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ORIGINAL RESEARCH REPORT

Prophylactic Pretransplant Ganciclovir to Reduce Cytomegalovirus Infection After Hematopoietic Stem Cell Transplantation

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Abstract

Objective/Background: **Cytomegalovirus (CMV) reactivation remains a serious complication after allogeneic hematopoietic cell transplantation (HCT) occurring in approximately 60−70% of CMV-seropositive HCT recipients. CMV reactivation leads to adverse outcomes including end-organ damage, graft-versus-host disease, and graft failure.**

Methods: **Ganciclovir was administered pretransplant at 5 mg/kg twice daily intravenously from the start of conditioning to Day T-2 to CMV-seropositive patients receiving their first allogeneic HCT. CMV DNA was monitored weekly until at least Day 100 posttransplant.**

Results: **A total of 109 consecutive patients were treated, median age 57 (range 20−73) years. Of these, 36 (33%) patients had a CMV reactivation within the first 105 days posttransplant with a median time of reactivation of 52.5 (range 36−104) days posttransplant. The cumulative incidence of CMV reactivation at Day 105 posttransplant was 33.1% (95% confidence interval: 24.4−42.0). One patient developed CMV disease.**

Conclusion: **The use of pretransplant ganciclovir was associated with low incidence of CMV reactivation and disease. These data suggest that pretransplant ganciclovir with preemptive therapy for viral reactivation may be a useful strategy to reduce CMV reactivation. Future prospective trials are needed to compare strategies for CMV prophylaxis.**

Keywords: Cytomegalovirus, Ganciclovir, Hematopoietic stem cell transplant, Prophylaxis

1. Introduction

Cytomegalovirus (CMV) is a human herpes double-stranded DNA virus known to be one of the most common opportunistic infections in immunocompromised allogeneic hematopoietic cell transplantation (HCT) recipients. CMV manifests as several pathologic entities in HCT patients ranging from reactivation with viremia without invasive disease to biopsy-proven CMV disease, affecting most commonly the lung and intestinal tract [1]. CMV disease can be associated with end-organ damage, graft failure, acute or chronic graft-versus-host disease (GVHD), and invasive fungal infection [2]. CMV reactivation has been associated with increased nonrelapse mortality approaching 25%

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[3,4]. Prevention of CMV reactivation and subsequent disease is an essential strategy to improve outcomes of HCT recipients.

CMV-seropositive recipients have a CMV reactivation incidence as high as 60–70% by Day 100 posttransplant [5,6]. Reactivation can also been seen in CMV-negative recipients who received a CMV-seropositive donor; these patients have a 32% reactivation rate [7]. Graft source influences CMV reactivation; in the absence of prophylaxis, CMV reactivation within 1 year of transplant occurs in up to 76% of CMV-positive patients receiving an umbilical cord blood (UCB) transplant [8]. Prevention of CMV disease has been performed by either prophylactic treatment or preemptive surveillance involving monitoring for detection of CMV in blood and then initiating treatment at the time of CMV viremia [9]. Prophylactic treatment has traditionally been associated with an increase in toxicity and cost, and late CMV disease; therefore, preemptive therapy has been more widely adopted [10,11]. Prophylactic ganciclovir has been investigated posttransplant, and results showed reduction in CMV reactivation and disease, but no significant reduction in mortality; however, these studies are outdated and therefore cautious interpretation to modern transplant practice is warranted [12–16]. Milano et al. [17] published an intensive strategy using pretransplant ganciclovir for patients who were seropositive and received an UCB transplant. This Phase II study demonstrated a lower CMV reactivation incidence for patients receiving the intensive strategy with pretransplant ganciclovir and posttransplant high-dose valacyclovir compared with a preemptive treatment strategy and standard posttransplant antiviral prophylaxis at 60% and 100%, respectively (hazard ratio: 0.27; 95% confidence interval [CI]: 0.15–0.48; $p < .001$). Hill et al. [18] published their results of a modified intensive strategy for patients receiving UCB transplants, removing pretransplant ganciclovir and giving posttransplant high-dose valacyclovir/acyclovir that revealed no difference in CMV reactivation or disease compared with patients who received pretransplant ganciclovir. In addition, the CMV terminase complex inhibitor letermovir, recently approved by the US Food and Drug Administration (FDA) and the European Union, has been shown to be effective for prophylaxis of CMV disease in allogeneic HCT patients. In a Phase III, randomized, placebo-controlled trial, letermovir prophylaxis led to a decreased incidence of clinically significant CMV infection (defined as CMV disease or CMV viremia requiring preemptive treatment) versus placebo at Week 24 (37.5% vs. 60.6%; $p < .001$) [19]. The use of letermovir may be limited by cost and drug–drug interactions.

Given the promising results in the UCB population, in January 2012, our institution implemented a strategy of pretransplant ganciclovir in all seropositive recipients. Patients receiving various donor sources received ganciclovir prior to transplantation (5 mg/kg intravenously [IV] administered twice daily from the start of conditioning to 2 days prior to transplantation).

2. Methods

2.1. Patients

We conducted a single-institution retrospective analysis of consecutive CMV-seropositive patients undergoing HCT at the University of Virginia between January 2012 and June 2019. This analysis was approved by the University of Virginia Institutional Review Board (IRB) for Health Sciences Research; given the retrospective nature of this research, the IRB elected to waive consent. Patients received pretransplant ganciclovir strategy if they had a positive immunoglobulin G for CMV based on enzyme-linked immunosorbent assay (seropositive). Patients who received any of the following donor options were included: matched related donor (MRD), matched unrelated donor (MUD), haplo-identical (haplo), or double umbilical cord blood transplant (UCB). Patients received either bone marrow, peripheral blood stem cells, or cord blood as graft sources. Exclusion criteria included patients who died in the first 14 days posttransplantation or patients who underwent treatment of CMV pretransplant for reactivation or infection. Patients were monitored weekly with serum CMV polymerase chain reaction (PCR) viral loads through Day 100 posttransplant. Historical controls obtained from the literature were used for comparison with CMV reactivation rates according to donor status. All patients received GVHD prophylaxis with calcineurin inhibitor-based treatment posttransplant.

2.2. Definitions

The primary outcome was defined as the cumulative incidence of CMV reactivation at 105 days posttransplant. CMV reactivation was defined as > 150 copies/mL by quantitative PCR. CMV disease was defined as detection of CMV by one or more appropriate diagnostic tests including culture,

immunohistochemical staining, or histopathology examination or positive tissue culture accompanied by documentation of signs and symptoms of the affected organ [1]. Other secondary outcomes included time to neutrophil recovery, time to platelet recovery, and incidence of acute and chronic GVHD per MAGIC: Mount Sinai Acute GVHD International Consortium and 2014 National Institutes of Health consensus criteria, respectively [20,21].

2.3. Transplantation practices

Choice of transplant donor, conditioning regimen, and GVHD prophylaxis were at the discretion of the treating physician, per established protocols. Transplant regimens including doses used for patients in this analysis are described in Appendix A.

All patients received calcineurin-based immunosuppressive therapy for the prevention of GVHD. Regimens included calcineurin inhibitors (cyclosporine and tacrolimus) and methotrexate or mycophenolate. Haploidentical patients received posttransplant cyclophosphamide with mycophenolate and a calcineurin inhibitor [22]. All patients received standard prophylactic antimicrobial and antifungal agents during follow-up.

2.4. Study treatment

All patients were given pretransplant ganciclovir at a dose of 5 mg/kg twice daily starting at the time of conditioning regimen and continuing until Day T-2, at which time patients received standard posttransplant antiviral prophylaxis for herpes simplex virus (HSV) and varicella-zoster virus (VZV) with acyclovir or valacyclovir.

2.5. Statistical analysis

Summary statistics such as frequency counts, percentages, medians, and ranges were used to describe the study population. Days from transplant to first CMV reactivation were estimated using the cumulative incidence function with death without CMV reactivation as a competing risk. The Fine–Gray subdistribution hazard model for competing risk data was used to assess and interpret the effect of covariates on the cumulative incidence functions. The Kaplan–Meier method was used to estimate the progression-free (PFS) and overall survival (OS) functions, and the log-rank test was used to compare differences in the time to event functions by use of pretransplant ganciclovir.

3. Results

3.1. Patient population

From January 2012 to June 2019, 170 consecutive patients underwent an allogeneic HCT. Of these, 112 patients were CMV seropositive prior to transplant. Of 112, 109 patients were included in this analysis. Three patients were excluded because pretransplant ganciclovir was not given. Patient characteristics are outlined in Table 1. The median age was 57 (range 20–73) years with 47.7% of patients being female. The most common diagnoses were acute myeloid leukemia in 51 (46.8%) patients and acute lymphocytic leukemia in 21 (19.3%) patients. The most common donor source was a MUD occurring in 40 (36.7%) patients, followed by MRD in 32 (29.4%) patients, UCB in 23 (21.1%) patients, and a haplo source in 14 (12.8%) patients. Graft sources included nine (8.2%) patients receiving bone marrow, 23 (21.1%) patients receiving cord blood units, and 77 (70.6%) patients receiving peripheral blood stem cells. The majority of patients

Table 1. Study Population Characteristics.

Characteristics	
Age, years	57 (20–73)
Female	52 (47.7)
Disease	
AML	51 (46.8)
ALL	21 (19.3)
MDS	9 (8.3)
MF	8 (7.3)
Other	20 (18.4)
Donor source	
MUD	40 (36.7)
MRD	32 (29.4)
UCB	23 (21.1)
Haplo	14 (12.8)
Graft source	
PBSCs	77 (70.6)
UCB	23 (21.1)
BM	9 (8.2)
Conditioning regimen	
RIC	88 (80.7)
MAC	21 (19.3)
CMV donor status	
Negative	55 (50.5)
Positive	54 (49.5)

Note. Values are presented as *n* (%) or median (range) depending on categorical versus continuous variable. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BM = bone marrow; CMV = cytomegalovirus; Haplo = haplo-identical; MAC = myeloablative conditioning; MDS = myelodysplastic syndrome; MF = myelofibrosis; MRD = matched related donor; MUD = matched unrelated donor; PBSCs = peripheral blood stem cells; RIC = reduced intensity conditioning; UCB = umbilical cord blood.

(n = 88) received reduced intensity conditioning, and 21 (19.3%) patients received myeloablative conditioning. Patients receiving CMV-positive donors represented 49.5% (54 patients), whereas patients receiving CMV-seronegative donors represented 50.5% (55 patients). The median number of days (ranges) patients received pretransplant ganciclovir according to donor was: 5 days (5–7) for haplo, 5 days (4–6) for MRD, 5 days (4–6) for MUD, and 5.5 days (3–7) for UCB.

3.2. CMV reactivation and CMV disease

The cumulative incidence of CMV reactivation at Day 105 posttransplant was 33.1% (95% CI: 24.4–42.0), with a median time to reactivation of 52.5 (range 36–104) days (Fig. 1). Five additional events of CMV reactivation occurred after Day 105 and within 1 year of transplant (range 157–279 days). There was one patient (0.9%) who had a CMV disease event during the first 105 days posttransplant. This patient had a proven case with CMV isolated from a duodenal biopsy at Day 60 posttransplant and ultimately succumbed 4 days later from complications related to acute GVHD [1]. One patient had CMV disease with biopsy-proven CMV pneumonitis within 1-year posttransplant at Day 170 [1]. The cumulative incidence of CMV reactivation at 1-year posttransplant was 38% (95% CI: 28.8–47.1). The cumulative incidence of CMV reactivation according to graft source is displayed in Fig. 2.

3.3. Engraftment and graft-versus-host disease

The median time to neutrophil count recovery (absolute neutrophil count > 500 K/μL) was 17 days, and was similar among donor sources (p = .06). However, median time to platelet count recovery (≥20 K/μL) was 17 days for MRD and MUD, 28 days for haplo, and 38 days for UCB (UCB vs. others, p = .06; Fig. 3). Acute GVHD had a cumulative incidence of 40.4% (95% CI: 31.1–49.5) at Day 100 posttransplant. Chronic GVHD had a cumulative incidence of 46.6% (95% CI: 36.2–56.3) by 2 years posttransplant.

3.4. Toxicity

The incidence of acute kidney injury (AKI) within 2 weeks posttransplant defined by previously published criteria was 7.3% [23]. None of the patients who experienced AKI required any type of renal replacement therapy, and events resolved with appropriate supportive care.

3.5. Overall and progression-free survival

The 1-year posttransplant PFS was 56.8% (95% CI: 46.7–65.8). The 1-year OS was 67.9% (95% CI: 57.9–76.0) and a 3-year OS estimate was 55.7% (95% CI: 43.6–66.2). CMV reactivation was not found to be associated with OS or PFS with or without adjustment for ganciclovir confirmed using Cox

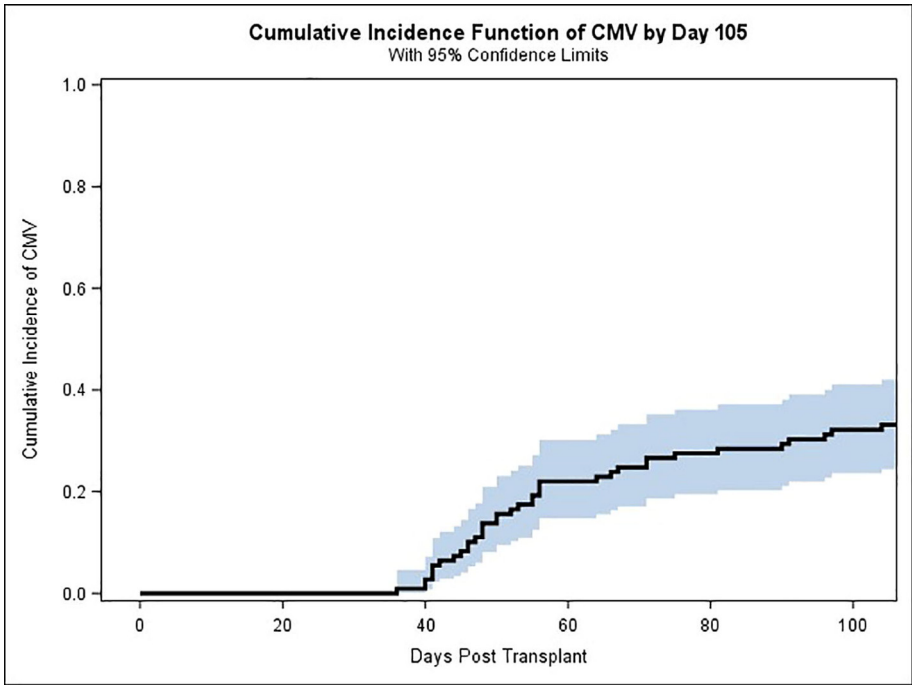

Fig. 1. Cumulative incidence of cytomegalovirus (CMV) reactivation 105 days posttransplant.

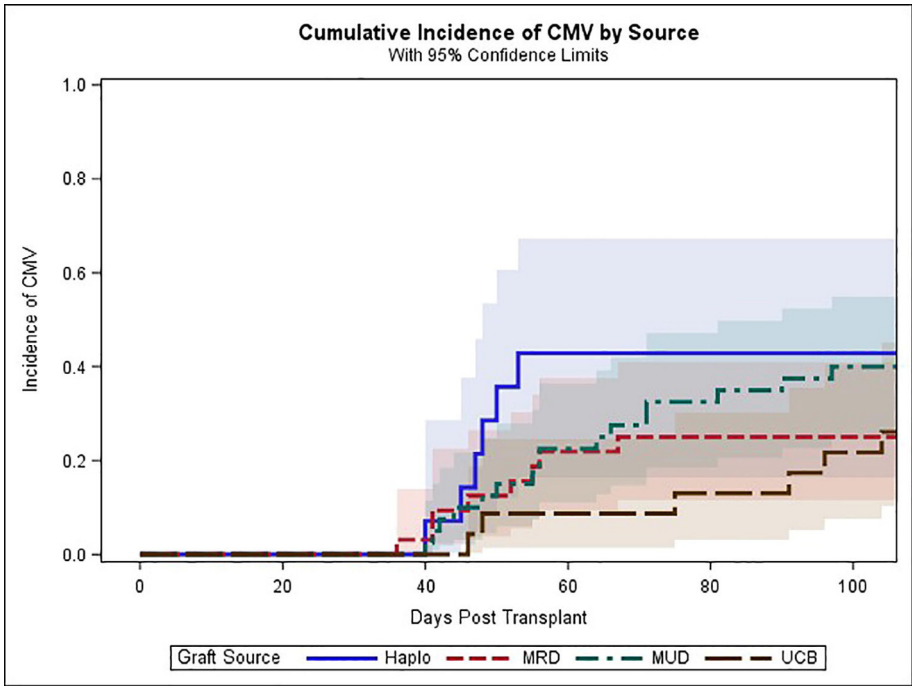

Fig. 2. Cumulative incidence of reactivation of cytomegalovirus (CMV) in days for patients according to graft source: haploidentical; umbilical cord transplant, UCB.

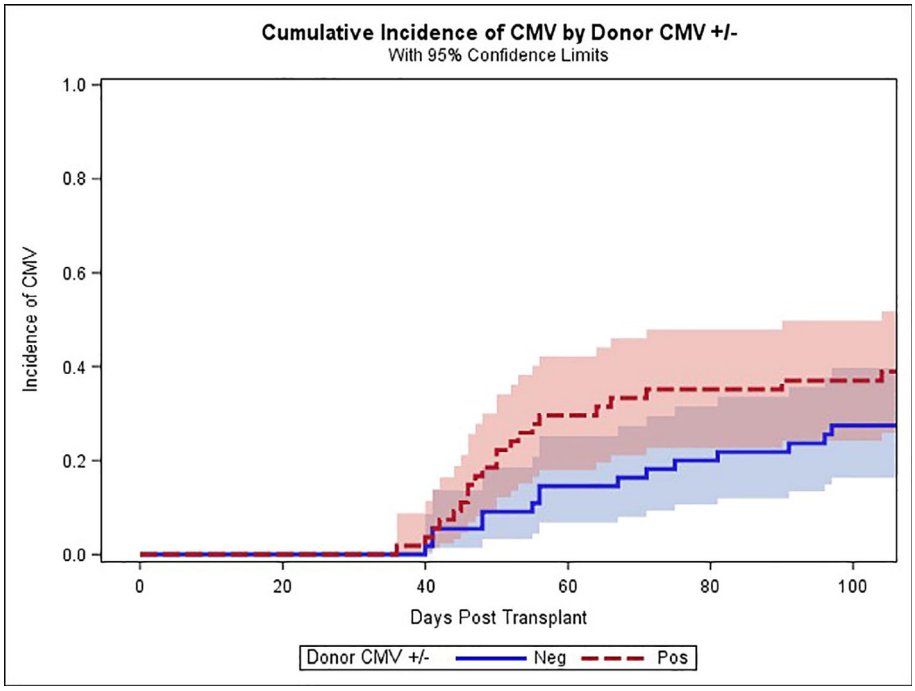

Fig. 3. Cumulative incidence of reactivation of cytomegalovirus (CMV) in days for seropositive patients according to donor CMV status. $p = 0.5$.

proportional hazard models with CMV status as a time-dependent covariate.

3.6. Univariable and multivariable analysis

In a univariable analysis, baseline factors of sex, age, donor CMV serostatus, diagnosis, conditioning regimen, and graft source were not found to be statistically associated with the cumulative incidence of CMV reactivation (Table 2). A multivariable analysis was explored but demonstrated no simultaneous associations with the cumulative incidence of CMV reactivation. Patients were also analyzed according to their donor CMV serostatus (Fig. 3).

4. Discussion

In this study, we analyzed the rate of CMV reactivation and CMV disease in all CMV-seropositive patients undergoing allogeneic transplantation. For recipient CMV-positive patients, our institution investigated a strategy of ganciclovir before transplantation with weekly preemptive screening. This approach had been successful in a cohort of UCB patients [17]. As an antiviral active against CMV, pretransplant ganciclovir may lead to elimination or reduction in CMV burden of patients who are CMV seropositive, potentially leading to a reduced risk of reactivation. We sought to determine if our CMV reactivation rates were improved compared with historical controls found in the literature. In this study, we show that pretransplant ganciclovir for CMV-seropositive patients, regardless of graft source, is associated with a low incidence of CMV reactivation and CMV disease, and minimal toxicity. In Phase III trial that evaluated letermovir (a CMV terminase inhibitor) versus placebo for CMV prophylaxis, the authors found a control CMV reactivation rate of 60.6% versus 37.5% for patients who received letermovir [19]. The reactivation incidence in our analysis (33%) appears to be comparable with the CMV incidence seen with letermovir and improved compared with historical controls, with no prophylaxis suggesting that pretransplant ganciclovir could be a helpful strategy in preventing reactivation of CMV. In our study, there was one occurrence of CMV disease before 105 days post-transplant. There was no evidence of delayed engraftment with patients who received ganciclovir. Our CMV reactivation rates were comparable across donor sources and lower than those of historical controls for haplo and UCB donor sources [17,24]. The lower rate of CMV reactivation in UCB patients compared with historical rates seen in the literature is consistent with the reduction in CMV reactivation in this population seen with Milano et al. [17]. In addition, the OS seen in this cohort is similar to what has been recently reported through CIMBTR: Center for International Blood and Marrow Transplant Research [25].

Other antiviral options may offer protection from CMV infection such as letermovir, which was approved by the US FDA and Health Canada in November 2017 and by the European Medicines Agency in August 2018 for CMV prophylaxis in adult CMV-seropositive allogeneic HCT recipients to be used after transplantation until Day 100. However, letermovir has significant interactions with commonly used immunosuppressive drugs due to effects on cytochrome P4503A leading to a half-dose reduction needed when given concomitantly with cyclosporine; letermovir does not have activity against other herpesviruses, including HSV and VZV [26,27]. Thus, additional prophylaxis against these viruses would be necessary.

Ganciclovir is potentially a less expensive alternative, with savings of $22,175, than letermovir for CMV prophylaxis especially in resource-limited

Table 2. Univariable Analysis for CMV Reactivation.

Variable	Fine–Gray *p*
Age	0.6
Sex (male)	0.1
Risk group	
Low (MRD/MUD)	0.5
High (Haplo/UCB)	
Disease group	
AML	0.3
MDS/MF	
Other	
ALL	
Graft source	
MRD	0.4
MUD	
Haplo	
UCB	
Donor CMV status	
Positive	0.5
Negative	
Flu conditioning	
Yes	0.3
No	

Note. The *p* values are reported from the Fine–Gray subdistribution hazard model used to interpret the covariates effect on the incidence of CMV. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CMV = cytomegalovirus; Flu = fludarabine; Haplo = haplo-identical; MDS = myelodysplastic syndrome; MF = myelofibrosis; MRD = matched related donor; MUD = matched unrelated donor; UCB = umbilical cord blood.

areas; however, this should not necessarily limit the use of letermovir for CMV prophylaxis. Ganciclovir is administered IV and therefore requires nursing care or home health care, which is a disadvantage compared with the oral option letermovir offers. In our resource-limited health care system, especially given the current coronavirus disease 2019 pandemic, it will be important to employ a safe, effective, and cost-efficient preventative strategy for CMV reactivation.

Limitations to our study include the retrospective nature of the analysis, the limited sample size, the heterogeneity of conditioning regimens, graft sources, and GVHD prophylactic regimens, and lack of a control group. We did not have an internal historical control group due to all CMV-seropositive patients receiving the pretransplant ganciclovir intervention at initiation of our program in 2012. There was significant heterogeneity in posttransplant acyclovir or valacyclovir dosing per the treating physician. Methods to detect CMV viremia varied over the time period studied. More sensitive PCR testing has been developed to detect CMV viral loads lower than 150 copies/mL. With only 36 CMV reactivation events by Day 105 posttransplant, there was limited power to assess the associations of baseline characteristics on the cumulative incidence function for CMV reactivation. OS and PFS were not found to be impacted by CMV reactivation, although this might be secondary to our reduced incidence of CMV reactivation events. Our study did not show an elevated CMV reactivation rate with UCB or haplo donor sources, likely due to our limited sample size. Furthermore, we did not study CMV-negative patients receiving a CMV-seropositive graft, and these patients were also excluded from Phase III letermovir study [19]. However, we believe our data is hypothesis generating as a strategy that might be compared with letermovir, or considered as an alternative when cost or significant drug interactions limit letermovir's use. Furthermore, potential future trials combining pretransplant ganciclovir with posttransplant letermovir may be warranted.

This retrospective analysis suggests that pretransplant ganciclovir followed by weekly preemptive screening is an effective way to reduce CMV reactivation and disease in CMV-seropositive patients undergoing allogeneic HCT. Additionally, ganciclovir appears to be safe with low incidence of AKI, no impact on engraftment, and a cost-effective alternative. The results of this analysis suggest that pretransplant ganciclovir should be considered in a prospective randomized trial to determine the optimal CMV preventative strategy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors would like to acknowledge the patients treated at the University of Virginia and their families.

Appendix A.

See Appendix Table 1.

Appendix Table 1. Conditioning regimens.

Donor	Intensity	Regimen
MRD/MUD	RIC	Fludarabine 30 mg/m^2 IV every24 hours X 5 doses (−6, −5, −4, −3, −2) Busulfan 0.8 mg/m^2 IV every 6 hours X 8 doses (−5, −4) OR Busulfan 1 mg/kg PO every6 hours X 8 doses (−5, −4)
	RIC	Fludarabine 25 mg/ m^2 IV every 24 hours X 5 doses (−6, −5, −4, −3, −2) Melphalan 70 mg/ m^2 IV every 24 hours X 2 doses (−3, −2)
	MAC	TBI 2 Gy twice daily X 6 doses (−6, −5, −4) Cyclophosphamide 60 mg/kg IV every 24 hours X 2 doses (−3, −2)
	MAC	Busulfan 0.8 mg/ m^2 IV every 6 hours X 16 doses (−7, −6, −5, −4) or Busulfan 1 mg/kg PO every 6 hours X 16 doses (−7, −6, −5, −4) Cyclophosphamide 60 mg/kg IV every 24 hours X 2 doses (−3, −2)
	MAC	Fludarabine 40 mg/ m^2 IV every 24 hours X 4 doses (−5, −4, −3, −2) Busulfan 0.8 mg/ m^2 IV every 6hours X 16 doses, (−5, −4, −3, −2) or Busulfan 1 mg/kg PO every 6 hours X 16 doses (−5, −4, −3, −2)
UCB	RIC	Fludarabine 40 mg/ m^2 IV every 24 hours X 5 doses (−6, −5, −4, −3, −2) Cyclophosphamide 50 mg/kg every 24 hours X 1 dose (−6) TBI 200 cGy X 1 dose (−1)
Haplo	RIC	Fludarabine 30 mg / m^2 IV every 24 hours X 5 doses (−6, −5, −4, −3, −2) Cyclophosphamide 14.5 mg/ m^2 IV every 24 hours X 2 (−6, −5) TBI 200 cGy X 1 (−1)
	RIC	ATG (rabbit) 0.5 mg/kg IV X 1 dose (−9), 2 mg/kg iv every 24 hours X 2 doses (−8, −7) Fludarabine 30 mg/ m^2 IV every 24 hours X 5 doses (−6, −5, −4, −3, −2) Cyclophosphamide 14.5 mg/ m^2 IV every 24 hours X 2 doses (−6, −5)
	MAC	Fludarabine 30 mg/ m^2 IV every 24 hours X 3 doses (−7, −6, −5) TBI 150 cGy BID X 8 (−4, −3, −2, −1)

Conditioning regimens Intravenous, IV; By Mouth, PO; Matched Unrelated Donor, MUD; Matched Related Donor, MRD; Umbilical Cord Blood, UCB; Haplo-identical, Haplo; Reduced Intensity Conditioning, RIC; Myeloablative Conditioning, MAC; Anti-thymocyte Globulin, ATG.

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