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Original Article

Ten-year epidemiology and risk factors of cytomegalovirus infection in hematopoietic stem cell transplantation patients in Taiwan

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Abstract *Background:* Cytomegalovirus (CMV) can cause infection and critical diseases in hematopoietic stem cell transplantation (HSCT) recipients. This study aimed to explore the cumulative incidence and risk factors for CMV infection and disease among HSCT recipients in Taiwan.
Methods: This retrospective cohort study using the Taiwan Blood and Marrow Transplantation Registry (TBMTR) included HSCT recipients between 2009 and 2018 in Taiwan. The primary outcome was cumulative incidence of CMV infection or disease at day 100 after HSCT. Secondary outcomes included day 180 cumulative incidence of CMV infection or disease, infection sites, risk factors for CMV infection or disease, survival analysis, and overall survival after CMV infection and disease.
Results: There were 4394 HSCT recipients included in the study (2044 auto-HSCT and 2350 allo-HSCT). The cumulative incidence of CMV infection and disease was significantly higher in allo-HSCT than in auto-HSCT patients at day 100 (53.7% vs. 6.0%, $P < 0.0001$ and 6.1% vs. 0.9%, $P < 0.0001$). Use of ATG (HR 1.819, $p < 0.0001$), recipient CMV serostatus positive (HR 2.631, $p < 0.0001$) and acute GVHD grades $\geq$ II (HR 1.563, $p < 0.0001$) were risk factors for CMV infection, while matched donor (HR 0.856, $p = 0.0180$) and myeloablative conditioning (MAC) (HR 0.674, $p < 0.0001$) were protective factors.
Conclusion: The study revealed a significant disparity in terms of the incidence, risk factors, and clinical outcomes of CMV infection and disease between auto and allo-HSCT patients. These findings underscore the importance of considering these factors in the management of HSCT recipients to improve outcomes related to CMV infections.

Introduction

Hematopoietic stem cell transplantation (HSCT) can improve survival by recovering bone marrow function after destroying diseased hematopoietic or tumor cells in patients with malignant and non-malignant disorders.[1] Despite advancements in post-transplantation management over decades, infections after HSCT remain a substantial risk of morbidity and mortality in HSCT recipients.[2]

Human CMV is among the significant pathogens that can develop into infection and critical end-organ diseases during the peri-engraftment period, especially among allogeneic hematopoietic stem cell transplantation (allo-HSCT).[3] The incidence of CMV reactivation after allo-HSCT carried out by previous reviews and studies was around 30–80%,

significantly higher compared to 0—39% among autologous (auto)-HSCT patients.[4—10]

Studies from Taiwan have demonstrated the incidence of CMV reactivation after allo-HSCT to be 45—55% and the incidence of CMV disease to be 5—6.8%.[11,12] However, the single-center design restricted the application from giving an overall estimation of CMV infection and CMV disease in Taiwan. In addition, data with respect to CMV disease burden after auto-HSCT were less conclusive and needed to be evaluated.

Apart from CMV incidence, risk factors for CMV reactivation and CMV disease among allo-HSCT were assessed by previous studies, and CMV serostatus positive, acute graft-versus-host disease (GVHD), mismatched donor, age, and T-cell depletion were reported to be associated with increased risk of CMV reactivation. Nevertheless, there were still inconclusive results considering the conditioning regimen.[7,13,14] Also, studies have demonstrated inferior survival outcomes after CMV infection,[15] despite that survival after CMV infection and disease has not been thoroughly evaluated.

As abovementioned, studies regarding the incidence of CMV infection and CMV disease are mostly limited to existing regional differences, specific hematopoietic malignancies,[8,9] relatively small sample sizes, and single-center design. Survival after CMV infection and disease has not been assessed comprehensively. Moreover, data concerning the incidence of CMV infection and CMV disease after auto-HSCT are scarce in Taiwan. Hence, in the current study, we aimed to explore the cumulative incidence of CMV infection and CMV disease in both auto- and allo-HSCT recipients using the TBMTR, which covered an estimated 95% of all patients who performed HSCT in Taiwan. We further sought to identify risk factors for CMV infection and CMV disease and evaluate the survival among allo-HSCT recipients in Taiwan.

Methods

Data source

The Taiwan Society of Blood and Marrow Transplantation Registry (TBMTR), operated by the society, is tasked to collect clinical data about HSCT from all 19 collaborative transplantation centers in Taiwan. Data quality control with regard to accuracy and consistency was regularly audited internally in the TBMTR. HSCT regimens were classified by established Center for International Blood and Marrow Transplant Research (CIBMTR) criteria.[16] The institutional review board approved the data collection and analysis of each participating hospital, with written informed consent obtained by the principles of the Declaration of Helsinki. This study was further approved by the Research Ethics Committee (REC) of the National Taiwan University Hospital (NTUH-REC No.201911005W).

Study design and patients

This was a retrospective cohort study based on TBMTR. Patients who underwent HSCT between January 2009 to December 2018 and registered in the TBMT database were collected. Patients with prior HSCT or who died 30 days post-HSCT were excluded; the remaining patients were included for analysis.

Outcome definitions

The primary outcome was cumulative incidences of CMV infection or disease at day 100 after HSCT among auto- and allo-HSCT patients. Secondary outcomes included cumulative incidences of CMV infection or disease, infection sites of CMV disease among allo-HSCT patients, risk factors for CMV infection or disease at day 180 among allo-HSCT patients, survival (overall survival, relapse-free survival, and non-relapse mortality) among allo-HSCT patients, and overall survival after CMV infection and disease. To provide data on different clinical scenarios, we analyzed cumulative incidences of CMV infection or disease at day 180 after HSCT among different subgroups (e.g., donor type, conditioning regimen, ATG used or not and GVHD prophylaxis regimen). We also evaluated incidence of CMV infection at day 180 after HSCT among allo-HSCT patients after excluding patients with donor CMV serostatus negative and recipient serostatus negative from the analysis. In addition, the cumulative incidence of relapse among allo-HSCT and auto-HSCT at 180 days were reported.

CMV infection was defined as the appearance of CMV viremia or positive culture requiring treatment, and the treatment threshold was determined according to the individual center and attending physician. Currently, ganciclovir and valganciclovir are the only anti-CMV medications covered by Taiwan's national health insurance. In treating CMV disease, ganciclovir is the drug of choice, with foscarnet being used as well, albeit with greater restrictions on its availability in Taiwan. CMV disease was defined as a proven CMV end-organ disease by documentation of CMV in tissue from the relevant organ by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization.[17] We also evaluated the infection sites of CMV disease among allo-HSCT patients on day 180. Infections within 30 days after the last episode were considered the same CMV disease episode, and patients with over one site of CMV diseases were collected. CMV disease infection sites were presented as numbers and percentages of all identified infection sites. Preceding CMV viremia in CMV disease was also collected. Regarding the risk factors of CMV infection and CMV disease, we assessed age, sex, type of donor, conditioning regimen, ATG use, CMV serostatus, and acute GVHD among allo-HSCT patients in our population.

Overall survival was defined as the time from HSCT to death, regardless of the cause. Relapse-free survival (RFS) was defined as the time from HSCT until the first relapse or death due to any cause, whichever was observed first. Non-relapse mortality (NRM) was defined as death without recurrent or progressive disease after HSCT. Among patients with CMV infection and CMV disease within 180 days after HSCT, we also reported the one-year overall survival after CMV infections and CMV diseases.

Statistical analysis

For baseline characteristics determined based on the day of HSCT, we provided descriptive analyses. Cumulative incidence functions were used to estimate the CMV infection,

CMV disease, and NRM. The follow-up period was calculated as the time from the HSCT date to the first documented CMV infection date or the last observation date (100 days and 180 days post-HSCT), death, relapse, and loss to follow-up. Kaplan–Meier analysis was used to plot the survival curves and log-rank tests to evaluate the statistical significance between defined groups. Cox proportional hazards model was applied to assess the factors associated with CMV infection or disease at univariate analysis and was presented as a hazard ratio with a 95% confidence interval. Significant factors were further evaluated in multivariate analysis. The Fine and Gray model[18] was also employed to determine the cumulative incidence of CMV infection and disease between auto- and allo-HSCT (death as competing risk). Differences were considered significant at $P < 0.05$. All models were checked to satisfy assumptions, and all statistical analyses were performed with IBM SPSS Statistics v25 (IBM Corp., Armonk, NY, USA).

Results

Basic characteristics

From 2009 to 2018, 4508 patients who underwent HSCT were identified in TBMTR. After excluding death within 30 days post-HSCT and patients with a history of HSCT, 4394 patients were included in the analysis (Fig. 1). The baseline characteristics of this cohort were summarized in Table 1. Among these, 2044 patients underwent auto-HSCT, and 2350 patients underwent allo-HSCT. The mean age was higher in auto-HSCT patients than allo-HSCT patients (48.2 vs. 38.6 years old). While most of the patients in auto-HSCT received a myeloablative conditioning regimen (94.7%), a lower proportion of patients in allo-HSCT received a myeloablative regimen (68.2%).

Among allo-HSCT recipients, 76.6% were CMV IgG positive, 5.6% were CMV IgG negative, and 17.8% with unknown serostatus. Among auto-HSCT recipients, 5.0% were CMV IgG negative, 52.6% were CMV IgG positive, and 42.4% were unknown serostatus. Regarding donor type and HLA compatibility, 40.2% of allo-HSCT recipients received HSCT from HLA-matched related donors, 20.8% from HLA-matched unrelated donors, 26.1% from HLA-mismatched unrelated donors, 6.6% from HLA-partial mismatched related donors and 6.0% from haplotype donors. For GVHD prophylaxis, cyclosporin was given in 2205 (93.8%) patients, methotrexate in 1512 (64.3%), mycophenolate mofetil in 577 (24.6%), and tacrolimus in 44 (1.9%) recipients. In addition, 62.3% of allo-HSCT patients received ATG.

Survival analyses among allo-HSCT patients

The cumulative probability of overall survival among allo-HSCT was 80.2% (95% CI 78.5–81.9) at day 180 and 51.3% (95% CI 48.9–53.7) three years after HSCT. Relapse-free survival among allo-HSCT was 69.9% (95% CI 68.0–71.8) at day 180 and 45.6% (95% CI 43.3–47.9) three years after HSCT. Non-relapse mortality was 10.7% (95% CI 9.3–12.1) at day 180 and 23.8% (95% CI 21.5–26.1) three years after HSCT (Table 2).

Cumulative incidence of CMV infection and CMV disease

The cumulative incidence of CMV infection on day 100 and day 180 after HSCT were both significantly higher in allo-

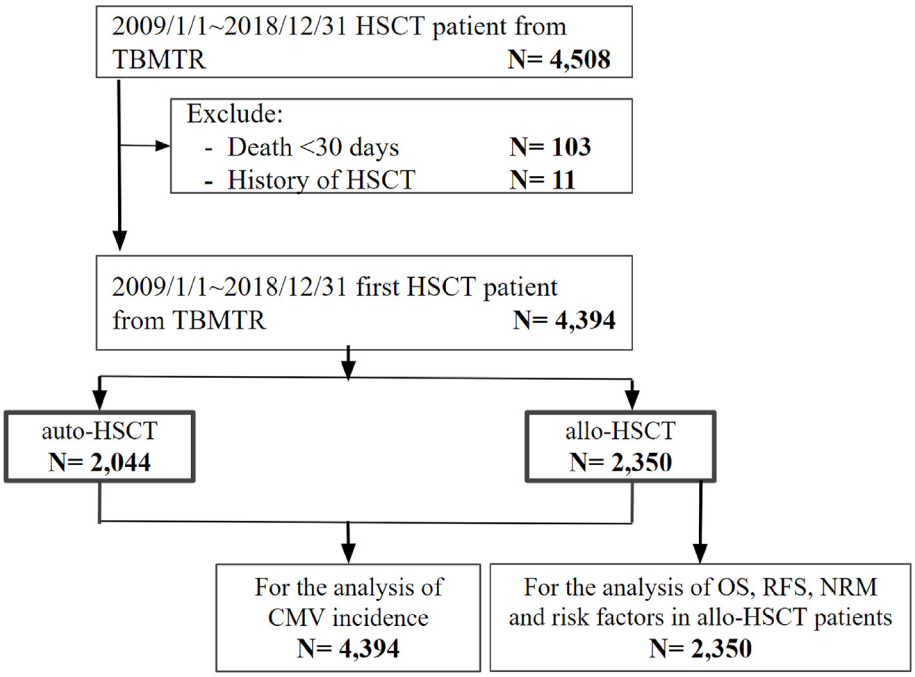

Figure. 1. Enrollment flowchart. Abbreviations: HSCT, Hematopoietic Stem Cell Transplantation; TBMTR, Taiwan Blood and Marrow Transplantation Registry; OS, Overall survival; RFS, Relapse-free survival; NRM, Non-relapse mortality.

Table 1 Baseline characteristics of Patients Undergoing Hematopoietic Stem Cell Transplantation From 2009 to 2018 in Taiwan (n = 4394).

Characteristics	auto-HSCT	allo-HSCT
HSCTs, actual No.	2044	2350
Male sex, n (%)	1190 (58.2)	1283 (54.6)
Age, mean (SD), ys	48.2 (15.5)	38.6 (16.2)
Age, n (%)		
0-9	58 (2.8)	119 (5.1)
10-19	64 (3.1)	196 (8.3)
20-29	189 (9.2)	396 (16.9)
30-39	197 (9.6)	477 (20.3)
40-49	346 (16.9)	467 (19.9)
50-59	682 (33.4)	473 (20.1)
≥60	508 (24.9)	222 (9.4)
Stem cell source, n (%)		
Peripheral blood only	2026 (99.1)	2128 (90.6)
Bone marrow only	6 (0.3)	73 (3.1)
Cord blood only	3 (0.1)	26 (1.1)
Peripheral blood plus bone marrow	2 (0.1)	111 (4.7)
Unknown	7 (0.4)	12 (0.5)
Conditioning regimen, n (%)		
Myeloablative	1935 (94.7)	1603 (68.2)
Non-myeloablative	45 (2.2)	733 (31.2)
Unknown	64 (3.1)	14 (0.6)
Underlying indication for HSCT, n (%)		
AML	27 (1.3)	1111 (47.3)
ALL	7 (0.3)	526 (22.4)
CML	0 (0.0)	85 (3.6)
NHL/HL	1044 (51.1)	153 (6.5)
MM	828 (40.5)	6 (0.3)
MDS/MPD	0.0	204 (8.7)
CLL	3 (0.2)	8 (0.3)
Aplastic anemia/ Thalassemia	0.0	182 (7.7)
Solid tumor	127 (6.2)	2 (0.1)
Others	8 (0.4)	73 (3.1)
CMV serostatus, n (%)		
Donor (+)/Recipient (+)	1076 (52.6)	1501 (63.9)
Donor (−)/Recipient (+)	−	299 (12.7)
Donor (+)/Recipient (−)	−	90 (3.8)
Donor (−)/Recipient (−)	102 (5.0)	42 (1.8)
Unknown	866 (42.4)	418 (17.8)
Donor HLA compatibility, n (%)		
HLA-matched related	N/A	946 (40.2)
HLA-matched unrelated	N/A	488 (20.8)
HLA-mismatched unrelated	N/A	613 (26.1)
HLA partial mismatched related	N/A	155 (6.6)
Haplotype	N/A	140 (6.0)
Unknown	N/A	8 (0.3)
$CD34^+$ cell[a] ($x10^6$), median (IQR)	4.6 (4.9)	5.6 (3.8)
ATG in conditioning, n (%)		
Yes	6 (0.3)	1463 (62.3)
GVHD prophylaxis, n (%)		
Cyclosporin	N/A	2205 (93.8)
Tacrolimus	N/A	44 (1.9)
Methotrexate	N/A	1512 (64.3)
Mycophenolate mofetil	N/A	577 (24.6)
aGVHD, n (%)	56 (2.7)	1241 (52.8)

(*continued on next page*)

Table 1 (*continued*)

Abbreviations. HSCTs, Hematopoietic Stem Cell Transplantations; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL/HL, non–Hodgkin lymphoma/Hodgkin lymphoma; MM, multiple myeloma; MDS/MPD, myelodysplastic syndrome/myeloproliferative disorders; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; ATG, anti-thymocyte globulin; GVHD, graft-versus-host disease; aGVHD, acute graft-versus-host disease.
[a] $CD34^+$ cell (10^6): data were missing in 144 auto-HSCT patients and 114 allo-HSCT patients.

Table 2 Overall Survival, Relapse-free survival, and Non-relapse mortality on 180-day and three years post HSCT among allo-HSCT patients (n = 2350).

Allo-HSCT	Cumulative Probability, % (95% CI)
Overall Survival	
180-days overall survival	80.2 (78.5–81.9)
3-years overall survival	51.3 (48.9–53.7)
Relapse-free survival	
180-days relapse-free survival	69.9 (68.0–71.8)
3-years relapse-free survival	45.6 (43.3–47.9)
Non-relapse mortality	
180-days Non-relapse mortality	10.7 (9.3–12.1)
3-years Non-relapse mortality	23.8 (21.5–26.1)

HSCT compared with auto-HSCT recipients (53.7% vs. 6.0%, $P < 0.0001$ and 55.6% vs. 6.3%, $P < 0.0001$) (Fig. 2-1 and 2-3, Table 3). The cumulative incidence of CMV disease on day 100 and day 180 after HSCT were also both significantly higher in allo-HSCT patients compared with auto-HSCT patients (6.1% vs. 0.9%, $P < 0.0001$ and 7.8% vs. 0.9%, $P < 0.0001$) (Fig. 2-2 and 2-4, Table 3). When we redefined death as the competing risk of CMV infection and CMV disease and analyzed using Fine and Gray model, the cumulative incidences of CMV infection and CMV disease were both slightly lower than the original results (Supplementary Table 1).

With respect to the cumulative incidence of CMV infection at day 180 in different subgroups, the results were showed in the Supplementary Table 2. Among allo-HSCT patients, after excluding 42 patients with donor CMV serostatus negative and recipient serostatus negative from the analysis, the cumulative incidence of CMV infection at 180 days was 58.7% (56.6%–60.8%), higher than the initially reported 55.6% (53.5%–57.7%). On the other hand, the cumulative incidence of relapse at 180 days was 21.2% (19.5%–23.0%) among allo-HSCT and 14.6% (13.0%–16.2%) among auto-HSCT patients.

Table 3 Cumulative probability of CMV infection and CMV disease at day 100 and day 180 among auto-HSCT and allo-HSCT patients.

	Cumulative Probability, % (95% CI)		p value
	Auto-HSCT	Allo-HSCT	
CMV infection, day 100	6.0 (4.9—7.1)	53.7 (51.6—55.8)	<0.0001
CMV disease, day 100	0.9 (0.4—1.3)	6.1 (5.1—7.2)	<0.0001
CMV infection, day 180	6.3 (5.3—7.4)	55.6 (53.5—57.7)	<0.0001
CMV disease, day 180	0.9 (0.5—1.4)	7.8 (6.7—9.0)	<0.0001

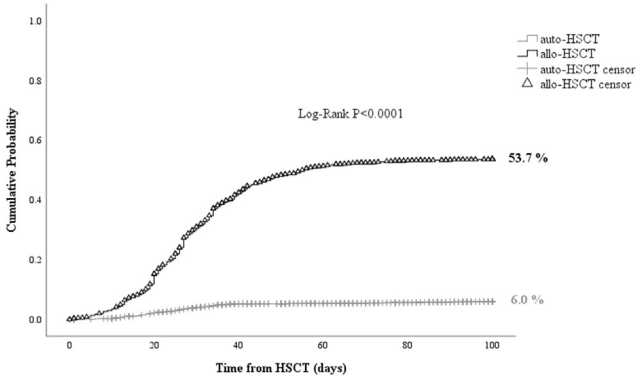

Figure. 2-1. CMV infection, day 100 among auto-HSCT and allo-HSCT patients.

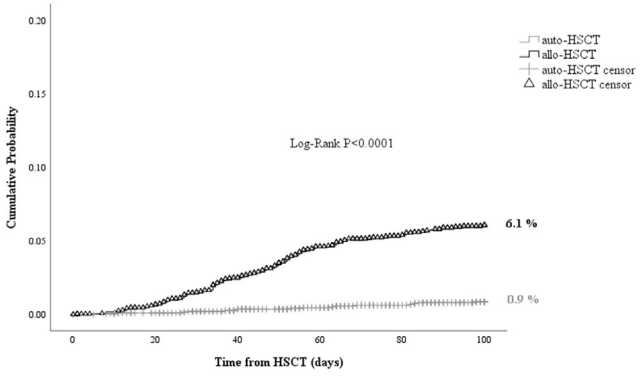

Figure. 2-2. CMV disease, day 100 among auto-HSCT and allo-HSCT patients.

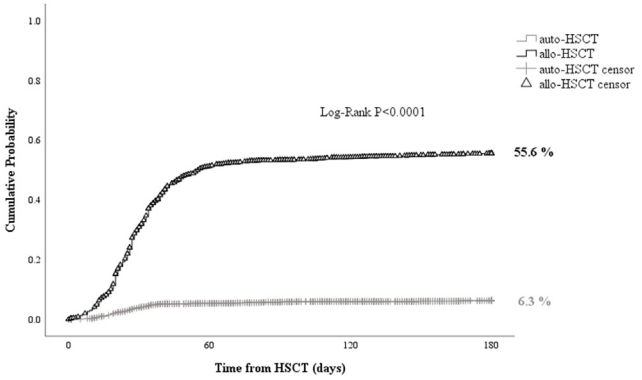

Figure. 2-3. CMV infection, day 180 among auto-HSCT and allo-HSCT patients.

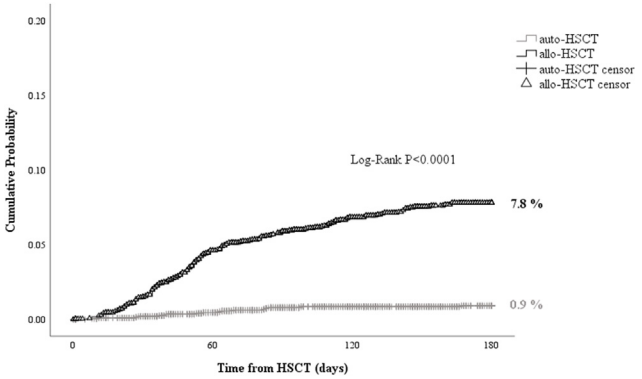

Figure. 2-4. CMV disease, day 180 among auto-HSCT and allo-HSCT patients.

The reported sites of CMV diseases among allo-HSCT patients before day 180 were analyzed and showed in Table 4.

Risk factors of CMV infection and CMV disease among allo-HSCT patients

Two thousand one hundred patients with completed risk factor profiles for CMV infections in the study population were included for univariate and multivariate analysis. In multivariate analysis of CMV infections (Table 5-1), matched donor, MAC, use of ATG, recipient CMV serostatus positive and acute GVHD grades $\geq$ II remained statistically significant after the significant univariate analysis results. At the same time, $\geq$45 years old was associated with the trend of higher risk in multivariate analysis. The univariate analysis also identified strong associations between CMV disease and matched donor, MAC, and acute GVHD grades $\geq$ II, and all remained statistically significant in multivariate analysis (Table 5-2).

Overall survival after CMV infection and CMV disease

Among patients with CMV infection and disease within 180 days after HSCT, the one-year overall survival after CMV

Table 4 Infection sites of CMV disease among allo-HSCT patients.

Disease site	n, (%)	No preceding CMV viremia, n
CNS	5 (2.7%)	1
Gastrointestinal Tract	89 (48.3%)	41
Respiratory Tract	60 (32.6%)	27
Genito-Urinary Tract	14 (7.6%)	13
Eyes	14 (7.6%)	7
Others[a]	2 (1.1%)	0

[a] 2 CMV diseases were identified at bone marrow.

infection was higher in auto-HSCT than allo-HSCT (Fig. 3-1). The one-year overall survival after CMV disease was also higher in auto-HSCT than in allo-HSCT (Fig. 3-2).

Discussion

As far as we know, this is the first nationwide study of CMV infection after HSCT in Taiwan, which provided the essential statistical power to analyze CMV incidence and risk factors after HSCT in a CMV endemic area. Because CMV reactivations most commonly occurred in the early phase after HSCT, we evaluated CMV incidence at day 100 and day 180 post-HSCT.

From the analysis, we found that the cumulative incidence of CMV infection has reached its highest value and remained stable at around 60 days after HSCT. For allo-HSCT, our findings were consistent with the results of a single-center cohort from Taiwan, which reported a cumulative incidence of CMV reactivation rate of 55% and a CMV disease rate of 5% at 100 days post allo-HSCT.[11] Our findings also showed similar results from another single-center study from Taiwan, with a cumulative incidence of CMV DNAemia of 39%–85% at day 180 post allo-HSCT.[38] Other cohorts from countries in East Asia, with CMV viremia rate of 54%–70% after HSCT, and a CMV disease rate of 7.5%, also showed compatible results from our study.[10,14,19,20] On the other hand, compared to the results from lower CMV seroprevalence countries, in which the CMV reactivation rate reported to be 4%–35% in allo-HSCT patients, our results were higher than the findings from their values.[15,21] For CMV cumulative incidence in auto-HSCT, our results were lower than the previous studies, which reported cumulative incidence of CMV reactivation ranging from 11.4%–31.4%, with CMV disease rate between 7.1%–7.4%, varying by the adopted diagnostic strategy of clinically driven approach or prospective surveillance strategy.[22,23] We also tested CMV incidences among allo-HSCT patients excluding CMV serostatus negative and recipient serostatus negative from the analysis, the results showed slightly higher incidences, which was as expected direction. This added information allowed us to understand better the burden of CMV infection in this patient population. Overall, our study provides a real-world evaluation of a highly prevalent area of CMV infection and disease after HSCT.

With regard to the infection sites of CMV diseases, half of the related organs were at the gastrointestinal tract

Table 5-1 Risk factors of CMV infection at day 180 among allo-HSCT patients (n = 2100).

Characteristics		Univariate		Multivariate	
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	≥45 vs. < 45	1.440 (1.285–1.613)	<0.0001	1.129 (0.991–1.287)	0.0691
Sex	Female vs. male	1.070 (0.955–1.198)	0.2430		
Type of donor	Matched vs. mismatched	0.643 (0.574–0.721)	<0.0001	0.856 (0.753–0.974)	0.0180
Conditioning regimen	MAC vs. non-MAC	0.585 (0.521–0.657)	<0.0001	0.674 (0.591–0.770)	<0.0001
ATG	Yes vs. no	1.860 (1.644–2.104)	<0.0001	1.819 (1.582–2.091)	<0.0001
Recipient CMV serostatus	Positive vs. Negative	2.753 (2.030–3.733)	<0.0001	2.631 (1.933–3.582)	<0.0001
Acute GVHD (grades II–IV)	Yes vs. no	1.566 (1.397–1.756)	<0.0001	1.563 (1.392–1.755)	<0.0001

Abbreviations. MAC, Myeloablative conditioning; GVHD, graft-versus-host disease.

Table 5-2 Risk factors of CMV disease at day 180 among allo-HSCT patients (n = 2100).

Characteristics		Univariate		Multivariate	
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	≥45 vs. < 45	1.104 (0.807–1.509)	0.5360		
Sex	Female vs. male	1.070 (0.955–1.198)	0.2430		
Type of donor	Matched vs. mismatched	0.599 (0.440–0.815)	0.0010	0.654 (0.480–0.891)	0.0070
Conditioning regimen	MAC vs. non-MAC	0.632 (0.462–0.863)	0.0040	0.693 (0.507–0.948)	0.0220
ATG	Yes vs. no	1.266 (0.911–1.757)	0.1600		
Recipient CMV serostatus	Positive vs. Negative	1.315 (0.671–2.576)	0.4250		
Acute GVHD (grades II–IV)	Yes vs. no	2.638 (1.933–3.600)	<0.0001	2.500 (1.829–3.416)	<0.0001

Abbreviations: MAC, Myeloablative conditioning; GVHD, graft-versus-host disease.

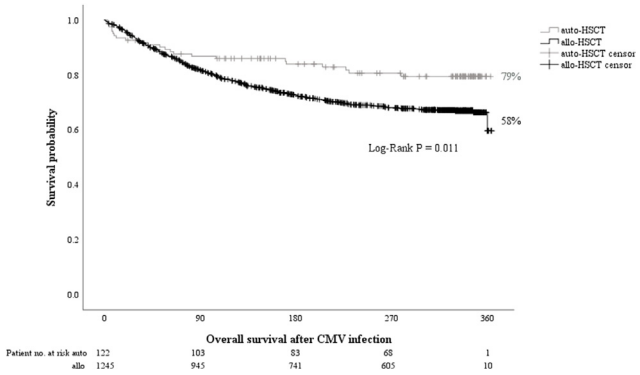

Figure. 3-1. Overall survival after CMV infection.

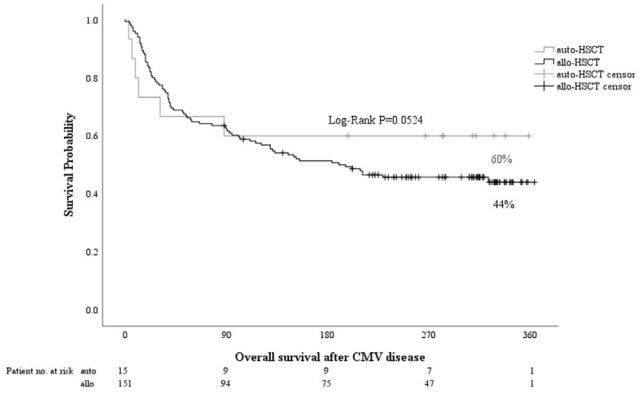

Figure. 3-2. Overall survival after CMV disease.

(Table 4), which was similar to the findings from previous studies.[14,24] Of all the CMV diseases, around half were with preceding CMV viremia. According to Boeckh et al. (2003),[25] CMV antigenemia during the first three months was a strong risk factor for CMV disease and survival. However, due to the low event rate in our studies, future studies are needed to evaluate the association of preceding CMV antigenemia and CMV disease in different affected organs.

In respect of transplant outcomes of overall survival (Table 2.), our study showed similar results compared with the allo-HSCT population in United States,[26] with the 3-year overall survival range from 49% to 62% in MDS, MPN, ALL, and AML adults. Our findings also provide near but higher results compared with a single-center study from Taiwan, with a 180-day overall survival of 74.4% among allo-HSCT patients.[11] For relapse-free survival, our results were equivalent to the results from Gu et al. (2021)[27] among peripheral T-cell lymphoma (three-year progression-free survival of 44%) and with the results from Scott et al. (2017)[28] among AML or MDS patients (18-month relapse-free survival of 47.3% in reduced intensity group and 67.8% in myeloablative group). As for non-relapse mortality, our cohort presented similar results from Tanaka et al. (2016)[29] among allo-HSCT patients from Japan (2-year non-relapse mortality of 16%) and from Gu et al. (2021)[27] (three-year non-relapse mortality rate of 27%).

In terms of risk factors for CMV infection or CMV disease in allo-HSCT, R + CMV serostatus, acute GVHD, mismatched donor, age over 40—50 years, and T-cell depletion were reported to be associated with increased risk of CMV reactivation after HSCT in the previous studies. Besides, R + CMV serostatus, acute GVHD, mismatched donor, and high viral load were associated with CMV disease after HSCT.[7,13,14] Our results were in accordance with the previous studies, except for conditioning regimens. The association between conditioning regimen and CMV infection was inconsistent in past studies. While most of the findings reported myeloablative regimens as a risk factor for CMV reactivation,[7,13] George et al. (2010)[30] reported that non-myeloablative regimens were an independent predictor of CMV reactivation, independent of the use of ATG or alemtuzumab. Nachbaur et al. (2003)[31] reported that non-myeloablative was associated with an increased risk of CMV infection, probably owing to the addition of anti-T-cell antibodies to the conditioning regimen. In another study by Nakamae et al. (2009),[32] they found that CMV disease rates were similar between myeloablative and non-myeloablative groups during the first 100 days after HSCT, but non-myeloablative recipients had an increased risk of late CMV disease (adj. HR 2.0, 95% CI 1.2—3.4). They suggested that this may be driven by less virologic surveillance and less use of late preemptive therapy in the early years of the study period because of the perception that infectious complications were less frequent. Two other single-center studies from Taiwan showed that myeloablative regimen was not associated with CMV reactivation after HSCT.[11,33] In our research, we found that myeloablative regimens were associated with a lower risk of CMV infection and CMV disease, independent of other risk factors. Further studies are required to assess the relationship between conditioning regimens and the risk of CMV reactivation.

As to overall survival after CMV infection and CMV disease, previous studies have shown that CMV infection was a major cause of mortality after allo-HSCT, by the reasons of bacterial and fungal co-infections, organ toxicities, and adverse effects of antiviral therapy.[34] On top of that, mortality associated with CMV diseases was reported to be 45—60% in HSCT recipients, despite antiviral treatment.[35] A study by Diaz et al. (2020)[36] showed that one-year survival among patients with CMV infections was 39% (24—53%), and one-year survival among patients with CMV diseases was 25% (0—66%). Yet, to our best knowledge, no study outlined the survival after CMV infection and CMV disease. In our study, which showed significantly lower survival of allo-HSCT compared to auto-HSCT after CMV infections (Fig. 3-1), and a lower trend of survival between allo-HSCT and auto-HSCT after CMV diseases (Fig. 3-2).

There are four medications approved by the US Food and Drug Administration (FDA) for CMV prophylaxis or therapy: foscarnet (1991), ganciclovir (1994), cidofovir (1996), and valganciclovir (2001). However, owing to their myelotoxicity and nephrotoxicity, pre-emptive therapy was the standard of care in the past era. Recently, a new class of anti-CMV medication, letermovir (LET), a viral terminase inhibitor, was approved by FDA in 2017 for prophylaxis of CMV infections, later approved by Taiwan FDA on December 2018 and received reimbursement on June 2020 for high-risk allo-HSCT patients. Unlike other anti-CMV medication classes, LET possesses the advantage of lower severe adverse effects. There was an increasing number of HSCT

patients who received LET for CMV prophylaxis in clinical settings; further analyses are expected to evaluate the effect of LET on our population.

Limitations

First, there were inherited biases for the retrospective nature of this study. Second, there were heterogeneities in CMV monitoring methods, monitoring schedules, preemptive treatment thresholds, and strategies for each institution and physician. Third, seventeen percent of allo-HSCT patients with missing data on CMV serostatus, which may undervalue the true prevalence in our population. Nevertheless, based on multivariate analysis, we found a two-fold risk of CMV infection in CMV seropositive patients compared with seronegative patients, which revealed a similar trend compared to the previous studies.[9,37] Furthermore, in this study, the main focus was to investigate the incidence and risk factors associated with CMV infection. Many of the potential risk factors such as age, gender, type of donor, conditioning regimen, use of ATG, or recipient CMV serostatus are time-invariant. Hence, we did not employ time-dependent variables in our multivariate analyses in order to avoid complicated analytic scenario. Future study may consider the potential impacts of time-variant covariates on clinical outcomes. Last, even with the importance of all centers' participation in collecting comprehensive nationwide HSCT patients' information, there were still centers that hadn't joined TBMTR due to limitations of technical resources. However, TMBTR already covered around 95% of all HSCT performed in Taiwan, which we believe is sufficient to represent our population.

Conclusions

In conclusion, we presented the first nationwide epidemiologic data on the incidence of CMV infection and CMV disease after HSCT among auto and allo-HSCT patients. We also demonstrated the risk factors of CMV infection and disease, along with overall survival, relapse-free survival, and non-relapse mortality among allo-HSCT patients in Taiwan. Plus, we presented overall survival after CMV infection and disease. Further analysis is required to address the prophylactic medication on the risk of CMV infection and survival outcomes in the high-risk population.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.02.005.