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Cytomegalovirus Load at Treatment Initiation is Predictive of Time to Resolution of Viremia and Duration of Therapy in Hematopoietic Cell Transplant Recipients

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Abstract

Background—Preemptive antiviral therapy relies on viral load measurements and is the mainstay of cytomegalovirus (CMV) prevention in hematopoietic cell transplant (HCT) recipients. However, optimal CMV levels for the initiation of preemptive therapy have not been defined.

Objectives—To evaluate the relationship between plasma CMV DNA levels at initiation of preemptive therapy with time to resolution of viremia and duration of treatment.

Study Design—Retrospective analysis of HCT recipients undergoing serial CMV PCR testing between June 2011 and June 2014 was performed.

Results—221 HCT recipients underwent preemptive therapy for 305 episodes of CMV viremia. Median time to resolution was shorter when treatment was initiated at lower CMV levels (15 days at 135–440 international units (IU)/mL, 18 days at 441–1000 IU/mL, and 21 days at >1000 IU/mL, $P < .001$). Prolonged viremia lasting >30 days occurred less frequently when treatment was initiated at 135–440 IU/mL compared to 441–1000 IU/mL and >1000 IU/mL (1%, 15%, 24%, $P < .001$). Median treatment duration was also shorter in the lower viral load groups (28, 34, 37 days, $P < .001$).

Conclusion—Initiation of preemptive therapy at low CMV levels was associated with shorter episodes of viremia and courses of antiviral therapy. These data support the utility of initiating preemptive CMV therapy at viral loads as low as 135 IU/mL in HCT recipients.

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Keywords

Cytomegalovirus; Quantitative Real-Time Polymerase Chain Reaction; WHO International Standard; Hematopoietic Cell Transplantation; Pre-emptive Therapy; viral load

1. Background

Cytomegalovirus (CMV) is a major cause of morbidity and mortality in hematopoietic cell transplant (HCT) recipients(1-3).Preemptive therapy strategies involving virologic monitoring and early intervention with antiviral therapy have been widely employed and successful in reducing CMV disease(4, 5).Quantitative nucleic acid amplification techniques have largely replaced pp65 antigenemia for early CMV detection and offer improved sensitivity without loss of specificity(6-8).Despite the widespread use of quantitative PCR, there is no consensus regarding the CMV level at which preemptive therapy should be initiated(9-11).Some studies have suggested a threshold of 500 copies/mL, others 1000 copies/mL, while others suggest different thresholds dependent on recipient risk(12-15).This lack of consensus translates into significant heterogeneity in clinical practice.

Attempts to establish broadly applicable quantitative values to guide preemptive therapy have been hampered by significant inter-assay quantification variability. To improve result generalizability between centers using different assays, the World Health Organization (WHO) developed the First WHO International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques, NIBSC code 09/162in 2010. Laboratories are now harmonizing quantitative CMV assays to the international standard and reporting results in international units (IU) rather than copies. While calibration to the WHO International Standard is an imperfect solution to inter-assay variability, the opportunity to provide comparable quantitative data across laboratories facilitates the development of guidelines with broadly applicable thresholds for diagnosing and managing CMV infection.

In the era of highly sensitive PCR assays and international calibration to the CMV WHO Standard, there is an unmet need to identify clinically relevant viral loads for the initiation of preemptive therapy in HCT recipients. In particular, the significance of low-level viremia and the impact of treatment initiation at various viral loads on clinically important outcomes require further investigation.

2. Objectives

To evaluate the relationship between CMV DNA levels in plasma at initiation of preemptive therapy, time to resolution of viremia, and duration of antiviral treatment in HCT recipients.

3. Study Design

3.1.Patient Population

We retrospectively reviewed results of quantitative CMV PCR testing in plasma performed at Stanford University Clinical Virology Laboratory. Between June 20, 2011 and June 30, 2014, 722 adult HCT recipients (age ≥18years) had 9610 tests performed. Of these, 256 HCT recipients, with 5578 CMV tests performed during monitoring for preemptive therapy,

had at least one positive test result in the assay's linear range (≥ 135 IU/mL) and were evaluated in our study.

3.2. Quantitative CMV Testing

Testing was performed using the *artus* CMV Rotor-Gene PCR (Qiagen, Germantown, MD) as previously described(16).Viral load values were expressed in international units (IU/mL) based on the test's calibration to the primary CMV WHO standard obtained from the National Institute for Biological Standards and Control (Hertfordshire, UK).

3.3. Data Collection and Definitions

Demographic and clinical data for each HCT recipient with at least one CMV PCR result of ≥ 135 IU/mL were collected through medical record review. CMV disease was defined as a consistent clinical presentation with CMV detected by immunohistochemistry or PCR on biopsied tissue. An episode of CMV viremia was defined as the time period beginning with a quantitative CMV PCR result of ≥ 135 IU/mL and ending with resolution of viremia to an undetectable level or detectable but <135 IU/mL for two consecutive tests. The primary outcome of this study was the time to resolution of viremia following initiation of antiviral therapy. Secondary outcomes included the incidence of prolonged CMV viremia, defined as detectable and quantifiable CMV DNA for >30 days, and the duration of antiviral therapy.

For each episode, the CMV DNA level immediately prior to the initiation of antiviral therapy and the duration of treatment were identified by chart review. Viral load treatment threshold, choice and dose of antiviral, and duration of treatment were at the discretion of the clinician. Intravenous ganciclovir 5mg/kg every 12 hours or oral valganciclovir 900mg twice daily were the most common agents used for preemptive therapy. These agents were dosed for renal function and continued until the resolution of viremia, followed by 1-3 weeks of maintenance therapy, per protocol. CMV genotypic drug resistance testing (Focus Diagnostics, Cypress, CA), as ordered by the clinician during the study period, was evaluated as available.

3.4. Data Analysis

To assess for associations between the primary outcome and CMV DNA level at treatment initiation, treatment episodes were stratified into groups by viral load. A viral load of 1000 IU/mL at treatment initiation was selected based on prior literature supporting a similar threshold (1000 copies/mL) for CMV preemptive therapy(13, 15).To identify a significant viral load division below 1000 IU/mL, we used principal component analysis and found 440 IU/mL as the middle point in the data that displayed the largest variance across groups for time to resolution of viremia(17).

Episodes were then separated into three groups by viral load at treatment initiation: 135-440 IU/mL, 441-1000 IU/mL, and >1000 IU/mL. Kaplan-Meier analysis was performed using resolution of viremia as the primary event, and significance was determined with the log-rank test. Patients were right-censored if there was a lack of documented resolution of viremia or completion of treatment within the study period. Multivariate Cox proportional hazards models were used to examine the relationship between the time to resolution of

viremia and viral load at treatment initiation, while adjusting for relevant baseline covariates. The multivariate model incorporated covariates found to have a P value $<.30$ in the univariate analysis. The hazard ratio and median time to resolution including 95% confidence intervals (CI) were calculated for each predictor. Where hazard ratios are shown, the category denoted by (1.00) was the reference group. Adjusted hazard ratios (AHR) >1.00 indicate a shorter time to resolution of viremia, whereas AHR values <1.00 indicates a longer time to resolution of viremia.

Continuous variables were compared between groups using the Kruskal-Wallis test and categorical variables were compared between groups using the Fisher's exact test. Statistical analysis was performed using STATA 13.0 (College Station, Texas). A P value $<.05$ was considered statistically significant.

4. Results

During the study period, 377 episodes of viremia developed among 256 HCT recipients. In 49 episodes, CMV viremia spontaneously resolved without treatment. 328 episodes among 221 HCT recipients were treated in response to aCMV PCR result of ≥ 135 IU/mL. 23 episodes were censored due to a lack of documented resolution of viremia or completion of treatment within the study period, resulting in a total of 305 treated episodes of viremia for primary and secondary outcome analysis. Treatment was initiated in 89 episodes at a viral load of 135-440 IU/mL [median 278 IU/mL, interquartile range (IQR) 202-343 IU/mL], 104 at 441-1000 IU/mL (median 618 IU/mL, IQR 481-773), and 112 at >1000 IU/mL (median 2111 IU/mL, IQR 1340-3590 IU/mL). The median duration between CMV tests during episodes was 7 days and was not significantly different between groups ($P = .54$). Patient characteristics stratified by CMV DNA level at treatment initiation were comparable (Table 1).

4.1. Time to Resolution of Viremia

Median time to resolution of viremia was significantly shorter when treatment was initiated at lower viral loads: 15 days for 135-440 IU/mL, 18 days for 441-1000 IU/mL, 21 days at >1000 IU/mL ($P < .001$; Table 2). Kaplan-Meier analysis also demonstrated a difference in time to resolution of viremia for each treatment group ($P < .001$; Figure 1). In a multivariate analysis, the association between viral load at treatment initiation and duration of viremia remained significant (Table 3). With the >1000 IU/mL group as reference, the AHR for shortened duration of viremia was 1.35 (95% CI, 1.02-1.79, $P = .03$) for those treated at 441-1000 IU/mL and 2.10 (95% CI, 1.55-2.85, $P < .001$) at 135-440 IU/mL. A shorter time to resolution of viremia was also associated with a matched donor and non-lymphoma indication for HCT.

4.2. Spontaneously Resolving Episodes

Median peak viral load for the 49 episodes that spontaneously resolved without antiviral therapy was 206 IU/mL, with a maximum peak viral load of 601 IU/mL. These episodes were matched to a comparison group of 84 episodes with an initial median viral load of 208 IU/mL (IQR: 167-288 IU/mL) that was followed by an increase in viral load to >440 IU/mL

within 7 days and initiation of preemptive therapy. These 84 episodes accounted for 40% of the 216 episodes where treatment was initiated at a viral load >440 IU/mL and had a median viral load of 1,110 IU/mL (IQR: 503-10,500 IU/mL) at treatment initiation. These two groups were similar when compared using the variables shown in Table 1 except that episodes with spontaneous resolution were significantly less likely to have new or worsening GVHD diagnosed within the prior month (4% vs 36%, $P<.001$). Furthermore, episodes that spontaneously resolved did not have CMV disease diagnosed during the episode of viremia (0% vs 10%, $P=.03$).

4.3. Prolonged Viremia

Consistent with the time to resolution of viremia, prolonged episodes of viremia lasting >30 days occurred less frequently in the lower viral load treatment groups (1% vs 15% vs 24%, $P<.001$; Table 2). The number needed to treat (NNT) to prevent one episode of prolonged viremia when treatment was initiated at 135-440 IU/mL was 7.1 compared to 441-1000 IU/mL and 4.3 compared to >1000 IU/mL. Genotypic drug resistance testing was performed during 16/44 (36%) of these prolonged episodes, resulting in the identification three UL97 mutations: one (C592G) in the 441-1000 IU/mL group and two (M460V, L595S) in the >1000 IU/mL group.

4.4. Treatment Duration

Median treatment duration for episodes in which therapy was initiated at 135-440 IU/mL, 441-1000 IU/mL, and >1000 IU/mL were 28, 34, and 37 days, respectively ($P<.001$; Table 2). Treatment was continued for a median duration of 14-16 days after resolution of viremia and was not significant across groups ($P=.18$; Table 2). Preemptive therapy was initiated with valganciclovir or ganciclovir in 88%, foscarnet in 4%, and alternating ganciclovir and foscarnet in 8% of episodes. Initial treatment did not differ across groups ($P=.78$).

5. Discussion

Despite the widespread use of CMV monitoring to guide preemptive antiviral therapy, clinical practice guidelines have yet to provide recommendations on when to initiate preemptive therapy in HCT recipients. Prior attempts at defining broadly applicable viral load thresholds have been limited by significant inter-assay quantification variability. However, the implementation of the CMV WHO International Standard for assay calibration now facilitates comparisons of viral load measurements across laboratories and may allow for clinically meaningful interpretation of these quantitative values.

This study emphasizes the clinical importance of CMV viral load at treatment initiation in HCT recipients undergoing preemptive therapy. We found that the initiation of preemptive therapy at lower CMV viral loads was associated with shorter episodes of viremia and decreased risk for prolonged viremia lasting >30 days. Prolonged viremia and high peak viral loads are associated with the development of antiviral resistance and CMV disease; thus, efforts towards minimizing duration of viremia may provide substantial clinical benefit (18-21). Additionally, preemptive therapy started at lower viral loads was associated with shorter treatment duration. Shorter exposure to antivirals, particularly ganciclovir and

foscarnet, may minimize toxicity such as leukopenia and acute renal injury, and reduces the need for frequent drug level monitoring for dose adjustments(22).

A limited number of previous studies evaluated CMV DNA levels at the initiation of preemptive therapy, though none have been designed to identify differences in time to resolution of viremia or duration of treatment. In the study by Einsele, *et al.*, which preceded the widespread use of quantitative CMV PCR in clinical laboratories, qualitative CMV PCR and viral culture were compared in a preemptive therapy strategy. The more sensitive PCR assay was found to result in earlier CMV detection and shortened duration of treatment(22). Two additional studies investigated the association of viral load at treatment initiation, reported in locally defined copies/mL, with a delayed virologic response. However, rather than time to resolution of viremia, delayed virologic response was defined as an increase in CMV DNA levels early after treatment initiation. While one study reported an association between higher viral loads at the initiation of therapy and a delayed virologic response, the other did not(14, 23).

Though the findings presented here demonstrate a benefit to starting preemptive therapy at CMV viral loads as low as 135 IU/mL, early antiviral therapy may lead to unnecessary treatment for episodes of CMV viremia that may have resolved spontaneously. In our study, the diagnosis of GVHD within the preceding month was associated with rising CMV levels and eventual treatment, though this criterion was insensitive for identifying patients who may benefit from early antiviral therapy. As might be expected, CMV disease was not diagnosed among episodes of CMV viremia that spontaneously resolved. Importantly, improved methods are needed for differentiating episodes of low level viremia that are likely to spontaneously resolve from those that will not. Other studies have suggested that measuring the rate of increase in CMV viral load allows the differentiation of these episodes(14, 24). However, this strategy would result in delayed initiation of therapy for patients whose viral loads continued to rise and, based on our findings, lead to longer episodes of viremia, increase the risk for prolonged viremia, and require longer courses of antiviral therapy.

In multivariate analyses, we also found that having a non-lymphoma indication or receiving an HLA-matched transplant was associated with a shorter duration of viremia. Differences in underlying immunologic function may explain these findings, though further work will be required to characterize the mechanisms that contribute to CMV resolution in these patients.

Limitations in our study involve practice patterns that were dictated by the provider, including selection of antiviral agent, dose, and duration. No drug level monitoring was performed to confirm standardized treatment and CMV genotypic drug resistance testing was performed in a minority of patients, which precluded a detailed analysis of the effect of resistance on outcomes. Additionally, provider initiation of preemptive therapy at low viral loads limited our ability to fully evaluate the natural history of low-level CMV viremia and better characterize episodes that may spontaneously resolve.

This study, to date, is the largest evaluation of CMV DNA levels in HCT recipients undergoing preemptive monitoring with CMV testing harmonized to the WHO International

Standard. We suggest that preemptive therapy may be started at CMV DNA levels as low as 135 IU/mL to reduce the time to resolution of viremia and the duration of therapy. Though findings in this study offer insight into the clinical benefits of initiating preemptive CMV therapy at low viral loads, further studies are needed to better discriminate patients with low level viremia that are likely to spontaneously resolve from those that require an immediate therapeutic intervention.

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Highlights

- Preemptive therapy is the basis of CMV prevention in HCT recipients.
- Retrospectively evaluated CMV levels at the initiation of preemptive therapy.
- The rapy initiation at low viral loads was associated with shorter time to resolution of viremia.
- Prolonged episodes of viremia lasting >30 days occurred less frequently.
- Therapy initiation at low viral loads was associated with shorter treatment duration.

Figure 1.

Kaplan-Meier estimates of time to resolution of CMV viremia by CMV DNA level at initiation of antiviral treatment. With the >1000 IU/mL group as reference, the adjusted hazard ratio was 1.35 (95% confidence interval, 1.02-1.79, $P = .03$) for the 441-1000 IU/mL group and 2.10 (95% confidence interval, 1.55-2.85, $P < .001$) for the 135-440 IU/mL group. The graph does not show 9 cases in the 441-1000 IU/mL and >1000 IU/mL groups where viremia resolved beyond 75 days.

Table 1
Demographic and Clinical Characteristics of Viremic HCT Recipients Stratified by CMV
DNA Levels at Initiation of Antiviral Therapy

Characteristic	135-440 IU/mL (n=89)	441-1000 IU/mL (n=104)	>1000 IU/mL (n=112)	P Value
Age, y ^a	55 (40-63)	57 (43-63)	57 (45-64)	.69
Day from transplant ^a	49 (29-129)	47 (27-101)	46 (28-92)	.44
Indication				.53
Acute leukemia	41 (46)	41 (39)	46 (41)	
Chronic leukemia	10 (11)	12 (12)	7 (6)	
Lymphoma	25 (28)	32 (31)	32 (29)	
Other ^b	13 (15)	19 (18)	27 (24)	
Conditioning regimen				.76
Myeloablative	35 (39)	37 (36)	37 (33)	
Nonmyeloablative	39 (44)	49 (48)	50 (45)	
Reduced intensity	15 (17)	17 (16)	25 (22)	
Match				.58
MRD	33 (37)	35 (34)	38 (34)	
MURD	28 (31)	39 (38)	41 (36)	
MMURD	23 (26)	27 (26)	31 (28)	
Haploidentical	4 (5)	1 (1)	0 (0)	
Autologous	1 (1)	1 (1)	2 (2)	
Stem cell source				.24
PBC	85 (96)	89 (86)	100 (89)	
BM	4 (4)	11 (11)	9 (8)	
Umbilical	0 (0)	3 (3)	3 (3)	
CMV serostatus				.27
D+/R+	55 (62)	66 (65)	61 (55)	
D+/R-	0 (0)	3 (3)	6 (5)	
D-/R+	33 (37)	32 (31)	43 (38)	
Autologous (R+)	1 (1)	1 (1)	2 (2)	
T-cell depletion	3 (3)	0 (0)	1 (1)	.11
ATG	46 (51)	57 (55)	65 (61)	.43
Steroids	58 (65)	56 (54)	67 (60)	.28
GVHD	29 (33)	38 (37)	41 (36)	.83

Abbreviations: HCT, hematopoietic cell transplant; CMV, cytomegalovirus; MRD, matched related donor; MURD, matched unrelated donor; MMURD, mismatched unrelated donor; PBC, peripheral blood cell; BM, bone marrow; ATG, anti-thymocyte globulin; D+, donor serology positive; D-, donor serology negative; R+, recipient serology positive; R-, recipient serology negative; GVHD, graft versus host disease

^aMedian (interquartile range), other table entries represent n (%).

^bIncluded myelodysplastic syndrome, myelofibrosis, aplastic anemia, multiple myeloma

Table 2
Outcomes of CMV Viremia Episodes in HCT Recipients Stratified by CMV DNA Levels at Initiation of Antiviral Therapy

Characteristic	<u>135-440 IU/mL</u> (n=89)	<u>441-1000 IU/mL</u> (n=104)	<u>>1000 IU/mL</u> (n=112)	P Value
Median days to viremia resolution (95% CI)	15 (10-17)	18 (13-19)	21 (20-25)	<.001 ^a
Prolonged viremia >30 days (%)	1 (1)	16 (15)	27 (24)	<.001
Median days on antiviral treatment (95% CI)	28 (26-30)	34 (31-37)	37 (34-40)	<.001 ^a
Median days of treatment after viremia resolution (IQR)	14 (9-21)	16 (10-24)	14 (9-22)	.18
CMV disease	5 (6)	9 (8)	8 (7)	.73

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic cell transplant; CI, confidence interval; IQR, interquartile range

^aPvalue by log-rank test

Table 3
Multivariate Analysis of Predictors for Time to Resolution of CMV Viremia Among HCT Recipients

		Multivariate Analysis^a	
Predictor	AHR	95% CI	P Value
CMV viral load			
135-440 IU/mL	2.10	(1.55-2.85)	<.001
441-1000 IU/mL	1.35	(1.02-1.79)	.03
>1000 IU/mL	(1.00) ^b		
Indication			
Acute leukemia	1.53	(1.09-2.14)	.01
Chronic leukemia	1.77	(1.12-2.80)	.01
Other	1.51	(1.04-2.19)	.03
Lymphoma	(1.00)		
Conditioning regimen			
Myeloablative	1.05	(.64-1.72)	.85
Nonmyeloablative	1.08	(.75-1.56)	.68
Reduced intensity	(1.00)		
Match			
MRD	1.99	(1.38-2.85)	<.001
MURD	1.48	(1.07-2.04)	.02
Haploidentical	1.61	(.59-4.39)	.36
Autologous	3.20	(.89-11.45)	.07
MMURD	(1.00)		
Stem cell source			
PBC	1.67	(.58-4.82)	.35
BM	1.30	(.40-4.15)	.66
Umbilical	(1.00)		
ATG			
No	1.02	(.63-1.66)	.93
Yes	(1.00)		
CMV serostatus			
D+/R+	1.15	(.89-1.48)	.27
D+/R-	1.19	(.58-2.45)	.64
D-/R+	(1.00)		
CMV disease			
No	1.17	(.74-1.85)	.50
Yes	(1.00)		
Steroids			

		Multivariate Analysis^a	
Predictor	AHR	95% CI	P Value
No	1.30	(.95-1.76)	.10
Yes	(1.00)		
GVHD			
Yes	1.07	(.80-1.44)	.64
No	(1.00)		

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic cell transplant; AHR, adjusted hazard ratio; CI, confidence interval; MRD; matched related donor; MURD, matched unrelated donor; MMURD, mismatched unrelated donor; PBC, peripheral blood cell; BM, bone marrow; ATG, anti-thymocyte globulin; D+, donor serology positive; D-, donor serology negative; R+, recipient serology positive; R-, recipient serology negative; GVHD, graft versus host disease

^aFinal model included covariates with a P value <.30 by univariate analysis with log-rank statistic

^bHazard ratio estimates within parentheses (1.00) indicate reference categories