A Low Incidence of Cytomegalo Virus Infection Following Allogeneic Hematopoietic Stem Cell Transplantation Despite a High Seroprevalence

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Abstract Cytomegalovirus (CMV) infection remains an important cause of morbidity and mortality following allogeneic stem cell transplantation (SCT). We wanted to study if the high sero-prevalence seen in our population translated into a high incidence of CMV infection following SCT. This is a retrospective analysis of patients who underwent allogeneic SCT between January 2008 and December 2012 at our centre. 475 patients underwent allogeneic SCT for malignant (46.5%) and non-malignant (53.5%) haematological disorders. 463 (97.4%) SCT recipients and 403 (84.8%) SCT donors were IgG seropositive for CMV. CMV reactivation within 100 days post SCT was seen in 174 (36.6%) at a median of 41 days (range 10–100) post SCT. Ganciclovir was used in 166 patients (95.4%) for a mean duration of 16 days (range 5–32). 157 patients (90%) responded to therapy. Sixty-six patients (42.3%) had secondary reactivation of the virus. Use of a male donor ($p = 0.000$), donor and recipient age > 15 ($p = 0.005$ and 0.000), unrelated donor ($p = 0.000$), degree of HLA mismatch ($p = 0.000$), occurrence of acute GVHD ($p = 0.000$) and steroid refractory acute GVHD ($p = 0.026$) were identified as risk factors for CMV reactivation while early neutrophil recovery (< 15 days) was found to be protective ($p = 0.004$). On multivariate analysis, male donor ($p = 0.042$), degree of HLA mismatch ($p = 0.006$), the occurrence of acute GVHD ($p = 0.000$) and steroid refractory acute GVHD ($p = 0.031$) continued to remain

significant. 5-year overall survival was significantly better in patients without CMV reactivation compared to those who developed reactivation of CMV (68.9 ± 3.7 vs $58.2 \pm 4.9\%$ $p = 0.004$). The incidence of CMV infection does not seem to be higher despite a high sero-prevalence of CMV. However, patients who developed CMV infection post SCT had inferior outcomes.

Keywords Cytomegalo virus · Stem cell transplantation · Seroprevalence

Introduction

Cytomegalovirus infection remains an important cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (SCT). SCT recipients remain at risk for CMV infection not only during the early post transplantation period (< 100 days), but also later (> 100 days). The virus persists in the host system because the viral genome encodes multiple proteins that interfere with major histocompatible (MHC) class I presentation of viral antigens [1]. CMV infection is defined as isolation of the CMV virus (CMV viremia) or detection of viral proteins (CMV antigenemia) or nucleic acid (CMV DNA/RNAemia) in any body fluid or tissue specimen [2]. CMV infection is seen in 30–80% of SCT recipients [3–6] and it can be primary (infection in a previously sero-negative individual) or can be reactivation (endogenous reactivation of latent virus in a seropositive patient) or reinfection (exogenous infection by a distinct strain in a seropositive patient) [2]. Studies have also shown that reactivation of CMV infection occurred more frequently in patients receiving a CMV positive graft and it was less severe than in patients receiving a CMV-negative graft [7]. In addition

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to end organ disease, CMV has repeatedly been associated with graft versus host disease (GVHD) and this has been considered both as the indirect immunomodulatory effects of this virus [8] and also secondary to the immunosuppressive therapy for GVHD. The sero-prevalence of CMV (IgG positivity) reported in the Indian population is between 95 and 97% and hence a higher incidence of CMV infection in SCT recipients is expected [9–11]. In this analysis, we studied the incidence of CMV infection following allogeneic SCT and the transplant related factors that influence it.

Patients and Methods

Consecutive patients who underwent allogeneic SCT between 2008 and 2012 at our centre were included in this analysis. Data on patient and donor demographics including diagnosis, conditioning regimen, degree of HLA match, donor and recipient pre transplant CMV viral sero status and antibody titres, transplantation details including conditioning regimen, GVHD prophylaxis, stem cell dose, neutrophil and platelet engraftment, presence of acute GVHD and its treatment were retrieved from medical records. Patients were followed up till their last available date of follow up and were evaluated for the development of early CMV reactivation or CMV disease in the first 100 days.

CMV monitoring and treatment: CMV monitoring was based on a real-time in house CMV-DNA polymerase chain reaction (PCR) assay done in whole blood in EDTA. The in-house assay was developed using Quantitect Multiplex PCR Norox master mix (Qiagen, GMBH, Germany) and primer–probe targeting 76 bp region of the MIE gene of CMV and this was previously reported by us [12].

CMV monitoring was done routinely in all allogeneic matched related donor stem cell recipients on day 28 post stem cell transplantation and then subsequently if clinically indicated. In case of matched unrelated donor stem cell transplants, CMV PCR assay was done on day 28 and then on a weekly basis till the patient was off all immunosuppression. CMV infection or reactivation was defined as the presence of CMV copies by DNA PCR in peripheral blood [2]. In patients suspected to have CMV disease, biopsies from respective organs (gut, lungs etc.) were taken whenever possible. Patients were identified as having CMV end organ disease if they had signs and symptoms of organ involvement and histopathological evidence of end organ involvement with viral cytopathic changes in these organs [2]. Pre-emptive therapy was started if the CMV copy number was more than $> 1000/\mu\text{L}$. Once pre-emptive therapy was started CMV PCR was repeated on 14th day of Ganciclovir, and if positive then twice weekly thereafter

till negative. Pre-emptive therapy was started with Ganciclovir (5 mg/kg twice a day) and given for a period of 2 weeks or till obtaining a negative PCR report. Patients who had CMV disease were also treated with Ganciclovir. Patients were supported with granulocyte colony stimulating factors (G-CSF) if they developed cytopenia secondary to Ganciclovir. In patients resistant to Ganciclovir or in those with cytopenia despite being on G-CSF, foscarnet was used for therapy. At our centre CMV specific immunoglobulins are not used and prophylactic Ganciclovir is not used in any circumstances.

Statistical analysis: All transplantation related risk factors for CMV infection were assessed using a Chi square test and a logistic regression test for multivariate analysis. The overall survival of patients who developed CMV infection with respect to non-infected patients was compared using a Kaplan–Meier graph and log rank test. A probability level of 5% ($p < .05$) was considered statistically significant. All statistical analysis was performed using SPSS software, version 16.0 (SPSS).

Results

Between January 2008 and December 2012, 506 patients underwent allogeneic SCT of which 475 patients who were alive for more than 3 weeks post SCT were included in this analysis. Baseline patient characteristics are summarised in Table 1. Patients underwent allogeneic SCT for both malignant (46.5%) and non-malignant (53.5%) haematological disorders. Antithymocyte globulin (ATG) was used as part of conditioning regimen in 20.4% cases (97 patients), 63 of which was ATGAM (equine ATG) and 34 Thymoglobulin (rabbit ATG). Four hundred and sixty-three (97.4%) stem cell recipients were seropositive for CMV while 403 (84.8%) donors were CMV IgG positive. The median cell dose infused was 11.58×10^6 CD34/kg (range 1–70). The median time to neutrophil engraftment was 15 days (range 8–28) and median time to platelet engraftment was 18 days (range 1–91). Acute GVHD was seen in 180 (38%) patients.

CMV infection within 100 days post SCT occurred in 174 patients (36.6%) at a median of 41 days (range 10–100) post SCT. Among the 174 patients who developed CMV infection post SCT, 8 patients (1.68%) developed biopsy proven CMV end organ disease (4 colitis, 2 esophagitis, 1 duodenitis and 1 CMV pneumonia). In patients with CMV infection, ganciclovir was used in 166 patients (95.4%) while the rest were treated with foscarnet and valganciclovir. The mean duration of antiviral therapy was 16 days (5–32 days). Response to therapy as defined by negative PCR was seen in 156 patients (90%) but 66 patients (42.3%) had secondary reactivation of the virus

Table 1 Baseline characteristics of all patients

Variables	Number
Total no of patients (n)	475
Recipient characteristics	
Median age (years)	21 (range 1–59)
Male: Female	306:169
Donor characteristics	
Median age (years)	25 (range 1–66)
Male : Female	266: 209
<i>Underlying condition</i>	
Malignant disorders	221 (46.5%)
Acute myeloid leukaemia	111
Acute lymphoblastic leukaemia	60
Chronic myeloid leukaemia	22
Myelodysplastic syndromes	22
Non hodgkin lymphoma	3
Juvenile myelomonocytic leukaemia	2
Myelofibrosis	1
Non malignant disorders	254 (53.5%)
Thalassemia major	145
Aplastic anaemia	81
Inherited bone marrow failure disorders	20
Paroxysmal nocturnal hemoglobinuria	4
Immunodeficiency disorders	4
<i>Donor type</i>	
Matched sibling donor	380 (80%)
Matched family donor	49 (7%)
Matched unrelated donor	82 (13%)
<i>Graft source</i>	
Peripheral blood (PBSC)	383 (80.6%)
Bone marrow(BM)	91 (19.6%)
Cord blood	1 (0.6%)
<i>Conditioning regimen</i>	
Myeloablative	313 (65.9%)
Non myeloablative	96 (20.2%)
Reduced intensity	66 (13.9%)
<i>GVHD prophylaxis</i>	
Cyclosporine—methotrexate	405 (85.3%)
Tacrolimus—methotrexate	50 (10.5%)
Cyclophosphamide	9 (1.9%)
Others	11 (2.3%)
<i>CMV status</i>	
R +/D+	397 (83.6%)
R +/D –	66 (13.8%)
R –/D +	6 (1.3%)
R –/D –	6 (1.3%)
Median cell dose	
MNC $\times 10^8/\text{Kg}$	6.13 (2–39)
CD 34 $\times 10^6/\text{Kg}$	11.58 (1–70)
<i>Median time to engraftment</i>	

Table 1 continued

Variables	Number
Neutrophil (ANC $> 0.5 \times 10^9/\text{L}$)	15.3 (8–28)
Platelets (Plt $> 20 \times 10^9/\text{L}$)	18 (1–91)

later. 5 patients did not clear the virus after 2 weeks of antiviral therapy while 12 patients expired while on therapy with Ganciclovir (7 patients died of grade IV acute GVHD, 4 died of bacterial sepsis and 1 patient died of probable fungal pneumonia). Grade IV neutropenia requiring stoppage of Ganciclovir was noted in 66 (38%) patients. The mean duration of cytopenia was 6 days (5–28 days). Ganciclovir was restarted in all but 10 patients who had prolonged and persistent neutropenia. Four patients died of CMV disease (3 CMV colitis and 1 CMV pneumonia).

A number of pre-transplant and transplant related factors were assessed to understand factors associated with increased risk of CMV reactivation (Table 2). On univariate analysis, male donor ($p = 0.000$), donor and recipient age > 15 ($p = 0.005$ and 0.000 respectively), unrelated donor ($p = 0.000$), degree of HLA mismatch ($p = 0.000$), occurrence of acute GVHD ($p = 0.000$) and steroid refractory acute GVHD ($p = 0.026$) were all found to be significant risk factors for CMV reactivation. Early neutrophil recovery ANC $> 0.5 \times 10^9/\text{L} < 15$ days was found to be protective against CMV reactivation ($p = 0.004$). Recipient gender, recipient and donor CMV serostatus, intensity of the conditioning regimen (myeloablative vs reduced intensity), use of ATG in conditioning, graft source, type of GVHD prophylaxis and grade of acute GVHD were not identified as significant factors. On multivariate analysis, use of a male donor ($p = 0.042$), degree of HLA mismatch ($p = 0.006$), the occurrence of acute GVHD ($p = 0.000$) and steroid refractory acute GVHD ($p = 0.031$) continued to remain significant.

We analysed the relationship between donor and recipient CMV serostatus and the occurrence of early CMV reactivation after SCT. There was no significant relationship with either the donor or the recipient CMV serostatus and CMV reactivation. In addition, we analysed the pre SCT donor and recipient IgG CMV titres to look for any relationship with CMV reactivation but no correlation with CMV titres could be identified (data not shown). Additionally we were also not able to find any association with the number of blood transfusions these patients had received pre and peri-transplantation.

Table 2 Risk factors for CMV reactivation (Univariate and multivariate analysis)

	CMV infection (+) n (%)	CMV Infection (–) n (%)	Univariate analysis			Multivariate analysis		
			RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>
Age (median years)	23 (1–59)	14 (1–58)	1.0	1.00–1.03	0.007			
Recipient gender								
Male	116 (37.9)	190 (62.1)	1.2	0.78–1.73	0.437			
Female	58 (34.3)	111 (65.7)						
Donor gender								
Male	118 (44.4)	148 (55.6)	2.2	1.47–3.21	0.000	1.7	1.02–3.02	0.042
Female	56 (26.8)	153 (73.2)						
Disease								
Non malignant	82 (32.3)	172 (67.7)						
Malignant low risk	43 (48.3)	46 (51.7)	1.9	1.19–3.20	0.007			
Malignant high risk	49 (37.1)	83 (62.9)						
Graft source								
PBSCT	141 (36.8)	242 (63.2)	1.0	0.64–1.67	0.866			
Bone marrow	33 (36.3)	58 (63.7)						
Cord blood	0	1						
Donor relation								
Matched related donor	136 (32.8)	279 (67.2)						
Matched unrelated donor	38 (63.3)	22 (36.7)	3.5	2.01–6.22	0.000			
HLA match								
Fully matched	129 (31.5)	281 (63.5)						
1 mismatch	39 (68.4)	18 (31.6)	4.7	2.66–8.56	0.000	2.9	1.29–6.22	0.009
2 or more mismatch	6 (75)	2 (25)	6.5	1.30–32.8	0.023			
Cond regimen								
Myeloablative	119 (38)	194 (62)	1.1	0.80–1.77	0.383			
Non myeloablative	55 (34)	107 (66)						
ATG in cond. regimen								
ATG used	34 (35.1)	63 (64.9)	0.9	0.57–1.46	0.717			
ATG not used	140 (37)	238 (63)						
CMV serology								
R + D+	147 (37)	250 (63)						
R + D–	27 (40.9)	39 (59.1)						
R–D+	0	6						
R–D–	0	6						
GVHD prophylaxis								
CSA-MTx	143 (35.3)	262 (64.7)						
Tac-MTx	22 (44)	28 (56)						
Cyclophosphamide	6 (66.7)	3 (33.3)						
Others	3 (27.3)	8 (72.7)						
Neutrophil recovery								
< 15 days	112 (42.1)	154 (57.9)	0.6	0.38–0.83	0.004	0.4	0.22–0.84	0.014
> 15 days	61 (29.3)	147 (70.7)						
Day 28 chimerism								
Full donor	152 (37.1)	258 (62.9)						
Mixed	20 (32.8)	41 (67.2)	0.8	0.46–1.46	0.517			
Acute GVHD								
aGVHD present	107 (59.4)	73 (40.6)	5.0	3.36–7.55	0.000			
No aGVHD	66 (22.5)	227 (77.5)						

Table 2 continued

	CMV infection (+) n (%)	CMV Infection (–) n (%)	Univariate analysis			Multivariate analysis		
			RR	95% CI	<i>p</i>	RR	95% CI	<i>p</i>
aGVHD severity								
Grade 1–2	53 (58.9)	37 (41.1)	1.0	0.57–1.89	0.879			
Grade 3–4	54 (60)	36 (40)						
aGVHD steroid response								
Responsive	77 (55)	63 (45)	2.4	1.11–5.40	0.026	2.8	1.24–6.43	0.014
Refractory	30 (75)	10 (25)						

CMV reactivation had an adverse effect on overall survival (OS) with a significantly lower 5 years OS of $58.2 \pm 4.9\%$ in patients with CMV reactivation compared to 5 years OS of $68.9 \pm 3.7\%$ ($p = 0.004$) without CMV reactivation (Fig. 1).

Fig. 1 Comparison of overall survival between patients who had CMV reactivation versus those who did not have CMV reactivation. CMV reactivation had an adverse effect on overall survival (OS) with a significantly lower 5 years OS of $58.2 \pm 4.9\%$ in patients with CMV reactivation compared to 5 years OS of $68.9 \pm 3.7\%$ ($p = 0.004$) without CMV reactivation

Discussion

Cytomegalovirus (CMV) reactivation remains a significant complication after allogeneic SCT. The pathogenesis of CMV reactivation is extremely complex and includes several interactions between the CMV virus and the immune system which is mediated by several mechanisms, including effects of the virus on the human leucocyte antigen expression, cytokine production and adherence molecules. Hematopoietic stem cell transplant recipients are at risk of CMV reactivation and disease both in the early (< 100 days) and in the late (> 100 days) post transplantation period. In particular, are those high-risk recipients who are on treatment with high-dose corticosteroids and other immunosuppressant or T cell depletion and anti-T-cell strategies including the use of Alemtuzumab and Antithymocyte globulin (ATG). The seroprevalence of CMV in the general population is high in a developing community compared to a developed country. In India the seroprevalence of CMV among healthy voluntary blood donors is estimated to be 95–98% [9, 10] compared to the Western world where it varies between 38 and 75% [11].

CMV seropositivity remains not only the main risk factor for CMV reactivation and disease but also, as indicated by various studies, surrogate markers for major mortality disadvantage among stem cell transplant recipients [11, 13]. In our study we found that 97.5% of the stem cell recipients and 84% of the stem cell donors were seropositive for CMV. Despite this high seroprevalence, it was interesting to note that only 36% of the stem cell transplant recipients develop CMV infection in the early post-transplant period. This is low in contrast to what is reported from the West where there is a high prevalence of CMV disease in the early post-transplant period in spite of having a low sero-prevalence in the general population. Van Baarle et al. [7] reported an incidence of 57.4% CMV

infection in a Dutch stem cell transplant cohort, whereas higher incidence of CMV infection (62%) was reported by Ljungman et al. [14] in a Swedish population who underwent allogeneic stem cell transplantation. The incidence of CMV reactivation post SCT is comparatively less in reports from Asian countries, as in a report from Korea which reported a lower incidence of CMV infection (42.2%) despite a higher seroprevalence in the recipients and donors [13]. An earlier report from India, had reported even less incidence (9.5%) of CMV infection at a median of 52 days in the post allogeneic stem cell transplant setting [15].

The relationship of donor sero-positive status and CMV sero-positive recipients (R+) in CMV infection and disease after allogeneic SCT remains controversial. CMV seropositivity of the recipient is an adverse factor especially in the setting of increased immunosuppression like mismatched or unrelated transplantation and graft vs host disease [16, 17]. Reactivation of an asymptomatic latent infection in the recipient by immunosuppression secondary to the transplantation and the immunosuppressive medications is well known and established. Ljungman et al. [18] had reported improved 5 years survival rate with decreased transplant related mortality in unrelated transplants involving a CMV seropositive donor and a CMV seropositive recipient. CMV seropositive recipients who receive grafts from CMV seronegative donors have an increased risk of CMV infection and disease. In contrast, CMV seronegative graft recipients from CMV seropositive donors are at low risk of CMV disease and have a much lower incidence of CMV disease.

The data on the use of Ganciclovir prophylaxis in the setting of R + D-stem cell transplant (where the recipient is seropositive and donor is seronegative) is controversial and more evidence is needed.

Other transplant related risk factors known to be associated with CMV reactivation include advanced age, conditioning regimen (use of total body irradiation, Fludarabine, ATG), mismatched and umbilical cord transplants, use of T cell depleted grafts and presence of acute GVHD [19, 20]. In our study male donor, mismatched transplantation, incidence of acute GVHD and the GVHD response to steroids were found to be significant risk factors for early CMV infection. However the use of ATG in conditioning regimen and severity of acute GVHD were not found to be associated with any increased risk.

Early CMV reactivation usually occur between 6 and 12 weeks after stem cell transplantation [21, 22]. In our patients CMV infection occurred in a median duration of 41 days (range 10–100 days) post-transplant. Ganciclovir, a nucleoside analogue of 2'-deoxyguanosine, competitively inhibits DNA synthesis and is the most commonly used anti CMV therapy [23]. It exhibits potent in vitro and

in vivo activity against the CMV virus. Majority of the patients in our group were treated with ganciclovir for a median of 16 days. The use of ganciclovir is often limited by the occurrence of hematologic side effects, primarily neutropenia and thrombocytopenia. Neutropenia has been reported in 30% of patients during ganciclovir therapy [24]. The use of prophylactic recombinant human G-CSF can decrease or in part prevent the neutropenia and facilitate an uninterrupted therapy with ganciclovir. In our series, majority of the patients (90%) responded to 2 weeks of ganciclovir therapy with clearance of the virus. Despite this, the presence of CMV reactivation by itself is associated with a higher morbidity and mortality and is usually associated with a lower overall survival as seen in our series. Newer strategies including the use of prophylactic drugs such as maribavir or immune augmentation using CMV specific T cells need to be explored in greater detail to reduce the incidence of CMV reactivation [25–27].

Our study has its limitations. As CMV viral copy numbers were monitored only on day 28 post stem cell transplantation and then on only when indicated, many cases of CMV reactivation may have been missed. The exact cause of the low CMV infection in Indian patients despite the high seroprevalence is not known. Well planned prospective randomised controlled studies with frequent monitoring of blood CMV viral copy numbers and serotyping of the viral strains are needed to correctly elucidate the cause.

It is still very early to comment on the futility of Ganciclovir prophylaxis in Indian patients. Large multicentre trials are required to make it more clear and to adapt it in standard practice.

Conclusion

CMV infection after allogeneic stem cell transplantation continues to be a major challenge. The incidence of CMV infection post allogeneic stem cell transplantation is low despite a very high sero-prevalence in the general population. Despite the lower incidence of CMV disease among SCT recipients early after transplantation, there is still a substantial mortality disadvantage.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to declare.

Informed Consent Informed consent was obtained from all human participants involved in this study. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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