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# Eltrombopag for Treating Thrombocytopenia after Allogeneic Stem Cell Transplantation

Cai Yuan[1], Angela M. Boyd[2], Jan Nelson[2], Rushang D. Patel[3], Juan C. Varela[3], Steven C. Goldstein[3], Sarfraz Ahmad[4], Xiang Zhu[5], Shahram Mori[3,*]

[1] *Department of Hematology and Oncology, University of Florida, Gainesville, Florida*
[2] *Pharmacy Department, Florida Hospital, Orlando, Florida*
[3] *Blood and Marrow Transplant Center, Florida Hospital Cancer Institute, Orlando, Florida*
[4] *Department of Gynecologic Oncology, Florida Hospital Cancer Institute, Orlando, Florida*
[5] *Center for Collaborative Research, Florida Hospital, Orlando, Florida*

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A B S T R A C T

Thrombocytopenia after allogeneic hematopoietic stem cell transplantation (allo-SCT) can pose significant problems in management of patients. Eltrombopag is a small-molecule thrombopoietin receptor agonist that has been approved for use in immune thrombocytopenic purpura and aplastic anemia; but its use after allo-SCT is limited. Between 2014 and 2017, we treated 13 patients with eltrombopag for poor platelet engraftment without evidence of relapse at the time of initiation, including 6 patients with primary platelet engraftment failure and 7 with secondary platelet engraftment failure. Eltrombopag was started at an initial dose of 25 or 50 mg per day, and dose adjustments were made in accordance with the manufacturer's recommendation. The cumulative incidence of platelet recovery to $\geq$50,000/$\mu$L without the need for transfusion for at least 7 days was defined as response. The overall response rate was 62% (n = 8). Of the 6 patients with primary isolated platelet failure, 3 (50%) responded, and of the 7 patients with secondary platelet failure, 5 (71%) responded. The median time to response was 33 days (range, 11 to 68 days). In addition, no significant differences in platelet recovery were noted in patients with adequate and decreased bone marrow megakaryocytic reserve (60% and 67%, respectively). Although eltrombopag was well tolerated, and no patient discontinued treatment because of adverse events, only 3 patients were alive at the end of the observation period, with relapse and graft-versus-host disease accounting for majority of the deaths. This suggested that despite the relatively good overall response rate to eltrombopag, inadequate platelet engraftment is a harbinger of poor outcome in allo-SCT.



## INTRODUCTION

Thrombocytopenia is a common complication after hematopoietic stem cell transplantation (SCT), with a reported incidence of 20% to 40% [1]. It is strongly associated with transplantation-related mortality and overall survival [1–3]. Various risk factors, including impaired graft function, drug toxicity, viral infection, disease relapse, thrombotic microangiopathy, and immune-mediated processes, have been described [4,5]. Currently, there is a lack of effective and reliable treatment for this potentially life-threatening complication. Repeated platelet transfusions, corticosteroids, intravenous immunoglobulin, and rituxan remain the mainstays of treatment [6] and are associated with increased risk of infection, higher costs, and decreased quality of life for patients.

Romiplostim and eltrombopag are thrombopoietin receptor (TPO-R) agonists that stimulate platelet production. Both drugs have been approved by the US Food and Drug Administration for the treatment of idiopathic thrombocytopenia purpura [7,8]. Eltrombopag is an oral nonpeptide agonist that binds to a transmembrane site on TPO-R, resulting in proliferation and differentiation of megakaryocytes (MegKs). Its safety and efficacy also have been reported in thrombocytopenia associated with hepatitis C infection [9] and severe aplastic anemia [10]. Several case reports have been published on the efficacy of sltrombopag for the treatment of thrombocytopenia after SCT [11–13]; however, in the majority of studies, patient numbers were limited and long-term patient outcomes were not reported. We evaluated our single-center experience to assess the safety and efficacy of eltrombopag in 13 consecutive (contemporaneous) allogeneic (allo-) SCT recipients. To the

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* Correspondence and reprint requests: Shahram Mori, MD, PhD, Blood and Marrow Transplant Center, Florida Hospital Cancer Institute, 2415 N. Orange Ave, Suite 601, Orlando, FL 32804
*E-mail address:* Shahram.Mori.MD@flhosp.org (S. Mori).

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best of our knowledge, this report is the largest case series reported to date in the peer-reviewed English literature.

## METHODS

### Patients

Between September 2014 and May 2017, a total of 13 consecutive allo-SCT recipients who developed persistent thrombocytopenia after transplantation and were treated with eltrombopag were identified retrospectively at the Florida Hospital Blood and Marrow Transplant Center. The treatment was stratified for patients who had prolonged primary platelet failure (PPF) or secondary platelet failure (SPF). Primary thrombocytopenia was defined as a requirement for platelet transfusion owing to inadequate platelet recovery ($<20 \times 10^9$/L) for ≥100 days after allo-SCT, and secondary thrombocytopenia was defined as inadequate platelet recovery ($<20 \times 10^9$/L) occurring after the initial engraftment of $>50 \times 10^9$/L without transfusions and in the absence of relapse of the original disease. All patients had normal liver function tests; an abnormal liver function test was defined as a serum aspartate aminotransferase or alanine transaminase level ≥2.5 times the upper limit of normal or a serum bilirubin level >2 mg/dL. This retrospective study was approved by the hospital's Institutional Review Board.

### Endpoints

The primary endpoint was platelet recovery to ≥50,000/mL for 7 consecutive days without the need for transfusion support. Secondary endpoints included adverse events associated with eltrombopag treatment and platelet recovery according to the number of bone marrow MegKs before starting treatment. Adverse events were graded using the National Cancer Institute's Common Toxicity Criteria. Clot sections stained with hematoxylin and eosin were used for the assessment of bone marrow MegKs.

### Eltrombopag Treatment

The initial dose of eltrombopag was either 25 or 50 mg/day at the discretion of the treating physician, and dose adjustments were made in accordance with the manufacturer's recommendations. Platelet transfusion was performed according to institutional guidelines. Clinically stable patients receive transfusions at a platelet count ≤10,000/$\mu$L. Transfusions at higher platelet levels were considered for some patients who had a planned invasive procedure, were receiving anticoagulation treatment, or had clinical bleeding.

### Statistical Analysis

The cumulative incidence of platelet recovery over time was analyzed using Cox regression, with death from any cause before the recovery as the competing risk factor. The days from starting eltrombopag to a platelet count >50,000/$\mu$L without transfusion were compared between the groups using the Wald chi-square test. All $P$ values were 2-tailed, and $P < .05$ was considered statistically significant. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, TX) software.

## RESULTS

### Patient Characteristics

Thirteen allo-SCT recipients with PPF and SPF were evaluated. Patient characteristics are summarized in Table 1. Indications for allogeneic HSCT were acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS) in 9 patients (48%), acute lymphoblastic leukemia in 2 patients (10%), Hodgkin lymphoma in 1 patient (8%), and aplastic anemia in 1 patient (8%). The median patient age was 53 years (range, 36 to 70 years). Six patients received myeloablative conditioning, and 7 patients received reduced-intensity conditioning. Bone marrow aspiration was performed in all patients before the start of eltrombopag treatment to rule out relapse of disease infiltration/fibrosis and viral inclusions. None of the patients treated had any evidence of classic active graft-versus-host disease (GVHD), and evaluation of peripheral blood was negative for cytomegalovirus. The number of MegKs was adequate in 10 patients (52%) and decreased in 9 patients (48%).

Table 2.

### Efficacy of Eltrombopag and Patient Outcomes

Eltrombopag was started at a median of 81 days after allo-SCT (range, 36 to 300 days). The median platelet count for the whole cohort was 18,000/$\mu$L, and the median time to primary endpoint was 33 days. Among the 13 allogeneic recipients, 8 patients (~62%) responded. In the whole cohort, the cumulative incidence of platelet recovery to ≥50,000/$\mu$L after eltrombopag treatment was 66%. Both patients with the PPF and SPF responded (Figure 1), although the response rate was higher in the patients with SPF (68% versus 49% in those with PPF). Three patients in the PPF cohort and 2 patients in the SPF cohort did not respond to eltrombopag.

In addition, both groups with adequate and decreased bone marrow MegK reserves responded (60% and 67%, respectively) although no significant conclusions can be drawn from this owing to the small sample size. At the time of last observation (August 2018), 10 of the 13 allo-SCT recipients (77%) had died; causes of death included leukemia relapse (40%), GVHD (30%), infection (30%), and graft failure (10%).

Eltrombopag was well tolerated, and no patient developed fibrosis, thrombosis, or other abnormalities related to the medication. Transient elevations in liver function tests (LFTs) and bilirubin that did not necessitate discontinuation of treatment were noted in 6 patients in both cohorts.

**Table 1**
Patient Characteristics and Responses

| Characteristic | Value |
|---|---|
| Age, yr, median (range) | 56 (36-70) |
| Sex, n (%) | |
| Male | 8 (61) |
| Female | 5 (39) |
| Disease, n (%) | |
| AML/MDS | 9 (69) |
| Acute lymphoblastic leukemia | 2 (15) |
| Hodgkin lymphoma | 1 (8) |
| Aplastic anemia | 1 (8) |
| Conditioning regimen, n (%) | |
| Allogenic | 13 (74) |
| Myeloablative | 6 (46) |
| Reduced intensity | 7 (54) |
| Starting platelet count $\times 10^9$/L, median (range) | 18 (1-33) |
| Initial bone marrow MegK, n (%) | |
| Adequate | 10 (77%) |
| Decreased | 3 (23%) |
| Time from SCT to treatment, d, median (range) | 81 (36-300) |
| Time to response, d, median (range) | 33 (11-68) |

## DISCUSSION

We report our single-center post-transplantation experience of 13 patients who received eltrombopag treatment for primary and secondary thrombocytopenia after allo-SCT. The cumulative incidence of platelet recovery to ≥50,000/$\mu$L was 68% after eltrombopag treatment. Response was seen in patients with primary thrombocytopenia and those with secondary thrombocytopenia alike. Eltrombopag improved platelet counts in both groups with adequate or low MegK reserves. Eltrombopag was well tolerated, and no patient experienced bone marrow fibrosis or severe adverse effects.

**Table 2**
Eltrombopag Recipients' Responses Based on Bone Marrow MegK Reserve

| Response | Adequate MegK (N = 10) | Inadequate MegK (N = 3) |
|---|---|---|
| Positive, n (%) | 6 (60) | 2 (67) |
| None, n (%) | 4 (40) | 1 (33) |

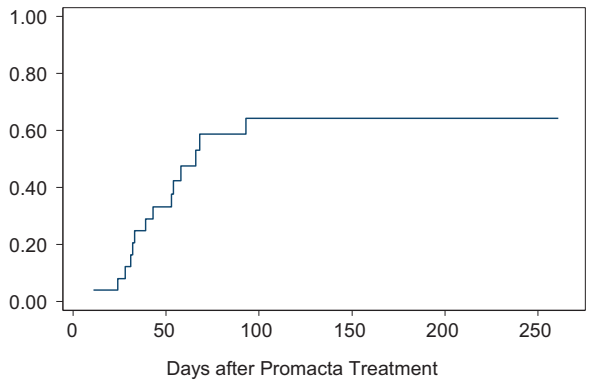


**Figure 1.** Cumulative incidence of platelet recovery.

Approximately 5% to 25% of patients experience inadequate or delayed platelet (primary) recovery following allo-SCT [14]. Some patients will experience secondary thrombocytopenia, defined as low platelet count after the initial platelet recovery without relapse of disease [15]. Generally, thrombocytopenia can be the result of impaired platelet production, increased platelet destruction, or both. The specific pathophysiological mechanisms of primary and secondary thrombocytopenia post-transplantation are still poorly defined and are likely multifactorial [15].

A flow cytometry analysis evaluating the frequency of bone marrow MegKs and their nuclear ploidy distribution in allo-HSCT recipients with or without prolonged thrombocytopenia showed an increased proportion of immature MegKs in patients with poor platelet engraftment [16]. TPO is a crucial cytokine for megakaryogenesis. Interestingly, there is some evidence of an inverse correlation between endogenous TPO levels and platelet counts after allo-HSCT. In one study, high endogenous TPO levels early post-transplantation was associated with worse 5-year OS and increased transplantation-related mortality [17].

Our review of the published literature identified 4 reports with a total of 9 patients treated with a TPO-R agonist for PPF following allo-SCT, as summarized in Table 3. Four of these patients achieved platelet transfusion independence. Including our cohort of patients with PPF, 67% of patients across the studies became transfusion-independent. Interestingly, the outcomes did not appear to be heavily skewed toward relapse, although the outcomes of these patients in our cohort were dismal. In the published reports of 35 patients with SPF treated with a TPO-R agonist (romiplostim or eltrombopag), 30 patients (88%) achieved transfusion independence, with no significant preponderance of relapse (Table 4). In our cohort, the median time to platelet recovery was 33 days, suggesting that eltrombopag has similar efficacy as romiplostim for SPF. In addition, the median time to transfusion independence was similar in patients with PPF and those with SPF in our cohort.

A relatively recent randomized phase II clinical trial in 53 allo-SCT recipients and 7 autologous SCT recipients treated with eltrombopag, presented in an abstract form (by Uday R, et al., *Blood* 2015; 126: Suppl. 1: A738), identified an overall response rate of 36% for the whole cohort. That study did not report patient outcomes following treatment, however.

Tanaka et al [11] reported that eltrombopag was a safe and effective treatment for 9 patients with persistent thrombocytopenia after allo-SCT, with response rates of 60% in patients with primary thrombocytopenia and 71% in those with secondary thrombocytopenia. In confirmation of that study, in our

**Table 3**
TPO-R Agonists for Persistent Isolated Thrombocytopenia following Allo-SCT in Patients Who Demonstrated Platelet Recovery to ≥50,000/μL

| Authors | Year of Publication | Number of Patients | Level of Bone Marrow MegKs before Treatment | Agent | Transfusion Independence | Days from Start of TPO-R Agonist to Response | Duration of Treatment | Patient Outcomes |
|---|---|---|---|---|---|---|---|---|
| Reid et al [19] | 2012 | 1 | Decreased | Eltrombopag | Achieved | Not reached | 6 wk | Relapse |
| Poon et al [27] | 2013 | 2 | Decreased in both | Romiplostim | Achieved in both | 126, 127 | 11 mo (not reported) | Alive |
| Fujimi et al [28] | 2015 | 1 | Decreased | Eltrombopag | Achieved | Not reported | 30 mo | Alive |
| Tanaka et al [11] | 2016 | 5 | Decreased in all | Eltrombopag | Achieved in 3, failed in 2 | Median, 183 (range, 91-195) | Median, 133 d (range, 49-273 d) | In whole cohort: relapses in 2, infection in 1 |
| Present study | 2019 | 6 | Decreased in 2, normal in 4 | Eltrombopag | Achieved in 3, failed in 3 | Median, 39 (range, 28-66) | Median, 33 d (range, 7-242 d) | 1 alive, 5 dead due to relapse in 2, GVHD in 2, and graft failure in 1 |

**Table 4**
TPO-R Agonists for Persistent Secondary Thrombocytopenia following Allo-SCT

| Authors | Year of Publication | Number of Patients | Level of Bone Marrow MegK before Treatment | Agent | Transfusion Independence | Days from Start of TPO-R Agonist to Response | Duration of Treatment | Patient Outcomes |
|---|---|---|---|---|---|---|---|---|
| Beck et al [29] | 2010 | 1 | Normal | Romiplostim | Achieved | Not reported | 4 wk | Not reported |
| Calmettes et al [30] | 2011 | 7 | Decreased in 5, increased in 2 | Romiplostim | Achieved in all | Median, 54 (range, 24-82) | Median, 13 wk (range, 4-16 wk) | 1 dead of relapse |
| Bollag et al [31] | 2012 | 1 | Decreased | Romiplostim | Achieved | Not reported | Not reported | Alive |
| Poon et al [27] | 2013 | 1 | Increased | Romiplostim | Achieved | 72 | Not reported | Alive |
| Deremer et al [32] | 2013 | 1 | Decreased | Romiplostim | Failed | Not recovered | 11 wk | Alive |
| Buchbinder et al [33] | 2014 | 1 | Decreased | Romiplostim | Achieved | Not reported | 6 mo | Alive |
| Maximova et al [34] | 2015 | 7 | Decreased in 5, increased in 2 | Romiplostim | Achieved in 6, failed in 1 | <28 | 4 wk | 6 alive and 1 dead of sepsis |
| Battipaglia et al [35] | 2015 | 2 | Decreased | Romiplostim | Achieved in 1 | Median, 14 (range, 7-35) | Median, 14 wk (range, 5-17 wk) | Died of infection |
| Tanaka et al [11] | 2016 | 7 | Decreased in 3, normal in 4 | Eltrombopag | Achieved in 6, failed in 1 | Median, 41 (range, 14-62) | Median, 98 d (range, 52-244 d) | In whole cohort: relapse in 2, infection in 1 |
| Present study | 2019 | 7 | Decreased in 1, normal in 7 | Eltrombopag | Achieved in 5, failed in 2 | Median, 33 (range, 11-68) | Median, 32 d (range, 19-323 d) | 2 alive, 5 dead due to relapse in 1, GVHD in 1, and infection in 3 |

cohort, response was better in the patients with secondary thrombocytopenia compared with those with primary thrombocytopenia. In both studies, no patients discontinued treatment because of adverse events or intolerability. In our study, the cumulative incidence of platelet recovery to $\geq$50,000/$\mu$L after eltrombopag treatment in the allogeneic recipients was 68%, similar to that reported by Tanaka et al [11]. Eltrombopag improved platelet counts regardless of the MegK reserve in bone marrow (60% and 67% in patient with adequate and decreased bone marrow respectively).

Bone marrow fibrosis is a rare potential adverse event associated with the use of TPO-R agonists, which may increase bone marrow reticulin in these patients [18]. As noted in other studies, none of our patients, including the deceased patients, showed evidence of bone marrow fibrosis following treatment with eltrombopag, and thus this was not considered a contributing factor to their outcomes [11,19]. Another concern with TPO-R agonists is the potential stimulation of myeloid leukemia cell proliferation through the TPO/TPO-R pathway [20–22]. However, other studies have reported that eltrombopag does not stimulate leukemia or MDS cell growth, but instead leads to a modest inhibition while continuing to stimulate normal megakaryopoiesis in patients with AML or MDS [23,24]. Furthermore, some studies have reported that eltrombopag may have an antileukemia effect that differs from its action on TPO-R [25,26]. In our present cohort, 3 allo-SCT recipients died of recurrent disease; however, whether the recurrent AML could be attributed to eltrombopag or whether the persistent thrombocytopenia was a harbinger of poor outcomes is difficult to determine.

This study has several limitations, including its retrospective nature and small number of patients. At our center, treatment with a TPO-R agonist is not standard treatment and depends on physician preference. Although we attempted to rule out other causes of thrombocytopenia, such as relapse of disease and infections, it is not possible to completely rule out impending relapse and development clinically silent GVHD as causes of thrombocytopenia. Nonetheless, this study adds to previous small studies supporting the safety and efficacy of eltrombopag following allo-SCT.

In conclusion, our results together with previously published studies suggest that eltrombopag can be a good therapeutic option after SCT for patients with persistent severe thrombocytopenia. In our limited study, although eltrombopag was well tolerated, unfortunately the majority of patients succumbed to relapse, GVHD, or infection. This suggests that despite a good overall response rate to eltrombopag, inadequate platelet engraftment heralds a poor outcome in allo-SCT recipients. Prospective studies are desirable to further evaluate the role of these agents in similar clinical settings.

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## SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.027.

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