Clinical Study

Cytopenia Occurrence in Kidney Transplant Recipients Within Early Post-transplant Period

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Abstract

Objective: This study assessed incidence, severity, and time to occurrence of drug-induced leukopenia/thrombocytopenia within 1st month after kidney transplantation.

Methods: This cross-sectional study was conducted on newly kidney transplant recipients from two hospitals, Iran. Patients with thrombocytopenia due to acute antibody-mediated rejection were excluded from the study. Demographic, clinical, and laboratory data of patients within the 1st month after transplantation were collected.

Findings: Of 213 patients, 14.1% and 66.2% experienced leukopenia and thrombocytopenia, respectively. Cytopenia happened more commonly among patients with thymoglobulin-containing regimen (for leukopenia: 24.6% vs. 0%, $P < 0.001$; for thrombocytopenia 84.4% vs. 41.8%, $P < 0.001$). Most leukopenia patients experienced Grades 1 and 2 of leukopenia (46.6% and 40% of patients). Most thrombocytopenic patients showed Grade 1 of thrombocytopenia (78.7%). Cumulative dose of thymoglobulin did not differ between patients with and without leukopenia (5.57 ± 1.13 vs. 5.9 ± 1.96 mg/kg; $P = 0.613$) or with and without thrombocytopenia (5.87 ± 1.86 vs. 5.56 ± 1.38 mg/kg; $P = 0.29$). Cytopenia were more common among recipients from deceased compared with from living donors (91.3% vs. 8.7% for leukopenia patients, $P = 0.001$; 69.9% vs. 33.1% for thrombocytopenia, $P = 0.02$). More patients with kidney from deceased donors received thymoglobulin in their immunosuppressive regimen (82% vs. 37%; $P < 0.001$). The median time to leukopenia and thrombocytopenia were 3 days and 1 day, respectively.

Conclusion: Among immunosuppressive and prophylactic antimicrobial agents, thymoglobulin is more related to cytopenia; therefore, thymoglobulin dose reduction is recommended as the first intervention to manage cytopenia without need for reduction of its cumulative dose. The higher prevalence of cytopenia among recipients from deceased donors may be related to the higher use of thymoglobulin in these patients.

KeyWords: *Kidney transplantation, leukopenia, thrombocytopenia, thymoglobulin*

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Introduction

Kidney transplantation (KT) as the treatment of choice for patients with renal failure improves patients' quality of life.[1] However, numerous complications within 1st weeks after transplantation have been reported that complicate administration of medications that are imperatives for prophylaxis of organ rejection or infection. Cytopenia is one of these complications. About 20%–63% of KT recipients will experience at least one episode of leukopenia/neutropenia.[2] It typically occurs around day 100 after transplantation and can last from 1 to 4 weeks.[2] Thrombocytopenia is also prevalent in the 1st year after KT. Most KT recipients show the lowest platelet count within the first 3 months after transplantation.[2] In this period, patients eventually receive induction therapy and higher doses of conventional immunosuppressive drugs to prevent or treat acute rejection.[3] Cytopenia may be due to drug toxicity, drug interactions,[4] viral infections,[5] or immune-mediated reactions[6-8] in these patients.

Several drugs may cause cytopenia within the 1st month after KT. Drug-induced leukopenia is reported with drugs that are prescribed for the prevention of organ rejection such as rabbit thymoglobulin,[9,10] mycophenolate mofetil (MMF),[11,12] some calcineurin inhibitors (CNIs) such as tacrolimus,[13] inhibitors of mammalian target of rapamycin such as sirolimus[14] and also by drugs for infection prophylaxis including trimethoprim-sulfamethoxazole (TMP-SMX)[15] and ganciclovir (GCV)/valganciclovir (VGCV).[16,17] Drug-induced

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thrombocytopenia is reported with drugs such as rATG,[18] and GCV, and VGCV,[16,19] CNIs,[20] MMF, and sirolimus.[3,14]

In cases of drug-induced thrombocytopenia, discontinuation or substitution of offending drugs will be helpful in treating thrombocytopenia.[2] Leukopenia in transplanted patients increases the risk of infection.[21] In some studies, neutropenia was associated with an increased risk for allograft loss and death.[22] There are limited approaches for managing the leukopenia after transplantation. If medications were the cause, the most effective way is dose reduction or discontinuation of precipitant drug;[3,23] however, this strategy may increase the risk of acute organ rejection in the case of decreasing MMF dose[3,21,24] or increase risk of infection in cases of discontinuation or dose reduction of GCV/VGCV.[24] Granulocyte-colony stimulating factors (G-CSFs) can be considered as the second-line of therapy.[2,21]

On the other hand, coadministrations of some medications that cause leukopenia/thrombocytopenia make it difficult to assess thoroughly the main causes of leukopenia and thrombocytopenia and to rule out nondrug etiologies. In clinical practice, recovery of leukopenia and thrombocytopenia after discontinuation of suspected agent is used as indirect evidence for diagnosis. Although drug-induced leukopenia and thrombocytopenia are common adverse effects following transplantation, however, published data are relatively scarce regarding incidence, significance, and management strategies of these side effects.[3] This study investigated incidence, severity, and time to the first occurrence of drug-induced leukopenia/thrombocytopenia within 1st month after KT. We also reviewed strategies (including medication dose adjustment, G-CSF administration) that responsible medical group of the transplantation centers applied for management of drug-induced leukopenia and thrombocytopenia.

Methods

This cross-sectional study was conducted in the KT wards of Imam Khomeini hospital complex affiliated to Tehran University of Medical Sciences and Milad Hospital, Tehran, Iran from May 2013 to the end of July 2015.

All newly KT recipients from deceased or living donors within first peritransplant hospitalization were included in the study. Patients who previously underwent transplantation surgery and were hospitalized following their hospital discharge after transplantation surgery were excluded from the study. Patients with thrombocytopenia due to acute antibody-mediated organ rejection were also excluded from the study.

All demographic, clinical, and laboratory data of the patients within 1st month after transplantation were collected from the patients' medical records. Details of drugs used in immunosuppressive protocol of each patient and daily laboratory tests (including complete blood counts) were recorded.

Thrombocytopenia and leukopenia were graded based on the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).[25] CTCAE has graded thrombocytopenia into four levels: grade 1 (less than lower limit of normal [LLN] to 75,000 cells/mm^3), Grade 2 (50,000–75,000 cells/mm^3), Grade 3 (25,000–50,000 cells/mm^3), and Grade 4 (<25,000 cells/mm^3). We considered 150,000 cells/mm^3 as LLN for platelet count based on the definitions of involved laboratories. The recovery time of thrombocytopenia in patients who received pharmacotherapy interventions to manage thrombocytopenia has been defined as the interval between the time of pharmacotherapy intervention and the time of platelet rise more than 150,000 cells/mm^3. Recovery time in patients without pharmacotherapy intervention has been defined as the interval between the time of thrombocytopenia and the time of increased platelet count to more than 150,000 cells/mm^3.

CTCAE has graded leukopenia into four levels: grade 1 (white blood cell [WBC] counts in the range of LLN - 3000 cells/mm^3), Grade 2 (2000–3000 WBC/mm^3), Grade 3 (1000–2000 WBC/mm^3), and Grade 4 (<1000 WBC/mm^3). We defined 4000 cells/mm^3 as LLN of WBCs based on the laboratories of our centers. Recovery time of leukopenia in patients with pharmacotherapy intervention has been defined as the interval between the time of intervention and the time of WBC rise over 4000 cells/mm^3. Recovery time in patients without intervention has been defined as the interval between the time of WBC decrease and the time of WBC rise to more than 4000 cells/mm^3.

Based on the regimen that was started in the day of transplantation, patients who fulfilled the inclusion criteria were divided into one of the four groups: rATG + MMF + GAN, MMF, MMF + GAN, or rATG + GAN. Each patient was given 500 mg intravenous methyl prednisolone immediately after transplant surgery as well as 250 mg and 125 mg on the 2nd and 3rd days postoperatively. Oral prednisolone was prescribed from day four after transplantation with dose reduction over time according to the center protocol. Patients who had MMF in their regimen received 1 g MMF preoperatively and then continued daily MMF administration. In the group of rATG + GAN, after discontinuation of rATG, the MMF was started. One of the CNIs, cyclosporine (desired whole blood through the level of 150–300 ng/ml) or tacrolimus, (desired whole blood through level of 8–12 ng/ml) was started from the 1st day posttransplantation for all patients.

All patients received TMP-SMX and clotrimazole for *Pneumocystis jirovecii* and candidiasis prophylaxis, respectively. Cytomegalovirus (CMV) prophylaxis was done preemptively or universal (with GCV in 1st day posttransplant and then changing to oral VGCV) based on the center protocol or preference of responsible physician. All drug dosages were adjusted based on patients' kidney function. We also recorded other drugs with potential bone marrow suppression adverse reaction (the only one was allopurinol).

Medical team of each of these two centers decided on the management of leukopenia or thrombocytopenia. The managements were dose adjustment or withholding of medications known to contribute to these adverse effects including rATG, MMF, GCV/VGCV, or SMX-TMP. Dose adjustments were based on guidelines and protocols of that center.

The study protocol was approved by the Local Ethics Committee of Tehran University of Medical Sciences (Number 5463). All patients were provided written consent form for using their clinical and laboratory data from their medical records.

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 19.0; SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to assess the normal distribution of all analyzed variables. The results are expressed as mean ± standard deviations or median (minimum-maximum). Comparisons were performed using the unpaired Student's *t*-test and Mann–Whitney U-test for variables with normal and skewed distribution, respectively. When study groups were more than two groups, One-way ANOVA and Kruskal-Wallis tests were used for analysis of variables with normal and skewed distribution, respectively. Chi-square and Fisher's exact tests were employed in the analyses of nominal variables in contingency tables. $P < 0.05$ were considered as statistically significant.

Results

Two hundred and thirteen kidney transplant recipients (133 males and 80 females) with mean age of 42.3 ± 13.3 years old who met the inclusion criteria were enrolled in this study. The most common causes of renal failure among these patients were hypertension (30.5% of cases) and diabetes mellitus (22.1% of cases).

Of these 213 patients, 76 (35.7%), 46 (21.6%), 46 (21.6%), 45 (21.1%) of patients received immunosuppressive regimen consisting rATG + GAN, rATG + MMF + GAN, MMF + GAN, and MMF, respectively.

As seen in Table 1, there was no significant difference between these four groups regarding demographic and clinical data except for cause of renal failure ant types of kidney donors. Hypertension and polycystic kidney disease were more prevalent causes of renal failure among patients in the two groups who were administered thymoglobulin compared with patients who did not receive thymoglobulin. In addition, more patients with kidney from deceased donors received thymoglobulin in their immunosuppressive regimen for induction therapy.

Of 213 patients, thirty patients (14.1%) experienced leukopenia. There was no difference between male and female patients in the rate of leukopenia (16.5% vs. 10%; $P = 0.225$).

Leukopenia happened more commonly among patients with rATG-containing immunosuppressive regimen (rATG + MMF + GAN and rATG + GAN; total number of patients in both groups = 122) compared with patients with regimens without rATG (MMF + GAN and MMF; total number of patients in both groups = 91) ($n = 30$ [24.6%] vs. $n = 0$ [0%]; $P < 0.001$). Most patients experienced Grades 1 and 2 of leukopenia (46.6% and 40% of leukopenia patients, respectively). Among 122 patients who received rATG, the total administered dose of rATG in patients with leukopenia ($n = 30$) showed no significant difference in comparison to patients without leukopenia ($n = 92$) (5.57 ± 1.13 vs. 5.9 ± 1.96 mg/kg of actual body weight; $P = 0.613$). The daily dose of rATG in patients in this study was administered into two ways: 1 mg/kg/day or 1.5 mg/kg/day. The incidence of leukopenia showed no significant difference between two different daily doses of rATG (24.3% of patients with 1 mg/kg/day and 26.3% of patients with 1.5 mg/kg/day regimen showed leukopenia; $P = 1$). There was no significant correlation between total dose of rATG and nadir of WBC count ($r = -0.031$, $P = 0.731$).

Except for age, there was no difference in demographic data between patients with and without leukopenia. Data have been summarized in Table 2. Among leukopenia-experienced patients, 91.3% and 8.7% of patients received their organs from deceased and living donors, respectively ($P = 0.001$).

The mean of the lowest WBC count within 1st month after transplantation was 6.95 ± 2.14 cells/mm^3 among patients without leukopenia versus 2.86 ± 0.77 cells/mm^3 among those with leukopenia. Nadir of WBC counts in leukopenia patients with ($n = 21$) and without pharmacotherapy interventions ($n = 9$) were 3.34 ± 0.32 versus 2.66 ± 0.83, respectively ($P = 0.003$).

Interventions to treat leukopenia are summarized in Table 2. The most frequent intervention was rATG dose reduction or discontinuation ($n = 16$ [in 53.3% of leukopenia patients]) followed by MMF dose adjustment (nine interventions (in 30% of patients). Nine patients also experienced leukopenia which improved without any intervention. Totally, eight patients required changes in more than one medication.

The median time to occurrence of leukopenia and leukopenia recovery after pharmacotherapy interventions was 3 days (ranges, 1–20 days) and 2 days (ranges, 1–5 days) after transplantation, respectively. The median of recovery time of leukopenia in patients with or without pharmacotherapy interventions did not differ (2 [ranges, 1–3] days vs. 1 [ranges, 1–3] days; $P = 0.466$).

There was no difference in the occurrence of leukopenia in patients who received tacrolimus compared to those who received cyclosporine (17 of 123 [13.8%] and 13 of 90 [14.4%], respectively; $P = 0.897$).

There was no significant difference between patients who received allopurinol within 1st month after transplantation and patients who did not receive allopurinol in terms of the occurrence of leukopenia (seven of 24 [29.16%] vs. 23 of 189 [12.17%], respectively; $P = 0.054$).

Of 213 patients, 141 patients (66.2%) experienced thrombocytopenia. Male and female patients shared similar rates of this phenomenon (63.9% vs. 70%; $P = 0.375$).

Thrombocytopenia occurrence was higher in regimens containing rATG (rATG + MMF + GAN and rATG + GAN; total number of patients in both groups = 122) in comparison with regimens without rATG (MMF + GAN and MMF; total number of patients in both groups = 91) ($n = 103$ [84.4%] vs. $n = 38$ [41.8%]; $P < 0.001$). Nevertheless, thrombocytopenia occurrence showed no significant difference between

Table 1: Demographic and clinical characteristics of kidney transplant recipients

Characteristic	rATG + MMF + GAN (*n*=46)	MMF + GAN (*n*=46)	MMF (*n*=45)	rATG + GAN (*n*=76)	*P*
Age (years)	42.45±14.57	44.56±13	40.64±13.71	41.82±12.52	0.549
Sex (male)	29 (63)	27 (58.7)	28 (62.2)	49 (64.5)	0.937
Weight (kg)	62.32±15.78	67.55±13.13	65.04±16.4	67.1±14.34	0.276
Height (cm)	162.78±11.07	164.84±10.89	163.57±16.44	165.89±10.85	0.520
BMI (kg/m^2)	23.21±4.38	24.9±4.19	25.71±4.19	24.29±3.95	0.128
Primary disease of ESRD					<0.001
Hypertension	16 (34.8)	9 (19.6)	10 (22.2)	30 (39.5)	
Diabetes mellitus	11 (23.9)	7 (15.2)	10 (22.2)	19 (25)	
ADPKD	2 (4.3)	4 (8.7)	0	10 (13.2)	
Renal stone	1 (2.2)	1 (2.2)	0	1 (1.3)	
Bladder reflux	3 (6.5)	0	0	1 (1.3)	
Others	4 (8.7)	25 (54.3)	24 (53.3)	4 (5.3)	
Unknown	9 (19.6)	0	1 (2.2)	11 (14.5)	
Donor type					<0.001
Deceased donor	29 (82.9)	17 (37)	16 (37.2)	51 (81)	
Living donor	6 (17.1)	29 (63)	27 (62.8)	12 (19)	
Missing data			26 patients		

Data have been presented as mean±SD or *n* (%) as indicated. SD=Standard deviation, ADPKD=Autosomal dominant, polycystic kidney disease, BMI=Body mass index, ESRD=End-stage renal diseases, IBW=Ideal body weight, GAN=Ganciclovir, MMF=Mycophenolate mofetil, rATG=Rabbit thymoglobulin

rATG + MMF + GAN regimen (n = 39) and rATG + GAN regimen (n = 64) (P = 0.933). No significant difference was observed between patients with and without thrombocytopenia regarding gender, age, weight, or body mass index (BMI) (P > 0.05). Among thrombocytopenia experienced patients, 69.9% and 33.1% received their organs from deceased and living donors, respectively (P = 0.02).

Most thrombocytopenic patients showed Grade 1 of thrombocytopenia (111 of 141 patients, 78.7%). Among others, 24 patients (17.02%), five patients (3.5%), and one patient (0.7%) showed Grades 2, 3, and 4 of thrombocytopenia, respectively. The mean of the least platelet count within 1 month after transplantation was 193.41 ± 41.71 cells/mm^3 among patients without thrombocytopenia versus 99.56 ± 29.24 cells/mm^3 among those with thrombocytopenia.

Pharmacotherapy interventions to treat thrombocytopenia have been summarized in Table 3. The most frequent intervention was rATG dose reduction or discontinuation (n = 49 (36.2%). In groups without rATG, thrombocytopenia in majority of patients improved without any intervention, and the only intervention was the dose reduction of MMF that was done only in three patients. No patient needed platelet transfusion.

As seen in Table 3, patients who received rATG showed significantly lower nadir platelet counts compared with patients whose immunosuppressive regimen lack thymoglobulin. The median time to occurrence of thrombocytopenia was 1 day after transplantation (ranges from 0 to 17 days after transplantation). The median time to thrombocytopenia improvement after pharmacotherapy intervention was 5 days (ranges, 1–21 days).

The median recovery time of thrombocytopenia in thrombocytopenic patients with intervention was longer than the recovery time of thrombocytopenic patients without pharmacotherapy intervention (4 days [range, 1–21 days] vs. 3 days [range, 1–8 days]; P = 0.003).

One hundred and twenty-two patients in this study received rATG (rATG + MMF + GAN or rATG + GAN regimen); of them, 103 patients experienced thrombocytopenia. The cumulative dose of rATG in patients with thrombocytopenia (n = 103) showed no significant difference in comparison to patients without thrombocytopenia (n = 19) (5.87 ± 1.86 vs. 5.56 ± 1.38 mg/kg of actual body weight; P = 0.29). The incidence of thrombocytopenia showed no significant difference between two different daily doses of rATG (85.4% of patients with 1 mg/kg/day and 78.9% of patients with 1.5 mg/kg/day regimen showed thrombocytopenia; P = 0.495). There was no significant correlation between total dose of rATG and nadir of platelet count (r = −0.043, P = 0.639).

There was no difference in the occurrence of thrombocytopenia between patients who received tacrolimus and who received cyclosporine (80 of 123 [65%] and 61 of 90 [67.8%], respectively; P = 0.77).

There was no significant difference between patients who received allopurinol within first 3 weeks after transplantation and patients who did not receive allopurinol in terms of the occurrence of thrombocytopenia (19 of 24 [79.2%] vs. 122 of 189 [64.6%], respectively; P = 0.176).

Discussion

Leukopenia and thrombocytopenia within first few days after transplantation are commonly encountered side effects in KT recipients; however, there are little data about their occurrence and severity. This study describes the key characteristics

Table 2: Clinical occurrence of leukopenia and its characteristics

Characteristics	rATG + MMF + GAN (*n*=46)	MMF + GAN (*n*=46)	MMF (*n*=45)	rATG + GAN (*n*=76)	*P*
leukopenia	9 (19.6)	0	0	21 (27. 6)	<0.001
Nadir WBC count	5.49±1.97	7.71±2.02	8.3±2.18	4.95±1.92	<0.001
Grade of leukopenia (cells/mm^3)					<0.001
1	2 (22.2)	0	0	12 (57.14)	
2	5 (55.5)	0	0	7 (33.3)	
3	2 (22.2)	0	0	2 (9.5)	
4	0	0	0	0	
The interval between transplantation and leukopenia (days)	3±1 3 (2-5)	leukopenia not reported	leukopenia not reported	4.67±4.57 3 (1-20)	0.313
The interval between intervention and recovery of leukopenia (days)*	2.67±1.22 3 (1-5)	leukopenia not reported	leukopenia not reported	1.5±0.7 1 (1-3)	0.293
Recovery time in leukopenia patients without intervention**	Intervention was done for all leukopenia patients	leukopenia not reported	leukopenia not reported	1.67±0.86 1 (1-3)	-
Type of intervention for leukopenia treatment					0.012
No intervention, 9 (30)	0	Leukopenia not reported	leukopenia not reported	9 (100)	
rATG, 9 (30)	2 (22.2)	Leukopenia not reported	leukopenia not reported	7 (77.8)	
MMF, 2 (6.7)	0	Leukopenia not reported	leukopenia not reported	2 (100)	
GAN, 1 (3.3)	1 (100)	leukopenia not reported	leukopenia not reported	0	
TMP-SMX, 1 (3.3)	0	leukopenia not reported	leukopenia not reported	1 (100)	
rATG + MMF, 1 (3.3)	1 (100)	Leukopenia not reported	leukopenia not reported	0	
rATG + GAN, 1 (3.3)	0	Leukopenia not reported	leukopenia not reported	1 (100)	
rATG + TMP-SMX, 1 (3.3)	0	Leukopenia not reported	leukopenia not reported	1 (100)	
MMF + TMP-SMX, 1 (3.3)	1 (100)	Leukopenia not reported	leukopenia not reported	0	
rATG + MMF + GAN, 2 (6.7)	2 (100)	Leukopenia not reported	leukopenia not reported	0	
rATG + MMF + TMP-SMX, 2 (6.7)	2 (100)	Leukopenia not reported	leukopenia not reported	0	

*The intervention was done in 21 patients, **There was no intervention in 9 patients. Data have been presented as mean±SD, median (minimum-maximum), or *n* (%) as indicated. SD=Standard deviation, GAN=Ganciclovir, MMF=Mycophenolate mofetil, rATG=Rabbit thymoglobulin, TMP-SMX=Trimethoprim-sulfamethoxazole, WBC=White blood cells

of leukopenia and thrombocytopenia within 1st month posttransplantation in KT recipients.

In this study, the incidence of leukopenia among KT recipients was 14.1%. In this survey, leukopenia occurrence was limited to patients who received rATG in their treatment regimen (24.6% of rATG-administered patients experienced leukopenia). The median time to onset of leukopenia was 3 days after transplantation with WBC nadir count in Grades 1 and 2 which resulted in rATG dose reduction or discontinuation.

The incidence of leukopenia after transplantation varies among studies and depends on the medication used in the posttransplant period.[3] In one study on 50 KT patients treated with quadruple immunotherapy (rATG, prednisone, azathioprine, and cyclosporine) leukopenia was reported in 4% of patients.[26] In another report, leukopenia was seen in 10%–14% of patients who treated with T-cell depleting antibody agents such as thymoglobulin.[9] In our study, about 25% of rATG-administered patients showed leukopenia that is higher than that reported previously.[11]

In a retrospective analysis of 102 kidney and pancreas transplant recipients, combined incidence of either leukopenia or neutropenia was reported in 58% of patients over a 1-year period. rATG was the most induction therapy that had been used in patients and fewer numbers of patients received alemtuzumab. Tacrolimus and MMF were prescribed as maintenance immunosuppression. Prophylactic antimicrobials including TMP-SMX or dapsone and VGCV also were prescribed for all patients. Initial intervention in most patients was a reduction of the MMF dose (66% of cases), followed by reduction of VGCV dose (17% of cases), or reduction in MMF and VGCV dose (12% of cases).[23] In addition, 49% of patients requiring these dose adjustments also received G-CSF.[23] Leukopenia/neutropenia due to the use of MMF is seen in 13%–35% of renal transplant recipients. Coadministered agents with myelosuppressive effects, such

Table 3: Occurrence of thrombocytopenia and its characteristics

Characteristics	rATG + MMF + GAN (*n*=46)	MMF + GAN (*n*=46)	MMF (*n*=45)	rATG + GAN (*n*=76)	*P*
Thrombocytopenia	39 (84.8)	20 (43.5)	18 (40)	64 (84.2)	<0.001
Nadir of platelet (cells/mm^3)	103.5±46.04	167.36±52.28	167.02±53.65	105.11±38.83	<0.001
Grade of thrombocytopenia					0.251
1	26 (66.7)	19 (95)	17 (94.4)	49 (76.6)	
2	10 (25.6)	1 (5)	1 (5.6)	12 (18.8)	
3	3 (7.7)	0	0	2 (3.1)	
4	0	0	0	1 (1.6)	
The interval between transplantation and thrombocytopenia (days)	1.31±0.8 1 (1-5)	2.4±3.81 1 (1-17)	1.4±0.85 1 (1-4)	1.75±1.64 1 (0-12)	0.313
The interval between intervention and recovery of thrombocytopenia (days)*	5.05±2.56 5 (1-12)	4±2.83 4 (2-6)	5 days after intervention Intervention was done in one patient; therefore the days between intervention and recovery of thrombocytopenia were constant	4.42±3.97 4 (1-21)	0.285
Recovery time in thrombocytopenic patients without intervention**	1.5±0.7 1.5 (1-2)	2.66±1.53 2.5 (1-5)	3.11±2.28 3 (1-8)	3.93±2.1 3 (1-8)	0.216
Types of interventions for thrombocytopenia treatment					<0.001
No intervention, 51 (36.1)	2 (3.9)	18 (35.3)	17 (33.3)	14 (27.5)	
rATG adjustments, 49 (34.75)	16 (32.7)	0	0	33 (67.3)	
MMF adjustments, 3 (2.1)	0	2 (66.7)	1 (33.3)	0	
rATG + MMF adjustments, 9 (6.4)	8 (88.9)	0	0	1 (11.1)	
rATG + GAN adjustments, 7 (4.9)	1 (14.3)	0	0	6 (85.7)	
rATG + TMP-SMX adjustments, 5 (3.5)	0	0	0	5 (100)	
MMF + GAN adjustments, 1 (0.7)	1 (100)	0	0	0	
MMF + TMP-SMX adjustments, 2 (1.4)	2 (100)	0	0	0	
rATG + MMF + GAN adjustments, 3 (2.1)	3 (100)	0	0	0	
rATG + MMF + TMP-SMX adjustments, 5 (3.5)	4 (80)	0	0	1 (20)	
MMF + GAN + TMP-SMX adjustments, 1 (0.7)	2 (66.7)	0	0	1 (33.3)	
rATG + GAN + TMP-SMX adjustments, 2 (1.4)	0	0	0	2 (100)	
rATG + MMF + GAN + TMP-SMX adjustments, 3 (2.1)	2 (66.7)	0	0	1 (33.3)	

*The intervention was done in 90 patients, **There was no intervention in 51 patients. Data have been presented as mean±SD, median (minimum-maximum), or *n* (%) as indicated. SD=Standard deviation, GAN=Ganciclovir, MMF=Mycophenolate mofetil, rATG=Rabbit thymoglobulin, TMP-SMX=Trimethoprim-sulfamethoxazole

as thymoglobulin and valganciclovir increase the risk of leukopenia in a dose-dependent manner.[4] In a small case series, an unexpected high incidence of agranulocytosis (37.5%) in patients treated with VGCV and MMF was observed.[27] Incidence of leukopenia with GCV/VGCV is reported in the range of 10%–85% in various studies.[16,28] VGCV prophylaxis

was associated with an increased frequency of leukopenia in MMF + tacrolimus-treated patients.[4] Reduction of VGCV, either alone or in combination with MMF, has been shown to be an effective measure in reducing the need for additional intervention.[3] In a small case series reported by Rerolle *et al.,* the initial reduction of VGCV dose was a successful treatment strategy in most cases even without a reduction in MMF dose.[27] It should be noticed that MMF-induced leukopenia is reversible, however, there have been increased the incidence of rejection in patients who have had MMF dosing interrupted.[21,24] Dose interruptions of prophylactic GCV or VGCV concomitant with close monitoring of CMV polymerase chain reaction testing (preemptive CMV strategy) could help to decrease the incidence of leukopenia in regimens containing MMF + GCV/VGCV. In another retrospective study on KT patients, 28% of patients experienced an episode of neutropenia within the 1st year after transplantation. All patients received induction therapy consisting basiliximab on days 0 and 4 posttransplant or rATG for 8 days posttransplant. The most frequent therapeutic intervention was a reduction in MMF dose. VGCV was discontinued in 20% of cases.[21]

In the present study, initial pharmacotherapy interventions to manage leukopenia were discontinuation or dose reduction of the rATG (53.3% of patients) in most patients followed by MMF dose adjustment solely or besides dose adjustment of other drugs (rATG, TMP-SMX, or GCV) (30% of patients). None of our patients needed G-CSF for management of leukopenia. However, in MMF + GAN group, none of our patients experienced leukopenia. In our study, VGCV discontinuation or dose adjustment was done in 6.7% of patients who experienced leukopenia.

Considering that no difference was seen in time to leukopenia recovery in patients with and without pharmacotherapy interventions, leukopenia occurrence only in rATG-administered patients, mild degree of leukopenia (Grades 1 and 2) in leukopenia-experienced patients, and no difference in cumulative dose of rATG between patients with and without leukopenia, it seems to be justifiable to reduce the daily dose of rATG as the first pharmacotherapy intervention in leukopenia KT recipients without reducing cumulative doses of rATG based on its indication or changing doses of other concomitant bone marrow suppressant drugs (such as MMF, GAN/VGCV) simultaneously with rATG dose adjustment.

Studies on prevalence, characteristics, and outcome of thrombocytopenia in KT recipients are little.[3] The incidence of thrombocytopenia (defined as a platelet count of <150,000 cells/mm^3) in our study was 66%. Because of difference in definition for thrombocytopenia, it is not precise to compare the incidence of this phenomenon in our study with other studies.

The prevalence of thrombocytopenia (defined as a platelet count <100,000 cells/mm^3) in 274 Chinese living donor recipients was 33.9% within the 1st year after transplantation. In that retrospective study, the lowest platelet count in most patients was in the first 3 months after transplantation. However, severe cases, which correlated with induction therapy and acute rejection episodes, were rare.[29] They found no significant association between thrombocytopenia and the immunosuppressive regimen.

In another study, the incidence of thrombocytopenia during quadruple immunosuppressive therapy (rATG, prednisone, azathioprine, and cyclosporine) after KT was 30%. One of the most significant factors for thrombocytopenia was rATG administration. Other factors were having low platelet count at admission, female gender, low body weight (<70 kg), and long prior dialysis treatment.[26] In the present study, the important factor related to thrombocytopenia incidence was administration of immunosuppressive regimens containing rATG (73% of thrombocytopenia-experienced patients were receiving rATG). There was not significantly different between male and female patients regarding thrombocytopenia.

In Heaf's study, thrombocytopenia more developed early and within 3 days after transplantation[26] which is consistent with our finding. Some studies reported that majority of thrombocytopenia events occur within 90 days after transplantation.[29]

In addition, we observed that among KT recipients who suffered thrombocytopenia, only a small proportion (4.25%) had a platelet count of <50,000 cells/mm^3. This finding was consistent with the findings of Xie *et al*. (4% of their patients).[29]

Another study compared short courses of rATG (1.5 mg/kg/day to a total dose of 7.5 mg/kg) and basiliximab in patients at high risk for acute rejection or delayed graft function who received a kidney transplant from a deceased donor. In that study, the major reasons for rATG dose reduction or discontinuation were leukopenia (defined as a WBC count of <2500 cells/mm^3) in 45.2% of patients, thrombocytopenia (defined as a platelet count of <80,000 cells/mm^3) in 11.9% of patients, or both in 14.3% of patients. On average, these conditions resolved by day 14 after transplantation. Immediately after transplantation, leukopenia and thrombocytopenia were more common among patients who received rATG than among those who received basiliximab.[30]

In the present study, time to start of thrombocytopenia and leukopenia was short (10–12) days and 3 (1–20) days, respectively) in patients who received rATG, and these conditions resolved by day 4 (1–21) and 2 (1–5), respectively.

The incidence rate of thrombocytopenia in our study was high, and induction treatment with rATG was a significant cause for thrombocytopenia, but most of our patients did not experience severe thrombocytopenia to need rATG discontinuation.

In this study, several other factors that may contribute to the incidence of leukopenia and thrombocytopenia were assessed. These factors included age, gender, BMI, donor type, and other medications including CNIs. We found that there was no statistically significant difference between patients with and without leukopenia or thrombocytopenia in terms of demographic characteristics. The only expectation was younger age of leukopenia patients.

In this study, patients who received transplantation from deceased donors were at higher risk of developing

thrombocytopenia and leukopenia within 1st month after transplantation. This result is compatible with findings of some other studies. In a study on 95 KT recipients (fifty from deceased donors and 48 from related living donors) with similar immunosuppressive regimen containing prednisolone and azathioprine, leukopenia rate was higher in recipients from deceased donors despite lower doses of azathioprine (18% vs. 6% of patients).[31] In another report on 153 KT recipients (113 from deceased and forty from living donors), hematologic abnormalities (anemia, thrombocytopenia, and leukopenia) were more common in KT recipients from deceased donors (51.3% vs. 27.5%).[32] In our study, more common cytopenia in deceased donor KT recipients may be related to more common use of rATG in these patients. rATG is used in some KT centers to decrease the dose of CNIs and risk of delayed graft function in kidney transplant recipients from deceased donors.[1]

Although some studies showed that tacrolimus administration may be related to neutropenia within 1st year after KT,[15,21] this study found no significant difference in the use of tacrolimus in patients with and without leukopenia or thrombocytopenia.

It is important to differentiate between lymphopenia and neutropenia among patients with leukopenia. Lymphopenia is most likely due to an induction therapy with a lymphocyte depleting agent (e.g., rATG) while posttransplant neutropenia is more associated with an increased risk for severe infections in the transplant population.[3] Unfortunately, differential test for WBC had not routinely done for our patients.

There are some limitations for this study. This study evaluated events of leukopenia and thrombocytopenia during 1st month after KT, which is often simultaneous with induction therapy period, while other studies often evaluated events of leukopenia and thrombocytopenia during 1 year posttransplant. Some of them excluded leukopenia during induction therapy. These differences make comparison between studies difficult. We found a broad definition for leukopenia and thrombocytopenia among studies, and they did not use a universal grading scale for these events. On the other hand, we missed checking neutrophil counts to compare with studies that investigated incidence and severity of neutropenia. In addition, we did not follow the long-term outcomes such as graft function, episodes of acute rejection, incidence of infection, and frequency of leukopenia and thrombocytopenia following the first occurrence of leukopenia and thrombocytopenia.

This study showed that among different immunosuppressive drugs and prophylactic antimicrobial agents, thymoglobulin administration is more related to thrombocytopenia and leukopenia; therefore, thymoglobulin dose reduction is recommended as the first intervention to manage thrombocytopenia and leukopenia without need for reduction of its cumulative dose based on indication. The higher prevalence of thrombocytopenia and leukopenia among kidney transplant recipients from deceased donors also may be related to higher use of thymoglobulin induction in these patients.

Authors' Contribution

Atefeh Jafari contributed in data analysis and manuscript drafting. Parisa Najivash contributed in data gathering. Simin Dashti-Khavidaki and Mohammad-Reza Khatami contributed in proposing idea, study design, data gathering, data interpretation and manuscript finalizing.

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Conflicts of interest

There are no conflicts of interest.

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