Extending duration of letermovir prophylaxis in haploidentical stem cell transplantation

Result from pivotal phase III studies demonstrated a significant reduction in clinically significant cytomegalovirus (CMV) infections (CS-CMVi)[1] in patients who received prophylactic letermovir for the first 14 weeks and 28 weeks after transplantation.[2,3] However, a significant proportion of participants developed late CS-CMVi after letermovir discontinuation and a small subset of patients underwent haploidentical donor stem cell transplantation (haplo-SCT). Moreover, it has been shown that post-transplantation cyclophosphamide (PTCy)-based graft-*versus*-host disease (GVHD) prophylaxis is associated with higher likelihood of developing CS-CMVi.[4] Consequently, the optimal duration of letermovir prophylaxis in haplo-SCT with PTCy-based GVHD prophylaxis remains unclear.

We retrospectively evaluated 43 consecutive adult patients undergoing haplo-SCT using fludarabine-based conditioning regimens with PTCy, tacrolimus, mycophenolate mofetil (MMF) and budesonide as GVHD prophylaxis, with CMV seropositive recipients or donors. MMF and budesonide were tapered off starting at day +90, while tacrolimus was continued for at least 6 months post-transplant. The study protocol was approved by the Institutional Review Board of the University of California, Irvine (IRB 20206215). The median follow-up time was 480 days (interquartile range [IQR], 288-793 days). The median age of donors was 35 years (IQR, 23-40 years). Ten patients (23.3%) developed human herpesvirus 6 reactivation, letermovir prophylaxis was interrupted by preemptive treatment with foscarnet in this group, for a median duration of 7 days (IQR, 6-10 days).[5] Patient characteristics are summarized in Table 1. Letermovir at 480 mg once daily was administered starting on day +7 and was extended up to 1-year post-transplant, due to perceived higher incidence of CS-CMVi after discontinuation at day 100 post-transplant and because adaptive immunity recovers approximately at 1-year post-transplant.[6] The plasma CMV DNA level was quantified by polymerase chain reaction (PCR) method and quantitative measurement range of CMV DNA assay was 50-156 million IU/mL (range, 1.70-8.19 log IU/mL). Preemptive treatment was initiated when detection of CMV DNA in plasma exceeded 50 IU/mL for two consecutive instances. Letermovir was resumed for secondary prophylaxis after completing preemptive treatment, with at least two consecutive undetected plasma CMV DNA. The median duration of letermovir exposure was 255 days (IQR, 179-344 days). Twenty-six patients (60.5%) developed at least one episode of CS-CMVi, with six patients (24%) receiving additional immunosuppressive agents (5 on corticosteroids and 1 on eculizumab plus rituximab). The median time to CS-CMVi post-transplant was 50 days (IQR, 11-213 days), with a median plasma level of CMV DNA of 160 IU/mL (IQR, 74-276 IU/mL). The median peak plas-

Table 1. Patient characteristics.

Characteristics	N=43
Median age in years (range)	50 (22-73)
Male/female, N	26/17
Median KPS (range)	90 (70-100)
Median HCT-CI (range)	2 (0-7)
DRI, N (%)	
Low	5 (11.6)
Intermediate	24 (55.8)
High	11 (25.6)
Very high	0 (0)
N/A	3 (7)
Diagnosis, N (%)	
AML	12 (27.9)
ALL	11 (25.6)
NHL, HL	9 (20.9)
MDS, MPN, MDS/MPN	8 (18.6)
AA	3 (7)
Intensity of conditioning regimen, N (%)	
Myeloablative	7 (16.3)
Reduced intensity	36 (83.7)
Type of conditioning regimen, N (%)	
Flu/Mel/TBI	26
Flu/Cy/TBI ± ATG	10
Flu/Mel/TT	7
Stem cell source, N (%)	
Peripheral blood	29 (67.4)
Bone marrow	14 (32.6)
ABO compatibility, N (%)	
Match	25 (58.1)
Minor mismatch	6 (14)
Major mismatch	11 (25.6)
Bidirectional mismatch	1 (2.3)
CMV serology, N (%)	
R+/D+	27(62.8)
R+/D-	15 (34.9)
R-/D+	1 (2.3)

AA: aplastic anemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ATG: anti-thymocyte globulin; CMV: cytomeglaovirus; Cy: cyclophosphamide; D: donor; Flu: fludarabine; KPS: Karnofsky Performance Scale; DRI: disease risk index; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; HL: Hodgkin lymphoma; MDS: myelodysplastic syndromes; Mel: melphalan; MPN: myeloproliferative neoplasm; N/A: not applicable; NHL: non-Hodgkin lymphoma; R: recipient; TBI: total body irradiation; TT: thiotepa.

ma level of CMV DNA was 665 IU/mL (IQR, 326-1,900 IU/mL) at a median of 79 days post-transplant (IQR, 35-215 days). The cumulative incidence of first CS-CMVi at day 100, 180, 270 and 365 were 34.9% (95% confidence interval [CI]: 21.2-48.9), 39.5% (95% CI: 25.1-53.6), 54.2% (95% CI: 38.1-67.7) and 63.1% (95% CI: 46.1-76.1), respectively (Figure 1). One patient (2.3%) developed CMV pneumonitis at 29 days post-transplant. CMV resistance testing was not performed during the first episode of CS-CMVi. Twenty-three (88.5%) patients with first CS-CMVi, including fourteen patients who had an initial plasma level of CMV DNA above 150 IU/mL, responded to first-line preemptive treatment with either foscarnet (N=11) or valganciclovir (N=12). However, three patients received maribavir as a salvage treatment due to refractory CS-CMVi. Twenty-four patients received letermovir as secondary prophylaxis after completing preemptive treatment. Eight of these patients (33.3%) subsequently developed a second CS-CMVi, with a 100-day cumulative incidence of failure from secondary prophylaxis at 29.4% (95% CI: 13.1-48.0) (Figure 1). The median duration of second CS-CMVi was 37 days after starting secondary letermovir prophylaxis (IQR, 14-42 days), with a median level of plasma CMV DNA at 64 IU/mL (IQR, 54-86 IU/mL). One patient out of eight developed a third episode of CS-CMVi on day 118 post-transplant, and subsequently died from COVID pneumonia on day 134 post-transplant. The median post-transplant day for letermovir discontinuation was 374 (IQR, 351-418 days), with 1-year cumulative incidence of letermovir discontinuation at 80.6% (95% CI: 63.0-90.4) (*Online Supplementary Figure S1*). The only factor associated with a lower risk of CS-CMVi was lower hematopoietic cell transplantation comorbidity index (HCT-CI) (subdistribution hazard ratio [SHR]=0.82; 95% CI: 0.68-0.99; *P*=0.04). No CMV-related mortality occurred.

Focusing on transplant outcomes, all patients achieved neutrophil engraftment at a median of 17 days post-transplant (IQR, 15-19 days). Forty-two patients (97.7%) achieved platelet engraftment at a median of 23 days post-transplant (IQR, 19-27 days), one patient died from pneumonia prior to platelet engraftment at day 206 post-transplant. There was no significant difference between patients with and without CS-CMVi with regards to median day post-transplant for neutrophil (17 *vs*. 16 days; *P*=0.97) and platelet (24 *vs*. 23 days; *P*=0.17) engraftment. Cox proportional hazards and subdistribution hazard model using CS-CMVi as a time-varying covariate, did not demonstrate differences in transplant outcomes between patients with and without CS-CMVi. The 1-year non-relapse mortality in subgroups with and without CS-CMVi were 23.0% (95% CI: 8.3-42.1) and 31.0% (95% CI: 11.2-53.6), respectively (SHR=0.13; 95% CI: 0.01-1.71; *P*=0.12). The 1-year cumulative incidence of relapse in subgroups with and without CS-CMVi were 11.5% (95% CI: 2.9-26.7) and 5.9% (95% CI: 0.4-23.5), respectively (SHR=1.86; 95% CI: 0.18-19.75; *P*=0.61). The 1-year progression-free survival (PFS) and overall survival (OS) between the cohort with and without CS-CMVi were 65.5% (95% CI: 42.1-81.3) *versus* 63.1% (95% CI: 35.3-81.6), (HR=0.48; 95% CI: 0.09-2.69; *P*=0.40) and 69.4% (95% CI: 45.9-84.3) *versus* 69.1% (95% CI: 40.7-85.9) (HR=0.28; 95% CI: 0.03-2.74; *P*=0.28), respectively. In addition, there were no differences in cumulative incidence of grade II-IV acute GVHD 7.7% (95% CI: 1.3-21.7%) *versus* 5.9% (95% CI: 0.04-23.5) at 100 days, (SHR=0.84; 95% CI: 0.05-14.04; *P*=0.90) and moderate to severe chronic GVHD 6.6% (95% CI: 0.4-25.7) *versus* 9.0% (95% CI: 0.6-32.8) at 2 years post-transplant, (SHR=0.59; 95% CI: 0.04-8.77; *P*=0.70) between patients with and without CS-CMVi (*Online Supplementary Figure S2*). After adjusting for age, sex, Karnofsky Performance Scale, HCT-CI and disease risk index, there were no differences in PFS (HR=0.94; 95% CI: 0.16-5.51; *P*=0.95) and OS (HR=0.45; 95% CI: 0.05-4.26; *P*=0.48) between the two groups.

Immune reconstitution was evaluated by analyzing peripheral blood absolute lymphocyte subset count including $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, and $CD3^-CD56^+$ lympho-

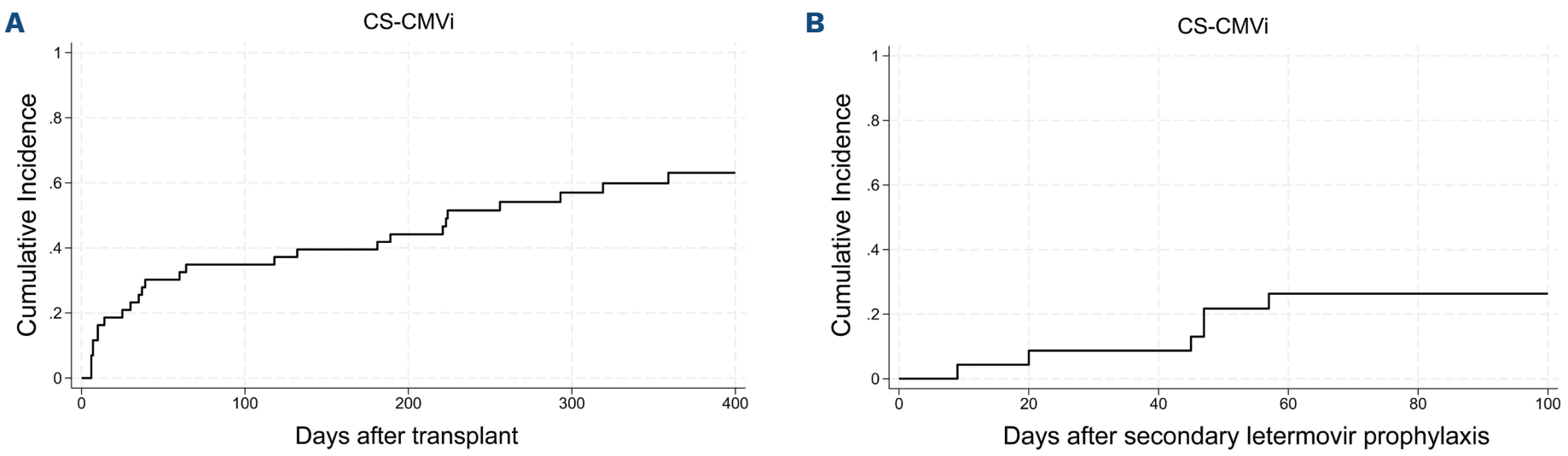

Figure 1. Cumulative incidence of clinically significance cytomegalovirus infection. (A) The cumulative incidence of clinically significant cytomegalovirus (CS-CMVi) infection at 1 year was 63.1% (95% confidence interval [CI]: 46.1-76.1). (B) The cumulative incidence of failure in secondary letermovir prophylaxis at 100 days was 29.4% (95% CI: 13.1-48.0).

cytes. Using a mixed effects linear model to account for multiple measurements per patient and multiple imputation method to impute missing lymphocyte subsets data, the occurrence of CS-CMVi was associated with lower $CD3^+$ (coefficient -79.65; *P*=0.03), $CD3^+CD4^+$ (coefficient -35.52; *P*=0.02), $CD3^+CD8^+$ (coefficient -60.23; *P*=0.02) and $CD19^+$ (coefficient -38.68; *P*=0.04) lymphocyte subsets at 1-year post-transplant. However, no association was found between CS-CMVi and $CD56^+$ lymphocyte recovery after transplant (coefficient 29.45; *P*=0.54) (Figure 2).

This reports demonstrated one of the longest durations of letermovir administration for CMV prophylaxis after transplantation. Despite a median duration of letermovir exposure of 255 days, the cumulative incidence of CS-CMVi was high at 63.1% throughout the first-year post-transplant. Significantly, 39.5% and 54.2% of patients experienced CMV reactivation by day 180 and day 270 post-transplant, respectively, demonstrating the need to further extend the duration of letermovir or to investigate a novel prophylaxis strategy other than letermovir. However, it remains unclear whether the consistent use of PTCy-based GVHD prophylaxis could be the main factor, and if the higher incidence and need to extend letermovir prophylaxis will be observed in HLA-matched donor transplants in the future, as PTCy is being extended to these transplants.[7,8] The incidence of CS-CMVi in our report was higher than in previous studies.[2,3] The inclusion of only haploidentical donors with PTCy-based GVHD prophylaxis and early preemptive treatment with a lower cutoff plasma CMV DNA level at 50 IU/mL, compared with other studies suggesting a cutoff of 137 IU/mL (150 copies/mL)[2,9] might be contributing to a higher incidence of CS-CMVi. We have found a consistent decrease in absolute T-cell subsets and B cells in CS-CMVi cohort which significantly associated

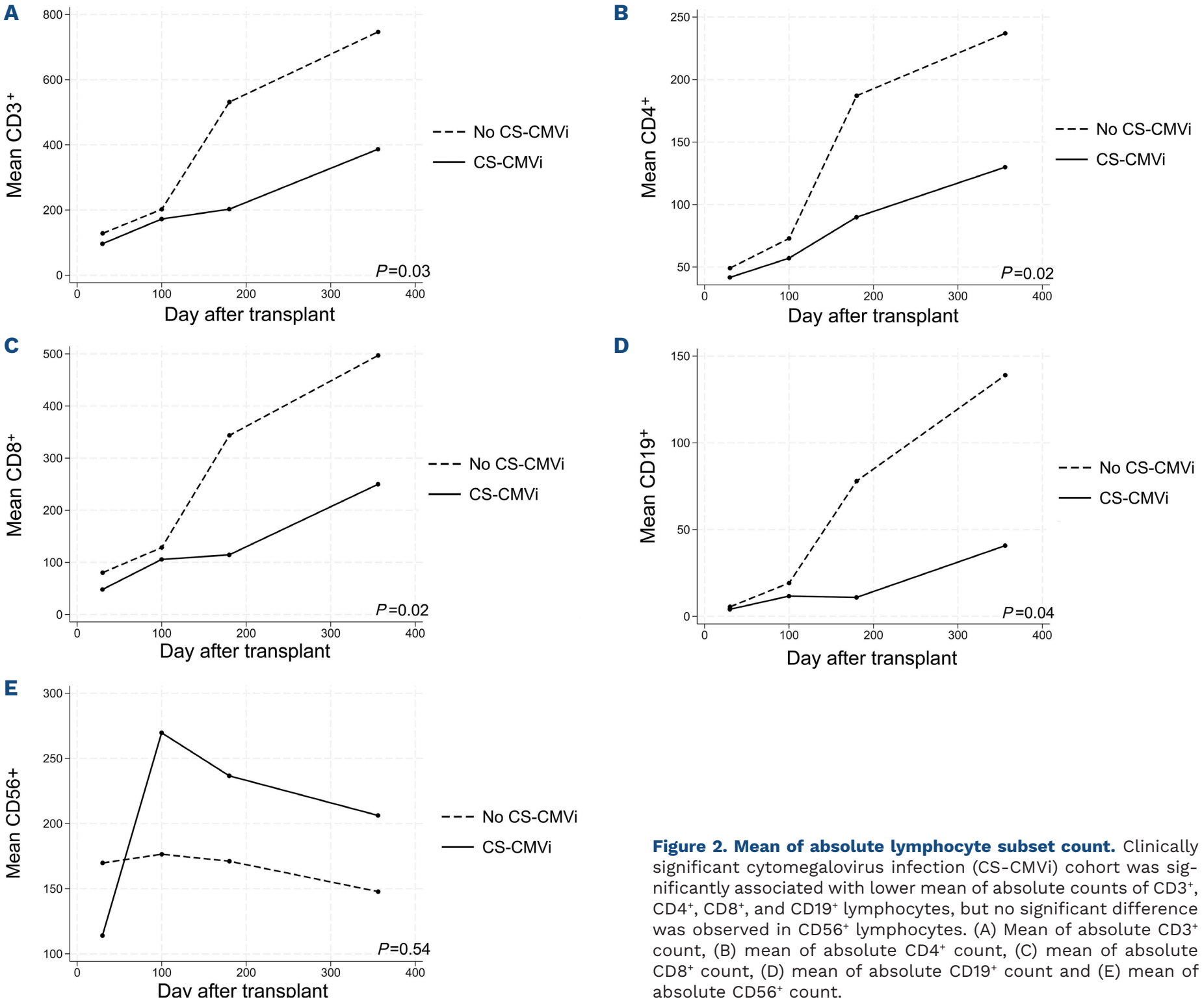

Figure 2. Mean of absolute lymphocyte subset count. Clinically significant cytomegalovirus infection (CS-CMVi) cohort was significantly associated with lower mean of absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ lymphocytes, but no significant difference was observed in $CD56^+$ lymphocytes. (A) Mean of absolute $CD3^+$ count, (B) mean of absolute $CD4^+$ count, (C) mean of absolute $CD8^+$ count, (D) mean of absolute $CD19^+$ count and (E) mean of absolute $CD56^+$ count.

with a higher HCT-CI, suggesting that either that patients with higher comorbidities have been less likely to develop an immune response or that CMV exerts a negative impact on immunologic reconstitution in these patients. Extending letermovir for CMV prophylaxis might overcome the negative impact of CS-CMVi, as our study showed no significant differences in transplant outcomes between the two groups of patients with and without CS-CMVi. Despite the apparent safety and tolerability of extending duration of letermovir prophylaxis, delay in recovery of CMV-specific immunity and letermovir resistance could be a concern associated with extending the duration prophylaxis.[10,11] Prospective randomized studies are needed in this group of patients as well as patients receiving PTCy-based GVHD prophylaxis to assess the need for extended duration. Additionally, a cost-effectiveness analysis would be useful to assess resource utilization.

In conclusion, our study reported real-world experience with extended letermovir prophylaxis in a cohort of haplo-SCT patients. CS-CMVi developed up to 1-year post-transplant suggesting that extending letermovir prophylaxis or novel prophylaxis strategy is needed. In addition, secondary prophylaxis with letermovir can be applied after completing preemptive treatment. Larger studies are needed to confirm these findings and assess the need to extend letermovir prophylaxis in human leukocyte antigen-matched transplants receiving PTCy-based GVHD prophylaxis.

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https://doi.org/10.3324/haematol.2024.285766

Received: May 4, 2024.
Accepted: July 3, 2024.
Early view: July 11, 2024.

Disclosures

No conflicts of interest to disclose.

Contributions

PV, PK and SC conceptualized and designed the study. PV performed data collection from the electrical medical records. PV, PK and SC analyzed the data and wrote the first draft of the manuscript. BL, SG, JD, JS, HN, EB, DJ, PK and SC took care of the patients. All authors edited and approved the final version of the manuscript.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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