ORIGINAL ARTICLE

PRE-TRANSPLANT GANCICLOVIR PROPHYLAXIS TO PREVENT CMV INFECTIONS IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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ABSTRACT

Background: The spectrum of human illness caused by cytomegalovirus (CMV) is diverse and mostly depended on the host. CMV infections in immunocompromised patients cause substantial morbidity and mortality, especially among transplant recipients. Most centers favor a pre-emptive approach for CMV in haematopoietic stem cell transplantation rather than a prophylactic approach to minimize toxicity from anti-viral agents. This study was done to determine the frequency of Cytomegalovirus reactivation and symptomatic infections with pre-transplant prophylactic ganciclovir versus no prophylaxis in patients undergoing allogenic haematopoietic stem cell transplantation. This study assessed the incidence of non-relapse mortality and overall survival for the first 100 days post-transplant in patients undergoing allogenic haematopoietic stem cell transplantation and receiving pre-transplant prophylactic ganciclovir versus those who received no prophylaxis.

Material and Methods: This Retrospective comparative observational study was conducted at the Department of Clinical Hematology and Bone Marrow Transplant, Shifa International Hospital, Islamabad, 01 Jan 2017 to 31 Jul 2021.A total of 106 patients, who underwent allogenic haematopoietic stem cell transplant, were included in this study for retrospective analysis between 2017 and 2021. Patients who received ganciclovir prophylaxis were placed in Group A while those that didn't were placed in Group B. Ganciclovir was administered at a dose of 5 mg/kg twice daily seven days prior to transplant and ceased on the day of transplant. All patients were placed on acyclovir 400 mg twice daily from day 0 to day 100 of transplant. Patients received a weekly or bi-weekly test for quantitative serum CMV PCR till day 100 post-transplant. CMV reactivation was defined as a viremia of greater than 150 IU/ml. Data was analyzed using SPSS 26.0.

Results: Ganciclovir prophylaxis was associated with a lower degree of CMV reactivation: 38 (61.3%) with prophylaxis versus 44 (89.8%) without prophylaxis, but with a higher rate of transplant related mortality, 14 (22.5%) with prophylaxis, vs. 4 (8.1%) without prophylaxis The increased transplant related mortality was likely due to primary engraftment failure in 7 (11.2%) with prophylaxis, while no cases of engraftment failure were seen without prophylaxis.

Conclusion: CMV prophylaxis with ganciclovir is effective in preventing CMV reactivation at the cost of increased transplant related mortality in the form of primary engraftment failure.

Keywords: Allogenic haematopoietic Stem cell transplantation, Cytomegalovirus, Ganciclovir prophylaxis

BACKGROUND

Cytomegalovirus (CMV), also known as human herpesvirus-5, is a globally endemic DNA virus which usually lies dormant in myeloid cells of the immune competent host, but is one of the most common pathogenic organisms in immune such as those undergoing allogeneic hematopoietic compromised stem cell under-going allogeneic hematopoietic stem cell transplantation (HSCT).[1] Manifestations vary from asymptomatic viremia or mild constitutional symptoms to life threatening organ involvement, including the lung, gastro-intestinal tract and the central nervous system.[2] CMV reactivation, in the context of HSCT, is associated with other complications, such as chronic graft versus host disease (GvHD), graft failure and increased incidence of concurrent infections, and results in an increase in non-relapse mortality (NRM), estimated to be about one quarter of affected patients, as such prevention of

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reactivation is of paramount importance in HSCT patients.[3]

Patients at high risk of reactivation include CMV-seropositive HSCT recipients and CMV-seropositive donors with 30–80% and 32% chance for reactivation by Day 100 post-transplant, respectively.[4,5] Measures to reduce risk of CMV reactivation include selecting a CMV-negative fully matched donor, utilization of leucocyte depleted blood for transfusion, surveillance to detect early CMV viremia for e.g., a once weekly CMV PCR, and early treatment and prophylactic administration of anti-viral medication.[6]

The prophylactic use of Ganciclovir to prevent CMV reactivation post-HSCT has been shown to decrease the frequency of CMV reactivation and overt disease, but this effect does not appear to translate into reduction in NRM.[7] Furthermore, the drug is known to cause bone marrow toxicity, making its employment during the transplant period rather undesirable, with particular concerns about delays in engraftment.[8] Alternatives such as Foscarnet are significantly nephrotoxic, while newer drugs like Letermovir are prohibitively expensive, and not readily available.[9,10] As such, in a prophylactic strategy, the best drug, and optimal dosing schedule is still up for debate, and it comes as no surprise that most centers adopt a pre-emptive testing approach, while employing standard doses of acyclovir or valacyclovir as antiviral prophylaxis for herpes simplex virus alone.[11]

The ideal scenario for employment of Ganciclovir in the setting of HSCT would entail a minimal risk of bone marrow suppression, no delays in engraftment, and prevention of CMV reactivation. Multiple, retrospective, non-randomized studies have not been able to resolve this issue conclusively.[12] This study was conducted to determine whether administration of pre-transplant ganciclovir was associated with decreased reactivation of CMV when compared to patients who were placed on standard post-transplant antiviral prophylaxis only in an attempt to ascertain whether prophylaxis is associated with benefits in terms of decreased activation and a reduction in non-relapse mortality. The effect of Ganciclovir vis-à-vis the time of neutrophil and platelet engraftment was also studied.

MATERIAL AND METHODS

This was a retrospective comparative observational study, conducted on records starting from 01 Jan 2017 to 31 Jul 2021 in the Department of Clinical Hematology and Bone Marrow & Stem Cell Transplant Unit, Shifa International Hospital, Islamabad on 106 patients who reported for allogeneic hematopoietic stem cell transplantation, after receiving informed consent from patients/guardians, and after receiving the appropriate ethical clearance. Informed consent for use of patients' data for future research purposes is obtained as standard practice in our institute. Patients of both genders between 4 to 65 years of age undergoing first allogeneic hematopoietic stem cell transplantation were included. Patients who had reactivation of CMV prior to transplant were excluded from the study.

We started using Ganciclovir pre-transplant prophylaxis in Dec 2018.Patients were assigned into one of two groups: patients who received Ganciclovir prophylaxis were placed in Group A (starting Dec 2018), while those who did not receive prophylaxis were placed in Group B (before Dec 2018). All data was collected from the electronic hospital record using a patient specific record number. Patients in Group A received Ganciclovir at a dose of 5 mg/kg twice daily in the 7 days prior to transplant, which was stopped at transplant. Patients of both groups were then placed on Acyclovir 400 mg twice daily, which was continued till day 100. NRM was defined as death post-transplant before Day-100 that was not preceded by recurrence or progression of primary disease for which transplant was done,[13] while CMV reactivation was defined as a viremia of greater than 150 IU/ml, as defined by Green *et al*.[14]

Data was analyzed using SPSS version 26.0. Mean and SD was calculated for quantitative variables specifically age, time to neutrophil and platelet engraftment, time post-transplant after which viremia occurred, degree of viremia, duration of treatment required, overall survival, and dose of stem cells given for transplant. Qualitative variables like gender, diagnosis, whether CMV reactivation occurred, whether patient required treatment for reactivation or not, CMV status after treatment, organ system affected by CMV, whether mortality occurred or not, and conditioning regimen used for transplant were recorded in terms of frequency and percentage. Chi square test was applied to all qualitative variables for associated, while the independent samples *t*-test was applied to compare quantitative variables. All variables were

compared between patients with CMV reactivation versus those without reactivation, using chi square test and independent samples t-test, for qualitative and quantitative variables, respectively. The *p* value of ≤0.05 was taken as significant. Kaplan-Meier curves were calculated to compare overall survival between the groups.

RESULTS

We studied a total of 111 patients, of whom 62 (55.9%) received prophylaxis while 49 (44.1%) did not. The mean age of the patients in our sample was 28.07 ± 13.16 years, with the majority of the sample being male i.e., 87 (78.4%) with a male to female ratio of 3.625 to 1. The group-wise demographic data, and breakdown according to diagnosis is showed in Table-1. None of the variables demonstrated statistical difference across groups.

All recipients and donors underwent evaluation for CMV antibody status, the results of which are displayed in Table-2. There was no difference between the two groups with regards to the pre-transplant CMV IgG and IgM status in either the donor or the recipient.

Patients were documented for different transplant characteristics, which are shown in Table-3. There were significant differences between the two groups with regards to conditioning regimens used. Group A had a higher mean dose of stem cells infused, the difference between the groups was statistically significant, (*p*=0.025) although both doses (6 and 8 million/kg recipient weight), would be deemed adequate. In Group B, platelet engraftment was delayed by mean duration of 3.57 ± 8.18 days, (*p*=0.044).

Patients were studied for outcomes and interventions related to CMV management, as shown in Table-4. CMV was more frequently detected in Group B, (*p*=0.001), and most of the cases in both groups had asymptomatic viremia: 38 (51.6%) in Group A versus 21 (42.8%) in Group B. However, the major difference was in the development of CMV enteritis: in Group B, 13 (26.5%) developed the complication vs. only 5 (8.1%) in Group A. Data for survival and post-transplant outcomes is shown in Table-5. In Group A, 7 (11.3%) patients suffered from engraftment failure, while no patients developed this complication in Group B, (*p*=0.015). Mortality at a hundred days post-HSCT was also higher in Group A than in Group B, 14 (22.6%) versus 4 (8.2%), respectively, (*p*=0.041). Kaplan-Meier curves were calculated for comparison between both groups for overall survival at 100 days post-HSCT, as well as overall survival till last follow-up, as shown in Figures-1 and 2. Survival was significantly reduced in Group A, as compared to Group B, in the first 100 days post HSCT, indicating a high transplant related mortality (TRM) as seen in Figure-1. This difference persisted till 34 months post HSCT, despite a longer follow-up period with Group B, as demonstrated in Figure-2.

Table-1: Pre-Transplant patient characteristics.

Variable	Group A	Group B	*p* value
Mean Age (years)	27.35 ± 13.42	28.98 ± 12.90	0.521
Gender			
Male	47 (75.8%)	40 (81.6%)	0.459
Female	15 (24.2%)	9 (18.4%)	
Diagnosis			
Aplastic Anaemia	15 (24.2%)	11 (22.5%)	
Acute Myeloblastic Leukemia	21 (33.9%)	17 (34.7%)	
B-Acute lymphoblastic leukemia	7 (11.4%)	5 (10.3%)	
T-Acute Lymphoblastic Leukemia	3 (4.9%)	4 (8.2%)	
Thalassemia Major	2 (3.2%)	4 (8.2%)	
Mixed Phenotype Leukemia	1 (1.6%)	2 (4.1%)	
Myelodysplastic Syndrome	2 (3.2%)	0 (0%)	0.485
Paroxysmal Nocturnal Haemoglobinuria	2 (3.2%)	1 (2.0%)	
Hodgkin Lymphoma	0 (0%)	1 (2.0%)	
Budd Chiari	0 (0%)	1 (2.0%)	
Myeloproliferative Neoplasm	0 (0%)	1 (2.0%)	
Fanconi Anaemia	0 (0%)	1 (2.0%)	
Chronic Myeloid Leukemia	2 (3.2%)	0 (0%)	
Myelofibrosis	2 (3.2%)	0 (0%)	

Haemophagocytic Lymphohistiocytosis	2 (3.2%)	0 (0%)	
Glanzmann's Thrombasthenia	1 (1.6%)	0 (0%)	
Multiple Myeloma	1 (1.6%)	0 (0%)	
Myeloid Sarcoma	1 (1.6%)	0 (0%)	
Diffuse Large B Cell Lymphoma	0 (0%)	1 (2.0%)	

Table-2: Pre-transplant CMV antibody status.

Variable	Group A	Group B	*p* value
Donor			
CMV IgM	6 (9.7%)	1 (2.0%)	0.1
CMV IgG	62 (100.0%)	49 (100.0%)	1.0
Recipient			
CMV IgM	1 (1.6%)	1 (2.0%)	0.866
CMV IgG	61 (98.4%)	48 (97.9%)	0.866

Table-3: Patient Transplant Characteristics.

Variable	Group A	Group B	*p* value
Conditioning Regimen			
Flu-Cy-ATG	14 (22.6%)	13 (26.5%)	
Bu-Cy	28 (45.2%)	19 (38.8%)	
Bu-Flu-Mel/Post-Cy	6 (9.7%)	8 (16.4%)	
Bu-Flu-Cy/Post Cy	0 (0%)	1 (2.0%)	
Bu-Flu-Cy-ATG	0 (0%)	3 (6.1%)	
Bu-Flu-Cy	2 (3.2%)	1 (2.0%)	
Flu-Mel	4 (6.5%)	4 (8.2%)	
Flu-Mel-Cy-ATG	1 (1.6%)	0 (0%)	
Bu-Flu-ATG	2 (3.2%)	0 (0%)	
Cy-TBI-ATG	1 (1.6%)	0 (0%)	
Flu-Cy-TBI	2 (3.2%)	0 (0%)	
Flu-Mel/Post- Cy	1 (1.6%)	0 (0%)	0.366
Bu-Flu-Thiotepa	1 (1.6%)	0 (0%)	
Transplant Parameters			
Stem Cell Dose (Million/kg)	8.32 ± 3.79	6.64 ± 3.99	0.025
Day of Neutrophil Engraftment	12.83 ± 3.07	14.06 ± 4.87	0.112
Day of Platelet Engraftment	14.18 ± 3.98	17.71 ± 12.16	0.044

Table-4: CMV related data.

Variable	Group A	Group B	*p* value
CMV Detection			
Yes	38 (61.3%)	44 (89.8%)	0.001
No	24 (38.7%)	5 (10.2%)	
Post-Transplant Day CMV Detected	26.69 ± 27.06	23.90 ± 16.24	0.525
CMV Copies on Initial Detection (Mean ± Range)	3548.1 ± 154551	3857.3 ± 64997	0.923
Type of CMV Disease			
Viraemia	32 (51.6%)	21 (42.9%)	
Hepatitis	1 (1.6%)	0 (0%)	
Oesophagitis	0 (0%)	1 (2.0%)	
Enteritis	5 (8.1%)	13 (26.5%)	0.007
Pneumonitis	1 (1.6%)	4 (8.2%)	
Retinitis	1 (1.6%)	3 (6.1%)	
Cystitis	0 (0%)	1 (2.0%)	
None	22 (35.5%)	6 (12.3%)	
Treatment for CMV Received			
Yes	20 (32.3%)	14 (28.6%)	0.676
No	42 (67.7%)	35 (71.4%)	
Time to Clear CMV (Days)	55.59 ± 28.60	59.77 ± 55.56	0.691
Treatment Duration (Weeks)	2.20 ± 0.616	2.57 ± 0.756	0.125
Biopsy Done	5 (8.1%)	8 (18.3%)	0.179

Biopsy Positive	2 (3.2%)	1 (2.0%)	0.702
Treatment Outcome			
Treated till Undetectable	17 (27.4%)	22 (44.9%)	0.002
Lost to Follow Up	2 (3.2%)	10 (20.4%)	
No Treatment Required	37 (59.7%)	13 (26.5%)	
Persistent Viraemia	6 (9.7%)	4 (8.2%)	

Table-5: post-transplant outcomes

Variable	Group A	Group B	*p* value
Engraftment Failure	7 (11.3%)	0 (0%)	0.015
Day-100 Mortality	14 (22.6%)	4 (8.2%)	0.041
Overall Mortality at Last Follow-Up	23 (37.1%)	17 (34.7%)	0.793
Mean Survival Duration Survival at Last Follow-Up (Months)	13.29 ± 9.70	32.04 ± 16.33	<0.001

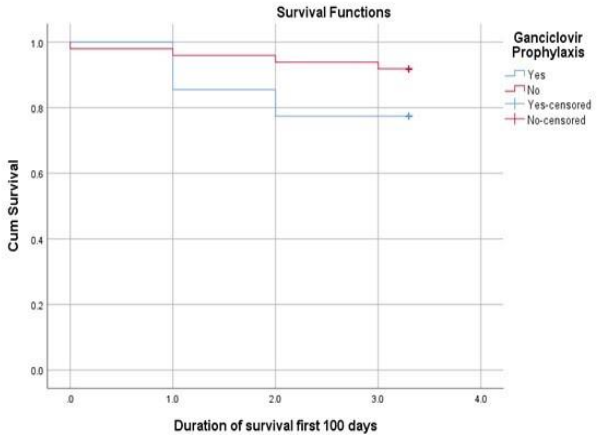

Figure-1: Overall Survival at 100 days post-HSCT.

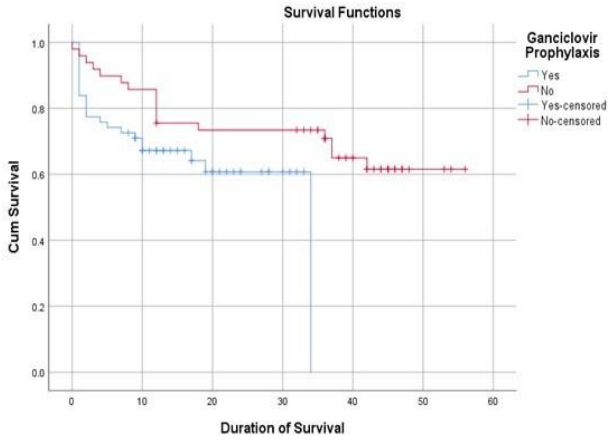

Figure 2: Overall Survival at Last Follow-Up)

DISCUSSION

We conducted this study to determine the frequency of reactivation of CMV disease, its types and effect on overall survival (OS) in patients who received prophylaxis for CMV versus those who did not receive any prophylaxis while undergoing HSCT. Ganciclovir is a readily available drug with antiviral activity against CMV, which has been used in a prophylactic role in patients with HSCT as early as 1993.[15,16] The aim of revisiting the issue was two-fold, the first was to determine whether the CMV reactivation rates in Pakistan were comparable to those available in literature internationally; whether the benefits of CMV prophylaxis translated to the Pakistani ethnicity, and secondly, to determine whether there was a short and long-term mortality benefit associated with ganciclovir prophylaxis during the conditioning period or vice-versa. This study demonstrated that there was indeed a reduced incidence of CMV reactivation in patients post-HSCT with pre-transplant ganciclovir prophylaxis, but with an increased risk of engraftment failure, a lower 100-day OS, and a lower OS at last follow-up.

Reed *et al* reported that 36 (33%) patients in their sample had CMV reactivation within the first 100 days of transplant, all of whom had been given ganciclovir prophylaxis which was less than half of the incidence in our sample (n=40, 64.5%).[8] This difference may be partially attributable to the difference in source of stem cell harvest; while Reed *et al* used different sources, our study was based exclusively on patients, who received harvests from peripheral blood, which is known to carry a higher incidence of reactivation.[17] Moreover, this study used higher resolution PCR (lower limit of detection 41 copies/mL), as opposed to Reed *et al*, which used detection methods limited to 150 copies/mL, which meant a higher number of cases with minimal viremia were detected in our study.[8] Hammerstrom *et al* saw a higher reactivation rate of CMV than in our study, with a frequency of up to 71%, with ganciclovir, during the first 100 days post-HSCT, which may be explained by the use of lower doses of

ganciclovir in that study, as well the higher dose of immunosuppression used, the transplants being haploidentical.[12] Variation in reactivation across literature may also be explained by the fact that the vast majority of our sample were already exposed to CMV, while this was not the case in other studies.[8,15,16] Goodrich *et al* reported that no patients developed CMV reactivation in their study arm with ganciclovir, while 9 (29%) patients on placebo suffered from CMV reactivation within 100 days post-HSCT, (p<0.001).[15]

Both Reed *et al* and Goodrich *et al* reported that there was no delay in engraftment in their study, which was not unexpected since both studies started their interventions post-engraftment. In the current study, there was no delay in engraftment with ganciclovir in patients who eventually engrafted, however, engraftment failure was seen in 7 (11.3%) cases of the therapeutic arm.[8] Hammerstrom *et al* did not report any graft failures in the ganciclovir arm, despite receiving a full course till Day -2, which conflicts in results with this study.(12) Winston *et al* initiated ganciclovir prophylaxis, as in our study, in their initial sample of 130 patients, however, they dropped patients who died during the study period i.e., 33 (25.4%) of whom 9 (6.9%) developed primary engraftment failure, all of whom were from the ganciclovir arm.[16] Engraftment failure, with pre-stem cell infusion ganciclovir prophylaxis is clearly an understudied problem, which requires further research.

This study showed a statistically significant difference in mortality at 100 days between patients receiving ganciclovir prophylaxis versus those who did not, 14 (22.6%) versus 4 (8.2%), respectively, (p=0.041), primarily occurring due to engraftment failure occurring in the ganciclovir arm. Goodrich *et al* reported that there was no significant difference between ganciclovir and placebo in terms of mortality at 100 days, however, Goodrich *et al* excluded patients who did not engraft from their analysis.[15] Winston *et al* noted that there was no difference in overall survival between ganciclovir and placebo: 29 (64%) patients were alive in the placebo group versus 28 (70%) in the ganciclovir prophylaxis group at 120 days post-HSCT, (p>0.2), indicating that there was no mortality benefit, a conclusion that was shared by Hammerstrom *et 0al*.[12,16]

Obstacles to developing an effective anti-viral regimen for prophylaxis include cost, availability and toxicity; ganciclovir and related compounds such as valganciclovir and even foscarnet are notorious for causing acute kidney injury and problems with delayed engraftment, engraftment failure and neutropaenia.[18-21] Thus, the search is on for a better, safer prophylactic modality, for which one possible alternative is letermovir which has been found to be effective, when compared to placebo, in terms of rates of CMV reactivation; 60.6% for placebo versus 37.5% with letermovir.[22]

This study was limited by its retrospective nature, as well as the difference in length of follow-up between the study and control arms. It was also limited by a small sample size and the management modalities relied upon the prevailing best clinical practice during that time period, which may have resulted in some degree of confounding. Clinically, drug resistance was encountered in one patient only and is not prevalent in our population.

CONCLUSION

Effective prevention of CMV reactivation is one of the goals of HSCT. Prophylactic employment of anti-CMV drugs have been proposed to reduce CMV-related morbidity and mortality. Multiple agents, some novel, have been suggested for use in this role, not all of which are available in the low-resource setting, while the rest are associated with significant toxicities. This study demonstrates that while ganciclovir is indeed effective in reducing CMV activation, transplant-related mortality is higher, primarily due to engraftment failure, which may require a re-evaluation of the practice of prophylaxis with this drug. Future research is necessary to study this aspect of HSCT in a prospective and randomized manner.

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