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Cytomegalovirus in Allogeneic Hematopoietic Transplantation: Impact on Costs and Clinical Outcomes Utilizing a Preemptive Strategy

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Abstract

Background: Cytomegalovirus (CMV) results in significant morbidity and mortality following hematopoietic cell transplantation (HCT). Establishing the cost and clinical impact are imperative to selecting appropriate CMV preventative strategies.

Methods: This is a retrospective cohort study of consecutive patients undergoing their first allogeneic HCT between January 1, 2009 and December 31, 2013. Detailed clinical and institutional cost data were obtained from the start of conditioning through one-year post-transplant. Baseline characteristics, resource utilization, costs and outcomes were compared between patients with and without clinically significant CMV infection (csCMVi).

Results: One-hundred seventy out of 388 (44%) patients developed csCMVi within one-year following HCT. Within the first post-transplant year, patients with csCMVi had significantly longer transplant lengths of stay (mean 91.7 vs. 78.3 days, $p<0.0001$) and more frequent and prolonged hospitalizations (mean 2.4 vs. 1.7 admissions, $p<0.0001$; mean 39.1 vs. 31.5 inpatient days, $p=0.001$) without significantly more admissions to the intensive care unit (28.2% vs. 21.6%, $p=0.408$). Use of granulocyte-colony stimulating factor was higher in patients with csCMVi (73.5% vs 54.1%, $p=0.0001$) though no significant differences were demonstrated in mean platelet or red blood cell transfusions. Total costs were also higher in patients with csCMVi (mean cost difference $45,811 (95% CI $26,385 - $67,544). However, the incidence of graft-versus-host disease (GVHD) and select infectious complications was not significantly different between the groups. There were no significant differences in one- and five-year post-transplant overall survival (OS) nor non-relapse mortality (NRM) between those with or without csCMVi, though relapse of underlying disease was significantly lower in the csCMVi group.

Conclusions: Allogeneic HCT patients with csCMVi had significantly greater medical resource utilization and costs than those without. However, clinical outcomes including GVHD, infections and mortality were similar in both groups. Future study is needed to determine the cost effectiveness of CMV preventative modalities.

Keywords

Cytomegalovirus; Hematopoietic Cell Transplantation; Costs

INTRODUCTION

Cytomegalovirus (CMV), a member of the Herpesviridae family of viruses, has been associated with significant morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT). Direct effects of CMV include end-organ disease involving almost any organ system (e.g., pneumonitis, colitis and retinitis), while potential indirect effects of CMV include increases in bacterial and fungal co-infections[1,2] and graft versus host disease (GVHD).[3] Further, positive CMV serostatus (in donors and recipients) and early CMV reactivation have been associated with poor transplant outcomes including higher non-relapse mortality (NRM) and lower overall survival (OS).[4–7] Late-onset CMV infection,

occurring greater than 100 days post-transplant, has also been associated with poor outcomes including an increased risk of death.[8,9]

In the absence of CMV-directed prophylaxis, reactivation occurs in 70–80% of seropositive recipients following allogeneic HCT, and primary infection can occur in at least 15% of CMV seronegative recipients with seropositive donors.[10] A pre-emptive strategy has been employed most commonly in lieu of universal prophylaxis to reduce exposure to CMV-directed antivirals and their associated toxicities including renal dysfunction and myelosuppression.[11] However, this strategy remains imperfect as antiviral exposure/toxicity occur alongside the potential for emergence of drug-resistant CMV, the latter reported in up to 14.5% of high risk HCT recipients during pre-emptive therapy.[12]

Identification of novel antiviral medications and other strategies (e.g., vaccination and adoptive transfer of CMV specific T-cells) for the prevention of CMV in transplant is paramount. Notable in this realm is the recent United States Food and Drug Administration approval of letermovir, an anti-CMV therapy that works via a unique mechanism targeting the viral terminase complex. This viral enzyme is involved late in the viral replication process and is unique to the virus, circumventing many of the issues of cross-resistance and toxicities associated with current CMV therapies.[13] In a phase three clinical trial utilizing letermovir for primary prophylaxis in 495 CMV seropositive adult allogeneic HCT recipients, letermovir met its primary efficacy endpoint with significantly fewer patients developing clinically significant CMV infection (csCMVi) through week 24, defined as CMV viremia necessitating preemptive therapy or CMV disease.[14] Patients in the letermovir arm also had lower all-cause mortality through week 24 though this did not achieve statistical significance through week 48. Further, letermovir was well-tolerated with no significant increase in adverse effects such as myelosuppression or nephrotoxicity encountered with traditional CMV antiviral therapies.

To design new CMV preventative approaches, observational studies are needed to determine the economic burden of CMV infection. The primary objective of this study is to estimate incremental medical resource use and costs associated with csCMVi through one-year following allogeneic HCT. Secondary objectives include an evaluation of the impact of csCMVi on HCT outcomes including non-CMV infections, GVHD as well as underlying disease relapse, NRM and OS at one and five years following transplant.

PATIENTS AND METHODS

Study Patients

This retrospective cohort study included all consecutive patients undergoing their first allogeneic HCT at Duke University Medical Center between January 1, 2009 and December 31, 2013 allowing for follow-up data up to five years post-transplantation. Patients were excluded from the study cohort if they had received the investigational agent brincidofovir post-transplant (N=8), utilized syngeneic donors (N=3), developed CMV viremia and/or disease within two months preceding allogeneic HCT (N=3) or underwent sequential organ transplant followed by HCT (N=1, lung-HCT transplant). The study focused on costs from the initiation of the transplant conditioning regimen through one year post-transplant as

beyond this time point, the majority of care is typically transferred back to local centers, and costs may not be accurately captured; however, transplant outcomes including survival were followed for up to five years. This study was approved by the Institutional Review Board of Duke University Health System (DUHS).

Data Extraction

Demographic and clinical data were abstracted from multiple sources including a prospectively maintained Duke Adult Blood and Marrow Transplant database, an institutional tool called Duke Enterprise Data Unified Content Explorer and manual review of electronic medical records. Institutional cost accounting data were provided by DUHS and represented all hospitalizations, emergency department visits, clinic visits, treatments, laboratory tests and procedures performed within the DUHS, inclusive of inpatient and outpatient settings.

Antimicrobial Prophylaxis

Throughout the study period, a preemptive strategy was employed for CMV management in allogeneic HCT recipients. Patients were monitored via plasma quantitative CMV polymerase chain reaction (PCR) using a DUHS laboratory-developed test incorporating the *artus* CMV PCR kit (Qiagen, Hilden, Germany) for amplification of a specific region of the CMV genome. Extraction of CMV DNA was performed on the MagNA Pure Compact (Roche), and amplification and detection were performed on the Lightcycler (LC) (Roche, Indianapolis, IN). Plasma CMV PCR evaluation occurred at least weekly beginning the first week post-transplant through a minimum of Day +100. Monitoring beyond Day +100 was continued at providers' discretion in patients receiving ongoing immunosuppression. CMV directed antiviral therapy (e.g., ganciclovir, foscarnet or valganciclovir) was recommended in patients with: (1) evidence of or concern for CMV disease; or (2) when the plasma CMV DNA PCR exceeded a designated threshold value. The recommended threshold value was greater than 250 copies/milliliter (mL) through April 2014 with modification thereafter to greater than 450 international units (IU)/mL following an update to the plasma CMV DNA PCR reporting. The minimum suggested duration for induction therapy was two weeks followed by an additional two weeks of maintenance therapy. Patients not receiving CMV-directed therapies were otherwise maintained on herpes virus prophylaxis with acyclovir. Recommended bacterial prophylaxis was ciprofloxacin through a minimum period of engraftment. Fungal prophylactic regimens included either fluconazole, voriconazole or posaconazole through at least Day +100. *Pneumocystis* prophylaxis consisted of sulfamethoxazole/trimethoprim during conditioning through Day −2 with resumption following engraftment or Day +30.

Clinical Definitions

Clinically significant CMV infection (csCMVi) was defined as CMV viremia for which preemptive therapy was applied or CMV disease consistent with the definition applied in recent CMV randomized controlled trials.[14] Assessment for CMV disease was based on standardized definitions proposed by Llungman, *et al*.[15] Delineation of a second or subsequent episode of csCMVi required a minimum of a two-week period following completion of CMV-directed therapy. CMV viral resistance was determined via a CMV

genotype demonstrating the presence of a UL97 or UL54 mutation confirmed in previous studies to confer antiviral resistance through marker transfer experiments.[16] Bacteremia was defined as a recognized pathogen from one or more blood cultures. More than one episode of bacteremia was recorded in the same patient only if it occurred after a minimum of two weeks from the previous positive blood culture in patients receiving directed therapy. Common skin commensals, as defined by the National Healthcare Safety Network,[17] were designated causes of bacteremia only if isolated from two or more blood specimens drawn on separate occasions meeting criteria that blood from at least two separate blood draws was collected on the same or consecutive calendar days, and from two separate blood draw sites. Proven and probable invasive fungal infections were based on modified criteria proposed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group.[18] These definitions were further modified to allow for inclusion of PCR testing from bronchoalveolar lavage specimens to identify probable *Pneumocystis jirovecii* pulmonary infections. Acute and chronic graft versus host disease were scored based on standardized criteria.[19–21]

Cost Assignment

We obtained detailed institutional cost accounting data representing direct and indirect (i.e., overhead) costs for all hospitalizations, emergency department visits, outpatient visits, medications, laboratory tests and procedures performed within the DUHS from 2009 to 2014. Investigation of both the DUHS cost data and use of anti-CMV medications documented in medical charts revealed that costs for inpatient use of anti-CMV treatments and outpatient administration of CMV immune globulin, cidofovir and intravenous immune globulin (IVIG) were well captured in the cost data. However, outpatient costs associated with foscarnet, ganciclovir and valganciclovir were incomplete because patients sometimes obtained these medications from pharmacies outside the DUHS. To account for costs of outpatient use of these medications, we applied unit costs derived from the DUHS data to medication dosing and duration information obtained from direct chart review, assuming full adherence.

The time period for the cost analysis began on the start date of the pre-transplant conditioning regimen and continued through one-year following the date of transplant. Two concerns arose. First, observed one-year costs would be underestimated for patients lost to follow-up. Second, to the extent that patients with csCMVi may be more likely to die (and incur no additional costs henceforth), csCMVi could inappropriately be interpreted as being cost-saving. To address these concerns, we calculated both actual costs as well as imputed costs to represent costs that would have been incurred had patients survived with complete one-year follow-up. To impute costs, we first computed mean daily costs for each day between Day 0 and Day +365 by csCMVi status using data from all patients up to their date of death/loss to follow-up. For patients who died or were lost to follow-up before Day +365, day- and csCMVi-specific mean costs were applied to remaining days through Day +365. Costs were summed and reported for three periods: from the start of conditioning to Day −1, Day 0 through Day +100 and Day +101 through Day +365. All costs were updated to 2018 U.S. dollars using the Consumer Price Index for Medical Care.[22]

Statistical analyses

Descriptive statistics were used to report baseline demographics, clinical characteristics, outcomes, medical resource use and costs. Percentages and numbers were reported for categorical variables. Means, standard deviations, medians and 25th and 75th percentiles were reported for continuous variables. In comparisons of baseline characteristics between patients with and without csCMVi, Chi-square tests were used for categorical variables, and Wilcoxon rank-sum tests were used for continuous variables.

Because medical costs are typically right-skewed, we applied nonparametric bootstrapping using the bias-corrected percentile method (2.5th and 97.5th percentiles) with 10,000 bootstrap replications to calculate the confidence intervals (CI) for differences in mean costs between patients with versus without csCMVi. Confidence intervals that exclude zero indicate statistically significant differences between unadjusted mean costs. To account for differences in baseline characteristics between patients with versus without csCMVi, we applied generalized linear models. For comparisons of medical resource use, the models were specified with negative binomial error distributions and log links; for comparisons of medical costs, models were specified with gamma error distributions and log links. Baseline covariates included age at transplant, gender, race, Karnofsky Performance Score (KPS),[23] disease, conditioning regimen, stem cell source and GVHD prophylaxis including T-cell depletion. Age and KPS were modeled as linear, continuous variables, and all other covariates were modeled as categorical dummy variables.

OS was defined as time to death from the day of transplant from any cause with surviving patients censored on the date of last follow-up and presented using the Kaplan Meier estimator. Comparisons of OS at one and five years between csCMVi and non-csCMVi patients and between patients with peak CMV DNA PCR values < 1000 copies/mL or ≥ 1000 copies/mL were based on log-rank tests. NRM was defined as death without evidence of disease relapse and examined using cumulative incidence estimates to account for competing risks. Grey's test was used to compare cumulative incidence curves between the groups at one and five years. All statistical analyses were conducted using SAS (SAS Institute, Version 9.4).

RESULTS

The cohort consisted of 388 adult allogeneic HCT recipients including 170 (43.8%) patients with csCMVi and 218 (56.2%) patients without csCMVi (Table 1). Eighteen patients were lost to follow-up during the first post-transplant year. Acute leukemia was the leading indication for allogeneic HCT across the cohort. Patients who developed csCMVi were more likely to have received a non-myeloablative conditioning regimen (90/170 [52.9%] vs 93/218 [42.7%], p=0.044) and T-cell depletion in the form of either anti-thymocyte globulin or alemtuzumab (91/170 [53.5%] vs 124/218 [43.1%], p=0.068). CMV seropositive recipients accounted for the vast majority (149/170 [87.6%]) of csCMVi cases with 149 of the 215 (69.3%) CMV seropositive recipients developing csCMVi (regardless of donor status). Twelve of the 57 (21.1%) CMV seronegative recipients who had seropositive donors developed csCMVi, and three of the 91 (3.3%) seronegative recipients with seronegative donors developed csCMVi.

Further details regarding the csCMVi episodes are shown in Table 2. Multiple episodes (≥ 1, range 2 to 5 episodes) were common, occurring in 77/170 (45.3%) of patients developing csCMVi. The first episode of csCMVi occurred a median of 33 days post-transplant (range four to 320 days) with 160 (94.1%) beginning prior to Day +100 and 10 (5.9%) beginning beyond Day +100. When comparing all 289 csCMVi episodes, 196 (67.8%) occurred prior to Day +100 and 93 (32.2%) occurred beyond Day +100. CMV disease occurred in 36/170 (21.2%) of patients with csCMVi and generally occurred later post-transplant (median onset 71.5 days [range 19–337 days]) and most commonly affected the gastrointestinal tract (25/36 [69.4%]). Repeated episodes of CMV disease were uncommon and documented in only one patient (1/36 [2.8%]) though disease involvement of more than one site was seen (5/36 [13.4%]). The most common antiviral therapies applied were ganciclovir (127/170 [74.7%]) followed by foscarnet (117/170 [68.8%]). Supplementary therapies such as IVIG and CMV immune globulin were utilized in 16.5% (28/170) of patients. Median total duration of CMV antiviral therapy across the one-year study period was 49 days (range 1–299 days). Figure 1 further demonstrates antiviral duration across csCMVi episodes. Genotypic assessment for antiviral resistance to CMV was performed in 29/170 (17.1%) patients with csCMVi and confirmed mutations predicting resistance were identified in 7/170 (4.1%).

Medical resource use during the study period, including blood, other support products and hospitalizations, is detailed in Table 3. There was a trend toward greater use of red blood cell (RBC) and platelet transfusions in patients with csCMVi (mean RBC transfusions 15.5 vs. 13.1, p=0.059; mean platelet transfusions 16.2 vs. 13.7, p=0.112) and these patients were significantly more likely to receive granulocyte colony stimulating factor (73.5% vs. 54.1%, p=0.0001). Further, patients with csCMVi had more frequent and prolonged hospitalizations throughout the study period. (2.4 vs. 1.7 mean admissions, p<0.0001; 39.1 vs. 31.5 mean inpatient days, p=0.001). However, there were no significant differences in ICU admissions. Mean total transplant length of stay, defined as the time between Day 0 and when patients were discharged to home after the acute peri-HCT care period, was also longer in patients with versus without csCMVi (mean 91.7 days +/− 31.5 vs. 78.3 days +/− 30.7, p<0.0001). The overall incidence of acute and chronic GVHD and infectious complications consisting of bacteremia and proven and probable invasive fungal infections was not significantly different between the two groups (Table 3).

The one- and five-year OS for the cohort was 56.7% and 35.8% with no significant difference between those with and without csCMVi (one-year OS p=0.807; five-year OS p=0.880, Figure 2). Similarly, there was no significant difference in one- and five-year NRM (one-year NRM p=0.221; five-year NRM p=0.132, Figure 3). However, patients with csCMVi had an overall lower cumulative incidence of disease relapse at one- and five-years post-transplant (one-year disease relapse 4.7% csCMVi vs. 11.5% without csCMVi, p=0.019; five-year disease relapse 5.9% csCMVi vs. 13.8% without csCMVi, p=0.012, Figure 4). When comparing patients with csCMVi based on peak CMV DNA PCR values < 1000 copies/mL versus ≥ 1000 copies/mL across episodes there was no significant difference in OS (one-year OS p=0.942; five-year OS p=0.101, Figure S1) or disease relapse (one-year disease relapse p=0.126; five-year disease relapse p=0.319, Figure S2) between these two groups. However, five-year NRM was significantly higher in those with peak

CMV DNA PCR values ≥ 1000 copies/mL (one-year NRM p=0.343; five-year NRM, p=0.024, Figure S3).

Actual and imputed costs are detailed in Tables 4a and 4b. Mean total actual and imputed one-year costs of allogeneic HCT for the entire cohort were $180,517 and $203,995, respectively. Total actual and imputed one-year costs were significantly higher in those with csCMVi versus those without csCMVi (cost difference $45,811 [95% CI $26,385 - $67,544] and $54,030 [95% CI $32,121 - $76,250] respectively). Further evaluation of the impact of multiple episodes of csCMVi is demonstrated in Table 4b wherein patients with more than one episode of csCMVi incurred higher actual and imputed costs across the study period than patients with one episode of csCMVi (cost difference $51,038 [95% CI $22,683 - $84,435] and $37,590 [95% CI $5,007 - $74,052] respectively). Evaluation of the impact of peak viral load attained on costs in those with csCMVi demonstrated no differences in costs associated with a CMV DNA PCR value < 1000 copies/mL versus ≥ 1000 copies/mL (data not shown). A separate analysis of actual and imputed costs across the same time periods in patients with a travel time less than or equal to one hour as opposed to greater than one hour from the medical center also did not demonstrate significant differences (data not shown).

DISCUSSION

Our cohort represents the largest published single center evaluation of the costs of CMV in allogeneic HCT. This large retrospective cohort study combines detailed cost accounting data with clinical data and chart review to present several insights into the economic burden of csCMVi: (1) patients with csCMVi have higher overall costs associated with HCT, approximately $45,000 (25%) added to the cost of HCT; (2) higher costs are incurred not just in the first 100 days but persist from days 101 to 365 after HCT when patients are typically discharged home from the transplant center; (3) higher costs are due to a combination of both direct treatment costs (e.g., antiviral therapies directed against csCMVi) and associated medical care (e.g., increased hospitalizations and length of stay). Findings from this study are comparable to other single center economic assessments of the impact of CMV in allogeneic HCT. However, these studies included smaller sample sizes, shorter follow-up periods and less detailed clinical and cost data.[24, 25] Jain, *et al*[24] compared 90 patients requiring CMV therapy in the first six months following allogeneic HCT to 44 patients who did not and estimated a mean additional cost between $58,000 to $74,000 per patient based on costs of antiviral therapy and estimated daily costs of inpatient hospitalization. In a retrospective cohort of 208 allogeneic HCT recipients, Robyn, *et al*.[25] found that recipients with greater than one CMV episode had a 25 to 30% increase in the costs associated with transplant though this evaluation was limited to inpatient costs only over a 12-month period post-transplant. In addition, while other investigators have demonstrated more substantial incremental costs of CMV in HCT recipients ($280,954 over a two-year period),[26] their analysis utilized the Truven Health MarketScan® database, thereby representing paid claims as opposed to the detailed cost accounting data provided in this study. This is an important distinction as our study provides a more accurate representation of the costs required to deliver care compared to negotiated payments, for which there is likely a higher mark-up for commercial payers.

The major advantage of our single-center design is the opportunity to use a detailed cost dataset to generate these findings; at the same time, this design has limitations with regard to drawing clinical conclusions. For example, while large for a single center study, the cohort of 388 patients is only a fraction of the thousands of patients in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry studies. Therefore, absence of statistically significant differences in the primary clinical findings in this study (e.g., no significant association between csCMVi and infections, GVHD, NRM and OS) may have occurred because the study was not powered to detect potential differences. However, large registry studies would not have access to the detailed patient-level cost data that is presented in the current study. Further, given the association of higher levels of CMV viremia with worse outcomes including OS and NRM[27] we explored the impact of higher levels of CMV viremia (using a viral load threshold of 1000 copies/mL) in those with csCMVi. While mortality, including NRM, was higher in those viral loads ≥ 1000 copies/mL we were unable to demonstrate a significant difference in one-year OS and NRM in this group. Interestingly, a significantly lower incidence of hematologic disease relapse was seen in patients with csCMVi in this cohort. Conflicting data are available regarding this putative beneficial effect of CMV. The reduction in hematologic disease relapse is consistent with that reported in other single center studies[28–34] most notably with AML, with corroboration in meta-analyses focusing specifically on the AML population.[35,36] However, this benefit has not been consistently confirmed, inclusive of a retrospective query of over 9000 patients within the CIBMTR registry.[4] Nonetheless, this observation necessitates close follow-up as we begin to incorporate primary prophylactic therapies such as letermovir with proven efficacy in preventing csCMVi.

Some clinical outcomes in this cohort may be reflective of center-specific practices such as the use of alemtuzumab (a common practice at the time of the evaluation) and may not apply to other centers. Another potential limitation of this study is the difficulty in capturing costs when patients return to the care of their local oncologist; however, the finding that costs were similar in patients who live less than an hour from the transplant center (and therefore more likely get the majority of their care at the transplant center) versus those who live more than an hour away suggests that this dataset accurately captured the majority of costs. Finally, while we were able to capture direct medical costs, not captured here are costs incurred by patients in terms of lower quality of life and delayed return to work associated with protracted durations of antiviral therapy.

In conclusion, csCMVi is associated with significant increases in costs throughout the first post-transplant year. As more data are generated on the clinical effectiveness of new CMV preventative strategies inclusive of antiviral prophylactic therapies such as letermovir, cost-effectiveness analyses will be needed to better understand their incremental value in caring for patients undergoing allogeneic HCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Cytomegalovirus following transplant has significant morbidity and mortality
- Implementation of efficacious preventative strategies is imperative
- Strategy selection requires an assessment of the economic impact of cytomegalovirus

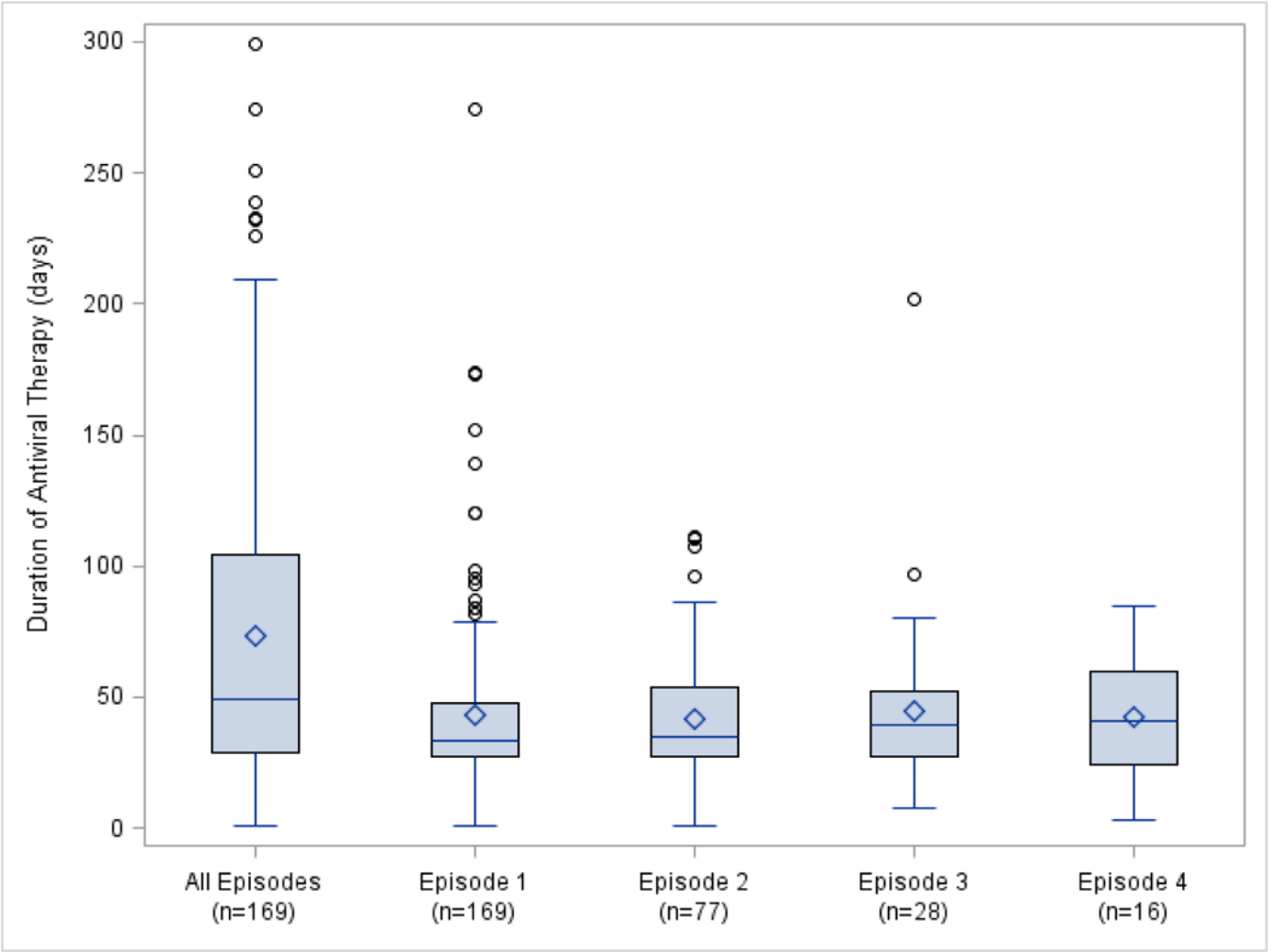

Figure 1. Duration of Cytomegalovirus-Directed Antiviral Therapy.

Bar in boxplot represents median antiviral duration. Diamond represents mean antiviral duration. Upper and lower limit of boxplot represent 75th and 25th percentiles, respectively. Whiskers represent values within 1.5*interquartile range and circles represent outliers. Boxplot for 'all episodes' represents cumulative duration of antiviral therapy.

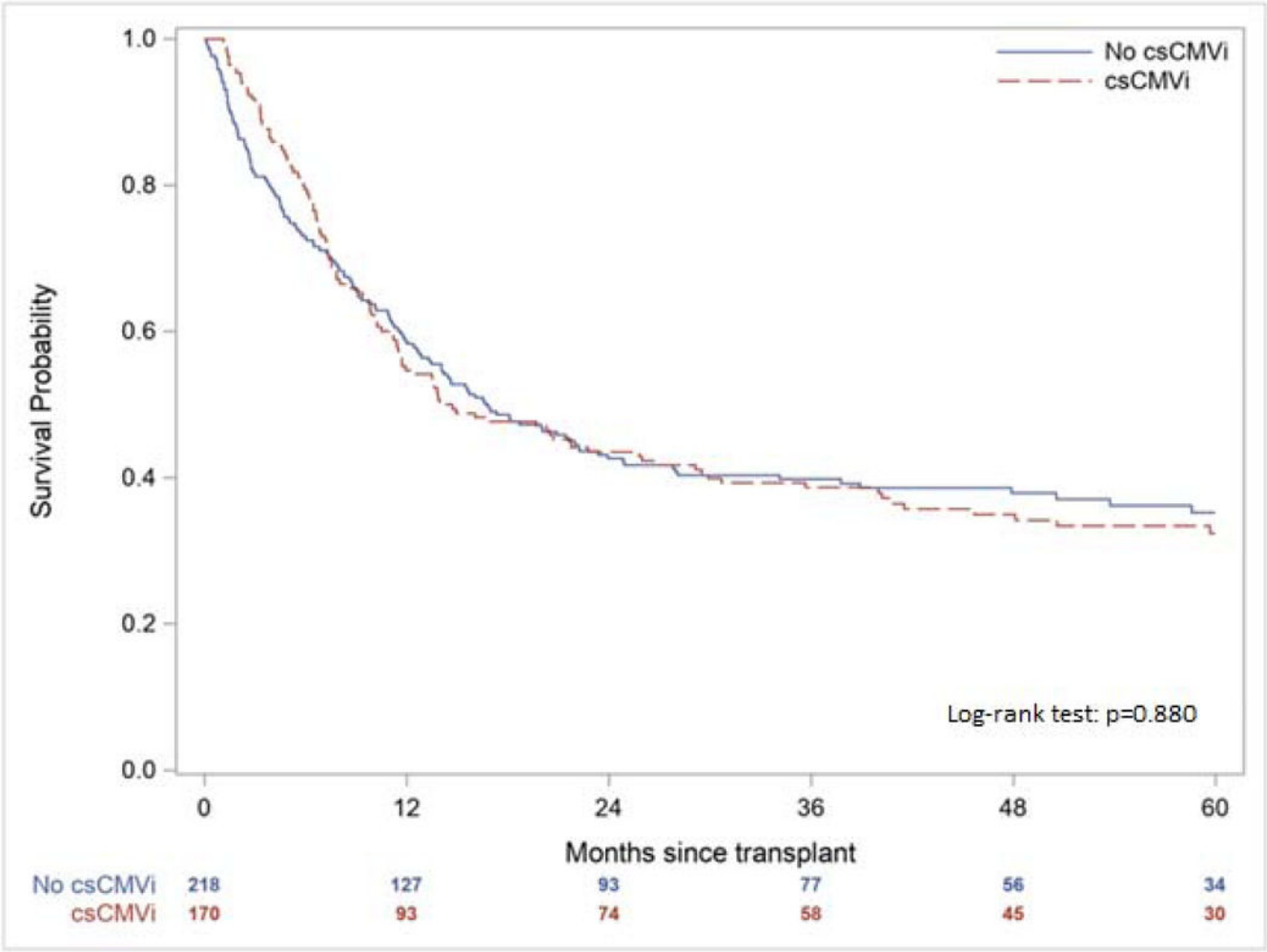

Figure 2.
Overall Survival According to the Presence of Clinically Significant Cytomegalovirus Infection (csCMVi)

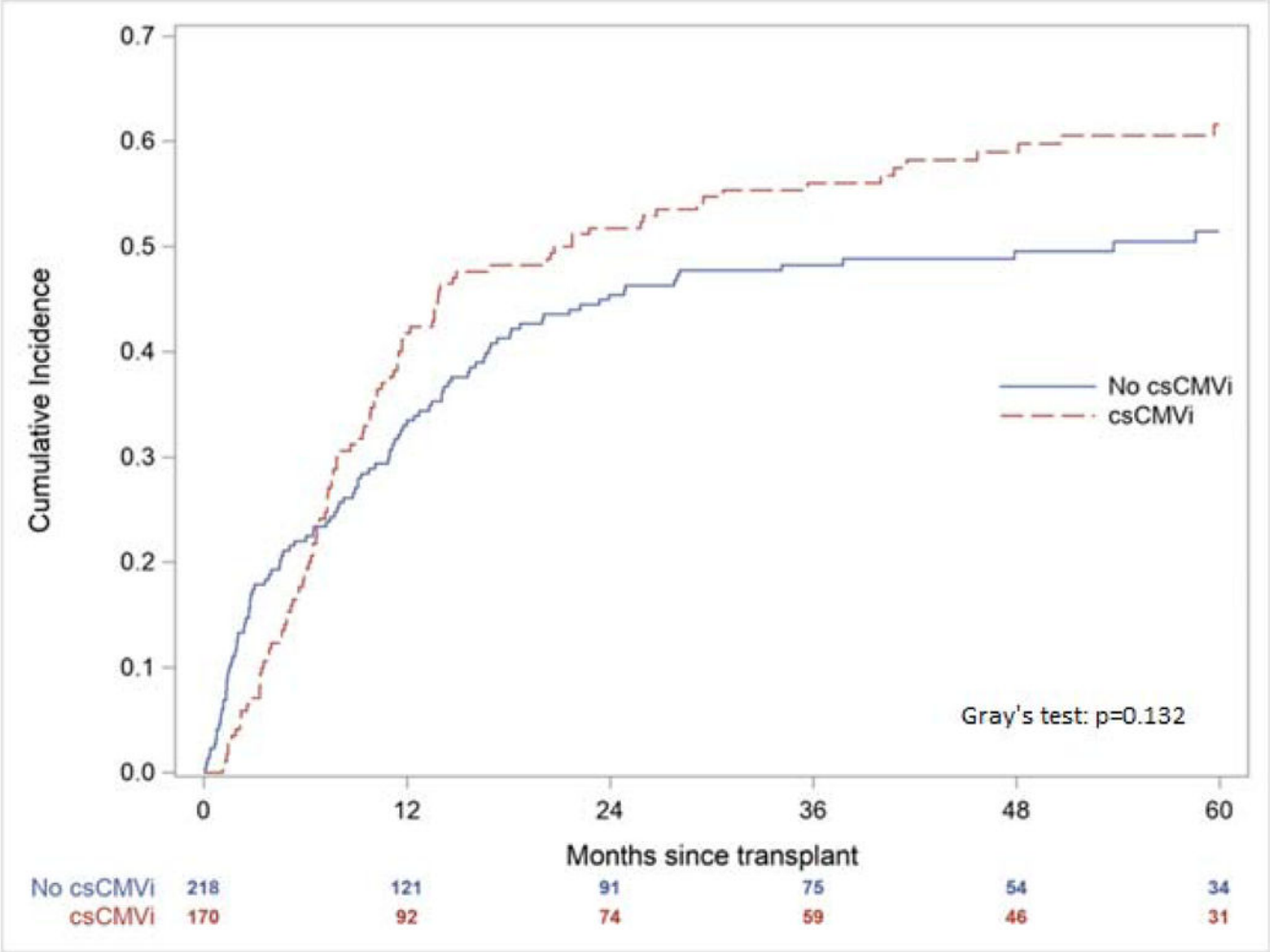

Figure 3.

Cumulative Incidence of Non-Relapse Mortality According to the Presence of Clinically Significant Cytomegalovirus Infection (csCMVi)

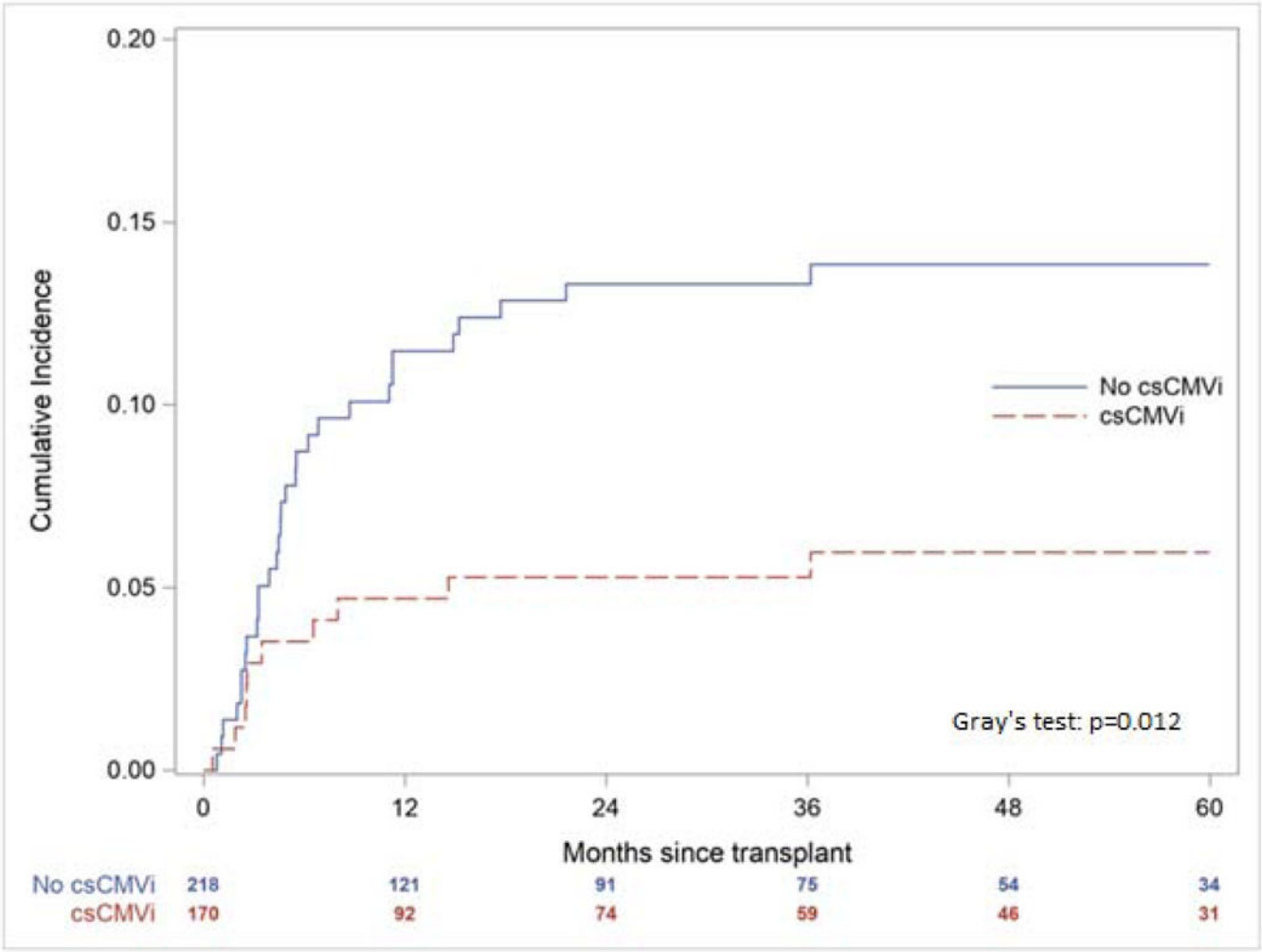

Figure 4.

Cumulative Incidence of Hematologic Disease Relapse According to the Presence of Clinically Significant Cytomegalovirus Infection (csCMVi)

Table 1.

Baseline Patient Characteristics

Characteristic	All patients (N=388)	With csCMVi (N=170)	Without csCMVi (N=218)	P-value[a]
Age (median)	51	52	51	0.477
Gender, female, no. (%)	157 (40.5)	75 (44.1)	82 (37.6)	0.195
Race, no. (%)				0.568
Caucasian	323 (83.2)	138 (81.2)	185 (84.9)	
African American	58 (14.9)	28 (16.5)	30 (13.8)	
Other	7 (1.8)	4 (2.4)	3 (1.4)	
Ethnicity (Non-Hispanic), no. (%)	383 (98.7)	167 (98.2)	216 (99.1)	0.463
Karnofsky Performance Status				
Median	90	85	90	0.146
100, no. (%)	50 (12.9)	23 (13.5)	27 (12.4)	
90, no. (%)	151 (38.9)	62 (36.5)	89 (40.8)	
80, no. (%)	99 (25.5)	33 (19.4)	66 (30.3)	
<=70, no. (%)	88 (22.7)	52 (30.6)	36 (16.5)	
Disease, no. (%)				0.531
Acute leukemia (AML+ALL)	183 (47.2)	82 (48.2)	101 (46.3)	
Lymphoma (HL+NHL)	81 (20.9)	39 (22.9)	42 (19.3)	
MDS/MPN	61 (15.7)	22 (12.9)	39 (17.9)	
Other	63 (16.2)	27 (15.9)	36 (16.5)	
Myeloablative Conditioning, no. (%)	205 (52.8)	80 (47.1)	125 (57.3)	0.044
HLA Matching/Donor Type, no. (%)				0.839
MUD	175 (45.1)	73 (42.9)	102 (46.8)	
MRD	107 (27.6)	47 (27.6)	60 (27.5)	
MMUD	71 (18.3)	34 (20.0)	37 (17.0)	
MMRD	35 (9.0)	16 (9.4)	19 (8.7)	
Haploidentical Donor, no. (%)	29 (7.5)	14 (8.2)	15 (6.9)	0.615
Stem Cell Source, no. (%)				0.126
Peripheral blood	295 (76.0)	131 (77.1)	164 (75.2)	
Bone marrow	27 (7.0)	7 (4.1)	20 (9.2)	
Cord blood	66 (17.0)	32 (18.8)	34 (15.6)	
GVHD prophylaxis, no. (%)				0.080
MTX/CNI alone	118 (30.4)	40 (23.5)	78 (35.8)	
MMF/CNI alone	80 (20.6)	37 (21.8)	43 (19.7)	
Alemtuzumab	155 (39.9)	79 (46.5)	76 (34.9)	
ATG	30 (7.7)	12 (7.1)	18 (8.3)	
Other	5 (1.3)	2 (1.2)	3 (1.4)	.
CMV status, no. (%)[b]				<0.0001
Donor Pos, Recipient Pos	109 (28.1)	76 (44.7)	33 (15.1)	
Donor Pos, Recipient Neg	57 (14.7)	12 (7.1)	45 (20.6)	
Donor Neg, Recipient Pos	106 (27.3)	73 (42.9)	33 (15.1)	

Characteristic	All patients (N=388)	With csCMVi (N=170)	Without csCMVi (N=218)	P-value[a]
Donor Neg, Recipient Neg	91 (23.5)	3 (1.8)	88 (40.4)	
Indeterminate/Unknown	25 (6.4)	6 (3.5)	19 (8.7)	

ALL, acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *ATG*, anti-thymocyte globulin; *CMV,* cytomegalovirus; *CNI,* calcineurin inhibitor; *csCMVi*, clinically significant cytomegalovirus infection; *GVHD*, graft-versus-host disease; *HL,* Hodgkin's lymphoma; *HLA*, human leukocyte antigen; *MDS*, myelodysplastic syndrome; *MMF,* mycophenolate; *MMRD*, mismatched related donor; *MMUD*, mismatched unrelated donor; *MPN*, myeloproliferative neoplasms; *MRD*, matched related donor; *MTX*, methotrexate; *MUD*, matched unrelated donor; *NHL*, Non-Hodgkin's lymphoma.

[a]P-values based on Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

[b]25 patients who had CMV status as 'Indeterminate/Unknown' include 18 patients with donor CMV negative and recipient indeterminate status and 7 patients with donor CMV positive and recipient CMV indeterminate status

Table 2.

Characteristics of Clinically Significant Cytomegalovirus Infection

Characteristic	N=170
csCMVi episodes	
csCMVi episodes per HCT recipient, median (IQI)	1 (1–2)
1, no. (%)	170 (100)
2, no. (%)	77 (45.3)
3, no. (%)	28 (16.5)
≥ 4, no. (%)	16 (9.4)
Time to first episode, median days (IQI)	33 (26–47)
CMV disease	
Any CMV disease, no. (%)	36 (21.2)
>1 episode, no. (%)[a]	1 (0.6)
>1 site, no. (%)[b]	5 (2.9)
Time to first CMV disease, median days (IQI)	71.5 (46–164)
CMV disease site, no. (%)	
Gastrointestinal	25 (14.7)
Proven upper GI	11 (6.5)
Probable upper GI	5 (2.9)
Proven lower GI	6 (3.5)
Probable lower GI	7 (4.1)
Pulmonary	10 (5.9)
Proven	3 (1.8)
Probable	7 (4.1)
Central nervous system	2 (1.2)
Proven	0
Probable	2 (1.2)
Antivirals applied (all episodes), no. (%)[c]	
Ganciclovir	127 (74.7)
Foscarnet	117 (68.8)
Valganciclovir	72 (42.4)
Cidofovir	6 (3.5)
Additional CMV-directed therapies	
Intravenous immunoglobulin	
Total patients receiving, no. (%)	19 (11.2)
Number of doses, mean (SD)	7.5 (6.1)
CMV immunoglobulin	
Total patients receiving, no. (%)	9 (5.3)
Number of doses, mean (SD)	3.4 (2.3)
Antiviral resistance, no. (%)	7 (4.1)

csCMVi, clinically significant cytomegalovirus infection; *CMV,* cytomegalovirus; *GI,* gastrointestinal; *HCT,* hematopoietic cell transplant; *IQI,* 25%−75% interquartile index; *SD,* standard deviation.

[a] 2 episodes of proven gastritis.

[b] More than one site of involvement included: 2 patients with proven upper and lower GI disease, 2 patients with proven upper and probable lower GI disease and 1 patient with probable upper GI disease and proven pneumonia.

[c] One patient died before receiving antiviral therapy.

Table 3.

Resource Utilization and Clinical Outcomes

Parameter	All Patients (N=388)	With csCMVi (N=170)	Without csCMVi (N=218)	Unadjusted p-value[a,b]	Adjusted p-value[a,c]
Transfusion/Support Products					
Red blood cells					
Mean units (SD)	14.1 (14.5)	15.5 (14.8)	13.1 (14.2)	0.077	0.059
Median units (IQI)	9 (5–19.5)	11.5 (6–21)	9 (4–17)		
Platelets					
Mean units (SD)	14.8 (20.4)	16.2 (21.6)	13.7 (19.3)	0.179	0.112
Median units (IQI)	7.5 (3–19)	8 (3–22)	7 (3–17)		
GCSF, no. (%)	243 (62.6)	125 (73.5)	118 (54.1)	0.0001	0.0001
Hospitalizations[d]					
Any inpatient admission, no. (%)	358 (92.3)	162 (95.3)	196 (89.9)	0.055	0.024
Inpatient admissions					
Mean number (SD)	2.0 (1.5)	2.4 (1.6)	1.7 (1.4)	<0.0001	<0.0001
Median number (IQI)	2 (1–3)	2 (1–3)	1 (1–2)		
Inpatient days					
Mean days (SD)	34.8 (26.5)	39.1 (27.5)	31.5 (25.3)	0.024	0.001
Median days (IQI)	32 (17–45)	35 (24–49)	29 (12–40)		
Intensive care unit stay, no. (%)	95 (24.5)	48 (28.2)	47 (21.6)	0.131	0.408
Transplant Length of Stay					
Mean days (SD)	84.2 (31.7)	91.7 (31.5)	78.3 (30.7)	<0.0001	<0.0001
Median days (IQI)	85 (65–95.5)	89 (75–103)	83.5 (61–92)		
Graft-versus-host Disease					
Acute GVHD, no. (%)	252 (64.9)	115 (67.6)	137 (62.8)	0.326	0.755
Grade of GVHD					
Grade 2 – 4	238 (61.3)	112 (65.9)	126 (57.8)	0.106	0.270
Grade 3 – 4	107 (27.6)	55 (32.4)	52 (23.9)	0.065	0.204
Site of GVHD					
Skin	186 (47.9)	83 (48.8)	103 (47.3)	0.758	0.644
Liver	17 (4.4)	6 (3.5)	11 (5.0)	0.472	0.587
Upper GI	126 (32.5)	58 (34.1)	68 (31.2)	0.542	0.672
Lower GI	130 (33.5)	65 (38.2)	65 (29.8)	0.083	0.063
Chronic GVHD, no. (%)	129 (33.2)	64 (37.6)	65 (29.8)	0.106	0.122
Grade of GVHD					
Grade 1	41 (10.57)	27 (15.9)	14 (6.4)	0.004	0.003
Grade 2	67 (17.27)	24 (14.1)	43 (19.7)	0.150	0.124

Parameter	All Patients (N=388)	With csCMVi (N=170)	Without csCMVi (N=218)	Unadjusted p-value[a,b]	Adjusted p-value[a,c]
Grade 3	21 (5.41)	13 (7.6)	8 (3.7)	0.093	0.134[e]
Site of GVHD					
Skin	86 (22.2)	42 (24.7)	44 (20.2)	0.289	0.320
Mouth	29 (7.5)	15 (8.8)	14 (6.4)	0.375	0.195
Eye	21 (5.4)	11 (6.5)	10 (4.6)	0.419	0.341
GI	49 (12.6)	26 (15.3)	23 (10.6)	0.166	0.385[e]
Liver	18 (4.6)	7 (4.1)	11 (5.0)	0.667	0.898[e]
Lung	7 (1.8)	1 (0.6)	6 (2.8)	0.150	NA
Joint	4 (1.0)	2 (1.2)	2 (0.9)	0.803	NA
Genital	1 (0.3)	1 (0.6)	0 (0.0)	0.978	NA
Renal	1 (0.3)	1 (0.6)	0 (0.0)	0.978	NA
Infections					
Bacteremia					
Any bacteremia, no. (%)	124 (32)	59 (34.7)	65 (29.8)	0.307	0.202
Onset of bacteremia					
Median transplant day (IQI)	22 (7.5–92)	27 (8–146)	16 (7–85)		
Invasive fungal infections					
IFI, no. (%)	34 (8.8))	20 (11.7)	14 (6.4)	0.069	0.117
Proven infection	21 (5.4)	12 (7.1)	9 (4.1)		
Probable infection	13 (3.4)	8 (4.7)	5 (2.3)		
Onset of IFI					
Mean transplant day (SD)	142.3 (118)	159.3 (108.5)	117.9 (130.5)	0.401	0.062
Median transplant day (IQI)	136 (24–266)	150.5 (48.5–282.5)	54 (12–210)		

csCMVi, clinically significant cytomegalovirus infection; *GCSF,* granulocyte colony stimulating factor; *GI,* gastrointestinal; *GVHD*, graft-versus-host disease; *IFI,* invasive fungal infection, *IQI,* 25%−75% interquartile index; *NA*, not applicable; *SD,* standard deviation.

[a] P-values based on generalized linear models with negative binomial distributions and log links.

[b] Independent variable included CMV status only.

[c] P-values adjusted for baseline demographic and clinical variables reported in Table 1.

[d] From start of conditioning through first post-transplant year

[e] P-value based on model including all baseline covariates excluding graft-versus-host disease prophylaxis.

Table 4a.

Costs Within the First Year of Allogeneic Hematopoietic Cell Transplantation

	All Patients (N=388)	Patients with csCMVi (N=170)	Patients without csCMVi (N=218)	Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
TOTAL COSTS (ACTUAL)[d]						
Tx start to D0[e]	***N=388***	***N=170***	***N=218***			
Mean (SD)	23,683 (15,423)	24,200 (17,093)	23,280 (14,010)	920 (−2,715 to 4,002)	1.040 (0.561)	1.074 (0.143)
Median (IQI)	20,488 (11,580–32,548)	19,957 (10,948–34,715)	21,195 (12,074–31,117)			
Maximum	130,258	130,258	74,757			
D0 to D100	***N=388***	***N=170***	***N=218***			
Mean (SD)	120,156 (75,615)	131,176 (75,635)	111,561 (74,648)	19,615 (4,296 to 34,125)	1.176 (0.012)	1.173 (0.004)
Median (IQI)	107,127 (66,686–156,599)	116,827 (73,907–168,452)	100,108 (61,780–143,872)			
Maximum	518,903	419,250	518,903			
D101 to D365	***N=328***	***N=154***	***N=174***			
Mean (SD)	43,388 (63,213)	56,166 (69,178)	32,078 (55,196)	24,088 (11,490 to 38,284)	1.750 (<0.001)	1.727 (0.001)
Median (IQI)	16,044 (4,009–62,328)	25,259 (8,223–79,294)	6,360 (2,886–39,378)			
Maximum	384,446	374,691	384,446			
D0 to D365	***N=388***	***N=170***	***N=218***			
Mean (SD)	156,834 (97,535)	182,056 (96,888)	137,165 (93,637)	44,891 (26,126 to 65,266)	1.327 (<0.0001)	1.349 (<0.0001)
Median (IQI)	136,877 (87,986–201,169)	164,004 (113,376–236,289)	114,841 (76,598–172,914)			
Maximum	573,064	573,064	533,683			
Tx start to D365	***N=388***	***N=170***	***N=218***			
Mean (SD)	180,517 (104,749)	206,256 (103,171)	160,445 (101,758)	45,811 (26,385 to 67,544)	1.286 (<0.0001)	1.316 (<0.0001)
Median (IQI)	162,154 (106,014–231,170)	190,438 (131,010–265,363)	146,392 (89,314–196,965)			
Maximum	606,680	606,680	591,894			
TOTAL COSTS (IMPUTED)[d]						
Tx start to D0[e]	***N=388***	***N=170***	***N=218***			
Mean (SD)	23,683 (15,423)	24,200 (17,093)	23,280 (14,010)	920 (−2,715 to 4,002)	1.040 (0.561)	1.074 (0.143)
Median (IQI)	20,488 (11,580–32,548)	19,957 (10,948–34,715)	21,195 (12,074–31,117)			
Maximum	130,258	130,258	74,757			

	All Patients (N=388)	Patients with csCMVi (N=170)	Patients without csCMVi (N=218)	Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
D0 to D100	***N=388***	***N=170***	***N=218***			
Mean (SD)	124,885 (76,730)	134,074 (76,465)	117,719 (76,346)	16,355 (32 to 30,814)	1.139 (0.040)	1.132 (0.026)
Median (IQI)	112,190 (69,809–163,625)	126,076 (76,511–170,900)	106,844 (65,956–153,568)			
Maximum	523,838	419,250	523,838			
D101 to D365	***N=388***	***N=170***	***N=218***			
Mean (SD)	55,428 (61,831)	76,079 (69,116)	39,324 (50,032)	36,755 (24,084 to 48,445)	1.935 (<0.0001)	1.887 (<0.0001)
Median (IQI)	39,324 (8,468–76,079)	71,807 (20,671–88,521)	33,785 (4,866–39,378)			
Maximum	384,446	374,899	384,446			
D0 to D365	***N=388***	***N=170***	***N=218***			
Mean (SD)	180,313 (103,760)	210,153 (103,784)	157,043 (97,828)	53,110 (32,005 to 73,454)	1.338 (<0.0001)	1.346 (<0.0001)
Median (IQI)	159,500 (108,901–231,451)	196,741 (139,355–273,785)	136,297 (89,097–204,216)			
Maximum	573,272	573,272	563,162			
Tx start to D365	***N=388***	***N=170***	***N=218***			
Mean (SD)	203,995 (110,437)	234,352 (109,161)	180,323 (105,764)	54,030 (32,121 to 76,250)	1.300 (<0.0001)	1.318 (<0.0001)
Median (IQI)	184,365 (124,650–254,238)	224,881 (156,627–303,504)	160,841 (108,102–227,824)			
Maximum	629,533	606,888	629,533			
INPATIENT COSTS (ACTUAL)[d]	***N=388***	***N=170***	***N=218***			
Mean (SD)	125,692 (100,187)	138,029 (96,828)	116,071 (101,916)	21,958 (2,373 to 41,900)	1.189 (0.273)	1.330 (0.069)
Median (IQI)	117,609 (51,336–175,831)	131,958 (64,209–189,114)	102,874 (46,456–158,113)			
Maximum	585,274	432,322	585,274			
OUTPATIENT COSTS (ACTUAL)[d]	***N=388***	***N=170***	***N=218***			
Mean (SD)	54,824 (46,404)	68,227 (47,174)	44,373 (43,090)	23,854 (15,044 to 33,237)	1.538 (0.001)	1.571 (0.001)
Median (IQI)	41,352 (20,237–79,089)	53,906 (32,777–101,806)	30,907 (15,310–67,450)			
Maximum	343,934	228,325	343,934			
INPATIENT COSTS (IMPUTED)[d]	***N=388***	***N=170***	***N=218***			

	All Patients (N=388)	Patients with csCMVi (N=170)	Patients without csCMVi (N=218)	Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
Mean (SD)	140,731 (104,640)	156,794 (102,272)	128,205 (104,986)	28,589 (8,301 to 48,625)	1.223 (0.165)	1.344 (0.039)
Median (IQI)	130,375 (61,812–191,571)	145,948 (84,962–209,882)	115,778 (50,595–177,739)			
Maximum	611,138	460,580	611,138			
OUTPATIENT COSTS (IMPUTED)[d]	***N=388***	***N=170***	***N=218***			
Mean (SD)	63,264 (45,164)	77,558 (45,279)	52,118 (41,907)	25,441 (16,934 to 34,301)	1.488 (<0.0001)	1.466 (<0.0001)
Median (IQI)	49,947 (31,153–87,094)	65,411 (43,829–109,173)	38,216 (24,143–72,156)			
Maximum	343,934	241,322	343,934			

Table 4b.

Costs in Patients with One or Multiple Episodes of Clinically Significant Cytomegalovirus Infection Within the First Year of Allogeneic Hematopoietic Cell Transplantation

	All Patients with csCMVi (N=170)	One Episode of csCMVi (N=93)	Multiple Episodes of csCMVi (N=77)	Mean Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
TOTAL COSTS (ACTUAL)[d]						
Tx start to Day 0[e]	***N=170***	***N=93***	***N=77***			
Mean (SD)	24,200 (17,093)	24,973 (17,673)	23,265 (16,430)	−1,708 (−6,974 to 3,490)	0.932 (0.500)	0.893 (0.148)
Median (IQI)	19,957 (10,948–34,715)	20,590 (12,678–34,623)	18,598 (8,945–34,715)			
Maximum	130,258	130,258	68,225			
D0 to D100	***N=170***	***N=93***	***N=77***			
Mean (SD)	131,176 (75,635)	128,602 (78,368)	134,285 (72,585)	5,683 (−15,551 to 29,792)	1.044 (0.637)	1.050 (0.553)
Median (IQI)	116,827 (73,907–168,452)	112,930 (65,905–162,351)	126,857 (76,511–182,858)			
Maximum	419,250	419,250	409,902			
D101 to D365	***N=154***	***N=78***	***N=76***			
Mean (SD)	56,166 (69,178)	35,248 (51,163)	77,635 (78,440)	42,387 (22,434 to 64,881)	2.203 (<0.0001)	2.549 (<0.0001)
Median (IQI)	25,259 (8,223–79,294)	13,815 (4,042–49,046)	53,083(16,838–122,479)			
Maximum	374,691	293,757	374,691			
D0 to D365	***N=170***	***N=93***	***N=77***			
Mean (SD)	182,056 (96,888)	158,165 (86,399)	210,912 (101,469)	52,746 (24,755 to 84,190)	1.333 (<0.001)	1.382 (<0.0001)
Median (IQI)	164,004 (113,376–236,289)	141,506 (102,795–212,543)	194,365 (144,507–258,350)			
Maximum	573,064	493,336	573,064			
Tx Start to D365	***N=170***	***N=93***	***N=77***			
Mean (SD)	206,256 (103,171)	183,139 (95,131)	234,177 (106,164)	51,038 (22,683 to 84,435)	1.279 (0.001)	1.324 (<0.001)
Median (IQI)	190,438 (131,010–265,363)	166,807 (117,618–236,717)	232,931 (161,847–286,777)			
Maximum	606,680	537,959	606,680			
TOTAL COSTS (IMPUTED)[d]						
Tx Start to D0[e]	***N=170***	***N=93***	***N=77***			

	All Patients with csCMVi (N=170)	One Episode of csCMVi (N=93)	Multiple Episodes of csCMVi (N=77)	Mean Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
Mean (SD)	24,200 (17,093)	24,973 (17,673)	23,265 (16,430)	−1,708 (−6,974 to 3,490)	0.932 (0.500)	0.893 (0.148)
Median (IQI)	19,957 (10,948–34,715)	20,590 (12,678–34,623)	18,598 (8,945–34,715)			
Maximum	130,258	130,258	68,225			
D0 to D100	***N=170***	***N=93***	***N=77***			
Mean (SD)	134,074 (76,465)	133,851 (79,906)	134,342 (72,610)	491 (−20,391 to 25,557)	1.004 (0.968)	1.011 (0.896)
Median (IQI)	126,076 (76,511–170,900)	121,998 (79,333–162,351)	126,857 (76,511–182,858)			
Maximum	419,250	419,250	409,902			
D101 to D365	***N=170***	***N=93***	***N=77***			
Mean (SD)	76,079 (69,116)	58,502 (49,560)	97,309 (82,550)	38,808 (18,517 to 61,525)	1.663 (0.001)	1.701 (0.001)
Median (IQI)	71,807 (20,671–88,521)	66,974 (16,561–76,079)	77,865 (28,591–158,012)			
Maximum	374,899	293,757	374,899			
D0 to D365	***N=170***	***N=93***	***N=77***			
Mean (SD)	210,153 (103,784)	192,353 (96,575)	231,651 (108,652)	39,298 (9,734 to 73,955)	1.204 (0.018)	1.255 (0.005)
Median (IQI)	196,741 (139,355–273,785)	183,747 (115,795–249,447)	216,443 (144,507–302,378)			
Maximum	573,272	493,336	573,272			
Tx start to D365	***N=170***	***N=93***	***N=77***			
Mean (SD)	234,352 (109,161)	217,326 (103,789)	254,916 (112,580)	37,590 (5,007 to 74,052)	1.173 (0.032)	1.217 (0.008)
Median (IQI)	224,881 (156,627–303,504)	212,749 (148,345–275,910)	247,446 (176,143–330,477)			
Maximum	606,888	537,959	606,888			
INPATIENT COSTS (ACTUAL)[d]	***N=170***	***N=93***	***N=77***			
Mean (SD)	138,029 (96,828)	128,843 (90,874)	149,124 (103,072)	20,280 (−8,108 to 53,033)	1.157 (0.465)	1.302 (0.211)
Median (IQI)	131,958 (64,209–189,114)	122,421 (62,878–180,642)	139,468 (85,831–205,432)			
Maximum	432,322	432,322	416,384			
OUTPATIENT COSTS (ACTUAL)[d]	***N=170***	***N=93***	***N=77***			

	All Patients with csCMVi (N=170)	One Episode of csCMVi (N=93)	Multiple Episodes of csCMVi (N=77)	Mean Cost Difference (95% CI)	Mean Cost Ratio (unadjusted p-value)[a,b]	Mean Cost Ratio (adjusted p-value)[a,c]
Mean (SD)	68,227 (47,174)	54,295 (44,460)	85,053 (45,071)	30,758 (15,774 to 43,536)	1.566 (0.002)	1.369 (0.021)
Median (IQI)	53,906 (32,777–101,806)	38,072 (26,990–68,359)	75,757 (48,933–114,996)			
Maximum	228,325	208,047	228,325			
INPATIENT COSTS (IMPUTED)[d]	***N=170***	***N=93***	***N=77***			
Mean (SD)	156,794 (102,272)	151,131 (97,804)	163,634 (107,669)	12,504 (−18,857 o 47,862)	1.083 (0.659)	1.193 (0.354)
Median (IQI)	145,948 (84,962 – 209,882)	143,217 (81,664 – 191,759)	151,552 (89,538 – 213,605)			
Maximum	460,580	434,318	460,580			
OUTPATIENT COSTS (IMPUTED)[d]	***N=170***	***N=93***	***N=77***			
Mean (SD)	77,558 (45,279)	66,196 (42,572)	91,282 (44,901)	25,086 (10,424 to 38,072)	1.379 (<0.001)	1.251 (0.008)
Median (IQI)	65,411 (43,829 – 109,173)	52,353 (34,576 – 85,201)	79,390 (51,559 – 120,041)			
Maximum	241,322	208,047	241,322			

CI, confidence interval; *csCMVi,* clinically significant cytomegalovirus infection; *D,* day; *IQI,* 25%−75% interquartile index; *SD,* standard deviation; *Tx,* transplant.

[a] P-values based on generalized linear models with gamma distributions and log links.

[b] Independent variable included CMV status only.

[c] Independent variables included CMV status and baseline demographic and clinical variables in Table 1 except HLA and donor and recipient CMV serostatus.

[d] All costs expressed in U.S. dollars.

[e] Cost does not include D0.