RESEARCH ARTICLE

Cytomegalovirus infection in autologous bone marrow transplantation: a retrospective analysis from a tertiary care centre in Pakistan

Farrukh Ali Khan[1], Fawad Qureshi[2], Urooj Haider Hashmi[3]

Abstract

Objective: To determine the frequency, management and outcome of cytomegalovirus infections in autologous bone marrow transplant recipients.

Method: The retrospective study was conducted at the Dow University Hospital, Karachi, in February 2025, and comprised medical record of patients who underwent autologous bone marrow transplant between February 1, 2019, and December 31, 2024. The data noted included age, gender, primary diagnosis, chemotherapy protocol, neutrophil and platelet engraftment, cytomegalovirus serology pre-transplant, and outcomes on day +30 and day +100. Data was analysed using SPSS 16.

Results: Of the 36 patients, 21(58.3%) were males and 15(41.7%) were females. The overall mean age was 35.29±11.79 years. The primary diagnosis in 21(58.3%) patients was Hodgkin lymphoma, 11(30.6%) had multiple myeloma, and 4(11.1%) had non-Hodgkin lymphoma. All the 36(100%) patients were seropositive for cytomegalovirus-immunoglobulin G pre-transplant. The median duration for neutrophil engraftment was 11 days (interquartile range: 14.75-10 days) and for platelet engraftment it was 12.5 days (interquartile range: 21-11 days). Of the total, 6(16.7%) patients had cytomegalovirus reactivation with a median time of 35 days (interquartile range: 42-19 days). Overall 30-day survival rate was 34(94.4%) and 100-day survival rate was 32(88.9%). The corresponding values in cytomegalovirus reactivation cases were 6(100%) and 5(83.3%), respectively.

Conclusion: There was a significant reactivation of cytomegalovirus in patients having undergone autologous bone marrow transplant, but since they were regularly monitored and treated pre-emptively, there was no major negative impact on the outcomes.

Key Words: CMV reactivation, Autologous bone marrow transplant.

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Introduction

Cytomegalovirus (CMV) infection is a major viral complication in bone marrow transplant (BMT) recipients, causing considerable morbidity, and contributing to transplant-related mortality. It can affect many different organ systems, causing retinitis, hepatitis, gastroenteritis, pneumonia, etc.[1,2] The incidence of CMV infection reported in autologous BMT (BMT) varies widely; from 4-9%1 to 17.6%.[3] This variation is due to the high incidence noted in routine monitoring of CMV viremia compared to those who are monitored based on clinical signs.[3]

CMV infection is diagnosed using serological tests, including CMV immunoglobulin G (IgG) and CMV IgM. CMV IgM indicates acute infection, and can remain positive for months. The negative serology does not necessarily rule out infection. Hence, CMV polymerase chain reaction (PCR) is considered the gold standard for its detection.[4]

[1-3]Department of Clinical Haematology and Bone Marrow Transplantation, Dow University of Health Sciences, Karachi

Correspondence: Farrukh Ali Khan **Email:** farrukh.ali@duhs.edu.pk

ORCID ID: 0009-0000-6100-1427

It has been noted that early infection of CMV is related to improved disease-free survival (DFS) in certain diseases, including chronic myelogenous leukaemia (CML), lymphoma and multiple myeloma (MM).[1, 5] However, it is associated with increased non-relapse mortality and decreased overall survival (OS) in myelodysplastic syndrome (MDS), CML, acute myeloid leukaemia (AML) and MM as well as in allogeneic BMT recipients.[1,6-8] Apart from the increased mortality and morbidity, the management of CMV infection entails a significant economic burden and a longer hospital stay.[9] Additionally, the risk of its reactivation is higher in patients diagnosed with MM compared to lymphoma.[10]

Its impact has been widely investigated in allogeneic BMT recipients as the incidence reported is higher in these patients. However, in a 2023 study, Mahar et al. reported that the incidence of CMV reactivation was rising among non-allogeneic BMT Pakistani patients. They reported it to be 23.6% with a median survival of 2 months.[4] They further highlighted the significant association of CMV reactivation with the use of steroids, the presence of active cancer, the use of monoclonal antibody, like rituximab, a history of radiation therapy and autologous BMT.[4]

In autologous BMT, patients undergo highly toxic chemotherapy followed by the infusion of stem cells, but their immune system remains severely compromised due to the underlying disease characteristics, and, as they are heavily treated before the transplant, they remain vulnerable to CMV infections. Yet, its monitoring is not a routine practice at many healthcare centres in the country. Hence, its reactivation and the impact of its reactivation and management is less well studied. Early detection and treatment can significantly reduce the risk for progression to severe CMV disease, organ damage and mortality.[11] The lack of uniform protocols, especially in a low-resource settings, makes its management even more challenging.

The current study was planned to determine the frequency, management and outcome of CMV infections in autologous BMT recipients.

Patients and methods

The retrospective study was conducted in February 2025 at the Department of Clinical Haematology and BMT, Dow University Hospital, Karachi, and comprised medical record of patients who underwent autologous BMT between February 1, 2019, and December 31, 2024. After approval from the institutional ethics review board, the sample size was calculated using PASS 1512 based on the test for one-sample proportion with 95% confidence interval (CI), 7% margin of error, and 4% incidence of CMV infection in autologous BMT.[1] Data was retrieved from the archives of the medical records section. Patients with incomplete records were excluded.

All the patients had been followed up for >100 post-transplant days. Data was collected on patients' demographics, primary diagnosis, previous lines of treatment, pre-transplant CMV status, conditioning regimen, CMV reactivation, its complications, treatment protocols, and patient outcomes on day +30 and day +100.

The patients were considered CMV seropositive pre-transplant if they were positive for serum CMV IgG or IgM. CMV reactivation / infection was labelled if they had detectable CMV deoxyribonucleic acid (DNA) by PCR with >500 copies/ml.[13] Due to limited data and unavailability of uniform protocol, the same cut-off was taken as was being followed in allogeneic BMT cases for starting treatment for CMV reactivation. All the patients were monitored for CMV infection by quantitative PCR for CMV DNA weekly for one month post-transplant, and then fortnightly until day +100. All the patients received the antiviral prophylaxis against herpes simplex virus, with oral acyclovir 400mg twice daily from day minus 3 until 6 months, but no antiviral prophylaxis was given against CMV.

Patients who had viral load of >500 copies/ml were treated with oral valganciclovir (or ganciclovir intravenous in patients who could not take oral drugs) until two consecutive CMV PCR results done one week apart were negative. Following this, the maintenance phase (valganciclovir 900mg once daily) was continued for 10-14 days. CMV myelosupression was defined as the presence of CMV viremia along with haemoglobin (Hb) <10g/dl, absolute neutrophil counts (ANC) $<1x10^9$/L and/or platelets $<50\times10^9$/L. CMV colitis/enteritis was defined as the presence of gastrointestinal symptoms along with the histopathological diagnosis of CMV infection.[3] CMV pneumonitis was defined as chest infiltrates on the radiograph along with microbiological evidence of CMV virus in bronchoalveolar lavage. CMV retinitis was defined by CMV virus isolation, along with characteristic appearance on fundoscopy and/or eye-related symptoms. Neutrophil engraftment was defined as ANC $>0.5x10^9$/L for 3 consecutive days post-BMT, and platelet engraftment was defined as platelets $>20x10^9$/L for 7 consecutive days post-BMT without platelet transfusion support.

Data was analysed later by using SPSS 16. Data was reported, as appropriate, as frequencies and percentages, mean ± standard deviation or median with interquartile range (IQR). The Kaplan-Meier curve was employed to evaluate the survival outcomes of patients in relation to their CMV status. $P<0.05$ was considered significant.

Results

Of the 36 patients, 21(58.3%) were males and 15(41.7%) were females. The overall mean age was 35.29±11.79 years. The primary diagnosis in 21(58.3%) patients was Hodgkin lymphoma (HL), 11(30.6%) had MM, and 4(11.1%) had non-HL (NHL). All the 36(100%) patients were seropositive for CMV-IgG and negative for IgM pre-transplant.

HL patients were treated with adriamycin-bleomycin-vinblastine-dacarbazine (ABVD), while NHL patients received rituximab-cyclophosphamide-adriamycin-vincristine-prednisolone (R-CHOP) as the first-line therapy. MM patients received lenalidomide-bortezomib-dexamethasone (VRD) as the first-line therapy. Overall, 9(25%) patients received single line of chemotherapy pre-transplant, while 19(52.8%) received two lines of chemotherapy, and 8(22.2%) received three or more lines. Majority of HL patients 14(38.89%) received brentuximab and bendamustine as the second-line therapy, while all 4 (11.11%) NHL patients received dexamethasone-

Table-1: Characteristics of the Patients with CMV reactivation.

	CMV Non reactivation (n = 30; 83.33 %)	CMV Reactivation (n = 6; 16.67%)	p Value
Age, years, median (IQR)	37.034 (11.89)	29.57 (9.71)	1.000
Males, n (%)	16 (53.33%)	5 (83.33%)	0.317
Females, n (%)	14 (46.66%)	1 (16.67%)	
Diagnosis, n (%)			0.002
Multiple Myeloma	11 (36.67%)	0 (0%)	
Hodgkin Lymphoma	16 (53.33%)	5 (83.33%)	
Non-Hodgkin Lymhoma	3 (10%)	1 (16.67%)	
Conditioning regimen, n (%)			
BendaEAM	19 (63.33%)	7(100%)	0.020
HD-Melphalan	11(36.67%)	0(0%)	
Neutrophilic engraftment, days, median (IQR)	11 (12-10)	17 (22-11)	0.007
Platelet Engraftment, days, median (IQR)	12 (19-11)	21 (35-14)	0.054
Total Number of Previous Treatment			
1	9 (30.00%)	0 (0%)	0.000
2	15 (50.00%)	4 (66.67%)	
3 or more	6 (20.00%)	2 (33.33%)	

cytarabine-cisplatin (DHAP) and from those diagnosed with MM only 1(2.78%) patient received carfilzomib-lenalidomide-dexamethasone (KRD) as the second-line therapy. Those with lymphoma 25(69.44%) patients received bendamustine-etoposide-cytarabine-melphalan (BendaEAM), and those with myeloma 11(30.56%) received high-dose melphalan as the conditioning regimen before transplant (Table).

The median duration for neutrophil engraftment was 11 days (IQR: 14.75-10 days) and for platelet engraftment it was 12.5 days (IQR: 21-11 days). Of the total, 6(16.7%) patients had CMV reactivation (Figure 1) with a median time of 35 days (IQR: 42-19 days). The median time of neutrophil engraftment in patients with CMV reactivation was 17 days (IQR: 22-11 days). All these 6(16.67%) patients received oral valganciclovir, while 2(5.55%) of them also received intravenous ganciclovir when they were unable to tolerate oral treatment. Further, 2(5.55%) patients developed symptoms of CMV disease; 1(2.78%) had colitis grade 3, who, despite receiving treatment, did not improve and was later found to have small intestinal bacterial overgrowth, while 1(2.78%) had grade 3 myelosupression, which was settled after anti-CMV therapy.

Overall 30-day survival rate was 34(94.4%) and 100-day survival rate was 32(88.9%). The corresponding values in CMV reactivation cases were 6(100%) and 5(83.33%), respectively (Figures 2-3). There was 1(2.76%) patient with CMV reactivation who died on day +42 owing to disseminated invasive fungal infection involving lungs

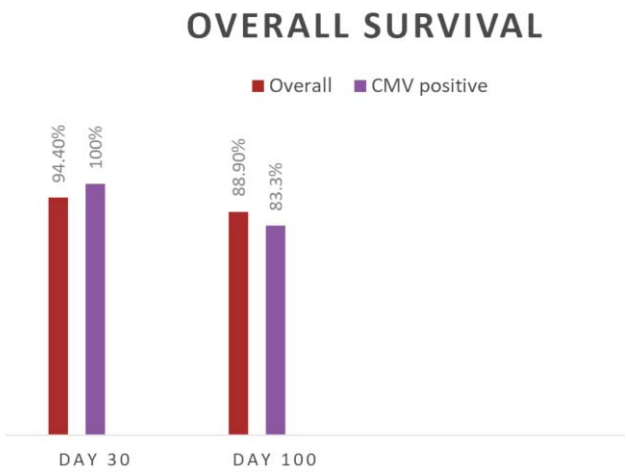

Figure-2: Overall Survival

and brain. The patient had a delayed neutrophil engraftment on day +22.

Among the 6(16.7%) CMV reactivation, 5(83.3%) had HL and 1(16.7%) had NHL. There was no significant association of CMV reactivation with disease status pre-transplant and gender (p>0.05).

Discussion

After the primary infection, CMV has the tendency to reside lifelong in host cells. The cluster of differentiation-

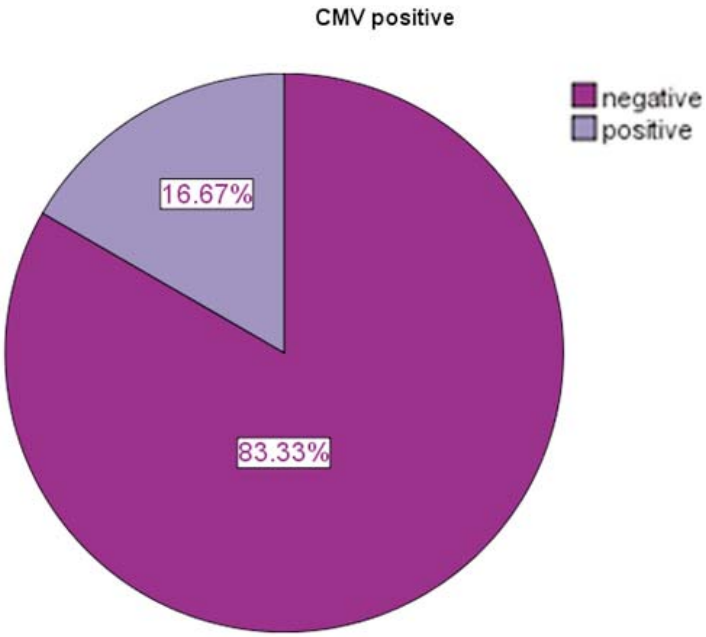

Figure-1: Frequency of CMV reactivation.

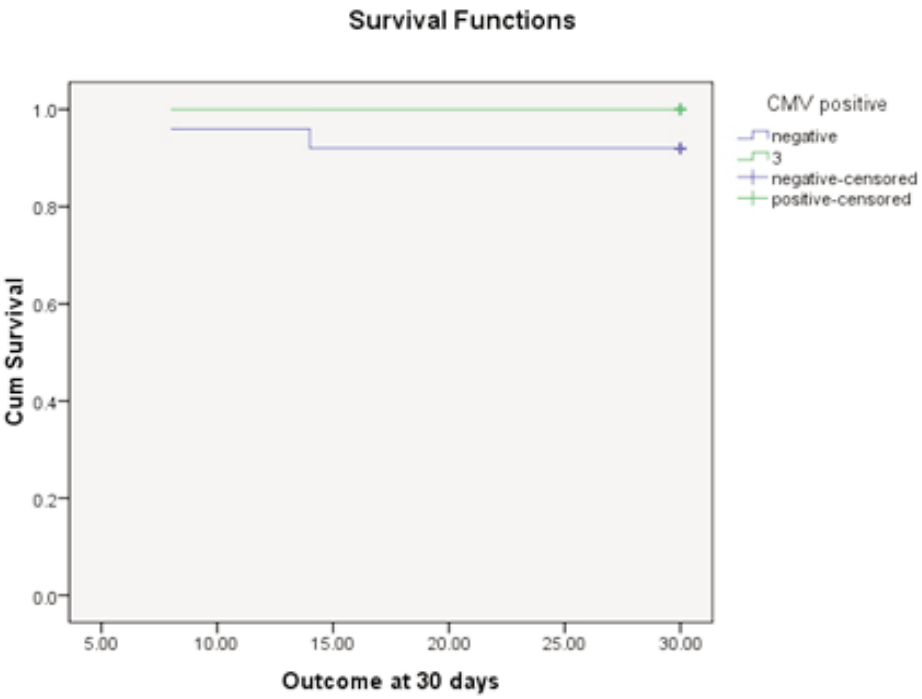

Figure-3A: Kaplan-Meier survival curve : Outcome at 30 days.

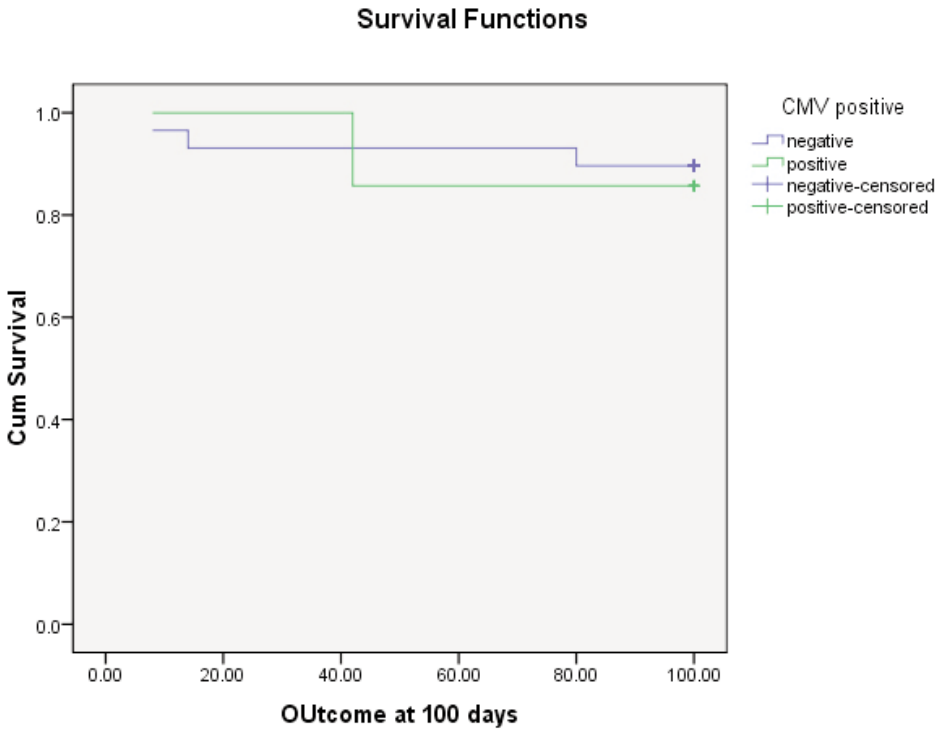

Figure-3B: Kaplan-Meier survival curve : Outcome at 100 days.

4+ (CD4+), CD8+ T-cells and natural killer cells are responsible for keeping it in check.[14] Hence, whenever there is a compromised cellular immunity, CMV virus tends to reactivate and can lead to life-threatening illnesses.[14] Apart from the allogeneic BMT patients who are at the highest risk of CMV reactivation, the other high-risk patients reported in the literature are those having received several lines of chemotherapy prior to transplantation, or who had been exposed to certain treatments, such as alemtuzumab, cladiribine or fludarabine. These patients were thought to be good candidates for monitoring and preventative treatment.[3] Furthermore, the use of steroids, monoclonal antibodies, radiation therapy, active malignancy and autologous BMT itself appear to play a role in its activation.[4]

Additionally, CMV virus also encodes certain proteins that target and hinder the host cellular immunity, which implies that it can indirectly lead to the development of other opportunistic infections, hence affecting the prognosis and outcome.[14]

Compared to the Western population, the incidence of CMV seropositivity pre-transplant is significantly higher in the Eastern Mediterranean region (90% vs 60%).[15] However, in the current cohort, it was 100%. Once infected, this virus becomes latent in the monocytes and macrophages, and can get reactivated in conditions associated with the immune

suppression. Al-Rawi et al. in 2015 reported that seropositive individuals had a greater chance of CMV reactivation (14.3 %) compared to seronegative patients (2.5%).[3] Due to high seropositivity rates prior to transplant, continued routine surveillance of the current patients was ensured, and 16.7% reactivation cases were detected.

Interestingly, the current findings were contradictory to previous reports stating CMV reactivation being higher in MM patients[10] who received autologous BMT. Besides, it has also been reported that MM patients treated with novel therapy, like bortezomib, or receiving tandem transplants, have significantly higher risk of developing symptomatic CMV reactivation.[14,16] All the current MM patients received bortezomib, but none developed CMV disease. One possible explanation for this discrepancy could be that all the MM patients were transplanted upfront, and, hence, had less exposure to chemotherapeutic drugs. No case of CMV reactivation was noted among patients who received single line of chemotherapy pre-transplant. However, this needs to be further evaluated with a larger sample size.

The duration of CMV monitoring after autologous BMT varies widely among centres due to comparatively lower pre-transplant seropositivity, less rates of reactivation, and occasional need of treatment. However, the current cohort of patients was monitored for 100 days post-transplant with a median duration of reactivation of 35 days. The rate of CMV reactivation was significant, although there was no significant impact on overall outcome, which suggests a possible role of early detection and pre-emptive management in decreasing mortality and morbidity. The current findings also explain the higher mortality reported previously among cancer patients, including those who underwent autologous BMT, among whom only symptomatic patients were tested and monitored.[4] The current study also observed that patients with delayed engraftment had higher chances of CMV reactivation. At the same time, there is a possibility of delayed engraftment that could be secondary to CMV reactivation, but since most of the patients with delayed engraftment received multiple lines of treatment before transplant, so delayed engraftment was expected in these patients.

The current study has limitations, like a retrospective design and a relatively small sample size, which may affect the generalisability of the findings. Prospective studies with a larger sample size are needed to validate the current findings.

Conclusion

There was a notably high rate (16.7%) of CMV reactivation among patients undergoing autologous BMT, and CMV seropositivity pre-transplant was 100%. Despite the reactivation, no significant differences were noted in patient outcomes, suggesting the positive impact of pre-emptive management on overall outcome.

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