Journal of Clinical Virology 120 (2019) 12–16

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Recommended foscarnet dose is not associated with improved outcomes in cytomegalovirus salvage therapy

Michael L. Spinner[a], Simon W. Lam[a], Christine E. Koval[b], Vasilios Athans[a,*,1]

[a] Department of Pharmacy, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, 44195, USA
[b] Department of Infectious Diseases, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, 44195, USA

ARTICLE INFO

Keywords:
Cytomegalovirus
Foscarnet
Dosing
Salvage therapy

ABSTRACT

Background: Cytomegalovirus (CMV) infection causes significant morbidity and mortality in transplant recipients. Ganciclovir and valganciclovir have proven efficacy but are limited by resistance and toxicity, whereas foscarnet typically retains activity when CMV has become resistant to other antivirals. Foscarnet dosing used in practice may be discordant with what is recommended in product labeling, as the result of an unconventional dosing nomogram or prescriber preference; however, it is unknown how discordant foscarnet dosing affects outcomes.

Objective: Our purpose was to characterize the relationship between initial foscarnet dosing intensity (relative to product labeling) and key effectiveness and safety endpoints.

Study design: This single-center, retrospective study included immunosuppressed adults with CMV viremia who received foscarnet between January 2012–July 2017. Subjects were divided into low dose (LD) and non-low dose (NLD) groups, according to foscarnet dose intensity. The primary endpoint was time-to-CMV eradication. Secondary endpoints included time-to-CMV clearance, acute kidney injury, hematologic toxicity, and mortality.

Results: Of 87 subjects, 38 met inclusion. Primary immunosuppression reasons were solid organ (63%) or hematopoietic cell transplant (29%). Seventeen and 21 subjects were in the LD and NLD groups, respectively. Median time-to-CMV eradication was 17 days (LD group) versus 13 days (NLD group), $p = 0.823$. Median time-to-CMV clearance was also non-significant ($p = 0.505$). There was no association between initial foscarnet dosing intensity and acute kidney injury, hematologic toxicity, or mortality (24% in both groups).

Conclusions: These findings suggest outcomes may be sensitive to other factors and underscore the need for further studies to improve understanding of foscarnet dosing in immunosuppressed patients.

1. Background

Cytomegalovirus (CMV) infection, once dubbed “the troll of transplantation”, causes significant morbidity and mortality in solid organ transplant (SOT) and hematopoietic cell transplant (HCT) recipients. [1–3] The CMV DNA polymerase inhibitors ganciclovir and valganciclovir are traditional first-line treatment options with proven efficacy; however, they are limited by treatment-emergent hematologic toxicity and mutational resistance [1,2]. Ganciclovir resistance, first clinically described in 1989, is mediated by point mutations in the UL97 viral kinase preventing drug phosphorylation and binding. Mutations in the CMV DNA polymerase (UL54) may also confer ganciclovir resistance, although less frequently [1,2].

Foscarnet (trisodium phosphonoformate) is a pyrophosphate analogue and reversible, competitive inhibitor that binds directly to DNA polymerase of CMV and other herpesviruses. Due to its unique mechanism of action and separate binding site, foscarnet often retains activity when CMV has become resistant to other antivirals. Foscarnet has been used to treat patients with AIDS-associated CMV retinitis, [4] ganciclovir-resistant or -refractory CMV infection, and ganciclovir intolerance [5–7]. Salvage therapy success rates have been reported as 65–70%, with limitations due to nephrotoxicity (incidence approaching 60%), hematologic toxicity, and electrolyte disturbances [4,6,7].

Foscarnet is renally eliminated and requires dose adjustment in the setting of acute or chronic kidney disease. The FDA-approved labeling for foscarnet includes renal dosing recommendations according to

* Corresponding author at: Clinical Pharmacy Specialist, Infectious Diseases, Department of Pharmacy, Hospital of the University of Pennsylvania, 3400 Spruce Street; Rhoads Building (Ground Floor), Philadelphia, PA, 19104, USA.
E-mail addresses: spinnem@ccf.org (M.L. Spinner), lams@ccf.org (S.W. Lam), kovalc@ccf.org (C.E. Koval), Vasilios.Athans@pennmedicine.upenn.edu (V. Athans).
[1] Department of Pharmacy, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA, 19104, USA.

https://doi.org/10.1016/j.jcv.2019.09.001
Received 12 June 2019; Received in revised form 19 August 2019; Accepted 2 September 2019

Table 1
FDA Product Labeling Foscarnet Dosing Recommendations.

Creatinine Clearance† (mL/min/kg)	Induction for CMV
> 1.4	90 mg/kg q12 h
> 1.0 – 1.4	70 mg/kg q12 h
> 0.8 – 1.0	50 mg/kg q12 h
> 0.6 – 0.8	80 mg/kg q24 h
> 0.5 – 0.6	60 mg/kg q24 h
≥0.4 – 0.5	50 mg/kg q24 h
< 0.4	Not recommended

† Calculated using Cockcroft-Gault formula and total body weight; CMV = cytomegalovirus.

Cockcroft-Gault creatinine clearance (CrCl) expressed in mL/min/kg (Table 1). [8] Although CrCl is typically expressed in mL/min, a *modified* Cockcroft-Gault equation was used in the pharmacokinetic study that formed the basis for the current FDA-approved dosing nomogram. [9,10] This study, which included pharmacokinetic data from 26 non-infected foscarnet recipients with varying degrees of renal function, proposed dose adjustments "to ensure that overall drug exposure would be similar among all subjects regardless of degree of kidney dysfunction" [10]. However, foscarnet is known to exhibit significant inter-patient pharmacokinetic variability, and the dosing nomogram does not appear to have been widely validated among infected patients with baseline renal dysfunction [11–13].

2. Objectives

The current foscarnet dosing nomogram is complex and based on an unconventional estimate of renal function, which may lead to errors in dose selection. In fact, a recent study identified that only one-third of foscarnet doses were within 10% of package insert recommendations. [14] Furthermore, prescriber preference may result in a dosing recommendation that is less or more aggressive than what is recommended by the FDA. The degree to which discordant foscarnet dosing impacts efficacy and toxicity is unknown. Therefore, the purpose of this study was to characterize the relationship between foscarnet dosing practices at our institution and pertinent effectiveness and safety endpoints.

3. Study design

This single-center, observational study was conducted between January 1, 2012 and July 1, 2017 at Cleveland Clinic, a 1400-bed tertiary academic medical center with robust oncology and transplant programs. Following institutional review board approval, subjects aged ≥18 years with an immunocompromising condition and documented CMV viremia [≥137 international units (IU)/mL] were screened for receipt of ≥ 48 h of foscarnet therapy. Included subjects were divided into two groups according to dose intensity, which was based on a comparison between actual administered foscarnet dose and package insert-recommended dose (Table 1). [8] Mean weight-based dose (mg/kg/day) was calculated for each subject over the first 5 days of foscarnet therapy using total body weight. The low dose (LD) group consisted of subjects receiving a mean actual dose that was more than 10 mg/kg/day below the recommended dose. The non-low dose (NLD) group consisted of subjects who received a mean actual foscarnet dose that either exceeded or was within 10 mg/kg/day below the usual recommendation. For example, if a subject's CrCl was 0.7 ml/min/kg and a dose of 60 mg/kg was administered every 24 h, the difference between actual daily dose (60 mg/kg/day) and recommended dose (80 mg/kg/day) was −20 mg/kg/day, resulting in a LD group assignment. The 10 mg/kg/day threshold was selected based on the smallest deviation a clinician may make when selecting a renally adjusted dose (Table 1) [8].

The primary endpoint was time-to-CMV eradication, defined as the time between pre-foscarnet viral load collection (i.e. CMV result immediately prior to foscarnet initiation) and attainment of a single negative or non-quantifiable CMV DNA result (< 137 IU/mL). Secondary endpoints included acute kidney injury (AKI), hematologic toxicity, time-to-CMV clearance, and mortality while receiving foscarnet. For this study, AKI was defined as a ≥25% reduction in CrCl between baseline (day 1) and end of foscarnet therapy. The following nephrotoxins were also noted if present concurrently: acyclovir, aminoglycosides, amphotericin B, cyclosporine, methotrexate, tacrolimus, and intravenous pentamidine. Subjects with baseline end-stage renal disease or renal replacement therapy were excluded from the AKI endpoint evaluation. Hematologic toxicity was a composite endpoint consisting of treatment-emergent anemia (hemoglobin < 13.0 g/dl for males, < 11.5 g/dl for females), leukopenia (< 3.7 cells/mm^3), or neutropenia (absolute neutrophil count < 1000 cells/mm^3) occurring between baseline and end of foscarnet therapy. Time-to-CMV clearance was defined as time between pre-foscarnet viral load collection and attainment of consecutively negative or non-quantifiable CMV DNA results. Data points were collected via manual chart review (patient demographics, reason for immunosuppression and/or transplant characteristics, immunosuppressive regimen, CMV infection characteristics, foscarnet regimen, concurrent nephrotoxins, and renal or hematologic-related laboratory results).

Categorical data were reported as n (%) and compared using either chi-square or Fisher's exact-tests, as appropriate. Continuous data were assessed for normality using the Shapiro-Wilk test and were compared by using the unpaired two-sample student's *t*-test with equal variances. The primary outcome of time-to-CMV eradication and secondary outcome of time-to-CMV clearance were evaluated using the Kaplan-Meier method with subjects censored at the last point of contact if no eradication or clearance was documented. Patients in the two dosing groups were compared using the log-rank test. Statistical significance was defined as a P value < 0.05, and analyses were performed using Stata software (Version 14.2, StataCorp LLC, College Station, Texas).

4. Results

After screening 87 subjects, 38 met inclusion criteria (Table 2). Twenty (53%) subjects were male and mean age was 51 ± 15 years. Reasons for immunosuppression were: 11 (29%) hematopoietic cell transplant, 9 (24%) lung transplant, 5 (13%) liver transplant, 4 (10%) renal transplant, 3 (8%) intestinal/multivisceral transplant, 3 (8%) non-transplant, 2 (5%) heart transplant, and 1 (3%) facial transplant. Of 35 subjects who received a SOT or HCT, mean time from transplant was 249 ± 74 days. Twenty-six (74%) transplant recipients were immunosuppressed with tacrolimus (mean trough 9.3 ± 4.3 ng/mL), 4 (11%) with cyclosporine (mean trough 206.5 ± 56.8 ng/mL), and 8 (23%) with mycophenolate (mean daily dose 1063 mg). Thirty-one (89%) transplant recipients were considered high risk according to CMV IgG status (donor seropositive/recipient seronegative SOT or recipient seropositive HCT).

Based on foscarnet dosing intensity, 17/38 (45%) and 21/38 (55%) subjects were assigned to the LD and NLD groups, respectively. Of 17 LD subjects, 15 (88%) received ganciclovir or valganciclovir immediately prior to foscarnet for a median duration of 16 (IQR 13–25) days. Of 21 NLD subjects, 17 (81%) received ganciclovir or valganciclovir immediately prior to foscarnet for a median duration of 15 (IQR 11–25) days. Mean foscarnet daily dose was 84 ± 38 mg/kg/day in the LD group and 100 ± 56 mg/kg/day in the NLD group (p = 0.330). Average deviation from package insert-recommended daily dose was -35 (range -93 to -12) mg/kg/day and +6 (range -8 to +39) mg/kg/day, respectively. Median (IQR) duration of foscarnet was 12 (6–22) days in the LD group and 14 (10–21) days in the NLD group (p = 0.210).

Rates of clinically diagnosed or biopsy-confirmed CMV organ

Table 2
Summary of Foscarnet Treatment Courses (N = 38).

No.	Age/ Sex	Reason for Immuno-Suppression	CMV Status	CMV Organ Disease	Baseline CMV Load (IU/mL)	Identified mutations	Baseline CrCl (mL/min)	Mean Foscarnet Dose Intensity (Δ mg/kg/day)†	Foscarnet Duration (days)	Time to Viremia Eradication (days)	Mortality During Foscarnet	AKI	CrCl, EOT (% change)	Hgb, EOT (g/dL)	WBC, EOT (cells/μL)	ANC, EOT (cells/μL)
Low Dose Group (n = 17)																
1	39/F	Kidney Txp	D+/R-	–	51,969	UL97: L595S	94	−46	33	19	N	Y	−28%	12.6	8.6	–
2	70/F	Lung Txp	D+/R-	Colitis	193,170	–	42	−13	3	–	N	Y	−27%	8.9	5.31	3.19
3	70/M	Liver Txp	D+/R-	–	21,485	UL54: A692S	79	−18	12	17	N	N	−10%	7.6	4.18	2.42
4	41/F	Stem Cell Txp	D-/R+	–	12,700	–	> 100	−93	16	35	N	N	+13%	11.1	4.72	4.06
5	46/M	Lung Txp	D+/R-	–	16,874	UL97: M460V UL54: L545S	63	−43	42	19	N	N	−11%	11.6	7.7	4.9
6	57/M	Lung Txp	D+/R-	–	39,306	UL97: M460V	56	−18	23	12	Y	Y	−26%	8.6	16.87	16.72
7	61/M	Stem Cell Txp	D-/R+	Colitis‡	3,094	–	> 100	−23	4	–	N	N	+19%	7.3	3.25	2.86
8	31/F	Stem Cell Txp	D+/R-	Pneumonitis	11,300	–	96	−19	20	11	Y	Y	−55%	8	0.11	0
9	48/M	Face Txp	D+/R-	–	34,200	–	> 100	−34	6	7	N	Y	−76%	6.9	5.77	4.37
10	68/M	Heart Txp	D+/R-	Colitis‡ Gastritis‡	519,563	–	37	−13	6	10	N	N	+67%	10.5	6.67	5.88
11	49/F	ILD	N/A	–	10,897	UL97: L595S	78	−63	14	–	Y	Y	−72%	8.5	11.25	–
12	67/M	Liver Txp	D+/R+	–	13,842	–	83	−58	4	7	N	N	−12%	8.5	0.3	–
13	58/F	Stem Cell Txp	D-/R+	Pneumonitis	2,562	–	RRT	−13	6	7	Y	RRT	RRT	9	3.52	3.27
14	58/F	Heart Txp	D+/R-	Colitis	89,879	–	56	−16	8	18	N	N	−23%	9.2	3.16	–
15	48/F	Stem Cell Txp	D+/R+	–	556	–	43	−12	7	–	N	N	+12%	10.6	0.71	0.6
16	59/M	Kidney Txp	D+/R-	–	13,482	UL97: C592G	46	−22	22	21	N	N	−6%	11.1	7.76	–
17	20/F	Stem Cell Txp	D+/R+	–	725	UL97: A594P	> 100	−84	43	4	N	N	+20%	11.3	4.51	2.4
Non-Low Dose Group (n = 21)																
18	49/M	Kidney Txp	D+/R-	–	120,536	UL97: Del596-602	56	−8	63	46	N	N	+12%	9.5	8.61	7.49
19	56/F	HIV	N/A	Colitis	2,278	–	RRT	+10	21	20	N	RRT	RRT	8	3.09	–
20	71/M	Lung Txp	D+/R-	–	719	UL97: L595W	28	0	33	30	N	Y	−44%	9.3	16.68	15.18
21	42/M	MV Txp	D+/R+	–	178,000	–	> 100	+11	13	–	Y	Y	−73%	11.5	0.54	0.42
22	56/M	Lung Txp	D+/R-	–	326	–	RRT	+2	14	4	N	RRT	RRT	9.2	10.58	6.67
23	58/F	Liver Txp	D+/R-	–	400,000	–	RRT	0	9	–	Y	RRT	RRT	9.2	10.85	9.77
24	69/M	Lung Txp	D+/R-	–	3,010	–	RRT	−7	10	–	N	RRT	RRT	6.9	0.59	0.46
25	53/M	Stem Cell Txp	D-/R+	–	281	–	> 100	−2	22	2	N	N	+9%	11.2	5.47	2.62
26	64/F	Lung Txp	D+/R-	–	19,156	UL97: A594V	43	+33	10	–	Y	N	+9%	8.7	8.56	8.34
27	57/M	Lung Txp	D+/R-	–	38,634	–	RRT	0	14	8	N	RRT	RRT	7.3	4.22	3.74
28	46/M	Liver Txp	D+/R+	Colitis Esophagitis	2,827	–	40	+3	8	13	N	N	+49%	7.6	3.44	3.11
29	20/F	Stem Cell Txp	D+/R+	–	3,360	UL97: A594P	> 100	−1	15	–	N	N	+56%	10.5	3.93	2.87
30	20/F	MCD	N/A	Colitis‡	65,974	–	RRT	−7	14	–	Y	RRT	RRT	6.9	28.52	22.53
31	58/F	Stem Cell Txp	D+/R+	Pneumonitis	2,861	–	RRT	+8	15	7	Y	RRT	RRT	11	1.83	1.1
32	65/M	Liver Txp	D+/R-	Colitis	28,178	UL54: R1052C	68	+39	10	11	N	Y	−49%	9.2	2.87	1.95
33	36/M	Stem Cell Txp	D+/R+	Colitis	6,419	–	78	+39	9	7	N	N	+13%	10.9	1.82	1.16
34	36/F	Intestinal Txp	D+/R-	–	154	–	> 100	0	21	7	N	N	−2%	11.2	5.96	3.5
35	36/F	Intestinal Txp	D+/R-	–	1,430	–	> 100	0	36	13	N	N	+1%	10.3	11.35	5.5
36	56/M	Lung Txp	D+/R-	–	326	–	RRT	+2	15	4	N	RRT	RRT	9.2	10.58	6.67
37	59/M	Kidney Txp	D+/R-	Duodenitis‡	1,255	UL97: C592G	34	−3	13	7	N	N	−24%	9.2	5.21	3.38
38	20/F	Stem Cell Txp	D+/R+	Duodenitis‡	34,836	UL97: A594P	> 100	+2	29	14	N	N	−20%	8.5	5.56	1.67

†Calculated as the mean daily difference between actual and recommended foscarnet dose during the first 5 days of therapy; ‡Biopsy-confirmed disease; AKI = acute kidney injury; CMV = cytomegalovirus; EOT = end of therapy; Hgb = hemoglobin HIV = human immunodeficiency virus; ILD = interstitial lung disease; MCD = minimal change disease; MV = multivisceral; RRT = renal replacement therapy at baseline; Txp = transplant; N/A = not applicable; (–) = death or discontinuation of foscarnet prior to eradication.

disease were comparable between groups [6/17 (35%) LD vs. 8/21 (38%) NLD; $p = 0.859$]. Prior to foscarnet initiation, 7/15 (47%) vs. 7/13 (54%) of subjects tested for CMV resistance were found to have mutations associated with reduced ganciclovir activity ($p = 0.705$). Eleven subjects had UL97 mutations, two subjects had UL54 mutations, and one subject had both UL97 and UL54 mutations. Subjects in the LD group had a mean pre-foscarnet CMV load of 60,918 ± 127,282 IU/mL compared to 43,360 ± 93,552 IU/mL in the NLD group ($p = 0.627$).

Median time-to-CMV eradication was 17 days (95% CI: 6–27 days) in the LD group and 13 days (95% CI: 9–17 days) in the NLD group ($p = 0.823$). Median time-to-CMV clearance was 24 days (95% CI: 17–32 days) in the LD group and 21 days (95% CI: 15–29 days) in the NLD group ($p = 0.505$). In the LD group, 11/17 (65%) subjects achieved CMV clearance, compared to 15/21 (71%) in the NLD group ($p = 0.657$). Mortality occurred in 24% of subjects in both groups during foscarnet treatment. Ten subjects could not be assessed for the primary endpoint. Five subjects died prior to eradication (1 LD vs. 4 NLD), 3 subjects had foscarnet discontinued prior to eradication (2 LD vs. 1 NLD), and 2 subjects had persistent viremia at the last point of contact (1 LD vs. 1 NLD). A Kaplan-Meier estimate of time-to-CMV eradication is displayed in Figs. 1.

One subject in the LD group and 8 subjects in the NLD group were excluded from the AKI assessment due to receipt of renal replacement therapy at baseline. After applying this exclusion, 12/16 (75%) LD group subjects and 12/13 (92%) NLD group subjects were found to have received at least one nephrotoxin concomitantly with foscarnet. At the end of foscarnet therapy, the rate of AKI was not significantly different between groups [6/16 (38%) LD vs. 3/13 (23%) NLD; $p = 0.454$]. There were no differences in the rate of new-onset leukopenia (24% vs. 14%; $p = 0.678$), neutropenia (8% vs. 10%; $p = 1.000$), or anemia (6% vs. 10%; $p = 1.000$).

5. Discussion

In this observational study, foscarnet dose intensity during the first 5 days of therapy was not positively associated with the surrogate endpoint of time-to-CMV eradication. We selected this endpoint for its objective nature, and because delayed viremia eradication has been correlated with meaningful clinical outcomes such as treatment failure and relapse. [2] Foscarnet doses greater than or equal to package insert recommendations did not hasten CMV eradication when compared to sub-recommended doses. There was also no clear association between initial foscarnet dose and overall treatment success (e.g. CMV clearance) or mortality. Collectively, these findings suggest that salvage therapy outcomes may be more sensitive to other factors, such as pre-treatment CMV load or immune status. However, patients in the NLD group were not found to have a significantly higher pre-foscarnet CMV load, and average calcineurin inhibitor trough levels were similar between the two groups (data not shown). Objective assessment of immune status was highly challenging, as the cohort was comprised of multiple types of transplant recipients on differing intensity of mono- or multi-drug regimens.

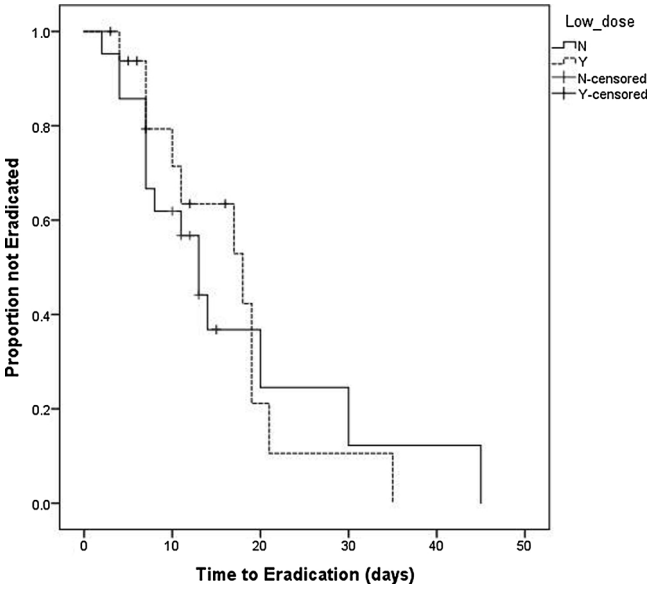

Fig. 1. Kaplan-Meier Estimate of Time-to-CMV Eradication. Median time-to-CMV eradication was 17 days (95% CI: 6–27 days) in the Low Dose group and 13 days (95% CI: 9–17 days) in the Non-Low Dose group ($p = 0.823$). Tick marks indicate censored data due to death or discontinuation of foscarnet prior to eradication. N = Non-Low Dose Group, Y = Low Dose Group, CMV = cytomegalovirus.

An alternative explanation is that an optimal foscarnet dosing strategy for CMV induction has not been determined. Based on foscarnet's *in vitro* activity against CMV [half maximal inhibitory concentration (IC_{50}) = 269 μM], investigational dosing regimens were historically designed to maintain plasma concentrations between 333 and 500 μM. [8,11] Foscarnet's complex pharmacokinetic profile renders this difficult due to multi-phase plasma clearance, which is also poorly understood in the setting of renal impairment. Steady state peak and trough concentrations of foscarnet during a 90 mg/kg q12 h regimen are 623 ± 132 μM and 63 ± 57 μM, respectively, indicating a high degree of interpatient variability and the potential for sub-inhibitory concentrations. [8,12] Given the low quality of data supporting current foscarnet dosing strategies, future studies should explore exposure-response relationships as well as the role for therapeutic drug monitoring.

We observed an overall AKI rate of 31% at the end of foscarnet therapy, which is within the range identified by similar retrospective studies (14–51%). [5,7] Foscarnet-induced renal impairment typically occurs after one week of therapy [1], as was the case in 78% of our identified AKI episodes. Interestingly, low dose foscarnet was not protective against AKI in our cohort, despite these patients receiving fewer concomitant nephrotoxins [15] and a shorter median duration of therapy [1]. Taken together, these findings suggest that variables other than foscarnet dose (e.g. acute illness or fluid status) may be more important predictors of nephrotoxicity in this complex population. Intravenous hydration is recommended prior to foscarnet infusion as a means to induce diuresis and minimize drug-induced tubular necrosis [8,16]. Within our institution's electronic health record, pre-hydration is embedded within the foscarnet order file. Although we did not confirm the administration of pre-hydration before each foscarnet dose administered in this study, it was assumed that clinicians did not routinely opt out unless the patient was adequately hydrated or volume overloaded.

Finally, rates of new-onset leukopenia, neutropenia, and anemia were not significantly reduced in patients receiving low dose foscarnet. While our study was not designed to make comparative conclusions about cytopenia incidence, the lack of consistent numerical trends implies that these end points are not strictly dose-dependent phenomena. In fact, a foscarnet dose-ranging study in 3 subjects with AIDS identified no hematologic toxicity at supratherapeutic doses (395–523 mg/kg/day). [17] By comparison, the maximum foscarnet daily dose in this study was 233 mg/kg/day. It is likely that rates of foscarnet-induced hematologic toxicity reported in the literature are overestimated as a result of underlying conditions (e.g. hematologic malignancy) or concomitant medications (e.g. mycophenolate).

Limitations of this study include single center retrospective design with a small sample size and lack of control for important confounders. Additionally, study subjects were grouped according to foscarnet dose administered during the first 5 days of therapy only. There is no evidence to suggest the first 5 days of foscarnet therapy is of particular clinical significance; however, we aimed to minimize the risk of

additional confounding presented by longer treatment courses. We hypothesized that initial dosing intensity would correlate to the rate of viremia eradication based on biological plausibility. Interestingly, in the current study the median duration of foscarnet therapy was shorter than the time-to-CMV eradication. This may signify that patients were switched to other therapies prior to eradication due to concerns surrounding toxicity or lack of efficacy. Retrospectively, we were often unable to determine the reason for a divergence between actual- and package insert-recommended foscarnet dose. It is likely that dosing discrepancies occurred due human error when interpreting complex foscarnet dosing recommendations, failure to make adjustments in the setting of changing weight or renal function, or prescriber preference. Lastly, the Non-Low Dose group contained a mixture of subjects receiving package insert-recommended doses and 'supratherapeutic' doses, which may have affected results. Only 5 subjects received doses significantly above package insert recommendations; therefore, a composite group was created to balance samples and enrich the dataset.

Few available CMV-active medications are supported by data for salvage therapy indications, ensuring that foscarnet will remain a necessary treatment option for the foreseeable future. Despite limitations, this study underscores the need for an improved understanding of foscarnet dosing in vulnerable populations. Foscarnet dosing for salvage therapy may not be an important predictor of clinical success or toxicity, therefore how should the clinician proceed? Given the uniquely error-prone nature of foscarnet dose selection, transplant centers are first encouraged to periodically educate prescribers on how to navigate the foscarnet dosing scheme. Pharmacist expertise should also be leveraged to reconcile dose discrepancies. A recent study by Pillinger and colleagues found that a pharmacist-managed foscarnet dosing service was able to improve package insert-concordant dosing nearly two-fold. [14] Second, we advocate for continued use of FDA-approved foscarnet renal adjustment nomogram until more robust data become available. Future investigations should seek to establish a pharmacokinetic-pharmacodynamic index (e.g. exposure-response relationship) for foscarnet. From there, prospective clinical trials are needed to "field test" novel dosing strategies for CMV salvage therapy indications.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

None declared.

Author contributions

All authors have contributed to the manuscript and approved the final version for submission.

Ethical approval

None.

CRediT authorship contribution statement

Michael L. Spinner: Conceptualization, Data curation, Methodology, Formal analysis, Writing - review & editing. **Simon W. Lam:** Conceptualization, Formal analysis, Methodology, Writing - review & editing. **Christine E. Koval:** Conceptualization, Methodology, Writing - review & editing. **Vasilios Athans:** Conceptualization, Data curation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Acknowledgments

None.

References

[1] C.S. Crumpacker, Cytomegalovirus (CMV) [chapter 140], Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., Saunders, Philadelphia, PA, 2015, pp. 1738–1753 e5.
[2] C.N. Kotton, D. Kumar, A.M. Caliendo, et al., The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation, Transplantation 102 (6) (2018) 900–931.
[3] H.H. Balfour, Cytomegalovirus: the troll of transplantation, Arch. Intern. Med. 139 (3) (1979) 279–280.
[4] G. Moyle, C. Harman, S. Mitchell, B. Mathalone, B.G. Gazzard, Foscarnet and ganciclovir in the treatment of CMV retinitis in AIDS patients: a randomised comparison, J. Infect. 25 (1) (1992) 21–27.
[5] R.K. Avery, R. Arav-Boger, K.A. Marr, et al., Outcomes in transplant recipients treated with foscarnet for ganciclovir-resistant or refractory cytomegalovirus infection, Transplantation 100 (10) (2016) e74–80.
[6] L.R. Minces, M.H. Nguyen, D. Mitsani, et al., Ganciclovir-resistant cytomegalovirus infections among lung transplant recipients are associated with poor outcomes despite treatment with foscarnet-containing regimens, Antimicrob. Agents Chemother. 58 (1) (2014) 128–135.
[7] B. Pierce, C.L. Richardson, L. Lacloche, A. Allen, M.G. Ison, Safety and efficacy of foscarnet for the management of ganciclovir-resistant or refractory cytomegalovirus infections: a single-center study, Transpl. Infect. Dis. 20 (2) (2017) e12852.
[8] Foscarnet Sodium Injection [package Insert], Clinigen Healthcare Ltd., Burton-on-Trent, UK, 2018 October.
[9] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, Nephron 16 (1976) 31–41.
[10] F.T. Aweeka, M.A. Jacobson, S. Martin-Munley, et al., Effect of renal disease and hemodialysis on foscarnet pharmacokinetics and dosing recommendations, J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 20 (4) (1999) 350–357.
[11] P. Chrisp, S.P. Clissold, Foscarnet, Drugs 41 (1) (1991) 104–129.
[12] A.M. Taburet, C. Katlama, C. Blanshard, et al., Pharmacokinetics of foscarnet after twice-daily administrations for treatment of cytomegalovirus disease in AIDS patients, Antimicrob. Agents Chemother. 36 (9) (1992) 1821–1824.
[13] The Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS, Arch. Ophthalmol. 114 (1996) 23–33.
[14] K.E. Pillinger, S. McClanahan, J. Arnall, et al., Expanding beyond vancomycin and aminoglycosides: a novel pharmacist-managed dosing service, Ann. Pharmacother. (2019), https://doi.org/10.1177/1060028019860515.
[15] J.M. Morales, M.A. Munoz, G. Fernandez Zatarain, et al., Reversible acute renal failure caused by the combined use of foscarnet and cyclosporine in organ transplanted patients, Nephrol. Dial. Transplant. 10 (6) (1995) 882–883.
[16] G. Deray, F. Martinez, C. Katlama, et al., Foscarnet nephrotoxicity: mechanism, incidence and prevention, Am. J. Nephrol. 9 (4) (1998) 316–321.
[17] E.A. Siedel, S. Koenig, M.A. Polis, A dose escalation study to determine the toxicity and maximally tolerated dose of foscarnet, AIDS 7 (7) (1993) 941–945.