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Original Article

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Hybrid Ganciclovir/Valacyclovir Prophylaxis Reduces CMV Reactivation in High-Risk Allogeneic Stem Cell Transplant Recipients

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ABSTRACT

Background: Cytomegalovirus (CMV) reactivation remains a critical concern following allogeneic hematopoietic stem cell transplantation (allo-HSCT), particularly in CMV-seropositive patients undergoing allo-HSCT from alternative donors. This study explored whether a hybrid CMV prophylaxis regimen would be more effective than the standard preemptive regimen in resource-limited settings where Letermovir is unavailable or cost-prohibitive.

Materials and Methods: This prospective single-center cohort study included adult patients with acute leukemia who received allo-HSCT from alternative donors between November 2018 and May 2022. The primary outcome was the evaluation of the CMV reactivation incidence in allo-HSCT patients receiving the hybrid CMV prophylaxis regimen comprising pretransplant ganciclovir followed by high-dose valacyclovir compared with the control patients who received the preemptive regimen. Secondary outcomes included overall survival (OS), disease-free survival (DFS), GVHD-free relapse-free survival (GRFS), and non-relapse mortality (NRM) between the two groups.

Results: A total of 80 patients, 34 receiving hybrid CMV prophylaxis and 46 received the preemptive protocol. The hybrid prophylaxis group exhibited a significantly lower incidence of CMV reactivation at 90 days post-transplantation (34% vs. 82%, $P = 0.000$). However, no statistically significant differences were observed in the overall survival, disease-free survival, or non-relapse mortality.

Conclusion: The hybrid regimen reduced CMV reactivation in high-risk HSCT recipients but did not improve survival outcomes, offering a practical alternative in settings with limited access to Letermovir.

Keywords: Cytomegalovirus prophylaxis; Allogeneic stem cell transplantation; Ganciclovir; Valacyclovir; Hybrid regimen; Preemptive therapy; CMV reactivation; Haploidentical transplant

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INTRODUCTION

Cytomegalovirus (CMV) reactivation remains a concern after allogeneic hematopoietic stem cell transplantation (allo-HSCT)[1,2]. Without CMV prophylaxis, 70-80% of seropositive HSCT recipients experience CMV reactivation, resulting in significant morbidity and mortality[3,4]. CMV infection is associated with increased transplant-related mortality [5].

Several risk factors that can increase the likelihood of CMV reactivation following allogeneic transplantation have been identified. These include recipient CMV seropositivity, in vivo or ex vivo T cell depletion, administration of high-dose steroids, use of post-transplant cyclophosphamide, transplantation from HLA-mismatched or unrelated donors, and GVHD [6-12].

Two major approaches, prophylactic and preemptive treatment, are currently used to prevent CMV disease. Prophylactic treatment typically involves administration of antiviral therapy starting on the day of transplantation and continuing through 100 days post transplantation. In contrast, preemptive therapy entails initiating antiviral treatment based on monitoring patients for early signs of CMV reactivation and starting treatment with antiviral medication once detected[13].

Various antiviral agents, such as ganciclovir and foscarnet, have been effective in reducing the incidence of CMV infection and disease, although their significant organ toxicity presents a substantial limitation for their use as prophylaxis [14-18]. Effective and safe anti-CMV prophylaxis can mitigate the risk of CMV reactivation and improve mortality rates following HSCT.

Letermovir decreases clinically significant CMV infection, exhibits a favorable toxicity profile, and has been approved for CMV prevention among adult CMV seropositive HSCT recipients. Letermovir may be a valuable option for CMV prevention in high-risk transplant patients, although the cost and resistance need to be considered[19]. Currently, maribavir is being studied in phase III trials [20-22].

Although effective, letermovir is associated with several barriers, such as high cost and emerging resistance, particularly in resource-constrained regions. This has spurred interest in alternative strategies using widely available antivirals, such as ganciclovir and valacyclovir, albeit with potential toxicity trade-offs. We hypothesized that a hybrid regimen combining pre-transplant ganciclovir with high-dose valacyclovir could balance the efficacy and accessibility in high-risk HSCT recipients.

Materials and Methods

Ethical Approval and Consent

This prospective cohort study was conducted at the Hematology-Oncology and Stem Cell Transplantation Research Center (HORCSCT), Tehran University of Medical Sciences, Iran. The protocol (IR.TUMS.HORCSCT.REC.1401.016) received ethical approval from the Institutional Review Board on March 15, 2022, and adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent.

Study Design and Patients

The study enrolled consecutive adult patients (aged 18 or older) with acute leukemia who underwent their first allogeneic stem cell transplant (allo-HSCT) from alternative donors—including haploidentical, mismatched unrelated, or unrelated donors—between November 2018 and May 2022. Key eligibility criteria required participants to meet the following:

1. CMV-seropositive status in either the recipient (R+) or donor (D+).
2. Transplantation during complete remission (CR1–CR3).
3. Presence of high-risk factors for CMV reactivation, such as receiving a transplant from an HLA-mismatched/haploidentical donor, undergoing T-cell depletion, or using post-transplant cyclophosphamide.

Patients were excluded if they met any of the following:

1. Both recipient and donor were CMV-seronegative.
2. CMV reactivation occurred prior to the transplant (day 0).
3. Previous history of allogeneic transplantation.

Based on evolving institutional protocols, participants were divided into two groups:

- Hybrid prophylaxis group (November 2018–December 2020; n=34): Patients received intravenous ganciclovir (5 mg/kg daily) from day -8 to -2 during conditioning. This was followed by oral valacyclovir (2 g every 8 hours, adjusted for kidney function) from day -1 to day +100, or intravenous acyclovir (500 mg/m² every 8 hours) if oral intake was impaired due to mucositis or swallowing difficulties.
- Preemptive therapy group (January 2021–May 2022; n=46): Treatment began only after CMV DNA levels reached ≥100 copies/mL. Induction therapy included oral valganciclovir (900 mg/m² twice daily for 7–14 days), followed by maintenance dosing (450 mg/m² twice daily) until two consecutive negative PCR results were achieved. Doses were adjusted for renal impairment.

All participants were monitored for CMV infection twice weekly via PCR until hospital discharge, then weekly until day +100. Follow-up continued through the end of 2023 to evaluate long-term outcomes and the effectiveness of each CMV management strategy.

Conditioning regimen, stem cell source, and GVHD prophylaxis

All patients in both groups received an identical myeloablative conditioning (MAC) regimen, followed by peripheral blood stem cell (PBSC) transplantation. This regimen consisted of intravenous busulfan (BU) 3.2 mg/kg/day administered from days -6 to -3, along with cyclophosphamide 60 mg/kg/day on days -2 and -1[23].

A combination of cyclosporine A (CyA) and methotrexate (MTX) were used for GVHD prophylaxis. CyA was administered intravenously at a starting dose of 1.5 mg/kg/day on day -2, which was then increased to 3 mg/kg/day from day +7 until oral administration was possible. On day +1, MTX was administered at 10 mg/m^2, followed by 6 mg/m^2 on days +3, +6, and +11. Additionally, as a component of the GVHD prophylaxis regimen for recipients of alternative donors, rabbit anti-thymocyte globulin (ATG) 2.5 mg/kg/day was used on days -3 and -2 and days -3 to -1, respectively. Furthermore, post-transplant cyclophosphamide 40 mg/kg/day on days +3 and +4 was administered to patients who received haploidentical grafts.

Supportive care, including the administration of fluconazole and trimethoprim/sulfamethoxazole to prevent Candida and Pneumocystis jirovecii infections, respectively, was similarly provided to all recipients in both groups. The patients received acyclovir 200 mg three times daily for prophylaxis against varicella-zoster and herpes simplex virus (HSV); nevertheless, during the mucositis period, 250 mg/m^2 intravenous acyclovir was substituted twice daily (adjusted for renal insufficiency).

Endpoints and Definitions

The primary objective of this study was to compare the incidence of CMV reactivation between the two groups. CMV reactivation was defined as the detection of CMV DNA in serum by PCR. Additionally, a high viral load was indicated by a CMV DNAemia level exceeding 1000 copies/ml.

The secondary endpoints included the incidence of grade III-IV acute GVHD (aGVHD) at 100 days, 2-year occurrence of extensive chronic GVHD (cGVHD), and probabilities of overall survival (OS), disease-free survival (DFS), GVHD-free, relapse-free survival (GRFS), and non-relapse mortality (NRM) over two years post-transplantation. Acute and chronic GVHDs were defined and graded based on Glucksberg's criteria[24] and the National Institutes of Health consensus guidelines [25].

OS was defined as the duration from HSCT to death regardless of disease recurrence and was terminated at the final follow-up. DFS was characterized as the period following transplantation with no evidence of active disease. GRFS was defined as the time duration in the absence of grade III-IV aGVHD, extensive cGVHD treated with systemic immunosuppressive therapy, or relapse. Death occurring due to any cause, except relapse, is denoted as NRM.

Statistical analysis

Continuous variables were reported as median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. Categorical variables were analyzed using the chi-square or Fisher's exact tests. Survival outcomes (OS, DFS, and GRFS) were estimated using Kaplan-Meier curves and compared using log-rank tests. The cumulative incidences of CMV reactivation, GVHD, and NRM were calculated using competing risk regression (Fine-Gray model), with death as a competing event. The follow-up duration was determined via reverse Kaplan-Meier estimation. All analyses were performed in Stata v17 (StataCorp), with two-sided $P < 0.05$ considered significant.

RESULTS

Study population

A total of 80 patients were enrolled in this study, with 34 patients receiving a hybrid CMV prophylaxis regimen and 46 receiving the preemptive regimen. There were no significant differences between the two groups regarding the demographic and clinical variables studied.

Most patients underwent transplantation from haploidentical donors, with 22 patients (64.71%) in the hybrid group and 25 patients (54.35%) in the preemptive group, followed by matched unrelated donors (MUD) occurring in 9 patients (26.47%) in the hybrid group versus 18 patients (39.13%) in the preemptive group. Most of the patients were transplanted in CR1. The median follow-up duration was 33.47 months (95% CI: 28.45-38.83). Table 1 summarizes the baseline characteristics of the patients and donors.

CMV reactivation

The hybrid prophylaxis group demonstrated a significantly lower incidence of CMV reactivation within 90 days post-transplant compared with the preemptive group [33.84% (95% CI: 20.33- 52.82) vs. 82.08% (95% CI:69.70-91.59); $P = 0.000$] (Figure.1). CMV reactivation occurred earlier in the preemptive group, with 74% (34/46) experiencing pre-engraftment reactivation versus 18% (6/34) in the hybrid group ($P < 0.001$) (Figure 2A). High-level viremia (>1,000 copies/mL) was also less frequent with hybrid prophylaxis (26% vs. 65%; $P = 0.001$) (Figure 2B).

Transplant outcomes

Neutrophil engraftment (absolute neutrophil count ≥500/µL for 3 consecutive days) and platelet recovery (≥20,000/µL without transfusion for 7 days) were comparable between the groups. As displayed in Table 2, the cumulative incidences of PLT engraftment on day 30 were comparable between the hybrid [81.55% (95% CI, 66.82- 92.49)] and preemptive groups [77.73% (95% CI, 64.80- 88.48)], P=0.38. The preemptive group had a neutrophil engraftment incidence of 84.78% (95% CI, 73.03-93.31) at day 30, as compared with the hybrid group [88.56% (95% CI, 74.25- 96.87)], p = 0.33.

Regarding mean (±SD) time to platelet or neutrophil recovery, there was no statistically significant difference between the two groups. It was 23.00 (±17.72) and 18.65 (± 14.4) days for platelet or neutrophils recovery in the preemptive group and 20.00 (±9.74) and 16.44 (±12.89) days in the hybrid group.

As shown in Table 2, the hybrid regimen recipients demonstrated a slightly superior 2-year OS to those administered the preemptive regimen, although the difference was not statistically significant (64.45% (95% CI: 45.94-78.03) vs. 60.55% (95% CI: 44.87-73.04), P= 0.75). Similarly, despite the higher probability rates of DFS and GFRS observed in the hybrid group than the preemptive group, these differences did not reach statistical significance (61.38% (95% CI: 42.91-75.46) vs. 56.1% (95% CI: 40.54-69.07), P= 0.55 for DFS and 33.83% (95% CI: 17.66-50.79) vs. 13.28% (95% CI: 5.09-25.44), P= 0.10 for GRFS).

In terms of GVHD, 9.68% (95% CI: 3.12-30.04) of the patients in the hybrid group developed grade III-IV acute GVHD, which was lower than the 14.39% (95% CI: 6.46-32.08) reported in the preemptive group, although this difference was not statistically significant (P = 0.59). Moreover, the cumulative incidence of extensive cGVHD during the two years was comparable between the groups (16.17% (95% CI: 6.04-43.30) for the hybrid group vs. 17.98% (95% CI: 7.39-43.74) for the preemptive group, P= 0.96) (Table 2).

Furthermore, the 2-year NRM rates also did not significantly differ between the two groups, although the hybrid cohort showed diminished rates compared to the preemptive group (17.85% (95% CI: 8.44-35.5) vs. 24.56% (95% CI: 14.37-40.06), P= 0.47) (Table 2). Additionally, the groups did not show any significant differences regarding the causes of death. Relapse was the leading cause of death in both groups, followed by infection.

Table 1. Baseline characteristics of high-risk allo-HSCT recipients stratified by CMV prophylaxis strategy

Protocol		Pre-emptive therapy	Hybrid prophylactic	P. V
Total, No (%)		46 (57.5)	34 (42.5)	
Median age, yr (range)		31.5 (25-39)	29.5 (23-41)	0.87
Male/female, No (%)		27/19 (58.7/41.3)	19/15 (55.88/44.12)	0.46
Donor type, No (%)	MOD	3 (6.52)	3 (8.82)	0.57
	MUD	18 (39.13)	9 (26.47)	
	Haplo	25 (54.35)	22 (64.71)	
Match status, No (%)	1locus mismatched	7 (15.22)	5 (14.71)	0.52
	Full match	14 (30.43)	7 (20.59)	
	Haploidentical	25 (54.35)	22 (64.71)	
Primary disease, No (%)	ALL	16 (34.78)	14 (41.18)	0.64
	AML	30 (65.22)	20 (58.82)	
Disease status, No (%)	CR1	26 (56.52)	18 (52.94)	0.77
	CR2	15 (32.61)	12 (35.29)	
	CR3	5 (10.87)	4 (11.76)	

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; MOD, matched other related donor; MUD, matched unrelated donor; Haplo, haploidentical donor; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission

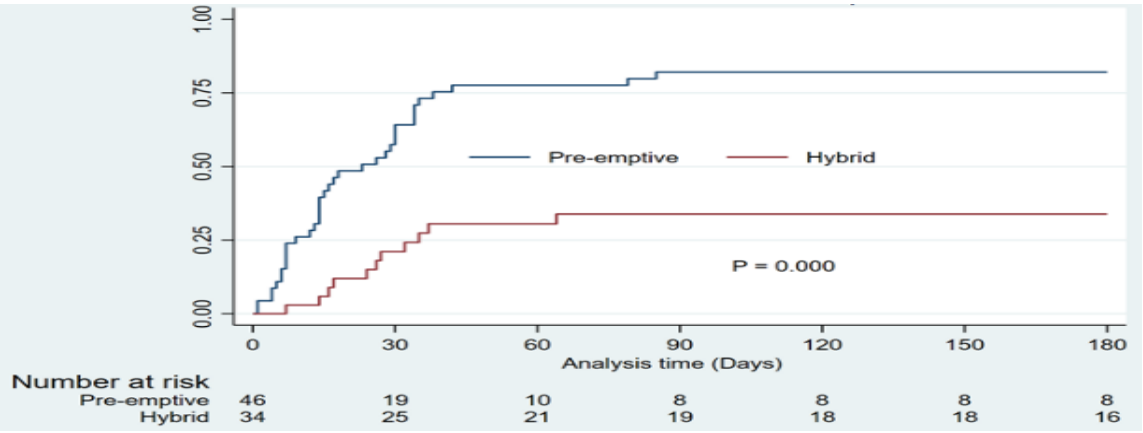

Figure 1. Cumulative incidence of CMV reactivation to day +180 by prevention strategy in high-risk allo-HSCT recipients (n = 80). P determined by the Gray test.

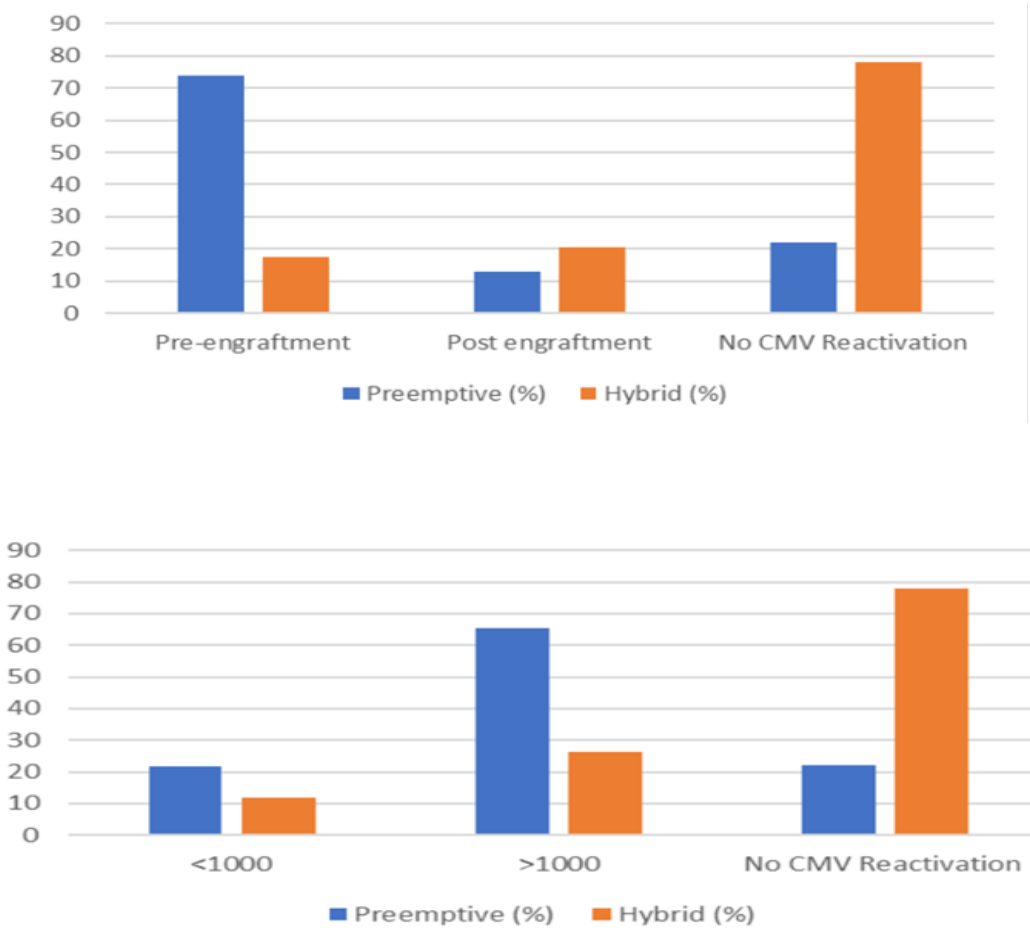

Figure 2. CMV reactivation characteristics by prophylaxis strategy. (A) Percent of CMV reactivation based of pre- and post-engraftment. (B) Distribution of CMV DNAemia levels (threshold: 1,000 copies/mL). Percentages reflect proportions within each group.

Table 2. Outcomes of high-risk allo-HSCT recipients by the CMV prophylaxis strategy

Protocol		Pre-emptive therapy	Hybrid prophylactic	P
Probability of OS (95% CI)	1-year	65.22 (49.64-77.04)	70.59 (52.24-82.96)	0.75
	2-year	60.55 (44.87-73.04)	64.45 (45.94-78.03)	
Probability of DFS (95% CI)	1-year	63.04 (47.46-75.16)	70.59 (52.24-82.96)	0.55
	2-year	56.1 (40.54-69.07)	61.38 (42.91-75.46)	
Probability of GRFS (95% CI)	1-year	33.06 (19.89-46.83)	41.35 (23.91-57.99)	0.10
	2-year	13.28 (5.09-25.44)	33.83 (17.66-50.79)	
Cum Incidence of NRM (95% CI)	1-year	21.86 (12.41-36.84)	17.85 (8.44-35.5)	0.47
	2-year	24.56 (14.37-40.06)	17.85 (8.44-35.5)	
Cum Incidence of 3-months CMV Reactivation (95% CI)		82.08 (69.70-91.59)	33.84 (20.33- 52.82)	0.00
Cum Incidence of aGVHD (III-IV) (95% CI)		14.39 (6.46-32.08)	9.68 (3.12-30.04)	0.59
Cum Incidence of Extensive cGVHD (95% CI)		17.98 (7.39-43.74)	16.17 (6.04-43.3)	0.96
Cum Incidence of Neutrophil engraftment at 28 days (95% CI)		84.78 (73.03-93.31)	88.56 (74.25-96.87)	0.33
Cum Incidence of PLT engraftment at 28 days (95% CI)		77.73 (64.80-88.48)	81.55 (66.82-92.49)	0.38

DISCUSSION

CMV infection remains a significant challenge for allo-HSCT recipients, particularly among CMV-seropositive individuals. This study compared the efficacy of a hybrid CMV prophylaxis regimen, consisting of pre-transplant ganciclovir followed by high-dose valacyclovir, with a standard pre-emptive strategy. The results demonstrated that the hybrid prophylaxis regimen significantly reduced CMV reactivation rates at 90 days post-transplantation and during the pre-engraftment period compared to the standard preemptive regimen without impacting OS, DFS, GVHD, or NRM. These findings align with and add to the growing body of literature on CMV prophylaxis.

While several studies have indicated the efficacy of prophylactic agents in reducing primary CMV infection and reactivation following transplantation, assessing their overall advantage has been difficult[14]. Similar to our results, a previous study reported that umbilical cord blood transplantation recipients administered the intensive regimen (pretransplant ganciclovir in combination with 2 g valacyclovir three times daily from day -1 through day +100) showed a significantly lower rate of CMV reactivation in comparison to the patients treated with the standard pre-emptive strategy [26].

In various HSCT populations, the use of ganciclovir before transplantation has been found to decrease CMV complications [27-30] and is thought to reduce the occurrence of early CMV reactivation following transplantation [30]. This outcome suggests that hybrid prophylaxis regimens are effective in reducing CMV reactivation in high-risk HSCT populations. Moreover, Hill et al. reported no significant differences in reactivation rates when comparing a modified intensive strategy to the original approach, indicating that both pre-transplant ganciclovir and high-dose valacyclovir contribute to lowering CMV reactivation[31].

The lower incidence of high-level viremia (CMV DNAemia > 1000 copies/ml) observed in our hybrid group (26.47% vs. 65.22% in the preemptive group, P = 0.001) echoes findings from Milano et al., which showed a reduction in high-level CMV viremia in intensive prophylaxis recipients[26], suggesting a

potential protective effect against the progression to overt CMV disease. Additionally, Hammerstrom et al. reported similar reductions in CMV reactivation among intensified prophylaxis recipients, supporting our results that hybrid prophylaxis may be effective in preventing significant CMV replication and its associated complications[32].

Consistent with previous studies mentioned above[26,32], the present study also reported that the choice of CMV prophylaxis strategy did not impact HSCT outcomes, suggesting that while the hybrid regimen effectively reduces CMV reactivation, it does not alter the long-term survival as well as the risk of GVHD (acute or chronic) and NRM in HSCT recipients.

Considering the toxicities related to the antiviral medications used in the prophylaxis regimens, it has been proposed that the administration of intermediate-dose valacyclovir during the peri-engraftment period may result in graft failure[27,33], though not previously reported in the literature. In our study, only one patient in the preemptive group developed graft failure, and the two groups did not differ in this regard. Similarly, previous studies using intermediate to high-dose valacyclovir also did not reveal any potential impact of higher doses of valacyclovir on the incidence of graft failure[26, 32].

In addition to clinical efficacy, economic considerations are crucial when selecting CMV prevention strategies, particularly in resource-constrained environments. Letermovir, an approved agent for CMV prophylaxis, has demonstrated efficacy in reducing clinically significant CMV infection and possesses a favorable safety profile. However, its high acquisition cost and limited availability in many healthcare settings may restrict its widespread adoption. In contrast, the hybrid regimen evaluated in this study utilizes established, widely accessible antivirals at substantially lower cost. Although our study did not include formal pharmacoeconomic analysis, the significantly reduced incidence of CMV reactivation observed with the hybrid strategy, combined with the affordability of its components, suggests a potentially cost-effective alternative to Letermovir in high-risk HSCT recipients. Future research incorporating detailed cost-effectiveness modeling is warranted to quantify the economic and clinical value of this approach relative to novel antiviral agents or adoptive T-cell therapy, especially for resistant CMV infections [34].

Our study's strengths can be attributed to its prospective design, balanced distribution of patients in two groups according to the baseline characteristics, and the inclusion of only high-risk patients for CMV reactivation. Nevertheless, the single-center small study population, missing molecular tests and disease risk stratification, and lack of data on CMV disease limit our analysis's findings.

CONCLUSION

The findings of this study suggest that a hybrid CMV prophylaxis regimen consisting of pre-transplant ganciclovir and high-dose valacyclovir is effective in reducing CMV reactivation without adversely impacting overall transplant outcomes, such as survival, GVHD, or NRM. These results are consistent with previous research, indicating that intensive prophylaxis strategies can be an effective alternative to standard prophylaxis CMV prophylaxis in high-risk HSCT recipients. Future research, including larger randomized controlled trials, is warranted to confirm these findings and further refine CMV prophylaxis strategies in allogeneic HSCT settings.

Ethics approval and consent to participate: The trial was performed under the Declaration of Helsinki and Good Clinical Practice. It was approved by the Ethics Committee of HORCSCT (IR.TUMS.HORCSCT.REC.1401.016) and written informed consent was obtained from the patients before enrollment.

Consent for publication: not applicable.

Data Availability: All datasets produced or analyzed during this investigation are included in the published article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. No commercial or financial relationships that could influence the research were present during this study.

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