Frequency of Thrombocytopenia and Leucopenia in Renal Transplant Recipients Taking Anti CMV Therapy

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ABSTRACT

Background: Cyto Megalo Virus (CMV) is among most frequently reported opportunistic infection causing morbidity and mortality in solid organ transplant recipients. Intravenous Ganciclovir is the recommended first line treatment strategy. Hematological complications have been reported as an important adverse effect of Ganciclovir therapy and therefore limits its optimal therapy. This study will provide data about the frequency of hematological adverse effects of anti CMV therapy in renal transplant recipients.
Objective: To determine the frequency of thrombocytopenia and leucopenia in renal transplant recipients taking anti CMV therapy
Materials & Methods: This was a cross sectional descriptive study and it was conducted at Department of Hematology at Sindh Institute of Urology And Transplantation (SIUT), Karachi for a period of 6 months i.e. from 1st November 2012 to 31st may 2013. Hundred 100 renal transplant recipients who were diagnosed as CMV positive on serological testing and taking Ganciclovir therapy, admitted in transplant ICU at SIUT were enrolled for the study after Informed consent. Patients with diagnosed hematological problem or having thrombocytopenia and leucopenia before taking Ganciclovir therapy were excluded. A structured Performa was used to collect data. Data was recorded including clinical history, age, gender and complete blood counts (CBC).Frequency of thrombocytopenia and leucopenia age and sex distribution were recorded.
Results: CBC parameters of all CMV positive renal transplant recipients taking Ganciclovir therapy were recorded before and after starting Ganciclovir therapy. Out of these 100 cases 43(43%) patients developed complications of anti CMV therapy. Thrombocytopenia developed in 24(24%). leucopenia developed in 31 (31%) patients of which 11% had leucopenia without neutropenia while 20% cases had leucopenia with neutropenia. Eleven 12 (12%) patients developed thrombocytopenia and leucopenia both as a complication of anti CMV therapy.
Conclusion: All the cases of hematological complications were diagnosed by simple laboratory methods .Of the 100 CMV positive patients taking Ganciclovir therapy 43 (43%) patients suffered complications (Thrombocytopenia and leucopenia) of anti CMV Therapy. More prolonged and follow-up studies are needed to define the true significance of these complications in post-transplant settings.

***Key words**: Renal Transplant Recipients, CMV infection, Anti CMV Therapy, Hematological complications*

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INTRODUCTION:

Standard of care for management of end stage renal disease is kidney transplantation in which a diseased kidney is replaced by a healthy kidney from a suitable healthy donor. Hosts immune system intends to reject the graft as it is foreign to the host[1]. Immuno suppressive therapy is used to suppress rejection of graft by host`s immune system. Immuno suppressive therapy has greatly reduced the incidence of early graft rejection but on the other hand these transplant recipients become prone to acquire opportunistic infections[2]. The transplanted patients don't exhibit usual symptoms of infection or disease as expected in a person with normal immune function so it is difficult to recognize infection in these patients. In solid organ transplant recipients (SOT) CMV is among the most frequently reported opportunistic infection that can cause significant morbidity and mortality in renal allograft recipients[3]. Reported incidence is between 20-60% depending upon various factors which include type of graft, immunosuppressive regimen and other risk factors. Mortality could approach 90%in some transplant settings[4]. According to researches 50-80% of the healthy immune competent patients are being infected with CMV, this rate is even higher in transplant recipients because of the immune suppression and in this group the CMV infection is an important cause of morbidity and mortality[5]. Around 75% solid organ transplant recipients acquire infection either through infected organ from a seropositive donor or by latent CMV virus reactivation[6]. Prophylaxis can be given to the patients who are at high risk of viral reactivation and preemptive therapy is indicated if viral replication has been diagnosed before appearance of full blown symptoms of disease. Anti-viral medications used in prophylaxis of CMV infection include oral and IV Ganciclovir, Valacyclovir, Acyclovir, valganciclovir and immunoglobulins however Ganciclovir and Valganciclovir are main drugs used in its treatment[7]. In the therapeutic settings of CMV disease, the recommended first line therapy is

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intravenous Ganciclovir[8]. Hematological complications have been reported as important adverse effect of Ganciclovir therapy and therefore limit its optimal therapy[9]. The reported incidence of leucopenia, thrombocytopenia and anemia in patients receiving Ganciclovir therapy is 21%, 47% and 64%, respectively[10].

Currently no published data is available in Pakistan on hematological adverse effects that have been described with variable frequency during the course of Ganciclovir therapy; however it has been frequently reported from other centers. So it is hoped that this study will help to generate local data and will contribute to evaluation of burden of this problem in Pakistan

MATERIALAND METHODS:

This is a prospective cross-sectional descriptive study carried out at Sindh Institute of Urology and Transplantation for a period of 6 months. Permission from the ethical review committee was taken by the researcher. All adult transplanted patients (above 18 yrs) of either sex who were diagnosed as CMV positive on serological test (using ELISA based kits of Roche) and taking anti CMV therapy were included.Patients having thrombocytopenia, leucopenia or anemia before starting Ganciclovir therapy, patients with diagnosed hematological problem and patients with diseases that may contribute to anemia, thrombocytopenia or leucopenia were excluded.

Informed consent was taken from the patient. A structured performa was used to collect data by the researcher. Data was collected through Consecutive Non probability sampling technique. Data included name, age, and gender along with date of transplant, date when the Ganciclovir therapy started and laboratory investigations of the patient. Once CMV serology of a transplanted patient was detected as positive, their initial CBC parameters were recorded at that time. 2ml venous blood samples was collected and delivered directly into vacutainer tubes containing Dipotassium EDTA at a concentration of 1.5±0.25mg/ml of blood. Samples were processed on SYSMEX XE-2100. After starting Ganciclovir therapy subsequent CBC parameters were recorded weekly for 2 to 4 weeks. The collected data was entered in SPSS (Version10.0) and analyzed by the researcher. Frequencies in percentages of thrombocytopenia and leucopenia were calculated among all patients taking Ganciclovir therapy. Frequencies in percentage were calculated for gender. Mean ±SD was calculated for age. Stratification was done with regard to age, gender and immunosuppressive regimen that the patient was taking.

RESULTS:

One hundred renal transplant recipients diagnosed as CMV positive on serology and taking Ganciclovir therapy were included in this study. Demographic features of all these patients showed that 70(70%) were male and 30(30%) patients were female. The mean age of all patients was 33.56 ± 9.9years, ranged from 18-58 years. Among all these patients 71 (71%) were aged below 40 years while 29(29%) were 40 years and above. the mean age of male patients was32.96±10.07 years ranged from 18-58yrs while the mean age of female patients was 34.9±9.81 ranged from 18-54yrs . Out of these 100 cases 43(43%) patients developed complications of anti CMV therapy. The mean age of these 43 cases was 31.57±9.65 ranged from 18-52 yrs. cases below 40 years were 33(78.6%)while cases 40 yrs and above were 9(21.4%). Male patients were25 (59.5%) while female were 17(40.5%). Thrombocytopenia developed in 24(24%). Leucopenia developed in31 (31%) patients from of which 11% had leucopenia without neutropenia while 20% cases had leucopenia with neutropenia. Out of these 42 cases 12 (12%) patients developed thrombocytopenia and leucopenia both as a complication of anti CMV therapy.

Total no. of patients who developed thrombocytopenia was 24(24%) of which 18 (18%) had mild while 6 (6%) had moderate thrombocytopenia. Demographic features of patients who develop Thrombocytopenia are shown in Table 1.Mean base line platelet was 227.3±63.21 with a range of 153-368.mean follow up platelet count (after taking Ganciclovir therapy) was 110.35±26.31 and range of 61-140.Total no of cases who developed leucopenia were 31(31%) and the mean age of these 31 cases was 33 ±10.42 with a range of 18-52 yrs.

Demographic features of patients who developed leucopenia are shown in Table 2.Mean base line TLC before starting Ganciclovir therapy was 8.62±3.29 with a range of 4-17. Follow up TLC count after starting Ganciclovir therapy was 2.67 ±0.629 with a range of 1.3-3.5. Mild neutropenia developed in 17 (56.7%) cases while 3(10%) patients developed moderate Neutropenia.

Table 1: Demographic features of patients who Developed Thrombocytopenia.

Total no of cases	24
Mean age ± SD	31.00 ± 7.97
Age range	18-45years
Cases below 40 yrs (%)	20(83.3%)
Cases 40yrs and above (%)	4 (16.7%)
Gender	
Male, n (%)	14(58.3%)
Female, n (%)	10(41.7%)
Baseline platelet mean± SD	227.88±63.17
Baseline platelet range	149-368
Baseline platelet mean± SD	149-368
Baseline platelet range	110.83±25.85
Follow up platelet mean± SD	110.83±25.85
Follow up platelet range	61-140

Table2: Demographic features of patients who developed Leucopenia

Total no of cases	31
Mean age ± SD	32.84±10.28
Age range	18-52years
Cases below 40 yrs (%)	23(74.2%)
Cases 40yrs and above (%)	8 (25.8%)
Gender	
Male, n (%)	18(58.1%)
Female, n (%)	3(41.9%)
Baseline TLC mean± SD	8.62±3.29
Baseline TLC range	4.0-17.0
Follow up TLC mean± SD	2.67±0.629
Follow up TLC range	1.3-3.5
Mild neutropenia, n (%)	17(56.7%)
Moderate neutropenia, n (%)	3(10%)

DISCUSSION:

Renal transplant recipients are prone to develop opportunistic infections because of iatrogenic immunosuppression. Infrequent opportunistic infections of clinical significance only in immunocompromised hosts that include infections due to Nocardia asteroides, Pneumocystis jirovecii (formerly P. carinii), Aspergillus spp, Cryptococcus neoformans, varicella zoster virus (VZV), cytomegalovirus (CMV), influenza, respiratory syncytial virus (RSV), Legionella spp and Rhodococcus equi. It is difficult to recognize infection in transplanted patients than in persons with normal immune function as transplanted patients don't exhibit the usual symptoms of a specific infection[10, 11]. CMV is the most frequently reported opportunistic infection occurring in 20-60% of transplant recipients. It is the important cause of death in immunocompromised subjects. SOT ((Solid organ Transplant) recipients who suffered from CMV disease have increased risk of developing acute and chronic graft rejection and death[12]

Most of donors as well as recipients have latent CMV infection at time of transplant .Antiviral medication which are used as prophylaxis to prevent CMV infection in transplant patients include IV and oral Ganciclovir, Valacyclovir, acyclovir valganciclovir, and IG. IV Ganciclovir is standard therapy used for Treatment and prevention of CMV disease but these agents have

several undesirable effects especially on blood cells and blood forming tissues .These adverse effects may further worsen by effects of immunosuppressive therapy and by immunomodulatory effect of CMV itself. Anemia, neutropenia and thrombocytopenia are among the major side effects of Ganciclovir therapy[13].

In this study 70% patients were male and 30% were female. The higher proportion of male is probably because most of the kidney transplant recipients were male. So many explanations have been suggested for these gender differences such as increased incidence of ESRD (end stage renal disease), more incidence of cardiovascular disorders among males, immunological dissimilarities and variances in health attitudes. [14] In our study 23%were found to have thrombocytopenia with 17% develop mild thrombocytopenia and 6% develop moderate thrombocytopenia Mean age of these patients was 31.48±7.79 severe thrombocytopenia did not develop in any patient Thrombocytopenia is a dose limiting side effect of Ganciclovir although this appears to be less common in SOT recipients[15]

In our study 30% patients develop leucopenia with mild neutropenia developed in 17% patients and moderate neutropenia developed in 3% patients while there was no patient with severe neutropenia. Both thrombocytopenia and leucopenia were present in 11% patients severity of neutropenia depends on viral load at time of initiation of therapy[16].

A randomized double blind trial was conducted by Edward Gane, et al to evaluate the safety and efficacy of oral Ganciclovir in the prevention of CMV disease in liver transplant recipients. Oral Ganciclovir was given to 150 patients and other 154 were selected to take matching placebo capsules out of 150 patients who were taking Ganciclovir, 5.4% patients develop leucopenia and 23% patients develop thrombocytopenia. Greater frequency of leucopenia in our study can be explained on the basis, that most of our patients were taking MMF (mycophenolate mofetil). The MMF may aggravate the risk of leucopenia (2346%), and thrombocytopenia (2438%). [17]Secondly primary dose limiting toxicity of Ganciclovir is myelosuppression[18,19]. Potential interaction between MMF and Ganciclovir may undesirably effect the blood system[20] So, MM f dosing should be maintained very carefully in patients who are at risk of CMV infection because both the factors that include CMV infection MMF dose reduction seems to increase the threat of acute, rejection[21]. Therefore, care must be taken in considering MMF dose reduction because of adverse reactions

A randomized, open-label trial was conducted between April 2004 and June 2006 to compare the efficacy of Oral valganciclovir with IV Ganciclovir in adult solid organ Transplant recipients with CMV disease. In that Study leucopenia was developed in 12.1% patients who were taking Ganciclovir therapy. Leucopenia was most frequent among all hematological complications which can be due to combined effect of MMF and Ganciclovir and secondly CMV itself play a role in hematologic problems seen after transplantation. [22] A retrospective study that was conducted in kidney transplant recipients who were taking treatment for CMV infection, reported the incidence of leucopenia and thrombocytopenia to be21%, and 47%, respectively[23].

Another study explained a correlation between early graft rejection and development of leucopenia after renal allograft transplantation[24, 25]. All these findings can be helpful for altering risk for undesired hematological side effects at start of antiviral therapy.

CONCLUSION

In this study leucopenia was common finding in patients taking Ganciclovir therapy. Adverse effects of anti CMV therapy were more common in patients below the age of 40 years. Adverse effects of anti CMV therapy on blood counts may limit its optimum therapy.All These events may get worsened by immunosuppression and by the immunomodulatory effects of CMV infection. Continuous monitoring of patient's blood counts is required during the course of anti CMV therapy. Severely decreased cell counts may lead to discontinuation of therapy

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