

Eltrombopag for Treatment of Thrombocytopenia Following Hematopoietic Stem Cell Transplantation

Hematopoetik Kök Hücre Nakli Sonrası Trombositopeni Tedavisinde Eltrombopag Kullanımı

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Abstract

Objective: This study aimed to evaluate the efficacy and safety of eltrombopag (ELT) in the treatment of thrombocytopenia following hematopoietic stem cell transplantation (HSCT).

Materials and Methods: Forty-eight patients treated with ELT for thrombocytopenia after allogeneic or autologous transplantation at the Erciyes University Bone Marrow Transplantation Center between July 2017 and July 2021 were evaluated retrospectively.

Results: Forty-eight HSCT recipients were included in this study. Thirty (62.5%) patients were evaluated as having experienced delayed platelet recovery (DPR) and 18 (37.5%) patients as having experienced secondary failure of platelet recovery (SFPR). The median platelet count before ELT treatment was $13 \times 10^9/L$ (range: $3-20 \times 10^9/L$). Twenty-three patients responded to treatment and the cumulative incidence of successful platelet recovery was 48%. Patients with both DPR and SFPR responded, but patients with DPR had a higher response rate (50% vs. 44%). The median platelet count of the 23 responding patients was $12 \times 10^9/L$ ($5-19 \times 10^9/L$) before treatment and $68 \times 10^9/L$ ($52-266 \times 10^9/L$) after treatment ($p < 0.0001$). While the number of bone marrow megakaryocytes before treatment was adequate in 22 (46%) cases, it was decreased in 26 (54%) cases. Patients with adequate bone marrow megakaryocytes had a better response rate than those without (77% vs. 23%, $p < 0.0001$). The group with adequate megakaryocytes responded to treatment at a median of 33 days (range: 9-174 days). Patients with decreased megakaryocytes responded at a median of 55 days (30-164 days) ($p = 0.002$). No drug-related side effects were observed in any patients.

Conclusion: This real-life experience demonstrates that ELT is an effective and safe treatment option for thrombocytopenia after HSCT. The adequacy of bone marrow megakaryocytes before ELT treatment was an important factor affecting response to treatment.

Keywords: Eltrombopag, Thrombocytopenia, Hematopoietic stem cell transplantation, Platelet recovery

Öz

Amaç: Transplantasyon sonrası trombositopeni tedavisinde eltrombopagin (ELT) etkinlik ve güvenliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Erciyes Üniversitesi Kemik İliği Nakil Merkezi'nde Temmuz 2017-Temmuz 2021 tarihleri arasında allojenik veya otolog transplantasyon sonrası trombositopeni nedeniyle ELT ile tedavi edilen 48 hasta retrospektif olarak değerlendirildi.

Bulgular: Bu çalışmaya 48 hematopoietik kök hücre nakli (HKHN) alıcısı dahil edildi. Otuz (%62,5) hasta gecikmiş trombosit iyileşmesi (DPR) ve 18 (%37,5) hasta ikincil trombosit iyileşme başarısızlığı (SFPR) olarak değerlendirildi. ELT tedavisinden önce medyan trombosit sayısı $13 \times 10^9/L$ (aralık, $3-20 \times 10^9/L$) idi. Yirmi üç hasta tedaviye yanıt verdi ve başarılı trombosit iyileşmesinin kümülatif insidansı %48 idi. Hem DPR hem de SFPR'li hastalar yanıt verdi, ancak DPR'li hastalarda yanıt oranı daha yüksekti (%50'ye karşı %44). Yanıt veren 23 hastanın medyan trombosit sayısı tedaviden önce ve sonra $12 (5-19) \times 10^9/L$ ve $68 (52-266) \times 10^9/L$ idi ($p < 0,0001$). Tedavi öncesi kemik iliği megakaryosit sayısı 22 (%46) hastada yeterli iken 26 (%54) hastada azalmıştı. Yeterli kemik iliği megakaryositleri olan hastalar, azalmış olanlara göre daha iyi bir yanıt oranına sahipti (%77'ye karşı %23, $p < 0,0001$). Yeterli megakaryositleri olan grup, tedaviye medyan 33 (aralık, 9-174) günde yanıt verdi. Megakaryositleri azalmış hastalar, ortalama 55 (aralık, 30-164) gün yanıt verdi ($p = 0,002$). Hiçbir hastada ilaca bağlı yan etki gözlenmedi.

Sonuç: Bu gerçek yaşam deneyimi, ELT'nin HKHN sonrası trombositopeni için etkili ve güvenli bir tedavi seçeneği olduğunu göstermektedir. ELT tedavisi öncesi kemik iliği megakaryositlerinin yeterliliği tedaviye yanıtı etkileyen önemli bir faktördü.

Anahtar Sözcükler: Eltrombopag, Trombositopeni, Hematopoietik kök hücre nakli, Trombosit iyileşmesi



Introduction

Hematopoietic stem cell transplantation (HSCT) is an effective treatment method used in the treatment of many malignant and non-malignant diseases today. After transplantation, engraftment is expected within weeks and blood parameters are anticipated to return to normal levels; however, some patients may suffer from cytopenia. The most frequently observed cytopenia following allogeneic and autologous transplantation is thrombocytopenia and it can be seen in up to 40% of patients after transplantation [1,2,3]. Many underlying causes including infections, side effects of drugs used, disease recurrence, alloantibodies, insufficient graft function, and microangiopathy can be identified [3,4,5]. Persistent thrombocytopenia after HSCT is an important cause of mortality and morbidity [1,2,6]. Thrombocytopenia may be severe in some patients and may continue for a long time. However, there is no standard approach for the treatment of these patients. Although it is only a temporary fix, transfusion support is used often to treat bleeding in such cases.

Eltrombopag (ELT) and romiplostim are thrombopoietin receptor agonists (rhTPO) that increase platelet production and are used in the treatment of idiopathic (immune) thrombocytopenic purpura in adults and children [7,8,9,10]. In the literature, it has been reported that ELT provides convenience with oral use, and it is also used in the treatment of aplastic anemia, low-risk myelodysplastic syndrome, and chemotherapy-associated thrombocytopenia [11,12].

There are various reports on the use of ELT in the treatment of post-transplant thrombocytopenia [13,14,15,16]. In this study, we aim to share our experiences with ELT treatment in 48 patients with delayed platelet recovery (DPR) or secondary failure of platelet recovery (SFPR) following HSCT.

Materials and Methods

Patients

The medical records of 634 patients who underwent HSCT at the Erciyes University Bone Marrow Transplantation Center between July 2017 and July 2021 were reviewed retrospectively. We identified 48 patients treated with ELT for thrombocytopenia after allogeneic or autologous transplantation. Successful neutrophil engraftment was achieved in all cases. Patients were classified into two groups as having experienced DPR or SFPR. Patients with primary graft failure were not included in the study and all patients were in remission. Signed written consent forms were obtained from all participating patients and the study was approved by the Ethics Committee of Erciyes University (2020/156).

Definitions

Neutrophil engraftment was defined as an absolute neutrophil count of $\geq 0.5 \times 10^9/L$ for 2 consecutive days. Platelet engraftment

was defined as a platelet count of $\geq 20 \times 10^9/L$ without transfusion for 3 consecutive days. DPR was defined as the absence of platelet engraftment on the 35th day after transplantation despite the occurrence of neutrophil engraftment [17]. SFPR was defined as a platelet count of $\leq 20 \times 10^9/L$ after platelet engraftment for more than 7 days [2,18]. Patients were excluded if they had secondary causes of thrombocytopenia such as drug-induced thrombocytopenia or viral infection-associated thrombocytopenia. Liver function test results were normal for all patients.

Bone marrow aspiration and biopsy were performed to evaluate bone marrow cellularity just before the ELT treatment was started. Megakaryocyte count was evaluated by bone marrow aspirate smear and a count of $\geq 8/mm^2$ was considered adequate [13]. Platelet recovery after ELT was defined as a platelet count above $50 \times 10^9/L$ for at least 7 days without the need for transfusion.

Eltrombopag Treatment

While the initial dose of ELT was typically 25 mg or 50 mg, the dose was increased by 25 mg per week based on the response status and the maximum dose reached was 150 mg. The drug doses given to the patients were adjusted according to their weekly blood counts. When the platelet count exceeded $100 \times 10^9/L$, the dose was reduced by 25 mg weekly. Platelet transfusions were performed according to institutional guidelines. Side effects were graded according to Version 4.0 of the National Cancer Institute Common Toxicity Criteria.

The efficacy of the treatment was determined by platelet count. The primary outcome was a platelet count of $\geq 50 \times 10^9/L$ for 7 consecutive days without transfusion. Secondary outcomes were the effect of bone marrow megakaryocyte count before ELT treatment on platelet recovery and treatment-related side effects.

Statistical Analysis

Continuous data conforming to normal distribution were expressed as mean \pm standard deviation, while continuous data not conforming to normal distribution were expressed as median and minimum-maximum and categorical data were expressed as percentages (%). Categorical data were compared using chi-square tests. The cumulative incidence of platelet recovery was analyzed using Cox regression. Days without transfusion from initiation of ELT to a platelet count of $> 50 \times 10^9/L$ were compared between groups using the Wald chi-square test. Data were analyzed with IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA). Values of $p < 0.05$ were considered significant.

Results

The clinical characteristics of the patients are summarized in Table 1. Forty-eight HSCT recipients were included in this study.

Thirty (62.5%) patients were evaluated as having experienced DPR and 18 (37.5%) patients as having experienced SFPR. There were 34 male patients, and the median age was 53 years (range: 21-69 years). Allogeneic stem cell transplantation was performed for 28 (58%) patients and 18 of those patients were diagnosed with acute myeloid leukemia. Myeloablative conditioning regimens were used for all patients undergoing allogeneic transplantation. Twenty-four patients of the allogeneic transplantation group had a sibling HLA-matched donor, while 4 patients had a haploidentical donor. Peripheral blood was used as a stem cell source in all cases. Cyclosporine and methotrexate were used most frequently for graft-versus-host disease (GVHD) prophylaxis, while post-transplant cyclophosphamide was preferred in cases of haploidentical transplantations. Autologous stem cell transplantation was performed for 20 (42%) patients and 12 of those patients were diagnosed with non-Hodgkin lymphoma. Neutrophil engraftment occurred in all patients at a median of 17 days (range: 8-24 days). Grade II-IV GVHD developed in 6 (12.5%) patients before ELT treatment. None of the patients had a previous history of using rhTPO. Bone marrow biopsy was performed for all patients before ELT treatment.

Outcomes of ELT treatment are listed in Table 2. ELT was started at a median of 57 days after HSCT (range: 36-513 days). The median platelet count before ELT treatment was $13 \times 10^9/L$ (range: $3-20 \times 10^9/L$). The starting dose of ELT was 50 mg per day for most patients, with a maximum dose of 150 mg per day.

Twenty-three patients responded to treatment and the cumulative incidence of successful platelet recovery was 48% (Figure 1). The cumulative incidences of platelet recovery

were 38% among patients with DPR and 50% among those with SFPR for allogeneic transplantation, respectively. The cumulative incidences of platelet recovery were 64% among patients with DPR and 33% among those with SFPR for autologous transplantation. Response rates were 55% and 43% among patients who underwent autologous and allogeneic transplantation, respectively. Patients with both DPR and SFPR responded, but patients with DPR had a higher response rate (50% vs. 44%). The median time to platelet recovery was 35 days (range: 9-174 days) and these patients had received ELT for a median of 77 days (15-293 days). No recurrence of thrombocytopenia was observed in any of these cases while ELT was reduced. The median platelet count of the 23 responding

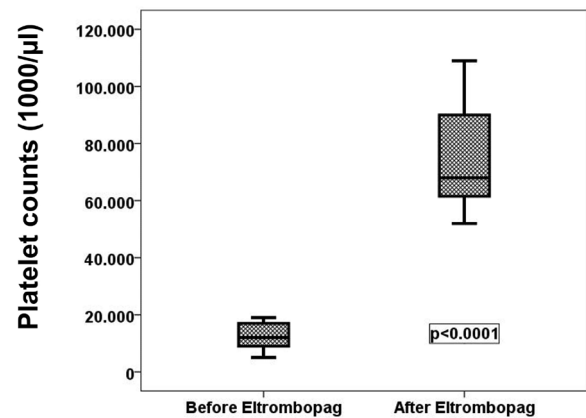


Figure 1. Median platelet count before and after eltrombopag treatment. The analysis included 23 responding patients ($p < 0.0001$).

Characteristic	Type of thrombocytopenia, n (%)		All, n (%)
	DPR (n=30)	SFPR (n=18)	
Age, years, median (range)	54.5 (21-69)	50.5 (31-63)	53 (21-69)
Sex			
Male	23 (77)	11 (61)	34 (71)
Female	7 (23)	7 (39)	14 (29)
Type of HSCT			
Allo-HSCT	16 (53)	12 (67)	28 (58)
Auto-HSCT	14 (47)	6 (33)	20 (42)
Disease			
AML	9 (30)	9 (50)	18 (37.5)
ALL	5 (17)	2 (11)	7 (14.5)
MM	6 (20)	2 (11)	8 (17)
HL	3 (10)	-	3 (6)
NHL	7 (23)	5 (28)	12 (25)
Neutrophil engraftment, day, median (range)	17 (10-24)	16 (8-23)	17 (8-24)
Grade II-IV GVHD	2 (7)	4 (22)	6 (12.5)

DPR: Delayed platelet recovery; SFPR: secondary failure of platelet recovery; HSCT: hematopoietic stem cell transplantation; Allo-HSCT: allogeneic HSCT; Auto-HSCT: autologous HSCT; AML: acute myeloblastic leukemia; ALL: acute lymphoblastic leukemia; MM: multiple myeloma; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; GVHD: graft-versus-host disease.

patients was $12 \times 10^9/L$ (range: $5-19 \times 10^9/L$) before treatment and $68 \times 10^9/L$ ($52-266 \times 10^9/L$) after treatment ($p < 0.0001$; Figure 2).

Among the 25 non-responders, ELT was discontinued in 11 cases due to death. It was continued for a median of 77 days among non-responder patients (range: 10-232 days).

While the number of bone marrow megakaryocytes before treatment was adequate in 22 (46%) cases, it was decreased in 26 (54%) cases. Patients with adequate bone marrow megakaryocytes had a better response rate than those without (77% vs. 23%). This finding was significant ($p < 0.0001$). The group with adequate megakaryocytes responded to treatment

at a median of 33 days (range: 9-174 days), while patients with decreased megakaryocytes responded at a median of 55 days (30-164 days) ($p = 0.002$; Table 3).

The treatment response was permanent in all patients and no platelet count below $50 \times 10^9/L$ was observed even after ELT was discontinued. The median follow-up time after discontinuation of ELT treatment was calculated as 365 days (range: 61-921 days). No drug-related side effects were observed in any patients. The patients were fully compliant with treatment and none of the patients had to discontinue the drug due to side effects.

Discussion

In this study, we have presented our single-center experience with 48 patients treated with ELT for primary and secondary platelet failure following HSCT. The cumulative incidence of platelet recovery after treatment with ELT was 48%. These patients, who needed continuous platelet transfusion, became transfusion-free in a median of 35 days. Furthermore, after discontinuation of ELT, platelet counts were maintained permanently in all responding patients.

The use of ELT is effective in thrombocytopenia that develops after autologous and allogeneic transplantation [13,19,20]. In our study, response to ELT was observed in both the autologous transplant and allogeneic transplant groups (55% vs. 43%). In

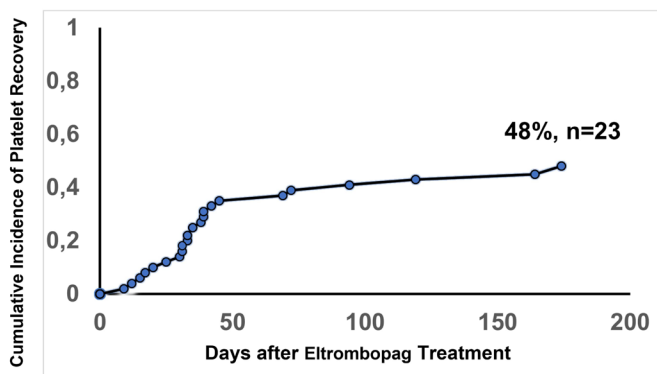


Figure 2. Cumulative incidence of platelet recovery (48%).

Table 2. Outcomes of eltrombopag treatment.	
Characteristics	Outcomes
Duration from transplantation to eltrombopag treatment, median (range), days	57 (36-513)
Starting dose of eltrombopag	
25 mg daily, n (%)	6 (12.5)
50 mg daily, n (%)	42 (87.5)
Maximum dose of eltrombopag	
75 mg daily, n (%)	3 (6)
100 mg daily, n (%)	17 (36)
125 mg daily, n (%)	4 (8)
150 mg daily, n (%)	24 (50)

Table 3. Bone marrow megakaryocytes of patients.			
Achievement of platelet response			
Yes, n (%)		23 (48)	
No, n (%)		25 (52)	
Days from starting eltrombopag to platelet response, median (range), days		35 (9-174)	
Duration of treatment among patients with platelet response, median (range), days		77 (15-293)	
Response	Adequate megakaryocytes (n=22)	Decreased megakaryocytes (n=26)	p
Positive response, n (%)	17 (77)	6 (23)	<0.0001
No response, n (%)	5 (23)	20 (77)	
Days from starting eltrombopag to response, median (range), days	33 (9-174)	55 (30-164)	0.002

their study, Yuan et al. [21] used ELT therapy for 13 patients with primary and secondary platelet failure. Response was observed in 50% of the patients with primary failure and 71% of those with secondary failure. In another study involving two groups of patients who underwent autologous and allogeneic transplantation, the response to ELT after transplantation was 100% and 61%, respectively. Hence, it was effective in cases of both primary and secondary platelet failure [22]. In our study, it was similarly observed that ELT was effective in both primary and secondary platelet failure. There was more platelet recovery in the group with primary failure (50% vs. 44%), but that finding was not statistically significant.

Tanaka et al. [13] administered ELT for the treatment of thrombocytopenia after allogeneic transplantation. Both groups of patients with prolonged thrombocytopenia and platelet recovery failure had positive results. Platelet recovery was in line with the amount of bone marrow megakaryocytes before treatment [13]. Similarly, patients with adequate megakaryocyte counts prior to initiation of ELT therapy had a higher platelet recovery rate than patients with decreased megakaryocytes in the present study (77% vs. 23%, $p < 0.0001$). Based on these results, it can be thought that the number of bone marrow megakaryocytes before treatment is a determining factor in the response to rhTPO agonists. Patients with adequate megakaryocytes responded to treatment in a shorter time than patients with inadequate megakaryocytes (33 days vs. 55 days, $p = 0.002$). A normal megakaryocyte count allows the platelet count to improve faster. In a study involving 13 patients, ELT was used for thrombocytopenia following allogeneic transplantation. The overall response rate was 62%. When evaluated in terms of bone marrow reserve, the ELT response was similar and sufficient in the group with lower megakaryocyte counts [21]. It remains to be determined whether higher doses of rhTPO agonists improve platelet recovery in patients with reduced megakaryocyte counts. We used a maximum dose of 150 mg of ELT for our patients.

Study Limitations

Our study has several limitations; it was a retrospective study and it included a small number of patients. In addition, the patient group was heterogeneous. Although we investigated other causes of thrombocytopenia for all patients, it was not always possible to exclude them completely. However, we think that our study nevertheless supports the safety and efficacy of ELT in the treatment of thrombocytopenia following HSCT.

Conclusion

The results that we have presented here demonstrate that ELT is an effective and safe treatment option for thrombocytopenia following HSCT. However, prospective randomized studies are

needed to demonstrate the efficacy and optimal dose of ELT in the treatment of post-transplant thrombocytopenia. Patients with normal megakaryocyte counts responded better and faster to ELT. Adequacy of bone marrow megakaryocytes before ELT treatment was an important factor affecting treatment response.

Ethics

Ethics Committee Approval: Signed written consent forms were obtained from all participating patients and the study was approved by the Ethics Committee of Erciyes University (2020/156).

Informed Consent: Signed written consent forms were obtained.

Authorship Contributions

Surgical and Medical Practices: Z.T.G., S.Ç., B.E., M.Ç., A.Ü., L.K.; Concept: Z.T.G., L.K., Design: Z.T.G., L.K.; Data Collection or Processing: Z.T.G., S.Ç., B.E.; Analysis or Interpretation: Z.T.G., S.Ç., B.E., M.Ç.; Literature Search: Z.T.G., S.Ç., B.E., M.Ç., A.Ü., L.K.; Writing: Z.T.G., S.Ç.

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

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