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Use of Cytomegalovirus Intravenous Immune Globulin for the Adjunctive Treatment of Cytomegalovirus in Hematopoietic Stem Cell Transplant Patients

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Abstract

Study Objective—To describe characteristics and clinical outcomes of hematopoietic stem cell transplant (HSCT) patients who received adjunctive Cytomegalovirus Intravenous Immune Globulin (CMV-IVIG) for probable or proven cytomegalovirus (CMV) disease.

Design—Retrospective cohort study.

Setting—A large, university-affiliated, tertiary-care medical center.

Patients—Thirty-five adult HSCT patients receiving at least one dose of CMV-IVIG for adjunctive treatment of probable or proven CMV disease over an eight-year period.

Measurements and Main Results—All-cause mortality at hospital discharge was the primary outcome. All patients received an allogeneic HSCT. Twenty-six patients had pneumonitis (74%), nine had enteritis (26%), and 29 had CMV viremia (83%). All patients received concomitant antiviral therapy; 31 (89%) received ganciclovir and 14 (40%) received foscarnet. All-cause mortality at hospital discharge was 49%. Patient characteristics associated with mortality included requiring intubation for CMV pneumonia (79% of non-survivors vs. 25% of survivors, p=0.016) and earlier disease onset following HSCT (median of 48 days for non-survivors vs. 106 days for survivors, p<0.001). In multivariable analysis, only requiring intubation for CMV pneumonia remained a significant risk factor for increased mortality. CMV-IVIG was attributed with a low rate of adverse events; mild hypertension (5.7%) and erythema/chills (2.9%) were most common.

Conclusions—The mortality rate in our population is similar to previous reports in the literature, and may be somewhat lower than rates reported with antiviral monotherapy. Our analysis suggests that factors associated with mortality include the need for intubation and, possibly, earlier onset of CMV disease following HSCT. CMV-IVIG appears to be well-tolerated in HSCT patients. These findings support further trials of CMV-IVIG efficacy in this setting.

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Keywords

Cytomegalovirus intravenous immune globulin; Cytomegalovirus disease; Hematopoietic stem cell transplantation

Introduction

Cytomegalovirus is a ubiquitous human herpes virus which has a prevalence in the general population of up to 70%.[1] In the solid organ transplant population, the occurrence of primary or reactivated infection is a major cause of morbidity and mortality following immunosuppression, and is the leading viral infectious complication in these patients.[2] Cytomegalovirus Intravenous Immune Globulin (CytoGam®; CSL Behring AG, Bern, Switzerland) is currently FDA approved in the United States for prophylaxis against CMV disease in solid organ transplant recipients.[3] A number of clinical studies support the efficacy of this therapy in preventing primary CMV infection in solid organ transplant recipients.[4] In the treatment of CMV disease, intravenous ganciclovir is the preferred therapeutic modality.[5–7] However, treatment failure rates in excess of 50% in most ganciclovir therapy trials, have led clinicians to utilize combination therapy with CMV-IVIG and ganciclovir for the treatment of CMV disease.[8, 9] Although this combination is utilized widely, clinical studies have yet to firmly establish whether the addition of CMV-IVIGto ganciclovir treatment has any benefit in reducing CMV disease mortality in the solid organ transplant population.[7, 10]

Since HSCT recipients also have an incidence of CMV disease of about 5–15% and treatment failure rates with antiviral monotherapy ranging from 50–100%, some clinicians use adjunctive CMV-IVIG treatment in this patient population.[11–15] One study described similar mortality rates between HSCT patients treated with antiviral monotherapy and patients who received CMV-IVIG in addition to antiviral therapy; however, indications for treatment were not strictly defined.[16] Only two studies, with a combined total of 29 patients, describing adjunctive CMV-IVIG therapy for HSCT patients with CMV disease are available in the literature.[17, 18] Therefore, studies providing additional support for a treatment regimen containing CMV-IVIG in the treatment of probable or proven CMV disease in HSCT patients are currently needed. The purpose of this study was to describe the characteristics and clinical outcomes of HSCT patients who received adjunctive CMV-IVIG for probable or proven CMV disease over an eight-year period at our institution.

Methods

Study Design

This single-center, retrospective cohort study evaluated patients who were hospitalized between January 1, 1999 and December 31, 2007 at Barnes-Jewish Hospital (BJH), a 1,250-bed tertiary-care medical center in St. Louis, MO.

Study Population

Study inclusion criteria included prior HSCT, age ≥18 years, and receipt of at least one dose of CMV-IVIG for adjunctive treatment of probable or proven CMV disease. Patients were excluded if they had received a solid organ transplant at any time or if CMV-IVIG was administered for any indication other than adjunctive treatment of CMV disease. This study was approved by the Human Research Protection Office at the Washington University School of Medicine in St. Louis.

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Definitions

The presence of probable or proven CMV disease was established by documentation of CMV disease by physician confirmed diagnosis, a bronchoalveolar lavage (BAL) sample positive for CMV and negative for other pathogens in a patient with pneumonitis, or with histopathological evidence of active CMV disease. Histopathological evidence consisted of the presence of virocytes and/or positive histochemical staining for CMV documented in the pathology report. Date of CMV disease diagnosis was determined to be the first date on which probable or proven CMV disease was established by the treating physician, or the date on which a subsequently positive sample establishing probable or proven CMV disease was obtained. Presence of CMV viremia was defined as at least one positive result on either a blood CMV culture or CMV polymerase chain reaction (PCR) assay within a window of seven days immediately prior to through seven days following the admission for CMV disease. At BJH, strict surveillance for CMV viremia via weekly PCR levels extends out to 180 days post-HSCT.[19] Maximum CMV PCR titer was the highest CMV titer identified during the viremic episode associated with CMV-IVIG administration. Quantitative CMV PCR has been available at BJH since October 2003. Duration of CMV viremia was defined as the time from the date on which the initial positive CMV assay was taken, until the day prior to the initial negative CMV assay was taken, for the viremic episode associated with CMV-IVIG administration. Resolution of CMV viremia and CMV virologic response were defined as at least one documented negative CMV assay. Concurrent antiviral therapy use was determined only for induction doses (ganciclovir 5mg/kg q12h and foscarnet 60mg/kg q8h, or their renal dose-adjusted equivalents) for the viremic episode associated with CMV-IVIG administration. CMV-IVIG dosing was 150mg/kg every other day from 1999 through 2001, and was changed to 150mg/kg twice weekly from 2002 through the end of the study period. Treatment prior to or within 24 hours of intubation (for pneumonitis) or CMV disease diagnosis (for enteritis) was defined as treatment with antiviral induction doses with or without concurrent CMV-IVIG administration. Finally, adverse events attributable to CMV-IVIG consisted of any chart-documented reaction that was associated with CMV-IVIG infusion.

The date of HSCT was the date hematopoietic stem cells were infused. For a patient to be considered human leukocyte antigen (HLA) matched to their donor, they must have had 6/6 (A, B, DR) or 10/10 (A, B, C, DR, DQ) haplotype matches. Diagnosis of acute graft-versus-host disease (GVHD) was determined per chart notation or histological examination within 100 days post-HSCT. Steroid use was defined as the number of days at a dose of 1mg/kg/day or greater, with a duration of at least 24 hours, during the immediate 100-day period post-HSCT. The Charlson Comorbidity Index was used to assess the comorbidities of the cohort at the time of HSCT.[20, 21]

Outcomes

The primary outcome measure was all-cause mortality at hospital discharge. Secondary outcomes included CMV virologic response, all-cause mortality at 30 days post-CMV-IVIG initiation, and identification of possible CMV-IVIG-related adverse effects.

Statistical Analysis

Univariate analysis was performed by comparing the survivors to non-survivors as defined by the primary outcome measure, all-cause mortality at hospital discharge, using the Chi-square or Fisher's exact tests for categorical variables, student's t-test for parametric continuous variables, and Mann-Whitney U test for non-parametric continuous variables. Multivariable regression analysis was performed including the two variables most predictive of mortality from the univariate analysis. A p-value of ≤ 0.05 was considered statistically

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significant. Statistical analysis was performed using SPSS Statistics® version 16 (SPSS; Chicago, IL).

Results

Forty-five patients were identified via a pharmacy informatics database when screening for the inclusion criteria. Upon chart review, 10 of these patients were excluded: six patients were found not to be HSCT patients, one never had probable or proven CMV disease, one had CMV-IVIG initiated for another indication, one patient never had any CMV-IVIG doses administered, and one had inadequate data available for evaluation. This resulted in 35 patients in the evaluable cohort.

Demographic information can be found in Table 1. The majority of patients were CMV IgG-positive at the time of transplantation (83%). All patients received an allogeneic HSCT. The majority of transplants were from unrelated donors (60%), HLA-matched (69%), and used peripheral blood as the source for the stem cell product (54%). All patients who received bone marrow stem cell product underwent their HSCT prior to 2005. A large percentage of patients (71%) developed acute GVHD within 100 days post-HSCT. Steroid use was frequent (94%), with a mean of 39 days (SD±20) of exposure during the immediate post-HSCT period. The Charlson Comorbidity Index had a median value of 2.5 (range 2–5).

CMV disease and treatment characteristics are found in Table 2. Twenty-nine patients (83%) had CMV viremia. The remaining six patients (17%) were determined through physician documentation to have probable or proven CMV disease in the absence of viremia. The maximum CMV titer in those patients where quantitative PCR was available was a median of 145,160 copies/mL (2000-4.7*10^6). Twenty-six patients had CMV pneumonitis (74%), while nine patients had CMV enteritis (26%). CMV disease diagnosis occurred at a median of 63 days following HSCT (range 0–369). Length of stay for the CMV disease admission was a mean of 24.9 days (SD±20.6). An average of 4 doses (SD±2.0) of CMV-IVIG was administered per patient. However, CMV-IVIG was initiated an average of 10 days (range 0–62) following the initial positive CMV assay result. Antiviral therapy consisted of ganciclovir for nearly all patients (89%) at some point during their treatment; however, some patients also received foscarnet therapy (40%), and these therapies were not mutually exclusive. Patients left the hospital following CMV disease treatment (either due to death, or discharge home) at a median of 82 days post-HSCT (range 22–386).

Outcome Measures

All-cause mortality at hospital discharge was 49%. For patients with CMV pneumonitis, mortality was 54% (14 of 26 patients), while in patients with CMV enteritis, the rate was 33% (3 of 9 patients). All-cause mortality at 30 days following initiation of CMV-IVIG was 51% (18 of 30 patients). CMV viremia resolved in 16 of 29 patients (55%). CMV-IVIG infusion was attributed with adverse reactions in three patients (8.6%). Two were mild hypertension, which spontaneously resolved without treatment. The third was a reaction of erythema and chills following the third dose administered to this patient. The patient was treated with hydrocortisone and diphenhydramine, with resolution. Subsequent infusions were premedicated with diphenhydramine and meperidine, and no further reactions were noted.

Analysis

Factors associated with all-cause mortality were absence of graft versus host disease ($p=0.027$), need for intubation due to CMV pneumonitis ($p=0.016$), and earlier time to CMV disease diagnosis following HSCT ($p<0.001$). Both the median Charlson Comorbidity Index

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at HSCT and the median of the maximum CMV PCR titer demonstrated a trend toward significance. When controlling for time to CMV disease diagnosis following HSCT and need for intubation due to CMV pneumonitis in a multivariable analysis (Table 3), only need for intubation remained predictive of increased mortality (p=0.042).

Discussion

There are little published data on the use of CMV-IVIG as adjunctive treatment of CMV disease in HSCT patients. In a study by Reed, et al., 25 consecutive patients with CMV pneumonitis diagnosed via biopsy or BAL were examined.[17] The primary outcome was all-cause mortality at hospital discharge, which was 48% in their cohort. In this study, five patients were under the age of 18, of whom four survived. Pediatric patients generally tend to have a more favorable prognosis than adult patients, and were not included within the population of our study.[22] A second study by Verdonck, et al., described four adult patients who had biopsy-proven CMV pneumonitis.[18] The primary outcome in this study was also all-cause mortality at hospital discharge. All patients in this cohort expired prior to hospital discharge. One additional study compiled a retrospective cohort of 24 patients from many European institutions who had received adjunctive CMV-IVIG for CMV pneumonitis.[23] However, varying antiviral and immunoglobulin regimens were used, and data from patients receiving CMV-IVIG were combined with those receiving IVIG for all outcomes, precluding detailed conclusions about the CMV-IVIG subgroup.

Various treatment regimens are employed for treating CMV disease in HSCT patients.[17, 18, 23] At BJH, immunotherapy with CMV-IVIG is primarily used in the treatment of CMV pneumonitis. Standard IVIG at 500mg/kg every other day[24, 25] or CMV-IVIG at 150mg/kg twice weekly is used concurrently with at least a 14-day induction course of ganciclovir 5mg/kg IV q12h for treatment in CMV pneumonitis. For CMV disease other than pneumonitis, immunotherapy (IVIG or CMV-IVIG) may be used in addition to antiviral monotherapy at the discretion of the treating physician. This protocol was followed routinely and consistently throughout the study period. The dosing strategy used for CMV-IVIG at BJH is supported by the maximum dosage recommended in the package labeling,[3] along with data suggesting that the half-life of CMV-IVIG in HSCT patients is between 1.5–7 days.[26, 27] Lack of consistent dosing strategies make interpretation of available studies and the broad application of any future prospective studies difficult.

Although previous studies have evaluated CMV-IVIG as adjunctive treatment in the context of proven CMV disease, we felt that it was clinically relevant to study patients with both suspected and proven disease. The morbidity and mortality of CMV disease is high and the histological standards for definitively diagnosing CMV disease are invasive and time-consuming.[28] In clinical practice, identifying patients at high risk for the development of CMV disease and patient characteristics associated with a high mortality rate may be more relevant for optimizing their treatment.

All-cause mortality at hospital discharge was 49% in our study. This is consistent with the results from the previous prospective studies described above in HSCT patients.[17, 18] Factors related to timing of treatment initiation, such as initiation of therapy prior to intubation for CMV pneumonia, time to initiation of CMV-IVIG following CMV disease diagnosis, and time to initiation of CMV-IVIG following discovery of viremia associated with CMV disease, consistently demonstrated no difference between survivors and non-survivors. This finding is in contrast to many other serious infectious diseases for which the early initiation of antiinfectives has been shown to confer benefit.[29–32] One possible explanation is that the time to initiation of the primary antiviral therapy has a greater impact than the initiation timing of adjunctive therapy, or that timing of adjunctive therapy has little

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or no impact on mortality at all. Another possible explanation may be that adjunctive CMV-IVIG was initiated early, or late, enough in all of our patients to equalize any effects that timing differences would have had on outcomes. Finally, our small sample size may simply be underpowered to detect a difference which may exist.

Severity of CMV disease was found to be more predictive of mortality, however. Intubation for CMV pneumonia was associated with mortality in both univariate and multivariable analysis, and higher maximum CMV PCR titers, although not available for every patient, trended towards significance in univariate analysis. Need for intubation as a predictor of mortality is a unique and potentially useful risk factor identified by our study, although the associated wide confidence intervals in multivariable analysis are evidence of the small cohort upon which this observation was made. Higher peak CMV PCR titer and a slower rate of decrease in CMV PCR titer during antiviral treatment has been associated with higher rates of CMV disease in HSCT patients,[33, 34] but not to increased mortality from CMV disease in general, to our knowledge. A greater Charlson Comorbidity Index score has similarly been shown previously to be a predictor of non-relapse mortality at one year in HSCT patients who underwent myeloablative conditioning regimens (67% for scores of one or two vs. 28% for scores of zero).[35]

Timing of CMV disease onset post-HSCT was a significant factor in predicting mortality in univariate analysis, but was not an independent predictor of mortality in multivariable analysis. There has been no previous description in the literature, to our knowledge, of lower mortality with later CMV disease diagnosis post-HSCT. One study identified a mortality rate of 46% in patients developing CMV disease at least 80 days post-HSCT, although lack of treatment details make comparison with other cohorts problematic.[36] In the study by Reed et al., no difference was found between survivors and non-survivors for this risk factor in univariate analysis.[17] Nevertheless, evaluation of this variable in further studies may identify it as a valuable risk factor.

The finding that the presence of GVHD was associated with a statistically significantly lower mortality appears contradictory. GVHD is generally considered a poor prognostic factor in HSCT patients, which leads to the need for intensive immunosuppressive regimens and higher rates of CMV disease.[37, 38] One possible explanation for this is that patients who survived simply had a longer period of time to develop GVHD than non-survivors. This hypothesis is plausible due to the significant difference between survivors and non-survivors in time to CMV disease post-HSCT.

There was a low incidence of adverse reactions attributed to the administration of CMV-IVIG in this study. Prospective studies of CMV-IVIG indicated an infusion-related adverse event rate of <6%.[3] The rate of 8.6% attributed to CMV-IVIG in our cohort is consistent with this finding, although the hypertensive reactions identified in our study were not one of the common infusion-related adverse events specifically described during clinical trials.[3] Reactions were minor and did not recur, although the patient experiencing erythema and chills received premedication with each subsequent administration. Adverse reactions related to nephrotoxicity are a concern with sucrose-containing immune globulin products, including CMV-IVIG.[39] However, renal dysfunction attributed to CMV-IVIG use was not identified in any patients in our study.

There are a number of limitations to this study. This study was a retrospective cohort analysis, and as such is only hypothesis-generating. Likewise, our intent to retrospectively study both probable and proven disease leads to some difficulty when comparing our cohort with those from prospective studies with strict case definitions. Direct comparison with previous studies is also complicated by the fact that our cohort includes patients treated for

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CMV enteritis, who have rarely been investigated when receiving this treatment regimen. As patients with CMV enteritis were not universally treated with adjunctive CMV-IVIG at our institution, this cohort may include a larger proportion of more acutely ill patients with this form of disease. Also, our study had too few patients to assess more than two variables on multivariable analysis or make powered conclusions regarding the outcome measures chosen. Despite the small sample size, our study is the largest to date to assess outcomes of CMV disease in HSCT recipients treated with adjunctive CMV-IVIG. Next, the adjunctive immunotherapy treatment protocol utilized for CMV disease at BJH changed during the study period. Although varying dosing schedules were used, univariate analysis of the primary endpoint was performed for these two periods and no significant difference was found between patients treated prior to the change compared with afterward (data not shown). This does not exclude the possibility that the presence of two dosing strategies could have had an effect on other variables evaluated. Finally, a full analysis of safety outcomes was precluded by restrictions of information available for chart review.

Conclusion

In summary, this study contributes to the available literature on adjunctive CMV-IVIG for probable or proven CMV disease in HSCT patients. We have demonstrated that the mortality rate in our population utilizing this therapy is similar to what has been previously reported, and may be somewhat lower than those rates reported with antiviral monotherapy. Additionally, we have identified risk factors in our population that are associated with worse clinical outcomes. Specifically, patients requiring intubation for CMV pneumonitis and, perhaps, earlier disease onset following HSCT were associated with increased mortality. Consideration of these factors in clinical decision-making may be beneficial in further optimizing outcomes with the use of adjunctive CMV-IVIG. Finally, our data indicate that CMV-IVIG is safe for use in the HSCT population. These findings support further trials of the efficacy of adjunctive CMV-IVIG for the treatment of CMV disease in the HSCT population.

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Table 1

Patient Demographics

Demographic Characteristic	N (%) (N=35)
Age, mean years (SD)	42.5 (±13.8)
Male	22 (63%)
Caucasian	31 (89%)
Underlying malignancy	
AML	17 (49%)
MDS	4 (11%)
CML	4 (11%)
Non-Hodgkin's Lymphoma	3 (9%)
ALL	2 (6%)
Other[a]	5 (14%)
CMV serologies (donor / recipient)	
Positive or negative / positive	29 (83%)
Positive / negative	2 (6%)
Negative / negative	4 (11%)
Allogeneic HSCT	35 (100%)
Unrelated donor	21 (60%)
HLA Matched	24 (69%)
Peripheral Blood HSCT	19 (54%)
Conditioning regimen	
Cyclophosphamide / Single-dose TBI (550cGy)	23 (65%)
Busulfan / Cyclophosphamide	6 (17%)
Fractionated TBI / Cyclophosphamide	3 (9%)
Other	3 (9%)
Graft versus host disease	25 (71%)
Skin	23 (66%)
Gastrointestinal	11 (31%)
Hepatic	5 (14%)
Steroid use, mean days (SD)	39 (±20)
Charlson Comorbidity Index at HSCT, median (range)[b]	2.5 (2–5)

SD – Standard deviation; AML – Acute Myelogenous Leukemia; MDS – Myelodysplastic Syndrome; CML – Chronic Myelogenous Leukemia; ALL – Acute Lymphoblastic Leukemia; CMV – Cytomegalovirus; HSCT – Hematopoietic Stem Cell Transplant; HLA – Human Leukocyte Antigen; TBI – Total Body Irradiation

[a] Other malignancies included aplastic anemia, prolymphocytic leukemia, and Hodgkin's lymphoma

[b] Age was not scored, as it was evaluated as a separate factor

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Table 2

CMV Disease and Treatment Characteristics

	N (%)
Demographic Characteristic	**(N=35)**
Viremia present	29 (83%)
Maximum CMV PCR titer, median copies/mL (range)[a]	145,160 (2000–$4.7*10^6$)
Duration of viremia, median days (range)	18 (3–85)
CMV Disease	
Pneumonitis	26 (74%)
Enteritis	9 (26%)
CMV Pneumonitis (N=26)	
Viremia present	20 (77%)
BAL CMV PCR or culture positive	7 (27%)
Intubated	14 (54%)
Treatment prior to intubation[b]	11 (79%)
Treatment within 24 hours of intubation[b]	12 (86%)
CMV Enteritis (N=9)	
Viremia present	9 (100%)
Histologically-observed inclusion bodies	7 (78%)
Treatment prior to CMV enteritis diagnosis	6 (67%)
Treatment within 24 hours of CMV enteritis diagnosis	8 (89%)
CMV disease diagnosis, median days post-HSCT (range)	63 (0–369)
Total CMV-IVIG doses administered, mean (SD)	4 (±2.0)
CMV-IVIG initiation, median days post-CMV disease diagnosis (range)	0 (0–15)
CMV-IVIG initiation, median days post-viremia (range)	10 (0–62)
Concomitant antivirals administered	
Ganciclovir	31 (89%)
Foscarnet	14 (40%)

CMV – Cytomegalovirus; PCR – Polymerase chain reaction; BAL – Bronchoalveolar lavage; HSCT – Hematopoietic stem cell transplant; CMV-IVIG – Cytomegalovirus intravenous immune globulin

[a] N=15, as this testing method was not available for the full cohort

[b] These characteristics were not mutually exclusive

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Table 3

Factors Associated with Mortality

Demographic Characteristic	Survivors N (%) (N=18)	Non-survivors N (%) (N=17)	Univariate Odds Ratio (95% CI)	Univariate P value	Multivariable Odds Ratio (95% CI)	Multivariable P value
Age, mean years (SD)	42.8 (±14.5)	42.2 (±13.5)		0.947		
Recipient CMV seropositivity	15 (83.3%)	14 (82.4%)	0.933 (0.161–5.42)	0.642		
HLA matched	12 (66.7%)	12 (70.6%)	1.2 (0.287–5.02)	0.546		
Unrelated donor	9 (50%)	12 (70.6%)	2.4 (0.596–9.67)	0.305		
Max CMV PCR titer, median copies/mL (range)[a]	38,840 (2000–730,000)	217,350 (48,600–$4.6*10^6$)		0.099		
Charlson Comorbidity Index, median (range)	2 (2–4)	3 (2–5)		0.069		
Graft versus host disease	16 (88.9%)	9 (52.9%)	0.141 (0.0244–0.811)	0.027		
Intubation required due to CMV pneumonitis[b]	3 (25%)	11 (78.6%)	11.0 (1.77–68.4)	0.016	12.2 (1.09–138)	0.042
CMV disease diagnosis, median days post-HSCT (range)	106 (20–369)	48 (0–90)		<0.001	0.959 (0.916–1.004)	0.075

SD – Standard deviation; CMV – Cytomegalovirus; HLA – Human leukocyte antigen; PCR – Polymerase chain reaction; HSCT – Hematopoietic stem cell transplant; CI –Confidence interval

[a] Survivors (N=9) and non-survivors (N=6), as this testing method was not available for the full cohort

[b] Survivors (N=12) and non-survivors (N=14), as only 26 patients had CMV pneumonitis