

Is CMV PCR Monitoring Necessary in Patients with Hematological Malignancy Receiving Chemotherapy? A Prospective Single-Center Study

Kemoterapi Alan Hematolojik Maligniteli Hastalarda CMV PCR İzlemi Gerekli midir?
Prospektif Tek Merkezli Bir Çalışma

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Abstract

Objective: This study aimed to evaluate cytomegalovirus (CMV) monitoring results in adult patients with hematological malignancies, identify risk factors associated with CMV reactivation, and emphasize the importance of regular CMV DNA monitoring using polymerase chain reaction (PCR).

Materials and Methods: In this prospective single-center study, 316 adult patients with leukemia or lymphoma receiving chemotherapy without hematopoietic stem cell transplantation were included. CMV DNA levels were monitored twice weekly during chemotherapy. Clinical and laboratory data were reviewed and associations between CMV reactivation and clinical and demographic parameters, including age, sex, malignancy type, neutropenia duration, lymphocyte count, and co-infections, were analyzed to identify independent risk factors.

Results: A total of 504 hospitalization episodes were recorded. CMV infection occurred in 9% of patients. CMV viremia was observed in 35 episodes, with 13 episodes showing both viremia and clinical CMV disease. Among the 13 cases of CMV disease, 4 were CMV retinitis and 9 CMV pneumonia. Antiviral therapy was administered in 29 episodes. Among 48 episodes of CMV viremia, 16 (33%) cases received preemptive therapy and 13 (27%) were treated for CMV disease. Post-neutropenia lymphopenia and concurrent infections were identified as independent risk factors for CMV reactivation.

Conclusion: This real-world study demonstrates that CMV infection is a significant threat during intensive chemotherapy in patients with hematological malignancies. Regular PCR-based CMV DNA monitoring allows early detection and timely intervention, potentially reducing morbidity and improving outcomes. These findings support routine

Öz

Amaç: Bu çalışma, hematolojik maligniteli erişkin hastalarda sitomegalovirüs (CMV) izlem sonuçlarını değerlendirmeyi, CMV reaktivasyonu ile ilişkili risk faktörlerini belirlemeyi ve polimeraz zincir reaksiyonu (PCR) yöntemi ile düzenli CMV DNA izleminin önemini vurgulamayı amaçladı.

Gereç ve Yöntemler: Bu prospektif, tek merkezli çalışmaya, kemoterapi alan ve hematopoietik kök hücre nakli yapılmamış 316 erişkin lösemi veya lenfoma hastası dâhil edildi. Kemoterapi sırasında CMV-DNA seviyeleri haftada iki kez izlendi. Klinik ve laboratuvar verileri incelendi; CMV reaktivasyonu ile yaş, cinsiyet, malignite tipi, nötropeni süresi, lenfosit sayısı ve eşlik eden enfeksiyonlar gibi klinik ve demografik parametreler arasındaki ilişkiler analiz edilerek bağımsız risk faktörleri belirlendi.

Bulgular: Toplam 504 hastaneye yatış epizodu kaydedildi. Hastaların %9'unda CMV enfeksiyonu görüldü. CMV viremi 35 epizotta gözlemlendi ve 13 epizotta hem viremi hem de klinik CMV hastalığı saptandı. On üç CMV hastalığı olgusundan 4'ü CMV retinitisi, 9'u CMV pnömonisi olarak tanımlandı. Antiviral tedavi 29 epizotta uygulandı. CMV viremi görülen 48 epizodun 16'sında (%33) önleyici tedavi, 13'ünde (%27) ise CMV hastalığı tedavisi uygulandı. Post-nötropeni lenfopeni ve eşlik eden enfeksiyonlar, CMV reaktivasyonu için bağımsız risk faktörleri olarak belirlendi.

Sonuç: Bu gerçek yaşam verisi, yoğun kemoterapi gören hematolojik maligniteli hastalarda CMV enfeksiyonunun ciddi bir tehdit oluşturduğunu göstermektedir. Düzenli PCR tabanlı CMV DNA izlemi, erken tespit ve zamanında müdahale ile morbiditeyi azaltabilir ve klinik sonuçları iyileştirebilir. Bu bulgular, yüksek riskli hematolojik



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Abstract

CMV surveillance of high-risk hematological cases to enhance patient management and clinical care.

Keywords: Cytomegalovirus, Leukemia, Lymphoma, Hematological malignancy, CMV reactivation

Öz

hastalarda rutin CMV izleminin hasta yönetimi ve bakımını iyileştirmek için desteklenmesi gerektiğini göstermektedir.

Anahtar Sözcükler: Sitomegalovirüs, Lösemi, Lenfoma, Hematolojik malignite, CMV reaktivasyonu

Introduction

Cytomegalovirus (CMV) infects many adults, causing a lifelong latent infection. Although CMV infection remains asymptomatic in most individuals, it constitutes a significant cause of morbidity and mortality in immunocompromised patients [1]. Due to the extensive use of immunosuppressive treatments, CMV infections have emerged as one of the most critical problems for patients with hematological malignancies globally [2,3]. However, routine CMV DNA monitoring is generally not required in patients with hematological diseases who are not receiving immunosuppressive therapy [3]. CMV infections can lead to life-threatening CMV-related diseases and graft rejections after bone marrow and solid organ transplantations. Furthermore, CMV can cause multiorgan disease in stem cell transplant recipients, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis. Therefore, antiviral prophylaxis and preemptive treatment strategies are applied for CMV in transplanted patients [4,5]. Data regarding CMV infection in non-transplanted patients are heterogeneous, complicating the determination of incidence and risk factors in this group. CMV infection/reactivation rates have ranged from 2% to 39% in previous studies [6,7,8]. Identified risk factors include high-dose corticosteroid use, severe disease state, poor performance status, and treatment regimens containing agents such as alemtuzumab, fludarabine, bortezomib, or rituximab [9].

CMV infection is rare in patients with hematological malignancies who have not undergone stem cell transplantation and studies in this field are limited. The purpose of this study was to evaluate the frequency of CMV reactivation and risk factors of CMV disease in this specific patient population.

Materials and Methods

Study Population

This prospective study was conducted in the Department of Hematology of the Erciyes University Faculty of Medicine between March 2020 and September 2021. Ethical approval was obtained from the Erciyes University Ethics Committee (approval no: 2020/130, date: 26.02.2020). All patients provided written informed consent prior to enrollment. The study included adult patients diagnosed with leukemia or lymphoma who developed absolute neutropenia lasting more than 3 days following

chemotherapy. Absolute neutropenia was defined as an absolute neutrophil count of less than 500/mm³. A total of 316 patients who met the inclusion criteria were enrolled consecutively.

Patients diagnosed with leukemia were classified as either in remission or relapsed/refractory based on bone marrow smear or biopsy results obtained after prior chemotherapy cycles. Newly diagnosed leukemia patients, including those receiving chemotherapy for the first time, were also included and received remission/induction or consolidation chemotherapy as appropriate. Post-treatment bone marrow evaluations were performed to determine their disease status as remission or relapsed. Patients whose disease status could not be assessed after chemotherapy were categorized as “continuing treatment.”

Similarly, lymphoma patients were evaluated for remission or relapsed/refractory status based on results from positron emission tomography/computed tomography (PET/CT) scans obtained after prior chemotherapy. Newly diagnosed patients were those receiving chemotherapy for the first time. Following treatment, PET/CT scans were performed to reassess disease status. Patients without post-treatment evaluations were also classified as “continuing treatment.”

High-dose corticosteroid use was defined as the administration of steroid therapy at doses greater than 1 mg/kg for at least 5 consecutive days. All corticosteroid dosages were standardized and converted to the prednisolone-equivalent dose for consistency in analysis.

CMV Monitoring and Definitions of CMV Infection and Disease

Following chemotherapy administration for patients diagnosed with leukemia and lymphoma, CMV polymerase chain reaction (PCR) monitoring was routinely performed twice weekly during hospitalization. CMV DNA was detected using a real-time PCR method. DNA isolation was carried out using the RTA Viral DNA Isolation Kit (RTA Laboratuvarları, Kocaeli, Türkiye) according to the manufacturer's instructions. The RTA Real-Time PCR Kit (RTA Laboratuvarları) was utilized for CMV PCR testing.

CMV DNA analysis was performed using plasma samples obtained from peripheral blood. The same DNA extraction method and PCR assay (RTA Viral DNA Isolation Kit and RTA Real-Time PCR Kit) were used consistently throughout the study period to ensure methodological uniformity.

A CMV DNA viral load exceeding 80 copies/mL was considered positive for CMV infection. CMV infection was evaluated based on clinical follow-up, radiological findings, the trajectory of viral load, and whether the virus was isolated from any tissue. Patients exhibiting clinical symptoms, radiological evidence of infection, or CMV manifestation in any organ were classified as having CMV disease. Cases not meeting these criteria were categorized as CMV DNAemia [10].

At admission, CMV immunoglobulin (Ig) M and IgG titers were assessed by enzyme-linked immunosorbent assay in all patients. In patients with CMV DNAemia or clinical suspicion of CMV disease, CMV DNA was also investigated by PCR from bronchoalveolar lavage, pleural fluid, and stool samples. Chest X-ray, thoracic CT, or orbital CT scans were performed as indicated. Findings were evaluated to determine the presence of CMV disease.

Patients diagnosed with CMV infection or disease received treatment with either ganciclovir (5 mg/kg every 12 h) or foscarnet (90 mg/kg every 12 h), with dosing adjusted based on renal function tests. Treatment success was defined as the resolution of clinical symptoms and laboratory findings, specifically conversion to negative CMV DNA status. Negative CMV DNA was defined as two consecutive negative test results or a single negative result without further testing due to discharge, provided that no subsequent positivity was detected during follow-up.

Complete blood count, neutrophil, and lymphocyte values were recorded and analyzed. Patients were stratified into three groups based on the timing of absolute neutropenia: before, during, and after neutropenia. CMV DNA positivity in relation to the onset of neutropenia and the day of clinical recovery were determined according to these groups. Neutropenia duration and total hospitalization time were also calculated. Absolute lymphopenia was defined as a lymphocyte count below 1000 cells/mm³.

Co-infection was defined as the occurrence of microbiologically or clinically documented infections caused by microorganisms other than CMV (including bacterial, viral, or fungal pathogens) during hospitalization. Prophylactic antifungal (posaconazole) and antiviral (acyclovir) therapies were administered in accordance with chemotherapy protocols that recommended their use.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation for normally distributed data and as median (minimum-maximum) for non-normally distributed data. Categorical (nominal) variables were presented as frequency and percentage [n (%)]. The impact of independent

variables on CMV viremia was evaluated using logistic regression analysis. Variables were first assessed in univariate analysis, and those found significant were subsequently included in multivariate analysis.

Categorical variables were compared using Pearson's chi-square test. For the comparison of non-normally distributed continuous variables, the Mann-Whitney U test was employed. Values of $p < 0.05$ were considered statistically significant.

Results

In this study, 316 leukemia and lymphoma patients were followed. These patients had a total of 504 hospitalization episodes. While 181 (57%) were male, 135 (43%) were female, and the median age was 55 (18-85) years. The study population's demographic and clinical characteristics are shown in Table 1.

Of the 504 hospitalization episodes, 179 (36%) corresponded to patients undergoing treatment during the initial diagnosis phase. The majority of patients were diagnosed with acute leukemia (n=199, 63%), followed by other hematological malignancies including lymphomas. In patients with leukemia, a total of 212 hospitalization episodes were associated with remission induction chemotherapy, while 131 episodes involved consolidation treatment protocols. Among patients with lymphoma, chemotherapy regimens varied across episodes: platinum-based therapies were administered in 33 episodes, gemcitabine-containing regimens in 17 episodes, rituximab-based treatment in 110 episodes, and other chemotherapeutic

Table 1. Demographic and clinical characteristics of the study population (n=316 patients).

Characteristics	Value
Sex, no. (%)	
Male	181 (57%)
Female	135 (43%)
Age, years	
	Median: 55 (range: 18-85)
Primary diagnosis, no. (%)	
Acute leukemia	199 (63%)
- Acute myeloid leukemia	149 (47%)
- Acute promyelocytic leukemia	13 (4%)
- B-cell acute lymphoblastic leukemia	37 (12%)
Lymphoma	117 (37%)
- Hodgkin lymphoma	19 (6%)
- Non-Hodgkin lymphoma	98 (31%)
Disease status*	
Newly diagnosed	179
In remission	147
Relapsed/refractory	178
*: Disease status refers to the status at the time of enrollment.	

combinations in 29 episodes. High-dose corticosteroid therapy was administered in 130 (26%) of the 504 chemotherapy episodes, either as part of the treatment protocol or as supportive care. The median cumulative corticosteroid dose, calculated in prednisolone equivalent, was 120 mg (range: 100-500 mg) (Table 2).

Among the 316 patients included in the study, 28 (9%) died during the post-chemotherapy period. The most frequently identified cause of death was septic shock, which was present in all fatal cases (100%), followed by bacterial pneumonia, observed in 21 of the 28 deceased patients (75%). Notably, 21 of the 28 patients who died had relapsed or refractory disease at the time of death.

CMV Monitoring Results

Serological screening revealed that all 316 patients were CMV-seropositive (CMV-IgG positive, CMV-IgM negative) at baseline. Real-time PCR was performed for every one of the 504 chemotherapy-related hospitalization episodes. Table 3 shows the CMV infection and treatment characteristics of the study population.

CMV DNA was detected in 48/504 episodes (9.5%). Of these, 35 episodes (7.0%) manifested as asymptomatic CMV DNAemia, whereas 13 episodes (2.6%) fulfilled the criteria for CMV disease (9 CMV pneumonia cases, 4 CMV retinitis cases). At the patient level, 28/316 individuals (8.9%) experienced at least one CMV event during the study period.

All patients in this study were managed using a preemptive CMV monitoring strategy based on routine twice-weekly CMV PCR testing. Antiviral therapy was initiated in 29 of the 48 CMV-positive episodes (60%). According to the definition of the

preemptive approach, all antiviral treatments initiated based on virological monitoring were considered preemptive therapy. Among the treated episodes, 16 received antiviral therapy due to increasing CMV DNAemia without clinical evidence of end-organ disease, whereas 13 episodes received antiviral therapy because of clinically overt CMV disease (9 CMV pneumonia cases, 4 CMV retinitis cases). The remaining 19 episodes (40%) with low-level CMV DNAemia were managed with close clinical and virological monitoring without immediate antiviral therapy.

Among the 29 treated episodes, CMV clearance and full clinical recovery were achieved in 13 (44.8%). Three episodes (10.3%) resulted in death despite antiviral therapy. In the remaining 13 episodes (44.8%), viraemia persisted; however, none of these patients progressed to CMV disease during follow-up.

CMV viremia was detected in 25 hospitalization episodes (7%) among patients with leukemia and in 23 hospitalization episodes (14%) among those with lymphoma. The frequency of CMV viremia was significantly higher in lymphoma-related episodes compared to leukemia-related episodes ($p=0.035$). Similarly, CMV disease occurred in 5 episodes (2%) associated with leukemia and in 8 episodes (5%) associated with lymphoma,

Table 2. Treatment characteristics during hospitalization episodes (n=504 episodes).

Characteristics	No. of episodes	Percentage (%)
Hospitalization episodes during initial diagnosis phase	179	36
Leukemia treatment episodes		
Remission induction chemotherapy	212	-
Consolidation treatment protocols	131	-
Lymphoma treatment episodes		
Platinum-based chemotherapy	33	-
Gemcitabine-containing regimens	17	-
Rituximab-based therapy	110	-
Other chemotherapy combinations	29	-
High-dose corticosteroid therapy	130	26

Table 3. CMV infection and treatment characteristics.

Characteristics	n/total	Percentage (%)
CMV detection via PCR (episode-based)		
Any CMV DNA positivity	48/504	9.5
Asymptomatic CMV DNAemia	35/504	7.0
CMV disease (total)	13/504	2.6
- CMV pneumonia	9	
- CMV retinitis	4	-
Antiviral treatment (among CMV + episodes)		
Any antiviral treatment	29/48	60.4
- Preemptive ganciclovir	16/48	33.3
- Overt CMV disease treatment	13/48	27.1
Observation without treatment	19/48	39.6
Treatment outcome (n=29 episodes)		
CMV clearance + full recovery	13	44.8
Death despite antiviral therapy	3	10.3
Persistent viraemia without CMV disease	13	44.8
CMV by underlying disease (episodes)		
CMV viremia in leukemia	25/343	7.0
CMV viremia in lymphoma	23/161	14.0
CMV disease in leukemia	5	2.0
CMV disease in lymphoma	8	5.0
CMV: Cytomegalovirus; PCR: polymerase chain reaction.		

demonstrating a statistically significant difference in disease prevalence between these two malignancy types ($p=0.038$).

Furthermore, both CMV viremia and CMV disease were found to be significantly more frequent in patients with refractory or relapsed disease compared to those in remission or undergoing first-line therapy ($p=0.006$ for viremia; $p=0.016$ for disease).

In our cohort, 16 patients with T-cell leukemia or T-cell lymphoma were followed during 36 chemotherapy-related hospitalization episodes. CMV reactivation was observed in four of these episodes: three episodes presented with CMV disease accompanied by viremia, while one episode developed isolated CMV viremia without clinical disease.

In univariate analysis, the following variables were found to be significantly associated with CMV viremia: lymphoma diagnosis, refractory disease status, administration of more than two lines of chemotherapy, rituximab-based treatment, lymphopenia prior to neutropenia, lymphopenia following neutropenia, and presence of co-infection. However, multivariate logistic regression analysis identified only post-neutropenic lymphopenia and co-infection as independent risk factors for CMV viremia. Specifically, patients who experienced lymphopenia after the neutropenic period had a 3.1-fold increased risk of developing CMV viremia compared to those without post-neutropenic lymphopenia ($p=0.011$). Additionally, the presence of co-infection was associated with a 6.4-fold higher risk of CMV viremia ($p=0.013$). Table 4 shows the results of the univariate and multivariate logistic regression analysis of risk factors for CMV viremia.

Co-infections and Results

Co-infection with microorganisms other than CMV was observed in 402 of 504 hospitalization episodes (80%). Neutropenic fever was the most frequently identified clinical presentation of co-infection, occurring in 391 episodes (78%). Among patients with neutropenic fever, microbiologically documented bloodstream infection was detected in a subset of cases. Gram-negative bacteria constituted the majority of isolates, followed by gram-positive organisms. The distribution of co-infections is summarized in Table 5.

A statistically significant association was identified between the presence of co-infection and CMV viremia ($p=0.002$). However, no statistically significant relationship was found between co-infection and CMV disease ($p=0.081$).

Discussion

Patients with hematological malignancies are at increased risk for infectious morbidity and mortality due to CMV reactivation. Although CMV-related life-threatening infections have been increasingly reported in this population, these occurrences are primarily attributed to the widespread use of immunosuppressive therapies and the adoption of novel treatment modalities. Many existing studies on CMV reactivation have focused on patients undergoing hematopoietic stem cell transplantation (HSCT) [11,12,13], whereas data on non-transplanted patients remain limited. In this context, our single-center experience offers valuable insight into CMV monitoring in patients with hematological malignancies who have not undergone transplantation.

Table 4. Logistic regression analysis of risk factors for CMV viremia.

Variable	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Sex	1.065	0.58-1.95	0.84	-	-	-
Diagnosis						
- Leukemia	Ref	-	-	Ref	-	-
- Lymphoma	0.447	0.22-0.92	0.03	0.504	0.19-1.32	0.16
Refractory disease	2.36	1.29-4.31	0.005	1.665	0.87-3.19	0.12
Remission-induction chemotherapy	0.734	0.39-1.36	0.33	-	-	-
Consolidation chemotherapy	0.541	0.25-1.19	0.13	-	-	-
Platinum-based therapy	1.339	0.45-3.98	0.60	-	-	-
Gemcitabine-based therapy	1.278	0.28-5.77	0.75	-	-	-
Rituximab-based therapy	1.926	1.01-3.66	0.045	1.129	0.41-3.14	0.82
First hospitalization	0.959	0.52-1.76	0.89	-	-	-
High-dose steroid	1.348	0.71-2.57	0.37	-	-	-
Pre-neutropenia lymphopenia	2.220	1.19-4.16	0.013	1.411	0.71-2.79	0.32
Post-neutropenia lymphopenia	4.531	1.99-10.33	<0.0001	3.097	1.29-7.43	0.011
Co-infection	6.462	1.54-27.08	0.011	6.403	1.47-27.89	0.013

CMV: Cytomegalovirus; OR: odds ratio; CI: confidence interval.

Table 5. Distribution of co-infections during hospitalization.

Infection type	n	%
Neutropenic fever	391	77.6
Bacterial pneumonia	80	15.9
Fungal pneumonia	74	14.7
Bacteremia	71	14.1
Catheter-related infection	34	6.7
Septic shock	28	5.6
Urinary tract infection	27	5.4
Neutropenic colitis	18	3.6
Perianal abscess	13	2.6
Oral candidiasis	8	1.6
Cellulitis	5	1.0
Rhinocerebral mucormycosis	4	0.8

HSCT is widely acknowledged as the foremost risk factor for CMV reactivation among patients with hematological malignancies. CMV reactivation rates among non-transplanted patients typically range from 5% to 16%, being generally lower than rates reported in transplanted cohorts [9,14,15]. For example, Han [16] reported an overall CMV antigenemia positivity rate of 9.3% in non-transplanted patients. Moreover, that study demonstrated a significantly higher incidence of CMV infections in patients with lymphoid malignancies compared to those with myeloid malignancies (13.6% vs. 3.9%, $p=0.001$). Consistent with these findings, our study observed an overall CMV infection rate of 9%, with higher reactivation rates and CMV disease frequency in lymphoma patients relative to those with myeloid malignancies. We suggest that the increased incidence in lymphoma patients may be related to the use of corticosteroids and immunosuppressive agents such as rituximab during their treatment regimens.

It should also be noted that the majority of lymphoma patients in our cohort had B-cell non-Hodgkin lymphoma and received rituximab-based treatment regimens, which may partially explain the higher frequency of CMV reactivation observed in this group. B-cell depletion and associated immune dysregulation may predispose patients to viral reactivation. In addition, 16 patients with T-cell leukemia or T-cell lymphoma were followed during 36 treatment episodes in our study, and CMV reactivation occurred in four of these episodes (three episodes with CMV disease accompanied by viremia and one episode with isolated viremia). However, the number of patients with T-cell malignancies was limited, preventing a detailed subgroup analysis.

In addition to the higher incidence of CMV reactivation in lymphoma patients, our study identified lymphopenia, particularly occurring after neutropenia, as a significant independent risk factor for CMV viremia. This finding underscores the importance of T-cell-mediated immunity in controlling

latent CMV infection. Persistent lymphopenia following chemotherapy may delay immune reconstitution, thereby facilitating viral reactivation. This aligns with prior studies that reported a correlation between low CD4+ T-cell counts and CMV reactivation risk, even outside of the transplant setting [17,18].

Another noteworthy finding of our study was the strong association between CMV viremia and co-infections. Co-infections were frequently observed in our cohort, reflecting the high infectious burden associated with intensive chemotherapy and prolonged neutropenia in patients with hematological malignancies. As shown in Table 5, neutropenic fever was the most common infectious complication, followed by bacterial pneumonia, fungal pneumonia, and bacteremia. In multivariate analysis, the presence of a concurrent non-CMV infection increased the likelihood of CMV viremia by more than sixfold. This suggests that the immune dysregulation caused by additional infectious insults may further compromise host defenses against latent viruses. Interestingly, however, we did not find a statistically significant association between co-infections and CMV disease [9,19]. This may indicate that while co-infections contribute to CMV viral replication, the development of overt end-organ disease may require additional host or pathogen-related factors.

Invasive fungal infections, particularly aspergillosis, have been reported in association with CMV reactivation in severely immunocompromised patients. In our cohort, fungal pneumonia was identified in 74 hospitalization episodes, indicating a substantial burden of fungal infections in patients undergoing intensive chemotherapy and prolonged neutropenia. However, we did not observe a clear temporal association between CMV reactivation and invasive fungal infection, including aspergillosis. In our cohort, antifungal prophylaxis was routinely administered according to chemotherapy protocols.

Refractory disease and exposure to more than two lines of chemotherapy were also associated with increased CMV reactivation risk in univariate analysis. These patients likely represent a subgroup with greater cumulative immunosuppression, highlighting the need for closer viral monitoring in later treatment phases. The use of rituximab was another variable associated with CMV viremia, potentially due to its B-cell-depleting effect and subsequent impairment of CMV-specific humoral and cellular immune responses [20,21].

Ganciclovir was the primary antiviral agent used for both preemptive therapy and treatment of active CMV disease. Approximately 45% of the CMV-positive episodes that received antiviral treatment achieved complete virological clearance and clinical recovery. However, some patients remained PCR-positive despite therapy and a subset unfortunately died, highlighting the challenges in managing CMV infection in severely immunocompromised individuals. These outcomes underscore

the need for individualized treatment strategies. Notably, one patient who did not respond to ganciclovir was successfully switched to foscarnet, emphasizing the importance of early detection and therapeutic flexibility in managing resistant cases.

Study Limitations

Despite the strengths of our prospective design, this study has several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings to broader populations with different demographic or clinical characteristics. Second, although we performed systematic CMV DNA monitoring, detailed immunological assessments such as quantification of CMV-specific T-cell responses were not conducted, which could have provided deeper insight into the mechanisms underlying CMV reactivation. Third, the study did not include a control group of healthy individuals or patients with hematological malignancies not receiving chemotherapy, which might have clarified the baseline risk of CMV reactivation in this population. Finally, antiviral treatment decisions were made based on clinical judgment and institutional protocols rather than randomized allocation, which may have introduced bias in treatment outcomes. Future multicenter studies with comprehensive immunological profiling and standardized therapeutic approaches are warranted to confirm and expand upon our findings.

Conclusion

In this prospective study of non-transplanted patients with hematological malignancies, CMV reactivation was identified as a significant complication, particularly among those with lymphoma, refractory disease, post-neutropenia lymphopenia, and concurrent infections. These findings emphasize the importance of routine CMV surveillance and early intervention in high-risk patient subsets to reduce morbidity and mortality. Given the multifactorial nature of CMV reactivation, individualized monitoring strategies and therapeutic approaches are warranted. Further multicenter prospective studies incorporating detailed immune function assessments are needed to optimize prevention and management of CMV infection in this vulnerable population.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Erciyes University Ethics Committee (approval no: 2020/130, date: 26.02.2020).

Informed Consent: All patients provided written informed consent prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.T.K., S.G., L.K.; Concept: Z.T.K., T.D., S.Ç., M.K., A.Ü., L.K.; Design: Z.T.K., T.D., S.Ç., M.K., A.Ü., S.G., L.K.; Data Collection or Processing: Z.T.K., S.Ç., L.K.; Analysis or Interpretation: Z.T.K., L.K.; Literature Search: Z.T.K., T.D., S.Ç., M.K., L.K.; Writing: Z.T.K.

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