Transplant Immunology 55 (2019) 101206

Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Analysis of genetic and clinical risk factors of post-transplant thrombocytopenia in kidney allograft recipients

Kyung Hee Choi[a], Youngil Chang[b], Tariq Shah[c,d], David I. Min[c,d,*]

[a] College of Pharmacy, Sunchon National University, Republic of Korea
[b] National Institute of Transplantation Foundation, Los Angeles, CA, United States
[c] Western University of Health Sciences, Pomona, CA, United States
[d] St. Vincent Medical Center, Los Angeles, CA, United States

ARTICLE INFO

Keywords:
Kidney transplantation
Thrombocytopenia
SDF1
PF4
Genetic polymorphisms

ABSTRACT

Background: Hematological abnormalities after transplantation are complications that may arise after renal transplantation, of which thrombocytopenia is associated with increased risk of bleeding and other complications. The development of thrombocytopenia is affected by various clinical conditions, and the stromal-derived factor 1 (SDF1) and platelet factor 4 (PF4) genes are known to be involved in the production or destruction of platelets. The purpose of this study was to investigate the prevalence of posttransplant thrombocytopenia and its association with other clinical conditions and genetic polymorphisms of SDF1 and PF4 genes a long time after transplantation.

Methods: This is a retrospective study that includes a total of 305 kidney transplant (KT) recipients between 2008 and 2012 at St. Vincent Medical Center, Los Angeles, CA. In this study, posttransplant thrombocytopenia was defined as a 30% reduction in platelet count from the baseline in the first week or a decrease of < 100 ($\times 10^3/\mu L$) within 1 year after KT. The subjects were divided into posttransplant thrombocytopenia and control groups. The chi-square test, *t*-test, and logistic regression were used for the analyses.

Results: In the first week, 65 patients had a 30% reduction in platelet count (21.3%). Gender, simultaneous kidney-pancreas transplantation, induction therapy (IT), and only alleles of rs2297630 of SDF1, among the SDF1 and PF4 genes, showed statistically significant differences. The rs2297630 alleles were consistently significant risk factors (non G vs. G: odds ratio = 0.445; 95% confidence interval, 0.224–0.884; $p = .021$) in the multiple logistic regression. In the 1-year study, 61 patients (20.0%) had platelet counts of $< 100 \times 10^3/\mu L$ and had statistically significant differences in patients who had delayed graft function and induction therapy.

Conclusions: In this study, non-G group of rs2297630 in SDF1 significantly increased the risk of post-transplant thrombocytopenia in the first week of kidney transplantation.

1. Introduction

Kidney transplantation (KT) is one of the most effective therapies in patients with end-stage kidney disease. However, blood disorders are common complications that may arise after transplantation, of which thrombocytopenia is associated with increased risks of bleeding and other complications that can result in significant morbidity and mortality [1,2].

Thrombocytopenia is one of the common complications after kidney transplantation. Thrombocytopenia has been variously defined as platelet (PLT) count reductions of < 50, 100, and $150 \times 10^3/\mu L$ or a 30% reduction from the baseline in previous studies [1–6]. It has been reported that thrombocytopenia occurs frequently within 1 year, and in most kidney recipients, PLT counts are lowest within 3 months after transplantation [3,7]. In the early stage of KT, all immune systems are strongly suppressed for prevention of organ rejection and blood-related counts may decrease to their lowest levels, thus, careful attention should be paid to the occurrence of complications.

The causes of post-transplant thrombocytopenia (PTT) have been known to be the results of myelosuppression, which is due to medications with immunosuppressive agents such as sirolimus, mycophenolate, rabbit anti-human anti-thymocyte globulin, prophylactic antibiotics such as sulfamethoxazole/trimethoprim or antiviral agents (i.e., ganciclovir, valganciclovir); other diseases such as viral infection and sepsis; or healthy status of the donor with autoimmunity and disseminated intravascular disease [1,2,7,8].

* Corresponding author at: Western University of Health Sciences, College of Pharmacy, 309 E. Second St., Pomona, CA 91766-1854, United States.
E-mail address: dmin@westernu.edu (D.I. Min).

https://doi.org/10.1016/j.trim.2019.04.001
Received 5 November 2018; Received in revised form 16 April 2019; Accepted 17 April 2019
Available online 19 April 2019

Recently, genetic factors have been revealed to affect bone marrow production; some of these factors are related to the development of immune or inherited thrombocytopenia [9,10]. The stromal-derived factor 1 (SDF1) and platelet factor 4 (PF4) genes are known to have an impact on platelet function [9–11]. The SDF1, which is the ligand for chemokine CXCR4, is an upregulator that enhances peripheral recruitment of cells to the sites of vascular and tissue injuries both in vitro and in vivo, thereby promoting repair mechanisms [12–14]. CXCR4 is expressed in various cell types such as hematopoietic stem cells, lymphopoietic cells, progenitor cells, endothelial/epithelial cell, and several tumor cells. SDF1 signals using CXCR4, its receptor, have been reported to have a direct effect on megakaryocyte (MK) cell proliferation, which augments platelet release [9,12,15,16]. PF1 is one of the first chemokine families discovered that is released from the activated platelets and binds to the heparin-causing neutralization of heparin-like molecules, thereby promoting coagulation [11,17,18].

To our knowledge, studies about factors that influence the prevalence of PTT have been limited to diseases, medications, or clinical characteristics [2,3,7], but are rarely conducted with the genetic polymorphisms related to the complications of platelet production or functions in KT. Therefore, we hypothesized that the genetic polymorphisms of SDF1 and PF4 are associated with the incidence of PTT. In this study, our objective was to investigate the prevalence of PTT and its association with the genetic polymorphisms of the SDF1 and PF4 genes, and other characteristics in consideration.

2. Materials and methods

This retrospective study was conducted as part of an overall genetic study that was approved by the Institutional Review Board for Human Subjects of Saint Vincent Medical Center, Los Angeles, California.

2.1. Study subjects

We reviewed the cases of 400 patients who received KT at St. Vincent Medical Center, CA, between January 2008 and December 2012. Among the 400 patients, 95 whose genomic DNAs were not available were excluded. The subjects' characteristics, clinical features, medications, laboratory data, and DNA genetic data were analyzed; then, their PLT counts were investigated after KT.

2.2. Thrombocytopenia

In this study, we investigated PLT counts, as PTT was defined as a 30% reduction in PLT counts from the baseline in the first week after KT. A total of 305 patients who had genetic data were divided into two groups. The study group was composed of those who met our definition of PTT; and the control group, of those who did not develop thrombocytopenia by definition. In addition, we considered another PTT group composed of patients who had PLT counts of $< 100 \times 10^3/\mu L$ within 1 year of KT, and compared with the results of PTT group in the first week after KT.

2.3. Genotyping analysis

Blood samples were collected from the patients, and genomic DNA was extracted using an extraction kit (QIAmp DNA Blood Mini Kit, Qiagen, Mississauga, Ontario, Canada). Genotyping using Taqman SNP genotyping analysis (ThermoFisher Scientific) was performed for the subject's genomic DNA sample in accordance with the manufacturer's protocol. In the genotyping analysis, the rs1801157 (C/T, intron) and rs2297630 (A/G, intron) alleles of SDF1 and the rs1435520 (A/C, UTR), rs1429637 (C/T, UTR), and rs442155 (A/G, intron) alleles of PF4 were included in this research.

2.4. Statistics analyses

The demographic and clinical characteristics of the subjects in the two groups are presented as mean, standard deviation (SD), and percentage, and analyzed using the *t*-test and chi-square test for continuous and discrete data, respectively, to determine the influencing factors of thrombocytopenia. To analyze the effect of polymorphisms on thrombocytopenia, a chi-square test for the genotypes were performed with the odds ratios.

After the univariate analysis for demographic and clinical features, we used as multivariable analysis to clarify the relationship between thrombocytopenia and several factors. The multiple logistic regression was used with adjusting features (the age, ethnicity with race, and gender) and the identified risk factors in the univariate analysis. The patients who developed thrombocytopenia within 1 year after KT were also evaluated using the same procedure, and then the outcomes were compared with each other. Data management and statistical analysis were performed using the IBM SPSS Statistical Analysis Software Program version 21 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study subjects

This study cohort originally consisted of 400 patients who received KT at St. Vincent Medical Center, Los Angeles, CA, between 2008 and 2012. Among the 400 patients who received KT, 305 who had genomic DNA data were included this study. The graph demonstrates a mild decrease in the average PLT count right after transplantation, which might be the influence of the administration of Bactrim, fluconazole, and ciprofloxacin as standard treatment for patients. However, the average PLT counts began to increase and normalize in the first week (Fig. 1). For the incidence of thrombocytopenia among the 305 patients, PLT count decreased to < 30% in the first week in 65 patients (21.3%) and to $< 100 \times 10^3/\mu L$ within 1 year in 61 patients (20.0%). Among these patients, only one patient in the 1 year cohort showed a trend of pancytopenia in WBC, PLT, and hemoglobin data [19].

3.2. Subjects' demographic and clinical characteristics

The characteristics of 305 KT recipients are summarized in Table 1. Of all the patients in this study, 33.3% were female; most were Hispanics (58.7%), followed by Asians (15.1%); and 12.8% had a previous transplantation, which showed no statistical differences between the control and PTT groups. The mean (± SD) age of the KT recipients was 47.7 ± 12.3 years, which was not statistically significantly different from that in the PTT group in the first week ($n = 65$, 47.6 ± 11.9 years, $p = .926$), but showed statistical significance in the PTT group within 1 year ($n = 61$, 50.8 ± 11.4 years, $p = .028$). The PTT group in the first week showed a significant difference in the patients who received simultaneous kidney-pancreas (SKP) transplantation (normal vs PTT; 7.9% vs 30.8%, $p < .001$), while the patients with delayed graft function (DGF) showed a statistically significant difference only in the PTT group within 1 year (normal vs PTT: 25.0% vs 57.4%, $p < .001$). Among the baseline characteristics, the deceased donors (normal vs PTT group in the first week; 69.6% vs. 86.2%, $p = .008$; within 1 year; 68.4% vs 91.8%, $p < .001$) and medications for induction therapy (normal vs PTT, $p < .001$) showed significant differences in both 1 week and within 1 year cohorts. We could not find any significant difference in previous transplantation, the causes of end stage renal disease (ESRD), and the medications for immunosuppressant therapy.

3.3. SDF1 and PF4 polymorphisms

The genotype frequencies of SDF1 (rs1801157 and rs2297630) and

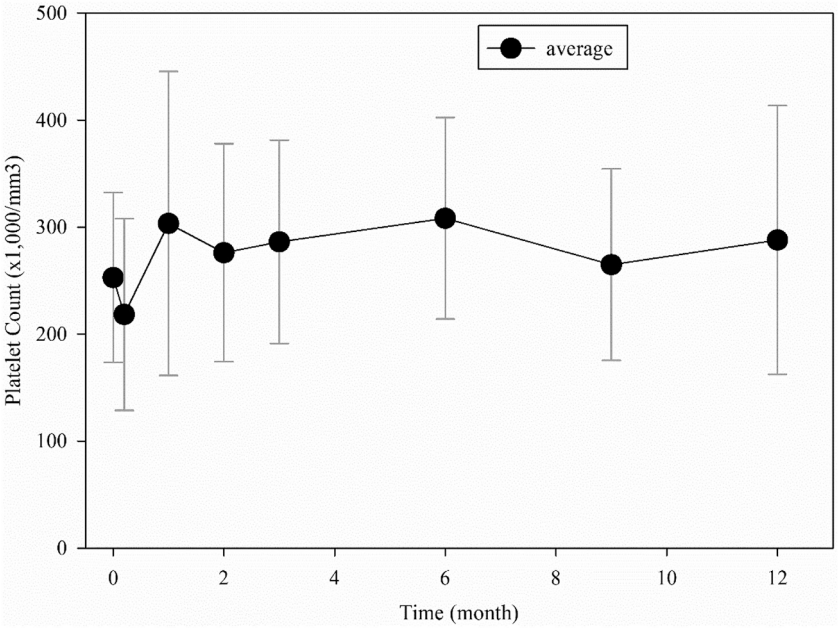

Fig. 1. The platelet counts after kidney transplantation.

Table 1
Demographic and clinical characteristics.

Characteristics	All patients (n = 305)	PTT after 1 week			PTT within 1 year		
		Normal (n = 240)	Thrombocytopenia (n = 65)	p-Value	Normal (n = 244)	Thrombocytopenia (n = 61)	p-Value
Age, years, mean ± SD	47.7 ± 12.3	47.8 ± 12.5	47.6 ± 11.9	.926†	47.0 ± 12.5	50.8 ± 11.4	**.028**†
Gender, male, n (%)	196 (64.3)	160 (66.7)	36 (55.4)	.092	158 (64.8)	38 (62.3)	.720
Ethnic with race group, n (%)				.564			.820
White Hispanic	179 (58.7)	139 (57.9)	40 (61.5)		143 (58.6)	36 (59.0)	
Asian	46 (15.1)	34 (14.2)	12 (18.5)		35 (14.3)	11 (18.0)	
Black non-Hispanic	26 (8.5)	24 (10.0)	2 (3.1)		22 (9.0)	4 (6.6)	
Mixed	29 (9.5)	23 (9.6)	6 (9.2)		25 (10.2)	4 (6.6)	
White non-Hispanic	24 (7.7)	19 (7.9)	5 (7.7)		18 (7.4)	6 (9.8)	
White unknown	1 (0.3)	1 (0.4)	0 (0.0)		1 (0.4)	0 (0.0)	
Previous transplantation, n (%)	39 (12.8)	33 (13.8)	6 (9.2)	.333	31 (12.7)	8 (13.1)	.932
SKP transplantation, n (%)	39 (12.8)	19 (7.9)	20 (30.8)	< **.001**	30 (12.3)	9 (14.8)	.607
Deceased donor, n (%)	223 (73.1)	167 (69.6)	56 (86.2)	**.008**	167 (68.4)	56 (91.8)	< **.001**
Cause of ESRD, n (%)				.116			.272
Diabetes	113 (37.0)	82 (34.2)	31 (47.7)		91 (37.3)	22 (36.1)	
Hypertension	89 (29.2)	70 (29.2)	19 (29.2)		67 (27.5)	22 (36.1)	
Miscellaneous	75 (24.6)	64 (26.7)	11(16.9)		64 (26.2)	11 (18.0)	
Unknown	28 (9.2)	24 (10.0)	4 (6.2)		22 (9.0)	6 (9.8)	
Delayed graft function, n (%)	96 (31.5)	75 (31.3)	21 (32.3)	.871	61 (25.0)	35 (57.4)	< **.001**
Allograft rejection, n (%)	15 (4.9)	12 (5.0)	3(4.6)	.899*	13 (5.3)	2 (3.3)	.743*
Induction therapy, n (%)				< **.001***			< **.001***
Anti-thymocyte globulin, rabbit	146 (47.9)	98 (40.8)	48 (73.8)		102 (41.8)	44 (72.1)	
IL-2 receptor antagonists	142 (46.6)	128 (53.3)	14 (21.6)		128 (52.5)	14 (23.0)	
Alefacept	3 (1.0)	3 (1.3)	0 (0.0)		2 (0.8)	1 (1.6)	
Unknown	14(4.6)	11 (4.6)	3 (4.6)		12 (4.9)	2 (3.3)	
Immunosuppressant therapy, n (%)				.778*			.720*
Tacrolimus, mycophenolate sodium	175 (57.4)	137 (57.1)	38 (57.1)		140 (57.4)	35 (57.4)	
Tacrolimus, mycophenolate mofetil	88 (28.9)	69 (28.8)	19 (28.8)		72 (29.5)	16 (26.2)	
Cyclosporin, mycophenolate sodium	12 (2.9)	10 (4.2)	2 (3.1)		8 (3.3)	4 (6.6)	
Cyclosporin, mycophenolate mofetil	12 (2.9)	8 (3.9)	4 (6.2)		10 (4.1)	2 (3.3)	
Miscellaneous	16 (5.2)	14 (5.2)	2 (3.1)		12 (4.9)	4 (6.6)	
Unknown	2 (0.7)	2 (0.7)	0 (0.0)		2 (0.8)	0 (0.0)	

SKP Transplantation: Simultaneous Kidney Pancreas Transplantation, ESKD; End Stage of Kidney Disease.
P < 0.05 is regarded of statistical significance.
* Analysis of Fisher's exact test.
† Analysis of t-test.

Table 2
Frequencies of genetic polymorphisms with normal or thrombocytopenia patients in kidney transplantation.

Characteristics		1 week				1 year			
Genotype	All patients, *n* (%)	Normal, *n* (%)	Thrombocytopenia, *n* (%)	$OR_{unadjusted}$ (95% CI)	*p*-Value*	Normal, *n* (%)	Thrombocytopenia, *n* (%)	$OR_{unadjusted}$ (95% CI)	*p*-Value*
SDF1									
rs1801157 C/T									
(*n* = 303)									
Non-T group	211 (69.6)	163 (68.2)	48 (75.0)	0.715	.293	168 (69.1)	43 (71.7)	0.886	.703
T group	92 (30.4)	76 (31.8)	16 (25.0)	(0.382–1.339)		75 (30.9)	17 (28.3)	(0.474–1.653)	
rs2297630 A/G									
(*n* = 304)									
Non-G group	68 (22.4)	47 (19.7)	21 (32.3)	**0.513**	**.030**	57 (23.5)	11 (18.0)	1.393	.363
G group	236 (77.6)	192 (80.3)	44 (67.7)	**(0.279–0.944)**		186 (76.5)	50 (82.0)	(0.680–2.853)	
PF4									
rs442155 A/G									
(*n* = 300)									
Non-G group	268 (89.3)	213 (89.9)	55 (87.3)	1.291	.557	214 (88.8)	54 (91.5)	0.743	.543
G group	32 (10.7)	24 (10.1)	8 (12.7)	(0.550–3.030)		27 (11.2)	5 (8.5)	(0.270–1.995)	
rs1429637 C/T									
(*n* = 298)									
Non-T group	192 (64.4)	154 (65.3)	38 (61.3)	1.186	.562	150 (62.8)	42 (71.2)	0.682	.226
T group	106 (35.6)	82 (34.7)	24 (38.7)	(0.666–2.112)		89 (37.2)	17 (28.8)	(0.366–1.270)	
rs1435520 A/C									
(*n* = 302)									
Non-C group	191 (63.2)	154 (65.0)	37 (56.9)	1.404	.233	151 (62.4)	40 (66.7)	0.830	.539
C group	111 (36.8)	83 (35.0)	28 (43.1)	(0.803–2.455)		91 (37.6)	20 (33.3)	(0.457–1.506)	

$OR_{unadjusted}$; unadjusted odds ratio; CI, confidence interval; SDF1, stromal-derived factor-1; PF4, platelet factor 4.
P < 0.05 is regarded of statistical significance.
* Analysis of chi-square test.

PF4 (rs1435520, rs1429637, and rs442155) in this study cohort are described in Table 2. In SDF1 SNP rs2297630, the non-G group (AA genotype) was showed a significantly increased incident risk of thrombocytopenia (unadjusted odds ratio [$OR_{unadjusted}$] = 0.513; 95% confidence interval [CI], 0.279–0.944; $p = .030$) as compared with SDF1 SNP rs2297630 G group.

Other genetic polymorphisms of SDF1 (rs1801157) and PF4 (rs1435520, rs1429637, and rs442155) did not show significantly statistical differences in the prevalence of PTT group in the first week. In the PTT patients within 1 year after KT, we could not find any statistically significant difference in the genetic polymorphisms of SDF1 (rs1801157 and rs2297630) and PF4 (rs1435520, rs1429637, and rs442155).

3.4. Multivariable logistic regression analysis

On the basis of the results of the analyses of the subjects' characteristics and polymorphisms, multivariable analysis was conducted with the statistically significant data and basic characteristics such as age, ethnicity with race, and gender. In the PTT group in the first week of SKP transplantation, deceased donor, induction therapy, and SDF1 SNP rs2297630 (non-G and G groups), were included the statistical analysis for age, ethnicity with race, and gender. Deceased donor, DGF, and induction therapy were also used with the three variables of basic characteristics for analysis in the PTT group within 1 year.

The significant risk factors that affected the prevalence of PTT in the first week were gender (female vs. male, $OR_{adjusted} = 0.487$; 95% CI, 0.256–0.926; $p = .028$), SKP transplantation (no vs. yes, $OR_{adjusted} = 3.598$; 95% CI, 1.620–7.988; $p = .002$), medication for induction therapy (IL2 receptor antagonist vs. rabbit anti-thymocyte globulin $OR_{adjusted} = 3.375$; 95% CI, 1.680–6.778; $p < .001$) and SDF1 SNP rs2297630 (non-G group vs. G group $OR_{adjusted} = 0.446$; 95% CI, 0.225–0.884; $p = .021$) (Table 3). In the PTT group within 1 year, the significant risk factors remained to be DGF ($OR_{adjusted} = 3.972$; 95% CI, 2.134–7.392; $p < .001$), induction therapy (IL2 receptor antagonist vs. rabbit anti-thymocyte globulin $OR_{adjusted} = 3.715$; 95% CI,1.889–7.305 $p < .001$) (Table 4).

Table 3
Risk factors of thrombocytopenia at 1 week after kidney transplantation (1 week)[a].

Variables	$OR_{adusted}$ (95% CI)	*p*-Value
Age, years	0.988 (0.961–1.016)	.404
Ethnic with race group		
White Hispanic	Reference	
Asian	2.725 (1.061–6.996)	.037
Black non-Hispanic	0.383 (0.079–1.861)	.234
Mixed	1.256 (0.416–3.796)	.686
White non-Hispanic	1.006 (0.313–3.230)	.992
Gender, female vs. male	0.488 (0.257–0.926)	**.028**
Simultaneous kidney pancreas, no vs. yes	3.622 (1.631–8.043)	**.002**
Deceased donor, no vs. yes	1.005 (0.400–2.522)	.992
Induction therapy, IL 2 antagonist vs. Rabbit anti-thymocyte globulin	3.375 (1.680–6.778)	**.001**
rs2297630, non-G group vs. G group	0.446 (0.225–0.884)	**.021**

$OR_{adjusted}$; adjusted odds ratio; CI, confidence interval.
P < 0.05 is regarded of statistical significance.
[a] Multivariable logistic regression with age, ethnicity, gender, simultaneous kidney pancreas, kidney transplantation from deceased donor, medication of induction therapy and rs2297630.

4. Discussions

In the early stage of organ transplantation, maintaining the organ well adapted to the recipients and minimizing the adverse effects that may occur after transplantation are highly important. Especially, the incidence of graft hematoma due to blood problems might increase the risk of rejection, graft loss, or recipient mortality [20]. In the previous reports, PLT counts would be lowest at 3 months after kidney transplantation and the baseline PLT count might decrease after operation [7], but we observed fast recovery of PLT counts after transplantation (Fig. 1) and see very short duration of declining overall PLT counts. So we focused on the PLT count reduction proportion in the first week

Table 4
Risk factors of thrombocytopenia within 1 year after kidney transplantation[a].

Variables	$OR_{adjusted}$ (95% CI)	*p*-Value
Age, years	1.016 (0.987–1.046)	.292
Ethnic with race group		
White Hispanic	Reference	
Asian	1.307 (0.521–3.277)	.569
Black non-Hispanic	0.840 (0.245–2.887)	.782
Mixed	1.049 (0.309–3.556)	.939
White non-Hispanic	1.038 (0.334–3.223)	.948
Gender, female vs. male	0.912 (0.463–1.797)	.790
Deceased donor, no vs. yes	1.766 (0.524–5.951)	.359
Delayed graft function, no vs. yes	3.972 (2.134–7.392)	< **.001**
Induction therapy, IL 2 antagonist vs. rabbit anti-thymocyte globulin	3.715 (1.889–7.305)	< **.001**

$OR_{adjusted}$; adjusted odds ratio; CI, confidence interval.
$P < 0.05$ is regarded of statistical significance.
[a] Multivariable logistic regression with age, ethnicity, gender, kidney transplantation from deceased donor, delayed graft function and medication of induction therapy.

after KT. We investigated the risk factors associated with the patients with thrombocytopenia, defined as those with PLT count reduction rate > 30% of that at baseline, which is similar to other studies on acute thrombocytopenia [4,5], and then compared them with those of patients with PTT within 1 year. We found that the potential risk factors of PTT in the first week included female gender, SKP transplantation, induction therapy with rabbit anti-thymocyte globulin, and SNP rs2297630 polymorphism (non-G group), the results of which differed in the PTT group within 1 year.

The prevalence of PTT was reported to be affected by various factors such as immunosuppressant therapy, antimicrobial agent, infections, acute rejection, DGF, and anemia [2,3,7,21]. In this study, the multivariable logistic regression analysis was conducted with the statistically significant variables identified from the univariate analysis and basic characteristics such as age, gender and ethnicity with race. We reconfirmed that the induction therapies such as rabbit anti-thymocyte globulin, or IL-2 receptor antagonists affected the prevalence of PTT, as in the previous studies [3,7,22], after alefacept was excluded in the multivariable logistic regression analysis owing to the small sample size of patients who received the medication ($n = 3$). We did not find the significance of the calcineurin inhibitor and mycophenolate in both PTT groups. However, especially rabbit anti-thymocyte globulin, a higher frequency ratio than those of IL-2 receptor antagonists was reported to be 12–25% of the prevalence of thrombocytopenia in the previous studies, which might be relate to its polyclonal nature [20,23,24]. By contrast, other studies suggested no significant difference in outcomes, including thrombocytopenia, among the induction therapy agents [23,25]. Gender did not show a significant difference in the PTT group within 1 year, similarly to the report by Xie et al. that gender was excluded as a risk factor for developing thrombocytopenia within 1 year in Chinese patients who received KT from living donors [3]. In the PTT group in the first week, male gender was showed lower prevalence than female gender in the multivariable analysis, although gender did not show statistical significance in the univariate analysis. This result was supported by the report published in 1993, in which female gender, low weight, and long dialysis duration influenced the occurrence of thrombocytopenia in KT patients who received quadruple inductive immunosuppressive medications. Moreover, the initial stage of thrombocytopenia developed within 3 days after operation [26].

In accordance with the results of previous research studies, we could deduce the genetic polymorphisms of SDF1 or PF4 association with the outcome of thrombocytopenia. SDF1 was related with the endothelial progenitor cells (EPCs), which are enhanced in angiogenesis and vasculogenesis; the SDF1α level promoted the mobilization and differentiation of EPC, and SDF1 polymorphism influenced the SDF1α levels [13,17,27–31]. Lee et al. reported that the SDF1 rs1801157 gene variation in the Korean donors showed a statistically significant protective effect on acute rejection [13]. The SDF1 rs22228014 polymorphism was reported to have no protective effect on acute rejection in KT recipients but was related to the PLT counts of Chinese patients with chronic immune thrombocytopenia [10,13]. In the study of Wang et al., the SDF1 rs1801157 polymorphism was identified as a factor that influenced the adverse outcome in KT recipients [32]. Chen et al. suggested that the SDF1 rs1801157 genotype significantly affected the prognosis of Chinese patients with nasopharyngeal carcinoma [33]. PF4 levels were high in atherosclerotic patients and reached significant levels in patients with atherosclerotic plaques, where it is released after platelet activation [18]. Bhatnagar et al. found that eight SNPs, including genotypes rs442155, rs1429637, and rs1435520, affected the serum PF4 levels related to platelet activity [34].

In this study, we found that the rs2297630 AA genotype was a significant factor for the prevalence of thrombocytopenia in the PTT group in the first week after KT, not within 1 year after KT. The other genetic polymorphisms (rs1801157, rs442155, rs1429637, and rs1435520) that we investigated did not significantly influence the outcome in the KT recipients. In accordance with the difference in pharmacogenomics as a factor that affected the occurrence of PTT, one of the main observational points after KT is to prevent PTT because the genomic differences are uncontrolled but predicted the risk factors. Therefore, the focus should be on different factors such as postoperative periods after KT, and genetic polymorphism must also be more deeply investigated as time and ethnicity.

This study had some limitations. First, we conducted the research with a retrospective design using medical records; thus, unintentional or unrecognized bias might have occurred while determining thrombocytopenia despite a well formative study design. Second, diverse antimetabolite dosages were not considered in this study, because we could not find any statistically significant difference in the immunosuppression combination therapies with prednisolone, calcineurin inhibitors and mycophenolate by univariate statistical analysis. Further studies are needed to determine the causation. A larger population group is needed to confirm that the genetic polymorphisms of SDF1 and PF4 are associated with the incidence of post-transplant thrombocytopenia with a larger sample size. However, this study is significant that it was conducted on various races including mainly Hispanics.

5. Conclusion

As the time passed after KT operation, the influencing factors associated with the prevalence of PTT differed, except induction therapy agents. The non-G group of rs2297630 increased the risk of PTT in the early stage after KT by about twice higher than did the G group genotypes. In addition, rabbit anti-thymocyte globulin, female gender and SKP transplantation were only associated with PTT in the early stage. On the other hand, DGF only affected the PTT that occurred within 1 year.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgments

This study has been supported in part by the Mendez National Institute of Transplantation, Los Angeles, California and the College of Pharmacy, and Western University of Health Sciences, Pomona, California.

Funding

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

References

[1] R. Reindl-Schwaighofer, R. Oberbauer, Blood disorders after kidney transplantation, Transplant. Rev. (Orlando) 28 (2) (2014) 63–75.
[2] KDIGO clinical practice guideline for the care of kidney transplant recipients, Am. J. Transplant. 9 (Suppl. 3) (2009) S1–155.
[3] L. Xie, et al., The prevalence and risk factors of thrombocytopenia after living-related renal transplantation in Chinese adult recipients, Transplant. Proc. 45 (1) (2013) 197–199.
[4] J.J. Orrick, et al., Thrombocytopenia secondary to linezolid administration: what is the risk? Clin. Infect. Dis. 35 (3) (2002) 348–349.
[5] Y. Takahashi, et al., Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy, J. Infect. Chemother. 17 (3) (2011) 382–387.
[6] J.M. Walenga, R.L. Bick, Heparin-induced thrombocytopenia, paradoxical thromboembolism, and other side effects of heparin therapy, Med. Clin. 82 (3) (1998) 635–658.
[7] Y. Yang, B. Yu, Y. Chen, Blood disorders typically associated with renal transplantation, Front Cell Dev Biol 3 (2015) 18.
[8] P. Ventura-Aguiar, J.M. Campistol, F. Diekmann, Safety of mTOR inhibitors in adult solid organ transplantation, Expert Opin. Drug Saf. 15 (3) (2016) 303–319.
[9] J.P. Salim, et al., Differential expression of SDF-1 receptor CXCR4 in molecularly defined forms of inherited thrombocytopenias, Platelets 28 (6) (2017) 602–606.
[10] M. Lyu, et al., Stromal cell-derived factor-1 rs2297630 polymorphism associated with platelet production and treatment response in Chinese patients with chronic immune thrombocytopenia, Platelets 27 (4) (2016) 338–343.
[11] P. Horsewood, J.G. Kelton, Investigation of a platelet factor 4 polymorphism on the immune response in patients with heparin-induced thrombocytopenia, Platelets 11 (1) (2000) 23–27.
[12] T. Hamada, et al., Transendothelial migration of megakaryocytes in response to stromal cell-derived factor 1 (SDF-1) enhances platelet formation, J. Exp. Med. 188 (3) (1998) 539–548.
[13] J.P. Lee, et al., Genetic predisposition of donors affects the allograft outcome in kidney transplantation; polymorphisms of stromal-derived factor-1 and CXC receptor 4, PLoS One 6 (2) (2011) e16710.
[14] L.M. Niswander, et al., SDF-1 dynamically mediates megakaryocyte niche occupancy and thrombopoiesis at steady state and following radiation injury, Blood 124 (2) (2014) 277–286.
[15] J.N. Thon, SDF-1 directs megakaryocyte relocation, Blood 124 (2) (2014) 161–163.
[16] W.J. Lane, et al., Stromal-derived factor 1-induced megakaryocyte migration and platelet production is dependent on matrix metalloproteinases, Blood 96 (13) (2000) 4152–4159.
[17] P. von Hundelshausen, et al., Heterophilic interactions of platelet factor 4 and RANTES promote monocyte arrest on endothelium, Blood 105 (3) (2005) 924–930.
[18] J.M. Fox, et al., CXCL4/platelet factor 4 is an agonist of CCR1 and drives human monocyte migration, Sci. Rep. 8 (1) (2018) 9466.
[19] B. Gayathri, K.S. Rao, Pancytopenia: a clinico hematological study, J. Lab. Physicians 3 (1) (2011) 15.
[20] T. de Nattes, et al., Antithymocyte globulin-induced hemolytic anemia and thrombocytopenia after kidney transplantation, Immunotherapy 10 (9) (2018) 737–742.
[21] I.V. Sonnerborg, et al., Severe transplantation-mediated Alloimmune thrombocytopenia in 2 recipients of organs from the same donor, Transplantation 101 (5) (2017) e190–e192.
[22] M.W. van den Hoogen, L.B. Hilbrands, Use of monoclonal antibodies in renal transplantation, Immunotherapy 3 (7) (2011) 871–880.
[23] D.C. Brennan, et al., Rabbit antithymocyte globulin versus basiliximab in renal transplantation, N. Engl. J. Med. 355 (19) (2006) 1967–1977.
[24] B. Charpentier, et al., A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine a in adult renal transplant recipients, Transplantation 75 (6) (2003) 844–851.
[25] S.D. Hwang, et al., Efficacy and safety of induction therapy in kidney transplantation: a network meta-analysis, Transplant. Proc. 50 (4) (2018) 987–992.
[26] J. Heaf, Bone marrow function during quadruple immunosuppressive therapy after renal transplantation, Clin. Nephrol. 40 (6) (1993) 332–338.
[27] T. Takahashi, et al., Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization, Nat. Med. 5 (4) (1999) 434–438.
[28] E. De Falco, et al., SDF-1 involvement in endothelial phenotype and ischemia-induced recruitment of bone marrow progenitor cells, Blood 104 (12) (2004) 3472–3482.
[29] R. Salcedo, et al., Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: in vivo neovascularization induced by stromal-derived factor-1alpha, Am. J. Pathol. 154 (4) (1999) 1125–1135.
[30] A. Whittaker, et al., Evidence for genetic regulation of endothelial progenitor cells and their role as biological markers of atherosclerotic susceptibility, Eur. Heart J. 29 (3) (2008) 332–338.
[31] Q. Xiao, et al., SDF1 gene variation is associated with circulating SDF1alpha level and endothelial progenitor cell number: the Bruneck study, PLoS One 3 (12) (2008) e4061.
[32] C.J. Wang, et al., Stromal cell-derived factor 1 gene polymorphism is associated with susceptibility to adverse long-term allograft outcomes in non-diabetic kidney transplant recipients, Int. J. Mol. Sci. 15 (7) (2014) 12495–12506.
[33] R. Chen, et al., CXCL12 genetic variants as prognostic markers in nasopharyngeal carcinoma, OncoTargets Ther. 8 (2015) 2835–2842.
[34] P. Bhatnagar, et al., Genetic variants in platelet factor 4 modulate inflammatory and platelet activation biomarkers, Circ. Cardiovasc. Genet. 5 (4) (2012) 412–421.