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Research paper

Eltrombopag treatment in thrombocytopenia following hematopoietic stem cell transplantation: A multicenter real-world experience

Ebru Kilic Gunes [a,*,1], Sureyya Yigit Kaya [b,2], Fatih Yaman [c,3], Mustafa Kemal Yeniay [d,4], Kurtulus Vural [e,5], Melda Comert [a,6], Omur Gokmen Sevindik [b,7], Neslihan Andic [c,8], Simten Dagdas [d,9], Ilknur Nizam Ozen [e,10], Leylagul Kaynar [b,11], Filiz Yavasoglu [c,12], Gulsum Ozet [d,f,13], Volkan Karakus [e,14], Meltem Ayli [a,15]

[a] University of Health and Sciences, Gulhane Training and Research Hospital, Department of Hematology, Ankara, Turkiye
[b] Istanbul Medipol University, Faculty of Medicine, Department of Hematology, Istanbul, Turkiye
[c] Eskisehir Osmangazi University, Faculty of Medicine, Department of Hematology, Eskisehir, Turkiye
[d] University of Health and Sciences, Ankara Bilkent City Hospital, Department of Hematology, Ankara, Turkiye
[e] University of Health and Sciences, Antalya Training and Research Hospital, Department of Hematology, Antalya, Turkiye
[f] Ankara Yildirim Beyazit University, Faculty of Medicine, Department of Hematology, Ankara Bilkent City Hospital, Ankara, Turkiye

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ABSTRACT

Introduction: Thrombocytopenia is among the most common complications following hematopoietic stem cell transplantation and is associated with increased mortality and morbidity with no standard treatment yet. In this multicenter and retrospective study, we aim to present our multi-center experience of Eltrombopag treatment in patients with isolated thrombocytopenia following HSCT.

Material-method: A total of 73 patients from 5 centers who underwent autologous or allogeneic stem cell transplantation, had no primary disease relapse, all of whom had neutrophil engraftment, complete chimerism, and who were diagnosed with Prolonged Isolated Thrombocytopenia (PIT) or Secondary Failure Of Platelet Recovery (SFPR) were included in the study. The patients were initiated on Eltrombopag at a dose of 50–150 mg. Complete response was defined as a platelet count $>50\times10^9$/L for 7 consecutive days with no transfusion support.

Results: A total of 50.3% of the patients underwent Autologous and 49.7% Allogeneic Stem Cell Transplantation, 54.8% were diagnosed with PIT, and 45.2% were diagnosed with SFPR, and the treatment with 50–150 mg/day Eltrombopag was initiated on the median day +42. Complete response was achieved in 71.2% of these patients on the median day 23 of the treatment. No significant effects of the initial dose (50–150 mg/day) were detected in the Complete Response in the multivariate analysis on response. An insufficient number of Megakaryocytes in

* Corresponding author.
E-mail address: ebrukilic83@hotmail.com (E. Kilic Gunes).
[1] Orcid ID: 0000-0001-8663-3172
[2] ORCID ID: 0000-0001-6732-8068
[3] ORCID ID: 0000-0002-0494-571X
[4] ORCID ID: 0000-0002-9059-4740
[5] ORCID ID: 0000-0001-5513-3802
[6] ORCID ID: 0000-0002-7798-4349
[7] ORCID ID: 0000-0001-9636-4113
[8] ORCID ID: 0000-0003-0510-4733
[9] ORCID ID: 0000-0003-0901-2043
[10] ORCID ID: 0000-0002-7787-2232
[11] ORCID ID: 0000-0002-2035-9462
[12] ORCID ID: 0000-0002-4017-4668
[13] ORCID ID: 0000-0003-2658-5987
[14] ORCID ID: 0000-0001-9178-2850
[15] ORCID ID: 0000-0001-5766-5642

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the bone marrow before Eltrombopag treatment was determined as an independent risk factor in determining the response (OR 3.57, 95% CI 1.21–10.55). The overall survival of the patients who did not respond to Eltrombopag was found to be significantly worse than that of patients who responded (p=0.022, HR:2.74, 95% CI 1.12–6.54). *Conclusion:* As a result of the present study, Eltrombopag treatment was found to be effective and safe in thrombocytopenia that develops following hematopoietic stem cell transplantation. It was concluded that its use may be more effective in patients with sufficient bone marrow megakaryocytes before the treatment and an initial dose of 50 mg/day may be appropriate in terms of cost, effectiveness, and toxicity. Large-scale randomized and controlled prospective studies are needed to determine the roles of Eltrombopag treatment in patients with post-transplant PIT and SFPR.

1. Introduction

Hematopoietic stem cell transplantation is a curative option employed in the treatment of many hematological diseases [1]. With the introduction of alternative donors and the increased use of reduced-intensity conditioning regimens, the field of application of Hematopoietic Stem Cell Transplantation (HSCT) is constantly expanding with the developments in preventive and supportive care, but it also includes many complications [2]. Following HSCT, prolonged cytopenia is a common cause of morbidity and a strong cause of transplant-related mortality [3]. The most common cause of cytopenia is still thrombocytopenia with a prevalence of 5–40%[4,5]. Previous studies showed that Transplant-Related Mortality (TRM) increases and overall survival reduces in those who have a platelet count $<50\times10^9$/L on day +100 following HSCT [2–4].

Multifactorial causes such as graft failure, the number of infused CD34+ stem cells, donor type, infections, drugs, microangiopathy, and alloimmunization can be considered in the etiology of post-transplant thrombocytopenia, as well as primary disease relapse[2,6].

Following HSCT, thrombocytopenia can be divided into two separate groups: Prolonged Isolated Thrombocytopenia (PIT) and Secondary Failure of Platelet Recovery (SFPR). PIT is defined as a platelet count $<20\times10^9$/L despite the presence of engraftment in other series following HSCT [7] and SFPR is defined as a platelet count below 20×10^9/L for 7 consecutive days following platelet engraftment without any relapse [2].

There is no approved treatment for the management of persistent thrombocytopenia following the transplantation and repeated transfusion support, growth factors, CD34+ stem cell reinfusion, mesenchymal stem cell transfusion, and a second allogeneic SCT are among the options [8,9]. However, there is still no consensus on the standard treatment approach and the present effective and reliable treatment options are limited.

Eltrombopag (EPAG) is a small-molecule oral thrombopoietin analog stimulating the differentiation of hematopoietic progenitor cells into Megakaryocyte (MGK) precursor cells and proliferation of precursor cells by binding to the transmembrane region of cMPL [10,11]. Also, EPAG prevents platelet apoptosis, contributing to platelet elevation [12]. EPAG is approved for the treatment of aplastic anemia, Immune Thrombocytopenia (ITP), and Hepatitis C-associated thrombocytopenia [13]. Recent studies have been published reporting that Eltrombopag, which is a thrombopoietin agonist, is effective in the treatment of post-transplant thrombocytopenia [7, 14–16]. However, prospective studies with a larger number of patients are needed for efficacy and safety data because of the limited number of patients in previous studies.

In this retrospective study, we aim to present our multi-center experience of Eltrombopag treatment in patients with isolated thrombocytopenia following HSCT.

2. Method

A total of 76 patients from 5 centers who received EPAG treatment because of thrombocytopenia following Allogeneic and Autologous Hematopoietic Stem Cell Transplantation (Autologous SCT) were screened in the present study. A total of 73 patients whose follow-up and treatment data could be accessed were included in the study after the inclusion and exclusion criteria were applied. Written consent was obtained from all patients. The Declaration of Helsinki Principles and good clinical practice protocols were adhered to in the study design, data collection, and analysis. Ethics committee approval was obtained for the study from the University of Health Sciences Gülhane Medical Faculty (14.03.2023; 46418926). The demographic data, primary diseases, transplant types, donor types, whether they had platelet engraftment, Eltrombopag initiation days, doses, EPAG responses, and toxicities of the patients were analyzed retrospectively.

2.1. Patients

All patients who had autologous or allogenic SCT in the 5 centers between November 2016 and January 2023 were screened. Among these patients, those who were given at least 2×10^6/kg CD34(+) stem cells in autologous transplants and at least 3×10^6/kg CD34(+) stem cells in allogeneic transplants, all with neutrophil engraftment, complete donor-type chimerism if allogeneic transplantation was performed, had a diagnose of Prolonged Isolated Thrombocytopenia (PIT) or Secondary Failure of Platelet Recovery (SFPR) and initiated EPAG, and whose follow-up and treatment data were complete were included in the study. All patients who underwent autologous and allogeneic stem cell transplantation were given Filgrastim treatment at a dose of 5 mcg/kg after day+5 until neutrophil engraftment.

Patients with recurrence or progression of primary hematological disease, previous EPAG treatments, impaired liver functions (patients with transaminase levels exceeding 2.5-fold the upper limit of normal, patients with bilirubin levels exceeding 2-fold the upper limit of normal), active Graft versus Host Disease (GvHD), those who were receiving systemic treatment for GvHD (except prophylaxis), patients with drug-induced thrombocytopenia or secondary thrombocytopenia because of viral infection, and patients with active thrombosis were not included in the study. Also, patients whose diagnosis and treatment data could not be accessed or who were lost to follow-up were excluded from the study.

All patients underwent bone marrow aspiration and biopsy before initial treatments. The presence of 8–12 MGK per mm^2 in the bone marrow was accepted as a sufficient number of MGK in the examination of bone marrow aspiration biopsy samples [17–19].

2.2. Definitions

Platelet Engraftment was defined as the time following transplantation needed to achieve a blood platelet count exceeding 20×10^9/L without transfusion support for 3 consecutive days.

Neutrophil Engraftment was defined as the first of three consecutive days of achieving a sustained peripheral blood neutrophil count of $>0.5\times10^9$/L.

Prolonged Isolated Thrombocytopenia (PIT) was defined as the PLT count being lower than 20×10^9/L on day +28 following the transplantation, even though neutrophil engraftment had developed [7].

SFPR was defined as a platelet count of $\leq20\times10^9$/L for more than 7

days following platelet engraftment without any relapse [2].

2.3. Eltrombopag treatment

Eltrombopag treatment was initiated at a dose of 50–150 mg/day. For those who did not respond, the dose was increased to a maximum of 150 mg/day. The selection of the initial dose and the dose increase were made every 7–14 days, if necessary, according to the decision or choice of the follow-up physician and the clinics' preferences.

Efficacy was evaluated in terms of Overall Response Rate (ORR), including complete response and partial response. Partial response was defined as the platelet level above 30×10^9/L but below 50×10^9/L without the need for platelet replacement, and complete response was defined as the platelet level above 50×10^9/L for 7 consecutive days without the need for platelet transfusions. Times to PR and CR were also evaluated. The factors that might affect complete response were also analyzed. Side effects that were observed following the Eltrombopag initiation were analyzed retrospectively according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 5).

3. Statistical analysis

Statistical assessment was performed using SPSS 23 for Windows (IBM SPSS Inc., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess whether the data fit normal distribution. Numerical variables with normal distribution were denoted as mean ± standard deviation, and those that did not fit a normal distribution were denoted as median min–max) values. Categorical variables are demonstrated as numbers and percentages. The distribution of numerical variables in two groups was evaluated with an independent samples t-test (numerical variables that fit abnormal distribution) or the Mann–Whitney U-test (numerical variables that did not fit a normal distribution). Comparison of categorical variables in groups was tested with Chi-square or Fisher exact chi-square tests. Survival plots were generated with Kaplan–Meier analysis and the log-rank test was used for testing the equality of survival curves. Analysis of predictors of survival was performed using the Cox regression test. Parameters with p values $\leq$0.15 in univariate tests were included in the multivariate analysis. Values of $p < 0.05$ were recognized to be significant in statistical analyses.

4. Results

A total of 73 patients who underwent autologous and allogeneic SCT were included in the present study. The demographic data and baseline characteristics of the patients are summarized in Table 1.

Autologous SCT was applied to 37 patients (50.3%) and allogeneic SCT was applied to 36 patients (49.7%). The median age of the patients was found to be 41 (18−70), and 47 (64.4%) were male and 26 (35.6%) were female. The median age of patients who underwent allogeneic SCT was 38 (18−66) years, 36.1% had Acute Myeloid Leukemia (AML), 27.8% had Acute Lymphoblastic Leukemia (ALL), 13.9% had Myelodysplastic Syndrome (MDS) and 11.1% had Lymphoma, and 11.1% were diagnosed with aplastic anemia. The median age of autologous SCT patients was 57 (18−70) years, 54.1% were diagnosed with Multiple Myeloma and 45.9% were diagnosed with Lymphoma.

Among the patients who underwent allogeneic SCT, 50% had a fully-matched sibling donor (MSD), 30.6% had a HLA fully-matched unrelated donor (MUD), 13.6% had a haploidentical donor, and 5.6% had a HLA a 9/10 matched unrelated donor (MMUD). Among those who underwent allogeneic SCT, 75% received myeloablative conditioning (MAC) and 25% received a reduced-intensity conditioning (RIC) regimen. Peripheral blood grafts were used as the stem cell source in all

Table 1
Baseline Patient Characteristics.

		Total Patients	Autologous HSCT	Allogeneic HSCT
Patients		73	37	36
Age (Median)	Years	41 (18−70)	57 (18−70)	38 (18−66)
Gender	Male	47 (64.4%)	22 (59.5%)	25 (69.4%)
	Female	26 (35.6%)	15 (40.5%)	11 (30.6%)
HSCT Indication	Multiple Myeloma	20 (27.3%)	20 (54.1%)	-
	AML	13 (17.9%)	-	13 (36.1%)
	ALL	10 (13.7%)		10 (27.8%)
	Lymphoma	21 (28.7%)	17 (45.9%)	4 (11.1%)
	Aplastic Anemia	4 (5.5%)	-	4 (11.1%)
	MDS	5 (6.9%)	-	5 (13.9%)
Donor Type	MSD			18 (50%)
	MUD			11 (30.6%)
	MMUD			2 (5.6%)
	Haploidentical			5 (13.8%)
Autologous HSCT Conditioning Regimen	Melphalan		20 (54.1%)	
	BEAM		9 (24.3%)	
	LEAM		5 (13.5%)	
	Other (TBI, Bu-Cy)		3 (8.1%)	
Allogeneic HSCT Conditioning Regimen	Cy-Bu			13 (36.1%)
	Flu-Bu			10 (27.9%)
	TBI-based			11 (30.5%)
	Other			2 (5.5%)
Intensity of Conditioning	Myeloablative	64 (87.6%)	37 (100%)	27 (75%)
	RIC	9 (12.4%)	-	9 (25%)
Post-Transplant Cyclophosphamide	Yes			20 (55.5%)
	No			16 (45.5%)
CD34 (+) cells infused	Median - 10^6/kg	5.4 (2–11.5)	5 (2–11.5)	6.1 (3.2–7.3)
Type of Thrombocytopenia	PIT	40 (%54.8)	26 (70.3%)	14 (39.9%)
	SFPR	33 (%45.2)	11 (29.7%)	22 (61.1%)
Neutrophil Engraftment	Median (days)	16 (9−57)	14 (9−34)	19 (10−57)
Bone Marrow Biopsy Before EPAG	Adequate Megakaryocytes	47 (64.4%)	25 (67.6%)	22 (61.1%)
	Inadequate Megakaryocytes	26 (35.6%)	12 (32.4%)	14 (38.9%)

AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia, MDS: Myelodysplastic Syndrome, MSD: Matched Sibling Donor, MUD: Matched Unrelated Donor, MMUD: Mismatched Unrelated Donor, RIC: Reduced Intensity Conditioning, EPAG: Eltrombopag. PIT: Prolonged isolated thrombocytopenia, SFPR: Secondary failure of platelet recovery

cases. On +3 and +4 days, Post-transplant cyclophosphamide was administered at a dose of 50 mg/kg/day as GvHD prophylaxis in 55% of patients who underwent allogeneic SCT. Patients who underwent allogeneic SCT were infused with a median of 6.1×10^6/kg CD34(+) stem cells (3–7.3×10^6/kg). The Neutrophil engraftment of the patients who underwent allogeneic SCT was observed on day +19.

After the allogeneic stem cell transplantation, EPAG treatment was started in 39.9% of the patients with a diagnosis of PIT and 60.1% with a diagnosis of SFPR. The MGK count was found to be sufficient in 61.1% of the patients in the bone marrow examination before EPAG treatment in patients who underwent allogeneic SCT.

Patients who underwent autologous SCT were infused with a median of 5.4×10^6/kg CD34(+) stem cells. The neutrophil engraftment of the patients who underwent autologous SCT was observed on the median day +14. EPAG was initiated for 70.3% of the patients who underwent autologous SCT with the diagnosis of PIT and 29.7% with the diagnosis of SFPR. In the bone marrow examination performed before the EPAG treatment of the patients who underwent autologous SCT, the MGK count was found to be sufficient in 67.6%.

Eltrombopag treatment was initiated for the patients on the median day +42 (28−218) following their transplantation. EPAG treatment was initiated on the median day +36 (28−218) for the autologous SCT group, and on the median day +66 (28−180) for patients who underwent allogeneic SCT. EPAG treatment was initiated significantly later than autologous SCT in the allogeneic SCT group ($p = 0.004$). This significant difference was considered to be the effect of the higher number of patients who were diagnosed with SFPR in the allogeneic SCT group (61% vs 28%; $p = 0.007$).

The median platelet count of the patients was found to be 14×10^9/L on the date of EPAG treatment. The initial dose was 50 mg/day in 54.7% of the patients and 150 mg in 45.3% of the patients. The initial dose was 50 mg in 64.8% of patients who underwent autologous SCT and in 52.7% of patients who underwent allogeneic SCT. No significant differences were detected between the initial doses of the patients who underwent autologous and allogeneic SCT ($p = 0.25$). The maximum EPAG dose was found to be 50 mg in 12.3% of the patients, 75 mg in 35.6%, and 150 mg in 52.1%. EPAG dose was increased in 42.4% of the patients.

Following EPAG, Partial Response (PR: plt>30×10^9/L) was achieved in 82.2% of patients and Complete Response (CR: plt>50×10^9/L) was achieved in 71.2% of the patients. Although the PR and CR rates were 89.2% and 79.4% in the autologous SCT group, they were 77.8% and 63.9% in the allogeneic SCT group, respectively. No significant differences were detected between the patients who underwent autologous and allogeneic stem cell transplantation in terms of the days to achieve complete response (22 vs 23 days, $p = 0.851$). Although CR was 73.2% in EPAG patients with a diagnosis of PIT, it was 68.8% in those with a diagnosis of SFPR. No significant effects of the transplant type (autologous/allogeneic) were detected on Complete Response ($p = 0.172$). Although PR was observed on the median day +14 (2–104 days) in patients following the EPAG treatment, CR was achieved on the median day +23 (7–266 days). No significant differences were detected between the patients who were diagnosed with PIT and SFPR in terms of the days to achieve Complete Response (median 23 vs 34 days, $p = 0.270$). The CR rates of the group in which EPAG was initiated within the first 60 days following the transplantation and the patients for whom EPAG was initiated following the day +60 after the transplantation were similar (71.4% vs 71.1%, $p = 0.977$). The maximum EPAG dose of the patients who had a Complete Response was 150 mg in 55.8%, 75 mg in 28.8%, and 50 mg in 15.4%. EPAG treatment data and treatment results of the patients are summarized in Table 2.

The analysis of the distribution of the patients who achieved CR with EPAG treatment according to subgroups is summarized in Table 3. No significant differences were detected in the subgroup analysis between age, gender, transplant type (autologous/allogeneic), number of infused CD34(+) stem cells, PIT/SFPR diagnosis, neutrophil engraftment day, initial EPAG dose, and EPAG maximum dose between the groups with and without a Complete Response. Also, no significant differences were detected between responsive and non-responsive patients in terms of donor type, conditioning regimen intensity, and post-transplant cyclophosphamide use in the analysis that was made with the patients who underwent allogeneic SCT. Although the complete response rate with EPAG was 73.1% in patients with sufficient MGK numbers in the bone marrow, it was found to be 42.9% in patients with insufficient MGK. The response rate in the patients with sufficient megakaryocytes in the bone marrow before the treatment was found to be significantly higher than the patients with insufficient megakaryocytes (73.1% vs 42.9%, p=0.015). While the MGK count was found to be sufficient in 75.6% of the in the PIT group, the MGK count was insufficient in 24.4% of the PIT patients. While the number of MGK was found to be adequate in 50% of the patients in the SFPR group, the number of MGK was inadequate in 50% of SFPR patients. Sufficient MGKs in the bone marrow was significantly higher in patients in the PIT group than in the SFPR group (75.6% vs 50%, $p = 0.023$).

Table 2
Eltrombopag Treatment.

		Total Patients	Autologous HSCT	Allogeneic HSCT
Patients		73	37	36
Plt count Before EPAG	Median – x10^9/L	14 (3−23)	14 (3−22)	14 (4−23)
Median Days from Transplant to EPAG treatment	Median – days	42 (28−218)	36 (28−218)	66 (28−180)
Initial EPAG dose	50 mg	40 (54.7%)	24 (64.8%)	19 (52.7%)
	150 mg	33 (45.3%)	16 (35.2%)	17 (47.3%)
EPAG dose increase	No	42 (57.6%)	22 (59.5%)	20 (55.6%)
	Yes	31 (42.4%)	15 (40.5%)	16 (44.4%)
Maximum EPAG dose	50 mg	9 (12.3%)	5 (13.5%)	4 (11.1%)
	75 mg	26 (35.6%)	13 (35.1%)	13 (36.1%)
	150 mg	38 (52.1%)	19 (51.4%)	19 (52.8%)
Partial Response to EPAG (plt> 30×10^9/L)	No	13 (17.8%)	5 (13.5%)	8 (22.2%)
	Yes	60 (82.2%)	32 (89.2%)	28 (77.8%)
Complete Response to EPAG (plt> 50×10^9/L)	No	21 (28.8%)	8 (21.6%)	13 (36.1%)
	Yes	52 (71.2%)	28 (79.4%)	23 (63.9%)
Median days to Partial response (plt> 30×10^9/L)	Median – days	14 (2−104)	12 (2−103)	15 (4−104)
Median days to Complete response (plt> 50×10^9/L)	Median – days	23 (7−266)	22 (7−249)	24 (12−266)
Median Duration of EPAG treatment	Median – days	75 (17−575)	70 (17−515)	83 (19−575)
Median Duration of Response	Median - Days	NR	NR	NR

Univariate analysis of the factors that affected the response to EPAG treatment is summarized in Table 4. A significant effect of sufficient bone marrow megakaryocytes before the treatment on EPAG response was detected in the univariate analysis (OR 3.61, 95% CI 1.21–10.04, p=0.017). An insufficient number of megakaryocytes in the bone marrow before EPAG treatment was determined to be an independent risk factor for determining EPAG response in multivariate analysis (OR 3.57, 95% CI 1.21–10.55).

At the end of a median follow-up period of 14 months as of the date of EPAG initiation, the median total survival (OS) was 16 months in

Table 3
Factors Affecting EPAG response.

		EPAG Responders	EPAG Non-responders	P value
Patients		52	21	
Age	Median	51 (20–66)	47 (18–70)	0.558
Gender	Male	34 (61.9%)	13 (65.4%)	0.779
	Female	18 (38.1%)	8 (34.6%)	
Type of Transplant	Autologous	29 (55.8%)	8 (38.1%)	0.172
	Allogeneic	23 (44.2%)	13 (61.9%)	
Type of Thrombocytopenia	PIT	30 (57.7%)	11 (52.4%)	0.679
	SFPR	22 (42.3%)	10 (47.6%)	
Intensity of Conditioning (Allo-only)	Myeloablative	18 (78.3%)	9 (69.2%)	0.548
	RIC	5 (21.7%)	4 (30.8%)	
Post-Transplant Cyclophosphamide (Allo-only)	Yes	12 (52.2%)	8 (61.5%)	0.587
	No	11 (47.8%)	5 (38.5%)	
CD34 (+) cells infused	Median – 10^6/kg	5.4 (2–11.5)	5.1 (3.2–11)	0.895
Neutrophil Engrafment	Median (days)	15 (9–34)	17 (9–57)	0.489
Initial EPAG dose	50 mg	27 (51.9%)	13 (61.9%)	0.438
	150 mg	25 (48.1%)	8 (38.1%)	
EPAG maximum dose	50–75 mg	25 (48.1%)	10 (47.6%)	0.972
	150 mg	27 (51.9%)	11 (52.3%)	
Bone Marrow Before EPAG	Adequate MGK	38 (73.1%)	9 (42.9%)	**0.015**
	Inadequate MGK	14 (26.9%)	12 (57.1%)	

Table 4
Univariate Analysis of Response.

		OR	CI (95%)	P value
Age		1.01	0.97–1.04	0.530
Gender	Male/Female	0.86	0.30–2.45	0.779
Type of Transplant	Auto/ Allo	2.04	0.72–5.77	0.172
Engraftment Failure	Primary/ Secondary	1.24	0.44–3.43	0.679
Donor Type	Allo-Only (MSD-MUD-MMUD)	0.88	0.46–1.67	0.698
Intensity of Conditioning	Allo-Only (MA/ RIC)	1.60	0.34–7.45	0.549
Post-Transplant Cyclophosphamide	Allo-Only	0.68	0.17–2.72	0.588
Allogeneic Conditioning	Cy/Bu-Flu-Bu/ TBI-based	0.89	0.65–1.22	0.475
Autologous Conditioning	Mel /BEAM /LEAM	0.92	0.67–1.28	0.655
CD34 (+) cells infused	Median x10^6/kg	0.96	0.75–1.22	0.765
Neutrophil Engrafment Day	Median - day	0.98	0.91–1.05	0.622
Bone Marrow Megakaryocytes	Adequate/ Inadequate	**3.61**	**1.25–10.04**	**0.017**
Initial EPAG dose	50/150 mg	0.66	0.23–1.87	0.439
EPAG Maximum Dose	50–75/150	1.01	0.36–2.80	0.972

OR: Odds Ratio, CI: Confidence Interval

patients who did not respond to EPAG treatment, and the median survival was not reached in patients who responded EPAG. The 2-year overall survival rate was found to be 61% in responded patients. The overall survival of the patients without EPAG response was found to be significantly worse than that of those with a response to EPAG (p=0.022, HR:2.74, 95% CI 1.12–6.54). The survival plot of the patients is given in Fig. 1.

When EPAG treatment was evaluated in terms of toxicity, no grade III-IV side effects were detected in the patients. Grade I-II dyspeptic complaints were detected in 4 patients (5.4%) and Grade I-II increase was detected in liver enzymes in 3 patients (4.1%). No thrombosis was detected in the patients during the follow-up period. EPAG treatment was tolerated well, and none of the patients discontinued treatment because of adverse events or intolerance.

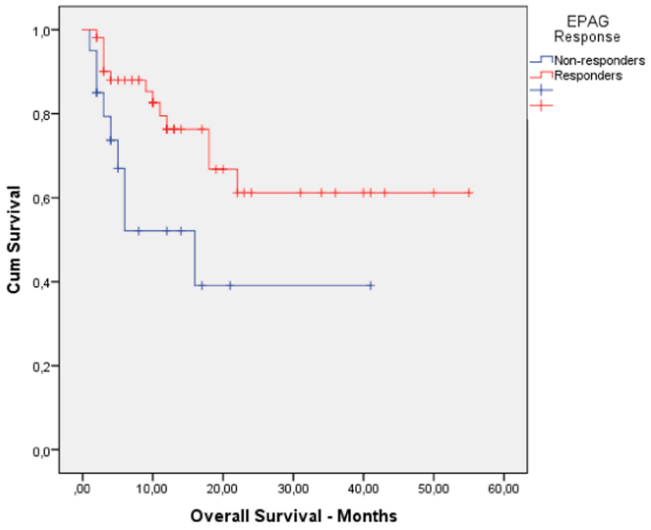

Fig. 1. Survival Plots of Responders and Non-Responders to EPAG treatment.

5. Discussion

Thrombocytopenia that develops following stem cell transplantation, as well as the elevated bleeding risk, poses a risk for patients, along with an increased serious morbidity and mortality with frequent platelet replacements. It is considered that EPAG might be a treatment modality that can provide transfusion independence in this patient group, reduce the need for new transplants, and avoid major financial losses and workforce loss [20,21].

A total of 73 patients from 5 centers (41 diagnosed with PIT and 32 diagnosed with SFPR) and initiated EPAG treatment following autologous and allogeneic SCT, were included in the present study. CR was achieved in 71.2% of these transfusion-dependent patients and transfusion independence was achieved on a median of 23 days after EPAG treatment.

Publications are reporting that EPAG is effective in thrombocytopenia that develops following both autologous SCT and allogeneic SCT [19,22]. In the present study, EPAG treatment was used following autologous SCT in 50.6% of the cases and following allogeneic SCT in 49.4% of them. The complete response rate was 79.4% in autologous SCT patients, and 63.9% in the allogeneic SCT group. In the study that

was conducted by Karataş et al., which included 25 patients, a response was achieved in 66.7% of the patient group who underwent allogeneic SCT, and in 50% of the patients who underwent autologous SCT [23]. Yuan et al. found that the EPAG response rate was 62% in 13 thrombocytopenic patients who underwent allogeneic SCT [24]. In their study, which included a total of 21 patients, 15 allogeneic SCTs and 6 autologous SCTs, who were diagnosed with PIT and SFPR following transplantation, treatment was initiated at doses of 25–150 mg on the median day 91, and the ORR was found to be 75% [21]. In the study of Kırcalı et al., a total of 39 patients were included (30 allogeneic SCT and 9 autologous SCT). EPAG treatment was initiated at a dose of 25–150 mg on the median 145th day following the transplantation and was used for a median of 82 days, and an 84.6% response was achieved [25]. In a recent meta-analysis, the response rate in the use of EPAG following HSCT was reported as 70–80% [2]. The response rates in our patient group are similar to the literature.

In a previous review that evaluated post-transplant EPAG treatment with a total of 122 patients from 8 case series and 5 case reports, treatment was initiated for 79 patients who had a diagnosis of PIT and for 43 patients who had a diagnosis of SFPR. Transfusion independence was achieved in 85 of a total of 122 patients, the platelet count was above 50×10^9/L, and the overall response rate (ORR) was determined as 70%. The response rate was 72% in patients diagnosed with PIT (n=56) and 67% in SFPR patients (n=29), which means that it positively affected both groups [2]. Tanaka et al. reported response rates of 60% and 72% in the PIT groups (n=5) and SFPR (n=7), respectively [19]. The CR rate was found to be 73.2% in our study in patients who were initiated with EPAG treatment with a diagnosis of PIT, and it was 68.8% in those who were diagnosed with SFPR, and a statistically significant effect of the indication for initial treatment (PIT or SFPR) could not be demonstrated on EPAG treatment response.

In a retrospective study that was conducted by Fei Yan et al., which included 34 transplant patients with PIT and SFPR, the median response time to EPAG in the SFPR group was found to be shorter when compared to the PIT group (31.5 days vs 7.5 days) [26]. In our study, with EPAG treatment, the median time to Complete Response was found to be 23 days in all patients, and no significant differences were detected in the time to Complete Response between those who were diagnosed with PIT and treatment initiated in the SFPR Group (median 23–34 days). The response was achieved on the median of the 35th day in the study of Güven et al., it was achieved on the median of the 41st day in the study of Karataş et al., it was achieved on the median of the 23rd day in the study of Fei Yan et al., and the response was achieved in the median of the 2nd month in the study of Sabrina et al. Survival was reported to be low in those who did not respond for more than 3 months [16, 27–29].

In a Phase II study, which compared EPAG and placebo in the treatment of prolonged thrombocytopenia following 53 allogeneic SCTs and 7 autologous SCTs, patients who had a platelet count $<20\times109$/L on the 35th day following the transplantation were included [18]. EPAG treatment was given to 42 patients, and a placebo was administered to 18 patients. EPAG was initiated at a dose of 50 mg/day and increased to a maximum of 150 mg for a total of 8 weeks. The secondary endpoint was set as plt$>50\times10^9$/L, and this response was achieved in 9 patients (21.4%) with EPAG treatment. This response rate was quite low when compared to our study. The reason for this was considered to be the inclusion of patients with acute and chronic GvHD, the use of bone marrow as a stem cell source in approximately half of the patients, the limited treatment duration, and especially the pre-treatment bone loss in 80% of the patients, the number of MGK in the marrow was insufficient which was shown to be an independent risk factor in our study regarding the treatment response.

In the study that was conducted by Güven ZT et al., which included 48 patients, a response was achieved in 77% of the patients who had sufficient bone marrow NSC counts, and the response was 23% in the group with decreased bone marrow MGK count, and a significant effect was detected regarding the presence of sufficient MGK in the bone marrow on the response [29]. Also, Tanaka et al. found that the success rate of EPAG treatment was significantly higher in the group with sufficient bone marrow MGK count [19]. The CR rate was found to be higher in patients with bone marrow-sufficient MGK in the study of Fu et al. [7] and the study of Fei Yan et al. [26]. In our study, the rate of achieving CR was found to be significantly higher in patients with sufficient MGK numbers. Also, multivariate analysis showed that sufficient MGK count in the bone marrow was an independent factor for determining EPAG treatment response.

The other TPO analog, Romiplostim, has also been evaluated in patients with post-transplant PIT or SFPR. As a result of the review in which 12 case series or reports were examined, Romiplostim treatment (at a dose of 1–10 μg/kg) was initiated in 49 patients with PIT or SFPR. The overall response rate (defined as plt$>50\times109$/L) was found to be 82%. Response occurred on a median of 31.5 days. While the ORR was found to be 59% in patients treated with a diagnosis of PIT, the ORR was found to be 94% in patients treated with a diagnosis of SFPR. There is no study comparing eltrombopag and romiplostim in terms of efficacy and safety in post-transplant thrombocytopenia [2].

Although the initial dose of EPAG was standardized in patients with Immune Thrombocytopenia (ITP) and Aplastic Anemia, this dose has not yet been optimized in thrombocytopenia following HSCT. It was shown in previous studies that Caucasians require higher doses of EPAG than East Asians [30]. The maximum EPAG dose was determined to be 12.5–50 mg in the study conducted by Tanaka et al. including 12 patients [19]. The maximum daily dose was found to be 25–75 mg by Tang et al. in China [28]. The maximum daily dose was found to be 25–75 mg in 8 Korean patients [30] and 50–150 mg per day in the Spanish series by Rivera et al. [31]. The initial dose was determined to be 12.5–150 mg in another analysis that included a total of 122 patients from 8 case series. In our study, patients were recruited from different centers, and the treatment dose selection was determined according to the preference of the physician, the patient's clinical condition, and treatment protocols, and the initial dose of EPAG was applied as 50–150 mg. No significant differences were detected between the rates of complete response with the EPAG initial dose (50–150 mg) or the maximum EPAG dose (50–150 mg). According to the results of our study, it can be recommended to start EPAG treatment at a dose of 50 mg in post-transplant PIT or SFPR patients because the initial dose does not change the Complete Response rates. However, large-scale prospective data are needed to determine the effective and safe initial dose for patients.

In the present study, following a median follow-up period of 14 months after the transplantation, the median OS was not reached in those who responded completely to EPAG treatment, and the median OS was found to be 16 months in those who did not respond. A significant effect of EPAG response was detected on overall survival. In a previous study conducted by Yamazaki et al., OS was found to be 75% in those who responded to EPAG and 27.3% in those who did not, and the difference was statistically significant (p=0.002) [6]. In the study of Karataş et al., OS was statistically and significantly longer in both autologous and allogeneic transplanted patients who responded to EPAG treatment than those who did not respond [23]. In the study that was conducted by Giammarco et al., a significant survival advantage was detected in patients who achieved a Complete Response following allogeneic SCT (1-year OS 89% vs 20%) [27]. Post-HSCT thrombocytopenia is an important, common, and multifactorial complication, increasing transplant-related mortality [2,3,32,33], and is a poor prognostic indicator in terms of morbidity and TRM [2].

Our study also showed that overall survival in patients who responded to EPAG treatment was significantly longer than in those who did not respond to treatment. In the previous studies, survival was powerfully influenced by the 100-day platelet count [3]: 4-year overall survival was 19% for patients with a platelet count $<30\times10^9$/L; and 72% for those with a platelet count $>50\times10^9$/L. According to our study, it was thought that especially in patients with EPAG response and those with a sufficient number of megakaryocytes in the bone marrow this

might be a probable factor that could affect the overall survival.

When compared to the studies in the literature conducted on the use of EPAG following transplantation, the present study is among the multicenter studies with the highest number of patients. The study had a retrospective design without a control group. Also, it was heterogeneous in terms of primary diseases, indications for initial EPAG treatment, and subgroups. More prospective randomized controlled studies are needed to determine the ideal EPAG dose and duration and the optimal time to start the treatment in this respect.

6. Conclusion

In the present study, EPAG treatment was found to be effective and safe in thrombocytopenia developing following hematopoietic stem cell transplantations. A sufficient number of MGKs in the bone marrow before the treatment was defined as an independent risk factor for predicting treatment response, and a total survival advantage was obtained in patients who responded to EPAG treatment. No differences were detected in the response rates between the initial doses of 50 mg/day and 150 mg/day, and it was found that starting patients with a dose of 50 mg/day in post-transplant thrombocytopenia may be appropriate in terms of cost, effectiveness, and toxicity. According to the results of our study, in patients who were diagnosed with PIT or SFPR after autologous/allogeneic transplantation, after performing a bone marrow biopsy for the assessment of Megakaryocyte count, Eltrombopag should be initiated at a dose of 50 mg/day, with a target platelet count of 50×10^9/L for 7 consecutive days without transfusion support. Depending on the patient's response to treatment, dose titration may be recommended every 7–14 days and increased to a maximum of 150 mg. In the maintenance phase, the optimal duration of treatment is still unclear but it may be recommended to continue with the lowest dose that will provide the target platelet count.

Randomized controlled prospective studies are needed to determine the roles of EPAG Treatment in patients with post-transplant PIT and SFPR.

Ethical approval

Ethical approval was waived by the local Ethics Committee of the University of Health Sciences Gulhane Faculty of Medicine with its approval dated 14.03.2023; and numbered 46418926, in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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CRediT authorship contribution statement

Leylagul Kaynar: Supervision, Investigation, Data curation, Conceptualization. **Ilknur Nizam Ozen:** Data curation, Conceptualization. **Simten Dagdas:** Investigation, Conceptualization. **Neslihan Andic:** Supervision, Data curation, Conceptualization. **Volkan Karakus:** Investigation, Data curation, Conceptualization. **Fatih Yaman:** Methodology, Data curation. **Gulsum Ozet:** Supervision, Investigation, Data curation, Conceptualization. **Sureyya Yigit Kaya:** Investigation, Data curation. **Filiz Yavasoglu:** Data curation, Conceptualization. **Ebru Kilic Gunes:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Omur Gokmen Sevindik:** Supervision, Data curation, Conceptualization. **Melda Comert:** Investigation, Data curation. **Kurtulus Vural:** Data curation. **Meltem Ayli:** Supervision, Methodology, Investigation, Data curation, Conceptualization. **Mustafa Kemal Yeniay:** Methodology, Data curation.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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