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MAJOR ARTICLE

Cytomegalovirus in Adult Allogeneic Blood and Marrow Transplant Patients Before or Around the Period of Neutrophil Recovery: A Single-Center, Retrospective, Descriptive Study

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Background. Few reports exist on pre-engraftment cytomegalovirus (CMV) DNAemia in allogeneic blood or marrow transplant (allo BMT) recipients. We describe this clinical entity, its management, and the potential effect of 3 different quantitative CMV deoxyribonucleic acid (DNA) tests used during the 6-year study period.

Methods. We performed a retrospective, single-center study of allo BMT recipients from 2010 to 2015 who developed CMV DNAemia before neutrophil recovery (absolute neutrophil count [ANC] <1000 cells/mm^3, "pre-engraftment CMV") or who became neutropenic concomitant with detectable CMV DNA ("peri-engraftment CMV"). Clinical data were collected from the electronic medical record.

Results. Among 1151 adult allo BMT patients, 73 developed CMV DNAemia before engraftment or while neutropenic after initial engraftment. Most patients were eventually treated (valganciclovir or ganciclovir, N = 68; foscarnet, N = 1); 4 were not treated. First CMV detection occurred at median day +12 (range, 0–48), but treatment was not started until median day +33 (range, 4–105) at median ANC of 760 cells/mm^3. Six patients had peak viral loads >5000 IU/mL; none had tissue-invasive disease. One developed ganciclovir resistance. No significant differences were observed upon stratification by quantitative CMV DNA test.

Conclusions. Cytomegalovirus DNA was detected in 6.3% of pre- and peri-engraftment allo-HSCT patients. Ganciclovir derivatives were commonly used for treatment despite risk of neutropenia. Treatment was typically deferred until CMV DNA and ANC rose. With rare exceptions, this treatment strategy did not appear to have adverse clinical consequences with respect to acute CMV. Different CMV DNA quantification tests used performed similarly from a clinical perspective despite different analytical performance characteristics.

Keywords. bone marrow transplant; CMV; pre-engraftment.

Cytomegalovirus (CMV) disease remains a significant infectious cause of morbidity and mortality in patients undergoing allogeneic blood or marrow transplant (allo BMT) despite advances in monitoring and treatment [1, 2]. Cytomegalovirus replication and disease are well recognized complications postengraftment, when the newly acquired immune system becomes functional [3]. Prophylaxis with valganciclovir or letermovir has been demonstrated to be effective in preventing postengraftment CMV disease [4, 5]; however, many centers have continued the strategy of serial monitoring of CMV deoxyribonucleic acid (DNA) in blood and preemptive therapy, in which infection is treated before disease onset. With preemptive therapy, postengraftment CMV DNA detection in blood (CMV DNAemia) of asymptomatic patients is far more common than CMV disease [3]. However, progressive, tissue-invasive infection of the gastrointestinal tract, lungs, liver, central nervous system, retina, or other sites can occur occasionally.

In contrast to postengraftment CMV infection, less is understood about CMV detection early after transplantation, from the period before engraftment to around the time neutrophil recovery. One study noted that CMV disease before engraftment was uncommon, occurring in approximately 1% of allo BMT recipients, but was associated with a high mortality rate [6]. A subsequent study demonstrated that CMV DNAemia was identified in a greater proportion of patients with CMV disease and at higher levels compared with controls [7]. Cytomegalovirus DNAemia was also detectable approximately 2 weeks before disease, suggesting that monitoring CMV

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DNA in plasma might help identify patients at risk of this pre-engraftment complication [7].

Extension of monitoring for CMV DNA into the pre-engraftment period has been facilitated by the ready availability of quantitative nucleic acid amplification tests for CMV DNA measurement (CMV qNAATs), which are now routine components of test menus at centers performing allo BMT. However many questions remain regarding pre-engraftment CMV DNAemia including its prevalence when monitoring is initiated immediately after allo BMT, its clinical characteristics, the risk of progression to tissue-invasive disease, and whether pre-engraftment CMV DNAemia should be treated and when. In addition, it is unclear which antivirals should be used in these medically tenuous patients, given the myelosuppressive potential of first-line therapy (ganciclovir, valganciclovir) and nephrotoxicity of second-line drugs (foscarnet and cidofovir).

At our center, post-allo BMT monitoring includes weekly CMV qNAAT from plasma starting at day 0 (day of receipt of the allo BMT). This practice allowed us to perform a retrospective, descriptive study of CMV DNAemia in neutropenic patients before engraftment and among those who became neutropenic again after engraftment (peri-engraftment neutropenia). The main aims of this study were to determine the prevalence of CMV DNAemia during pre- and peri-engraftment neutropenia, define its clinical characteristics, and describe therapeutic practices such as whether CMV DNAemia was treated, clinical parameters at treatment initiation (CMV DNA level and absolute neutrophil count [ANC]), and treatment regimens. Furthermore, we sought to assess whether clinicians' decisions to treat (or to wait), depending on the viral load and ANC, had any adverse effects in terms of development of tissue-invasive CMV disease or high peak viral loads. Finally, CMV DNA quantitative testing evolved during the 6-year study period to exploit the diagnostic gains afforded by improved automation and by the adoption of a US Food and Drug Administration-approved assay that incorporated a new international standard for CMV qNAAT calibration [8, 9]. The utilization of different assays at our center allowed us to compare clinical features and treatment characteristics of pre-/peri-engraftment CMV DNAemia in 3 sequential eras during the study period when 3 CMV qNAATs with varying performance characteristics were in use, in order to discern the clinical impact of deploying assays with slightly different functionality.

METHODS

Clinical Record Review

Subjects who underwent allo BMT between January 2010 and December 2015 were identified through 2 databases of adult allo BMT recipients at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins Hospital. Two groups of first-time allo BMT patients were selected for inclusion, one group with detectable CMV DNAemia occurring before neutrophil recovery (defined as ANC <1000 cells/mm^3, n = 60) and a second, smaller group with peri-engraftment neutropenia (n = 13) who developed recurrent neutropenia after neutrophil recovery, with their first episode of CMV DNAemia detectable after recurrent neutrophil decline. These latter patients were included because the treatment dilemma in this group was similar to that in patients with pre-engraftment CMV. Patients who had undergone a prior allo BMT were excluded.

Data collected from retrospective medical record review included age, gender, underlying disease, allograft type, donor/recipient CMV serostatus, conditioning regimen, CMV qNAAT results, ANCs at specific time points (at time CMV DNA was detectable, at time CMV DNA was greater than assay's lower limit of quantification [LLOQ], and at time of treatment initiation), CMV treatment (what antiviral agent was used, if any, and treatment duration), CMV disease within 100 days of allo BMT, and death within 6 months of allo BMT. This study was approved by the Johns Hopkins Medicine Institutional Review Board.

Cytomegalovirus Management in Allogeneic Blood or Marrow Transplant

Post-allo BMT CMV DNA monitoring at this center includes weekly CMV qNAAT from plasma, starting from day 0 (date of allo BMT). In the electronic medical record, CMV DNA ≥LLOQ was flagged as an abnormal result. Once this occurred, management was per clinician choice and included decisions such as CMV DNA monitoring frequency (could increase to twice weekly), initiation of preemptive treatment, CMV antiviral drug selection, duration of preemptive treatment (until CMV qNAATs results were either <LLOQ or undetectable), and duration of CMV DNA monitoring after treatment cessation.

Cytomegalovirus Quantitative Nucleic Acid Amplification Tests

Three different qNAATs were used sequentially during the 6-year study period (Table 1) [10]. Testing eras 1 and 2 were reported in copies/mL, whereas era 3 was calibrated according to the CMV WHO International Standard and reported in IU/mL [9]. Validation studies performed before test implementation demonstrated a mean difference in CMV DNA measurement of -0.12 $\log_{10}$ for era 2 qNAAT versus era 1 (era 2 qNAAT values were on average 0.12 $\log_{10}$, or 1.3-fold, greater than era 1 qNAAT) and 0.31 $\log_{10}$ for era 3 qNAAT versus era 2 qNAAT (era 3 qNAAT values were on average 0.31 $\log_{10}$, or 2-fold, less than era 2 qNAAT).

Statistical Analysis

Descriptive statistics (means, medians) were analyzed with Stata version 14. Associations between discrete variables (such as assay era) and continuous variables (such as the day posttransplant when CMV DNA was first detectable) were tested using one-way analysis of variance. $P < .05$ was considered significant.

Table 1. Clinical CMV qNAATs During Study Period

	Era 1	Era 2	Era 3
Dates	January 1, 2010 (study start)–May 1, 2012	May 2, 2012–April 2, 2013	April 3, 2013–December 31, 2015 (study end)
Test • Extraction • Amplification • Real-time PCR reagents	Laboratory developed test BioRobot M48 (QIAGEN) SDS 7500 (Applied Biosystems) Artus (QIAGEN)	Laboratory developed test (7) QIASymphony (QIAGEN) RGQ (Rotorgene, QIAGEN) Artus (QIAGEN)	COBAS AmpliPrep (extraction)/ COBAS TaqMan (real-time PCR) CMV (Roche Molecular Diagnostics) Test system approved by the US Food and Drug Administration
LLOQ	300 copies/mL	100 copies/mL	137 IU/mL[a]
LOD	100 copies/mL	50 copies/mL	91 IU/mL

Abbreviations: CMV, cytomegalovirus; LLOQ, lower limit of quantification; LOD, limit of detection; PCR, polymerase chain reaction; qNAAT, quantitative nucleic acid amplification tests

[a]Conversion from copies to IU between tests used in era 2 and era 3, 1.09 copy/IU as per era 3 validation studies using clinical plasma samples.

A sensitivity analysis was performed, either including or excluding patients (n = 13) who initially engrafted then again became neutropenic by the time their CMV DNAemia was detected. The analysis that excluded these patients included only those who had detectable CMV DNAemia before initial neutrophil recovery (n = 60).

RESULTS

Patients

During the study period, 73 of 1151 (6.3%) adult patients who underwent allo BMT met the case definitions of CMV DNA detection in plasma with ANC <1000 (pre- or peri-engraftment). Demographic information and basic clinical characteristics were retrieved (Table 2). The conditioning regimen type and donor and graft types in these 73 patients mirrored that seen in the total 1151 patient cohort; most patients with pre- or peri-engraftment CMV DNA had received nonmyeloablative conditioning regimens (78%) and haploidentical allografts using posttransplant cyclophosphamide (PTCy) (82%). Cytomegalovirus serologic status was documented for all recipients and for 70 of 73 (96%) of donors (Table 2). Most recipients were CMV immunoglobulin (Ig)G seropositive (R+, 68 of 73, 93%). Donor CMV IgG serology was positive in 43 of 73 (D+, 59%) and negative in 27 of 73 (37%). The greatest proportion of patients were D+/R+ (55%) (Table 2).

Table 2. Patient Demographic and Clinical Characteristics (n = 73)

Median age (years)	52 (23–76)
Gender	
Male	39 (53%)
Female	34 (47%)
Donor/Recipient CMV Serology	
Recipient seropositive (total)	68 (93%)
Recipient seronegative (total)	5 (7%)
Donor seropositive (total)	43 (59%)
Donor seronegative (total)	27 (37%)
Donor serology missing	3 (4%)
D+/R+	40 (55%)
D-/R+	25 (34%)
D+/R−	3 (4%)
D−/R−	2 (3%)
Induction Regimen	
Myeloablative	16 (22%)
Nonmyeloablative	57 (78%)
Allograft Type	
Matched related	7 (9%)
Haploidentical	60 (82%)
Unrelated donor	5 (7%)
Cord blood	1 (1%)

Abbreviations: CMV, cytomegalovirus; D, donor, R, recipient.

Clinical Features of Pre-/Peri-Engraftment Cytomegalovirus Among All Case Patients and Stratified by Testing Era

To better understand the clinical entity of pre-/peri-engraftment CMV, clinical features related to plasma CMV DNA detection were characterized. Overall, CMV DNAemia was first detectable at a median of 12 days posttransplant (range, 0–48 days) and rose to levels above the LLOQ at a median of 28 days posttransplant (range, 0–49 days). The median ANC at which CMV DNA became detectable and measurable (>LLOQ) was less than 500 cells/mm^3. The median peak CMV DNA of the pre-/peri-engraftment episode was <1000 copies/mL, but it ranged considerably (790–84 300 copies or IU/mL). Only 6 patients (8%) had peak CMV DNA >5000 (data not shown). Stratified analysis according to test era to determine the effect of qNAAT demonstrated no significant difference between the 3 testing eras for the following parameters: day posttransplant and ANC at which CMV DNA was first detectable, day posttransplant and ANC at which CMV DNA was first above the LLOQ, or peak CMV DNA of the episode (Table 3). In addition, a sensitivity analysis demonstrated no significant difference in these results when excluding the group of 13 patients who had initially engrafted and then had become neutropenic again by the time that CMV DNA was detected.

Treatment of Pre-/Peri-Engraftment Cytomegalovirus Among All Case Patients and Stratified by Testing Era

Most patients with CMV DNAemia in the pre- and peri-engraftment period were eventually treated with antiviral drugs

Table 3. Clinical Features of CMV Among All Patients and Stratified by Testing Era

	All Patients (n = 73)	Era 1 Patients (n = 20) (<300 copies/mL)	Era 2 Patients (n = 14) (<100 copies/mL)	Era 3 Patients (n = 39) (<137 IU/mL)	
	Median (Range)	Median (Range)	Median (Range)	Median (Range)	*P* Value
Day posttransplant when CMV first detectable	12 (0–48)	10 (2–48)	13 (3–38)	12 (0–34)	.72
Day posttransplant when CMV > LLOQ	28 (0–49)	28 (9–48)	28 (3–45)	30 (0–49)	.79
ANC when CMV first detectable (cells/mm^3)	110 (20–4030)[a]	76 (50–1647)	90 (20–1340)	125 (20–4030)	.99
ANC when CMV first > LLOQ	423 (20–2560)[a]	416 (50–1632)	610 (20–2560)	350 (20–1660)	.76
Peak CMV DNA of episode (copies/mL or IU/mL)	790 (137–84 300)	1127 (300–22 122)	449 (211–2489)	829 (137–84 300)	.46

Abbreviations: ANC, absolute neutrophil count; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; LLOQ, lower limit of quantification.

[a]Upper end of range is >1000 because the cohort includes peri-engraftment patients with recovered ANCs who again became neutropenic after plasma CMV was detected.

(69 of 73, 95%) (Table 4). Most patients (69 of 73, 95%) were started on CMV treatment on the basis of preemptive CMV PCR monitoring (Table 4), but treatment initiation was deferred until after engraftment (median 33 days posttransplant) (Table 5) relative to initial detection (median 12 days posttransplant) (Table 3). Valganciclovir (41 of 69, 59% of treated patients; 41 of 73, 56% of all case patients) and intravenous (IV) ganciclovir (27 of 69, 39% of treated patients; 27 of 73, 37% of all case patients) were used most commonly. Only one patient received foscarnet initially. Cytomegalovirus Ig was used at some point in the course of treatment in 6 (8%) patients. Four patients (4 of 73, 5%) were managed with continued monitoring and no antiviral therapy. At initiation of therapy, the median CMV DNA level was 656 copies or IU/mL and the median ANC was 760 cells/mm^3 (compared with median 110 cells/mm^3 at initial detection of CMV). The median treatment duration was 34 days (Table 5).

Stratified analysis according to test era to determine the effect of qNAAT on treatment of pre-/peri-engraftment CMV demonstrated no significant differences in the 3 testing eras for the following parameters: day posttransplant when treatment was started, CMV DNA level when treatment was started, and ANC on the day treatment was started (Table 5). There was also no significant association between the peak CMV DNA level and the day posttransplant on which treatment was started ($P = .99$) or the peak CMV DNA level and the ANC at which treatment was started ($P = .56$, data not shown). However, for treatment duration, there was a trend toward significance between era 2, when a qNAAT with the lowest LLOQ and limit of detection (LOD) was in use, and eras 1 and 3 (<300 copies/mL and <137, respectively). The median duration of treatment in era 2 was 36 days, compared with 31 and 34 days for era 1 and era 3, respectively ($P = .04$) (Table 5).

Table 4. Patient Treatment Information (n = 73)

Initial Agent Used to Treat CMV DNAemia[a]	Number (%)
Valganciclovir	41 (56%)
Ganciclovir	27 (36%)
Foscarnet	1 (1%)
No treatment	4 (6%)

Abbreviations: CMV, cytomegalovirus.

[a]CMV immunoglobulin was used at some point of treatment in 6 (8%) patients.

Acute Cytomegalovirus-Related Outcomes

No patients in this cohort developed biopsy-proven tissue-invasive CMV disease within the first 100 days posttransplant. Fifty-nine (80%) patients were alive at 6 months. Stratified analysis according to test era demonstrated that there was no significant association between survival at 6 months and the day posttransplant on which treatment was started ($P = .17$). In addition, there was no significant association between survival at 6 months and the ANC at which treatment was started ($P = .62$).

There was no significant association between the ANC at start of treatment and the time from transplant until neutrophil engraftment (ANC >500; $P = 1.0$), nor was there a significant association between treatment/no treatment and time to engraftment ($P = .9$). However, all but 4 patients in this cohort were treated for CMV.

One patient developed ganciclovir-resistant CMV during a recrudescence of CMV DNAemia, approximately 3 months into the course of CMV treatment. This patient's CMV DNA level peaked at 53 900 IU/mL during initial treatment with valganciclovir, fell to a level that was detectable but not quantifiable (<137 IU/mL) while on IV ganciclovir, and rose again in the setting of graft-versus-host disease (GVHD) and oncologic relapse. Cytomegalovirus DNAemia persisted in the 3000–4000 IU/mL range, and foscarnet treatment was required due to the development of ganciclovir resistance, with UL97 mutations M460V and A594V detected by direct sequencing. Four additional patients were tested for antiviral resistance and were not found to have UL97 resistance mutations.

Table 5. CMV Treatment Among All Patients and Stratified by Testing Era

	Era 1 (<300 copies/mL) (n = 20)	Era 2 (<100 copies/mL) (n = 14)	Era 3 (<137 IU/mL) (n = 39)		Total (n = 73)
	Median (Range)	Median (Range)	Median (Range)	*P* Value	Median (Range)
Day posttransplant when treatment initiated	29 (10–50)	29 (4–48)	36 (4–105)	.23	33 (4–105)
CMV DNA level at treatment initiation (copies/mL or IU/mL)	1127 (428–4262)	439 (175–1660)	736 (159–22 900)	.46	656 (159–22 900)
ANC at treatment initiation (cells/mm^3)	492 (28–1590)	890 (60–5840)	1070 (50–9680)	.11	760 (28–9680)
Treatment duration (days)	31 (9–66)	36 (25–392)	34 (11–243)	.04	34 (9–392)
Days of treatment until 2 consecutive undetectable CMV qNAAT results	33 (20–80)	34 (17–228)	37 (12–341)	.38	34 (12–341)

Abbreviations: ANC, absolute neutrophil count; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; qNAAT, quantitative nucleic acid amplification test.

DISCUSSION

In this descriptive study, pre- or peri-engraftment CMV DNAemia occurred in 6.3% of adult allo BMT recipients. Treatment of this entity is not protocolized at our center; therefore, this study offered the opportunity to document approaches to its management. Studies of postengraftment CMV infection have suggested treatment initiation at levels ranging from 135 IU/mL to 1000 copies/mL or based on the doubling time of DNA levels [11–14]. However, there is still a lack of consensus on treatment thresholds in the pre-engraftment population. Although the biology of those with pre- versus peri-engraftment CMV DNAemia may be distinct, we chose to include both groups in this study because the clinical management dilemma is similar in these 2 populations. The sensitivity analysis performed, excluding the smaller peri-engraftment group, did not change the overall analysis of results.

Our study demonstrated that most providers at our center elected preemptive treatment. However, therapy was typically deferred approximately 3 weeks, suggesting that clinicians waited for the CMV DNA level and/or ANC to rise before initiating treatment. It appeared that treatment was deferred until there was evidence that CMV might become clinically problematic and/or that the bone marrow had recovered sufficiently to potentially withstand the adverse effects of ganciclovir and valganciclovir, which were used in almost all patients despite the potential for bone marrow toxicity. This deferred treatment strategy did not appear to adversely affect short-term outcomes relating to acute CMV infection, because only 8% of patients developed viral loads over 5000 copies or IU/mL, and no patient developed biopsy-proven tissue-invasive CMV. The relative lack of high-viral-load CMV and end-organ involvement suggests that CMV DNAemia remained manageable even when treatment was deferred until after the ANC rose, to avoid hematologic toxicity. In addition, the timing of treatment did not appear to affect the time to engraftment. Despite these findings, careful management of these patients is still warranted, because occasional patients can develop complex CMV syndromes including ganciclovir resistance, as seen in 1 patient in our cohort.

Pre-engraftment CMV was first described in the premolecular era [6], and it was noted to be associated with significant disease and mortality. There is a paucity of published data on pre-engraftment CMV in the current era, in which CMV DNA is monitored routinely with sensitive quantification assays. Our findings along with a recent report by Solano et al [15] clarify some aspects of pre-engraftment CMV in the current clinical era. Unlike the original report [6], CMV disease seems to be uncommon among individuals with detectable CMV DNA in this setting. We observed no CMV end-organ disease before engraftment among 73 patients with pre-engraftment DNAemia. Likewise, Solano et al [15] found only 1 patient among 29 with pre-engraftment CMV with nonfatal CMV esophagitis before engraftment (day 18 after transplant). In addition, pre-engraftment CMV DNAemia occurs more commonly among CMV-seropositive than CMV-seronegative recipients. In our study, 68 patients (93%) were CMV-seropositive recipients among 73 patients with pre/peri-engraftment CMV. Likewise, in a univariate analysis, Solano et al [15] found that recipient seropositivity had the greatest odds ratio (4.6; 95% confidence interval, 0.59–35.58) among pretransplant variables associated with pre-engraftment CMV and trended as a risk factor (P = .14). These findings suggest that pre-engraftment CMV reactivation is more likely to be recipient-derived rather than donor-transmitted.

Other aspects of pre-engraftment CMV remain unclear, as highlighted by differences in findings between our study and the report by Solano et al [15]. Prevalence appears to be variable; in our study, it was lower than in the previous report (~6.5% versus ~15%). Whether this relates to differences in patients or transplant approaches (for example, virtually all of our patients receive PTCy as GVHD prophylaxis) is unknown. Moreover, Solano et al [15] showed that in a subset of patients, CMV DNAemia develops much earlier than previously recognized; approximately one quarter of all pre-engraftment episodes initiated before infusion. We were unable to study this further because CMV DNA monitoring is initiated at the time of bone marrow or peripheral blood-derived stem cell infusion at our center.

Cytomegalovirus qNAATs have been demonstrated to perform variably, demonstrating quantitative bias, varying quantification ranges, and differences in sensitivity [16]. The introduction of an international biological standard preparation of CMV intended for use as a global calibrator has improved quantitative agreement. However, interassay differences in quantification persist [17, 18], suggesting that the international standard's goal of harmonization has not been achieved yet. Interassay differences could affect the clinical description and management of any CMV-mediated syndrome. A previous study demonstrated that a shift from an unstandardized laboratory-developed qNAAT to a more sensitive commercial test that reports results in international units per milliliter had minimal clinical impact [19]. Our study offered the unique opportunity to describe clinical aspects and management practices of pre-engraftment CMV over 3 eras during which assays with small differences in LOD and LLOQ were used. We observed no significant differences in the clinical features of pre-engraftment CMV stratified by testing era. The lone difference in CMV treatment parameters was a predictable one—slightly longer median duration of treatment in era 2, when a qNAAT with the lowest LOD and LLOQ was in use. The small number of pre-engraftment CMV cases during each era precludes definitive conclusions regarding the clinical impact of different tests. However, the data are somewhat reassuring in that they suggest that the clinical performance of the 3 assays was fairly similar, which is consistent with previous findings [19].

This study has several limitations, the first of which is its retrospective and descriptive nature. No control group without CMV DNAemia was used for comparison of mortality outcomes. Because most patients were eventually treated at low levels of CMV, and only 4 patients were untreated, conclusions cannot be made about the natural history of untreated low-level CMV DNAemia in this patient population. Low absolute numbers of patients in each testing era meant that results could be skewed by outliers. For this reason, medians instead of means were compared for continuous variables. Because our center performs few cord blood transplants, these conclusions are not likely to apply to such patients. Finally, almost all of our patients receive PTCy GVHD prophylaxis, so these data may not apply to other GVHD prophylaxis strategies.

CONCLUSIONS

This study describes recent practices for monitoring and preemptive treatment of pre-/peri-engraftment CMV DNAemia, in neutropenic recipients of a first allo BMT at a single institution. Most patients received treatment for low but quantifiable levels of CMV DNAemia with ganciclovir or valganciclovir despite the potential bone marrow suppression caused by these antiviral agents. Treatment was generally initiated after a period of watching and waiting during which both the ANC and viral load rose. This strategy did not appear to increase the risk for tissue-invasive disease, because no biopsy-proven invasive disease occurred in this cohort. However, the occasional experience of individual patients with complex courses means that pre-engraftment CMV is not always clinically mild, and it should not be viewed as inconsequential. Furthermore, because most patients in this cohort did eventually get treated, these data should not be interpreted to mean that treatment is not necessary. Additional prospective studies are necessary to further define appropriate thresholds for treatment of pre-engraftment CMV.

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