RESEARCH ARTICLE

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Overview of Cytomegalovirus Positive Patients Post-Peripheral Blood Stem Cell Transplant at Malaysia Tertiary Hospital

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ABSTRACT

Background and Objectives: Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality after Peripheral Blood Stem Cell Transplant (PBSCT). This study aimed to determine the characteristics and the outcomes of CMV-positive patient's post-PBSCT.

Materials and Methods: The study population was CMV-positive post-PBSCT diagnosed by quantitative Polymerase Chain Reaction (PCR) from January 2014 until June 2016. The data was retrieved retrospectively using Integrated Laboratory Management System (ILMS) and medical records.

Results: A total of 64 medical records who received peripheral blood stem cell transplant were reviewed and 30 cases (46.9%) with CMV positive. They had PBSCT between 2009 and June 2016. Mean age was 34.8± 11.14. Twenty-three (76.7%) patients underwent allogeneic and 7 (23.3%) underwent autologous PBSCT. Most of the diagnoses were Acute Myeloid Leukemia (AML) (36.7%), Acute Lymphoid Leukemia (ALL) (20.0%) and Non-Hodgkin Lymphoma (16.7%). Pre-transplant CMV Immunoglobulin G (IgG) serology was positive in 29 patients (96.7%). Post-PBSCT CMV DNA titer was detected low in 16 (53.3%) and high in 14 (46.7%). The median duration to detect CMV positivity post-PBSCT was 29 days(IQR 14.75-55.75). Interestingly, 25 (83.3%) patients were positive within 100 days. All patients had resolution of viremia within 24 weeks after the treatment. Three patients (10%) died between 1-13 months post-PBSCT. Four patients (13.3%) had CMV end-organ disease 1-5 months with median 32 days (IQR 30.75-62.25) post-PBSCT. Two patients (6.67%) had clinical diagnosis of CMV disease. Others developed complications such as mucositis (66.7%) and neutropenic sepsis (43.3%).

Conclusion: Mortality rate was low (10%) among CMV-positive post-PBSCT patients. Regular monitoring for CMV viral load to patients at risk of CMV infection is required. The complications of mucositis and neutropenic sepsis can be successfully treated medically.

Keywords: Cytomegalovirus, Viral load, Peripheral Blood Stem Cell Transplantation.

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INTRODUCTION

Cytomegalovirus (CMV) infection is still a major cause of morbidity and mortality after Peripheral Blood Stem Cell Transplantation (PBSCT). CMV infection is defined as evidence of CMV replication regardless of symptoms and signs[1,2]. It also can define as any attributable symptoms and signs either a viral syndrome (the presence of signs and symptoms of disease and the confirmation of viral replication in the peripheral blood detected by antigenemia assay or molecular techniques) or as tissue invasive disease (the presence of specific symptoms in a target organ and histological findings demonstrating the cytopathic effect of the virus in tissue. In these instances, there may or may not be evidence of viral replication in the peripheral blood[1,2].The antigenemia assay is a useful and reliable indirect method for the diagnosis and prediction of human CMV end organ disease.

Clinical manifestations vary widely and should be diagnosed according to established, internationally accepted, standardized criteria.1 Primary CMV infection is when infection occurs in a CMV IgG-negative patient and CMV reactivation when patient or donor is known to be CMV antibody positive. Most patients will reactivate latent virus rather than acquire primary infection post Hematopoietic Stem Cell Transplant (HSCT).

In uncomplicated CMV infection, organ-specific signs and symptoms are absent, although non-specific symptoms, such as fever and malaise, may occur[1,2].If left untreated, asymptomatic CMV infection can progress to CMV disease, most commonly affecting the lung, gastrointestinal tract, eye, liver or central nervous system. CMV pneumonia is the most serious complication with > 50% mortality.

The pathogenesis of CMV infection and disease is complex with several interactions between CMV and immune system. The interaction is mediated through several mechanisms, including the virus having effects on Human Leukocyte Antigen (HLA) expression, cytokine production, and expression of adherence molecules. These interactions can explain the increased risk of secondary bacterial and fungal infections in patients with CMV infection[3]. Another possible effect of the interaction with the immune system is the described association between CMV and acute and chronic Graft Versus Host Disease (GVHD)[4-6]. However, CMV infection has been reported as a risk factor for acute GVHD in patients receiving T cell-depleted grafts and for chronic GVHD[7-10].

CMV reactivation and infection incidence is more frequent after allogeneic stem cell transplant than after autologous stem cell transplant[11]. Serology is useful in determining the serological status of the donor and recipient prior to transplantation to thereby define the post-transplant risk. CMV reactivation may occur in up to 70% of high-risk patients, such as those with positive serology who received a transplant from a negative donor[12]. In HSCT, reactivation usually occurs within the first 30 days after transplantation and in those who develop GVHD.

Viral load quantification in CMV by quantitative PCR is the main alternative option for the diagnosis of viral replication. This test is carried out using the real-time PCR technique which provides better accuracy, a faster response time, higher efficiency and lower risk of contamination compared with conventional PCR[13].

The aim of this research is to study the outcome of CMV infection in post-PBSCT patients.

MATERIALS AND METHODS

The study conducted in Hospital Canselor Tuanku Muhriz from September 1st, 2015-September 1st, 2016. This hospital is a 900-bedded, research-oriented tertiary care hospital affiliated to the Universiti Kebangsaan Malaysia. This study received approval from the Research Ethic Committee FF-2016-220. The data of CMV-positive patients retrieved from January 2014 to June 2016 by using Integrated Laboratory Management System (ILMS). All respondents` medical record that fulfilled the criteria set and retrieved the data retrospectively. Our unit sample was post peripheral blood stem cell transplant patient. Inclusion criteria were patients who underwent peripheral blood stem cell transplant with CMV-positive diagnosed by quantitative Polymerase Chain Reaction (PCR) from January 2014 until June 2016 using Integrated Laboratory Management System (ILMS). The exclusion criteria were incomplete medical records. Data collected were introduced and processed by statistical software Statistical Package for the Social Sciences (SPSS) Version 20.0. Descriptive statistics of demographic and clinical data of the sample were calculated. We analyzed data using SPSS statistical software for Windows version 20.0.

RESULTS

A total of 64 medical records were universally reviewed and 30 cases (46.9%) fulfilled the criteria. Mean age was 34.8± 11.14. There was equal distribution between genders. Most of the patients went for PBSCT was diagnosed with Acute Myeloid Leukemia (AML) (11, 36.67%), followed by acute lymphoid leukemia (ALL) (6, 20%), Non-Hodgkin Lymphoma (5, 16.67%), Chronic Myeloid Leukemia (4, 13.3%), Hodgkin lymphoma (2, 6.67%), Myelodysplastic Syndrome (1, 3.33%) and Multiple Myeloma (1, 3.33%). Out of 30 patients, 14 patients (46.67%) underwent PBSCT on 2014 and the number was reduced to 4 (13.33%) on 2015 and 2 (6.67%) on 2016.

Relationship between CMV infection and CMV disease with type of transplant

Out of 23 patients went for allogeneic PBSCT, 3 (13.0%) developed CMV disease while 1 out of 7 patients (14.3%) went for autologous PBSCT developed CMV disease. This shows that both type of transplant have equal chance of getting CMV disease. However, this could be underestimated because the sample of autologous is small as compared to allogeneic.

Pre-transplant CMV serology

Pre-transplant CMV serology was routinely checked for screening. There was only one patient (3.33%) with seronegative CMV IgG while the rest were seropositive CMV IgG. Meanwhile, all the patients were seronegative CMV IgM showing no acute CMV infections pre-PBSCT.

Relationship between CMV viral load and mortality

In total, there were three mortalities out of 30 patients (10%). One of them had high CMV viral load while the other two had low CMV viral load. Based on Fisher exact test, ($p = 0.552$); $p > 0.05$. No significant association between mortality and CMV viral load.

Relationship between CMV viral load and CMV disease

Out of 14 patients who had high CMV Viral load, there were two patients (14.3%) had CMV disease while two out of 16 patients (12.5%) who had low CMV viral load developed CMV disease. Thus, there was equal chance to get CMV disease despite of the CMV viral load they had. The CMV diseases that the patients had were CMV pneumonitis and CMV colitis with equal distribution in both viral loads.

Time interval between transplant and CMV viremia

The median of time interval between transplant and CMV viremia was 29 days (IQR: 14.75-55.75). This shows that most of the patients developed CMV viremia within 1-month post-PBSCT. Out of 30 patients, there were 26 patients (86.67%) developed CMV viremia within 250 days post-PBSCT. There was a patient who developed CMV viremia after 5 years of transplant. This might not the patient first episodes as we did not have the date on CMV viremia before the year of 2014. There was also a patient who had CMV viremia before the transplant. This might be due to the immunosuppressive effect of the treatment he/she received before the transplant which makes him vulnerable to CMV infection.

Time interval between viremia and resolution

Every patient might have multiple episodes of CMV viremia in their life post-PBSCT. The time interval was calculated for each episode of CMV viremia. Thus, the median of time interval between CMV viremia and resolution for each episode was 4 weeks (IQR: 1-8). This shows that most of the CMV viremia will be cleared within one months of treatment. However, there were two patients who achieved resolution within 21-25 weeks post-PBSCT with proper treatment.

Time interval between transplant and CMV disease

From four patients who had CMV diseases, three (75%) of them developed CMV disease approximately within 30 days post-PBSCT. However, the other patient was diagnosed to have CMV disease after 5 months of PBSCT which suggestive of late onset CMV disease.

Other opportunistic infections post-PBSCT

Most of the patients who went for PBSCT were immunocompromised. Thus, they were vulnerable to other infections. A total of 13 (43.33%) patients had bacterial infections such as Streptococcus pneumoniae, Escherichia coli and Klebsiella sp. While, there were 6 (20.00%) patients had fungal infections such as Candida albicans, Cryptococcus neoformans and Aspergillus sp.. There were four (13.33%) patients had both bacterial and fungal infections. Out of that, there were 7 (23.33%) patients who never had any other infections.

Complications post-PBSCT

The most common complication was mucositis which affected 20 (66.67%) patients followed by GVHD which affected 16 (53.33%) patients. The GVHD mainly affect the skin in 11 patients, while 5 patients developed GVHD in gut and liver each. Other than that, there were 13 (43.3%) patients who developed neutropenic sepsis, 7 (23.33%) patients developed pneumonia and four patients (13.33%) developed thrombocytopenia.

DISCUSSION

CMV infection / viremia is highly associated with morbidity and mortality in patients post-Peripheral Blood Stem Cell Transplant (PBSCT). CMV disease is diagnosed when patient presented with signs and symptoms of organ involvement together with detection of CMV using validated method with appropriate clinical specimen. Our study had shown there was no difference between incidence of CMV disease among allogenic (13.3%) and autologous (14.0%) PBSCT. It was reported that the incidence of CMV disease in allogenic hematopoietic transplant was about 30% and 5% in autologous transplant[14]. Several authors from mid-1999s demonstrated that CMV disease was rare after autologous Hematopoietic Stem Cell Transplant (HSCT). In comparison, our study could be underestimated because the number of patients who underwent for autologous PBSCT was small compare to allogenic transplant.

A total of four out of 30 patients (13.3%) CMV viremia post-PBSCT developed CMV disease. Two of them detected to have high viral load while the other two had low viral load. Our findings indicated there was no association between CMV viral load and CMV disease since it was proven that patient who had low positive CMV viral load also develop CMV disease. However, it was also reported that both high CMV viral load in the initial phase of active infection and the rate of increase in viral load correlate with CMV disease[15].

The time interval for CMV disease to develop post-transplantation was approximately 30 days. About 75% of CMV disease patients developed the disease within 30 days and only one (25%) manifested late at day 150 post-transplantation. This result is consistent with other research which showed that CMV disease occurs mainly between 30-90 days post-transplant and is rare after 180 days[16]. Most cases of late CMV disease occur between 4-12 months after transplant[17]. There was other study revealed the risk factors of CMV late disease include CMV infection or disease during first 3-month post-transplant,

low CD4 T-cell count, undetectable CMV-specific T-cell immunity, and Graft Versus Host-Disease (GVHD) or T-cell depletion in the graft or the use of anti T-cell agents[18].

Our study had shown there was no association between viral load and mortality since we found that 6.67% of our patients died with detection of low viral load and 3.33% died with high viral load. None of them died due to CMV disease. In contrast, there was one study reported that high CMV viral load was associated with increased risk of early death (day 0-60 post transplantation)[19].

Serology test has role to predict the risk to get the disease[20]. Other study done regarding serological status in solid organ transplant with risk CMV disease, revealed that serological mismatch (D+/R-) has highest risk for CMV disease while (D+/R-) and (D-/R+) are both classified under intermediate risk. The lowest risk (<5%) for CMV disease is when both recipient and donor are seronegative (D-/R-)[21]. In our study, 14.3% of match seropositive donor and recipient developed CMV disease though being classified under intermediate risk.

There was 23 (76.7%) patients developed additional infections other than CMV infection post-PBSCT. This could be associated with indirect immunosuppressive effect of CMV infection or chemotherapy. CMV also has indirect immunosuppressive effects, leading to an increased incidence of fungal and bacterial infection[22].

Many of our patients had more than one complication post-PBSCT. The most common complications they developed were mucositis followed by GVHD and neutropenic sepsis. These complications may be attributed by immunosuppressive effect of chemotherapy given pre and post-transplant. Oral mucositis is found in 15-40% of patients treated with conventional chemotherapy in 70-90% of patients undergoing HSCT[23]. CMV has indirect immunosuppressive effects leading to higher rates of both acute and chronic GVHD[24].

Small number of sample size is the limitation of our study. This may contribute to underestimation and inaccuracy of CMV infection cases among PBSCT. Therefore; further study with larger sample size should be carried out for more accurate result. CMV disease can appear in the absence of CMV viremia20. However, our study didn't have data on negative CMV viremia therefore comparison with the incidence of CMV disease and positive CMV viremia could not be made. Other than that, there is no establish guidelines on utility of CMV viral load or cut off point to determine CMV disease thus we suggest in the future to have a protocol or guidelines that would be used worldwide. This helps for early detection of CMV disease as well as can start early preemptive therapy that will reduce the mortality among CMV viremia patients.

CONCLUSION

Mortality rate was low (10%) among CMV positive post-PBSCT patient's despite of various complications. We advocate regular monitoring of CMV viral load among patients at risk of CMV infection. This is important to assist the pre-emptive therapy and to monitor the response to anti-viral treatment although those with end-organ disease may not have high viremia.

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