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Outcomes of Refractory Cytomegalovirus Infection in the First Year after Allogeneic Hematopoietic Cell Transplantation

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Outcomes of refractory (Rf) cytomegalovirus (CMV) infection (CMVi) after hematopoietic cell transplantation (HCT) are poor owing to limited treatment options and treatment related toxicities. Maribavir, an orally bioavailable CMV antiviral, was recently approved for treatment of Rf-CMVi. Real-world studies quantifying the burden of Rf-CMVi prior to maribavir provide a benchmark for evaluating the net value of novel treatments. Here we report the incidence, clinical outcomes, and healthcare resource utilization (HRU) associated with Rf-CMVi in the first year post-HCT in a cohort of CMV-seropositive HCT recipients (R+) who underwent HCT between January 1, 2014, and December 31, 2017, at Memorial Sloan Kettering Cancer Center and were managed exclusively by preemptive therapy. CMVi was defined as CMV viremia treated preemptively. Rf-CMVi was defined as a <1 $\log_{10}$ decrease and CMV viral load >1000 U/mL after ≥ 14 days of appropriately dosed therapy. Welldays were defined as alive days not hospitalized and off CMV antivirals by 1 year post-HCT. The impact of Rf-CMVi on mortality and HRU was examined in multivariable models. Of the 286 R + patients, 145 (50.7%) developed CMVi (99 no Rf-CMVi and 46 Rf-CMVi). Compared with the no Rf-CMVi group, the Rf-CMVi group had higher rates of CMV EOD (23.9% versus 10.1%; $P = .030$), CMV-related mortality (9.5% versus .0%; $P = .002$), and all-cause mortality (33.3% versus 15.6%; adjusted $P = .049$). Rf-CMVi was an independent predictor for readmission (adjusted odds ratio [aOR], 3.24; 95% confidence interval [CI], 2.19 to 4.87; $P < .0001$); CMV-related readmission (aOR, 9.48; 95% CI, 5.83 to 15.80; $P < .0001$), and decreased well days (adjusted arithmetic mean ratio, .72; 95% CI, .58 to .89; $P = .001$) in the first year post-HCT. Rf-CMVi is associated with increased mortality and increased HRU at 1 year after HCT. Improved therapies for Rf-CMVi have the potential of improving HCT outcomes and reducing HRU.

INTRODUCTION

Cytomegalovirus (CMV) infection is associated with increased mortality after hematopoietic cell transplantation (HCT) [1] with a dose-response relationship between CMV viral load (VL) and mortality [2,3]. The term "refractory CMV infection" (Rf-CMVi) is used by clinicians to describe a lack of clinical and/or virologic response to standard therapy regardless of the presence of resistance-conferring mutations on genotypic analysis [4]. Consensus definitions for Rf-CMVi have been developed for clinical trial design [5].

Before letermovir prophylaxis, reported rates of Rf-CMVi ranged between 19% and 39% [6–8]. Rf-CMVi has been associated with CMV end-organ disease (EOD) [7,9,10], CMV-related mortality [9], and increased nonrelapse mortality [7]. Maribavir, an orally available CMV antiviral, was recently approved by the Food and Drug Administration for treatment of Rf-CMVi. In a randomized study, maribavir had better safety and efficacy compared to current DNA polymerase inhibitors [11,12]. The impact of maribavir on long-term HCT outcomes has yet to be evaluated. Quantifying the real-world impact of Rf-CMVi on HCT outcomes and health resource utilization (HRU) is useful in guiding clinical decisions for novel treatments.

We analyzed a cohort of CMV-seropositive HCT recipients (R+) managed exclusively by the preemptive approach at Memorial Sloan Kettering Cancer Center. Rf-CMVi was defined

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using the virologic criteria used in the clinical trials of maribavir [11,12]. Here we report the incidence, clinical outcomes, and impact of Rf-CMVi on HRU in the first year after HCT.

METHODS

Study Cohort

We included adult R+ recipients of first allogeneic peripheral blood or bone marrow HCT between January 2014 and December 2017 at Memorial Sloan Kettering Cancer Center. Patients who had multiple myeloma, had participated in randomized trials for CMV prevention, had received letermovir for primary CMV prophylaxis, or had received CMV-active antivirals for indications other than CMVi prior to meeting the criteria for Rf-CMVi were excluded.

Demographic data, clinical characteristics, and outcomes were extracted from the electronic medical records and institutional databases. Patients were followed through 1 year post-HCT or death, whichever occurred first. The study was reviewed and approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board.

Institutional Standards of Care

Graft Manipulation and Graft-versus-Host Disease Prophylaxis

Ex vivo T cell depletion was performed by $CD34^+$ selection as described previously [13]. Recipients of T cell-depleted (TCD) allografts did not receive additional pharmacologic graft-versus-host disease (GVHD) prophylaxis. The majority of unmodified HCT recipients received tacrolimus with or without methotrexate, and most haploidentical HCT recipients received post-transplantation cyclophosphamide [14,15].

CMV Monitoring

Pre-HCT CMV IgG for donors and recipients was determined by automated semiquantitative ELISA (VIDAS; Biomerieux, Durham, NC). Plasma CMV DNA was determined via a quantitative PCR assay (Roche Diagnostics, Basel, Switzerland). The lower limit of detection was 136 IU/mL, and the linear range was 137 to 9,100,000 IU/mL. Patients were routinely monitored by CMV PCR if the recipient (R) or donor (D) was CMV seropositive, starting at day 14 post-HCT and continued at least weekly through day 100 and then at least once every 2 weeks through day 180 or immune reconstitution, whichever occurred later. CMV monitoring started before day 14 for patients with documented CMV infection prior to HCT or clinical concern for CMV infection or EOD. CMV resistance genotyping (Eurofins-Viracor, Lee's Summit, MO) was ordered at the clinician's discretion, typically if CMV VL failed to decrease by >1 $\log_{10}$ after at least 2 weeks of stable induction therapy or rose after initial suppression on appropriate induction therapy. The VL threshold for CMV genotyping was $\geq$1000 IU/mL.

Anti-Infective Prophylaxis and CMV Management

All patients received acyclovir prophylaxis (400 mg twice daily) from admission for HCT through at least 12 months post-HCT. Antibacterial and antifungal prophylaxis has been described previously [16].

CMV infection was managed exclusively by preemptive therapy (PET) [17]. In brief, PET was started for $\geq$1 CMV VL $>$137 IU/mL in recipients of unmodified allografts from mismatched donors or TCD HCT regardless of donor type. For recipients of unmodified HCT, PET was initiated for $\geq$2 consecutive CMV VL $>$300 IU/mL with a rising trend obtained 3 to 4 days apart.

First-line PET was valganciclovir (900 mg orally every 12 hours) or ganciclovir (5 mg/kg i.v. every 12 hours). A foscarnet induction dose (90 mg/kg i.v. every 12 hours) was used in patients with a contraindication to valganciclovir or ganciclovir. Induction therapy was continued for minimum of 14 days or until viral clearance, whichever occurred later. EOD was treated with induction treatment for 2 to 4 weeks, until clinical improvement and viral clearance. Patients who remained immunosuppressed after clearance of viremia received maintenance antiviral therapy (valganciclovir 900 mg orally every 24 hours, ganciclovir 5 mg/kg i.v. every 24 hours, foscarnet 90 mg/kg every 24 hours).

Definitions

CMVi was defined as any level of CMV viremia treated with PET. Rf-CMVi was defined as failure to achieve >1 $\log_{10}$ decrease in CMV VL and CMV VL $>$1000 IU/mL after at least 14 days of appropriately dosed PET. Resistant CMVi required meeting criteria for Rf-CMVi plus genotypic documentation of $\geq$1 resistance-associated mutation(s) in UL54 and/or UL97 [5,18,19]. Patients with CMVi were categorized into 2 mutually exclusive groups as Rf-CMVi or no Rf-CMVi.

Time to CMV viremia clearance was calculated at the number of days from the start of PET to the first day of 2 consecutive CMV VL values below the lower limit of detection from HCT. CMV EOD was scored as described previously [20]. In general, gastrointestinal disease was confirmed by biopsy, whereas sampling of bronchoalveolar lavage or cerebrospinal fluid was used for pneumonitis and central nervous system involvement, respectively. CMV retinitis was defined by characteristic appearance on fundoscopy. CMV-related mortality was defined when CMV caused or contributed to death. Death from any other cause was considered a competing risk for CMV-related mortality. CMV-related readmission was defined as any admission with a length of stay (LOS) $>$48 hours after discharge from the index hospitalization for HCT for any of the following: management of CMV viremia, EOD, or PET initiation during the readmission. Well days (for patients with CMVi) were the number of days alive, not hospitalized, and off CMV antivirals by 1 year post-HCT. Acute GVHD was scored by standard criteria [21].

Statistical Methods

Our primary objective was to identify predictors for Rf-CMVi in multivariable models. Our secondary objective was to quantify the impact of Rf-CMVi on clinical outcomes and HRU in the first year after transplantation. Our primary endpoints were CMV EOD, CMV-related mortality; all-cause mortality, and HRU including readmissions, LOS, CMV-related readmissions, CMV-related LOS, and well days in the first year post-HCT.

Descriptive statistics were used to tabulate demographics and clinical characteristics. Numeric data were expressed as median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. Categorical data were expressed as number and percentage and compared using the chi-square test or Fisher's exact test as appropriate. The cumulative incidence function and Gray's test were used to estimate and compare the incidence of EOD and CMV-related mortality. Death from all causes and other than CMV infection were considered competing risks for EOD and CMV-related death, respectively. The Kaplan-Meier estimates and log-rank tests were used to estimate and compare time to CMV viremia clearance and all-cause mortality. Patients were censored at 1 year post-HCT or date of last follow-up, whichever occurred first. To account for early death, the CMV-related and all-cause mortality was estimated with the landmark method at day 100. Pairwise comparisons were adjusted using the Benjamini-Hochberg procedure.

Univariable and multivariable models were performed to assess risk factors for clinical and HRU outcomes. Models included a multinomial logistic regression model for Rf-CMVi, Fine-Gray subdistribution hazard model for EOD and CMV-related mortality, Cox proportional hazard model for all-cause mortality, logistic regression model for all-cause and CMV-related readmission, and generalized linear model with a gamma distribution for LOS, CMV-related LOS, and well days. Variables entered in the models were patient characteristics including age, sex, race and underlying disease, and transplant characteristics including donor type, donor CMV serostatus, stem cell source, conditioning regimen, total body irradiation, antithymocyte globulin (ATG), HCT-comorbidity index, GVHD prophylaxis, acute GVHD, and absolute lymphocyte count (ALC) at day 30. Additional covariates, including VL at PET initiation, days to PET from CMV viremia, and first antiviral type, were entered in the analysis for patients who received PET only. The Pearson correlation coefficient was calculated to avoid multicollinearity. Possible interactions between Rf-CMVi and other covariates were investigated by adding respective interaction terms. All tests were 2-sided with a significance level of .05. All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; (https://www.rproject.org/).

RESULTS

Study Population

During the study period, 616 adults underwent first marrow or peripheral blood HCT (Supplementary Figure S1). We excluded 274 patients with negative (R-) or equivocal CMV IgG and 30 R+ patients with multiple myeloma as an underlying disease. In addition, 26 R+ patients were excluded because they participated in randomized trials for CMV prevention, received letermovir for primary CMV prophylaxis, or received investigational antivirals with anti-CMV activity before meeting the criteria for Rf-CMVi. The remaining 286 patients were categorized into 3 mutually exclusive groups: Rf-CMVi (N = 46), no Rf-CMVi (N = 99), and no CMVi (N = 141). Out of 46 patients with Rf-CMVi, 44 were tested for CMV resistance mutations (a total of 209 resistance tests) (Supplementary Figure S1). By 1 year post-HCT, CMV resistance mutations were confirmed in 6 patients, in 4 patients identified before day 180, and in 4 patients after day 180 post-HCT. Four patients had ganciclovir resistance, 1 patient had foscarnet resistance, and 1 patient had cidofovir resistance.

Table 1 summarizes the baseline clinical characteristics of the 3 groups. Patients with Rf-CMVi were more likely to have received ATG (P= .003) and ex vivo TCD HCT (P= .001).

Table 1
Baseline Characteristics of CMV R^+ Recipients (N = 286)

Characteristic	Total (N = 286)	Rf-CMVi (N = 46)	No Rf-CMVi (N = 99)	No CMVi (N = 141)	*P* Value
Demographic					
Age, yr, median (IQR)	60 (47-67)	58 (45-66)	58 (45-67)	61 (49-67)	.462
Age group, n (%)					.954
18-39 yr	44 (15.4)	8 (17.4)	16 (16.2)	20 (14.2)	
40-64 yr	144 (50.3)	21 (45.7)	50 (50.5)	73 (51.8)	
65+ yr	98 (34.3)	17 (37.0)	33 (33.3)	48 (34.0)	
Sex, n (%)					.602
Female	123 (43.0)	22 (47.8)	39 (39.4)	62 (44.0)	
Male	163 (57.0)	24 (52.2)	60 (60.6)	79 (56.0)	
Race, n (%)					.016
White	219 (76.6)	35 (76.1)	64 (64.6)	120 (85.1)	
Asian	21 (7.3)	4 (8.7)	12 (12.1)	5 (3.5)	
African American	23 (8.0)	4 (8.7)	13 (13.1)	6 (4.3)	
Other/unknown	23 (8.0)	3 (6.5)	10 (10.1)	10 (7.1)	
Clinical					
Underlying disease, n (%)					.160
AML/ALL/CML/MDS	212 (74.1)	37 (80.4)	72 (72.7)	103 (73.0)	
Lymphoma/CLL	55 (19.2)	4 (8.7)	19 (19.2)	32 (22.7)	
MPD/nonmalignant	19 (6.6)	5 (10.9)	8 (8.1)	6 (4.3)	
Donor type, n (%)					.004
Matched related	83 (29.0)	11 (23.9)	26 (26.3)	46 (32.6)	
Matched unrelated	162 (56.6)	22 (47.8)	53 (53.5)	87 (61.7)	
Mismatched	20 (7.0)	6 (13.0)	9 (9.1)	5 (3.5)	
Haploidentical	21 (7.3)	7 (15.2)	11 (11.1)	3 (2.1)	
Donor CMV serostatus, n (%)					.384
Negative	111 (38.8)	22 (47.8)	36 (36.4)	53 (37.6)	
Positive	175 (61.2)	24 (52.2)	63 (63.6)	88 (62.4)	
Stem cell source, n (%)					.341
Bone marrow	48 (16.8)	7 (15.2)	21 (21.2)	20 (14.2)	
Peripheral blood	238 (83.2)	39 (84.8)	78 (78.8)	121 (85.8)	
Conditioning regimen intensity, n (%)					.003
Ablative	156 (54.5)	34 (73.9)	59 (59.6)	63 (44.7)	
Reduced	102 (35.7)	8 (17.4)	29 (29.3)	65 (46.1)	
Nonablative	28 (9.8)	4 (8.7)	11 (11.1)	13 (9.2)	
ATG, n (%)					<.0001
No	165 (57.7)	12 (26.1)	52 (52.5	101 (71.6)	
Yes	121 (42.3)	34 (73.9)	47 (47.5)	40 (28.4)	
HCT-comorbidity index, n (%)					.490
0	46 (16.1)	8 (17.4)	13 (13.1)	25 (17.7)	
1-2	84 (29.4)	16 (34.8)	33 (33.3)	35 (24.8)	
3+	156 (54.5)	22 (47.8)	53 (53.5)	81 (57.4)	
GVHD prophylaxis, n (%)					<.0001
Ex vivo T cell depletion	92 (32.2)	30 (65.2)	37 (37.4)	25 (17.7)	
Tacrolimus-MTX ± other	160 (55.9)	7 (15.2)	47 (47.5)	106 (75.2)	
PTCy + other	34 (11.9)	9 (19.6)	15 (15.2)	10 (7.1)	

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; MTX, methotrexate; PTCy, post-transplantation cyclophosphamide.

Supplementary Table S1 provides pairwise comparisons of baseline characteristics.

Multivariable Predictors for Rf-CMVi

To identify specific risk factors for Rf-CMVi, patients with no Rf-CMVi composed the reference group (Figure 1). Owing to the high correlation of ATG with GVHD prophylaxis (.74), ATG was not entered into the model.

In multivariable multinomial regression models, the strongest predictor for Rf-CMVi was TCD HCT (adjusted odds ratio [aOR], 12.60; 95% confidence interval [CI], 6.24 to 25.60; $P<$ .001), followed by haploidentical donor HCT (aOR, 4.82; 95% CI, 1.65 to 14.10; $P=$ .004). Myeloproliferative or nonmalignant disorders and reduced-intensity conditioning regimens also were associated with increased risk. In contrast, factors associated with decreased risk for Rf-CMV were CMV-seropositive donor (aOR, .49; 95% CI, .35 to .70; $P<$ .001) and incremental increase of ALC at D30 (aOR, .49; 95% CI, .32 to .74; $P<$ .001). In addition, African American race and HCT-comorbidity index 1 to 2 were associated with decreased risk for Rf-CMVi.

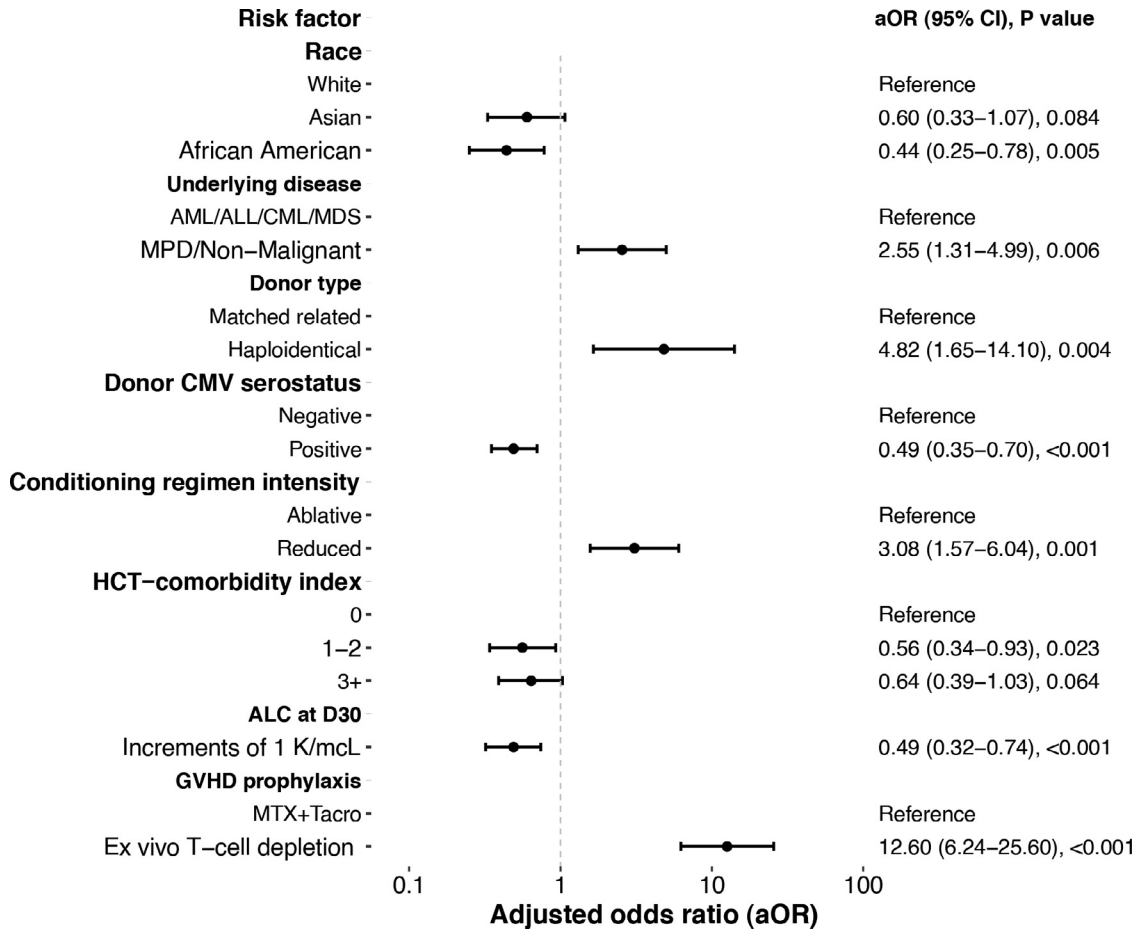

Figure 1. Multivariable risk factors for Rf-CMVi. Risk factors for Rf-CMVi were assessed in multivariable multinomial logistic regression models. No Rf-CMVi was set as the reference. Points show aORs, and whiskers show 95% CIs. AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; MTX, methotrexate.

Viral Kinetics

The median maximum CMV VL of the Rf-CMVi group was .9 $\log_{10}$ IU/mL higher than that for the no Rf-CMVi group (median $\log_{10}$, 3.8 [IQR, 3.4 to 4.2] versus 2.9 [IQR, 2.7 to 3.3]; $P < .0001$) (Figure 2A). Similarly, the CMV averaged area under the curve by day 100 post-HCT was larger in the Rf-CMVi group (median, 1.9 [IQR, 1.6 to 2.4] versus 1.0 [IQR, .8 to 1.3]; $P < .0001$) (Figure 2B). The time from onset of CMV viremia to clearance was delayed in the Rf-CMVi group compared with the no Rf-CMVi group (median, 67 days [IQR, 43 to 122 days] versus 26 days [IQR, 21 to 33 days]; $P < .0001$). Overall, 88.7% patients in the Rf-CMVi group achieved clearance of CMV viremia, compared with 98.9% in the no Rf-CMVi group ($P < .0001$) (Figure 2C).

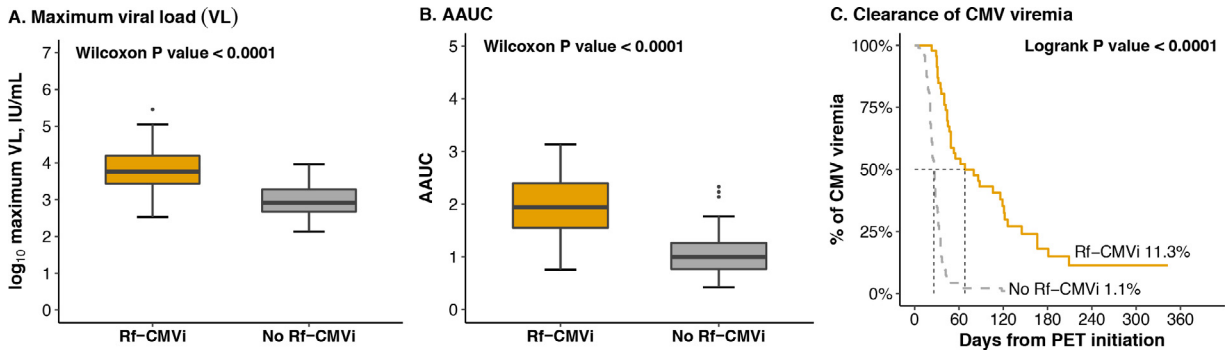

Figure 2. Comparison of viral kinetics between the Rf-CMVi and no Rf-CMVi groups. (A) Maximum CMV VL $\log_{10}$ IU/mL by day 100. (B) Averaged area under the curve (AAUC) of the CMV VL by day 100. Horizontal lines, boxes, whiskers, and dots represent median, IQR, range, and outliers, respectively. *P* values were calculated with the Mann-Whitney *U* test. (C) Kaplan-Meier curve of time to clearance of first CMV viremia by 1 year post-HCT. Patients were censored at death, 1 year post-HCT, or last follow-up, whichever occurred first. *P* values were calculated using the log-rank test.

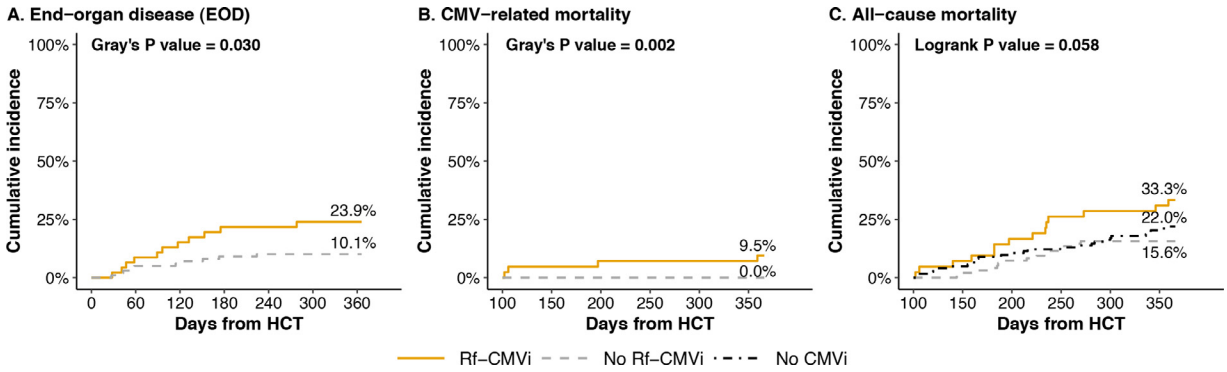

Figure 3. Cumulative incidence of CMV EOD (A), CMV-related mortality (B), and all-cause mortality (C) by 1 year post-HCT. For CMV EOD, death was considered a competing risk. *P* values were calculated using Gray's test. For CMV-related mortality, deaths from other causes were competing risk events. *P* values were calculated using Gray's test. For all-cause mortality, *P* values were s calculated using the log-rank test. Pairwise comparisons were adjusted using the Benjamini-Hochberg procedure. To account for early death, the CMV-related and all-cause mortality were estimated with the landmark method at day 100.

Clinical Outcomes

Twenty-one of 145 patients with CMVi (14.5%) developed EOD by 1 year post-HCT, including 11 (23.9%) in the Rf-CMVi group and 10 (10.1%) in the no Rf-CMVi group (*P*= .030) (Figure 3A). The adjusted hazard ratio (aHR) for Rf-CMVi was 2.56 (95% CI, 1.00 to 6.53; *P*= .049) when adjusting for age, sex, race, donor CMV serostatus, HCT- comorbidity index, and ALC at day 30. The gastrointestinal tract was involved in 53% of all EOD cases. The time from HCT to diagnosis of EOD was similar in the 2 groups (median, 96 days [IQR, 53 to 143 days] versus 86 days [IQR, 46 to 144 days]; *P*= .698).

CMV-related mortality was 9.5% in the Rf-CMVi group and 0% in the no Rf-CMVi group (*P*= .002) (Figure 3B). Because there were no CMV-related deaths in the no Rf-CMVi group, the aHR could not be assessed. At 1 year post-HCT, all-cause mortality was 33.3% for the Rf-CMVi group, 15.6% for the no Rf-CMVi group, and 22.0% for the no CMVi group (P = .058) (Figure 3C). The pairwise comparison between the Rf-CMVi and no Rf-CMVi groups was .049.

CMVi was explored as a predictor for all-cause mortality in multivariable models. No Rf-CMVi was set as a reference. Rf-CMVi was found to increase the probability of death (aHR, 2.80; 95% CI, 1.30 to 6.03; *P*= .008) when adjusting for age, sex, HCT-comorbidity index, ALC at day 30, and GVHD prophylaxis.

Healthcare Resource Utilization

By 1 year post-HCT, 163 patients (57.0%) required readmission. The need for readmission was greater in the Rf-CMVi group compared with the no Rf-CMVi group (80.4% versus 61.6%; *P*= .024). The impact of Rf-CMVi on readmission, LOS, and well days were examined in multivariable models, with the no Rf-CMVi group as the reference. The aOR for readmission was 3.24 (95% CI, 2.19 to 4.87; *P*< .0001). The adjusted arithmetic mean ratio [aAMR] for inpatient LOS was 1.25 (95% CI, .98 to 1.61; *P*= .081) (Figure 4A, Table S2).

Among the 145 patients with CMVi, 40 (27.6%) had ≥1 CMV-related readmission, including 25 of 46 (54.3%) in the Rf-CMVi group and 15 of 99 (15.2%) in the no Rf-CMVi group (*P*< .0001). The aOR for CMV-related readmission was 9.48 (95% CI, 5.83 to 15.80; *P*< .0001) (Figure 4B, Table S2). The LOS for

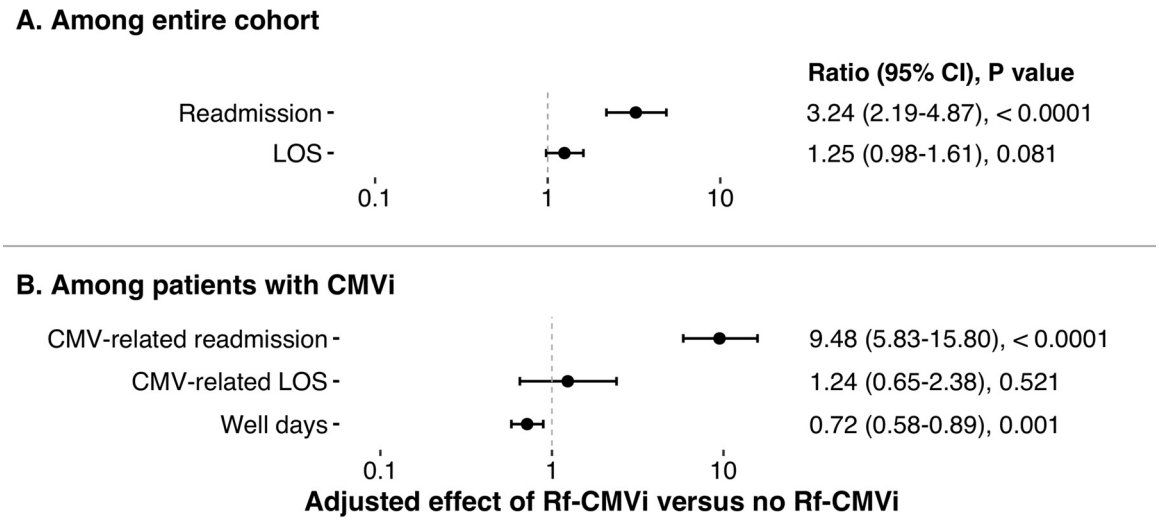

Figure 4. Adjusted effect of Rf-CMVi on readmissions and hospital LOS in the first year post-HCT (A) and in the entire cohort (B) among patients with CMVi. Points show aORs, and whiskers show 95% CIs. Multivariable logistic regression models were performed for all-cause and CMV-related readmissions. Multivariable generalized linear models with gamma distribution were used to determine LOS, CMV-related LOS, and well days (defined as days alive, out of hospital, and off CMV antivirals by 1-year post-HCT).

CMV-related readmissions was similar in the 2 groups (P= .521) (Figure 4B, Table S2).

We next compared the number of well days (defined as days alive, out of hospital and off CMV antivirals by 1 year post-HCT) in the 2 groups. The patients in the Rf-CMVi group had fewer well days compared with the no Rf-CMVi group (median, 244 days [IQR, 163 to 276 days] versus 320 days [IQR, 266 to 330 days]; P< .0001). After adjusting for covariates, Rf-CMVi was associated with a 28% decrease in well days (aAMR, .72; 95% CI, .58 to .89; P= .001) (Figure 4B, Table S2).

CMV Antiviral Utilization

The onset of CMV viremia post-HCT was earlier in the Rf-CMVi group compared with the no Rf-CMVi group (median, 22 days [IQR, 16 to 29 days] versus 26 days [IQR, 18 to 32 days]; P= .079), as was the start of PET (median, 32 days [IQR, 26 to 40 days] versus 37 days [IQR, 30 to 44 days]; P = .013) (Table 2).

By 1 year post-HCT, the median number of antiviral days was >2-fold higher in the Rf-CMVi group compared with the no Rf-CMVi group (median, 92 days [IQR, 58 to 111 days] versus 43 days [IQR, 32 to 65 days]; P< .0001) (Table 2). More patients in the Rf-CMVi group required 2 anti-CMV antivirals (65.2% versus 25.3%; P< .0001) (Table 2). Additional therapies for Rf-CMVi included CMV-specific T lymphocytes (CTLs) in 10 patients and investigational maribavir in 3 patients. Two patients with no Rf-CMVi also received CMV CTLs.

DISCUSSION

The management of Rf-CMVi after HCT is challenging owing to the paucity of effective treatments and the associated toxicities [4,10]. Although profound immunosuppression rather than pharmacologic failure may initially cause Rf-CMVi, the development of virologic resistance as a sequalae of Rf-CMVi may further compromise outcomes [7,9]. There is no standardized approach for the management of Rf-CMVi (in the absence of resistance), and variability across centers may reflect differences in patient populations and local practices. Quantitating the HRU associated with Rf-CMVi provides a benchmark for assessing the net value of novel therapies.

We analyzed a cohort of CMV R+ recipients from a tertiary care center managed exclusively with PET. Our main findings can be summarized as follows: (1) Rf-CMVi occurred in approximately one-third (31.7%) of patients treated with PET for CMVi ; (2) compared with no Rf-CMVi, patients with Rf-CMVi had more CMV EOD (10.1% versus 23.9%), CMV-related mortality (0% versus 9.5%), and all-cause mortality (22.0 versus 33.3%) at 1 year post-HCT; (3) in multivariable models, Rf-CMVi was an independent predictor for readmission, CMV-related readmission, and increased LOS. We next discuss the implications of our findings.

Table 2
Comparison of CMV Antiviral Use between the Rf-CMVi and No Rf-CMVi Groups in the First Year Post-HCT

CMV Antiviral Use	Rf-CMVi (N = 46)	No Rf-CMVi (N = 99)	*P* Value
Days to PET from HCT, median (IQR)	32 (26-40)	37 (30-44)	.013
Total antiviral days, median (IQR)	92 (58-111)	43 (32-65)	<.0001
Total foscarnet days, median (IQR)	36 (27-47)	25 (15-34)	.027
Type of CMV antiviral, n (%)			<.0001
(val)GCV only	13 (28.3)	60 (60.6)	
(val)GCV + foscarnet	30 (65.2)	25 (25.3)	
Foscarnet only	3 (6.5)	14 (14.1)	

Only treatment episodes of >48 hours (2 days) duration were counted.

The incidence of Rf -CMVi in our cohort is comparable to previous studies using similar definitions [6,7,9]. Sassine et al. [22] reported an incidence of 11% before letermovir prophylaxis, with a steep decrease to 2% after letermovir prophylaxis. The lower incidence could be explained in part by the use of consensus definitions for Rf-CMVi [5]. I. The maximum CMV VL and averaged area under the curve by day 1000 were higher in the Rf-CMVi group compared with the no Rf-CMVi group. Both parameters have been associated with increased mortality in the first year post-HCT [2,3]. In multivariable analyses, ex vivo T cell depletion and a haploidentical donor were associated with an increased risk for Rf-CMVi, whereas CMV donor seropositivity and an incremental increase in lymphocyte count at day 30 post-HCT were associated with decreased risk. These findings are in in agreement with reported risk factors for CMV infection in general [17,23]. African American CMV R+ recipients were more likely than white recipients to have CMVi (73.9% versus 45.2%); however, African American race was associated with decreased risk for Rf-CMVi in multivariable models. We previously identified African American race as a risk factor for CMV infection [17]. An association between African race and high-grade CMV viremia, but not with CMV infection, also has been reported [24]. At present, the basis for these findings is not clear; host- and transplantation-related confounding variables likely are contributing factors.

Notably, only 6 patients (13%) with Rf-CMVi had confirmed CMV genotypic resistance, underscoring the importance of immune reconstitution for virologic control. Studies focusing exclusively on resistant CMV likely underestimate the impact of CMV on HCT outcomes and HRU. DNA polymerase inhibitors have dose-dependent toxicities, and foscarnet and cidofovir have been associated with organ dysfunction after transplantation [4,10,17,25]. In addition, administration of foscarnet is resource-intensive, requiring prolonged infusion time, hydration and electrolyte replacement, and monitoring. In our cohort, twice as many patients in the Rf-CMVi group received foscarnet compared with the no Rf-CMVi group. Rf-CMVi was an independent predictor for CMV-related readmissions and increased hospital LOS. CMV-related readmissions are associated with increased cost [26]. Notably, Rf-CMVi was associated with 28% fewer well days after adjusting for covariates. Although outpatient foscarnet administration may alleviate readmissions, infusion time and monitoring requirements remain extensive.

Maribavir, an orally bioavailable CMV antiviral with a multimodal mechanism of action [27,28], was recently approved by the Food and Drug Administration for treating Rf-CMVi. In a randomized, open-label trial, maribavir was well-tolerated and associated with less myelosuppression and nephrotoxicity compared with ganciclovir and foscarnet, respectively [11]. The use of off-the-shelf CMV-specific CTLs is another approach in a late stage of development for treating CMV, with a potential added benefit of durable immune restoration [29,30]. CMV viremia post-HCT has been associated with greater expansion of CD8 T cells compared with no CMV viremia [31]. In contrast, persistent CMV viremia has been associated with lower CD4 and CD8 cell counts compared to nonpersistent viremia [3,6]. Future well-designed comparative studies of pharmacologic and cellular therapy modalities are needed to optimize CMV treatment.

The limitations of our study are inherent to its retrospective and observational design. Resistance testing, choice, and duration of antivirals were at the discretion of the treating

clinicians. Detailed histories of immunosuppressants were not captured; however, we did adjust for GVHD in our multivariable models. Readmissions and LOS reflect our institutional practices during the study period and may differ across geographic areas or centers. Acknowledging these limitations, our study provides real-world quantitative data on the impact of Rf-CMV in on the outcomes and HRU and underscores the need for improved treatment options.

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Authorship statement: E.K. designed the research, collected and analyzed data, and wrote the manuscript. P.D.Z. designed the research, collected data, and critically reviewed the manuscript. Y.S. analyzed and interpreted data and wrote the manuscript. J.F. performed data collection. R.T., C.C., and M.A.P. provided a critical review of the manuscript. A.S. and G.A.P. contributed to and supervised all aspects of the study. E.K. and P.D.Z. are co-first authors. A.S. and G.A.P. are co-senior authors.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.04.016.

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