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Impact of Preemptive Therapy for Cytomegalovirus on Toxicities after Allogeneic Hematopoietic Cell Transplantation in Clinical Practice: A Retrospective Single-Center Cohort Study

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A B S T R A C T

(Val)ganciclovir (vGCV) or foscarnet (FCN) as preemptive therapy (PET) for cytomegalovirus (CMV) after allogeneic hematopoietic cell transplantation (HCT) is associated with myelosuppression and nephrotoxicity, respectively. We analyzed a cohort of CMV-seropositive (R^+) HCT recipients managed preemptively at a single center. The objectives of our study were to (1) quantify the frequencies of neutropenia and acute kidney injury (AKI) through day +100 (D100) post-HCT and at PET discontinuation and (2) assess the impact of PET on neutropenia and AKI in multivariate models. This was a retrospective cohort study of adult CMV R^+ recipients who underwent allo-HCT at Memorial Sloan Kettering Cancer Center from March 18, 2013, through December 31, 2017, and were managed with PET. Patients were grouped by receipt of PET (PET and no PET). Neutropenia and AKI were defined by Common Terminology Criteria for Adverse Events version 4. Frequencies of toxicities by D100 were compared between relevant groups. The impact of PET on toxicities was examined in univariate and multivariate Poisson/negative binomial regression models. Of 368 CMV R^+ HCT recipients, 208 (56.5%) received PET. Neutropenia by D100 occurred in 41.8% and 28.6% patients in PET and no PET, respectively ($P = .0009$). PET increased the risk of neutropenia (adjusted relative risk = 1.81; 95% confidence interval [CI], 1.48 to 2.21; $P < .0001$) in multivariate analyses. AKI by D100 occurred in 12.0% and 7.8% patients in PET and no PET, respectively ($P = .19$). PET increased the risk of AKI by 2.75-fold (95% CI, 1.71 to 4.42; $P < .0001$). When PET recipients were grouped by first antiviral, neutropenia by D100 occurred in 34.8% and 48.9% of vGCV and FCN recipients, respectively, ($P = .08$), and AKI occurred in 13.0% and 34.0% of vGCV and FCN recipients, respectively ($P = .001$). At discontinuation of vGCV or FCN, neutropenia was present in 11.2% versus 2.1% patients, respectively ($P = .08$), and AKI was present in 1.9% of versus 12.8% patients respectively ($P = .005$). Preemptive therapy for CMV increased the risk of neutropenia and AKI in the first 100 days post-HCT by 1.8-fold and 2.8-fold, respectively. Our results underscore the need for safer antivirals for CMV management in HCT recipients.

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Cytomegalovirus (CMV) infection is the most common clinically significant viral infection following hematopoietic cell transplantation (HCT), occurring in 40% to 90% of CMV R^+ recipients [1-4]. Risk factors for CMV infection includ HLA-mismatched or CMV-seronegative donor, T cell depletion (TCD), and graft-versus-host disease (GVHD). CMV infection has been associated with bacterial and fungal infections, end-organ dysfunction, GVHD, and worse overall survival [2,5-7]. The preemptive therapy (PET) strategy entails routine monitoring for CMV replication in whole blood or plasma by sensitive quantitative PCR assays and initiation of CMV antiviral therapy when CMV viremia occurs. There are no validated viral load thresholds for initiation of PET. Universally acceptable thresholds are difficult to establish due to variability across assays and testing material (whole blood or plasma) [8]. PET is usually given until resolution of CMV infection; however, a longer duration may be given to prevent CMV recurrence in the absence of CMV immune reconstitution [6,9-13].

Ganciclovir and valganciclovir (vGCV) are effective as PET but are associated with exposure-dependent myelosuppression

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[14,15]. Absolute neutrophil count (ANC) $<1{,}000/mm^3$ and $<500/mm^3$ occurred in 30% to 58% and 11% to 33% patients, respectively, in clinical trials of ganciclovir prophylaxis in HCT recipients [6,16,17]. Ganciclovir-induced neutropenia was associated with a 4-fold increased risk of nonviral infections [16] and increased mortality [18]. Due to substantial myelosuppression and lack of survival benefit, vGCV prophylaxis has not been widely adopted in HCT recipients. Oral valacyclovir is less myelosuppressive, albeit less effective compared to ganciclovir [16,19-21]. In a retrospective study where ganciclovir was used for PET, 80 of 160 (50%) patients developed ganciclovir-related neutropenia, including 39 patients with grade 3 and 41 patients with grade 4 neutropenia [22].

Foscarnet (FCN) has been shown to be as effective as ganciclovir for PET [12]; however, it is nephrotoxic and requires intravenous administration, making it less desirable as a prophylactic agent. Deterioration in renal function was reported in 27% of HCT recipients treated with FCN [23]. In a different study, 50% of patients had a decline in serum creatinine (sCr) clearance [12]. Among solid organ or HCT recipients treated with FCN for resistant CMV, 51.2% had a >20% increase in sCr at discontinuation of FCN [24]. Higher rates of nephrotoxicity have been reported in the setting of concomitant nephrotoxic medications [25]. In addition, electrolyte abnormalities related to FCN require aggressive supplementation, which affect patients' quality of life and pose a burden on health care resources. Thus, the use of FCN for PET is limited to patients who have contraindications to vGCV.

The toxicities of PET in contemporary clinical practice have not been quantified in detail. In real life, the choice of antivirals for PET is based on baseline laboratory values and potential risk of toxicity, assessed by the clinicians. As opposed to clinical trials, clinical decisions in real life are dynamic and individualized. PET entails a strategy rather than a fixed dose and duration of a specific antiviral guided by prespecified endpoints. We analyzed a cohort of CMV-seropositive recipients who received their first HCT from March 2013 through 2017 at our institution and were treated preemptively for CMV. The purpose of our study was to estimate the impact of PET on neutropenia and acute kidney injury (AKI) in the first 100 days post-HCT. In addition, we report the frequency and patterns of PET utilization and compare the frequencies of toxicities at discontinuation of first PET between PET recipients who received vGCV or FCN.

METHODS

Study Population

Retrospective review was conducted in adult CMV R^+ recipients of first peripheral blood (PB) or bone marrow HCT at Memorial Sloan Kettering Cancer Center from March 18, 2013, through December 31, 2017. Patients who received cord blood allograft, participated in clinical trials of CMV antivirals, or received antivirals with anti-CMV activity for non-CMV indications were excluded from the analyses. Data were extracted from the electronic medical record and hospital databases. The study was reviewed by the Memorial Sloan Kettering Institutional Review Board and was granted a waiver of authorization (IRB #16-920).

Conditioning Regimens and Graft Manipulation

Conditioning regimens for acute leukemia or myelodysplastic syndrome, including myeloablative and reduced intensity, have been previously described [26,27]. Briefly, patients with acute leukemia in first complete remission and those with myelodysplastic syndrome received ex vivo TCD/CD34-selected HCT unless contraindicated or insurance refused coverage. TCD was performed by the CliniMACS $CD34^+$ reagent system (Miltenyi Biotec, Gladbach, Germany) [28]. Patients undergoing HCT for lymphoma generally received conventional HCT after reduced-intensity conditioning regimens with low-dose total body irradiation or busulfan and fludarabine [26]. Patients with multiple myeloma received ex vivo T cell depleted allografts as described [29].

GVHD Prophylaxis

Recipients of ex vivo TCD allografts did not receive additional pharmacologic GVHD prophylaxis. Recipients of conventional allografts received GVHD prophylaxis with tacrolimus (or sirolimus) + mycophenolate mofetil ± methotrexate [30] or tacrolimus (or sirolimus) + mycophenolate mofetil + posttransplant cyclophosphamide (post-CY) for haploidentical donor allografts [31].

CMV Management

Patients were managed per institutional standards of care. CMV R^+ recipients were routinely monitored for CMV at least weekly from D 14 through D100. CMV monitoring started prior to D14 for patients with a history of CMV infection prior to HCT or clinical concern for CMV infection or end-organ disease. Patients were categorized into 2 CMV risk groups: high risk (HR) included conventional HCT from haploidentical or mismatched donors or TCD HCT, regardless of donor type. Low risk (LR) comprised conventional matched related donor HCT. Thresholds for PET initiation were ≥2 consecutive viral loads >300 IU/mL for LR patients and ≥1 CMV viral loads >137 IU/mL or 2 consecutive detectable (at any level) viral loads for HR patients. For patients with adequate counts (ANC $>2{,}000/mm^3$, platelets count $>100{,}000/mm^3$), induction dose vGCV (valganciclovir 900 mg per os [PO] q12h or ganciclovir 5 mg/kg i.v. q12h) was the preferred PET. When vGCV was contraindicated, foscarnet (90 mg/kg i.v. q12h) induction was initiated.

After 1 to 2 weeks of induction and documented viral suppression, maintenance doses of the same agent (valganciclovir 900 mg PO q24h, ganciclovir 5 mg/kg i.v. q24h, or foscarnet 90 mg/kg i.v. q24h) were used based on patient risk. In rare instances of early, low-level CMV viremia, maintenance doses were used with close monitoring of CMV viral load. Dosing of valganciclovir, ganciclovir, and foscarnet was adjusted for patients' renal function according to package inserts.

Supportive Care

Bacterial and fungal prophylaxis have been previously described [32,33]. The preferred prophylaxis against *Pneumocystis jirovecii* was trimethoprim/sulfamethoxazole starting on D21. Patients unable to tolerate or allergic to trimethoprim/sulfamethoxazole received inhaled pentamidine or oral atovaquone. Acyclovir (400 mg PO q12h or 250 mg/m^2 i.v. q8h) was administered for prevention of herpes simplex virus and varicella zoster virus starting from admission for HCT [20]. Treatment with growth factors (granulocyte-colony stimulating factor [G-CSF]) was administered as part of transplant protocol routinely starting D7 once daily until neutrophil engraftment. In case of neutropenia occurring after engraftment, G-CSF treatment was at the discretion of the treating physician.

Laboratory Methods

CMV IgG levels were determined using an automated semiquantitative ELISA (VIDAS; Biomerieux, Inc., Durham, NC). Routine monitoring for CMV was performed by the CobasAmpliprep/CobasTaqman plasma quantitative PCR assay (Roche Diagnostics, Basel, Switzerland). The linear range of quantification was >137 to 9.1×10^6 IU/mL [34].

Definitions

CMV infection was defined as ≥1 detectable CMV viral load. CMV end-organ disease (EOD) was scored as previously described [35].

Patients were categorized into 2 mutually exclusive groups based on receipt of PET by D100. PET recipients were further categorized into 2 treatment categories (vGCV or FCN), based on the first PET antiviral they received.

A course of PET was defined as the administration of a single antiviral class (vGCV or FCN) with interruption ≤3 days. Changes in formulation (ie, ganciclovir to valganciclovir or vice versa) and/or dose modification (induction versus maintenance) or dose adjustments (for renal function or toxicity) were at the discretion of the clinician within the same PET course. Switching to a different antiviral class at any time or reinitiation of the same antiviral class after >3 days of interruption was considered a new course. Neutrophil engraftment was defined as ANC $\geq 500/mm^3$ for 2 consecutive measurements. GVHD diagnosis and grading were based on consensus guidelines [36].

Toxicity Definitions and Grading

Neutropenia and AKI were graded by the Common Terminology Criteria for Adverse Events version 4 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Patients with ≥1 value of ANC $<1{,}000/mm^3$ or sCr >2.0 × baseline sCr from D21 to D100 were considered to have neutropenia or AKI, respectively. To compare toxicities between PET and no PET groups, we excluded patients who died before D21. For the remaining patients, toxicity was assessed weekly from D21 through D100 or death. A toxicity episode was defined as ≥1 value of ANC $<1{,}000/mm^3$ or sCr >2.0 × baseline sCr (sCr on D21) for each week interval. The maximum number of episodes for each toxicity was 11 per patient.

Toxicities at discontinuation of first PET were defined as ANC $<1{,}000/mm^3$ or sCr >2.0 × baseline sCr (sCr at start of PET) for neutropenia and AKI, respectively. The absolute change in laboratory values was calculated as the difference between values at the end and start of first PET.

Table 1
Baseline Characteristics of the Cohort (N = 368)

Characteristic	N	(%)
Age, years, median (IQR)	59	(48-66)
Age groups, years		
18-39	52	(14.1)
40-64	201	(54.6)
≥65	115	(31.3)
Sex		
Female	155	(42.1)
Male	213	(57.9)
Race		
White	265	(72.0)
African American	31	(8.4)
Asian	26	(7.1)
Hispanic/Latino	24	(6.5)
Other/unknown	22	(6.0)
Underlying disease		
AML/ALL/CML/MDS	231	(62.8)
Lymphoma	51	(13.9)
Multiple myeloma	39	(10.6)
Other*	47	(12.8)
Donor type		
Matched related	117	(31.8)
Mismatched related	22	(6.0)
Matched unrelated	192	(52.2)
Mismatched unrelated	37	(10.1)
Donor CMV serostatus		
Negative	145	(39.4)
Positive	223	(60.6)
Stem cell source		
Bone marrow	49	(13.3)
Peripheral blood	319	(86.7)
Conditioning regimen intensity		
Ablative all chemotherapy	175	(47.6)
Ablative containing TBI	51	(13.9)
Reduced	111	(30.2)
Nonablative	31	(8.4)
GVHD prophylaxis		
Tacrolimus/sirolimus + MMF (±MTX)	178	(48.4)
Tacrolimus/sirolimus + MMF + post-CY	34	(9.2)
Ex vivo CD34-selected TCD	156	(42.4)
GVHD grade		
0-1	237	(64.4)
2-4	127	(34.5)
NA	4	(1.1)
CD34 dose (10^6/kg)		
≤6.4	179	(48.6)
>6.4	189	(51.4)
Maximum viral load (IU/mL)		
≤300	169	(45.9)
>300	193	(52.4)
NA	6	(1.6)
ATG		
No	183	(49.7)
Yes	185	(50.3)
CMV risk†		
Low	176	(47.8)
High	192	(52.2)

Values are presented as number (%) unless otherwise indicated.
AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; TBI, total body irradiation; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; ATG, anti-thymocyte globulin.

* Myeloproliferative disorder (13), chronic leukemia (12), acute leukemia mixed phenotype (9), aplastic anemia (9), immune deficiency (1), paroxysmal nocturnal hematuria (1), and other hematologic malignancy (2).

† Low CMV risk included matched related allografts; high CMV risk included conventional haploidentical or mismatched allografts or T cell depleted allografts.

Statistical Methods

The sample size was determined by the size of the cohort. Descriptive statistics were used to summarize demographic and clinical characteristics, CMV infection, CMV EOD, PET exposure, G-CSF use, and toxicities attributed to PET. Categorical variables were compared using the chi-squared tests, and continuous variables were compared using Mann-Whitney rank-sum tests between relevant groups.

The incidences of CMV infection and PET use were estimated using the cumulative incidence analysis. Univariate and multivariate analyses were performed to identify risk factors for PET use and risk factors for neutropenia and AKI in the first 100 days for the entire cohort and risk factors for toxicities among PET recipients. To identify risk factors for PET use, we used logistic regression.

Due to overdispersion, negative binomial regression was used to assess the impact of PET on neutropenia and AKI by D100. PET was included as a variable in the models. Additional variables included patient characteristics (age, sex, race, underlying disease), transplant characteristics (donor type, donor CMV status, stem cell source, conditioning regimen intensity, GVHD prophylaxis, CD34 cell dose), acute GVHD by D100, and virologic characteristics (maximum CMV viral load by D100). As the variable of interest, PET use was kept in the multivariable models regardless of significance. To adjust for different follow-up time, the period from the first laboratory test to the last test within D21 to D100 or death per recipient was included as an offset in the negative binomial regression.

To define risk factors for toxicities among PET recipients, we included all the above variable in the multivariable models and also included first drug type, time to first PET, and numeric laboratory values at the start of first PET, including WBC (K/mm^3), ANC (K/mm^3), platelets (K/mm^3), and sCr (mg/dL).

For all performed multivariate analyses, variables with $P < .3$ in the univariate models entered the multivariate models. Forward stepwise selection was used to keep variables with $P < .1$ in the final models. Statistical analyses were performed with R, version 3.5.1 (R foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

During the study period, 394 CMV R^+ patients received their first PB or marrow HCT. Twenty-six patients were excluded from the analyses because they received investigational antivirals with anti-CMV activity (brincidofovir or maribavir) or received foscarnet or cidofovir for treatment of human herpes virus 6 (HHV-6) or adenovirus, respectively. The study cohort consists of the remaining 368 CMV R^+ HCT recipients.

Table 1 shows the baseline characteristics of the cohort. The median age was 59 years, and the indication for HCT was leukemia or myelodysplastic syndrome in 62.8% of patients; 86.7% patients received peripheral blood HCT and 61.5% patients received a myeloablative conditioning regimen. In total, 156 (42.4%) patients received ex vivo TCD/CD34-selected grafts, and 192 (52.2%) patients were high risk for CMV. Supplementary Table S1 shows the baseline characteristics for patients by CMV risk category.

Incidence of CMV Infection and PET Utilization

Of 368 patients in our cohort, 273 (76.4%) developed CMV infection by D100. Among patients with CMV infection, 208 (76.2%) received PET (Figure 1). The remaining 65 patients did not receive PET because they did not meet viral load thresholds for PET initiation or died shortly after detection of CMV

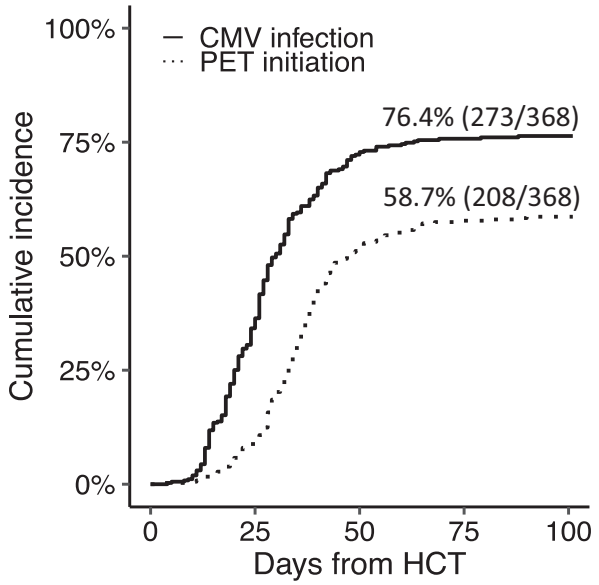

Figure 1. Time to CMV infection and PET initiation. Cumulative incidence of CMV infection and PET initiation by D100 for entire cohort (N = 368). CMV infection occurred at a median of 26 days (IQR, 18 to 33) after HCT. PET initiation occurred at a median of 35 days (IQR, 28 to 41) after HCT.

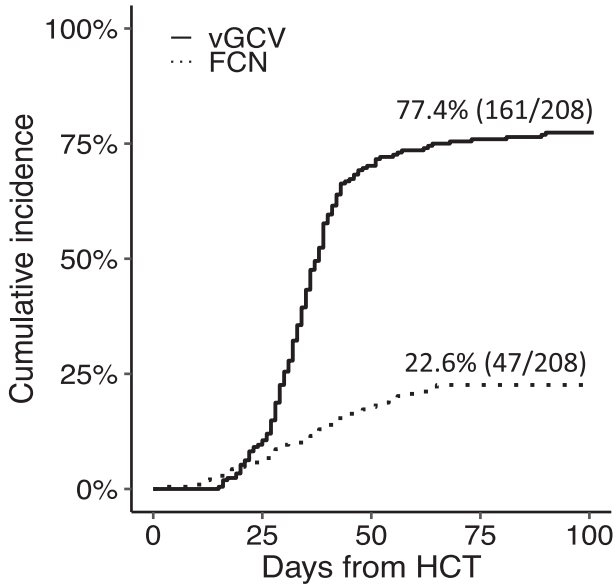

Figure 2. Time to first course of vGCV and FCN among PET recipients. Cumulative incidence of vGCV and FCN initiation as first PET by D100 among PET recipients (n = 208). vGCV was initiated at a median of 34 days (IQR, 29 to 40) after HCT. FCN was initiated at a median of 36 days (IQR, 24 to 48) after HCT.

viremia. When we stratified patients by CMV risk, the incidences of CMV infection and PET were 67.5% and 34.9%, respectively, for LR and 84.3% and 80.0%, respectively, for HR patients. HR patients started PET earlier post-HCT compared with LR patients (median, 32 days [interquartile range (IQR), 27 to 38] versus 41 [36 to 51], respectively, $P < .0001$) (Supplementary Figure S1).

CMV resistance by D100: Seven patients had mutations conferring CMV resistance. Five patients had UL97 mutations (conferring ganciclovir resistance), and 2 patients had UL54 mutations conferring resistance to FCN (with coresistance to cidofovir in 1 patient).

CMV EOD by D100: Twelve patients developed CMV EOD (4.4% of patients with CMV infection). The median time from HCT to EOD was 45 days. EOD involved the gastrointestinal tract in 10 patients and lungs in 2 patients. Among patients with EOD, the maximum CMV viral load was a median of 5,232 IU/mL compared with a median of 1,177 IU/mL for patients without EOD ($P = .08$). None of the patients with EOD were found to have confirmed resistance to any of the PET agents.

PET Courses

Of the 208 PET recipients, 161 (77.4%) started on vGCV and 47 (22.6%) on FCN. Figure 2 shows the cumulative incidence of vGCV or FCN initiation among PET recipients. Supplementary Figure S2 shows the cumulative incidence of vGCV or FCN initiation by CMV risk.

We next examined the sequence of antivirals for patients who received multiple PET courses and the average time to initiation and average duration for each PET course. In total, 144 patients (69.2%) received only 1 course of PET (vGCV in 120 and FCN in 24), 46 (22.1%) patients received 2 courses, and 18 (8.7%) received more than 2 PET courses. Of patients receiving vGCV as first PET, 34 (21.1%) were later switched to FCN, while of patients receiving FCN as first PET, 21 (44.7%) were later treated with vGCV (Figure 3A,B).

For the first PET course, 179 patients received induction and 28 received maintenance. Of the 179 patients who started on induction, 108 also received maintenance. Of the 28 patients who started on maintenance, 12 were switched to the induction dose due to rising CMV viremia. Doses of first PET were renally adjusted in 15 patients (5 receiving FCN and 10 receiving vGCV).

Risk Factors for PET Initiation

We examined risk factors for PET use in our cohort in univariate and multivariate models. In univariate analysis, race, underlying disease, donor HLA match, conditioning regimen, and TCD/CD34-selected HCT were risk factors for PET. In multivariate analysis, only African American, Asian, or Hispanic/Latino race; HLA-mismatched donor; and TCD/CD34-selected HCT remained significant (Table 2).

Impact of PET on Toxicities by D100

To assess the impact of PET on toxicities, PET was entered as a variable in multivariable models. To exclude episodes of AKI and neutropenia associated with conditioning and pre-engraftment complications (such as sepsis), we assessed toxicities weekly starting from D21 (week 4) through D100 or death, whichever came first. After excluding 6 patients who died before D21, 362 patients were included in the final model, including 208 in the PET group and 154 in the no PET group.

Neutropenia

Eighty-seven (41.8%) patients in the PET group and 44 (28.6%) patients in the no PET groups developed neutropenia by D100 ($P = .0009$) (Table 3). G-CSF utilization was higher in the PET group compared to the no PET group, with 154 patients (74%) of PET group receiving G-CSF from D7 postengraftment to D100 post-HCT, compared to 82 patients (51.3%) in the no PET group ($P = .04$). The median number of G-CSF orders was 5 for the PET group and 3 for the no PET group ($P = .01$) (Supplementary Table S2).

Next, we evaluated the impact of PET on the number of neutropenia episodes in univariate and multivariate models. PET was entered as a categorical variable in the model. In

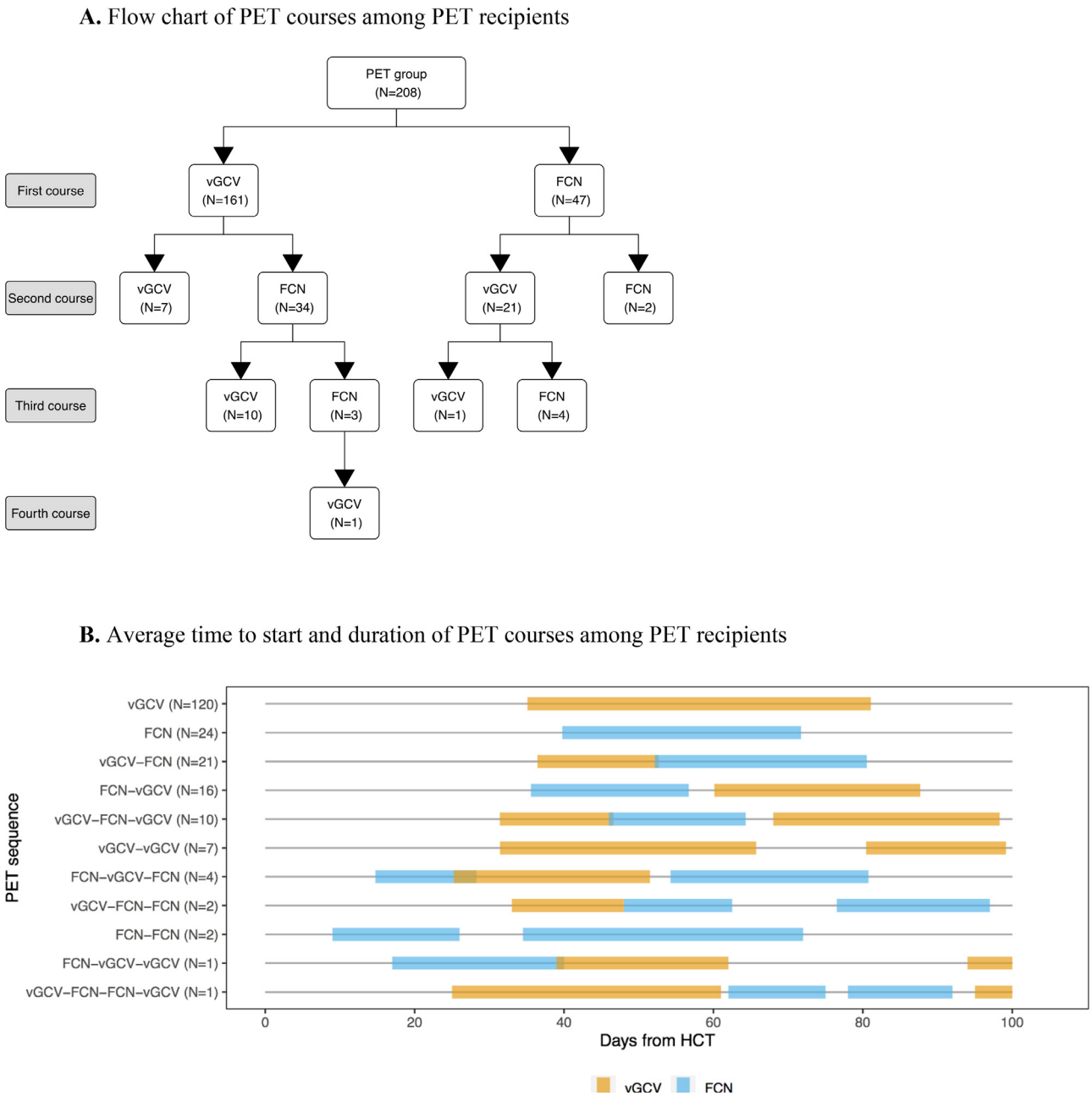

Figure 3. (A) Flowchart of PET courses among PET recipients by type of antiviral. Overall, 144 patients received only 1 PET course, 46 received 2 courses, and 18 received >2 courses. (B) Average time to start and duration of vGCV (marked orange) and FCN (marked blue) courses. Each line represents a unique PET course sequence.

multivariate analyses, PET use was associated with increased neutropenia (adjusted relative risk [RR] = 1.81; 95% confidence interval [CI], 1.48 to 2.21; $P < .0001$) (Figure 4A). Additional risk factors for neutropenia were age group 40 to 64 years (RR = 1.4; 95% CI, 1.05 to 1.88; $P = .02$), lymphoma (RR = 1.62; 95% CI, 1.21 to 2.17; $P = .001$) and "other" as underlying diseases (RR = 1.92; 95% CI, 1.47 to 2.51; $P < .0001$) , matched unrelated donor allograft (RR = 1.51; 95% CI, 1.23 to 1.86; $P < .0001$), CMV seropositive donor (RR = 1.39; 95% CI, 1.15 to 1.66; $P = .0005$), nonablative conditioning (RR = 1.79; 95% CI, 1.27 to 2.53; $P = .0009$), and GVHD grade ≥2 (RR = 1.24; 95% CI, 1.02 to 1.5; $P = .03$). In contrast, PB (versus marrow) allograft was associated with decreased neutropenia risk (RR = 0.73; 95% CI, 0.55 to 0.96; $P = .03$). Detailed results of univariate and multivariate analyses are shown in Supplementary Table S3A.

Acute Kidney Injury

Of the 362 patients, 37 (10.2%) had ≥1 episode of AKI, including 25 (12.0%) in the PET group and 12 (7.8%) in the no PET group ($P = .19$) (Table 3).

Next, we evaluated the impact of PET on the number of AKI episodes in univariate and multivariate analyses. In multivariate analyses, PET increased the risk for AKI episodes by 2.75-fold (95% CI, 1.71 to 4.42; $P < .0001$) (Figure 4B). Additional risk factors for AKI were age between 40 and 64 years (RR = 2.06; 95% CI, 1.06 to 4.00; $P = .03$) and post-CY GVHD prophylaxis (RR = 3.57; 95% CI, 1.88 to 6.76; $P < .0001$). In contrast, male sex (RR = 0.42; 95% CI, 0.28 to 0.63; $P < .0001$) and TCD allograft (RR = 0.42; 95% CI, 0.26 to 0.69; $P = .0007$) were associated with decreased risk prophylaxis. Detailed results of univariate and multivariate analyses are shown in Supplementary Table S3B.

Table 2
Univariate and Multivariate Risk Factors for PET (N = 368)

Factor	Univariate			Multivariate		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Race						
White	Reference			Reference		
African American	3.4	(1.4-8.1)	.01	3.1	(1.1-8.2)	.03
Asian	4.1	(1.5-11.3)	.01	4.6	(1.5-13.8)	.01
Hispanic/Latino	3.0	(1.1-7.7)	.03	2.7	(1.0-7.9)	.06
Other/unknown	1.0	(0.4-2.4)	.97	0.9	(0.3-2.5)	.86
Underlying disease						
AML/ALL/CML/MDS	Reference					
Lymphoma	0.6	(0.3-1.1)	.11			
Multiple myeloma	7.0	(2.4-20.3)	.0004			
Other	0.7	(0.4-1.3)	.27			
Donor type						
Matched related	Reference			Reference		
Mismatched related	5.8	(1.6-20.7)	.01	13.3	(3.5-50.7)	.0001
Matched unrelated	1.0	(0.6-1.6)	.96	1.3	(0.7-2.2)	.38
Mismatched unrelated	2.9	(1.2-6.6)	.01	2.9	(1.1-7.4)	.03
Conditioning regimen intensity						
Myeloablative	Reference					
Reduced	0.3	(0.2-0.4)	<.0001			
Nonmyeloablative	0.5	(0.2-1.0)	.04			
Ex vivo CD34 selected T cell depletion						
No	Reference			Reference		
Yes	5.6	(3.5-9.0)	<.0001	6.9	(4.2-11.4)	<.0001

OR indicates odds ratio.

Toxicities among PET Recipients

Neutropenia: We compared the frequencies of grade 3 (ANC $<1{,}000/mm^3$) and grade 4 (ANC $<500/mm^3$) neutropenia from the start of PET through D100 between patients who received vGCV or FCN as first PET. Frequencies of grade 3 and 4 neutropenia were similar between vGCV and FCN recipients (Table 4).

AKI: We compared the frequencies of grade 2 (sCr) $>2.0\times$ and grade 3 (sCr $>3.0\times$ baseline sCr) AKI from the start of PET through D100 between patients who received vGCV or FCN as first PET. AKI occurred more frequently among FCN recipients. Twelve (7.5%) vGCV recipients had grade 2 AKI compared with 11 (23.4%) FCN recipients ($P = .002$) (Table 4). A similar number of patients in both groups had grade 3 AKI. Among patients with grade 3 AKI, 2 patients required renal replacement therapy (grade 4 AKI).

Toxicities at Discontinuation of First PET

To provide a more direct measure of toxicities attributed to PET, we evaluated toxicities at discontinuation of first PET. We compared the proportion of patients meeting criteria for neutropenia and/or AKI at first PET discontinuation. We also report the absolute change in ANC and sCr value at the discontinuation of PET from start of PET.

At discontinuation of first PET, neutropenia occurred in 11.2% of patients who received vGCV compared with 2.1% of those who received FCN ($P = .08$) (Figure 5A). Compared to ANC at PET initiation, ANC decreased with a median of −0.7 (IQR, −2.6 to 0.3) K/mm^3 at discontinuation of vGCV as first PET but increased with a median of 1.3 (IQR, 0.1 to 3.7) K/mm^3 at discontinuation of FCN as first PET ($P < .0001$) (Figure 5B).

Table 3
Frequency of Neutropenia and AKI by D100 among All Patients Alive by D21 (N = 362)

Neutropenia	Overall (N = 362)	PET (n = 208)	No PET (n = 154)	*P* Value
Neutropenia*				
Number (%) of patients	131 (36.2)	87 (41.8)	44 (28.6)	.0009
Number of episodes	258	170	88	
Mean (SD)	0.7 (1.2)	0.8 (1.2)	0.6 (1.2)	.06
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	.008
AKI†				
Number (%) of patients	37 (10.2)	25 (12.0)	12 (7.8)	.19
Number of episodes	89	67	22	
Mean (SD)	0.2 (0.9)	0.3 (1.1)	0.1 (0.5)	.04
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	.17

* Neutropenia episode was defined as ≥1 value of ANC $<1{,}000/mm^3$ assessed for each week interval from D21 through D100 or death. Recipients with at least 1 episode during the follow-up period were defined as neutropenia patients.

† AKI episode was defined as the maximum value of sCr $>2.0\times$ baseline sCr (sCr on D21) assessed for each week interval from D21 through D100 or death. Recipients with at least 1 episode during follow-up period were defined as AKI patients.

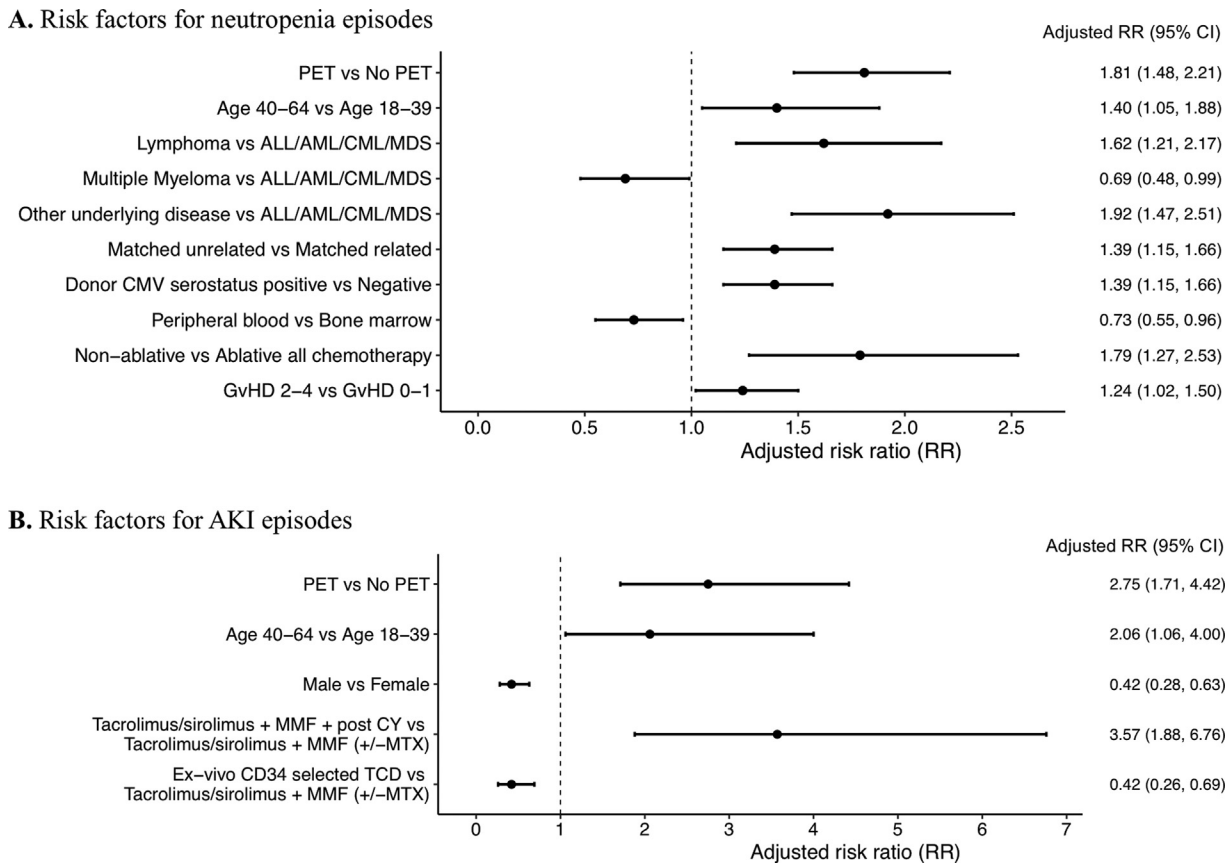

Figure 4. Forest plot of risk factors for neutropenia (A) and AKI (B) episodes. Adjusted RR and 95% CI from multivariate negative binomial regression models evaluating risk factors for neutropenia (A) and AKI (B) episodes among entire cohort (N = 357). PET was entered to the model as a categorical variable. Six patients who died before D21 post-HCT and 5 patients who had no maximum viral load values were excluded from the analyses.

AKI was more common at discontinuation of FCN compared to vGCV. AKI was present in 1.9% and 12.8% of patients at discontinuation of vGCV and FCN, respectively (P = .005) (Figure 6A). sCr at discontinuation of vGCV was same as baseline (sCr change of 0; IQR, −0.1 to 0.1 mg/dL). In contrast, compared to baseline, the change in sCr at discontinuation of FCN was a median of 0.1 (IQR, 0 to 0.4) mg/dL (P < .0001) (Figure 6B).

Table 4
Frequency of Neutropenia and AKI by D100 among PET Recipients

Characteristic	vGCV* (N = 161)	FCN* (N = 47)	*P* Value
	No. (%)	No. (%)	
Neutropenia			
Grade†			
3	38 (23.6)	14 (29.8)	.39
4	18 (11.2)	9 (19.1)	.15
3 + 4	56 (34.8)	23 (48.9)	.08
AKI			
Grade‡			
2	12 (7.5)	11 (23.4)	.002
3	9 (5.6)	5 (10.6)	.32
2 + 3	21 (13.0)	16 (34.0)	.001

* Patients were grouped according to antiviral used as first PET.
† Occurrence of ≥1 value below threshold as defined by Common Terminology Criteria for Adverse Events version 4.0 from start of PET through D100 or death (whichever occurred first). Grade 3 defined as ANC <1,000 and ≥500/mm^3 and grade 4 as ANC <500/mm^3.
‡ Occurrence of ≥1 value below threshold as defined by Common Terminology Criteria for Adverse Events version 4.0 from start of PET through D100 or death (whichever occurred first). Grade 2 AKI was defined as sCr >2.0 and ≤3.0 × baseline sCr, and grade 3 was defined as >3.0 × baseline sCr. Baseline sCr was defined as sCr at start of first PET.

Multivariate Risk Factors for Toxicities in the PET Group

We conducted multivariate analyses to identify predictors for neutropenia or AKI by D100 among the 208 PET recipients. After adjusting for other variables, factors associated with more neutropenia episodes were FCN as first PET (RR = 1.45; 95% CI, 1.10 to 1.91; P = .01), diagnosis of lymphoma (RR = 1.64; 95% CI, 1.21 to 2.23; P = .002), CMV seropositive donor (RR = 1.32; 95% CI, 1.07 to 1.64; P = .01), maximum CMV viral load >300 IU/mL (RR = 1.56; 95% CI, 1.10 to 2.2; P = .01), and lower platelet counts at PET start (RR = 0.98, 95% CI, 0.95 to 0.99; P = .02).

Factors associated with more AKI episodes were FCN as first drug (RR = 5.49; 95% CI, 3.03 to 9.9; P < .0001), age group 40 to 64 years (RR = 5.04; 95% CI, 2.01 to 12.65; P = .0006), reduced (RR = 3.27; 95% CI, 1.37 to 7.82; P = .01) or nonmyeloablative conditioning regimen (RR = 6.08; 95% CI, 2.17 to 17.04; P = .0006), GVHD prophylaxis with post-CY (RR = 10.38; 95% CI, 4.39 to 24.51; P < .0001), and CD34 dose >6.4 × 10^6/kg (RR = 3.79; 95% CI, 2.16 to 6.63; P < .0001).

DISCUSSION

Rates of cytopenia and nephrotoxicity have been quantified in clinical trials of vGCV and FCN [12,13,16,18,21,23,37]. In clinical practice, multiple factors may influence the types and frequencies of toxicities. Treatment decisions and modifications are dynamic and reflect evolving clinical events. In the

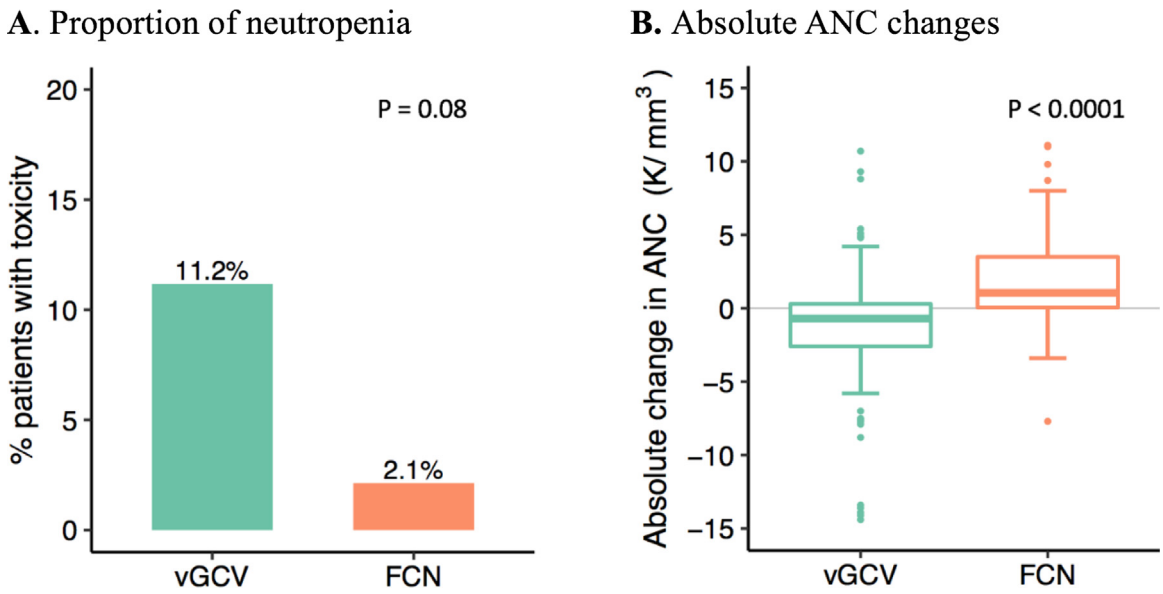

Figure 5. Proportion of neutropenia (A) and absolute ANC changes (B) at discontinuation of first PET. (A) Proportion of patients with neutropenia at end of vGCV (n = 161) and FCN (n = 47) as first PET. (B) Absolute change in ANC (K/mm^3) from start of first PET to discontinuation of first PET for vGCV and FCN.

end, treatment is tailored to the individual patient. We aimed to characterize toxicities associated with PET in the first 100 days post-HCT in a cohort treated preemptively in a single institution. Approximately half of our patients were considered "high risk" for CMV and 42.5% received ex vivo TCD HCT.

We show variability with regard to first PET selection, sequence, and duration of antivirals, highlighting the differences between clinical trials and the "real world." In agreement with published literature, multivariate risk factors for PET were allograft from mismatched donor, T cell depletion, and diagnosis of multiple myeloma [38-40]. In addition, we show that nonwhite race was an independent risk factor for PET.

Our primary objective was to evaluate the impact of PET on neutropenia and AKI by D100. To exclude toxicities associated with conditioning or early complications, we excluded patients who died before D21 and assessed toxicities from D21. By D100, more PET recipients had ≥1 episode of neutropenia compared to no PET (41.8% versus 28%; *P* = .0009). Similar rates of neutropenia (40% to 60%) have been reported in clinical trials of ganciclovir in HCT patients [6,16,17]. When we compared utilization of G-CSF between PET and no PET recipients, a greater proportion of PET recipients received G-CSF (74% versus 51.3%) for a greater number of G-CSF doses (median 5 versus 3) compared to no PET recipients. In multivariate models, PET increased the risk of neutropenia 1.8-fold after adjusting for transplant characteristics and duration of follow-up. While our study was limited to the first 100 days, neutropenia has been reported as a negative predictor of overall survival and nonrelapse mortality by 1 year [18].

We next examined the impact of PET on AKI. By D100, the proportion of patients with ≥1 episode of AKI was similar between PET and no PET group (12.7% and 7.8%; *P* = .19). The

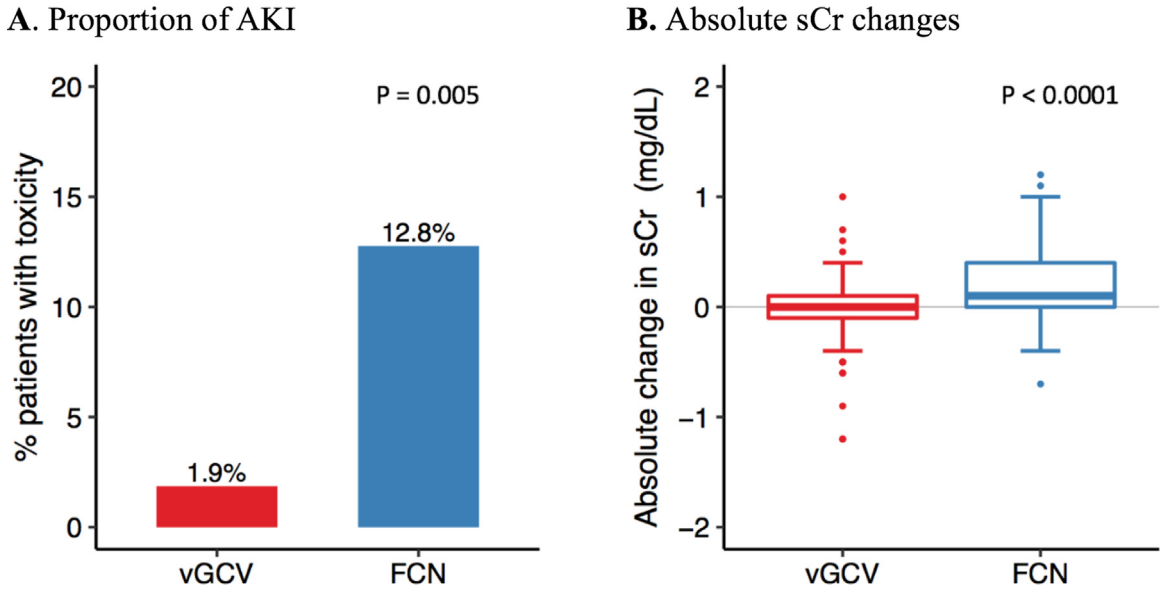

Figure 6. Proportion of AKI (A) and absolute sCr changes (B) at discontinuation of first PET. (A) Proportion of patients with AKI at end of vGCV (n = 161) and FCN (n = 47) as first PET. (B) Absolute change in sCr (mg/dL) from start of first PET to discontinuation of first PET for vGCV and FCN.

number of AKI episodes, however, was higher among PET recipients. In multivariate models, PET recipients had a 2.8-fold increased risk for AKI compared to no PET patients. Use of post-transplant cyclophosphamide for GVHD prophylaxis was associated with a 3.75-fold increased risk ($P < .0001$) while T cell depletion was associated with decreased risk (RR = 0.42; $P = .0007$) compared to calcineurin-based regimens. We have previously shown that T cell depletion was associated with less chronic kidney disease at 2 years post-HCT compared to calcineurin-based GVHD prophylaxis [41].

Next, we compared the frequencies of toxicities by D100 between patients who received vGCV or FCN as first PET course and examined the association of each antiviral with toxicities. The frequency of neutropenia was similar between patients who received vGCV or FCN. Surprisingly, in multivariate analysis, FCN (as opposed to vGCV) as first PET was associated with neutropenia. This finding could be partially explained by preferential use of FCN in patients with cytopenias. To get a more direct assessment of treatment-emergent neutropenia, we examined ANC counts at discontinuation of first PET. More vGCV recipients (11.2%) versus FCN recipients (2.1%) had ANC $<1{,}000/mm^3$ at first PET discontinuation. In a recent randomized trial, 18% of HCT recipients treated with valganciclovir had ANC $<1{,}000/mm^3$ compared to 5% of patients treated with maribavir for CMV [42]. Ganciclovir induces neutropenia by dose-dependent inhibition of DNA-polymerase in hematopoietic progenitor cells [43]. Ganciclovir is mainly eliminated through the kidney by glomerular and tubular secretion with a large fraction of unchanged ganciclovir found in urine [44]. Thus, differences in the metabolism of vGCV by sex and race [45] may result in different GCV exposures and could partially explain differential risk for neutropenia in certain groups.

Nephrotoxicity is a well-recognized side effect of FCN and may occur more frequently in the setting of concomitant nephrotoxic medications or pre-existing renal impairment [23-25]. In our cohort, FCN was used as first PET in 22% of patients. The frequency of AKI was approximately 3 times higher among FCN versus vGCV recipients (34% versus 13%, respectively, $P = .001$). In multivariate analysis, FCN as first PET was associated with a 5.5-fold increased risk for AKI compared to vGCV after adjusting for other factors associated with renal toxicity.

In summary, we show that PET recipients had a 1.8- and 2.8-fold increased risk for neutropenia and AKI, respectively, by D100. The direct impact of toxicities on health care resource utilization and cost was beyond the scope of our study and would likely vary across centers and geographic regions. In addition, neutropenia and AKI may influence selection of immunosuppressants for GVHD or anti-infective prophylaxis agents (eg, trimethoprim/sulfamethoxazole for *P. jirovecii*), which may affect HCT outcomes beyond the first 100 days post-HCT.

Implementation of letermovir for CMV prevention was associated with a 90% decrease in PET utilization by D100 [46]. The impact of letermovir on rates of neutropenia and AKI needs to be factored in cost-benefit analyses. Maribavir, currently developed for CMV treatment, has not been associated with neutropenia and nephrotoxicity to date [42,47], making maribavir a safer alternative to currently available antivirals for treatment of CMV [42]. Nonpharmacologic approaches such adoptive transfer of CMV-specific T cells or vaccination currently under investigation have not been associated with toxicities and have the potential of inducting long-term immunity against CMV [1].

Our study has several limitations inherent to its observational, retrospective design. Practice and patient differences among and within centers may affect rates and outcomes of observed toxicities. The direct impact of CMV infection on neutropenia or AKI could not have been evaluated in our study [48].

Acknowledging these limitations, our study provides a real-world quantification of clinically relevant toxicities associated with preemptive therapy for CMV after HCT. Our findings underscore the challenges of PET administration and support the need for safer alternative strategies for prevention or treatment of CMV post-HCT.

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Conflict of interest statement: GAP is an investigator for Merck and Shire and has received grant support, and consulting and other fees from Merck & Co. SG serves as a member of Advisory Board for AMGEN, ACTINUUM, CELGENE, Johnson & Johnson, JAZZ Pharmaceutical, TAKEDA, NOVARTIS, KITE, and SPECTRUM Pharma. He has received research funding from AMGEN, ACTINUUM, CELGENE, Johnson & Johnson, MILTENYI, and TAKEDA. MAP reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.03.019.

REFERENCES

1. Sellar RS, Peggs KS. Therapeutic strategies for the prevention and treatment of cytomegalovirus infection. *Expert Opin Biol Ther*. 2012;12(9):1161–1172.
2. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol*. 2016;3(3):e119–e127.
3. Huang YT, Neofytos D, Foldi J, et al. Cytomegalovirus infection after CD34(+)-selected hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(8):1480–1486.
4. Milano F, Pergam SA, Xie H, et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. *Blood*. 2011;118(20):5689–5696.
5. Boeckh M. Complications, diagnosis, management, and prevention of CMV infections: current and future. *Hematol Am Soc Hematol Educ Program*. 2011;2011:305–309.
6. Broers AE, van Der Holt R, van Esser JW, et al. Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. *Blood*. 2000;95(7):2240–2245.
7. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. *Blood*. 2016;127(20):2427–2438.
8. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood*. 2009;113(23):5711–5719.
9. Barkam C, Kamal H, Dammann E, et al. Improving safety of preemptive therapy with oral valganciclovir for cytomegalovirus infection after

allogeneic hematopoietic stem cell transplantation. *Bone Marrow Res*. 2012;2012: 874601.
10. de la Camara R. CMV in hematopoietic stem cell transplantation. *Mediterr J Hematol Infect Dis*. 2016;8:(1) e2016031.
11. Ljungman P, de la Camara R, Cordonnier C, et al. Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. *Bone Marrow Transplant*. 2008;42(4):227–240.
12. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood*. 2002;99(4):1159–1164.
13. Takenaka K, Eto T, Nagafuji K, et al. Oral valganciclovir as preemptive therapy is effective for cytomegalovirus infection in allogeneic hematopoietic stem cell transplant recipients. *Int J Hematol*. 2009;89(2):231–237.
14. Takahata M, Hashino S, Nishio M, et al. Occurrence of adverse events caused by valganciclovir as pre-emptive therapy for cytomegalovirus infection after allogeneic stem cell transplantation is reduced by low-dose administration. *Transplant Infect Dis*. 2015;17(6):810–815.
15. Ruiz-Camps I, Len O, de la Camara R, et al. Valganciclovir as pre-emptive therapy for cytomegalovirus infection in allogeneic haematopoietic stem cell transplant recipients. *Antiviral Ther*. 2011;16(7):951–957.
16. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med*. 1993;118(3):173–178.
17. Winston DJ, Ho WG, Bartoni K, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients: results of a placebo-controlled, double-blind trial. *Ann Intern Med*. 1993;118(3):179–184.
18. Salzberger B, Bowden RA, Hackman RC, Davis C, Boeckh M. Neutropenia in allogeneic marrow transplant recipients receiving ganciclovir for prevention of cytomegalovirus disease: risk factors and outcome. *Blood*. 1997;90 (6):2502–2508.
19. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. *Ann Intern Med*. 2015;162(1):1–10.
20. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143–1238.
21. Winston DJ, Yeager AM, Chandrasekar PH, Snydman DR, Petersen FB, Territo MC. Randomized comparison of oral valacyclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. *Clin Infect Dis*. 2003;36(6):749–758.
22. Venton G, Crocchiolo R, Furst S, et al. Risk factors of ganciclovir-related neutropenia after allogeneic stem cell transplantation: a retrospective monocentre study on 547 patients. *Clin Microbiol Infect*. 2014;20(2):160–166.
23. Bacigalupo A, Boyd A, Slipper J, Curtis J, Clissold S. Foscarnet in the management of cytomegalovirus infections in hematopoietic stem cell transplant patients. *Expert Rev Anti Infect Ther*. 2012;10(11):1249–1264.
24. Avery RK, Arav-Boger R, Marr KA, et al. Outcomes in transplant recipients treated with foscarnet for ganciclovir-resistant or refractory cytomegalovirus infection. *Transplantation*. 2016;100(10):e74–e80.
25. Jacobsen T, Sifontis N. Drug interactions and toxicities associated with the antiviral management of cytomegalovirus infection. *Am J Health Syst Pharm*. 2010;67(17):1417–1425.
26. Hobbs GS, Kaur N, Hilden P, et al. A novel reduced intensity conditioning regimen for patients with high-risk hematological malignancies undergoing allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2016;51 (7):1010–1012.
27. Montoro J, Ceberio I, Hilden P, et al. Ex vivo T cell-depleted hematopoietic stem cell transplantation for adult patients with acute myelogenous leukemia in first and second remission: long-term disease-free survival with a significantly reduced risk of graft-versus-host disease. *Biol Blood Marrow Transplant*. 2020;26(2):323–332.
28. Huang YT, Kim SJ, Lee YJ, et al. Co-infections by double-stranded DNA viruses after ex vivo T cell-depleted, CD34(+) selected hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(10):1759–1766.
29. Smith E, Devlin SM, Kosuri S, et al. CD34-selected allogeneic hematopoietic stem cell transplantation for patients with relapsed, high-risk multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22(2):258–267.
30. Ceberio I, Devlin SM, Sauter C, et al. Sirolimus, tacrolimus and low-dose methotrexate based graft-versus-host disease prophylaxis after non-ablative or reduced intensity conditioning in related and unrelated donor allogeneic hematopoietic cell transplant. *Leuk Lymphoma*. 2015;56(3):663–670.
31. Ahmed S, Kanakry JA, Ahn KW, et al. Lower graft-versus-host disease and relapse risk in post-transplant cyclophosphamide-based haploidentical versus matched sibling donor reduced-intensity conditioning transplant for Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2019;25(9):1859–1868.
32. Rosillo C, Avila AM, Huang YT, et al. Sequential systematic anti-mold prophylaxis with micafungin and voriconazole results in very low incidence of invasive mold infections in patients undergoing allogeneic hematopoietic stem cell transplantation. *Transplant Infect Dis*. 2018;20(4):e12897.
33. Seo SK, Xiao K, Huang YT, et al. Impact of peri-transplant vancomycin and fluoroquinolone administration on rates of bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients: a 12-year single institution study. *J Infect*. 2014;69(4):341–351.
34. Babady NE, Cheng C, Cumberbatch E, Stiles J, Papanicolaou G, Tang YW. Monitoring of cytomegalovirus viral loads by two molecular assays in whole-blood and plasma samples from hematopoietic stem cell transplant recipients. *J Clin Microbiol*. 2015;53(4):1252–1257.
35. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017;64(1):87–91.
36. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15(6):825–828.
37. Einsele H, Ehninger G, Hebart H, et al. Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. *Blood*. 1995;86(7):2815–2820.
38. Hamilton BK, Rybicki L, Sekeres M, et al. Racial differences in allogeneic hematopoietic cell transplantation outcomes among African Americans and whites. *Bone Marrow Transplant*. 2015;50(6):834–839.
39. Pinana JL, Martino R, Barba P, et al. Cytomegalovirus infection and disease after reduced intensity conditioning allogeneic stem cell transplantation: single-centre experience. *Bone Marrow Transplant*. 2010;45(3):534–542.
40. Cohen L, Yeshurun M, Shpilberg O, Ram R. Risk factors and prognostic scale for cytomegalovirus (CMV) infection in CMV-seropositive patients after allogeneic hematopoietic cell transplantation. *Transpl Infect Dis*. 2015;17(4):510–517.
41. Glezerman IG, Devlin S, Maloy M, et al. Long term renal survival in patients undergoing T-Cell depleted versus conventional hematopoietic stem cell transplants. *Bone Marrow Transplant*. 2017;52(5):733–738.
42. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. *N Engl J Med*. 2019;381(12): 1136–1147.
43. Sommadossi JP, Carlisle R. Toxicity of 3′-azido-3′-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro. *Antimicrob Agents Chemother*. 1987;31 (3):452–454.
44. Sommadossi JP, Bevan R, Ling T, et al. Clinical pharmacokinetics of ganciclovir in patients with normal and impaired renal function. *Rev Infect Dis*. 1988;10(suppl 3):S507–S514.
45. Fletcher C, Sawchuk, Chinnock R, de Miranda B, Balfour P, Jr HH. Human pharmacokinetics of the antiviral drug DHPG. *Clin Pharmacol Ther*. 1986;40(3):281–286.
46. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med*. 2017;377 (25):2433–2444.
47. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, double-blind, phase 2 study. *Clin Infect Dis*. 2019;68(8):1255–1264.
48. Randolph-Habecker J, Iwata M, Torok-Storb B. Cytomegalovirus mediated myelosuppression. *J Clin Virol*. 2002;25(suppl 2):S51–S56.