Original Article

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The Efficacy of Eltrombopag Treatment in Patients who developed Platelet Engraftment Failure after Allogeneic Stem Cell Transplantation: A Single Center Experience

Allojenik Kök Hücre Nakli Sonrası Trombosit Engrafman Yetersizliği Gelişen Hastalarda Eltrombopag Tedavisinin Etkinliği: Tek Merkez Deneyimi

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ABSTRACT

Objective: Persistent thrombocytopenia is a common complication of allogeneic stem cell transplantation (ASCT). Treatment of platelet engraftment failure after ASCT remains controversial. Drugs, such as eltrombopag, are used for this purpose. Eltrombopag is an Food and Drug Administration -approved oral thrombopoietin receptor agonist. We aim to present the results of 12 patients treated with eltrombopag in our center for severe thrombocytopenia after ASCT.

Methods: From January 2018 to February 2020, a total of 56 patients underwent ASCT. Twelve patients had persistent thrombocytopenia following ASCT. All patients received eltrombopag.

Results: Primary platelet engraftment failure developed in six of 12 patients who developed persistent thrombocytopenia after ASCT. Secondary platelet engraftment failure developed in six of them. After eltrombopag treatment, eight (66.7%) patients achieved transfusion independence, whereas four patients (33.3%) could not. The maximum platelet count after the eltrombopag treatment was median 118.000 (range: 24,000-253,000)/μL. The median time from the start of eltrombopag until the platelet count was >50,000/μL was 18 (range: 14-112) days. The median duration of treatment with eltrombopag was 70 (range: 26-180) days. Eltrombopag was discontinued in all patients who survived and had full platelet recovery.

ÖZ

Amaç: Kalıcı trombositopeni, allojenik kök hücre transplantasyonunun (AKHN) yaygın komplikasyonlarından biridir. AKHN sonrası trombosit engrafman yetersizliğinin tedavisi hala tartışmalıdır. Eltrombopag bu amaçla kullanılan ilaçlardan biridir. Eltrombopag, FDA onaylı oral trombopoietin reseptör agonistidir. AKHN sonrası şiddetli trombositopeni nedeniyle merkezimizde eltrombopag ile tedavi edilen 12 hastanın sonuçlarını ortaya koymayı amaçladık.

Yöntemler: Kök hücre nakil merkezimizde ocak 2018'den şubat 2020'ye kadar 56 hastaya AKHN yapıldı. Oniki hastada AKHN sonrası kalıcı trombositopeni gelişti. Tüm hastalar eltrombopag aldı.

Bulgular: AKHN sonrası inatçı trombositopeni gelişen 12 hastanın altısında birincil trombosit engrafman yetersizliği, altısında ise ikincil trombosit engrafman yetersizliği gelişti. Eltrombopag tedavisi sonrası sekiz hasta (%66,7) transfüzyon bağımsızlığına ulaşılırken dört hastada (%33,3) ulaşılamadı. Eltrombopag tedavisinden sonra maksimum trombosit sayısı medyan 118.000 (aralık: 24.000-253,000)/μL oldu. Eltrombopag başlangıcından trombosit sayısı >50.000/μL olana kadar geçen süre medyan 18 (aralık:14-112) gün idi. Eltrombopag ile medyan tedavi süresi 70 (aralık: 26-180) gün oldu. Yaşayan ve tam trombosit iyileşmesi olan tüm hastalarda eltrombopag kesildi.

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Conclusion: Thrombocytopenia after ASCT is a condition that should be treated as it can lead to life-threatening bleeding.

Keywords: Hematopoietic stem cell transplantation, platelet engraftment failure, eltrombopag

Sonuç: AKHN sonrası kalıcı trombositopeni, yaşamı tehdit eden kanamalara yol açabileceği için tedavi edilmesi gereken bir durumdur.

Anahtar Sözcükler: Allojenik kök hücre nakli, trombosit engrafman yetersizliği, eltrombopag

Introduction

Persistent thrombocytopenia is a common complication of allogeneic stem cell transplantation (ASCT) (1). Its causes are not well understood. Poor graft function, viral infections such as cytomegalovirus (CMV), impaired platelet production due to side effects of immunosuppressive or antiviral drugs, increased destruction associated with infection and immune-mediated processes, or a combination of these mechanisms may play a role (2). A platelet count >20,000/μL for three days after transplantation is considered platelet engraftment. There are two forms of thrombocytopenia after ASCT. Primary platelet engraftment failure is characterized by the absence of initial donor cell engraftment (donor cells less than 95%); peripheral blood platelet count < $20x10^9$/L by day +28 after allo-HSCT from peripheral blood or bone marrow progenitors in the absence of relapse (3). It is seen in 5%-20% of transplantations. If the posttransplant platelet count reaches 50,000/μL and then persistently decreases to <20,000/μL, it is called secondary platelet engraftment failure (SPEF). Its prevalence is around 20% (4).

There is evidence which is proving that eltrombopag can induce hematopoiesis with a non-competitive activation of c-MPL. In immune thrombocytopenia, TPO levels are at the upper or near the upper limit of the mean, while they increase significantly in aplastic anemia (5).

Romiplostim and eltrombopag, which are FDA-approved thrombopoietin receptor agonists, stimulate platelet production, especially in immune thrombocytopenia (6,7). The efficacy and safety of eltrombopag have been demonstrated in a study by Wong et al. (8) in immune thrombocytopenic purpura (ITP) and a study by Townsley et al. (9) severe aplastic anemia. Given the similarity between severe aplastic anemia and graft failure, it was suggested that eltrombopag therapy could also be successful in graft failure (10). Recently, several articles with small numbers of cases showing the efficacy of eltrombopag in persistent thrombocytopenia developed after HSCT have been published (11-13).

Herein we reported the results of 12 patients treated with eltrombopag in our center with severe thrombocytopenia after HSCT retrospectively.

Method

From January 2018 to February 2020, 119 patients had hematopoietic stem cell transplantation in our center's bone marrow transplantation unit. Fifty-six patients underwent ASCT, and 12 of them developed persistent thrombocytopenia. Our study was approved by the Bezmialem Vakıf University ethics committee.

Endpoint: The endpoints were determined as platelet levels >50,000/μL after initiating treatment with eltrombopag either permanently after cessation of drug or need to continue therapy and no response after four months therapy at a dose of 150 mg/day.

Eltrombopag Treatment

Eltrombopag was initiated at a dose of 50 mg/day in seven patients. The eltrombopag dose was increased by 50 mg weekly to attain a final dose of 150 mg/day. Due to the lack of platelet response in patients who received a daily dose below 150 mg, three patients were started with 100 mg, and two patients were directly started at 150 mg/day. Eltrombopag was given to all patients with a maximum dose of 150 mg. After the platelet count exceeded 150,000/μL, it was planned to taper first by decreasing 50 mg and 25 mg. When a decrease in platelet count was also detected during the cessation period, the dose was increased to the previous dose again. Platelet transfusions were performed when the platelet count was <15,000/μL in clinically stable patients and had no fever and bleeding symptoms and in patients with signs of bleeding, even if the platelet count was between 20,000/μL and 50,000/μL.

Statistical Analysis

Average values, standard deviation, median lowest, highest values, frequency, and ratio values were used in the descriptive statistics. The distribution of the variables was checked by the Kolmogorov-Smirnov test. The Wilcoxon test was used to analyze quantitative dependent data. The SPSS 22.0 program was used for the analyses. The Kaplan-Meier method was used for survival analysis.

Results

In a total of 12 patients who developed persistent thrombocytopenia after ASCT, 10 were men, and two were women. The median age was 40.5 (range: 19-67) years. Platelet engraftment failure was observed in 12 out of 56 patients (21.4%). The diagnoses of these patients were acute lymphoblastic leukemia (n=3; 25%), acute myeloid leukemia (n=6; 50%), Hodgkin lymphoma (HL, n=1; 8.3%), myelodysplastic syndrome (MDS, n=1; 8.3%) and non-HL (NHL, n=1; 8.3%). Nine patients had ASCT from a sibling donor (one of which was haploidentical), and three patients from an unrelated donor. Nine of the donors were a full match, two donors had one mismatch, and one donor had two mismatches

peripheral stem cell source, and myeloablative regimens were used in all patients. The median given stem cell number was 6.65 (4.7-9.3) x10^6/kg. Neutrophil engraftment could be achieved in all patients. The median time to neutrophil engraftment was 20 (9-27) days). Six patients developed PPEF, and the SPEF occurred in the other six patients. Cyclophosphamide was used in four patients after transplantation. Transfusion independence was achieved in three of these patients. Patient-donor blood groups were the same in seven patients and different in five patients. Before eltrombopag, the frequency for transfusion was once a week in two patients, 1-2 times a week in seven patients, and more than two times a week in three patients. A decreased number of megakaryocytes in the bone marrow were seen in six patients, whereas it was normal in the other six patients. The median time from transplant to eltrombopag initiation was 69 (range: 48-128) days. After eltrombopag treatment, eight patients achieved transfusion independence. The median platelet count four months after the start of eltrombopag treatment was 118.000 (range: 24,000-253,000)/μL. The median time for the platelet count to reach 50,000/μL was 18 (range: 14-112) days. The median duration of treatment with eltrombopag was 70 (range: 26-180) days. Currently, five of these patients are alive, and seven died due to septicemia. Eltrombopag treatment was discontinued in all patients who survived and had full platelet recovery. Patient characteristics are summarized in Table 1.

The patients' response rates were evaluated according to their status before eltrombopag are summarized in Table 2.

The duration of achieving transfusion independence in responders was 61.9 days (36.4-87.3)(Figure 1).

The duration of achieving transfusion independence in patients who had one or fewer transfusions per week before eltrombopag was significantly shorter than those with two or more platelet needs before eltrombopag [46.5 and 83.4 days (HR: 0.255, 95% CI: 0.050-1.29, p=0.045] (Figure 2).

In the group whose patient-donor blood group was compatible [34.1 and 86.1 days HR: 5.071, 95% CI, p=0.040], the time to achieve transfusion independence was significantly shorter than the group without blood group compatibility (Figure 3).

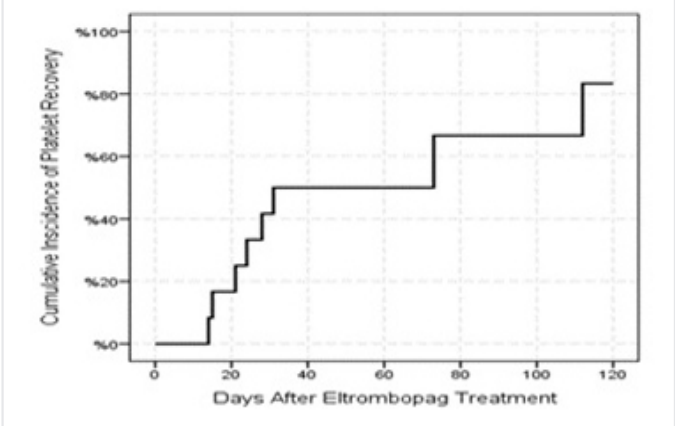

Figure 1. Cumulative transfusion independence

There was no significant difference regarding the time to achieve transfusion independence in primary and secondary failure. The time to achieve transfusion independence in patients who had a normal megakaryocyte count in their bone marrow was significantly shorter than those who had a low megakaryocyte count [85.0-38.8 days, HR: 3.667, 95% CI 0.698-19.25, p=0.045] (Figure 4).

The duration of achieving transfusion independence in the group using posttransplant cyclophosphamide (47.7 and 68.7 days, p>0.05) did not differ from the group that did not use cyclophosphamide (Figure 5).

The transfusion frequency decreased in three of four patients who did not respond to eltrombopag therapy. According to our study, a dose of eltrombopag <150 mg/day was not effective.

In the last outpatient visit, the median number of platelets was 80.500 (range: 19,000-210,000)/μL and was statistically significant (Table 3) (Figure 6).

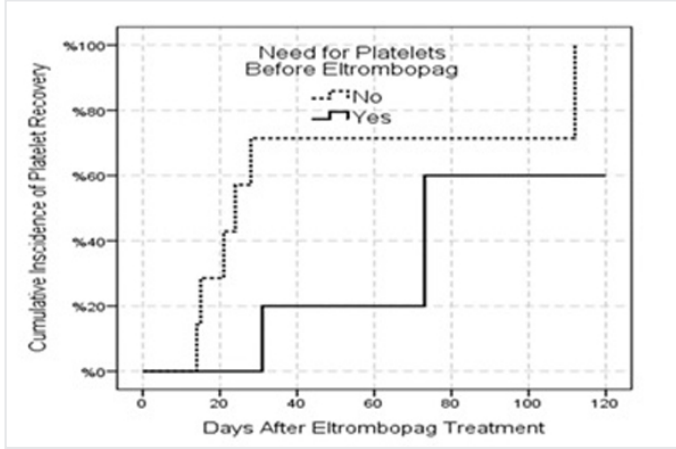

Figure 2. Need for platelets before eltrombopag

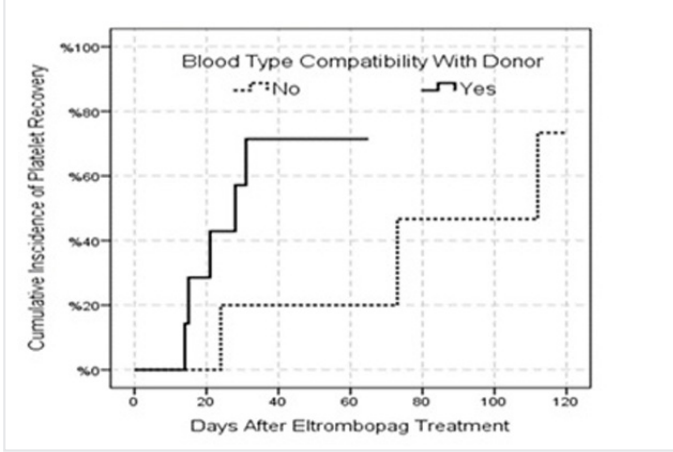

Figure 3. Patient-donor blood group compatibility

Table 1. Patient characteristics

		Min - Max			Median	Mean ± SD/n-%		
Patient age at transplantation		19.0	-	67.0	40.5	42.1	±	12.9
Gender	Female					2		16.7%
	Male					10		83.3%
Disease	ALL					3		25.0%
	AML					6		50.0%
	Hodgkin's lymphoma					1		8.3%
	MDS					1		8.3%
	NHL					1		8.3%
Donor	Sibling					8		66.7%
	Unrelated					3		25.0%
	Sibling haploidentical					1		8.3%
HLA	1 mismatch					2		16.7%
	2 mismatch					1		8.3%
	Match					9		75.0%
Stem cell source	Peripheral blood					12		100.0%
CD34+ cell dose x 10^6		4.7	-	9.3	6.7	6.5	±	4.6
Neutrophil engraftment time (days)		9.0	-	31.0	20.0	19.3	±	5.4
Patient-donor blood Group compatibility	Compatible					7		58.3%
	Not compatible					5		41.7%
Thrombocytopenia Status	PPEF					6		50.0%
	SPEF					6		50.0%
Platelet transfusion Before starting Eltrombopag	Once per week					2		16.7%
	2 times per week					7		58.3%
	>2 per week					3		25.0%
Megakaryocyte count Before starting eltrombopag	Decreased					6		50.0%
	Normal					6		50.0%
Starting dose of eltrombopag	100 mg					3		25.0%
	150 mg					2		16.7%
	50 mg					7		58.3%
Max dose of eltrombopag	150 mg					12		100.0%
The time until the start of the eltrombopag after ASCT (days)		48.0	-	128.0	69.0	75.7	±	25.3
Achievement of transfusion independence	Yes					8		66.7%
	No					4		33,3%
Final status	Alive					5		41.7%
	Dead					7		58.3%
Treatment time (days)		26.0	-	180.0	70.0	78.0	±	48.1

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, MDS: Myelodysplasticsydrome, NHL: non-Hodgkin lymphoma, HLA: Human leucocyte antigen, PPEF: Primary platelet engraftment failure, SPEF: Secondary platelet engraftment failure, ASCT: Allogeneic stem cell transplantation, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Response rates to treatment

		Transfusion independence (-)				Transfusion independence (+)			
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median
Age		47.3	±	11.0	51.5	39.5	±	13.7	39.5
Gender	Female	0		0.0%		2		25.0%	
	Male	4		100.0%		6		75.0%	
Patient-donor blood group compatibility	Compatible	2		50.0%		3		37.5%	
	Not compatible	2		50.0%		5		62.5%	
Thrombocytopenia status	PPEF	2		50.0%		4		50.0%	
	SPEF	2		50.0%		4		50.0%	
Platelet transfusion before starting eltrombopag	(-)	1		25.0%		6		75.0%	
	(+)	3		75.0%		2		25.0%	
Platelet count before starting eltrombopag		14,000	±	4,243	15,000	20,000	±	6,866	21,500
Max platelet count after eltrombopag		39,000	±	11,165	42,000	16,5125	±	54,186	166,000
Days from starting eltrombopag to platelet 50.000/µL						26.5	±	33.9	18.0

PPEF: Primary platelet engraftment failure, SPEF: Secondary platelet engraftment failure, SD: Standard deviation

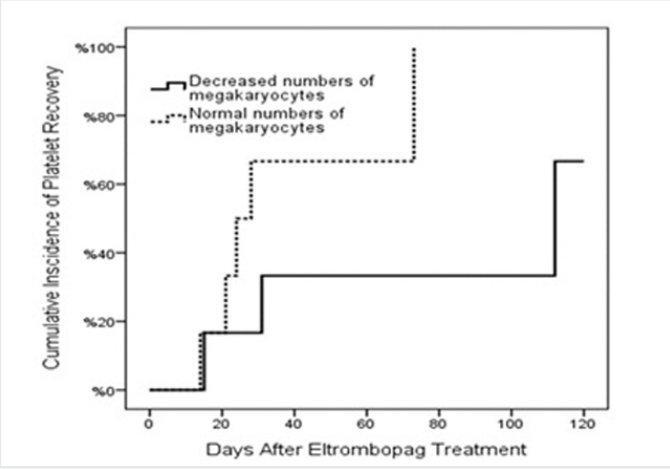

Figure 4. Megakaryocyte counts before starting eltrombopag

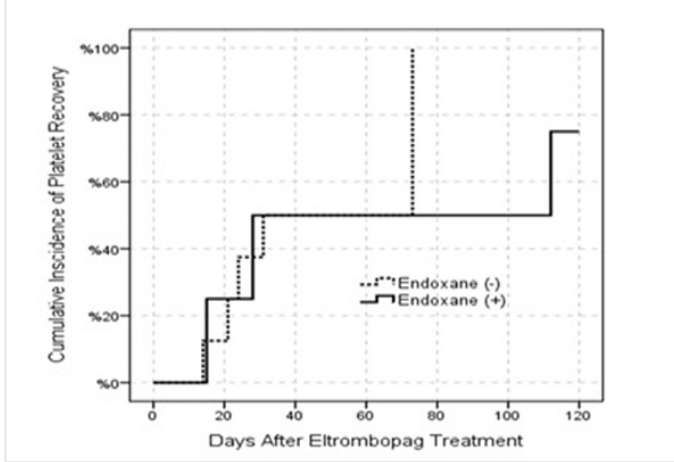

Figure 5. Using cyclophosphamide after ASCT

ASCT: Allogeneic stem cell transplantation

Discussion

Engraftment failure after ASCT has been a life-threatening complication with a rate of 5%-27% (14-16). After hematopoietic stem cell transplantation, two types of engraftment failure can be observed: PPEF and SPEF (3,4). Various methods have been tried to activate engraftment. These are growth factors, CD34+ stem cell enhancement, mesenchymal stem cells, and a second ASCT (16-19). However, none of these methods was completely effective. Eltrombopag, a thrombopoietin receptor agonist, has recently been started to be used.

In this article, we wanted to share our experience with eltrombopag in a patient who developed thrombocytopenia after ASCT. In our ASCT patients, platelet engraftment failure was found to be 21.4%. Eltrombopag treatment provided transfusion independence in 66.7% of patients and it was discontinued in all living patients. The dose was increased to 150 mg/day in all patients.

Bielski et al. reported that the post-ASCT PPEF prevalence was 3% (3). In three separate reports, two of four patients reported as PPEF were treated with romiplostim and the other two were treated with eltrombopag. Transfusion independence was

Table 3. Platelet counts before and after eltrombopag

	Min - Max			Median	Mean ± SD			p	
Platelet count (x10³)/µL									
Before eltrombopag	5.0	-	27.0	18.5	18.0	±	6.6	0.002	w
After eltrombopag	19.0	-	210.0	80.5	89.5	±	62.4		

Min: Minimum, Max: Maximum, SD: Standard deviation

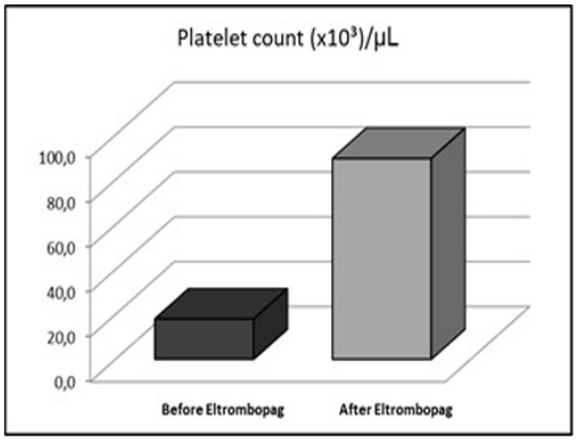

Figure 6. Platelet count before and after eltrombopag

achieved in all four patients (20-22). Tanaka et al. (12) treated five PPEF patients with eltrombopag and reported that they achieved transfusion independence in 60% of the patients. Transfusion dependence continued in two patients, but the frequency of transfusions decreased (12). We treated six patients diagnosed as PPEF with eltrombopag. Transfusion independence was achieved in four (66.7%) patients, and transfusion frequency decreased in the other two patients.

Bruno et al. (4) reported the prevalence of SPEF as 20%. Twenty-two patients identified as SPEF in seven different reports treated with romiplostim and transfusion independence was achieved in 91% of patients (20,23-28). Tanaka et al. (12) described a transfusion independence rate of 86% with six patients in a total of seven SPEF patients treated with eltrombopag. Six patients were diagnosed with SPEF and treated with eltrombopag in our patient group (max dose of 150 mg/day). Transfusion independence was achieved in four (66.7%) of these patients. Transfusion frequency decreased in one of the two nonresponder patients.

Tang et al. (11) treated 12 patients with poor graft function after ASCT with eltrombopag. In this study, eltrombopag was started at 25 mg/day and a maximum dose of 75 mg/day. A complete response (CR) was achieved in 66.7% of these patients. In our study, transfusion independence (CR) was achieved in 66.7% of patients.

Two of four patients for whom transfusion independence could not be achieved had grade ≥2 gastrointestinal tract GvHD. This was observed in three of four patients in the study by Tanaka et al. (12). Gastrointestinal absorption disorders might be effective in this condition.

In our study, the response to eltrombopag therapy was significantly better in patients who need a lower frequency of transfusions and had donor-patient blood group compatible transplantations. In addition, transfusion independence was achieved in five (83%) patients with normal bone marrow megakaryocyte counts. However, transfusion independence was achieved in only three (50%) of six patients with reduced bone marrow megakaryocyte counts (Figure 5). A study conducted by Tanaka et al. (12) supports this result. In the same study, the response to eltrombopag treatment was significantly higher in patients with secondary platelet failure than those with primary failure (12). However, in our study, there was no difference between the two groups.

Eltrombopag was well tolerated in all 12 patients. Side effects, such as cataracts, thrombosis, or 3/4 degree of toxicity and treatment-related mortality identified in the "EXTEND" (8) and "RAISE" phase III studies (29). These studies demonstrated the efficacy and safety of eltrombopag in patients with ITP. In various studies, it has been reported that eltrombopag does not induce leukemia or MDS cell growth (30). None of our patients had a transformation of leukemic or myelodysplastic syndrome. The efficacy and safety of eltrombopag have been demonstrated in ITP and aplastic anemia in various studies (8,9).

Study Limitations

The small number of cases is a limitation of this study.

Conclusion

Thrombocytopenia that develops after ASCT is a condition that should be treated as it can lead to life-threatening bleeding. Recently, the administration of eltrombopag USA after ASCT has become widespread and is effective and safe. It can be considered an effective option in the treatment of this difficult condition. Despite a small patient population, eltrombopag was an effective and safe treatment option for persistent thrombocytopenia that developed after allogeneic stem cell transplantation. Patient-donor blood group compatibility, pre-eltrombopag transfusion frequency, and pre-eltrombopag bone marrow megakaryocyte count may help predict the response to eltrombopag. Further studies with more patients are necessary to assess its full potential.

Ethics

Ethics Committee Approval: Our study was approved by the Bezmialem Vakıf University ethics committee.

Informed Consent: Patient consent was not obtained because the study was retrospective.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E., A.T.A., Concept: A.E., Design: A.E., Data Collection or Processing: A.E., Analysis or Interpretation: A.T.A., Literature Search: A.E., Writing: A.E

Conflict of Interest: No conflict of interest was declared by the authors.

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