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Cytomegalovirus Infection Post-hematopoietic Stem Cell Transplant: Incidence, Risk Factors, and Outcome in an Omani Cohort

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ABSTRACT

Objectives: To estimate the incidence, risk factors, and outcome of cytomegalovirus (CMV) infection during the first year following hematopoietic stem cell transplant (HSCT) among Omani patients. ***Methods***: This retrospective study included allogenic HSCT recipients between January 2006 and December 2018. We investigated the possible factors associated with CMV infection and CMV impact on one-year mortality. ***Results:*** Among 556 recipients of allogenic HSCT, 308 (55.4%) were male, the median age was 12 years, and 366 (65.8%) had benign conditions. One-year after transplants, the prevalence of CMV infection was 59.4%, and that of CMV disease was 1.8%. Multivariate analyses revealed significant relationships between CMV infection and haploidentical transplant ($p = 0.006$), graft versus host disease ($p = 0.013$), myeloablative conditioning ($p = 0.001$), and patient age ≥ 12 years ($p < 0.001$). CMV infection was associated with an increased risk of one-year mortality ($p = 0.001$). One-year overall mortality was 8.3%. ***Conclusions:*** The incidence of CMV infection in this Omani cohort was comparable with earlier findings, but the disease incidence and overall mortality were lower. Older age, haploidentical transplant, myeloablative conditioning, and graft versus host disease were significantly associated with a higher risk of CMV infection. In addition, CMV infection was associated with an increased risk of overall mortality in the first year post-transplant. Our findings support early initiation of preemptive therapy at low-level CMV viremia.

Cytomegalovirus (CMV) is a highly prevalent herpesvirus. CMV immunoglobulin G (IgG) positivity has been found to be 60% in the European population and as high as 90% in the Eastern Mediterranean Region (EMR) population.[1,2] CMV causes prolonged latent infection and a wide spectrum of clinical presentations.[3] In immunocompromised patients, it can cause significant morbidity and mortality. CMV infection is present in 60% of seropositive allo-hematopoietic stem cell transplant (HSCT) recipients, which can result in invasive end-organ diseases, such as enteritis and pneumonitis.[4,5] Despite major advances in early diagnosis and management, seropositivity for CMV seems to be a risk factor for transplantation-related mortality in patients who receive a transplant from related donors.[6]

Current prevention strategies that utilize antiviral agents, such as ganciclovir or foscarnet, as preemptive therapy at the onset of viremia have sharply decreased the incidence of CMV end-organ diseases during the first three months after HSCT to 3–6% compared to 30% in the past.[7–9] Generally, there is a preference for preemptive over prophylactic treatment, mainly due to the side effects of the available anti-CMV drugs.[10] There is no consensus as to the cutoff CMV viral load for starting the preemptive therapy; however, it is typically initiated upon the first detection of CMV infection by a rapid detection method such as the pp65 antigenemia assay, pp67 messenger RNA assay, or DNA assay. Quantitative real-time polymerase chain reaction (PCR) assays for CMV DNA are increasingly preferred because of their high sensitivity and specificity and help monitor response

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to treatment. In the preemptive therapy strategy, all allogeneic HSCT recipients are monitored for CMV viral load every week till day 100 post-transplant.[11]

Internationally, the mortality rate of HSCT recipients due to CMV disease is very high, at nearly 46%.[2] The corresponding figures for the EMR are lacking. HSCT service in Oman started in 1995 at Sultan Qaboos University Hospital (SQUH), Muscat. SQUH continues to be the only center in Oman offering the facility and performs allogeneic and autologous HSCT for 4–29 cases yearly. Due to limited bed availability, some patients are sent abroad to undergo the procedure.[12]

We aimed to estimate the incidence of CMV infection/disease in HSCT recipients during the first year post-transplant and investigate the risk factors for CMV infection as well as the clinical outcomes.

METHODS

This was a retrospective observational cohort study of all allogenic HSCT recipients (n = 576) over 12 years (January 2006 to December 2018) who underwent the transplant either at SQUH or abroad and then were followed up at SQUH on their return (usually around day 30 post-transplant). Their one-year post-transplant medical history was collected. We excluded nine HSCT recipients who had CMV infection within three months prior to the transplant and eleven recipients whose records lacked regular CMV viral load testing data.

The patient records revealed that they were managed as per the following protocol adopted by SQUH: routine surveillance was conducted weekly for all HSCT recipients by testing plasma by CMV quantitative real-time PCR (COBAS AmpliPrep/ COBAS TaqMan CMV test) for the first 100 days post-transplant and clinically indicated afterward. CMV infection was defined as the detection of viral nucleic acid in plasma. Recipients with CMV infection underwent enhanced surveillance by monitoring their CMV viral load twice weekly if preemptive therapy had not been started yet. CMV disease was identified if it met the case definition of proven or probable CMV disease: the presence of compatible symptoms or signs and CMV documentation by histopathology or detection of CMV DNA by real-time PCR in tissue from the affected organ or fluid based on the clinical scenario.[12] Clinically significant CMV infection was considered CMV disease or CMV infection leading to preemptive therapy. The local CMV viral load cutoff to consider preemptive therapy was 500 copies/mL (454.5 IU/mL). However, preemptive therapy was started at any detectable CMV viral load for T-cell-depleted transplants.

We used *t*-tests and chi-square tests to compare nominal and ordinal variables between recipients with and without CMV infection. A multivariate logistic regression model was used to identify factors independently predictive of post-HSCT CMV infection. Kaplan-Meier and cumulative incidence estimation methods were used to estimate one-year overall mortality rates associated with CMV infection post-HSCT. Cox proportional hazard regression, providing hazard ratios, and 95% CI, were used to assess predictors of one-year overall mortality. A p-value ≤ 0.050 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Ethical approval was obtained from the medical research ethics committee at SQU on March 7, 2019 (Ref. MREC #1867/ 2019).

RESULTS

The final subjects of this study were 556 HSCT recipients, of whom 308 (55.4%) were male. Their median age was 12 years with an interquartile range (IQR) of 5–22 years. Nearly two-thirds (366; 65.8%) had benign conditions such as beta thalassemia (24.8%), sickle cell disease (16.5%), aplastic anemia (4.3%), primary immunodeficiency (6.1%), and hemophagocytic lymphohistiocytosis (3.8%) [Table 1]. Malignant conditions were found in 190 (34.2%) participants, including acute lymphoblastic leukemia (15.5%), acute myeloid leukemia (12.6%), lymphoma (3.2%), and chronic myelogenous leukemia (2.9%). The vast majority (458; 82.4%) received their transplants from matched related donors. Myeloablative conditioning was given to 405 (81.2%) patients while reduced intensity conditioning (RIC) was given to 94 (18.8%). The median day of engraftment was day 13 (range = 2–33). Graft versus host disease (GVHD) was observed in 246 (44.2%) patients within one year post-transplant, among whom 115 (46.7%) had multiple organs involvement, while the rest had skin

Table 1: Recipients' demographic and clinical characteristics.

Characteristics	n	%
Age, years		
< 12	276	49.6
≥ 12	280	50.4
Sex		
Male	308	55.4
Female	248	44.6
Underlying disease		
Beta thalassemia	138	24.8
SCD	92	16.5
ALL	86	15.5
AML	70	12.6
Lymphoma	18	3.2
HLH	21	3.8
Aplastic anemia	24	4.3
Fanconi anemia	17	3.1
Primary immunodeficiency	34	6.1
CML	16	2.9
Others*	40	7.2
HLA matching		
Matched	458	88.2
Haploidentical	61	11.8
HSCT source		
Bone marrow	138	27.6
PBSC	362	72.4
Conditioning regimen		
Myeloablative	405	81.2
RIC	94	18.8

SCD: sickle cell disease; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; HLH: hemophagocytic lymphohistiocytosis; CML: chronic myelogenous leukemia; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplant; PBSC: peripheral blood stem cells; RIC: reduced intensity conditioning.
**Other diseases present: myelodysplastic syndromes, multiple myeloma, neuroblastoma, osteopetrosis, paroxysmal nocturnal hemoglobinuria, hemoglobin S-Oman, epidermolysis bullosa, and bone marrow failure.*

GVHD (62; 25.2%), gastrointestinal (41; 16.7%), or liver (18; 7.3%) involvement. CMV serostatus was not assessed in this study because it was documented only in 259 (46.6%) recipients (who had positive CMV immunoglobulin G).

Out of the 556 recipients, 330 (59.4%; 95% CI: 55.200–63.400) experienced CMV infection within one year post-transplant, while the incidence of clinically significant CMV infection was 155 (27.9%; 95% CI: 24.200–31.600). CMV infection occurred at a median of 37 days after graft infusion (IQR = 24–56). The median CMV viral load at the time of the first detection of CMV infection was 150 copies/mL (IQR = 17–336 copies/mL). The median day of starting preemptive therapy was day 46 post-transplant. Ganciclovir was used as the initial agent in 97/155 (62.6%) recipients, valganciclovir in 37 (23.9%), and foscarnet in 18 (11.6%). The median time till the occurrence of viremia was longer (four weeks) in recipients who received preemptive therapy, and their median highest viral load reached 3313 copies/mL during the viremic phase. In contrast, among the recipients who did not receive preemptive therapy, the median time of viremia was shorter (two weeks) and their highest viral load was 150 copies/mL. The majority of 330 infected patients (261; 79.1%) had only one CMV infection episode during one year post-transplant.

Univariate and multivariate analyses were used to characterize the clinical variables that were associated with overall CMV infection and clinically significant CMV infection post-HSCT [Tables 2 and 3]. Univariate analysis of overall CMV infection showed a significantly increased risk of overall CMV infection with myeloablative conditioning compared to RIC ($p = 0.002$) and haploidentical donor versus human leukocyte antigen matched donor ($p = 0.003$). GVHD and age group ≥ 12 years ($p < 0.001$) were associated with a higher incidence of CMV infection. There was no evidence to support the increased risk of CMV infection in recipients receiving HSCT for malignancy ($p = 0.102$) versus benign disease or anti-thymocyte globulin based conditioning regimen ($p = 0.580$). Multivariate analysis further demonstrated a statistically significant relationship between overall CMV infection and myeloablative conditioning (odds ratio (OR) = 2.548, 95% CI: 1.480–4.388; $p = 0.001$), GVHD (OR = 1.721, 95% CI: 1.120–2.647; $p = 0.013$), haploidentical transplant (OR = 2.740, 95% CI: 1.342–5.587; $p = 0.006$), and age ≥ 12 years (OR = 3.155, 95% CI: 1.984–5.025; $p < 0.001$). Clinically significant CMV infection analysis showed similar results apart from the age variable failed to demonstrate clinically significant association in multivariate analysis [Table 3].

The incidence of CMV disease among the total study population was 1.8% (10; 95% CI: 0.690–2.900), and among those who had CMV infection, it was 3.0% (10; 95% CI: 1.200–4.800). Out of the 10 cases of CMV disease, five developed CMV pneumonitis, four had CMV colitis, and one developed CMV multisystem involvement (CMV pneumonitis, colitis, and retinitis). In the five recipients, CMV disease was confirmed by

Table 2: Analysis of CMV infection (overall vs. clinically significant) among HSCT recipients.

Risk Factor	Overall CMV infection, n (%)	*p*-value	Clinically significant CMV infection, n (%)	*p*-value
Sex				
Male	179 (58.1)	0.544	81 (26.4)	0.544
Female	151 (60.9)		74 (29.8)	
Age, years				
< 12	137 (49.6)	< 0.001	66 (23.9)	0.038
≥ 12	193 (68.9)		89 (31.9)	
Underlying disease				
Benign	208 (56.8)	0.102	95 (26.0)	0.195
Malignant	122 (64.2)		60 (31.6)	
HLA matching				
Matched	253 (55.2)	0.003	105 (23.0)	< 0.001
Haploidentical	46 (75.4)		36 (59.0)	
Conditioning regimen				
Myeloablative	256 (63.2)	0.002	124 (30.7)	0.002
RIC	43 (45.7)		14 (14.9)	
ATG use				
Yes	136 (58.4)	0.580	67 (28.8)	0.613
No	157 (61.1)		68 (26.6)	
HSCT source				
Bone marrow	72 (52.2)	0.025	25 (18.1)	0.001
PBSCT	229 (63.3)		117 (32.4)	
GVHD				
Yes	172 (69.9)	< 0.001	103 (41.9)	< 0.001
No	158 (51.6)		52 (17.0)	

CMV: cytomegalovirus; HSCT: hematopoietic stem cell transplant; HLA: human leukocyte antigen; RIC: reduced intensity conditioning; ATG: anti-thymocyte globulin; PBSCT: peripheral blood stem cell transplantation; GVHD: graft versus host disease.

Table 3: Logistic regression of CMV infection risk factors among HSCT recipients.

Risk factors	Overall CMV infection			Clinically significant CMV infection		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age, years						
≥ 12 vs. < 12	3.155	1.984–5.025	< 0.001	0.614	0.988–2.681	0.056
HLA matching						
Haploidentical vs. matched related	2.740	1.342–5.587	0.006	4.115	2.141–7.937	< 0.001
Conditioning regimen						
Myeloablative vs. RIC	2.548	1.480–4.388	0.001	2.876	1.359–6.086	0.006
Underlying disease						
Benign vs. malignant	0.696	0.434–1.115	0.132	0.722	0.433–1.204	0.212
HSCT source						
BM vs. PBSCT	1.069	0.653–1.748	0.791	0.666	0.365–1.217	0.186
GVHD						
Yes vs. no	1.721	1.120–2.647	0.013	< 0.001	1.628–4.177	2.608

CMV: cytomegalovirus, ; HSCT: hematopoietic stem cell transplant; OR: odds ratio; HLA: human leukocyte antigen; RIC: reduced intensity conditioning; BM: bone marrow, PBSCT: peripheral blood stem cell transplantation; GVHD: graft versus host disease.

histopathology, while the other five were diagnosed with probable/possible CMV disease upon detection of CMV DNA in tissue/fluid. The median day for CMV disease was day 50 post-transplant (IQR = 35–195). The median initial viral load was 3547.5 copies/mL (IQR = 1812.8–4229.5), and the median

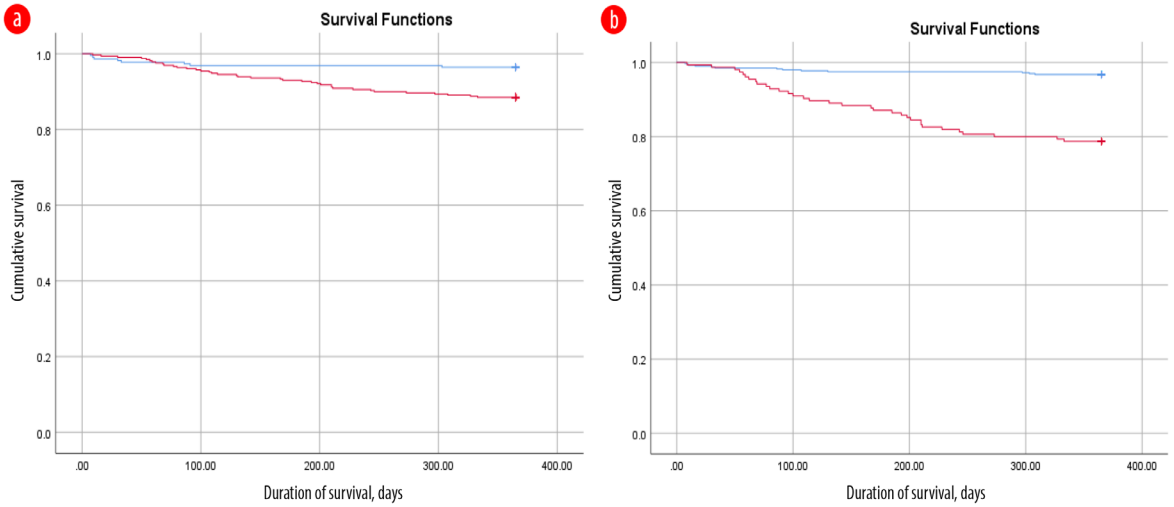

Figure 1: Comparative durations of survival for patients with (red line) and without cytomegalovirus (CMV) infection (blue line). CMV infection was associated with increased overall mortality ($p = 0.001$). **(a)** Survival time with all levels of CMV infection was significantly lower than without CMV infection ($p = 0.001$); **(b)** survival time with clinically significant CMV infection was significantly lower ($p < 0.001$) compared to those free of CMV infection.

duration of CMV viremia was six weeks. Ganciclovir was used for induction therapy for seven recipients, while three received foscarnet. For maintenance therapy, valganciclovir was used for eight recipients, while two continued on ganciclovir. The median duration of induction and maintenance therapy was two and three weeks, respectively. Ganciclovir resistance was confirmed by molecular testing in two recipients with CMV disease.

The overall one-year mortality was 8.3% (46; 95% CI: 6.000–10.600). CMV infection was associated with increased overall mortality ($p = 0.001$). Survival time was significantly lower among recipients with overall ($p = 0.001$) and clinically significant CMV infection ($p < 0.001$) compared to those free of CMV infection [Figure 1].

DISCUSSION

To our knowledge, this is the largest cohort study of CMV infection post-HSCT in the EMR. The overall incidence of CMV infection in all allo-HSCT recipients in the current cohort was 59.3%, which was within the 39–60% range reported in the literature.[13–15] However, the incidence of clinically significant CMV infection (i.e., CMV infection that required preemptive therapy or led to CMV disease) was 27.9%. The estimate of clinically significant CMV infection varies between institutions depending on which CMV viral load cutoff is used to initiate preemptive therapy. In one study, clinically significant CMV infection was reported at 59%, which is higher when compared to our finding that could be attributed to starting preemptive therapy at any detectable CMV level in that center.[16]

In our center, a CMV viral load of 500 copies/mL was taken as the cutoff to start preemptive therapy. The exceptions were T-cell-depleted recipients for those the therapy was started at any detectible CMV level. Since we had a good number (60.4%) of patients with highest detectable viral loads < 500 copies/mL, preemptive therapy was only given for 47.0% of CMV-infected recipients.

GVHD was a significant contributing factor for CMV infection in our study population, in line with several studies.[12–14] Immunosuppressive effects of GVHD and its treatment play major roles in CMV replication. In addition, recipients who had a haploidentical transplant or received myeloablative conditioning were at higher risk of developing CMV infection than those who had human leukocyte antigen-matched transplants or received RIC. This might be attributed to administration of higher doses of myeloablative chemotherapy, leading to irreversible cytopenia and prolonging the recovery period of adaptive T-cell immunity.[17] However, anti-

thymocyte globulin use did not show any significant association between both groups.

In our cohort, older age was significantly associated with overall CMV infection (though not with clinically significant CMV infection), but studies elsewhere have varied in determining the role of age.[14,15,18] For example, Sousa et al,[14] and Lin et al,[15] did not find the recipients' age a significant risk factor for CMV infection. This might be attributed to the relatively higher age distribution in these studies. However, Takenaka et al,[18] went in line with our finding that older age was an independent risk factor for CMV infection. This corresponds to an age-dependent rate of CMV seropositivity in the general population and different indications of HSCT among age groups where malignancy may be the major indication for HSCT in older recipients. In young recipients, the main indication would be hereditary blood diseases such as beta thalassemia and sickle cell disease, which accounted for most of our cohort due to high levels of consanguinity in the Omani population. We did not find a significant association between the prevalence of CMV infection and the nature of the underlying disease (malignant vs. benign) or the source of HSCT (bone marrow vs. peripheral blood stem cell).

The incidence of CMV disease in our one-year cohort post-transplant was 1.8%, much lower than the incidence of 8–16% reported in the literature.[13,17,19] The risk of CMV disease in our cohort was low because of the strict CMV routine surveillance and the initiation of preemptive therapy at low-level viremia. On the other hand, a high CMV viral load was associated with an increased risk of CMV disease.[13] We have also found that the overall one-year mortality in our cohort (8.3%) was much lower than the 30–61% rates reported in other studies.[13,19] This can be explained by the age distribution and underlying disease, as the younger age group and benign primary diseases accounted for the majority of our cohort. However, overall mortality was higher among recipients with CMV infection, which could be a primary or a secondary outcome. CMV infection can also be attributed to multi-organ failure by cytopathic effect or a marker for illness severity.[19]

The major limitations of this study were its retrospective and observational nature, which prevented us from assessing the association between CMV serostatus and CMV infection due to missing data.

CONCLUSION

The incidence of CMV infection post-HSCT in this relatively young Omani cohort was comparable to the levels elsewhere, while those of CMV disease and overall mortality were lower. Older age, haploidentical transplant, myeloablative conditioning, and GVHD were significantly associated with a higher risk of CMV infection and with an increased risk of overall mortality in the first year post-transplant. Given the impact of CMV infection on HSCT recipients and the lack of consensus on the CMV level where preemptive therapy needs to be started, our findings support early initiation of preemptive therapy at low-level CMV viremia.

Disclosure

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