Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

Granulocyte colony-stimulating factor usage in drug-induced neutropenia after kidney transplantation: a single-center experience

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Abstract

Introduction. Granulocyte colony-stimulating factor (G-CSF) therapy is commonly used in kidney and liver transplant recipients with severe neutropenia. However, rapid and high increases in neutrophil counts of some patients may occur during treatment. This retrospective study aimed to determine the efficacy and safety of G-CSF treatment in neutropenic kidney transplant recipients.
Methods. Eight kidney transplant recipients treated with G-CSF for drug-induced neutropenia (neutrophil count <1000 cells/μL) were included in the study. Daily renal function tests, leukocyte (WBC) and absolute neutrophil counts were measured.
Results. The median duration of G-CSF treatment was 4 days (2-5). The median WBC and neutrophil counts elevated from 1130 and 565 cells/μL to 4400 and 1950 cells/μL after treatment, respectively (p=0.012). The median peak WBC and neutrophil counts during treatment were 18,045 and 16,445 cells/μL, respectively. The WBC counts returned to normal limits after a median of 22 days from the maximum value. No acute rejection was observed within three months of discontinuation of treatment.
Conclusions. G-CSF may be a useful therapeutic alternative for kidney recipients with severe neutropenia. It seems reasonable to withdraw G-CSF treatment when WBC and neutrophil counts reach certain cut-off values during treatment.

Turk J Int Med 2020;2(1): 11-18

Keywords: Filgrastim, granulocyte colony-stimulating factor, kidney transplantation, leukopenia, neutropenia.

Received: December 4, 2019; Accepted: January 10, 2020; Published Online: January 29, 2020

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Introduction

Post-transplant neutropenia is a common complication in kidney recipients. The incidence of neutropenia may range from 14.5% to 28% in the first year after transplantation.[1,2] It may be caused by immunosuppressive therapy (thymoglobulin, mycophenolate or sirolimus), antimicrobial therapy (trimethoprim/sulfamethoxazole, valacyclovir, valganciclovir or ganciclovir), bacterial and viral infections.[1,3-9] In drug-induced neutropenia, identification of the responsible drug is often difficult, and regression of neutropenia after drug discontinuation can be used as indirect evidence.[9]

Leukopenia or neutropenia in kidney transplant recipients is associated with a high risk of serious infections that may lead to septicemia. Although there is no widely accepted guideline on treatment strategies, most physicians often prefer to reduce the dose or discontinue the causative drug.[2] However, interventions to immunosuppressive drugs may cause graft loss.[10] Discontinuation of mycophenolic acid for more than 6 days may be associated with a high rate of allograft rejection.1 Another approach can be the usage of everolimus or azathioprine instead of mycophenolic acid rather than a reduction in the dosage of mycophenolic acid in patients with persistent neutropenia.[11,12] Tacrolimus-induced neutropenia is less recognized, and may be improved by discontinuing tacrolimus and switching to cyclosporine.[13] Recombinant human granulocyte colony stimulating factor (G-CSF) is a hematopoietic growth factor that selectively stimulates neutrophil colony formation and neutrophil cell differentiation.[14] G-CSF has been used successfully to reverse neutropenia in kidney and liver transplant recipients.[15-18] However, some patients may respond very quickly to the initial dose and the neutrophil counts may increase significantly.[19,20] This study aimed to determine the efficacy of G-CSF in persistent neutropenic recipients after kidney transplantation.

Methods

Neutropenic kidney transplant recipients were retrospectively identified among 170 adult patients who underwent kidney transplantation in our center between January 2012 and May 2014 in our center. Ten out of 170 patients treated with G-CSF for persistent neutropenia and/or leukopenia. Posttransplant leukopenia and neutropenia were defined as the count of white blood cells (leukocytes, WBC) below 3000 cells/μL and the absolute neutrophil count below 1000 cells/μL, respectively.[1,21-23] Two patients with sepsis were excluded from the study. Eight transplant recipients (5 males and 3 females) receiving G-CSF treatment for drug-induced neutropenia were included in this study. Primary diseases were Alport syndrome in 2 patients, focal segmental glomerulosclerosis in 2 patients, diabetes mellitus in 2 patients and unknown etiology in 2 patients. There was no history of hepatitis or acute rejection in all patients. Two patients had a history of ganciclovir treatment for CMV DNA positivity. The patients with persistent neutropenia were given a daily dose of 5 μg/kg filgrastim (recombinant human G-CSF, 30 or 48 MIU = 300 or 480 μg) subcutaneously. Demographic and clinical features of the patient, changes in WBC, neutrophil and creatinine values before and after treatment were obtained from the medical records.

All statistical analyses were performed using the IBM SPSS Software package of version 23.0 (IBM Corp, Armonk, NY, USA). The data was given as mean ± standard deviation (SD) or median (min:max). The numerical variables were compared with Wilcoxon signed-rank test within group. The relation between the variables was estimated with Pearson correlation test. Statistical significance was defined by $p < 0.05$.

Results

The dialysis types were hemodialysis in 3 patients and peritoneal dialysis in 4 patients. One patient underwent preemptive transplantation. The median duration of dialysis of seven patients was 38.6 months (6.5-196). Among the patients, 3 received a living donor and 5 deceased donor transplant. The transplant age of patients were 38.2±16.5 years. The mean body mass index at the time of transplantation was 20.9±4.7 kg/m^2. The median number of human leukocyte antigen (HLA) mismatch was 2.5 (1-4). The mean donor age was

51.3±13.4 years. Immunosuppressive regimens of eight patients consisted of cyclosporine (n=4) or tacrolimus (n=4) combined with mycophenolate mofetil and prednisolone. The induction therapy was performed with ATG in 2 patients and basiliximab in 6 patients.

The median duration of neutropenia after transplantation was 2.8 months (1.25-16.1). When leukopenia and/or neutropenia developed, the dose of mycophenolate was initially reduced in all patients. If WBC values continued to fall, it was discontinued. If there is any possible responsible drug, it is also discontinued. When leukopenia improved, mycophenolate treatment was restarted by reducing the dose. The cause of neutropenia was attributed to mycophenolate in 4 patients, teicoplanin in 2 patients, ganciclovir in 1 patient and valganciclovir in 1 patient. Six months after transplantation, one patient with CMV-DNA 282 copies/mL was treated with intravenous ganciclovir. CMV-DNA was negative (<20 copies/mL) after the treatment. On the 17th day of the treatment, the drug was discontinued when persistent neutropenia developed, and then the patient was given 4 doses of G-CSF after 5 days.

The median duration of G-CSF usage for post-transplant neutropenia was 4 days (5 days in 2 patients, 4 days in 4 patients, 3 days in 1 patient and 2 days in 1 patient). The mean dose of G-CSF was 1747±434 µg. The baseline WBC and absolute neutrophil values were 1271±856 (560-3170) and 565±333 (60-1080) cells/µL, respectively. The WBC and absolute neutrophil counts elevated to 5933±5187 (1780-17,300) and 4033±4247 (1340-12,700) cells/µL after G-CSF treatment, respectively (p=0.012). The mean peak WBC and absolute neutrophil counts were measured 20,158±12,556 (3080-44,600) cells/µL and 17,232±11,417 (2720-38,100) cells/µL after median 9.5 days (6-20), respectively. In 5 patients, WBC count increased above 4000 cells/µL after cessation of G-CSF treatment. WBC (8176±2426 cells/µL) and neutrophil (6201±2146 cells/µL) counts returned to normal ranges on average 17 days after discontinuation of G-CSF treatment. The changes in WBC and neutrophil counts are given in Figure 1.

All patients had a median serum creatinine level of 1.75 mg/dL (1.1-2.91) at 1 month after kidney transplantation. The baseline median creatinine levels of patients at the time of neutropenia were 1.5 mg/dL (1.1-2.4), and there was no significant difference between the mean serum creatinine levels at the time of neutropenia and 1 month after transplantation (p=0.441). Serum creatinine levels were measured as 1.53±0.52 mg/dL on the day after G-CSF discontinuation (p=0.115), 1.57±0.6 mg/dL on the day of peak WBC (p=0.262) and 1.75±0.66 mg/dL on the day that WBC returned to normal ranges (p=0.499) (Figure 2). These levels were comparable with the mean serum creatinine levels during neutropenia. No acute rejection episode was observed during the 3-month follow-up period after discontinuation of G-CSF. There was no a significant correlation between total G-CSF dose and treatment duration with

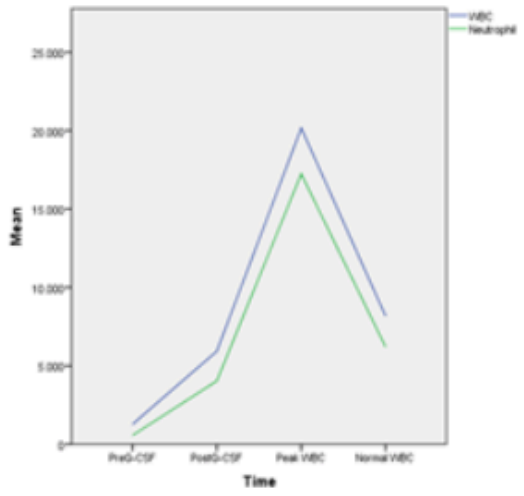

Figure 1. The changes in WBC and neutrophil counts after G-CSF treatment

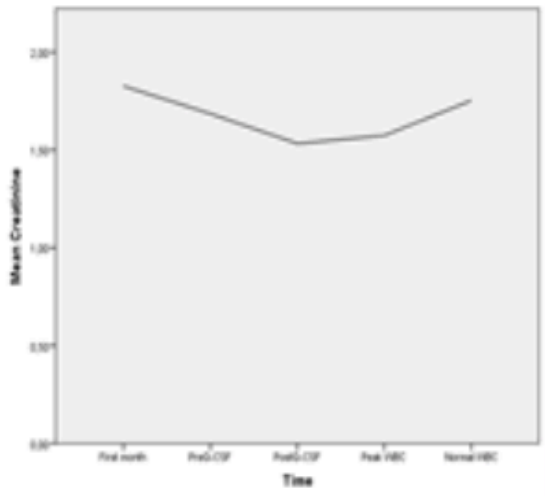

Figure 2. The changes in serum creatinine levels after G-CSF treatment

several variables including age, gender, presence of diabetes mellitus, history of CMV infection, calcineurin type, baseline serum creatinine level, baseline and peak WBC and neutrophil values ($p>0.05$). The neutropenia duration was positively correlated with pre-transplant body mass index value (r:0.836, p=0.010). None of the patients had bone pain associated with G-CSF usage.

Discussion

Incidence of combined leukopenia or neutropenia in kidney and/or pancreas transplant recipients can be as high as 58%.[21] The rate of neutropenia is reported to be 28% in the first year after transplantation.[1] In a study, the incidence of leukopenia was higher in patients receiving alemtuzumab (42% vs. 9% by antithymocyte globulin induction) and/or in patients had rapid steroid withdrawal in the early post-transplant period (44% vs. 16% in those without steroid withdrawal).[21] Neutropenia can be associated with many factors including thymoglobulin induction, tacrolimus, mycophenolate mofetil, female gender, Caucasian ethnicity, ischemic heart disease, donor cytomegalovirus positivity, and later year of transplant, deceased donor, expanded donor criteria, delayed graft function, higher panel reactive antibody and HLA mismatch.[2] In another study, the causes of 100 post-transplant neutropenia episodes in 50 recipients (14 kidney, 35 liver and 1 combined kidney and liver transplant) were ganciclovir (28%), CMV (21%), chemotherapy (12%), sepsis (11%), azathioprine (5%), interferon (3%) and others (20%).[24] The occurrence of neutropenia was found to be associated only with combined tacrolimus and mycophenolate treatment in a study.[1] Our study included drug-induced neutropenic patients, and neutropenia in half of the patients was associated with mycophenolate. The occurrence of neutropenia in our patients was similar to the previous reports.[1,2,25-27] The median duration of neutropenia after transplantation was 2.8 months.

Our findings and the results of other studies indicated that G-CSF treatment was safe and effective in reversing persistent leukopenia or neutropenia in solid organ transplant patients without no serious adverse effects.[8,14-18,20-22,24,27,28] The elevation of total WBC count in G-CSF-treated patients is mainly due to a specific increase of neutrophil granulocytes.[14] Our patients received G-CSF treatment for a median of 4 days. The median WBC and neutrophil counts elevated from 1130 and 565 cells/μL to 4400 and 1950 cells/μL after the treatment, respectively. In 62.5% of the patients, WBC count increased to over 3000 cells/μL when G-CSF treatment was discontinued. The rate of treatment failure was 12.5%. Because only one patient could not achieve the desired WBC response (peak value: 3080 cells/μL), however, the maximum neutrophil count of 2720 cells/μL was more reasonable and acceptable. The median peak WBC and neutrophil counts were 18,045 and 16,445 cells/μL in all patients, respectively. The WBC counts returned to normal ranges after a median of 22 days from the maximum value. In other retrospective study, 15 patients (13.3%) were treated with G-CSF for a median 2 days.[1] The mean duration of neutropenia did not differ between patients receiving G-CSF or not (16±14 vs. 26±23 days). In patients treated with G-CSF, the time to reach an absolute neutrophil count above 1000/μL was significantly shorter than in patients not receiving G-CSF (1.5±0.5 days). In another study including 25 patients who underwent either a kidney or a combined kidney and pancreas transplant, 35 neutropenia episodes were treated with a mean of 2.9 doses of G-CSF per episode without precipitate or aggravate allograft rejection.[20] The mean number of days to peak WBC after initiation of treatment was 4.6 days. In a retrospective cohort study in which 30 leukopenia episodes (2000 cells/μL) were evaluated in 19 kidney transplant recipients treated with G-CSF, the therapy was discontinued when the counts above 4000 cells/μL were reached,[14] and all patients responded to the therapy. The median duration of treatment per episode was 1 day (1-8). WBC counts increased from 1756±582 cells/μL to a peak of 8723±3038 cells/μL in 2.7±1.8 days (1-8) after the first G-CSF usage.14 When compared to historical control group, leukopenic episodes in treated patients were significantly shorter (1.29 days vs. 7 days), and bacterial infections occurred at a significantly lower rate.[14] In the largest retrospective study of 100 neutropenia episodes in 50 patients undergoing kidney or liver transplantation, WBC count increased to above

5000 cells/μL in 93% of patients within 3.7 days after G-CSF support for a mean of 10 days.[24] In 6 (7%) out of 7 cases that did not reach this count, G-CSF treatment lasted less than 4 days. In a retrospective study of 102 kidney and pancreas transplant recipients over 1 year, Hartmann et al.21 found 59 patients (58%) with total WBC <3000 cells/μL or absolute neutrophil count <2000 cells/μL, and 21 patients received G-CSF at some point during their management. Leukopenia was successfully treated with an average of 3.1 doses of G-CSF. Similar to our observations, a total G-CSF dose of four or less was sufficient in the majority of patients (85%). Hamel et al.[29] retrospectively evaluated 32 leukopenic (WBC <3000 cells/μL) kidney transplant recipients who started G-CSF treatment on mean 98±38 days after transplantation. The median time to WBC count recovery was 9 days (4-14) following a mean 2.1±1.9 doses of G-CSF. This time is longer than previously reported in the literature.[20,24,27,30] The mean interval from the onset of leukopenia to the initiation of G-CSF treatment was 15±16 days. In post-hoc analysis, WBC count recovery times were similar in patients with or without G-CSF therapy delays (median 10 vs. 5 days). The recovery time at 7 and 14 days was similar between patients receiving at least one dose of G-CSF and not receiving any dose (median 9 vs. 8.5 days).[29] Similar to the findings of Zafrani et al.1, there was no difference in time to WBC count recovery in patients with therapy delays in therapy or those who did not receive any G-CSF dose.[29] In the other study, 28 neutropenic patients were treated with a mean of 1.79 doses (1-5) of G-CSF (300 or 480 μg) without infection or acute rejection.[30] Overall, 87.5% of the cases reached a WBC count of at least 3000 cells/μL within 7 days of hospital discharge.

Although some studies did not find a difference between the rates of infection or acute rejection in patients with and without leukopenia,[21] neutropenia has long been recognized as a risk factor for the development of infection in solid organ transplant recipients.[15] Seven neutropenic patients in the era when G-CSF was not in use had more infectious episodes, more aggressive antibiotic therapy, longer hospital stay and higher mortality rates (57% vs. 14.3%) than those treated with G-CSF.[16] However, eight patients (16%) under G-CSF treatment in the cohort of Turgeon et al.[24] died from infection. They observed that patients with leukopenia secondary to drugs tolerated G-CSF well and received an appropriate WBC response. On the contrary, the outcome in patients receiving G-CSF treatment for sepsis associated leukopenia was particularly poor.[24] In one study, the frequency of infection requiring hospitalization or opportunistic infection was 14% in kidney recipients with leukopenia.[29] Our two patients were excluded in this study due to sepsis-induced leukopenia. Both patients who were given 1 and 5 doses of G-CSF died from infection. In sepsis models, G-CSF increases number of circulating granulocytes, decreases tumour necrosis factor (TNF) production and improves survival. A possible mechanism responsible for a lower rate of rejection in patients treated with G-CSF may be a significant reduction in serum TNF levels associated with G-CSF therapy.[31,32] In comparison to the 49 previous liver transplant recipients who did not receive G-CSF, 37 liver transplant recipients receiving G-CSF (5-10 mcg/kg/day) for the first 7-10 days after transplantation had a lower rates of acute rejection (22% vs. 51%), a decreased number of sepsis episodes per patient (0.92±1.5 vs. 2.18±2.8) and a lower percentage of sepsis-related mortality (8% vs. 22%).[31]

Many studies have reported an association between mycophenolate dose reductions and increased rates of acute rejection following kidney transplantation.[1,33,34] Discontinuation of mycophenolic acid due to neutropenia increases the risk of acute rejection, especially after a 6-day interruption, but this may not lead to reduced renal function at 1 year. The time from onset of neutropenia to discontinuation of the drug is associated with the duration of neutropenia.[1] Since steroid therapy affects mycophenolate mofetil bioavailability, tapering steroid dose may result in higher mycophenolate mofetil exposure.[35] In a retrospective cohort of 41,705 adult transplant patients, 6043 (14.5%) patients had neutropenia and leukopenia, and 740 (12.2%) of these patients received G-CSF. Post-transplant neutropenia was associated with a 1.59-fold loss of graft and 1.74-fold increased risk of death, but G-CSF did not increase the risk of graft loss.2 However, the use of G-CSF in transplant patients may increase the risk of rejection by overstimulating the immune system via leukocyte precursors.[30,36,37]

Colquhoun et al.[38] only reported 1 clinically and biopsy-documented rejection episode among 18 liver transplant recipients who received G-CSF for reversal of neutropenia. Similarly, G-CSF treatment has been reported to be associated with deterioration of graft function in a kidney recipient.[36] The results of several studies in mouse models of acute renal failure indicate contradictory effects of G-CSF on renal function, because G-CSF can attenuates or worsens renal injury in different settings.[39] Anupama et al.[37] described a kidney transplant patient with biopsy-proved acute tubular injury probably due to G-CSF therapy for profound leukopenia. The patient developed acute kidney injury with severe musculoskeletal pain four days after receiving G-CSF, and returned to near baseline creatinine in two weeks. The pathophysiology of this injury may be due to the cytokine nature of G-CSF.[40] In the cohort of Turgeon et al.[24], eight rejections (8%) were seen during G-CSF treatment or within 2 months of treatment. One kidney transplant patient (3.8%) had refractory rejection episodes previously and creatinine level was already high at the start of G-CSF treatment. Among liver and kidney–liver transplant recipients, 7 episodes of rejection (9.5%) within one year of transplant occurred during or following G-CSF, and 3 of them were biopsy proven. No correlation was found between the presence of rejection during or following G-CSF treatment and the peak WBC count, or the length or daily dose of G-CSF.[24] In the majority of studies, the use of G-CSF in solid organ transplant recipients did not increase the frequency of rejection episodes even in the early period with a higher risk of rejection.[14,15,20,26,29] In a relatively large population including a control group, the significant decrease of serum creatinine levels during the treatment period also reflected the concomitant improvement of graft function.[14]

Besides being expensive, G-CSF usage may be associated with several adverse events including bone pain and rare instances such as splenic rupture, allergic reactions, flares of underlying autoimmune disorders, acute myeloid leukemia, myelodysplastic syndrome, lung injury and vascular events in healthy bone marrow donors or persons with chronic neutropenia or cancer.[41] However, in transplant patients with lymphoma, G-CSF treatment may probably be less effective and cause suboptimal WBC increases.[42]

G-CSF is often used as a second-line treatment after discontinuation of potentially responsible drugs. In addition, the use of G-CSF in patients with severe neutropenia reduces the risk of serious infections such as CMV infections, and can provide better outcomes and cost savings. Kidney transplant recipients are also well tolerated for short-term therapy periods of up to 4 days. The decision to start or to continue G-CSF therapy should be based on the measurement of absolute neutrophil count rather than total WBC count.[14] Because leukopenia or neutropenia can be rapidly resolved in patients after G-CSF. In our study, the WBC count of 3 patients given G-CSF for 3, 4 and 5 days was 2280, 2780 and 1780 cells/μL at the end of treatment, respectively. Although the treatment was discontinued when the WBC count was below 4000 cells/μL, the peak leukocyte count reached 28,200 and 19,300 cells/μL in 2 patients. In the third patient, the WBC count increased from 1190 to 1780 cells/μL after 5 doses of G-CSF, but the peak leukocyte value was 3080 cells/μL. Approximately 2 months later, the WBC value was measured as 5490 cells/μL. In another patient, WBC count was after 2 doses of G-CSF elevated from 1280 to 4000 cells/μL. However, the peak leukocyte count was 24,100 cells/μL after 10 days. The peak WBC count increased to 44,600 cells/μL in one patient on the 6th day after 4 doses of G-CSF treatment. The WBC values of the patients returned to normal range median 9.5 days (1-58) after the maximum WBC value and median 22 days (8-65) after the first G-CSF dose.

Conclusions

The usage of short-term G-CSF in kidney transplant recipients appears to be safe and effective without acute rejection episode. It accelerates the recovery of neutropenia in severe neutropenic recipients and may be a good therapeutic alternative in addition to changes in immunosuppression and prophylaxis drugs. As yet, there are no published guidelines on management of neutropenia in kidney transplant recipients. When total WBC and absolute neutrophil counts rise to 2000-3000 cells/μL and 1000-1500 cells/μL, respectively, it seems reasonable to withdraw G-CSF treatment. However, it may be more appropriate for the

transplant physician to make individual decisions based on the severity of neutropenia, graft function, infection and acute rejection risk. Randomized controlled trials are still needed to determine minimum effective dose and therapeutic duration of G-CSF in this population.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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