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Preemptive Therapy for Cytomegalovirus Reactivation Post-hematopoietic Cell Transplantation is Associated with Significant Morbidity and Resource Utilization

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Introduction

Cytomegalovirus (CMV) is a double-stranded DNA (dsDNA) virus that causes persistent and latent infections in humans. While CMV normally remains latent in infected healthy individuals, in immunocompromised patients, such as allogeneic hematopoietic cell transplant (HCT) recipients, virus reactivation can lead to potentially life-threatening infections, characterized by pneumonia, gastrointestinal (GI) disease, hepatitis, and (to a lesser extent) retinitis.[1]

Randomized clinical trials of ganciclovir (Cytovene®, GCV) prophylaxis have shown a significant reduction in early CMV disease, but no survival benefit due to the increased occurrence of invasive fungal and bacterial infections and late onset CMV disease.[4,5] In contrast, PrT with GCV showed both a reduction in disease and a survival benefit, although still associated with an increased risk of bacterial and fungal infections.[1,6,7] While the current standard of care in the HCT population relies on PrT using GCV, or its prodrug, valganciclovir (Valcyte®, vGCV), as first-line therapy to reduce the severity of CMV disease, the use of both drugs is limited by high rates of neutropenia, with concomitant increased risk of bacterial and fungal infections, as well as anemia and thrombocytopenia requiring transfusion.[8] The second-line anti-CMV drugs, foscarnet (Foscavir®, FOS) and intravenously administered (IV) cidofovir (CDV, Vistide®) are also associated with significant toxicities. Thus, there are detrimental patient outcomes, medical resource utilization, and financial costs associated with the treatment and management of PrT-related toxicities. The availability of new anti-CMV drugs that can be administered prophylactically to allogeneic HCT recipients without significant myelotoxicity has the potential to shift the current emphasis away from PrT to CMV prophylaxis.

CMX001 is a novel, orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate that is converted intracellularly into the active antiviral, cidofovir diphosphate (CDV-PP). CMX001 is absorbed in the small intestine, circulates in the periphery, and is delivered to target organs throughout the body. Inside cells, CMX001 is cleaved by intracellular enzymes to release CDV, which is anabolised by intracellular kinases to CDV-PP. CDV-PP has a long intracellular half-life estimated at ~ 6.5 days. CMX001 has demonstrated in vitro antiviral activity against all five families of dsDNA viruses that affect humans, including herpesviruses such as CMV, polyomaviruses, such as BK virus, papillomaviruses, adenoviruses and orthopoxviruses.

Methods

In a recently completed, multi-center, randomized, double-blind, placebo-controlled, dose-escalation study designed to evaluate CMX001 for the prevention and control of CMV infection in 230 R+ HCT recipients (Study CMX001-201, ClinicalTrials.gov identifier: NCT00942305), CMX001, at total weekly doses of 100 to 200 mg, was shown to be active and tolerated as a CMV prophylactic agent.[10] Of the 230 subjects enrolled in the study, 50 (21.7%) had CMV viremia at entry. Subjects who developed CMV infection that required preemptive anti-CMV treatment or CMV disease at any time during the treatment period (9 to 11 weeks, through approximately 100 days post-transplant) were required to be discontinued from study treatment (i.e., CMX001 or placebo) and followed for a period of 4 weeks, while subjects who completed the treatment period were followed for a period of 8 weeks. Once study treatment was discontinued, subjects were allowed to be treated with PrT for CMV infection/disease, per institutional standard of care, at the discretion of the responsible investigator. We report here the results of an analysis to characterize the tolerability profile of PrT during the follow-up (FU) period and inform the discussion on the potential economic and human impact of initiating PrT in the HCT population. Clinical laboratory values, relevant adverse events (AEs) (i.e., hematologic toxicity, infections, renal toxicity, etc.), concomitant medications and other procedures were compared between those subjects who did and those who did not receive PrT during the post-treatment FU period.

Description of Analysis

- Subjects who received anti-CMV PrT, defined as receiving at least one dose of GCV, vGCV, FOS or IV CDV for the explicit treatment of CMV infection/disease during the FU period, were identified.
- The FU period was defined as the last day of study treatment through the last day on study, i.e., completion of the +4-week or +8-week post-treatment visit, as applicable.
- Baseline measures for changes in clinical laboratory values were defined as the last value on or before the last day of study treatment. The maximal decrease in ANC was determined using the minimum value reported after the last day of study treatment. The maximal increase in serum creatinine was determined using the maximum value reported after the last day of study treatment. Only subjects with ≥ 1 on-treatment and ≥ 1 FU value were included in the analysis.
- Based on the known toxicities of existing anti-CMV medications, relevant AEs were defined as those events mapping to the blood and lymphatic disorders, infections/infestations and renal and urinary disorders using the MedDRA® coding dictionary. AEs were only counted if they began after the last day of study treatment.
- P-values were determined using Fisher's exact test for binary data and an independent t-test (pooled) for continuous data.

Results

Analysis Population: Seventy subjects (30.4%) received PrT for the treatment of CMV infection or disease. Of these, 67 subjects (95.7%) were treated within the 100-day post-transplant period and 56 subjects (80.0%) were treated within 9 days of stopping study treatment. The incidence of subjects requiring PrT was greatest in the lowest CMX001 dose group (40 mg administered once-weekly [QW]), which was essentially inactive with regard to anti-CMV activity, at 12/25 subjects (48.0%) and in the pooled placebo group at 20/59 subjects (33.9%). In these 2 groups, 7/25 subjects (28.0%) and 12/59 subjects (20.3%), respectively, entered the study with preexisting CMV viremia.

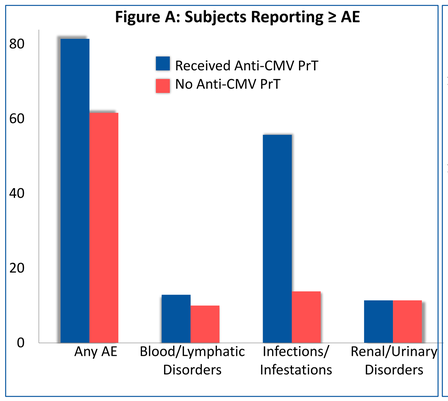
Preemptive Therapy: The vast majority of subjects (68/70, 97.1%) received GCV, vGCV, or both, with 10 (14.3%) subjects receiving FOS and 4 (5.7%) subjects receiving IV CDV. Fifty-two (74.3%) subjects received 1 drug, 16 (22.9%) subjects received 2 drugs, and 2 (2.9%) subjects received 3 drugs.

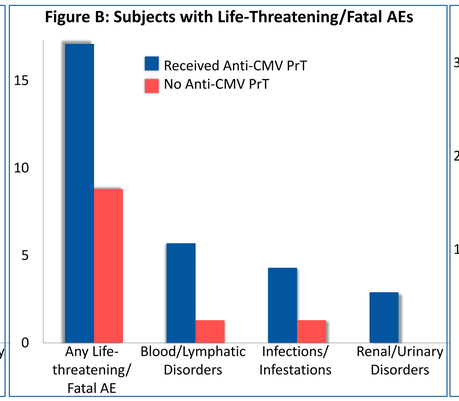
Demographics/Baseline Characteristics: The demographic/baseline characteristics of the two groups are summarized in Table 1. The demographics of the two groups are comparable. As might be expected, the group requiring PrT intervention included a higher proportion of subjects with risk factors for CMV reactivation (i.e., unrelated and/or mismatched donor and receipt of a myeloablative conditioning regimen).

Duration of Follow-up: The duration of FU between the two groups is summarized in Table 2. Of note, there is an inherent bias in this analysis, since the subjects who completed study treatment were followed for up to twice as long as subjects who discontinued study treatment prematurely (i.e., 8 weeks vs. 4 weeks) and, therefore, had more time to report potentially adverse findings. Consequently the analysis below is conservative as the follow-up period is shorter for subjects who received anti-CMV PrT versus those who did not.

Clinical Laboratory Values of Interest: More subjects receiving anti-CMV PrT experienced decreases in their ANC and a greater magnitude of decline, compared to subjects who did not receive PrT. Mean increases in serum creatinine values and the number of subjects with a > 20% increase in serum creatinine were also higher in subjects receiving anti-CMV PrT, but did not achieve statistical significance.

Granulocyte Colony-Stimulating Factor: A higher percentage of subjects receiving anti-CMV PrT required G-CSF, although the difference was not statistically significant. In contrast, a lower percentage of subjects receiving anti-CMV PrT required blood or blood product transfusion, although the difference was again not statistically significant. The latter observation is explained by the different durations of follow-up in the two groups, with a 2.6% incidence of transfusion per subject-week in the group receiving anti-CMV PrT, as compared to a 2.3% incidence of transfusion per subject-week in the group that did not receive anti-CMV PrT.





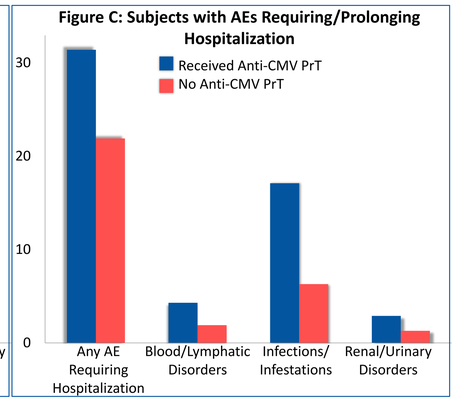


Table 1

	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)
Age, years		
Mean	50.5	50.7
Median	51.5	50.5
Min, Max	25, 69	21, 71
Gender, n (%)		
Female	28 (40.0)	70 (43.8)
Male	42 (60.0)	90 (56.3)
Race, n (%)		
Asian	2 (2.9)	10 (6.3)
Black	3 (4.3)	4 (2.5)
White	62 (88.6)	145 (90.6)
Other	3 (4.3)	1 (0.6)
Weight (kg)		
Mean	79.0	77.2
Median	78.6	77.9
Min, Max	40.8, 146.9	40.6, 131.9
Transplant Characteristics, n (%)		
Unrelated Donor	47 (67.1)	77 (48.1)
Adult Mismatch	15 (21.4)	18 (11.3)
Myeloablative Conditioning	52 (74.3)	95 (59.4)

Table 2

	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)
Duration of Follow-up (Days)		
Mean (SD)	30.9	45.4 (19.4)
Median	28	53
Q1, Q3	27, 33	31, 57
Min, Max	3, 63	1, 144
Subjects Followed for Specified Period (n, [%])		
≥ 2 weeks	66 (94.3%)	147 (91.9%)
≥ 4 weeks	52 (74.3%)	136 (85.0%)
≥ 6 weeks	9 (12.9%)	104 (65.0%)
≥ 8 weeks	5 (7.1%)	63 (39.4%)

Table 3

	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)	P-value
Absolute Neutrophil Count (G/L)			
Maximal ANC Decrease:			
N	**68**	**149**	
Mean (SD)	**2.0 (2.9)**	**0.7 (2.0)**	
Median	**1.4**	**0.5**	**0.0002**
Min, Max	-6.5, 11.4	-4.4, 8.1	
Subjects with: ((n (%))			
Any decrease in ANC	**56 (82.4%)**	**100 (67.1%)**	**0.02**
> 2 G/L decrease in ANC	**28 (41.2%)**	**27 (18.1%)**	**0.0006**
ANC decreased to < 1.5 G/L	25 (36.8%)	51 (34.2%)	0.76
Serum Creatinine (µmol/L)			
Maximal Creatinine Increase			
N	68	150	
Mean (SD)	6.9 (32.2)	3.3 (37.1)	
Median	4.5	8.0	0.50
Min, Max	-53.0, 142.0	-283.0, 142.0	
Subjects with: ((n (%))			
> 20% increase in creatinine	23 (33.8%)	36 (24.0%)	0.14

Table 4

Primary System Organ Class Preferred Term [a]	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)
≥ 1 AE (all grades [b]), n (%)	**57 (81.4%)**	**97 (60.6%)**
≥ 1 Life-threatening/Fatal AE [c], n (%)	**12 (17.1%)**	**14 (8.8%)**
Blood and Lymphatic System Disorders, n (%)		
Any AE in category	**4 (5.7%)**	**2 (1.3%)**
Lymphopenia	1 (1.4%)	0
Neutropenia	0	1 (0.6%)
Pancytopenia	2 (2.9%)	0
Thrombocytopenia	2 (2.9%)	1 (0.6%)
Infections and Infestations, n (%)		
Any AE in category	**3 (4.3%)**	**2 (1.3%)**
Cellulitis	1 (1.4%)	0
Escherichia sepsis	0	1 (0.6%)
Klebsiella bacteremia	1 (1.4%)	1 (0.6%)
Pneumonia	1 (1.4%)	1 (0.6%)
Septic shock	1 (1.4%)	0
Renal and Urinary Disorders, n (%)		
Any AE in category	**2 (2.9%)**	**0**
Renal failure	2 (2.9%)	0

[a] AEs were linked to system organ class and preferred term by MedDRA® coding dictionary, v.12.1
[b] Grades 1 to 5, per CTCAE
[c] Life-threatening = grade 4 and fatal = grade 5, per CTCAE

Table 5

Primary System Organ Class Preferred Term [a]	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)
≥ 1 AE Requiring/Prolonging Hospitalization, n (%)	**22 (31.4%)**	**35 (21.9%)**
Blood and Lymphatic System Disorders, n (%)		
Any AE in category	**3 (4.3%)**	**3 (1.9%)**
Anemia	1 (1.4%)	1 (0.6%)
Febrile neutropenia	0	2 (1.3%)
Lymphopenia	1 (1.4%)	0
Pancytopenia	1 (1.4%)	0
Thrombocytopenia	1 (1.4%)	0
Infections and Infestations, n (%)		
Any AE in category	**12 (17.1%)**	**10 (6.3%)**
Bacteremia	1 (1.4%)	1 (0.6%)
Cellulitis	1 (1.4%)	0
Citrobacter infection	1 (1.4%)	0
Clostridium difficile infection	1 (1.4%)	0
Epstein-Barr virus infection	1 (1.4%)	0
Escherichia sepsis	0	1 (0.6%)
Klebsiella bacteremia	1 (1.4%)	1 (0.6%)
Metapneumovirus infection	0	1 (0.6%)
Pneumonia	1 (1.4%)	2 (1.3%)
Pneumonia, Legionella	0	1 (0.6%)
Pseudomonal bacteremia	1 (1.4%)	0
Sepsis	1 (1.4%)	1 (0.6%)
Septic shock	1 (1.4%)	0
Serratia bacteremia	0	(0.6%)
Sinusitis	1 (1.4%)	0
Staphylococcal bacteremia	0	1 (0.6%)
Staphylococcal infection	1 (1.4%)	0
Stenotrophomonas infection	0	1 (0.6%)
Streptococcal bacteremia	1 (1.4%)	0
Renal and Urinary Disorders, n (%)		
Any AE in category	**2 (2.9%)**	**2 (1.3%)**
Hematuria	0	2 (1.3%)
Renal failure	2 (2.9%)	0

[a] AEs were linked to system organ class and preferred term by MedDRA® coding dictionary, v12.1

Table 6

	Received Anti-CMV PrT (n = 70)	No Anti-CMV PrT (n = 160)	P-value
Received G-CSF, n (%)	11 (15.7%)	17 (10.6%)	0.28
Received Transfusion, n (%)	8 (11.4%)	24 (15.0%)	0.54

Conclusion

The results of this post hoc analysis support the conclusion that PrT for CMV is associated with significant morbidity and greater resource utilization post-HCT, especially given the inherent negative bias of a reporting period for subjects who completed study treatment that was twice as long for subjects who discontinued study treatment prematurely. Anti-CMV PrT was associated with higher rates of life-threatening/fatal AEs and hospitalizations due to the myelosuppression, nephrotoxicity, and secondary bacterial and fungal infections. There is a clear and unmet medical need for new antiviral compounds that are safe and effective to replace current anti-CMV PrT in order to improve HCT outcomes and decrease HCT-related costs. Of note, the incidence of anti-CMV PrT in subjects who received placebo or the essentially inactive 40 mg QW CMX001 dose was 32 out of a combined 84 subjects (or 38.1%). The rate of preemption in the CMX001 cohort with the greatest anti-CMV activity, 100 mg twice-weekly, was 22.0% (11/50); 9 (18.0%) of these subjects had CMV viremia upon study entry. This "burden of care" aspect will be explored further in a Phase 3 clinical trial evaluating CMX001 for the prevention of CMV infection in adult R+ HCT recipients, in which all subjects will be followed through 24 weeks post-transplant.

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