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Eltrombopag for the Treatment of Poor Graft Function Following Haematopoietic Cell Transplantation: Real-Life Data

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Background: Eltrombopag has an off-label indication for haematopoietic cell transplantation in patients experiencing delayed thrombocyte recovery and/or thrombocytopaenia.

Aims: To present our centre's experience of using this agent not only for post- haematopoietic cell transplantation thrombocytopaenia but also for poor graft functioning in the post-haematopoietic cell transplantation setting.

Study Design: Retrospective cross-sectional study.

Methods: Thirty-nine patients who had persistent cytopaenia following haematopoietic cell transplantation and treated with eltrombopag at our centre between October 2011 and December 2021 were retrospectively identified. During this period, 9 (23.1%) and 30 (76.9%) patients who underwent allogeneic transplantations, respectively, received eltrombopag.

Results: The female-to-male ratio was 12:27, and the median transplant age was 49 (18-70) years. Eight (20.5%) patients had isolated thrombocytopaenia, 19 (49.4%) had bi-lineage cytopaenia and 12 (30.1%) had pancytopaenia. Patients received a median of 50 mg/day (25-150 mg/day) of eltrombopagfor a median duration of 82 (24-386) days. Nine (23.1%) patients had autologous haematopoietic cell transplantation, and 30 (76.9%) had allogeneic haematopoietic cell transplantation (14 unrelated, 9 sibling and 7 haploidentical). The median donor age was 32 (20-67) years. The median follow-up was 16.4 (1.8-84.3) months. The median pre-treatment platelet count was $11x10^9$/l (1-23), which increased to $41x10^9$/l (6-150). The median platelet count increment was $29.5x10^9$/l ($p = 0.001$). The pre-treatment median neutrophil count was $1.19x10^9$/l (0.39-5.1), which increased to 2.35 $x10^9$/l (0.1-5.33) ($p = 0.05$), and the pre-treatment median haemoglobin was 8.3 (6.2-14) g/dl, which increased to 10 (6.2-14) g/dl ($p = 0.001$) with eltrombopag. No eltrombopag-related hepatotoxicity occurred; however, 1 (2.6%) patient failed to continue treatment because of two consecutive episodes of deep venous thrombosis. Six (15.4%) patients were unresponsive to eltrombopag and dependent on blood product transfusions. After a median time of 82 days, 61.5% of the patients discontinued eltrombopag successfully.

Conclusion: The results confirmed that eltrombopag could provide a rapid, sustained response in patients with poor graft functioning after haematopoietic cell transplantation. This finding is essential given the high rate of non-relapse mortality caused by poor graft functioning after haematopoietic cell transplantation.

INTRODUCTION

Haematopoietic cell transplantation (HCT) is a well-proven treatment for various haematological diseases, and it is continuously evolving along with improving cellular technologies, conditioning regimens and preventive/supportive care. Despite developments in the HCT era, poor graft function (PoGF) is still a multifactorial complication after allo-HCT, occurring between 5% and 20% of the patients.[1,2] Prolonged damage to the stem cell niche in the microenvironment of the bone marrow and failure to restore the normal haematopoietic stem and progenitor cells (HSPCs) in allografts with donor chimerism may result in engraftment failure. Currently, efficient and reliable treatment options are limited for this life-threatening HCT complication.

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Persistent thrombocytopaenia following HCT is not rare and may cause fatal bleeding. Predictive factors facilitating thrombocytopaenia could be graft versus host disease (GvHD), infections (cytomegalovirus, etc.), immune-mediated factors, drug-related factors (ganciclovir, valganciclovir, etc.), disease relapse and thrombotic microangiopathy.[3,4] Post-transplant thrombocytopaenia could be classified either as prolonged isolated thrombocytopaenia (PIT) or secondary failure of platelet recovery (SFPR). PIT is defined as adequate engraftment of all peripheral blood lineages, except platelets, being under $20x10^9$/l, or dependence on thrombocyte suspension transfusions for over 60 days post-HCT.[5] On the contrary, SFPR is defined as losing independence on platelet transfusions after allo-HCT for seven consecutive days with the number of thrombocytes under $20x10^9$/l from over $50x10^9$/l.[6] PIT and SFPR were reported to occur in 12%-20% and 20%-40%, respectively.[5,6]

Recently, the effect of thrombopoietin agonists [romidepsin and eltrombopag (EPAG)] has been sought for the self-renewal and maintenance of HSPCs. EPAG is an oral thrombopoietin receptor agonist molecule, and with it, multi-lineages responses were reported in severe aplastic anaemia (SAA), which led to the approval by US Food and Drug Administration.[7,8]

Various reports and studies have included a small number of patients and published the role of EPAG in refractory or prolonged thrombocytopaenia following allo-HCT[9-14] and auto-HCT.[15,16] Based on the results, promising outcomes with significant transfusion independent of platelet recovery were obtained. However, as mentioned above, EPAG restores trilineage haematopoietic cell lines and, thus, may benefit patients with various cytopaenias caused by post-HCT and PoGF.

In this retrospective study, we aimed to summarise our single-centre experience in the use of EPAG for PoGF treatment.

MATERIALS AND METHODS

Patients

A total of 39 patients who had persistent PoGF-induced cytopaenia following HCT and treated with EPAG at our centre between October 2011 and May 2021 were retrospectively identified. PoGF was diagnosed based on the presence of 2 or 3 of the following criteria along with transfusion dependence: post-HCT 1) haemoglobin below 10 g/dl, 2) thrombocyte count below $30x10^9$/l and 3) neutrophil count below $1x10^9$/l.[1]

This retrospective study was approved by the local institutional review board of our centre and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent for EPAG use as an off-label agent. To rule out any haematologic disorders, a bone marrow biopsy was acquired for donors aged > 65 years.

Assessments

The characteristic and clinical data for each patient were retrospectively collected. The effectiveness of EPAG was evaluated by achieving transfusion independence, which required haemoglobin of > 8 g/dl, platelet count of > $20x10^9$/l and neutrophil count of > $1x10^9$/l. Several additional factors that may predict the response to EPAG therapy, including age, sex, diagnosis of the recipient, disease status at the time of the transplant, donor type, conditioning regimen, source of stem cells used and HLA matching, were also assessed.

EPAG was initiated at 12.5 mg dose, which gradually increased in accordance with the results of previous studies. However, six (15.4%) patients were unresponsive to EPAG, even though some of them were prescribed higher doses (up to 150 mg/day) but never reached transfusion independence (Table 3).

Polymerase chain reaction was performed to evaluate donor/recipient chimerism via a panel of highly polymorphic short tandem repeats.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA). The characteristics of the patients were presented as median (range) for continuous variables and frequencies (percentages) for categorical variables. When comparing two groups, Pearson's chi-square test or Fisher's exact test was performed for categorical variables, and the Wilcoxon rank-sum test for the continuous variables; p-values of <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Demographics of the 39 patients with PoGF included in the study are shown in Table 1.

In this study, 30 (76.9%) patients received myeloablative conditioning, whereas 9 (23.1%) received reduced intensity conditioning regimens. To exclude active/relapsed disease or myelofibrosis, bone marrow biopsy was acquired from all patients before EPAG treatment. None of the patients had reticulin fibrosis higher than grade II according to the EUMNET 2007 criteria. At the time of EPAG initiation, none of the patients had evidence of cytomegalovirus reactivation.

All patients who underwent allo-HCT had full split and T-cell donor chimerism on day 28 of HCT, and the engraftment of cells on day 28 was as follows: neutrophil count ≥ $0.5x10^9$/l,

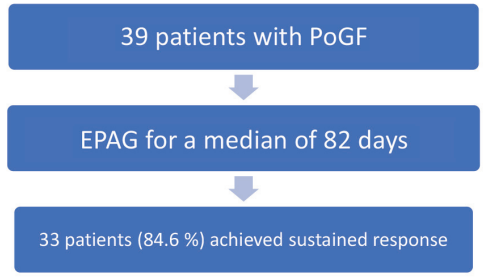

FIG. 1. Eltrombopag (EPAG) response rates in patients with poor graft function (PoGF)

with a median interval from HCT of +12 (9-21) days. Moreover, 16 (41.1%) patients achieved a platelet count ≥ 20x10^9/l, with a median interval from HCT of +13 (range: 8-16) days; however, platelet recovery was not reached in 23 (58.9%) patients before EPAG treatment.

Furthermore, 8 (20.5%) patients had isolated thrombocytopaenia, 19 (49.4%) had bi-lineage cytopaenias, involving thrombocytes and leucocytes or erythrocytes, and 12 (30.1%) had pancytopaenia before EPAG therapy and after day 28 of HCT. EPAG was initiated (median time) on day 145 post-HCT (31-300 days) and continued for a median period of 82 (range: 24-386) days. In addition, 33 (84.6%) patients received EPAG alone, whereas 1 (2.6%) was additionally treated with synthetic erythropoietin and 5 (12.9%) others with granulocyte colony-stimulating factors (G-CSF).

Outcomes and Efficacy

In this study, 33 (84.6%) patients responded to EPAG treatment, and 6 (15.4%) were unresponsive and remained dependent on transfusions. The characteristics of the non-responders are shown on Table 3. Fifteen patients (38.5%) were continuing their EPAG therapy at the time of the data cut-off for the study.

TABLE 1. Patient Characteristics

Age, median (range)	49 (18-65)
Sex (Female/Male)	12/27
HCT indication	
Aplastic anaemia	7 (17.9%)
Acute myeloid leukaemia	10 (25.6%)
Chronic myeloproliferative disease/myelofibrosis	2 (5.1%)
Chronic lymphocytic leukaemia	1 (2.6%)
Hodgkin's lymphoma	1 (2.6%)
Chronic myeloid leukaemia	2 (5.1%)
Acute lymphoblastic lymphoma	5 (12.9%)
Combined immunodeficiency	1 (2.6%)
Blastic plasmacytoid dendritic cell neoplasm	1 (2.6%)
Non-Hodgkin lymphoma	2 (5.1%)
Multiple myeloma	7 (17.9%)
HCT	
Allogeneic-related	9 (23.1%)
Allogeneic-unrelated	14 (35.9%)
Haploidentical	7 (17.9%)
Autologous	9 (23.1%)
Donor age, median (range)	32 (20-67)
Conditioning	
Myeloablative	30 (76.9%)
Reduced intensity	9 (23.1%)
Stem cell source	
Peripheral blood	33 (84.6%)
Bone marrow	6 (15.4%)
CD34 (+) cells infused (x10^6/kg)	5.18-12.53
Platelet count before EPAG, median (range)	11x10^9/l (1-23)
Neutrophil count before EPAG, median (range)	1.35x10^9/l (0.66-5.1)
Haemoglobin before EPAG, median (range)	8.3 g/dl (6.2-14)
Blood marrow megakaryocytes before EPAG	
Decreased/scattered	34 (87.1%)
Normal	5 (12.9%)
Median time between transplant to EPAG initiation (range)	145 (31-300)
Reticulin fibrosis grade before EPAG	
0	27 (69.1%)
1	5 (12.9%)
2	5 (12.9%)
Not evaluated	2 (5.1%)

EPAG, eltrombopag; HCT, haematopoietic cell transplantation.

In patients treated with EPAG, the median thrombocyte count increased from $11x10^9$/l at baseline to $41x10^9$/l. Haemoglobin went up from 8.3 g/dl at baseline to 10.4 g/dL, and the neutrophil count increased from $1.35x10^9$/l to $2.55x10^9$/l (Table 2).

The overall estimated 1-year overall survival rates were 75% for EPAG responders (n = 33) and 66.7% (n = 6) for non-responders ($p = 0.3$), which was not statistically significant. Fifteen patients died within the follow-up period, and mortality causes were GvHD in 4 (26.7%) patients, infections/sepsis in 3 (20%), haemorrhagic cystitis in 2 (13.3%) and disease progression in 6 (40%).

EPAG was easily tolerated by all participants, and in accordance with the Common Terminology Criteria for Adverse Events v5.0[17] criteria, none of the patients had grade 3 or 4 EPAG-related toxicity. The most common side effect of EPAG is an increase in liver function tests; fortunately, no patient on EPAG with or without GvHD developed this abnormality. One patient had to discontinue EPAG because of two consecutive episodes of grade 2 venous thromboembolism and was never reintroduced to EPAG. Five patients (12.9%) experienced an increase in fibrosis (a maximum of grade I) grading in follow-up bone marrow biopsies; however, this did not translate into any clinical consequence that requires discontinuation of the agent. None of the patients experienced a relapse of the underlying disease while on EPAG, suggesting that EPAG did not stimulate possible residual disease and malignant cells in this cohort.

TABLE 2. Patient Outcomes

Parameter	Median (range)	*p*-value
Platelet count increase	$30x10^9$/l (3-141)	***0.001***
Neutrophil increase	$0.9x10^9$/l (0-2.67)	***0.011***
Haemoglobin increase	2.7 g/dl (0-4.1)	***0.001***
Post-treatment platelet count	$41x10^9$/l (1-150)	
Post-treatment neutrophil count	$2.55x10^9$/l (0.34-5.33)	
Post-treatment haemoglobin	10.4 g/dl (8-13)	
Duration of EPAG treatment (days)	82 (24-386)	
Adverse effects		
Venous thromboembolism	1 (2.6%)	
Progress in reticulin fibrosis	5 (12.9%)	
Transfusion independence	33 (84.6%)	

Among the six patients unresponsive to EPAG, one patient developed chronic GvHD with liver and gastrointestinal system (GIS) involvement, three had GIS GvHD and one experienced rapidly progressive disease (MM). One of the patients (atypical CML-haploidentical transplant) had very refractory haemorrhagic cystitis caused by BK virus reactivation. For one of these patients, the EPAG dose was progressively increased up to 150 mg per day, whereas in the other five, the dose was not further increased by the treating physician's choice to avoid thromboembolic complications and toxic hepatitis in these heavily medicated patients.

DISCUSSION

This study reports the single-centre experience on the use of EPAG to rescue PoGF after HCT. In this study, 33 (84.6%) patients obtained response and achieved transfusion independence, and the results showed that EPAG can be safely administered at a dose of 150 mg/day up to 7 months after HCT without any significant increase in grade 3 or 4 adverse events.

The mechanism underlying the efficacy of EPAG in SAA is still unclear and is thought to be caused by the expression of c-Mpl in $CD34^+$ HSPCs, trilineage haematopoiesis stimulation and its immunomodulatory effect by preventing interferon and tumour necrosis factor release.[18] This effect was presumed to stem from driving haematopoietic progenitor cells into haematopoiesis. A phase I/II study on EPAG efficacy in relapsed/refractory SAA (NCT00922883) reported that 44% of the patients showed a haematologic response of one or more cell lineages with single-drug treatment.[18] The efficacy of EPAG in SAA, where the bone marrow is hypocellular, has led to its use in the management of post-HCT cytopaenias. Persistent cytopaenias after HCT should be related to reduced bone marrow cellularity and complete donor chimerism without evidence of relapsed disease. The largest data up to now on EPAG use in 48 patients with PoGF was from the study by Giammarco et al.,[19] where EPAG (50-150 mg) was used for a median of 120 days and showed an overall response of 75% and complete resolution of cell counts in 24 patients. This multicentre study included PIT as their inclusion criteria for PoGF. In our cohort, EPAG was used for the treatment of PoGF, and we obtained increases in not only thrombocyte count but also haemoglobin level (2.7 g/dl) and neutrophil count ($0.9x10^9$/l). Most of these patients were not on G-CSF treatment, and nutritional anaemia was also ruled out.

TABLE 3. Characteristics of the Non-responders

	Patient age	Donor age	HCT indication	HCT type	Maximum dose	Treatment duration	GvHD development
1	32	30	AA	Matched unrelated	25 mg	264 days	GIS
2	57	-	MM	Autologous	25 mg	237 days	-
3	55	26	CML	Haploidentical	100 mg	60 days	GIS
4	56	33	AML	Haploidentical	150 mg	266 days	GIS, liver
5	34	37	AML	Matched related	75 mg	119 days	-
6	46	41	Ph(+) B- ALL	Matched unrelated	125 mg	100 days	GIS

AA, aplastic anaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; GIS, gastrointestinal system; GvHD, graft versus host disease; MM, multiple myeloma; Ph(+) B- ALL, Philadelphia chromosome positive B- acute lymphoblastic leukaemia

Yamazaki et al. reported that PIT was associated both with thrombocyte production impairment and increased turnover of platelets,[9] whereas Zhang et al.[10] demonstrated a significant reduction in ploidy and megakaryocyte immaturity. EPAG can recruit HPSCs from the quiescent state. The aetiologies responsible for prolonged thrombocytopaenia include primary isolated thrombocytopaenia, most of which relates to engraftment failure and SFPR, in which cytomegalovirus and BK virus reactivation, ganciclovir and valganciclovir treatments or GvHD play roles. Tanaka et al. published their experience of 12 patients with isolated thrombocytopaenia (five PIT and seven SFPR) and showed that 66.7% of the patients became transfusion independent with EPAG (12.5-50 mg). Eight responders who had a median therapy duration of 116 days sustained independency after EPAG withdrawal. The results of our study revealed that EPAG was successfully discontinued in 61.5% (n = 24) of the patients, without losing response to treatment during data cut-off. Ahmed et al. used EPAG up to 150 mg/day for up to 8 weeks for prolonged thrombocytopaenia after stem cell transplantation and concluded in their phase II trial that EPAG achieved a thrombocyte count of 50,000 and higher than those of placebo.[20]

Before choosing the ideal donor for a patient, transplant teams must evaluate donor candidates in many aspects. Post-transplant cytopaenias may result from undiagnosed clonal haematopoiesis of indeterminate potential (CHIPs) engrafted from the donor.[21] As CHIP occurs mainly in older people, the median age of our donor cohort was 32 (20-67) years.

Cellular therapies such as CD34+ selected stem cells, mesenchymal stem cells and second allo-HCT have also been sought for the treatment of PoGF with encouraging response rates.[22-25] Nevertheless, EPAG treatment does not necessitate re-accessing the donor, or an apheresis centre, and this makes it a unique agent in the daily routine practice of clinicians.

In conclusion, our results confirmed that EPAG could provide a sustained response in patients with PoGF after allo- and auto-HCT. This finding is appealing considering the high rate of non-relapse mortality caused by PoGF. However, our study is a retrospective trial and consists of a rather small patient group. In addition, PoGF studies specify diverse cytopaenia thresholds. Although The European Society for Blood and Marrow Transplantation was the first to define PoGF, it did not provide any specific cytopaenia thresholds.[26] In our study, we had to establish cytopaenia cut-offs along with transfusion dependence. Despite conflicts in the definition of PoGF, our data revealed that 8 (88.9%) of all auto-HCT recipients and 24 (80%) of allo-HCT recipients responded to EPAG. Prospective, randomised trials with larger cohorts are warranted to make a precise clinical decision. EPAG is a bone marrow inducing agent; thus, it should be applied with precaution in patients with an increased relapse risk.[27]

Ethics Committee Approval: Ankara University Medical School Ethics Committee/ 2022000036-2022/36.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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