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Letermovir for prevention of cytomegalovirus reactivation in haploidentical and mismatched adult donor allogeneic hematopoietic cell transplantation with post-transplant cyclophosphamide for graft-versus-host disease prophylaxis

A Lin[1], **J Flynn**[2], **L DeRespiris**[1], **B Figgins**[1], **M Griffin**[1], **C Lau**[1], **A Proli**[1], **SM Devlin**[2], **C Cho**[2,4], **R Tamari**[3,4], **AA Jakubowski**[3,4], **EB Papadopoulos**[3,4], **SA Giralt**[3,4], **MA Perales**[3,4], **SK Seo**[4,5], **B Shaffer**[3,4]

[1]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

[3]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA

[4]Department of Medicine, Weill Cornell Medical College, New York, NY, 10065, USA

[5]Infectious Disease Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA

Abstract

Cytomegalovirus (CMV) is serious viral infection in allogeneic hematopoietic cell transplantation (allo HCT) recipients. November 2017, the novel CMV DNA terminase complex inhibitor letermovir was approved for prophylaxis of CMV infection in CMV-seropositive allo HCT recipients. Here, we sought to determine the effectiveness of letermovir in preventing CMV infection in CMV-seropositive patients undergoing haploidentical or mismatched adult unrelated donor allo HCT using post-transplant cyclophosphamide-based graft-versus host-disease prophylaxis. Sixty-four patients were transplanted between 2014 and 2019 of whom 32 received letermovir and 32 did not receive letermovir. The day 180 cumulative incidence of CMV infection requiring therapy was 45.3% (95% conf. interval 32.7% − 57.1%) in the entire cohort, 68.8% (48.9% - 82.2%) in the patients that did not receive letermovir, and 21.9% (9.5% − 37.6%, P < 0.001) in patients that received letermovir. Adjusting for regimen intensity, disease histology, and age, the hazard ratio for CMV infection was 0.19 (0.08 – 0.47, P < 0.001) in patients that received primary prophylaxis with letermovir. The one-year cumulative incidence of treatment related mortality was similar between patients with and without letermovir treatment (16.9% *versus*

Corresponding author: Andrew Lin, Department of Pharmacy, Memorial Sloan Kettering, Medical Center, 1233 York Ave SR-307, New York, NY 10065 (lina@mskcc.org).

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18.9%) as was overall survival (64.0% *versus* 49.0%, respectively). Persistent CMV infection requiring >28 days of therapy was more common in patients that did not receive letermovir (31.2% *versus* 6.2%, P = 0.02). In summary, letermovir was effective at preventing CMV infection in this high-risk population of HLA mismatched allo HCT recipients.

Introduction

Cytomegalovirus (CMV) is a common viral infection in recipients of allogeneic hematopoietic cell transplantation (allo HCT).[1,2] Untreated CMV infection results in significant morbidity and mortality in this population, necessitating the use of pre-emptive anti-viral therapies in patients with detectable viremia.[3,4] CMV-active antiviral agents have significant adverse effects including myelosuppression (ganciclovir and valganciclovir), or renal injury (foscarnet), among others, leading to additive toxicities in allo HCT recipients requiring treatment for CMV.[5] November 2017, the novel CMV DNA terminase inhibitor letermovir was approved for prophylactic use in CMV-seropositive allo HCT recipients on the basis of a phase 3 trial demonstrating a significant reduction in CMV infection through week 24 after allo HCT in patients taking letermovir versus placebo (18.9% vs 44.3%, P<0.001).[6,7] The majority of subjects in this study received an allograft from an HLA matched donor and received standard, calcineurin inhibitor based, graft-versus-host disease (GVHD) prophylaxis.

Human leukocyte antigen mismatched adult donors, including haploidentical donors and mismatched unrelated donors (MMUD), are frequently used as allo HCT donors when combined with post-transplant cyclophosphamide (PT-Cy).[8] PT-Cy results in an *in vivo* lymphodepletion of alloreactive donor lymphocytes, theoretically sparing quiescent, non-alloreactive donor cells.[9] Clinical evidence suggests that PT-Cy results in some impact to the either the recipient or donor CMV-specific lymphocyte pool: CMV reactivation after PT-Cy based GVHD prophylaxis is approximately 10–20% more frequent when compared to recipients receiving methotrexate and calcineurin inhibitor based GVHD prophylaxis and HLA matched related or unrelated donor allografts.[2,10,11]

The clinical effectiveness of letermovir in higher risk populations, such as HLA mismatched donor with PT-Cy based GVHD prophylaxis, is not widely reported at this time.[12] Here, we compared the CMV-specific outcomes in adult patients undergoing either related haploidentical or HLA-mismatched (≤ 7/8 matched at HLA-A, -B, -C, -DRB1) unrelated donor allo HCT with PT-Cy based GVHD prophylaxis who did and did not receive primary CMV prophylaxis with letermovir.

METHODS

Patient population, clinical CMV monitoring, and letermovir prophylaxis

Subjects were CMV-seropositive adult allo HCT recipients treated at Memorial Sloan Kettering Cancer center between 2014 – 2019 using either an HLA MMUD (≤ 7/8 matched at HLA-A, -B, -C, -DRB1) or a related haploidentical donor. All recipients received GVHD

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prophylaxis with PT-Cy as is previously described.[13] The study was reviewed and approved by the Institutional Review Board and Privacy Board.

CMV viremia and disease were assigned according to standard guidelines.[14] Plasma CMV viral load (VL) was monitored by quantitative CMV polymerase chain reaction (PCR) (COBAS® AmpliPrep /COBAS® TaqMan® CMV Test, Roche Diagnostics) according to the manufacturer's guidelines.[15] CMV blood PCR was monitored on day +5 and continued weekly until day +100, then every 1–2 weeks for months 3–6 post allo HCT. The limit of detection of this assay is 137 IU/mL and values below this limit (i.e. low-detected) were considered negative for the purposes of this analysis. Primary letermovir prophylaxis was instituted at 7 days post-allo HCT unless there were extenuating clinical circumstances. The goal duration of letermovir prophylaxis was 6 months in this and other high-risk patient populations. Each patient's duration of letermovir prophylaxis was occasionally shorter if insurance coverage was limited to 100 days and/or for patient compliance and pill burden issues. Letermovir was discontinued and systemic anti-CMV therapy was instituted when there were 2 consecutive values of CMV VL > 300 IU/mL or a single CMV VL > 1000 IU/mL. The CMV treatment thresholds for initiation of pre-emptive therapy and monitoring frequency were the same before and after letermovir became available. Standard supportive care measures included chemoprophylaxis for herpes simplex virus, *Pneumocystis jirovecii*, and fungi as per institutional guidelines.[4]

Statistical considerations and study endpoints

The primary outcome was the proportion of patients who developed clinically significant CMV reactivation (CMV viremia requiring pre-emptive therapy or CMV disease; CS-CMVi). Persistent CMV infection was defined as detectable CMV viremia despite >28 days of anti-CMV specific therapy, excluding patients who had interrupted CMV specific therapy. The primary endpoint was evaluated by comparing the cumulative incidence of CS-CMVi in the study groups. Death or relapse were considered as competing events for this and the following endpoints as appropriate. We examined the role of clinically significant covariates using a competing risk regression framework. Overall survival (OS) was determined using the Kaplan-Meier method. Treatment-related mortality (TRM) and persistent CMV were evaluated using cumulative incidence. Wilcoxon rank sum and Fisher's exact tests were used to compare the frequency of clinical covariates between the study groups. Analyses were performed using R version 3.6.1.

RESULTS

Patient characteristics

Baseline characteristics of the sixty-four study patients are summarized in Table 1. Complete 180-day follow-up was available for all subjects. Thirty-two CMV-seropositive patients received letermovir as primary prophylaxis. From January 2018 onward, all patients eligible to receive letermovir for primary prophylaxis were treated. The median age was 63 years (range, 26–75) and 66% (42/64) were men. Approximately half of the patients received a myeloablative preparative regimen and the majority (72%) were haploidentical T-cell replete transplants. Rates of grade II-IV acute GVHD were similar in patients who did

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and did not receive letermovir prophylaxis (56% vs. 66%, respectively, P = 0.387). Severe grade 3–4 acute GVHD was rare in this population. Additionally, glucocorticoid exposure ≥ 1 mg/kg prednisone or equivalent for acute GVHD treatment did not impact CS-CMVi. Clinical co-variates were similar between patients that did or did not receive letermovir prophylaxis (Table 1) except for graft source: Letermovir recipients were more likely to receive peripheral blood-derived allografts reflecting a trend towards increased use of that collection strategy over time at our center.

Letermovir administration and incidence of CMV-specific outcomes

Primary letermovir prophylaxis was started at a median of 7 days (range, 5–12) after allo HCT. At initiation, 29 patients had an undetectable CMV VL, 2 patients had a detectable CMV VL <137 IU/mL, and one patient had a CMV VL of 151 IU/mL. The median duration of letermovir prophylaxis was 191 days (range, 16 to 796) with 7 patients continuing letermovir at last follow-up. Twenty-four of 32 patients (75%) continued letermovir prophylaxis beyond 14 weeks after allo HCT. Transplant characteristics did not influence the hazard for CMV infection requiring treatment in this smaller cohort (Table 2). Recipients with a diagnosis that required more intensive prior lymphodepletion, including lymphoma or non-malignant disorders, had a non-significant trend towards increased hazard for the primary endpoint (hazard ratio (HR): 2.1, 95% CI: 0.9 – 5.2, P= 0.26) when compared to recipients with a diagnosis of acute leukemia. Competing risk regressions were adjusted for covariates in this population regardless of their significance in univariate analysis.

The primary endpoint of 180-day cumulative incidence of CMV infection requiring therapy in patients that did not receive letermovir prophylaxis was 68.8% (95% CI: 48.9% - 82.2%) compared with 21.9% (95% CI: 9.5% - 37.6%) in patients that did receive letermovir prophylaxis (P < 0.001), (Figure 1). Duration of CMV viremia in patients who did or did not receive letermovir is outlined in Figure 2. Overall, only seven patients who received letermovir developed CS-CMVi. Of this group, five of the patients had this occur while receiving letermovir prophylaxis. Three of these patients had additional CMV resistance testing via conventional PCR followed by genotypic sequencing (ViraCor-IBT Laboratories). There were no documented mutations (e.g. at UL56) that would have conferred letermovir resistance amongst letermovir recipients. Pre-emptive therapy was successfully administered to all seven patients with either valganciclovir or foscarnet (figure 2). There was no difference in overall-survival (OS) or TRM in patients that did or did not receive letermovir (Figure 3).

Late CMV infection, persistent CMV viremia, and end-organ disease

Of the three patients who had a detectable or quantifiable CMV VL at the time of letermovir initiation, two patients required pre-emptive therapy for CMV viremia. Notably three patients had CS-CMVi occur in the period beyond 14-weeks after allo HCT but two of the patients had discontinued letermovir before CS-CMVi occurred. Overall, only 1 of 24 (4.2%) developed CS-CMVi if they remained on letermovir beyond the 14-week mark after allo HCT.

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In this population, the cumulative incidence of persistent CMV in recipients that did not receive letermovir prophylaxis was 31.2% (95% CI: 16.1% − 47.7%) compared to 6.2% (95% CI: 1.1% − 18.4%, P = 0.02). Only two documented cases of CMV end-organ disease were described in this population (one patient treated with letermovir prophylaxis developed pneumonitis after discontinuing letermovir and one patient developed CMV colitis without letermovir prophylaxis).

DISCUSSION

In this study we demonstrate that primary letermovir prophylaxis was effective in preventing CS-CMVi in CMV-seropositive recipients of allo HCT from haploidentical or MMUD who received PT-Cy as GVHD prophylaxis. The cumulative incidence of CMV reactivation in recipients of haploidentical donor allo HCT with PT-Cy based GVHD prophylaxis is 50–80%.[16–19] These results are similar to other high risk allo HCT recipients including those undergoing T-cell depletion or receiving HLA mismatched umbilical cord blood allografts.[20,21] In this study, we observed a similar rate of CMV reactivation in patients that did not receive letermovir, whereas the cumulative incidence of CS-CMVi in letermovir recipients was significantly decreased. In this population, letermovir was well tolerated as there were no discontinuations due to treatment-emergent adverse events. Of note, persistent CMV infection was significantly reduced with utilization of letermovir prophylaxis. We and others have previously described persistent CMV infection (detectable CMV viremia for greater than 28 days despite optimal therapy) as a significant risk factor for TRM.[22] Our findings are also in line with another large, 2020 report highlighting the efficacy of letermovir in high risk populations (e.g. umbilical cord blood and haploidentical allo HCT recipients).[23] Overall, these results further suggest that letermovir reduces the incidence of CMV related complications in patients who are at high risk for CMV specific complications.

The optimal duration of letermovir prophylaxis, especially in higher risk allograft recipients, remains an unanswered question. This is of interest when considering high-risk populations such as presented here. At 14-weeks post allo HCT the patients who received letermovir prophylaxis had a similar incidence of CS-CMVi compared to the registration trial at 12.5% (4/32) vs. 7.7%, respectively. Marty et al. noted additional post-prophylactic CMV events starting around week 18, likely representing ongoing or new periods of CMV risk beyond day + 100.[7] In this population, late CS-CMVi was rare if letermovir prophylaxis was continued beyond 14 weeks, occurring in only one patient (4.2%). These findings support the use of prolonged letermovir primary prophylaxis. There is some concern that letermovir prophylaxis of any duration only delays CS-CMVi until after prophylaxis is completed. An ongoing randomized clinical trial to evaluate efficacy and safety of letermovir prophylaxis when extended to 200 days after alloHCT (NCT03930615) should provide further data in this regard as there are key secondary endpoints evaluating the effect of extended prophylaxis at 38- and 48-weeks post allo HCT. Additionally, there is value in preventing CS-CMVi from occurring at all. CMV reactivation is associated with an increased risk of invasive fungal infections.[24] Another report indicates letermovir may reduce mortality by preventing or delaying CS-CMVi in HCT recipients.[25] Our study size may have been too small to capture this effect.

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There are some imitations inherent to the retrospective and observational nature of our study. The sample size was relatively small. Since this was a real-world study, we relied on patient reports of adherence. While acknowledging these limitations, our data provide real-world data of the effectiveness of letermovir in a population at high-risk of CMV reactivation and complications. Haploidentical allo HCT recipients only comprised 16% of the registry trial, but this study triples the number of patients in this high-risk group.[20] Additional studies are needed to quantify the impact of letermovir on the reduction of days and toxicity of pre-emptive therapy, readmissions, hospital length-of-stay, and overall long-term survival in these and other high-risk patients.

In summary we found that letermovir resulted in a significant reduction in the need for CMV specific therapy but did not impact TRM or OS in this population. These results support the efficacy of letermovir for CMV prevention for the first 14 weeks in CMV-seropositive adult recipients of allo HCT and continued efficacy when given beyond 14 weeks in HLA mismatched allograft recipients using PT-Cy based GVHD prophylaxis. Results of a larger trial using prolonged letermovir use in this population are necessary to determine the standard of care in HLA mismatched allo HCT recipients.

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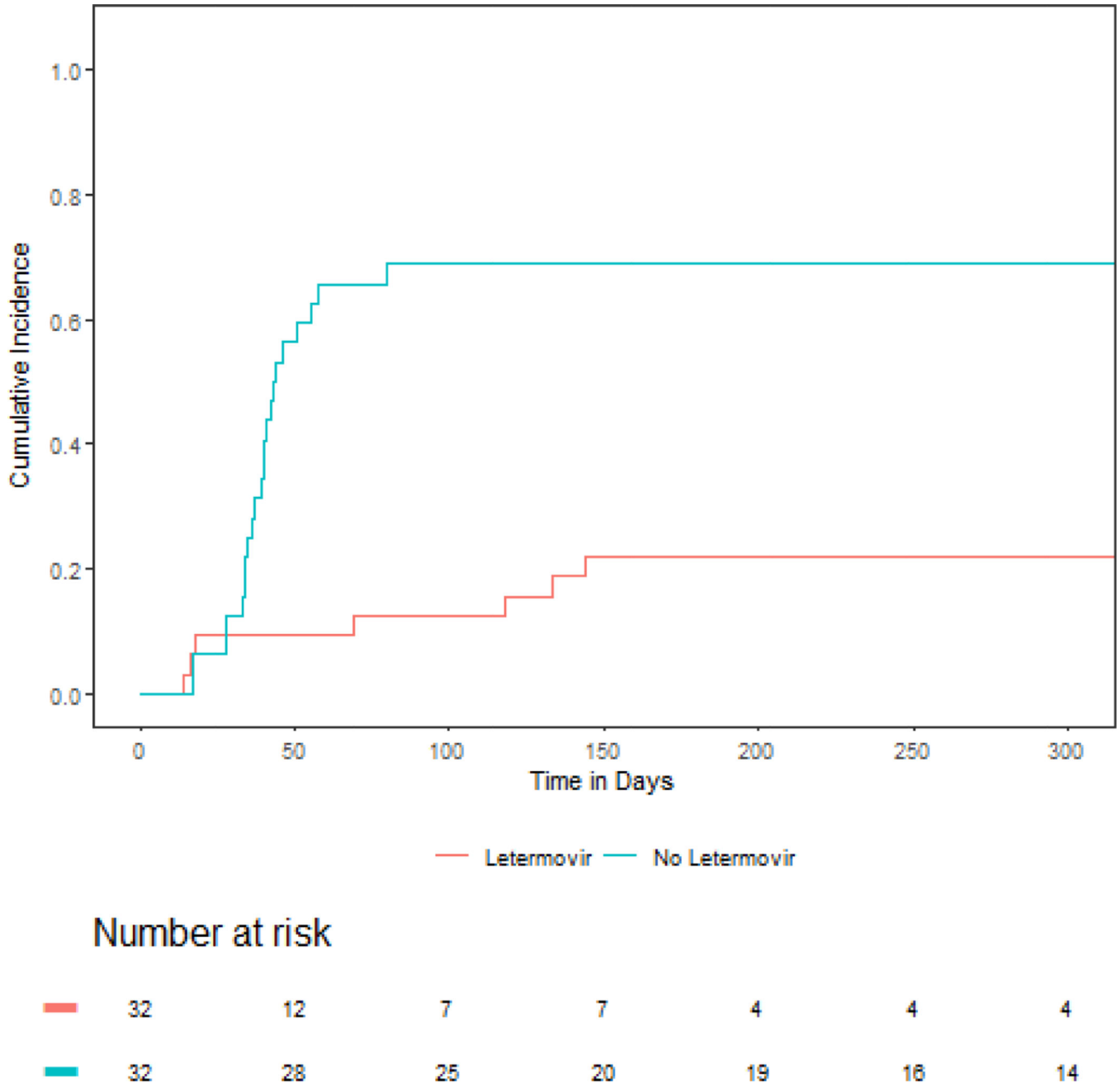

Figure 1:
Cumulative incidence of clinically significant CMV infection in patients that received letermovir primary prophylaxis (red) *versus* patients that did not receive primary prophylaxis (blue).

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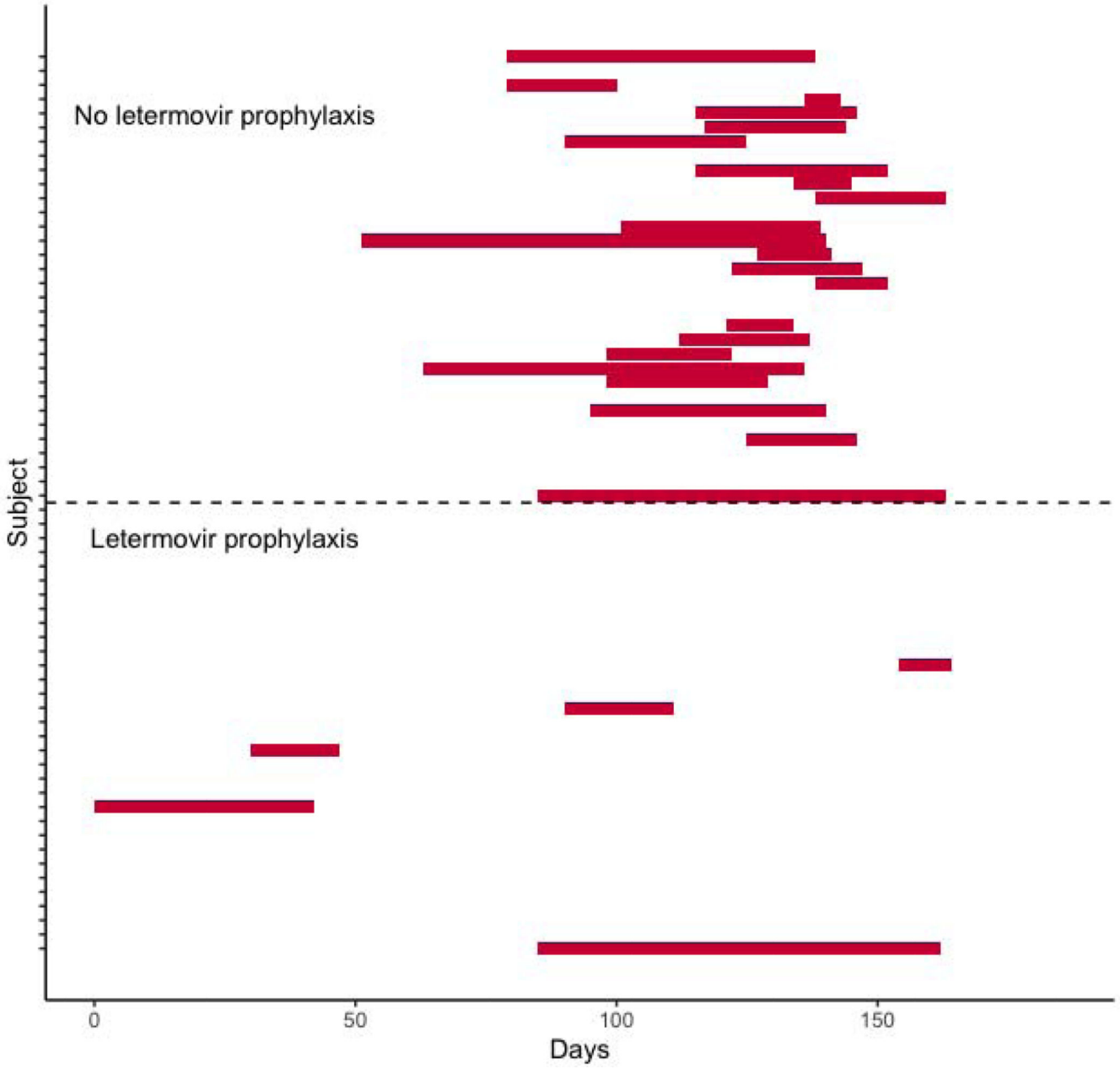

Figure 2:
Duration of anti-viral therapy in patients that received or did not receive letermovir. The red bars indicate the time of CMV specific pre-emptive or therapeutic therapy administration relative to the infusion of the allograft stem cell product on day 0.

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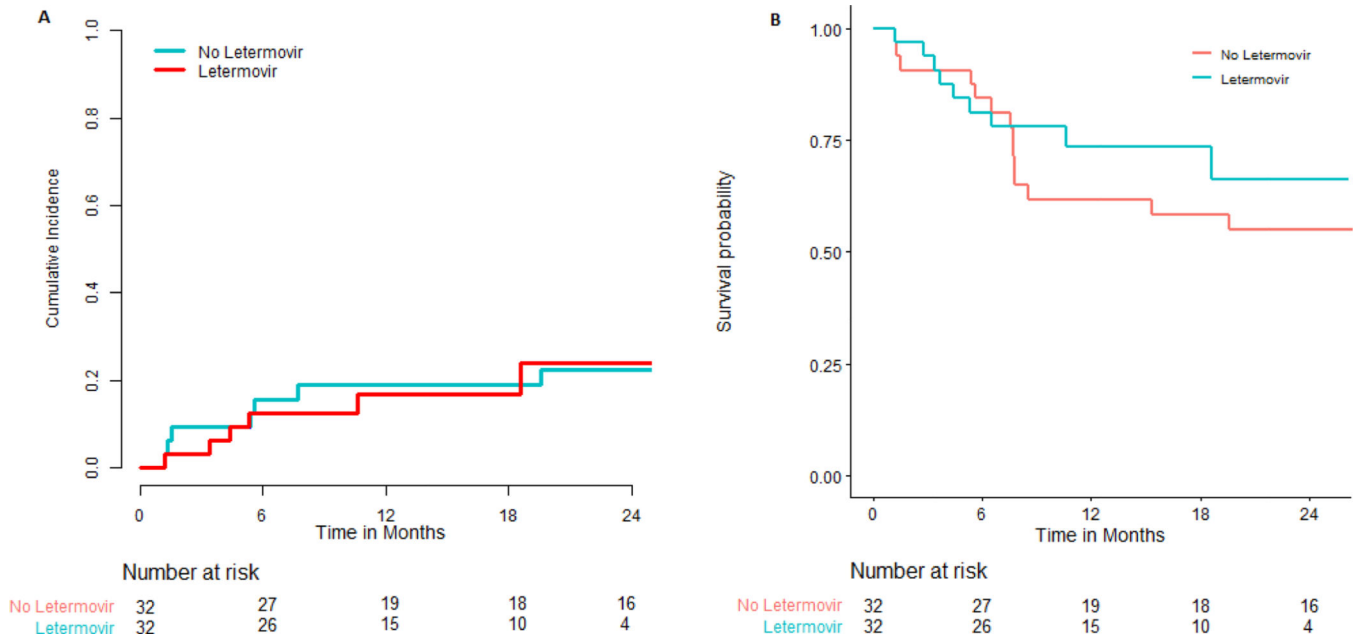

Figure 3:

Cumulative incidence of treatment-related mortality (A) and Kaplan-Meier estimates of overall survival (B) in subjects.

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Table 1.

Characteristics of patients who received post-transplant cyclophosphamide as graft-versus-host disease prophylaxis

Characteristic	Overall, N = 64	No Letermovir, N = 32	Letermovir, N = 32	P value
Regimen				0.6
Busulfan based	3 (4.7%)	1 (3.1%)	2 (6.2%)	
Nonmyeloablative Fludarabine, Cyclophosphamide, TBI based	20 (31%)	12 (38%)	8 (25%)	
Ablative – Fludarabine, TBI based	1 (1.6%)	0 (0%)	1 (3.1%)	
Melphalan based	40 (62%)	19 (59%)	21 (66%)	
Disease histology				0.12
Acute leukemia	22 (34%)	11 (34%)	11 (34%)	
Lymphoid malignancy	22 (34%)	8 (25%)	14 (44%)	
Myelodysplastic or proliferative syndrome	16 (25%)	9 (28%)	7 (22%)	
Non-malignant diagnosis	4 (6.2%)	4 (12%)	0 (0%)	
Age	63 (26, 75)	65 (26, 75)	61 (26, 75)	<0.001
Gender				0.8
Female	22 (34%)	12 (38%)	10 (31%)	
Male	42 (66%)	20 (62%)	22 (69%)	
HLA				0.4
Related haploidentical	46 (72%)	25 (78%)	21 (66%)	
Unrelated mismatched	18 (28%)	7 (22%)	11 (34%)	
Source				0.024
Bone marrow derived	34 (53%)	22 (69%)	12 (38%)	
Peripheral blood derived	30 (47%)	10 (31%)	20 (62%)	
Conditioning intensity				0.2
Myeloablative	35 (55%)	20 (62%)	15 (47%)	
Non-myeloablative	18 (28%)	6 (19%)	12 (38%)	
Reduced intensity	11 (17%)	6 (19%)	5 (16%)	
CMV serostatus				0.5
D^-/R^+	32 (50%)	18 (56%)	14 (44%)	
D^+/R^+	32 (50%)	14 (44%)	18 (56%)	

[1] Statistics presented: n (%); median (minimum, maximum)

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Table 2:

Univariate associations of clinical covariates with CMV infection requiring pre-emptive therapy

Variable	HR (95% CI)	P value
Age	1.02 (0.98–1.05)	0.35
Letermovir		<.001
No	Reference	
Yes	0.21 (0.09–0.49)	
Disease Histology		0.26
Acute leukemia	Reference	
Lymphoid or non-malignant diagnosis	2.13 (0.86–5.23)	
Myelodysplasia or myeloproliferative syndrome	1.69 (0.64–4.44)	
Regimen		0.61
Non-myeloablative fludarabine, cyclophosphamide, TBI-200	Reference	
All others	0.82 (0.39–1.74)	
Donor		0.684
Related haploidentical	Reference	
Unrelated mismatched adult	1.17 (0.54–2.53)	
Graft Source		0.479
Bone marrow	Reference	
Peripheral blood	0.77 (0.37–1.59)	
CMV serostatus		0.9
D^-/R^+	Reference	
D^+/R^+	1.05 (0.51–2.14)	