	37 (84.1)	
UCB	1 (1.6)	7 (15.9)	
CMV-status recipient, n (%)			
Positive	62(100)	40(90.9)	0.057
Negative	0	4(9.1)	
Donor, n(%)			0.006*
HID	49(79.0)	21(47.7)	0.001*
MSD	2(3.2)	3(6.8)	0.693
MUD	8(12.9)	12(27.3)	0.062
mMud	3(4.8)	8(18.2)	0.058
Use of ATG, n(%)	61 (98.4)	42 (95.5)	0.762
Use of Pt-cy, n(%)	61 (98.4)	44 (100)	1.000
Grade II-IV aGvHD, n (%)			0.117
Yes	18 (29.0)	7 (15.9)	
No	44 (71.0)	37 (84.1)	
Risk factors number for csCMVi, n (%)			0.861
2~3	47 (14.5)	34 (31.8)	
4~5	15 (61.3)	10 (45.5)	
Total OS, n (%)	52 (83.9)	42 (95.5)	0.117
OS with 2~3 risk factors, n (%)	43(91.5)	32(94.1)	0.987
OS with 4~5 risk factors, n (%)	9(60.0)	10(100)	0.022*
Total csCMVi, n(%)			<0.001*
Yes	43 (69.4)	8 (18.2)	
No	19 (30.6)	36 (81.8)	
csCMVi during +100d, yes n(%)	40(64.5)	5(11.3)	<0.001*
csCMVi after +100d, yes n(%)	9(14.5)	4(9.1)	0.401
CMV disease, n(%)			0.020*
Yes	8 (12.9)	0 (0.0)	
No	54 (87.1)	44 (100.0)	
Granulocyte engraftment (days), M(range)	12(9–18)	12(9–28)	0.442
Platelet engraftment (days), M(range)	13(8–50)	12(9–111)	0.474
Maximum value of CMV replication (copies IU/mL), M(range)	3400(442–871,000)	810(441–6820)	0.057
Time to occur csCMVi(days), M(range)	32(18–281)	64(7–209)	0.153
During time of csCMVi(days), M(range)	11(1–65)	1(1–8)	0.001*
Frequency of csCMVi(times), M(range)	1(0–6)	0(0–3)	NA

Abbreviations: PB, Peripheral blood; BM, Bone marrow; UCB, Umbilical cord blood; HID, Haploidentical donor; MRD, Matched related donor; MUD, Matched unrelated donor; mMud, Mismatched unrelated donor; GvHD, graft-versus-host disease; csCMVi, clinically significant CMV infection; OS, overall survival; M, Median; *P<0.05; NA, Not Applicable.

CMV reactivation had no difference between letermovir group and control group (Table 1, $p > 0.05$). Our analysis revealed no significant difference in the incidence of grade II–IV aGvHD between letermovir and control group ($p > 0.05$). The administration of letermovir did not prolong the time to granulocyte and platelet engraftment and no discontinuations occurred due to severe toxicity, indicating that letermovir is safe and does not exacerbate bone marrow toxicity.

Patient Characteristics in AA

We showed baseline characteristics of patients with AA in Table 2. A total of 43 patients was analyzed. All patients received high-dose ALG or ATG as conditioning therapy, 29 of whom received pt-cy additionally, and the difference of conditioning therapy between the two groups was not statistically significant ($p > 0.05$). There was only one (6.3%) patient experienced csCMVi in letermovir group, which was significantly less than that in the control group (18, 66.7%; $p < 0.001$). The maximum CMV replication loads in letermovir group was 441 copies/mL, which subsequently turned negative, indicating the efficacy of letermovir prophylaxis in patients with AA. Letermovir did not prolong the time to granulocyte and platelet engraftment in pediatric patients with AA, emphasizing that letermovir can avoid bone marrow toxicity again.

Overall Survival and Cumulative Incidence of csCMVi

We compared the CMV absolute copies between letermovir and control group, found that CMV median loads were much higher in control group than that in letermovir group (Figure 2). The median follow-up period of patients were 1135 days and 333 days in control and letermovir group. 10(16.1%) and 2(4.5%) patients died in control group and letermovir group, respectively, and the overall survival (OS) rate was 83.9% and 95.5% ($p = 0.15$; Figure 3A). Notably, letermovir improved OS in patients presenting with 4 to 5 risk factors for CMV infection (Table 1, Figure 3B), suggesting a greater

Table 2 Patients Characteristics in AA

Variables	Control (n=27)	Letermovir (n=16)	P value
Age, x±SD	7.83±3.37	7.38±3.12	0.666
Gender, n(%)			0.044*
Male	17 (63.0)	5 (31.3)	
Female	10 (37.0)	11 (68.7)	
AA, n(%)			0.667
NSAA	1 (3.7)	2 (12.5)	0.635
SAA	6 (22.2)	4 (25.0)	1.000
VSAA	20 (74.1)	10 (62.5)	0.649
Use of ATG, n(%)	27 (100)	16 (100)	1.000
Use of pt-cy, n(%)	27 (100)	16 (100)	1.000
Donor, n(%)			0.529
Non-MSD	25 (92.6)	13 (93.2)	
MSD	2 (7.4)	3 (18.8)	
Grade II-IV aGVHD, n (%)			0.869
Yes	7 (25.9)	3 (18.8)	
No	20 (74.1)	13 (82.2)	
Granulocyte engraftment(days), x±SD	12.6±1.7	11.9±1.2	0.101
Platelet engraftment(days), M(range)	11 (8–31)	12 (9–13)	0.550
Time to occur CMV viremia(days), M(range)	35.5 (24–64)	117	NA
Total csCMVi, n (%)			<0.001*
Yes	18 (66.7)	1 (6.3)	
No	9 (33.3)	15 (81.8)	
csCMVi during +100d, yes n(%)	18(66.7)	0(0.0)	<0.001*
csCMVi after +100d, yes n(%)	1(3.7)	1(6.3)	1.000
CMV disease, n(%)			0.522
Yes	2 (7.4)	0 (0.0)	
No	25 (92.6)	16 (100.0)	
Maximum value of CMV replication (copies IU/mL), M(range)	2760 (538–13,400)	441	NA
Frequency of csCMVi(times), M(range)			
During time of CMV viremia(days), x±SD	12.2±2.5	1	NA

Abbreviations: NA, Not Applicable; M(range), Median(range); * P<0.05.

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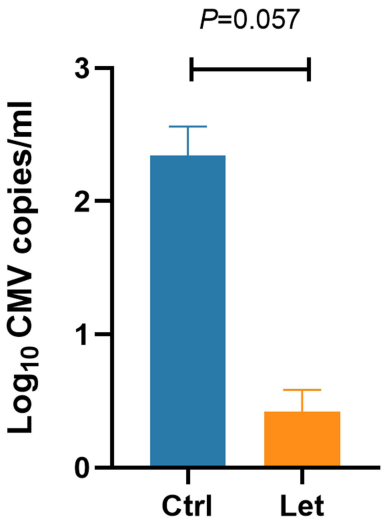

Figure 2 The highest CMV-DNA loads in the letermovir and control group.

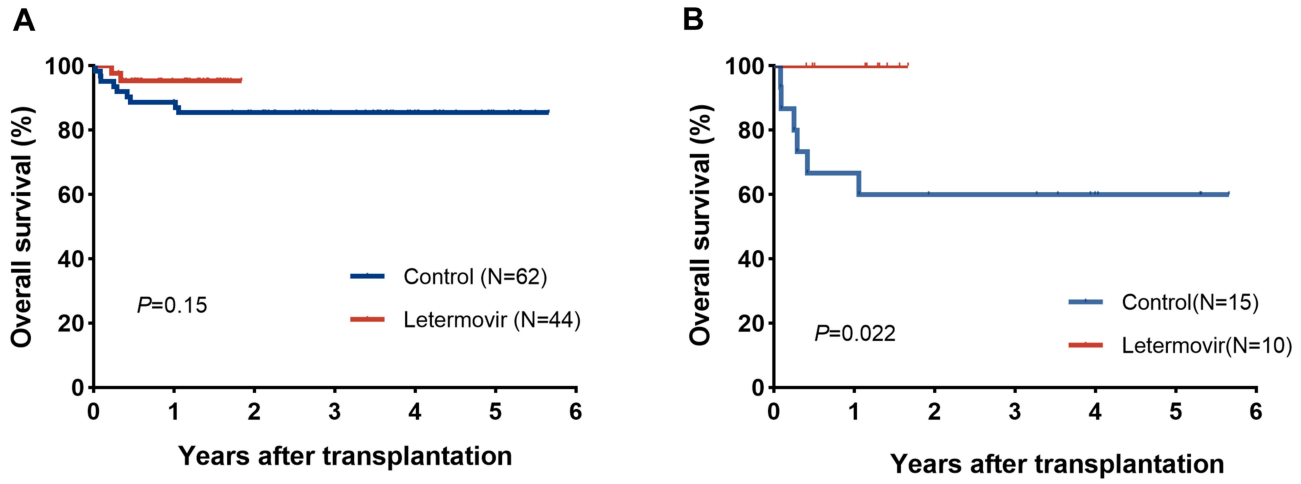

Figure 3 Overall survival after HCT between the two groups. **(A)** Kaplan–Meier plot shows OS for the letermovir group (red solid line) and control group (blue solid line; *p*=0.15). (**B**) OS of patients with 4–5 risk factors in the letermovir group and the control group(*p*=0.022).

benefit for patients with a higher number of risk factors. In terms of infection-related mortality, 4 of 10 and 1 of 2 children succumbed to infection in control group and letermovir group, respectively. Additionally, 5 (11.3%) children in the letermovir group and 40 (64.5%) children in the control group experienced csCMVi during day 100 of posttransplant ($p < 0.001$, Figure 4).

Risk Factors for csCMVi

Overall, 11.3% (7/62) and 4.5% (2/44) of the children died within the 24-week in the control group and letermovir group, respectively. One patient was CMV-related death in control group and 0 patient in letermovir group. The non-CMV-related causes of death were TA-TMA and severe acute hemolytic anemia in letermovir group and were co-infections (n = 2), relapsed hematological diseases (n = 2) and severe intestinal GVHD in control group.

Preliminary data suggested that 50% to 70% of CMV infections following HSCT arised within the initial 100 days after graft infusion, and late-onset infections are strongly associated with early-onset cases.[23] Consequently, we examined the risk factors for csCMVi specifically during 100 days after HSCT. Until day 100 post-transplant, 45 pediatric patients developed csCMVi and the incidence of csCMVi was 42.5% (45/106), which occurred in 11.1% (5/44) of the patients in

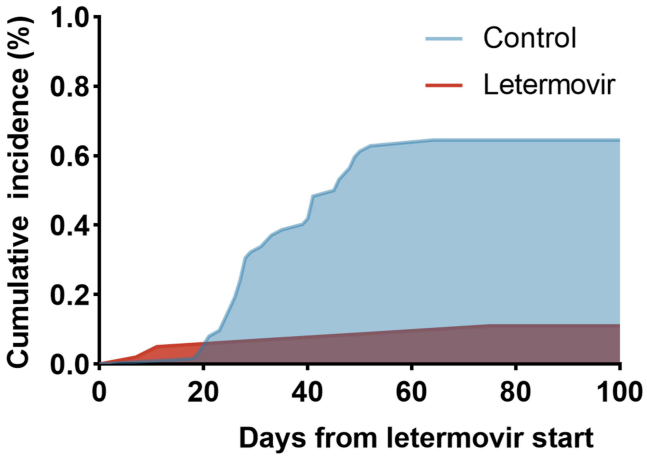

Figure 4 Cumulative incidence of csCMVi during 100 days after HCT. Letermovir group vs control group (11.3% vs 64.5%). Kaplan–Meier plot shows CI for the letermovir group (blue line) and control group (red line; $p<0.05$).

letermovir prophylaxis group and 64.5% (40/62) in control group ($p < 0.05$). Children with grade II–IV aGvHD had a higher incidence of csCMV viremia than those without, which was 60.0% (15/25) and 37.0% (30/81), respectively ($p < 0.05$). Univariate cox-regression analysis indicated that using letermovir prophylaxis and grade II–IV aGvHD were the independent variable related to csCMVi until day 100 after HCT (Table 3). According to the multivariate cox-regression

Table 3 Univariate Cox-Regression Analysis of csCMVi During 100 days After HSCT

Variables	csCMVi (n=45)	Non-csCMVi (n=61)	Univariate COX Regression		
			HR	95% CI	P
Age, x±SD	7.1±0.5	7.4±0.5	0.971	0.896–1.052	0.472
Gender, n(%)			1.141	0.631–2.062	0.662
Male	26 (41.3)	37 (58.7)			
Female	19 (44.2)	24 (55.8)			
Diagnosis, n(%)					0.530
AA	18(41.9)	25(50.1)	1.117	0.615–2.028	0.716
Malignant	21 (44.7)	26 (55.3)	0.829	0.461–1.489	0.530
Other non-malignant	6(41.9)	10(50.1)	1.172	0.496–2.770	0.717
Stem cell source, n(%)			0.436	0.106–1.801	0.251
PB/PB+BM	43 (43.9)	55 (56.1)			
UCB	2 (25.0)	6 (75.0)			
Donor, n(%)					0.332
HID	34 (48.6)	36 (51.4)	0.538	0.272–1.063	0.074
MSD	1 (20.0)	4 (80.0)	2.775	0.379–20.000	0.316
MUD	6 (30.0)	14 (70.0)	1.683	0.712–3.977	0.235
Mmud	4 (36.4)	7 (63.6)	1.274	0.456–3.561	0.644
Neutrophil engraftment, M(range)	12 (9–28)	12 (9–27)	0.930	0.826–1.046	0.224
Platelet engraftment, M(range)	12 (8–50)	13 (9–111)	0.989	0.957–1.023	0.527
CMV-status recipient, n (%)			0.691	0.256–1.861	0.464
Positive	44 (43.1)	58 (56.9)			
Negative	1(25.0)	3(75.0)			
Letermovir, n(%)			0.119	0.047–0.304	<0.001*
No	40 (64.5)	22 (35.5)			
Yes	5 (11.1)	39 (88.9)			
Grade II-IV aGvHD, n(%)			1.92	1.031–3.578	0.040*
No	30 (37.0)	51 (63.0)			
Yes	15 (60.0)	10 (40.0)			

Abbreviations: NA, Not Applicable; * P<0.05; M(range), Median(range).

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Table 4 Multivariate Cox Regression of csCMVi During 100 days After HSCT

Variables	CMV Positive (n=45)	CMV Negative (n=61)	Multivariate Cox Regression		
			HR	95% CI	P
Letermovir, n(%)			0.074	0.025–0.217	<0.001*
No	40 (88.9)	22 (36.1)			
Yes	5 (11.1)	39 (63.9)			
Grade II-IV aGVHD, n (%)			2.122	0.723–6.221	0.171
No	30 (66.7)	51 (83.6)			
Yes	15 (33.3)	10 (16.4)			

Notes: *P<0.05.

analysis, letermovir as CMV prophylaxis was the only independent variable associated with preventive factor of csCMV viremia (Table 4). Unfortunately, the use of letermovir had no effect on the frequency of csCMVi (Table S1, Table S2). We analyzed the protective effect of letermovir in patients with varying numbers of risk factors, and the risk factors for CMV reactivation in each patient were presented in Table S3. Our findings indicated that as the number of high-risk factors increases, the HR value decreases, suggesting a stronger protective effect of letermovir against csCMVi (Figure 5).

Discussion

In this study, we retrospectively assessed the efficacy and safety of letermovir for CMV prophylaxis in children undergoing HCT at a single center. To the best of our knowledge, this represents the largest cohort of pediatric HCT patients in China receiving letermovir prophylaxis. Our findings demonstrated that letermovir significantly reduces the incidence of csCMVi. Grade II–IV GvHD was identified as a high-risk factor for csCMVi, while letermovir emerged as the only independent protective factor against csCMVi, and the value increased with the number of high-risk factors increases. This study provides strong evidence that letermovir effectively prevents early-stage CMV infection in pediatric patients post-transplant, based on data from the large cohort.

Letermovir represents an important innovation in CMV prophylaxis following HCT. Several studies have shown that letermovir reduced the incidence of csCMVi in adult patients[16,17] and its use as CMV prophylaxis has been included in clinical guidelines.[13,14] However, published data on the efficiency and safety of letermovir prophylaxis in pediatric patients remain limited and optimal dosing for this population has not yet been fully established. The recommended dosing, based on a Phase II clinical trial,[20] is tailored to factors such as age, weight, and concomitant use of cyclosporine. One study reported that letermovir may cause side effects such as leukopenia, neutropenia, nauseated or vomiting.[24] In our study, all patients tolerated letermovir well, and no patients required discontinuation of the drug due to adverse reactions, confirming that the dosage used in our cohort aligns with a favorable toxicity profile.

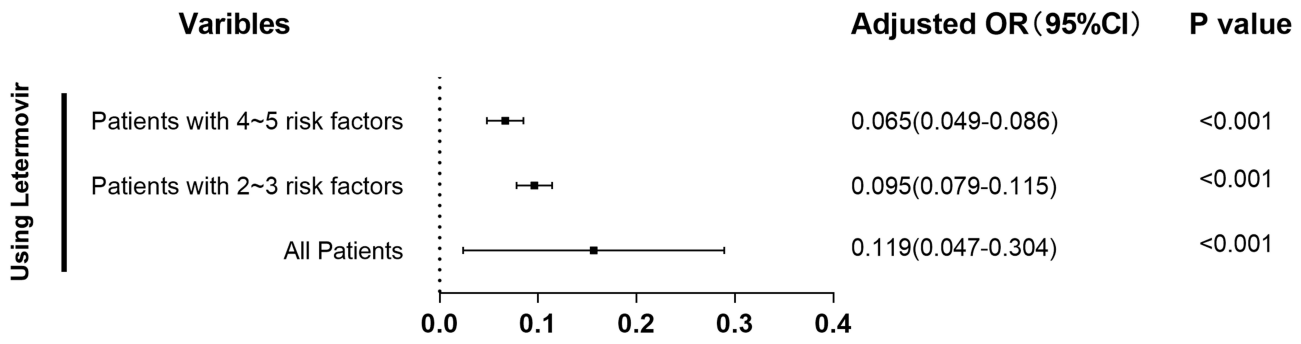

Figure 5 Forest plot of the protective effect of letermovir. Univariate cox-regression analysis the protective value of letermovir against csCMVi in patients with different high risk factors.

Previous studies have shown that letermovir is associated with a reduced incidence of CMV infection in pediatric patients,[19,25,26] consistent with the data presented in our study. Five patients experienced breakthrough CMV infection during the prophylactic period. Compared to the control group, the letermovir group demonstrated lower transient viral load and milder symptoms, indicating the potential of letermovir to reduce the reactivation of CMV. Furthermore, we found that letermovir had no effect on the all-cause mortality of patients after transplantation, which is consistent with the findings of Pang et al,[27] contradicts the results of a Phase III clinical trial.[13] This discrepancy may be attributed to the relatively small sample size in our study. Although letermovir is approved for CMV prophylaxis, current clinical data are insufficient to support its use as a treatment rather than solely as a preventive measure, particularly given its low resistance threshold.[28] Further research is necessary to optimize its therapeutic benefits.

In our study, aplastic anemia (AA) comprised nearly half of all patients. Children with AA are at higher risk for CMV infection after HCT due to the unique conditioning regimen, which includes post-transplant cyclophosphamide (Pt-Cy) and high-dose antithymocyte globulin (ATG). These treatments delay immune reconstitution, thereby increasing the risk of CMV reactivation.[29] Actually, letermovir significantly reduced the incidence of csCMVi, consistent with previous studies demonstrating the benefits of letermovir prophylaxis in patients with AA.[30] Furthermore, given the impaired hematopoietic function of the bone marrow in these patients, we are particularly concerned about whether letermovir impacts the engraftment of neutrophils and platelets. Our result indicated that letermovir can avoid bone marrow toxicity.

Five patients experienced breakthrough CMV infection during letermovir prophylaxis in our study. Previous researches have identified subclinical CMV replication and the development of aGvHD during letermovir treatment as significant risk factors for CMV breakthrough infection.[31,32] As the specific inhibitor of the pUL56 subunit of CMV terminase complex, several researches have reported the letermovir resistance.[33] Chou et al[34] highlighted the critical role of genotyping validation in identifying CMV genetic variants during a letermovir clinical trial. Furthermore, early detection of CMV drug resistance mutations (DRMs) through advanced next-generation sequencing techniques can facilitate more rapid adjustments in antiviral treatment strategies.[35]

Significant progress has been made in using letermovir for CMV prophylaxis following HCT within the initial 100 days. However, findings from a phase III clinical trial indicated that letermovir prophylaxis may be linked to an increased incidence of CMV reactivation after day 100.[13] Late-onset CMV disease is most commonly observed in patients with prolonged periods of low-level, untreated viremia and has been independently linked to increased mortality within two years post-HCT.[36] Chris et al[37] demonstrated that letermovir prophylaxis is associated with a reduction in T-cell numbers and an increase in NK cell numbers, which may contribute to CMV reactivation upon the drug's discontinuation. The resulting changes in the proportions of NK and T cells could potentially facilitate CMV reactivation. Thus, evaluating HCMV-specific immunity after the cessation of letermovir prophylaxis may help identify patients at risk for clinically significant CMV infection. Domenico et al[12] showed that extending letermovir prophylaxis to 200 days post-HCT is both effective and safe in reducing the incidence of late-onset csCMVi at risk patients. Another study highlighted differences between early (0–1 day) and late (2–27 days) initiation of letermovir prophylaxis for CMV viremia.[38] However, letermovir does not fully address or significantly alter the persistent issue of late-onset CMV following the completion of prophylaxis, serving as a preventive measure rather than a transformative solution.[39] In this study, four patients experienced csCMVi after discontinuation of letermovir. These patients had received cyclosporine therapy for the prevention of GVHD, which led to a reduction in the use of letermovir. Currently, further research is needed to determine whether the reduced dose of letermovir affects the occurrence of long-term csCMVi.

The limitations of our study include the inherent limitations of its retrospective design, and letermovir was approved for application in 2022 so the follow-up time may be not enough. Despite these drawbacks, our study provides real-world evidence supporting the advantages and safety of letermovir for CMV prophylaxis in pediatric patients undergoing HCT. This could benefit children post-HCT by reducing CMV infection risk and potentially contribute to extending its approval in pediatric populations. However, late-onset CMV disease remains a significant concern following the discontinuation of letermovir around 100 days, highlighting the need for improved preventive strategies. Well-conducted, prospective, randomized studies on extending the duration of letermovir are essential.

Conclusion

Letermovir is both effective and safe for CMV prophylaxis in pediatric patients following HCT, especially in patients with more risk factors of csCMVi. Grade II–IV GvHD increases the risk of csCMVi, while letermovir prophylaxis reduces the risk.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files, which are available to authorized users.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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