Open Access

OBM Transplantation

LIDSEN Publishing Inc.

Research Article

Oral Versus Intravenous Anti-CMV Preemptive Strategies in Allogeneic Stem Cell Transplant Patients with CMV Reactivation: Experience from the National Center of Bone Marrow Transplantation, Tunis, Tunisia

Nour Ben Abdeljelil [1], Rimmel Yosra Kanoun [1,*], Roua Hsasna [1], Rabeb Jaied [1], Sabrine Mekni [1], Siwar Frigui [2], Lamia Torjemane [1], Dorra Belloumi [1], Ines Turki [1], Rihab Ouerghi [1], Insaf Ben Yaiche [1], Wafa Achour [2], Saloua Ladeb [1], Tarek Ben Othman [1]

1. National center of bone marrow transplantation, Department of hematology and transplantation, Tunis, Tunisia; E-Mails: nour.abdejlil@gmail.com; kanounrimmelyosra@gmail.com; hsasna.roua@gmail.com; jaiedrabeb@gmail.com; sabrina.mekni@fmt.utm.tn; lamia_torjemane@yahoo.fr; dorrabelloumi@gmail.com; ines.turki.ba@gmail.com; rihabouerghi89@gmail.com; benyaicheinsaf@gmail.com; ladebsaloua63@gmail.com; tarek.benothman@fmt.utm.tn
2. National center of bone marrow transplantation, Central laboratory, Tunis, Tunisia; E-Mails: siwar.frigui@fmt.utm.tn; wafaachour@gmail.com

* **Correspondence:** Rimmel Yosra Kanoun; E-Mail: kanounrimmelyosra@gmail.com

Academic Editor: Nidhi Sharma

OBM Transplantation
2023, volume 7, issue 3
doi:10.21926/obm.transplant.2303195

Received: April 12, 2023
Accepted: July 28, 2023
Published: September 12, 2023

Abstract

Cytomegalovirus (CMV) infection is a common and severe complication following allogeneic stem cell transplantation (ASCT) and requires effective preemptive antiviral therapy. Both oral and intravenous (IV) antiviral agents effectively reduce CMV viral load and achieve viral clearance. Studies comparing oral and IV anti-CMV preemptive treatment in ASCT patients with CMV reactivation showed a potential difference in treatment response and safety profiles between the two administration routes. We retrospectively compared the efficacy and safety of oral with intravenous (IV) anti-CMV preemptive therapy in ASCT recipients with CMV reactivation. A descriptive retrospective study included patients who received their first ASCT between January 2018 and June 2022. The monitoring oral load was assessed weekly

using a quantitative polymerase chain reaction in plasma. Fifty-five patients developing 72 CMV reactivations were included. The median age was 29 years (range, 6-50). The main underlying diseases were acute leukemia and aplastic anemia. Before ASCT, 96% of patients were at high risk of CMV reactivation. CMV reactivations were observed at a median of 43 days (range, 16-270) post-ASCT. The median viral load at CMV reactivation was 248 copies/mL (range, 150-4800). The first-line preemptive treatment was oral in 51 (71%) of the episodes (Valganciclovir, n = 40; Leflunomide, n = 11) and IV in 21 (29%) of the episodes (Foscarnet, n = 16; Ganciclovir, n = 5). Response to first-line therapy was not statistically significant between the two groups (74% vs 76%, p = 0.88). Thirteen (25%) and 5 (24%) episodes needed second or subsequent-line therapy in the oral and IV groups, respectively. The hematological toxicity was significantly higher in the oral group (61% vs 29%, p = 0.01). The mean duration of hospital stay per patient in the oral and IV groups was 7 days and 49 days ($p < 10^{-3}$), respectively. More non-CMV documented infections were observed in the IV group (38% vs 4%, p = 0.001). After a median follow-up of 18 months (range, 2-55), the 2-year-overall survival, event-free survival and cumulative incidence of non-relapse mortality were 85%, 75% and 6%, respectively. Our results showed that the oral preemptive therapy for CMV reactivations after ASCT was as effective as IV formulations and needed less hospital stay time. However, it is associated with more hematological toxicity.

Keywords
Cytomegalovirus reactivation; allogeneic stem cell transplantation; viral load; preemptive therapy

1. Introduction

Cytomegalovirus (CMV) reactivation is a common and potentially serious complication after allogeneic hematopoietic stem cell transplantation (ASCT) and remains a major cause of morbidity and mortality in recipients of ASCT [1]. It occurs in 30-70% of seropositive recipients, usually within 100 days after transplantation [2]. Immunosuppressant drugs and graft versus host disease (GVHD) are the major risk factors for CMV reactivation [3]. Monitoring of CMV reactivation by weekly quantitative PCR (qPCR) DNA in plasma allows for early detection. It enables the initiation of preemptive antiviral therapy which plays a crucial role in managing CMV reactivation and preventing CMV disease [4]. Two commonly used administration routes for antiviral drugs are oral and intravenous (IV). The choice between oral and IV administration should consider various factors, including patient characteristics, comorbidities, renal and gastrointestinal function, and the availability of resources. This study compares the efficacy and safety of oral versus IV anti-CMV preemptive strategies in ASCT patients with CMV reactivation. Because of the high incidence of CMV seropositivity in the Tunisian population and no published data on CMV reactivation in our center, we compared the outcomes of CMV reactivations in ASCT recipients receiving either oral or IV anti-CMV preemptive therapies.

2. Materials and Methods

This is a retrospective study, analyzing all consecutive CMV reactivations after ASCT, which were treated preemptively at the national center of bone marrow transplantation in Tunisia from January 2018 to June 2022. Fifty-five patients developing 72 CMV reactivations were evaluated. All patients with hematological malignancies received a myeloablative conditioning regimen based on chemotherapy or total body irradiation and a transplant from HLA-identical sibling donors. Graft-versus-host disease (GVHD) prophylaxis consisted of Cyclosporine and a short course of Methotrexate, no other anti-GVHD prophylaxis was used. High-dose Acyclovir was used as antiviral prophylaxis from day + 1 until the introduction of the preemptive therapy, then after till day + 180.

Patients who experienced CMV reactivation requiring preemptive oral or IV antiviral treatment were included. We excluded patients with positive qPCR but less than 150 copies/ml, patients with CMV disease and patients who had experienced spontaneously resolved CMV reactivation.

The institutional ethics committee has approved this study and all patients provided written informed consent.

2.1 Diagnosis of CMV Reactivation

Monitoring of CMV infection was performed weekly after transplantation, from day +15 until day +100 (and once every two weeks until day +180 in patients on steroids for GVHD), by real-time quantitative polymerase chain reaction (qPCR) in EDTA plasma (Cobas AmpliPrep/COBAS TaqMan), with 56 UI/mL as the limit of detection and 137 UI/mL as the limit of quantification (1 copy = 0.91 UI). Reactivation was considered positive if qPCR was ≥150 copies/mL. The response was defined by undetectable qPCR.

2.2 Preemptive Anti-CMV Strategies

Preemptive therapy was selected according to the patient's hematological and renal status. Initial preemptive therapy was given for at least two weeks. Patients who did not respond to the first-line therapy after 2 weeks of treatment or developed severe toxicity were switched to a second- or subsequent-line therapy. In our center, the preemptive therapy was started if qPCR ≥150 copies/mL in patients on steroid therapy or if qPCR ≥150 copies/mL with increasing load in two consecutive tests in patients without steroid therapy. Preemptive therapy is stopped if patients have undetectable qPCR in two consecutive tests or develop severe toxicity. Patients were assigned to the "oral group" if they received Valganciclovir (VGCV) or Leflunomide (LF) and to "intravenous (IV) group" if they were treated with Foscarnet (FSC) or Ganciclovir (GCV).

2.3 Toxicity During the First-Line Treatment

The toxicity was graded according to the common toxicity criteria for adverse events version 4.0.

2.4 Non-CMV Documented Infection

Clinically documented infection (CDI) was defined as a fever in connection with unambiguous diagnostic signs of localized infection without microbiological proof or if inaccessible for examination; and microbiologically documented infection (MDI) was defined as a fever with

plausible pathogenic evidence (in the microbiological/time context) in addition to identified localized infection, or if blood culture was positive for pathogenic agents without a localized infection [5].

2.5 Statistical Analysis

The patient characteristics between the oral and IV groups were compared by using Fisher's exact test or the χ^2 statistic for categorical variables. Probabilities of the overall survival (OS) and the event-free survival (EFS) were estimated by using the Kaplan-Meier method. Events for EFS included relapse, death and non-relapse mortality (NRM). NRM was defined as death by any cause without prior relapse and was estimated by cumulative incidence (CI). Univariate comparisons of OS and EFS probabilities were performed by using the log-rank test, and Gray's test was used for univariate analysis of the CI. P-values were based on two-sided hypothesis tests. Alpha was set at 0.05.

3. Results

3.1 Baseline Characteristics

A total of 72 episodes of CMV viremia occurred in 55 patients. The baseline characteristics of the 55 patients are presented in Table 1. The sex ratio was 1.5, and the median age was 29 years (range, 6-50 years). All patients were at high risk of CMV reactivation according to serological status. The underlying diseases were acute leukemia (n = 38), aplastic anemia (n = 10), myelodysplastic syndrome (n = 3), chronic myeloid leukemia (n = 2), lymphoma (n = 1) and myelofibrosis (n = 1). Patients in the oral group were younger (p = 0.02) and had more acute GVHD (p = 0.02). The median duration of hospital stay was longer in the IV group without significant differences (44 vs 27 days, respectively, p = 0.24). Patients in the IV group experienced more non-CMV documented infections (38% vs 4%, p = 0.001).

Table 1 Patients' characteristics.

	Oral formulation	**Intravenous formulation**	**P**
Number of patients	37 (67%)	18 (33%)	
Number of episodes	51 (71%)	21 (29%)	
Gender			
Female	13 (35%)	9 (50%)	0.29
Male	24 (65%)	9 (50%)	
Age			
<18 years	5 (14%)	8 (44%)	**0.02**
≥18 years	32 (86%)	10 (55%)	
Diagnosis			
Aplastic anemia	4 (11%)	6 (33%)	
Acute myeloid leukemia	14 (38%)	4 (22%)	0.41
Acute lymphoid leukemia	13 (35%)	7 (39%)	
Others	6 (16%)	1 (6%)	

CMV donor/recipient status			
D+/R+ or D-/R+	36 (97%)	17 (94%)	1.00
Others	1 (3%)	1 (6%)	
Conditioning regimen			
TBI-based (TBI-VP16, TBI-Cy)	8 (22%)	5 (28%)	
CT-based (Bu-Cy, Fluda-Bu, TBF)	25 (67%)	7 (39%)	0.05
Non-myeloablative (hATG-Cy, rATG-Fluda-Cy)	4 (11%)	6 (33%)	
Stem cell source			
BM	17 (46%)	6 (33%)	0.63
Peripheral blood	20 (54%)	12(67%)	
Sex-mismatch			
Female to male	11 (30%)	7 (39%)	0.50
Other	26 (70%)	11 (61%)	
Viral load at first reactivation (copies/mL)			
Median	183	356	0.30
Range	150-4800	150-4477	
Median time of onset of first CMV viremia			
Median (days)	46	32	0.12
Range	18-210	16-270	
First CMV reactivation			
< day +100	40 (78%)	18 (86%)	0.74
≥ day +100	11 (22%)	3 (14%)	
Concurrent non-CMV documented infections	2 (4%) colitis (n = 1) nephritis (n = 1)	8 (38%) bacteremia (n = 3) fungemia (n = 1) CRBSI (n = 2) pneumonia (n = 2)	**0.001**
Duration of hospital stay			
mean (days)	7	49	**$<10^{-3}$**
Acute GVHD grade ≥II	28 (55%)	8 (38%)	**0.02**

TBI: Total body irradiation, CT: Chemotherapy, BM: Bone marrow, CMV: Cytomegalovirus, CRBSI: Catheter related blood stream infection, GVHD: Graft-versus-host disease, Others: myelodysplastic syndrome (n = 3), chronic myeloid leukemia (n = 2), lymphoma (n = 1) and myelofibrosis (n = 1), TBI-based: TBI-VP16, TBI-cyclophosphamide, CT-based: busulfan. iv-cyclophosphamide, Fludarabine- Cyclophosphamide, thiotepa-busulfan-fludarabine. hATG-Cy: horse anti-thymocyte globulin-cyclophosphamide, rATG-Fluda-Cy: rabbit anti-thymocyte globulin-fludarabine-cyclophosphamide.

3.2 CMV Characteristics in the Entire Cohort

The median time of viremia onset in the 72 episodes was 43 days (range, 16-270 days) after ASCT. Fifty-eight episodes (80%) were detected before day 100 after ASCT. Forty-two (58%) patients experienced a single episode and 13 (18%) patients experienced 2 or 3 episodes of viremia. In all the episodes combined, the median viral load at diagnosis was 248 copies/ml (range, 150-4800),

183 (range, 150-4800) and 356 (range,150-4477) in the oral and IV groups respectively (p = 0.30). Thirty-six (65%) patients had acute GVHD grade ≥II and were on steroid therapy before CMV reactivation. With a median follow-up of 18 months (range, 2-55), the 2-year OS, EFS (Figure 1) and the 2-year CI of NRM (Figure 2) were 81%, 75% and 6%, respectively.

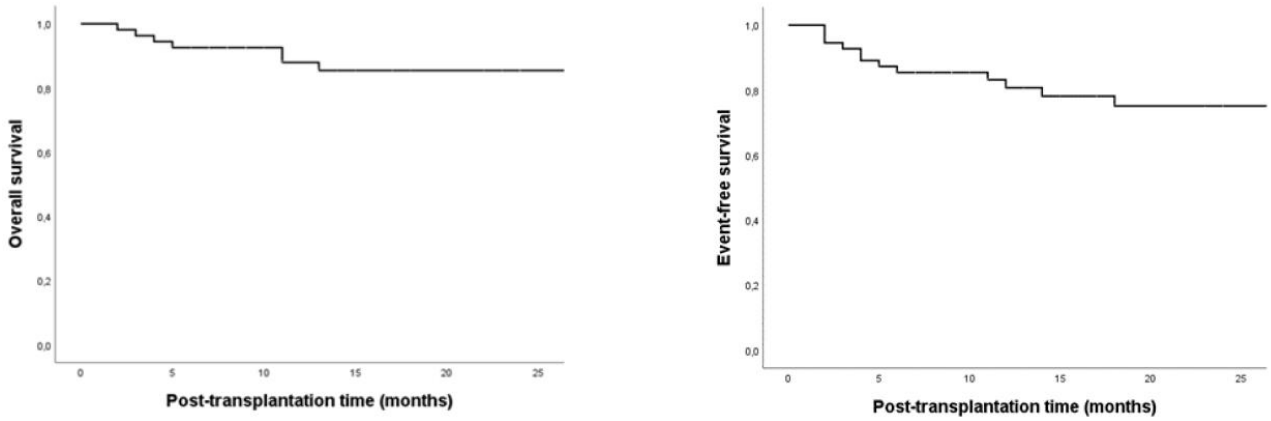

Figure 1 Estimate of overall survival and event-free survival in the entire cohort.

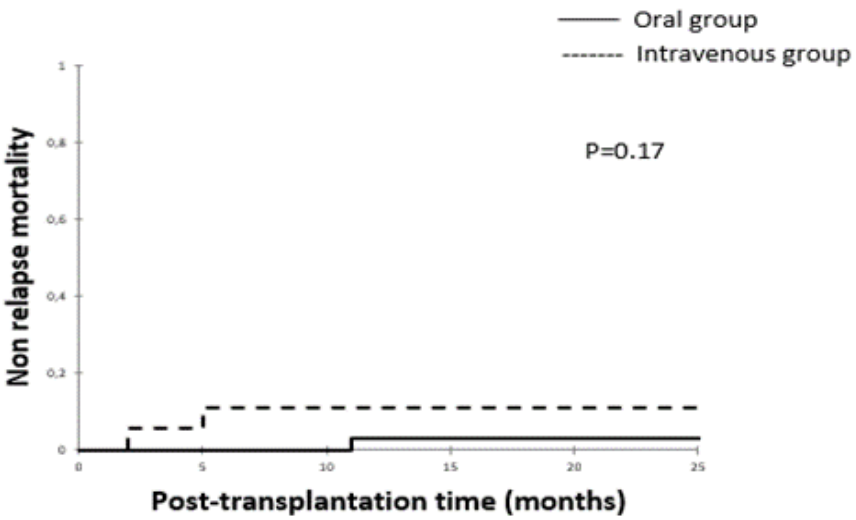

Figure 2 Cumulative incidence of non-relapse mortality in oral and intravenous groups.

3.3 Efficacy of Oral Versus Intravenous Anti-CMV Treatment

The first-line preemptive treatment was VGCV in 40 (55%), FSC in 16 (20%), LF in 11 (15%) and GCV in 5 (7%) episodes. First-line preemptive therapy was successful in 38 of 51 (74%) and 16 of 21 (76%) of the episodes (p = 0.88), at a median of 28 days (range, 7-50) and 21 days (range, 7-42) in the oral and IV CMV groups (p = 0.37), respectively. The median duration of the first-line preemptive therapy was 21 days (range, 2-69) and 15 days (range, 4-32) in oral and IV groups (p = 0.08), respectively. Among the 72 episodes, 18 (25%) required a second- or third-line therapy and all cleared the virus: (5/5) in the IV group and (13/13) in the oral group (Table 2, Table 3). No patients developed CMV end-organ disease.

After a median follow-up of 18 months (range, 2-55), there was no statistically significant difference in terms of OS, EFS and NRM (88% vs 80%, p = 0.79), (72% vs 83%, p = 0.48) and (3% vs 11%, p = 0.17) between oral and IV group, respectively.

Table 2 Strategy in oral group.

First-line	Second-line	Third-line
VGCV (n = 40)	LF (n = 1)	FSC (n = 1)
	FSC (n = 4)	
	GCV (n = 3)	FSC (n = 2)
LF (n = 11)	VGCV (n = 3)	
	FSC (n = 2)	

VGCV: Valganciclovir, LF: Leflunomide, FSC: Foscarnet, GCV: Ganciclovir

Table 3 Strategy in IV group.

First-line	Second-line
FSC (n = 16)	GCV (n = 1)
GCV (n = 5)	FSC (n = 4)

FSC: Foscarnet, GCV: Ganciclovir

3.4 Safety of Preemptive Therapy

Hematologic toxicity was observed in 20 (61%) and 6 (29%) of the episodes treated by oral and IV formulations (p = 0.01), respectively. Neutropenia and thrombocytopenia grade ≥3 were observed in 10 (20%) vs 3 (14%) and 11 (21%) vs 1 (5%) of the episodes in the oral and IV groups, respectively. No patients developed renal toxicity after the first-line therapy by FSC. Treatment discontinuation was necessary in 17 episodes (13 with VGCV and 4 with LF) in the oral group, and in 3 episodes in the IV group, respectively. In the univariate analysis, factors associated with toxicity were: age ≥18 years (p = 0.03), acute GVHD before CMV reactivation (p = 0.007), high-dose steroids (p = 0.03), early reactivation (p = 0.06) and oral treatment (VGC or LF) (p = 0.01).

Patients in the IV group experienced more non-CMV documented infections (38% vs 4%, p = 0.001), related to 2 infections in the oral group (1 colitis, 1 nephritis), and 8 in the IV group (3 bacteremias, 1 fungemia, 2 catheters related bloodstream infection, 2 pneumonia).

The mean duration of hospital stays per patient in the oral and IV groups was 7 days and 49 days, respectively ($p < 10^{-3}$).

4. Discussion

Cytomegalovirus reactivation is a significant complication in ASCT patients and is potentially associated with end-organ disease, leading to increased morbidity and mortality. Preemptive antiviral therapy is crucial in managing CMV reactivation [6, 7]. However, the optimal route of administration remains debated. Our study compares the efficacy and safety of oral versus IV anti-CMV preemptive strategies in allogeneic SCT patients with CMV reactivation. The choice between oral and IV anti-CMV preemptive antiviral agents, such as valganciclovir, ganciclovir and foscarnet

should consider various factors, including patient-specific characteristics, the severity of CMV reactivation, drug tolerability, and resource availability.

Oral administration offers the advantages of convenience, and reduced healthcare costs. It allows patients to self-administer the medication without the need for healthcare professionals. This aspect is particularly beneficial in outpatient settings or when patients are discharged. Furthermore, oral medications generally have a good safety profile and are associated with minimal adverse effects. In contrast, IV administration allows for better drug bioavailability, especially in patients with gastrointestinal complications or poor oral absorption. We included 55 consecutive recipients who developed 72 episodes of CMV reactivation and received preemptive therapy with either oral (VGC and LF) or IV anti-CMV formulations (FSC and GCV).

All patients in the IV group and 94% of the oral group responded and converted to a negative qPCR after the first- or second-line therapy. The remaining patients (6%) required a third-line therapy with FSC, and all responded. The differences between the two groups were not statistically significant regarding OS, EFS and NRM. These results aligned with other studies using oral VGC or IV formulations (GCV or FSC), demonstrating a response rate above 90% after 2 weeks of therapy and less than 5% of CMV disease [8-14]. Ganciclovir and foscarnet are two commonly used IV antiviral agents for CMV management. These medications have effectively reduced CMV viral load and prevented disease progression in allogeneic SCT patients. Intravenous therapy is particularly useful in cases where oral medications are contraindicated, such as gastrointestinal dysfunction. Additionally, foscarnet allows for flexibility in dose adjustment based on renal function, which is crucial as this antiviral agent can cause nephrotoxicity. In our institution, oral formulations were used as the preferred primary preemptive therapy in patients without cytopenia or symptomatic digestive acute GVHD, because they offer advantages such as hospital avoidance, sparing renal function and reduced cost. In our study, the baseline CMV loads in the oral and IV-treated groups were comparable, indicating similar anti-CMV activity. However, Gokarn et al. found that oral preemptive therapy with LF is more effective in patients with a lower CMV burden ($<2 \times 10^3$ copies/mL [15]. In a small retrospective study including 15 patients, eleven patients (73%) had completed a 28-day therapy with VGCV, and all patients had complete clearance of the virus with a median time of 6 days (range 4-18 days). In this study, six patients (40%) experienced hematological toxicity, specifically neutropenia and/or thrombocytopenia, which resulted in the discontinuation of the drug in four cases [16]. In a prospective study by Liu Kai-yan et al., among 54 patients treated, 89% (48/54) responded to VGCV and no significant toxicity was observed in this study [17].

CMV reactivation has been identified as an independent prognostic factor for worse outcomes following ASCT, as it is associated with substantial morbidity and mortality [18, 19]. In our study, despite the high-risk profile of our patients and the presence of acute GVHD and steroid therapy, the 2-year OS, EFS and NRM were favorable (81%, 75% and 6% respectively) with statistically no significant difference observed between the oral and IV treatment groups. The encouraging results observed in our study can be attributed to the implementation of early preemptive therapy initiated at a relatively low CMV burden (≥150 copies/ml). This hypothesis is supported by a retrospective study including 174 ASCT recipients, wherein 109 patients (63%) experienced CMV viremia. The study revealed a strong correlation between a peak viremia level of ≥150 IU/mL and a decreased likelihood of spontaneous clearance (relative risk, 0.16; 95% confidence interval, 0.1-0.27), regardless of established clinical risk factors such as CMV donor serostatus, exposure to anti-thymocyte globulin, and underlying lymphoid malignancy. The median time for viremia clearance

was significantly shorter in patients who initiated therapy at a CMV level of 350 IU/mL compared to those who started at a higher level (44% versus 57%; p = 0.42) [20]. However, patients in the oral group experienced an increased incidence of grade 3-4 neutropenia and thrombocytopenia, compared to the IV group in which most received FSC. Few patients were treated by GCV (76% vs 24%) avoiding myelosuppression. However, the treatment discontinuation due to grade 3-4 neutropenia was manageable with hematopoietic growth factors. Patients in the IV group experienced developed more non-CMV documented infections than the oral group.

Our study was not designed to evaluate the pharmacoeconomic cost difference between the oral and IV routes of antiviral treatment. Ueno Rie et al. conducted cost-effectiveness analyses to evaluate the financial impact of oral and IV anti-CMV preemptive strategies. This analysis considered direct costs, such as drug acquisition costs, hospitalization expenses, and outpatient visit fees, as well as indirect costs associated with CMV-related complications, extended treatment duration, or readmissions. The incremental cost associated with IV therapy was relatively higher [21].

Despite these positive results, our study has several limitations related to its retrospective design, the small sample size, and the low threshold load chosen to start preemptive therapy. In our practical experience, 65% of our patients with acute GVHD and a low qPCR showed a rapid increase in the viral load, when on steroid therapy. As a consequence, the course of CMV infection can be rapidly progressive and ultimately fatal [22-25]. However, the exact threshold for treatment is still an area of controversy, different thresholds have been used and vary according to the severity of immunosuppression and different centers [9, 26-28]. In a recent survey conducted by the infectious disease working party of the European Bone Marrow Transplantation (EBMT), there was large variability on the threshold of CMV viremia used to start preemptive therapy; however, the preference was for a CMV load $>10^3$ copies/mL [29].

5. Conclusions

In our study, oral and IV anti-CMV preemptive strategies showed efficacy in managing CMV reactivation in ASCT patients. However, the oral formulation was associated with fewer non-CMV documented infections and hospital stays, but more hematological toxicity. Randomized studies are needed to establish standardized guidelines and evaluate the long-term outcomes associated with each strategy to improve the management of CMV reactivation in this vulnerable patient population. Similarly, a larger study, including pharmacoeconomic evaluation, is warranted to assess these two strategies.

Acknowledgments

The authors thank all medical staff who supported this study and participated in the management of the patients.

Author Contributions

Nour Ben Abdeljelil: Manuscript editing, writing, study design**. Rimmel Yosra Kanoun**: Collected and analyzed the data, interpretation of data, Manuscript writing. **Roua Hsasna and Rabeb Jaied:** obtained data. **Sabrine Mekni**: data analysis, interpretation of data. **Siwar Frigui**: Obtained data. **Lamia Torjemane**: study design. **Dorra Belloumi, Ines Turki, Rihab Ouerghi and Insaf Ben Yaiche**:

organization and maintenance of data. **Wafa Achour**: study concept. **Saloua Ladeb**: review, editing, and visualization. **Tarek Ben Othman**: critical revision, and final approval of the manuscript.

Funding

The authors declared that this study received no financial support.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Locatelli F, Bertaina A, Valentina Bertaina V, Merli P. Cytomegalovirus in hematopoietic stem cell transplant recipients - management of infection. Expert Rev Hematol. 2016; 9: 1093-1105.
2. Melendez-Munoz R, Marchalik R, Jerussi T, Dimitrova D, Nussenblatt V, Beri A, et al. Cytomegalovirus infection incidence and risk factors across diverse hematopoietic cell transplantation platforms using a standardized monitoring and treatment approach: A comprehensive evaluation from a single institution. Biol Blood Marrow Transplant. 2019; 25: 577-586.
3. Hakki M. Moving past ganciclovir and foscarnet: Advances in CMV therapy. Curr Hematol Malig Rep. 2020; 15: 90-102.
4. Cui J, Zhao K, Sun Y, Wen R, Zhang X, Li X, et al. Diagnosis and treatment for the early stage of cytomegalovirus infection during hematopoietic stem cell transplantation. Front Immunol. 2022; 13: 971156.
5. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis. 1997; 25: 551-573.
6. Ozdemir E, Saliba RM, Champlin RE, Couriel DR, Giralt SA, de Lima M, et al. Risk factors associated with late cytomegalovirus reactivation after allogeneic stem cell transplantation for hematological malignancies. Bone Marrow Transplant. 2007; 40: 125-136.
7. Jang JE, Hyun SY, Kim YD, Yoon SH, Hwang DY, Kim SJ, et al. Risk factors for progression from cytomegalovirus viremia to cytomegalovirus disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2012; 18: 881-886.
8. Pande A, Dubberke ER. Cytomegalovirus infections of the stem cell transplant recipient and hematologic malignancy patient. Infect Dis Clin. 2019; 33: 485-500.
9. Einsele H, Ljungman P, Boeckh M. How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation. Blood. 2020; 135: 1619-1629.
10. Reusser P, Einsele H, Lee J, Volin L, Rovira M, Engelhard D, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood. 2002; 99: 1159-1164.
11. Hakki M, Aitken SL, Danziger-Isakov L, Michaels MG, Carpenter PA, Chemaly RF, et al. American Society for Transplantation and Cellular Therapy series: #3—prevention of cytomegalovirus infection and disease after hematopoietic cell transplantation. Transplant Cell Ther. 2021; 27: 707-719.

12. Ayala E, Greene J, Sandin R, Perkins J, Field T, Tate C, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2006; 37: 851-856.
13. van der Heiden PL, Kalpoe JS, Barge RM, Willemze R, Kroes AC, Schippers EF. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. Bone Marrow Transplant. 2006; 37: 693-698.
14. Ruiz-Camps I, Len O, de la Cámara R, Gurguí M, Martino R, Jarque I, et al. Valganciclovir as pre-emptive therapy for cytomegalovirus infection in allogeneic haematopoietic stem cell transplant recipients. Antivir Ther. 2011; 16: 951-957.
15. Gokarn A, Toshniwal A, Pathak A, Arora S, Bonda A, Punatar S, et al. Use of leflunomide for treatment of cytomegalovirus infection in recipients of allogeneic stem cell transplant. Biol Blood Marrow Transplant. 2019; 25: 1832-1836.
16. Busca A, de Fabritiis P, Ghisetti V, Allice T, Mirabile M, Gentile G, et al. Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. Transpl Infect Dis. 2007; 9: 102-107.
17. Liu KY, Wang Y, Han MZ, Huang H, Chen H, Liu QF, et al. Valganciclovir for pre-emptive therapy of cytomegalovirus viraemia after hematopoietic stem cell transplantation: A prospective multi-center trial. Chin Med J. 2010; 123: 2199-2205.
18. Teira P, Battiwalla M, Ramanathan M, Barrett AJ, Ahn KW, Chen M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: A CIBMTR analysis. Blood. 2016; 127: 2427-2438.
19. Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: A retrospective cohort study. Lancet Haematol. 2016; 3: e119-e127.
20. Camargo JF, Kimble E, Rosa R, Shimose LA, Bueno MX, Jeyakumar N, et al. Impact of cytomegalovirus viral load on probability of spontaneous clearance and response to preemptive therapy in allogeneic stem cell transplantation recipients. Biol Blood Marrow Transplant. 2018; 24: 806-814.
21. Ueno R, Nishimura S, Fujimoto G, Piao Y, Takenaka K. The clinical and economic burden of cytomegalovirus management post allogeneic hematopoietic stem cell transplantation in Japan-A retrospective database study. Curr Med Res Opin. 2019; 35: 2089-2096.
22. Miyao K, Terakura S, Ozawa Y, Sawa M, Kohno A, Kasahara S, et al. Comparison of transplantation outcomes after foscarnet and ganciclovir administration as first-line anti-cytomegalovirus preemptive therapy. Transplant Cell Ther. 2021; 27: 342.e1-342.e10.
23. Fang J, Su Y, Zavras PD, Raval AD, Tang Y, Perales MA, et al. Impact of preemptive therapy for cytomegalovirus on hospitalizations and cost after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2020; 26: 1937-1947.
24. Johnsrud JJ, Nguyen IT, Domingo W, Raval AD, Tang Y, Narasimhan B, et al. The changing impact of cytomegalovirus among hematopoietic cell transplant recipients during the past decade: A single institutional cohort study. Transpl Infect Dis. 2022; 24: e13825.
25. Chanswangphuwana C, Wudhikarn K, Watanaboonyongcharoen P, Kansuwan P, Sukperm A, Bunworasate U. Prognostic factors and impact of CMV reactivation on acute myeloid leukemia

patients after HLA-matched myeloablative allogeneic stem cell transplantation in a high CMV prevalence country. Hematol Transfus Cell Ther. 2022. doi: 10.1016/j.htct.2022.01.006.
26. Tan SK, Waggoner JJ, Pinsky BA. Cytomegalovirus load at treatment initiation is predictive of time to resolution of viremia and duration of therapy in hematopoietic cell transplant recipients. J Clin Virol. 2015; 69: 179-183.
27. Damlaj M, Khalid F, Alahmari B, Alaskar A, Ghazi S, Johani S, et al. Optimal pre-emptive cytomegalovirus therapy threshold in a patient population with high prevalence of seropositive status. Curr Res Transl Med. 2020; 68: 131-137.
28. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009; 113: 5711-5719.
29. Cesaro S, Ljungman P, Tridello G, Mikulska M, Wendel L, Styczynski J, et al. New trends in the management of cytomegalovirus infection after allogeneic hematopoietic cell transplantation: A survey of the Infectious Diseases Working Pary of EBMT. Bone Marrow Transplant. 2023; 58: 203-208.