Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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To cite this article: Rie Ueno, Shinichi Nishimura, Go Fujimoto, Yi Piao & Katsuto Takenaka (2019) The clinical and economic burden of cytomegalovirus management post allogeneic hematopoietic stem cell transplantation in Japan – a retrospective database study, Current Medical Research and Opinion, 35:12, 2089-2096, DOI: 10.1080/03007995.2019.1649379

To link to this article: https://doi.org/10.1080/03007995.2019.1649379

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 12, 2089–2096
https://doi.org/10.1080/03007995.2019.1649379
Article FT-0357.R1/1649379

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ORIGINAL ARTICLE

The clinical and economic burden of cytomegalovirus management post allogeneic hematopoietic stem cell transplantation in Japan – a retrospective database study

Rie Ueno[a], Shinichi Nishimura[a], Go Fujimoto[a], Yi Piao[b] and Katsuto Takenaka[c]

[a]MSD K.K., Tokyo, Japan; [b]IQVIA Solutions Japan K.K., Tokyo, Japan; [c]Department of Hematology, Clinical Immunology and Infectious Diseases, Graduate School of Medicine, Ehime University, Toon, Japan

ABSTRACT

Introduction: Reactivation of cytomegalovirus (CMV) infection is a major threat and it causes significant morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). There remains, however, a paucity of evidence regarding the economic burden of current CMV management in Japan. The aim of this study is to characterize the healthcare resource utilization (HCRU) and cost incurred for CMV management post allo-HSCT, using a Japanese hospital claims database.

Methods: Patients who underwent allo-HSCT between April 2010 and March 2018 were identified and followed up for 180 days.

Results: In total, 916 patients were included for analysis and categorized into CMV (−) group and CMV (+) group based on the presence of a CMV episode within 100 days post allo-HSCT. A CMV episode was defined as evidence of receiving at least one dose of the following anti-CMV drugs, ganciclovir, foscarnet, or valganciclovir. The mean (± standard deviation [SD]) total length of stay was 93.6 (± 43.7) days in the CMV (+) group, which was significantly longer than 55.9 (±40.6) days in the CMV (−) group, and this trend was more pronounced in patients with multiple CMV episodes. The mean (±SD) total medical cost within 180 days post allo-HSCT was US$122,328 (±56,977) in the CMV (+) group, while the mean total medical cost was US$75,344 (±43,821) in the CMV (−) group. Moreover, transfusion and antimicrobial use was observed as the major medication cost component, which is suggestive of the indirect effect of CMV episodes.

Conclusion: This study demonstrated that CMV episodes post allo-HSCT were associated with increased HCRU and cost.

ARTICLE HISTORY
Received 5 July 2019
Revised 19 July 2019
Accepted 21 July 2019

KEYWORDS
Cytomegalovirus; allogeneic hematopoietic stem cell transplantation; medical cost; healthcare resource utilization

Introduction

Human cytomegalovirus (CMV) is an opportunistic pathogen and widely carried among populations. The CMV seroprevalence in Japan is ~80–90%[1], which is higher than western countries[2–5]. In most cases, infected persons are asymptomatic. However, reactivation of the virus as a result of reduced cellular immunity can lead to a significant increase in virulence in immunocompromised patients, such as recipients of hematopoietic stem cell transplantation (HSCTs)[6]. A Japanese study has shown that reactivation of CMV occurred in ~50% of recipients who were CMV seropositive after allo-HSCT[7]. CMV reactivation exhibits a wide spectrum of clinical manifestations, including pneumonia, gastroenteritis, retinitis, and hepatitis[8]. Until now, clinicians have adopted a pre-emptive therapy (PET) in which detection of CMV viremia triggers antiviral treatment (e.g. ganciclovir) to prevent end-organ CMV diseases[9]. Previous studies have indicated that CMV reactivation is a major post-allo-HSCT complication and is associated with overall mortality or non-relapse mortality after allo-HSCT[7,10,11]. Moreover, recent studies have indicated that CMV reactivation and any level of viremia could also be associated with post-allo-HSCT mortality, suggesting the limitation of CMV management with PET[5,7,8].

CMV reactivation is not only associated with negative clinical outcome, but also correlated with increased economic burden. Previously, a single-site study in the US compared outcomes and post-transplant treatment cost between 44 patients who never required PET and 90 treated patients undergoing allo-HSCT. Those patients who required PET incurred an additional cost of antiviral medication ($58,000–$74,000 per patient), and additional days of hospitalization (13.9 days per patient)[12]. On the other hand, a recent French single-institution study also examined an association between CMV reactivation and cost incurred post allo-HSCT in 208 adult patients. In this study, the cost of transplant after 12 months increased with the number of

CONTACT Rie Ueno rie.ueno@merck.com Medical Affairs, MSD K.K., Japan, Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan

Supplemental data for this article is available online at https://doi.org/10.1080/03007995.2019.1649379.

CMV episodes (€99,793, €104,815, and €125,080 with no CMV episode, 1 CMV episode, and ≥2 CMV episodes, respectively)[13]. However, those previous studies were limited by a small population size and lack of details of healthcare resource utilization incurred after transplantation.

This study aimed to demonstrate the economic burden of CMV episodes post-allo-HSCT using a large hospital claims database, and to better characterize the healthcare resource utilization associated with the current CMV management.

Methods

Data source

Data for this study was obtained from the commercially available hospital claims database; Medical Data Vision (MDV). This database has been used in previous health economic studies[14–17]. MDV contains anonymized healthcare claims data from patients' outpatient and inpatient visit, including information on demographic, diagnosis, drug prescription, examination, surgery, laboratory, and medical procedures. It is derived from ~359 acute hospitals throughout Japan. This sample represents ~22% of the hospitals that use the Diagnosis Procedure Combination (DPC) claims-based bundled payment system in Japan. The DPC is a flat-fee system, similar to the Diagnosis-Related Group (DRG) classification system in the US, was introduced to Japan in April 2003 for use at large hospitals[18]. As of March 2018, it consists of ~22 million patient records. "Universal National Health Insurance System" was established and it applies to the entire population in Japan. This study was approved by the Merck & Co., Inc. (Kenilworth, NJ), Center for Observational and Real-world Evidence Review Board (approval number: ID1314).

Study design and study population

This is a retrospective cohort study and the study population comprised adult patients (≥18 years of age) who underwent the first allo-HSCT between April 1, 2010 and March 31, 2018. The first allo-HSCT date was defined as the index date. Among the study population, patients who aged 18 and over were included at the time of the index date. Patients were excluded when they met at least one of the following criteria: (1) who underwent autologous stem cell transplantation during the study period; (2) who cannot be followed up for 180 days post-index date (i.e. follow-up period; patients with evidence of inpatient death were retained); (3) who cannot be traced back for 180 days pre-index date (i.e. look-back period); and (4) who have more than one allo-HSCT during the follow-up period.

This study defined the presence of CMV episodes as evidence of receiving at least one dose of the following anti-CMV drugs: ganciclovir, foscarnet, or valganciclovir. Presence of switching-over to another anti-CMV drug within 6 days from the last dose of previous treatment was defined as drug switch. Receiving the same or different type of anti-CMV drugs at least 7 days apart from the last dose of previous treatment was defined as another CMV episode.

Patients were categorized into two groups: (1) no CMV episode [hereinafter referred to as CMV (−)]; (2) having at least one CMV episode [CMV (+)] within 100 days post-index date. The period of 100 days was selected as the cut-off, as published evidence suggests allo-HSCT recipients are at higher risk of CMV reactivation during this period[9].

Based on the number of CMV episodes, the CMV (+) group was further stratified into two groups; (a) having only one CMV episode [CMV (1)] and (b) having two or more CMV episodes [CMV (≥2)]. Baseline characteristics (e.g. age, gender), indications for allo-HSCT, and source of stem cell were collected at the time of the index date, and Charlson comorbidity index (CCI) was measured during the look-back period. The anti-CMV drug treatment patterns were examined: such as the time to the first CMV episode and subsequent CMV episodes after the index date, duration of CMV episodes, type of anti-CMV drugs prescribed, and number of switching in anti-CMV drugs.

Outcome measures

The main outcomes from this study are HCRU and medical cost within 180 days after allo-HSCT in the CMV (+) group and CMV (−) group. The period of 180 days was selected because it represents the time for which most of the HCRU are used[13]. HCRU was classified into the following categories: number of hospitalizations, number of readmissions, total hospital stays, number of outpatient visits, duration of medication use, duration of blood product use, and number of clinical examinations. Types of medication were included but were not limited to immunosuppressant drugs (e.g. prednisolone), anti-CMV drugs, and antimicrobials (refer to detailed list of medications in Supplementary Table S1). Clinical examination defined in this study included X-ray, computed tomography (CT) scan, esophagogastroduodenoscopy, colonoscopy, bronchoscopy, retinal examination, and CMV antigenemia test. Medical costs were presented based on cost categories listed in the DPC data such as medication, examination, surgery/procedure, and others (e.g. basic hospitalization fee). Furthermore, cost was also shown as HCRU categories as well. Cost was converted to US dollars ($) by the exchange rate in March 2018 (1US$ = 106 Japanese yen).

Statistical analysis

Categorical variables were presented as the count and percentage of patients in each category; continuous variables were summarized by providing the mean, standard deviation (SD), and median. The analysis mainly focused on data reported in 180 days post allo-HSCT. A sensitivity analysis of cost and HCRU was carried out excluding patients who died within 180 days after allo-HSCT. Demographic and clinical characteristics were described and presented by the number of CMV episodes. Statistical comparisons were performed across different groups using ANOVA for continuous variable, Wilcoxon rank sum test for median, and Chi-square and

Table 1. Baseline characteristics of included patients.

Characteristics	Total ($n = 916$)	CMV (−)[a] ($n = 177$)	CMV (+)[b] ($n = 739$)
Age at index date, years			
Median (IQR)	54 (40–62)	51 (38–60)	55 (42.5–62)
Gender, *n* (%)			
Female	397 (43.3)	83 (46.9)	314 (42.5)
Male	519 (56.7)	94 (53.1)	425 (57.5)
Indication of allo-HSCT, *n* (%)			
AML	472 (51.5)	98 (55.4)	374 (50.6)
ALL	169 (18.5)	26 (14.7)	143 (19.4)
Myelodysplastic syndrome	276 (30.1)	53 (29.9)	223 (30.2)
Lymphoma	291 (31.8)	52 (29.4)	239 (32.3)
Multiple myeloma and plasma cell neoplasms	31 (3.4)	9 (5.1)	22 (3.0)
CLL	1 (0.1)	1 (0.6)	0 (0)
Aplastic anemia	48 (5.2)	13 (7.3)	35 (4.7)
CML blast crisis	30 (3.3)	7 (4.0)	23 (3.1)
ATL or ATLL	225 (24.6)	30 (17.0)	195 (26.4)
Stem cell source, *n* (%)			
Bone marrow	232 (25.3)	40 (22.6)	192 (26)
Peripheral blood	174 (19)	45 (25.4)	129 (17.5)
Cord blood	510 (55.7)	92 (52.0)	418 (56.6)
Charlson Comorbidity Index (CCI)			
Median (IQR)	5 (3–6)	5 (3–6)	5 (3–6)

[a]Having no CMV episode within 100 days post-index date.
[b]Having at least one CMV episode within 100 days post-index date.
Abbreviations. CMV, cytomegalovirus; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATL or ATLL, adult T-cell leukemia/lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem cell transplantations; IQR, interquartile range.

Fisher's exact test for categorical variable. A significance level was set at $\alpha = 0.05$ (p-value $< .05$) for statistical test. All the statistical analysis was performed using SAS version 9.4 (SAS institute, Cary, NC).

Results

Patient demographic and clinical characteristics

A total of 1446 patients were identified as the study population. Of these, 916 patients who met the eligibility criteria were included in this study (Supplementary Figure S1) and were categorized into two groups of CMV (−) ($n = 177$) and CMV (+) ($n = 739$). The CMV (+) group was divided into CMV (1), with 359 patients, and CMV (≥2), with 380 patients.

Baseline patient demographic and clinical characteristics were identified as shown in Table 1. The median age of the overall patients was 54 (interquartile range [IQR] = 40–62) years old, of which 56.7% were male and 43.3% were female. In terms of the indication of allo-HSCT, 472 patients (51.5%) received allo-HSCT for acute myeloid leukemia, 291 (31.8%) for acute lymphocytic leukemia, and 276 (39.1%) for myelodysplastic syndrome. The number of patients who received bone marrow, peripheral blood, and cord blood as a stem cell source was 232 (25.3%), 174 (19.0%), and 510 (55.7%), respectively. The median CCI score was 5 (3–6) for the overall population.

CMV episodes and drug treatment patterns

Among the 752 patients who had at least one CMV episode, 479 patients had at least two CMV episodes, and 246 patients had three or more CMV episodes during the 180 days post allo-HSCT. Furthermore, 98% (739 patients) of the patients who had at least one CMV episode experienced the first episode within 100 days (Figure 1).

The pattern of CMV episodes and anti-CMV drug use in CMV (+) patients over the first 180 days post allo-HSCT are shown on Table 2. The median time to the first CMV episodes from the index date was 26 (15–40) days. The median time to the subsequent CMV episodes from the previous CMV episode was 20 (13–30) days. Ganciclovir was the most frequently utilized ($n = 515$, 69.7%) among anti-CMV drugs prescribed over the 180 days post-allo-HSCT, followed by valganciclovir ($n = 387$, 52.4%) and foscarnet ($n = 366$, 49.5%). Treatment switches were reported in 314 (42.5%) patients. The mean (± standard deviation [SD]) number of anti-CMV drugs switch was 1.4 (±2.9) for the CMV (+) group. Those results show a potential challenge in the CMV management.

Healthcare resource utilization and cost analysis

The summary of inpatient and outpatient encounters is shown in Supplementary Table S2. In comparison with the CMV (−) group, the mean number of hospitalizations (1.4 ± 0.7 vs 1.2 ± 0.5; $p = .0014$) and the total hospital days (93.6 ± 43.7 vs 55.9 ± 40.6 days; $p < .0001$) were significantly elevated in the CMV (+) group. In addition, 28.0% of patients in the CMV (+) group had at least one or more readmissions, which was higher than the CMV (−) group (14.7%).

As shown in Supplementary Table S3, patients in the CMV (+) had increased mean duration of immunosuppressant drugs (157.8 ± 75.2 vs 101.5 ± 76.1 days; $p < .0001$) and a longer mean duration of antimicrobial use (192.7 ± 64.9 vs 125.2 ± 78.3 days; $p < .0001$) compared to those in the CMV (−) group. Notably the mean duration of intravenous antifungal use was significantly longer in the CMV (+) group (56.0 ± 37.6 vs 30.2 ± 23.4 days; $p < .0001$). Mean duration of blood product utilization was significantly longer in the CMV

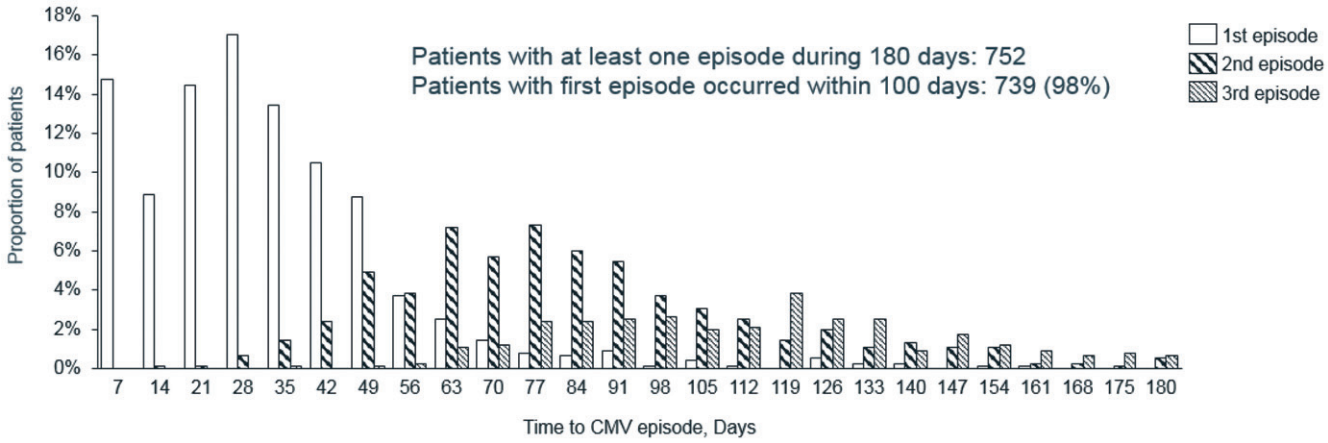

Figure 1. The time of occurrence of 1st, 2nd and 3rd episode after index date. CMV (−): having no CMV episode within 100 days post-index date; CMV (1): having only one CMV episode within 100 days post-index date; CMV (≥2): having more than or equal to two CMV episodes within 100 days post-index date.

Table 2. Pattern of CMV episodes and anti-CMV drug use in CMV (+) patients over the first 180 days post-allo-HSCT.

Category	CMV (+)[b] ($n = 739$)	CMV (1)[c] $n = 359$	CMV (≥2)[d] $n = 380$
Time to CMV episode after allo-HSCT			
Median time to presentation of 1st episode, days (IQR)	26 (15–40)	26 (11–43)	26.5 (17.5–36)
Median time to end of 1st episode, days (IQR)	55 (41–70)	62 (49–87)	50 (36–62)
Median duration of 1st episode, days (IQR)	22 (12–41)	29 (14–59)	21 (10.5–31)
Number of patients with presentation of 2nd and subsequent episodes, *n*	477	97	380
Median time to presentation of 2nd and subsequent episodes from the previous episode, days (IQR)	20 (13–30)	31 (17.7–42)	19 (12.5–26)
Number of patients being prescribed with anti-CMV drug, *n* (%)			
Ganciclovir	515 (69.7)	223 (62.1)	292 (76.8)
Foscarnet	366 (49.5)	183 (51.0)	183 (48.2)
Valganciclovir	387 (52.4)	144 (40.1)	243 (64.0)
The number of medication switching, mean ± SD	1.4 ± 2.9	1.3 ± 2.7	1.5 ± 3.1
0, *n* (%)	425 (57.5)	219 (61.0)	206 (54.2)
1, *n* (%)	116 (15.7)	43 (12.0)	73 (19.2)
≥2, *n* (%)	198 (26.8)	97 (27.0)	101 (26.6)

[a]Having no CMV episode within 100 days post-index date.
[b]Having at least one CMV episode within 100 days post-index date.
[c]Having only one CMV episode within 100 days post-index date.
[d]Having more than or equal to two CMV episodes within 100 days post-index date.
Abbreviations. CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantations; IQR, interquartile range; SD, standard deviation.

(+) group than the CMV (−) group for both red blood cells (12.2 ± 11.0 vs 7.1 ± 6.6 days; $p < .0001$) and platelets (29.2 ± 25.6 vs 17.2 ± 16.5 days; $p < .0001$). For clinical examinations (Supplementary Table S4), 85.5% and 99.1% of patients in the CMV (+) group had a CT exam and CMV antigenemia test, respectively, which was higher than the 68.4% and 83.1% in the CMV (−) group. Furthermore, 13.1% of patients underwent colonoscopy and 2.3% of patients had bronchoscopy in the CMV (+) group, compared with 4.0% and 0.6% in the CMV (−) group, respectively.

The mean total medical cost in 180 days post-allo-HSCT is shown in Table 3. In comparison to the CMV (−) group, the CMV (+) group had significantly higher mean cost (US$75,344 ± 43,821 vs 122,328 ± 56,977; $p < .0001$). The mean of medical cost in the CMV (≥2) group was higher than in the CMV (1) group (US$115,177 ± 54,878 vs 129,084 ± 58,159; $p = .0009$). As shown in Figure 2, inpatient cost constituted the majority of the total medical cost, which increased as the number of CMV episodes increased. Figure 3 shows the total medical costs based on categories listed in the DPC data. In the CMV (+) group, medication cost (e.g. anti-CMV drugs, immunosuppressant drugs, antimicrobials, blood products) was the major cost component. A detailed cost breakdown is listed in Table 4. Costs related to anti-CMV drugs, blood products, and antimicrobials were significantly higher in the CMV (+) group than in the CMV (−) group.

Those findings suggest a significant economic impact of CMV management in Japan.

Sensitivity analyses: cost and healthcare resource utilization

In this study, due to the limitations of the database, a sensitivity analysis was conducted, as shown in Figure 4 and Supplementary Table S5.

This study excluded patients who died within 180 days post-allo-HSCT out of concerns that the presence of unequal number of inpatient deaths in each group could affect the HCRU and cost outcomes. Supplementary Table S5 demonstrates that patients in the CMV (+) had increased total mean length of stay (96.4 ± 43.9 vs 74.1 ± 39.7 days; $p < .0001$). The mean total medical cost was also increased as the number of CMV episodes increased (Figure 4).

The findings of sensitivity analysis were consistent with those from the main analysis demonstrating an increase in HCRU and cost with CMV episodes.

Table 3. Total cost in 180 days after allo-HSCT.

Category	CMV (−)[a] (*n* = 177)	CMV (+)[b] (*n* = 739)	*p*-value	CMV (+)		
				CMV (1)[c] (*n* = 359)	CMV (≥2)[d] (*n* = 380)	*p*-value
Total (inpatient + outpatient)						
Mean	$75,344	$122,328	<.0001	$115,177	$129,084	.0009
SD	$43,821	$56,977		$54,878	$58,159	
Median	$63,218	$107,036	<.0001	$103,264	$110,644	.0009
25% percentile	$50,475	$84,957		$80,895	$89,896	
75% percentile	$91,650	$148,818		$138,886	$158,886	

[a]Having no CMV episode within 100 days post-index date.
[b]Having at least one CMV episode within 100 days post-index date.
[c]Having only one CMV episode within 100 days post-index date.
[d]Having more than or equal to two CMV episodes within 100 days post-index date.
Abbreviations. CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantations; SD, standard deviation.

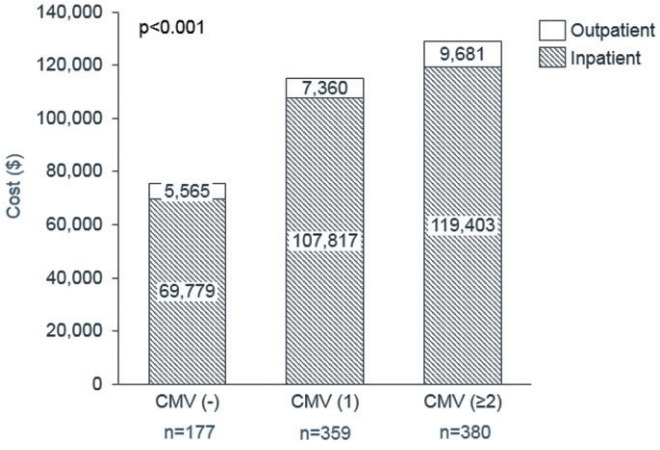

Figure 2. Mean total cost in 180 days after allo-HSCT. The *p*-value represents the statistical test results between three groups. CMV (−): having no CMV episode within 100 days post-index date; CMV (+): having at least one CMV episode within 100 days post-index date; CMV (1): having only one CMV episode within 100 days post-index date; CMV (≥2): having more than or equal to two CMV episodes within 100 days post-index date.

Discussion

Among the 916 patients included in this study, over 80% of patients had CMV episodes in 180 days after allo-HSCT, 98% of which had CMV episodes within 100 days. It was also found that the first CMV episode occurred in ∼ 30 days post-allo-HSCT. Two or more episodes of CMV occurred in over 50% of patients post-allo-HSCT, which may suggest a potential challenge in the CMV management. This study also revealed that patients who had CMV episodes had higher medical cost and HCRU, and both cost and HCRU increased as the number of CMV episodes increased.

In a previous US study, patients who required PET incurred an additional cost of USD 58,000–74,000 within the first 6-months post-HSCT. However, it is a single center study using a small sample size, and the breakdown of the cost increase was not described in detail[12]. Another retrospective study in France demonstrated that the occurrence of CMV episodes was significantly associated with increased costs. Whereas the difference was not obvious with only one CMV episode, two or three CMV episodes contributed to an ∼25–30% increase in medical cost. Nevertheless, this is a single-center study with a small sample size. The details of the resource utilization contributing to the cost increase were not discussed[13].

In this study, we used a large Japanese hospital claims database including 916 patients to evaluate the HCRU and cost of current CMV management with PET, as well as the detailed breakdown of those. In our study, the total medical cost was ∼60% higher in the CMV (+) than the CMV (−) group, and 12% higher in CMV (≥2) than CMV (1), which suggests a significant economic impact of CMV management in Japan. The length of hospitalization was longer in the CMV (+) group than in the CMV (−) group, which is likely contributing to the overall increase in inpatient cost. Also, the medication cost (e.g. anti-CMV drugs, immune-suppressant drugs, antimicrobials, blood products) is the major cost component of the total cost. A sensitivity analysis excluding patients who died within 180 days post-allo-HSCT further

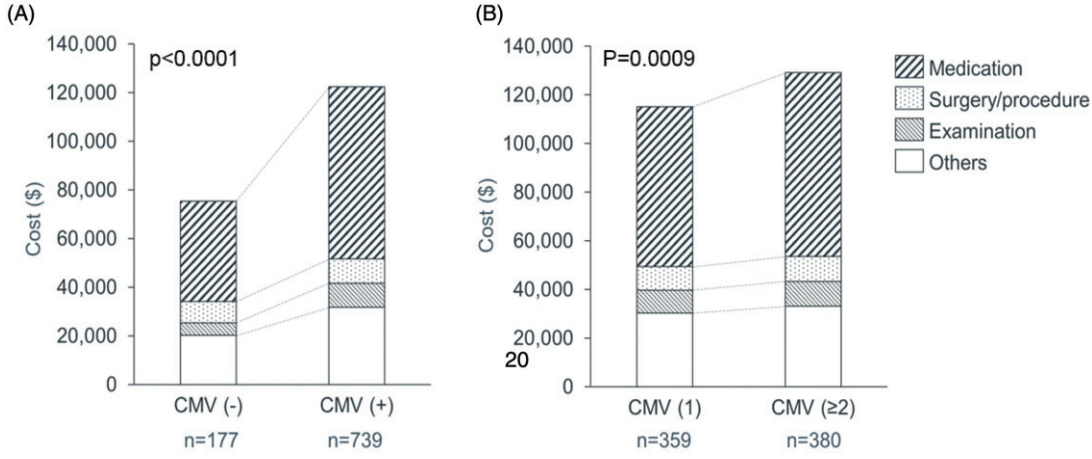

Figure 3. Mean total cost in 180 days after allo-HSCT stratified by cost categories listed in DPC data. (A) CMV (−) and CMV (+). (B) CMV (1) and CMV (≥2). The *p*-value represents the statistical test results of mean total cost. CMV (−): having no CMV episode within 100 days post-index date; CMV (1): having only one CMV episode within 100 days post-index date; CMV (≥ 2): having more than or equal to two CMV episodes within 100 days post-index date.
Abbreviations: CMV, cytomegalovirus; DPC, diagnosis procedure combination.

Table 4. Detailed cost component of medication in 180 days after allo-HSCT.

Category	CMV (–)[a]	CMV (+)[b]	*p*-value	CMV (+)		
	(*n* = 177)	(*n* = 739)		CMV (1)[c] (*n* = 359)	CMV (≥2)[d] (*n* = 380)	*p*-value
Anti-CMV drug						
Mean	$112	$4,039	<.0001	$3,625	$4,430	.0029
SD	$528	$3,680		$3,902	$3,416	
Median	$0	$2,942	<.0001	$1,986	$3,309	<.0001
25% percentile	$0	$1,412		$800	$1,999	
75% percentile	$0	$5,671		$5,209	$6,070	
Immunosuppressant drugs						
Mean	$2,153	$2,630	<.0001	$2,491	$2,761	.0192
SD	$1,869	$1,569		$1,627	$1,502	
Median	$1,737	$2,238	<.0001	$2,055	$2,402	.0008
25% percentile	$774	$1,555		$1,437	$1,698	
75% percentile	$2,908	$3,380		$3,186	$3,480	
Antimicrobial						
IV Antifungal						
Mean	$4,292	$9,276	<.0001	$8,842	$9,686	.2236
SD	$4,695	$9,415		$9,375	$9,448	
Median	$2,786	$6,907	<.0001	$6,444	$7,210	.1373
25% percentile	$1,439	$2,716		$2,552	$2,877	
75% percentile	$4,905	$1,2376		$12,259	$12,523	
PO Antifungal						
Mean	$2,533	$3,907	<.0001	$3,798	$4,009	.468
SD	$3,531	$3,934		$4,180	$3,689	
Median	$862	$2,501	<.0001	$2,074	$2,967	.0771
25% percentile	$0	$514		$309	$792	
75% percentile	$3,718	$6,944		$6,745	$7,016	
Carbapenems						
Mean	$416	$608	.0014	$590	$625	.5234
SD	$501	$755		$748	$763	
Median	$243	$413	.017	$381	$428	.5991
25% percentile	$0	$0		$0	$0	
75% percentile	$678	$878		$871	$892	
Other broad-spectrum antimicrobials						
Mean	$226	$477	<.0001	$471	$483	.8169
SD	$418	$688		$649	$725	
Median	$0	$186	<.0001	$228	$136	.3462
25% percentile	$0	$0		$0	$0	
75% percentile	$283	$772		$741	$783	
Anti-MRSA antimicrobials						
Mean	$581	$1,077	<.0001	$992	$1,157	.1332
SD	$951	$1,492		$1,425	$1,551	
Median	$267	$639	<.0001	$476	$765	.0129
25% percentile	$0	$21		$0	$82	
75% percentile	$767	$1,488		$1,298	$1,554	
Blood products						
Red blood cells						
Mean	$861	$1,604	<.0001	$1,586	$1,620	.8305
SD	$1,192	$2,134		$2,261	$2,010	
Median	$502	$969	<.0001	$960	$990	.633
25% percentile	$0	$0		$0	$0	
75% percentile	$1,171	$2,174		$2,096	$2,307	
Platelets						
Mean	$14,086	$23,072	<.0001	$20,915	$25,110	.0093
SD	$14,029	$21,948		$20,265	$23,270	
Median	$9,112	$15,824	<.0001	$15,071	$16,766	.0146
25% percentile	$6,028	$9,477		$8,289	$1,0497	
75% percentile	$15,824	$29,242		$2,6607	$3,3826	

[a]Having no CMV episode within 100 days post-index date.
[b]Having at least one CMV episode within 100 days post-index date.
[c]Having only one CMV episode within 100 days post-index date.
[d]Having more than or equal to two CMV episodes within 100 days post-index date.
Abbreviations. CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantations; IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus; PO, per oral; SD, standard deviation.

supports the finding that the CMV (+) group had higher total medical costs than the CMV (−) group.

The duration of medication use was longer in the CMV (+) group than the CMV (−) group. Increased antimicrobial use, especially antifungals use, might be related to the indirect-effect of CMV reactivation[19,20]. Duration of immunosuppressants used for post-HSCT graft vs host disease (GvHD) management was longer in the CMV (+) group than the CMV (−) group. This might be suggestive of increased risk of GvHD during CMV episodes post-allo-HSCT, as stated previously[21]. Similarly, our study found that the duration and utilization of transfusion of red blood cells and

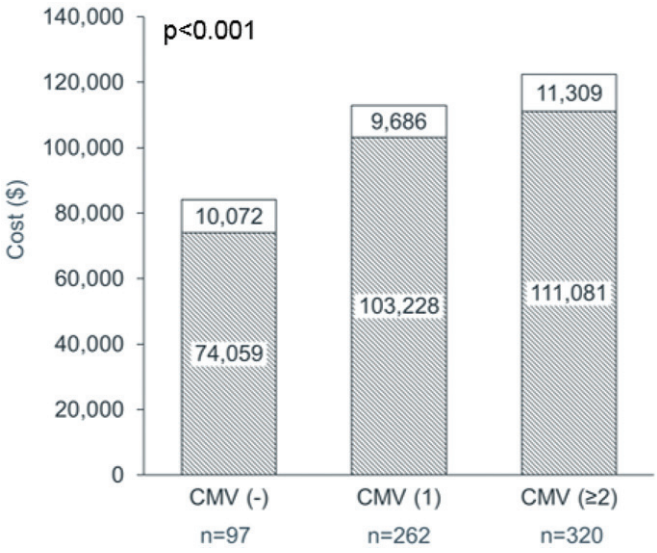

Figure 4. Sensitivity analysis of cost in 180 days after allo-HSCT. Excluding patients who died within 180 days post allo-HSCT.

platelets were higher in the CMV (+) group than in the CMV (–) group. As the duration of ganciclovir use was longer in the CMV (+) group than in the CMV (−) group, the increase in transfusion utilization might be attributable to the myelosuppressive effect of ganciclovir as stated previously[22–24].

This study has several limitations. First, CMV reactivation cannot be defined within MDV database based on diagnostic testing due to lack of the test results; thus, indications for anti-CMV drug use (i.e. prophylactic use, pre-emptive therapy, and CMV-disease treatment) cannot be specified. Second, quantitative CMV PCR assay is not reflected in the database because only the CMV antigenemia test is widely used for post-HSCT CMV monitoring and reimbursed by the national health insurance in Japan. As the CMV antigenemia test cannot be conducted during the pre-engraftment neutropenic phase, a sensitivity analysis excluding patients with CMV episodes within 14 days post-HSCT was performed[25,26]. The findings of the sensitivity analysis were consistent with those from the main analysis demonstrating an increase in HCRU and cost with CMV episodes (data not shown). Third, since this study is descriptive in nature, patient characteristics, such as severity-of-illness, and GvHD were not adjusted between different groups. Forth, misclassification may exist in the database if the claims data were recorded incorrectly. Fifth, we cannot capture healthcare claims in uncontracted hospitals. Lastly, the findings of the present study may be limited to Japanese clinical-settings.

Previous large-database studies indicate an association between post-HSCT mortality (e.g. non-relapse mortality or overall survival) and CMV episodes in the era of pre-emptive therapy[7,11]. To evaluate other aspects of the current CMV management, we analyzed the economic burden using a large anonymized hospital claims database and revealed that 60% of the total medical cost increased in the CMV (+) compared to the CMV (−) group post-allo-HSCT, which indicates a significant economic impact of current CMV management. More research is needed to capture the economic impact of post-allo-HSCT CMV management, including the prophylaxis strategies.

Transparency

Declaration of funding

This study was supported by funding from MSD K.K., Tokyo, Japan.

Declaration of financial/other relationships

R.U., S.N., and G.F. are employees of MSD K.K. Y.P. was an employee of IQVIA Solutions Japan K.K. at the time this study was conducted and is currently an employee of AstraZeneca K.K. K.T. received speaker honoraria from MSD K.K. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

Data availability

The data that support the findings of this study are available from MDV. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://www.mdv.co.jp/english/links.html with the permission of MDV.

Acknowledgements

The authors would like to thank Tetsuya Nishida in the Department of Hematology of Nagoya University Hospital, for his contributions to the study design and providing clinical expert opinions. The authors also thank William Kuan, Dilinuer Ainiwaer, and other staff of IQVIA Solutions Japan K.K. for their substantial contributions to statistical analysis, and writing and editorial assistance, provided under contract with MSD K.K., Tokyo, Japan.

ORCID

Shinichi Nishimura http://orcid.org/0000-0001-6013-8296

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