

Cytomegalovirus Infection and Treatment in Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective Study from a Single Institution in an Endemic Area

Allojeneik Hematopoietik Kök Hücre Transplantasyonunda *Sitomegalovirüs* Enfeksiyonu ve Tedavisi: Endemik Bir Alanda Tek Merkezden Retrospektif Bir Çalışma

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Abstract

Objective: Although *Cytomegalovirus* (CMV) infection is a major complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), the risk factors for CMV reactivation and treatment failure in CMV endemic areas have remained unclear. This study investigated the risk factors for CMV reactivation among allo-HSCT recipients in an area where CMV is highly endemic.

Materials and Methods: Medical records of 82 allo-HSCT recipients from a CMV endemic area were retrospectively reviewed. The patients were stratified into two groups: those with CMV reactivation (n=32) and those without CMV reactivation (n=50). We investigated possible variables associated with CMV reactivation and treatment failure.

Results: Univariate analyses showed that non-remission disease status [hazard ratio (HR): 2.15; p=0.032] and ≥grade III acute graft-versus-host disease (GVHD) (HR: 3.07; p=0.002) were associated with CMV reactivation. Multivariate analysis further demonstrated that older age (HR: 1.03; p=0.029) and ≥grade III acute GVHD (HR: 2.98; p=0.012) were associated with CMV reactivation. Overall survival time seemed lower among patients with CMV reactivation than among patients without CMV reactivation, although the difference was not statistically significant (p=0.165). The absence of ≥grade III acute GVHD was associated with successful CMV treatment in the current study (odds ratio: 4.40; p=0.008).

Conclusion: Prophylactic anti-CMV therapy might need to be considered for allo-HSCT recipients who have ≥grade III GVHD.

Keywords: Allogeneic hematopoietic stem cell transplantation, *Cytomegalovirus*, Graft-versus-host disease, Taiwan

Öz

Amaç: *Sitomegalovirüs* (CMV) enfeksiyonu, allojeneik kök hücre transplantasyonu (allo-KHT) sonrası majör bir komplikasyon olmasına rağmen CMV'nin endemik olduğu alanlarda CMV reaktivasyonu ve tedavi başarısızlığı için risk faktörleri belirsizliğini korumaktadır. Bu çalışma CMV'nin büyük ölçüde endemik olduğu bir alanda allo-KHT alıcılarında CMV reaktivasyonu için risk faktörlerini araştırmıştır.

Gereç ve Yöntemler: CMV endemik olduğu bir alandan 82 allo-KHT alıcısının tıbbi kayıtları retrospektif olarak incelendi. Hastalar iki gruba ayrıldı: CMV reaktivasyonu olan (n=32) ve CMV reaktivasyonu olmayan (n=50). CMV reaktivasyonu ve tedavi başarısızlığı ile ilişkili olası değişkenler araştırıldı.

Bulgular: Tek değişkenli analiz CMV reaktivasyonunun remisyon-olmayan hastalık durumu [risk oranı (RO): 2,15; p=0,032] ve ≥grade III akut graft versus host hastalığı (GVHH) (RO: 3,07; p=0,002) ile ilişkili olduğunu gösterdi. Çok değişkenli analiz ayrıca CMV reaktivasyonunun ileri yaş (RO: 1,03; p=0,029) ve ≥grade III akut GVHH (RO: 2,98; p=0,012) ile ilişkili olduğunu gösterdi. Genel sağkalım CMV reaktivasyonu olan hastalarda CMV reaktivasyonu olmayan hastalardan daha düşük görünmekle birlikte fark istatistiksel olarak anlamlı değildi (p=0,165). Bu çalışmada, ≥grade III akut GVHH yokluğu başarılı CMV tedavisi ile ilişkili idi (olasılık oranı: 4,40; p=0,008).

Sonuç: Profilaktik anti-CMV tedavisinin ≥grade III GVHH olan allo-KHT alıcılarında dikkate alınması gerekebilir.

Anahtar Sözcükler: Allojeneik hematopoietik kök hücre transplantasyonu, *Sitomegalovirüs*, Graft versus host hastalığı, Tayvan

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) not only improves survival times in patients with acute myeloid leukemia [1] and acute lymphoid leukemia [2], but may also be the only curative therapy for very severe aplastic anemia [3]. Nonetheless, the morbidity and mortality that are associated with allo-HSCT limit its clinical application and efficacy. In addition to graft-versus-host disease (GVHD), infection remains one of the most important complications after allo-HSCT [4]. The incidence of each infection in allo-HSCT recipients varies depending on the time since transplantation. During the neutropenic phase, the principal pathogens are bacteria and *Candida* species. In contrast, *Cytomegalovirus* (CMV) reactivation is the major infectious complication between 30 and 100 days after transplantation. Infections in the late phase are relatively heterogeneous, which is associated with the presence and severity of GVHD [5].

Among the different infectious complications that occur in patients undergoing allo-HSCT, the clinical entity of CMV infection is unique. Reactivation of CMV appears in 60% of seropositive allo-HSCT recipients. Without appropriate treatment, asymptomatic CMV reactivation eventually progresses to symptomatic CMV diseases, which can result in death, especially in immunocompromised hosts. Typically, CMV mainly affects the lungs and gastrointestinal tract [6]. However, CMV retinitis is also common, occurring in 5% of high-risk pediatric allo-HSCT recipients [7].

Although the incidence of symptomatic CMV diseases has decreased significantly because of universal prophylaxis or preemptive therapy, this life-threatening complication still develops in 30% of all allo-HSCT recipients [8]. In addition, CMV seroprevalence is quite endemic [9]. The strategies of CMV prophylaxis and treatment can be entirely different for allo-HSCT recipients in CMV endemic areas and those in non-endemic areas. Moreover, it remains unclear whether ganciclovir in combination with CMV immunoglobulin is more effective than ganciclovir alone for the treatment of CMV reactivation; further investigation is necessary.

We conducted this retrospective study to address these issues, specifically by investigating the risk factors for CMV reactivation among allo-HSCT recipients in an area where CMV is highly endemic. We additionally compared the overall survival (OS) time in patients with and without CMV reactivation. Finally, factors associated with CMV treatment failure were also analyzed.

Materials and Methods

Patients

The review board of Taichung Veterans General Hospital approved this study. According to the regulations of the

institutional review board, informed consent was not required from the patients because of the retrospective study design. Medical records were evaluated for 86 consecutive ≥ 18 -year-old patients who received allo-HSCT at our institution for various hematological diseases from February 2010 to November 2015. Patients without regular follow-up ($n=2$) and those who died before successful engraftment ($n=2$) were excluded. The remaining 82 patients were included in the analyses of this study. The median follow-up time for these 82 patients was 513 days (range: 23 to 2045 days). The clinical characteristics of all of the patients are shown in Table 1. The mean \pm standard deviation age of our study cohort was 41.98 ± 14.57 years. Acute myeloid leukemia (47.6%) was the major underlying disease that required allo-HSCT. Regarding CMV serostatus, 92.68% (76/82) of recipients were CMV-seropositive before allo-HSCT, while 85.37% (70/82) of donors were CMV-seropositive. Complete remission could not be defined in patients with aplastic anemia ($n=9$) and chronic myeloid leukemia ($n=3$). The median OS time was not reached in this study cohort.

Conditioning Regimen

In this study, the non-myeloablative conditioning regimen was provided irrespective of the patient's underlying disease. It consisted of total body irradiation (TBI) (200 cGy, day -7) and the administration of fludarabine (30 mg/m²/day, from day -6 to day -2) and cyclophosphamide (10 mg/kg/day, from day -5 to day -2). As compared with the non-myeloablative regimen, the myeloablative regimens in the current study were relatively heterogeneous. A TBI-based conditioning regimen (TBI: 1200 cGy, 6 fractions, from day -6 to day -4; cyclophosphamide: 60 mg/kg/day, from day -3 to day -2) was used for patients with acute lymphoblastic leukemia. BuCy₂ was routinely delivered to patients with acute myeloid leukemia, myelodysplasia syndrome, or chronic myeloid leukemia [10]. Lymphoma patients who received a myeloablative preparative regimen were conditioned using BEAM [11]. In terms of haploidentical transplantation, we followed the Johns Hopkins protocol [12].

Graft-Versus-Host Disease Prophylaxis

We used cyclosporine as the major immunosuppressant. A trough level of 150-250 ng/mL was the targeted concentration. Myfortic acid was used since day -2 at a dose of 720 mg twice daily and was generally discontinued on day 60. With the exception of the patients undergoing haploidentical transplantation, patients received short-course methotrexate at 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11. Antithymoglobulin (ATG) was routinely given to patients without matched sibling donors at 2 mg/kg/day from day -4 to -2.

Cytomegalovirus Monitoring and Treatment

Our allo-HSCT protocol did not contain CMV antiviral prophylaxis. Because Taiwan is an endemic area for CMV infection, blood

donation volunteers do not routinely check their CMV serostatus. Since getting CMV-negative blood products is difficult, to avoid further CMV infection, all allo-HSCT recipients in our study only received leukodepleted and irradiated blood products if blood transfusion was needed. We used quantitative polymerase chain reaction with a COBAS AmpliPrep/COBAS TaqMan CMV system (Roche Molecular Systems, Inc., Branchburg, NJ, USA) to detect the serum CMV viral load. The cutoff of negativity was set as <3333 copies/mL after internal adjustment and validation. Serum CMV viral load was generally monitored once every 1 to 2 weeks. CMV treatment with ganciclovir at 5 mg/kg/day was initiated preemptively in patients with a serum CMV viral load of >3333 copies/mL or with symptomatic CMV infection. Further, 81.3% (26/32) of patients with CMV reactivation also received CMV immunoglobulin simultaneously at a dose of 10,000 units per day on every other day, for a total of five doses. CMV treatment was defined as having been successful if the symptoms of CMV infection disappeared completely and the serum viral load became negative.

Efficacy Assessments

The patients were stratified into two groups: those with CMV reactivation (n=32) and those without CMV reactivation (n=50). Clinical characteristics, causes of death, and OS were compared between these two groups of patients. We attempted to identify variables associated with CMV reactivation and the failure of CMV treatment. Only the first episode of CMV reactivation was investigated in the current study.

Statistical Analysis

Student t-tests and Fisher exact tests were used to compare nominal and ordinal variables between patients with and without CMV reactivation. Differences in OS were assessed using the log-rank test. Cox proportional hazards regression was used to investigate variables that were potentially associated with CMV reactivation and successful CMV treatment, as quantified in terms of hazard ratios (HRs) and accompanying 95% confidence intervals (CIs). Data are summarized as mean \pm standard deviation where appropriate. $P < 0.05$ was regarded as indicating statistical significance. All statistical analyses were conducted using SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results

Comparisons of Clinical Characteristics between Patients with and without *Cytomegalovirus* Reactivation

Patients without CMV reactivation were younger than patients with CMV reactivation (38.74 ± 13.29 years vs. 47.03 ± 15.23 years; $p = 0.011$). Additionally, more patients in the no-CMV-reactivation group received myeloablative conditioning regimens (78.0% vs. 53.1%; $p = 0.032$). Sex ($p = 0.899$), underlying

diseases ($p = 0.951$), donor types ($p = 0.332$), CMV serology status ($p = 0.176$), ATG use ($p = 0.076$), presence of \geq grade III acute GVHD ($p = 0.940$), and disease status before allo-HSCT ($p = 0.101$) did not differ significantly between the two groups of patients (Table 1).

Risk Factors Associated with *Cytomegalovirus* Reactivation

The average time until the first CMV reactivation was 42.1 ± 31.0 days. Univariate analyses showed that a disease status of non-complete remission (HR: 2.15; 95% CI: 1.07 to 4.43; $p = 0.032$) and \geq grade III acute GVHD (HR: 3.07; 95% CI: 1.53 to 6.16; $p = 0.002$) were associated with CMV reactivation. Multivariate analysis further demonstrated that older age (HR: 1.03; 95% CI: 1.00 to 1.06; $p = 0.029$) and \geq grade III acute GVHD (HR: 2.98; 95% CI: 1.27 to 6.95; $p = 0.012$) were significantly associated with increased risks of CMV reactivation (Table 2).

Patients with *Cytomegalovirus* Reactivation Had a Trend Toward Inferior Overall Survival

The median OS time for patients with CMV reactivation was 508 days. However, median OS time was not reached during the follow-up period in patients without CMV reactivation. Although a trend toward inferior OS times was observed in patients with CMV, the difference was not significantly significant ($p = 0.165$) (Figure 1).

Cause of Death Analyses

Overall, 36 patients (43.9%) died in our study cohort. The mortality rates of patients with and without CMV reactivation were 53.1% (17/32) and 38.0% (19/50), respectively. For patients with CMV reactivation, CMV infection remained the major cause of death, accounting for 41.2% (7/17) of deaths. In contrast,

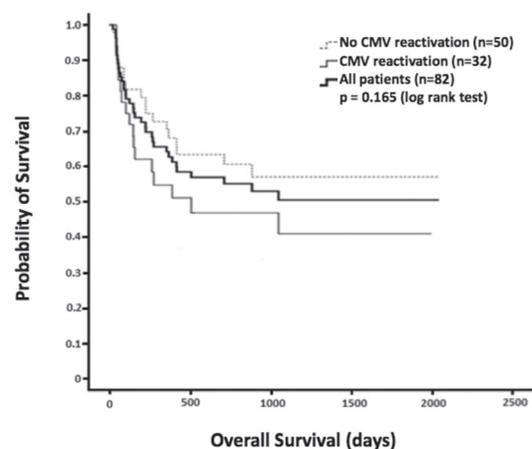


Figure 1. The median overall survival time for patients with *Cytomegalovirus* (CMV) reactivation was 508 days. However, the median survival time was not reached during the follow-up period for patients without CMV reactivation. Although a trend toward inferior overall survival was observed in patients with CMV reactivation, the difference was not statistically significant ($p = 0.165$).

Table 1. Comparisons of clinical characteristics between patients with and without *Cytomegalovirus* reactivation.

		All patients		CMV reactivation		No CMV reactivation		
		n=82		n=32		n=50		p
Age, years	Mean ± SD	41.98±14.57		47.03±15.23		38.74±13.29		0.011*
Sex (n, %)								0.899 ^s
	Male	43	52.4%	16	50.0%	27	54.0%	-
	Female	39	47.6%	16	50.0%	23	46.0%	-
Diagnosis (n, %)	-	-	-	-	-	-	-	0.951 ^s
	AML	39	47.6%	16	50.0%	23	46.0%	-
	ALL	20	24.4%	8	25.0%	12	24.0%	-
	Lymphoma	8	9.8%	2	6.3%	6	12.0%	-
	CML	3	3.7%	1	3.1%	2	4.0%	-
	Aplastic anemia	9	11.0%	4	12.5%	5	10.0%	-
	Multiple myeloma	2	2.4%	1	3.1%	1	2.0%	-
	MDS	1	1.2%	0	0.0%	1	2.0%	-
Donor type (n, %)	-	-	-	-	-	-	-	0.332 ^s
	Matched sibling	27	32.9%	7	21.9%	20	40.0%	-
	Matched, unrelated	21	25.6%	9	28.1%	12	24.0%	-
	Mismatched, unrelated	29	35.4%	13	40.6%	16	32.0%	-
	Haploidentical	5	6.1%	3	9.4%	2	4.0%	-
CMV serology (n, %)	-	-	-	-	-	-	-	0.176 ^s
	D+/R+	66	80.5%	23	71.9%	43	86.0%	-
	D+/R-	4	4.9%	1	3.1%	3	6.0%	-
	D-/R+	10	12.2%	7	21.9%	3	6.0%	-
	D-/R-	2	2.4%	1	3.1%	1	2.0%	-
Conditioning regimen	-	-	-	-	-	-	-	0.032 ^s
	Myeloablative	56	68.3%	17	53.1%	39	78.0%	-
	Non-myeloablative	21	25.6%	11	34.4%	10	20.0%	-
	Haploidentical	5	6.1%	4	12.5%	1	2.0%	-
TBI or chemo-based regimen (n, %)	-	-	-	-	-	-	-	0.963 ^s
	TBI-based	19	23.2%	8	25.0%	11	22.0%	-
	Chemo-based	63	76.8%	24	75.0%	39	78.0%	-
ATG (n, %)	-	-	-	-	-	-	-	0.076 ^s
	Yes	56	68.3%	26	81.3%	30	60.0%	-
	No	26	31.7%	6	18.8%	20	40.0%	-
Disease status (n, %)	-	-	-	-	-	-	-	0.101 ^s
	CR	52	63.4%	20	62.5%	32	64.0%	-
	Non-CR	18	22.0%	10	31.3%	8	16.0%	-
	Others	12	14.6%	2	6.3%	10	20.0%	-

Table 1. Continued.

≥Grade 3 aGVHD (n, %)	-	-	-	-	-	-	-	0.940 [§]
	Yes	17	20.7%	6	18.7%	11	22.0%	-
	No	65	79.3%	26	81.3%	39	78.0%	-

CMV: *Cytomegalovirus*, SD: standard deviation, AML: acute myeloid leukemia, ALL: acute lymphoid leukemia, CML: chronic myeloid leukemia, MDS: myelodysplastic syndrome, D: donor, R: recipient, TBI: total body irradiation, ATG: antithymoglobulin, CR: complete remission, aGVHD: acute graft-versus-host disease.
*indicates Student t-test; [§]indicates Fisher exact test.

Table 2. Risk factors associated with *Cytomegalovirus* reactivation.

		Univariate			Multivariate				
		HR	95% CI		p	HR	95% CI		p
Age		1.01	0.99	1.04	0.273	1.03	1.00	1.06	0.029
Sex	Male vs. female	1.26	0.65	2.44	0.489	1.08	0.53	2.21	0.838
Donor type	Donors other than matched sibling donors vs. matched sibling donors	2.21	0.97	5.05	0.060	1.83	0.76	4.44	0.179
CMV serology	Donor (+) vs. donor (-)	1.02	0.4	2.63	0.968	0.79	0.27	2.31	0.661
	Recipient (+) vs. recipient (-)	1.36	0.33	5.64	0.677	0.62	0.13	2.97	0.55
Conditioning regimen	Myeloablative ^a vs. non-myeloablative	2.03	0.88	4.66	0.097	2.37	0.89	6.33	0.085
ATG	Yes vs. no	0.67	0.34	1.32	0.247	0.93	0.41	2.13	0.865
Disease status	Non-CR vs. CR	2.15	1.07	4.34	0.032	1.10	0.64	1.91	0.732
≥Grade 3 aGVHD	Yes vs. no	3.07	1.53	6.16	0.002	2.98	1.27	6.95	0.012

^aMyeloablative regimen includes conventional myeloablative regimens and regimen specific for haploidentical allogeneic hematopoietic stem cell transplantation.
CMV: *Cytomegalovirus*, HR: hazard ratio, CI: confidence interval, ATG: antithymoglobulin, CR: complete remission, aGVHD: acute graft-versus-host disease.

52.6% of deaths in patients without CMV reactivation were attributable to relapse of the underlying disease. The average OS time was 142.4±92.5 days among patients who died of CMV infection and 285.6±210.7 days among patients who died of their underlying diseases (Table 3).

Variables Associated with Successful *Cytomegalovirus* Infection Treatment

Because of the limited number of patients in the study cohort, we only conducted univariate analyses, the results of which are shown in Table 4. Briefly, the absence of ≥grade III acute GVHD was the only variable that was significantly associated with successful CMV treatment in the current study (odds ratio: 4.40; 95% CI: 1.48 to 13.15; p=0.008). Notably, use of CMV immunoglobulin was not significantly associated with CMV treatment success (odds ratio: 2.57; 95% CI: 0.58 to 11.50; p=0.217).

Discussion

CMV serostatus is the most important factor for CMV reactivation in patients undergoing allo-HSCT [13]. In an analysis of a Portuguese cohort that comprised 85.81% CMV-seropositive recipients and 73.27% CMV-seropositive donors,

Table 3. Causes of death in patients undergoing allogeneic hematopoietic stem cell transplantation.

	CMV reactivation, (n=17)	No CMV reactivation, (n=19)
	n (%)	n (%)
CMV infection	7 (41.2)	0 (0)
GVHD	2 (11.8)	7 (36.8)
Underlying diseases	6 (35.3)	10 (52.6)
Others	2 (11.8)	2 (10.5)

CMV: *Cytomegalovirus*, GVHD: graft-versus-host disease.

Sousa et al. [14] observed that 60.3% of patients developed CMV infection after allo-HSCT. In our study, 92.68% of recipients and 85.37% of donors were CMV-seropositive, but the incidence of CMV reactivation was only 39.02%. One possible explanation for this lower incidence of CMV reactivation could be the lower incidence of acute GVHD in the present study. Acute GVHD occurred in 70.8% of patients in the Portuguese cohort, yet only 20.73% (17/82) of our patients had ≥grade III acute GVHD. Moreover, among all of the variables investigated in the present study, ≥grade III acute GVHD was the only variable that was a significant risk factor for CMV reactivation in both

Table 4. Variables associated with successful *Cytomegalovirus* treatment by univariate analysis (n=32).

		OR	95% CI		p
Age		0.99	0.96	1.02	0.548
Sex	Male vs. female	0.89	0.34	2.31	0.809
Donor type	Donors other than matched sibling donors vs. matched sibling donor	4.58	0.61	34.56	0.140
CMV serology	Donor (+) vs. donor (-)	1.67	0.48	5.83	0.422
	Recipient (+) vs. recipient (-)	22.87	0.01	56,684.9	0.432
Condition regimen	Myeloablative ^a vs. non-myeloablative	1.84	0.65	5.26	0.254
ATG	Yes vs. no	0.36	0.12	1.07	0.066
Disease status	Non-CR vs. CR	2.08	0.77	5.60	0.148
CMV viral load (copies/mL)	<10,000 vs. ≥10,000	1.26	0.29	5.54	0.762
Use of CMV immunoglobulins	Yes vs. no	2.57	0.58	11.50	0.217
≥Grade 3 aGVHD	No vs. yes	4.40	1.48	13.15	0.008

^aMyeloablative regimen includes conventional myeloablative regimens and regimen specific for haploidentical allogeneic hematopoietic stem cell transplantation.
 CMV: *Cytomegalovirus*, OR: odds ratio, CI: confidence interval, ATG: antithymoglobulin, CR: complete remission, aGVHD: acute graft-versus-host disease.

univariate (p=0.002) and multivariate (p=0.012) analyses (Table 2). Our result is confirmed by a study of Cohen et al. [15], in which GVHD was also identified as a risk factor for first CMV reactivation in allo-HSCT recipients (HR=5.091, p=0.021).

In addition to GVHD, conditioning regimens could be also associated with CMV reactivation in patients receiving allo-HSCT. However, evidence concerning the association between conditioning regimens and CMV reactivation has been inconsistent. Although Cohen et al. [15] identified the myeloablative preparative regimen as a risk factor, George et al. [13] considered the non-myeloablative regimen to be an independent predictor of CMV reactivation. Interestingly, the type of preparative regimen did not correlate with CMV reactivation in our study. Additionally, our data did not demonstrate an association between the use of ATG and CMV reactivation, either. This result, however, is not consistent with the prior findings of Wu et al. [16]. Small study cohort and short follow-up time could be among the reasons for these inconsistent findings, suggesting that further studies are required.

Previous studies also investigated whether CMV reactivation results in inferior outcomes in allo-HSCT patients. Sousa et al. [14] found that CMV infection was associated with inferior median post-transplantation survival in allo-HSCT recipients. However, the data from our cohort did not show a statistically significant difference in OS between patients with and without CMV reactivation. This result is similar to the prior findings of Liu et al. [17], who found no survival disadvantage for patients with CMV infection (p=0.699) or CMV disease (p=0.093). Notably, CMV infection is not entirely a poor prognostic predictor for allo-HSCT. On the contrary, CMV reactivation is considered

to reduce the risk of relapse in patients with acute myeloid leukemia after allo-HSCT [18,19]. This protective effect might partially reverse the inferior outcomes of CMV reactivation in patients undergoing allo-HSCT. Additionally, the good efficacy of CMV treatment could potentially also be responsible for the non-inferiority of OS in patients with CMV infection. In our study cohort, the rate of successful CMV treatment for the first reactivation was as high as 87.50%.

In terms of CMV treatment, although the rates of clearance of CMV viremia are similar with oral valganciclovir and ganciclovir in the post-allo-HSCT population [20], ganciclovir remains the drug of choice in our allo-HSCT setting. Moreover, most of the patients with CMV reactivation (81.3%) in our study cohort were treated with CMV immunoglobulin simultaneously. However, whether CMV immunoglobulin could facilitate successful CMV treatment remains controversial. A study by Ranganathan et al. [21] revealed that prophylactic CMV immunoglobulin decreased risk of CMV infection, but not CMV disease, after lung transplantation in pediatric patients. The univariate analyses of our data also did not demonstrate a significant association between the use of CMV immunoglobulin and the success of CMV treatment (odds ratio: 2.57; 95% CI: 0.58 to 11.50; p=0.217). More studies are required to identify the role and efficacy of CMV immunoglobulin in allo-HSCT.

Among the 32 patients with first CMV reactivation in our study cohort, treatment failure occurred in four patients (4/32, 12.50%). This result raises another important issue: the identification of individuals who are at higher risk of treatment failure and possibly require CMV prophylaxis. CMV prophylaxis by valganciclovir appears to fail as a means of improving CMV disease-free and invasive infection-free survival in allo-HSCT

recipients [22]. A phase 2 study by Chemaly et al. [23] showed that letermovir prophylaxis effectively reduced the incidence of CMV infection after allo-HSCT. Its impact on OS, however, was not clear. CMV antiviral prophylaxis was not part of the routine of our allo-HSCT protocol. Notably, our results showed that patients with \geq grade III GVHD were more refractory to CMV treatment (odds ratio: 4.40; 95% CI: 1.48 to 13.15; $p=0.008$), suggesting that patients with \geq grade III GVHD could potentially benefit from valganciclovir prophylaxis. However, more evidence is needed before jumping to any conclusions.

The major limitations of the current study are its retrospective study design and the small number of patients. In addition, the active immunosuppressants of each patient at the time at which either CMV or GVHD occurs are very heterogeneous. The current study could not precisely identify the impact of immunosuppression on CMV reactivation. Moreover, the role of CMV immunoglobulin in either preemptive or targeted treatment remains uncertain after our analyses. Studies with prospective and randomized-control designs, focusing on more particular clinical scenarios, are urgently needed for this unmet clinical need.

Conclusion

Older age, non-complete remission disease status, and \geq grade III GVHD were risk factors for CMV reactivation in allo-HSCT recipients. The presence of \geq grade III acute GVHD could be associated with CMV treatment failure. Prophylactic anti-CMV therapy needs to be considered in allo-HSCT recipients with \geq grade III GVHD.

Ethics

Ethics Committee Approval: Institutional Review Board of the Taichung Veterans General Hospital (TCVGH-IRB) Taiwan, CE16033B; Informed Consent: Informed consent was not required due to retrospective study.

Authorship Contributions

Concept: H.C.L., C.L.J.T.; Design: H.C.L., C.L.J.T.; Data Collection or Processing: H.C.L., S.M.H., W.L.H., C.W.C., K.H.C., Z.Y.S., C.L.J.T.; Analysis or Interpretation: K.H.C., C.L.J.T.; Literature Search: H.C.L., S.M.H., W.L.H., C.W.C., K.H.C., Z.Y.S., C.L.J.T.; Writing: C.L.J.T.

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