Received: 4 April 2024 | Revised: 24 August 2024 | Accepted: 20 September 2024

https://doi.org/10.1016/j.rpth.2024.102578

ORIGINAL ARTICLE

Efficacy and safety of hetrombopag in the treatment of recombinant human thrombopoietin–resistant thrombocytopenia after allogeneic hematopoietic stem cell transplantation

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Handling Editor: Dr Bethany Samuelson Bannow

Abstract

Background: Thrombocytopenia after allogeneic hematopoietic cell transplantation is a challenging clinical problem. Recombinant human thrombopoietin (rhTPO) and thrombopoietin receptor agonists are increasingly used in posttransplant thrombocytopenia. However, the use of hetrombopag in patients with posttransplant thrombocytopenia, especially in patients with resistance to rhTPO, has not yet been reported.

Objectives: The present study aimed to investigate the efficacy and safety of hetrombopag in patients with rhTPO-resistant posttransplant thrombocytopenia.

Methods: This retrospective study included 21 patients with rhTPO-resistant posttransplant thrombocytopenia who received hetrombopag from August 2021 to July 2022. The primary endpoint was the overall response rate, including partial response and complete response (CR). We also evaluated the predictors of hetrombopag efficacy and adverse events.

Results: The overall response rate to hetrombopag was 81%, and the CR rate was 62%. The median time from hetrombopag initiation to response and CR were 16 and 31 days, respectively. Decreased megakaryocytes in bone marrow negatively correlated with CR to hetrombopag (P = .03). All the patients tolerated hetrombopag well without any significant increase in adverse events. At the last follow-up, 71% of responders had discontinued hetrombopag and sustained their best response.

Conclusion: Our results suggested that hetrombopag is an effective treatment option to promote platelet recovery in patients with posttransplant thrombocytopenia, even in patients resistant to rhTPO.

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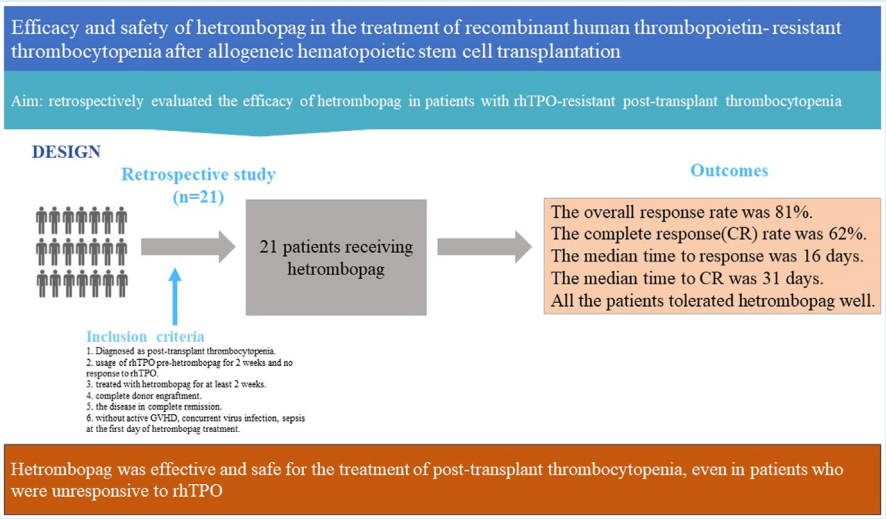

KEYWORDS
allogeneic hematopoietic stem cell transplantation (allo-HSCT), efficacy, hetrombopag, recombinant human thrombopoietin (rhTPO), thrombocytopenia

Essentials

- Posttransplant thrombocytopenia (PTT) is a common and potentially fatal complication.
- Recombinant human thrombopoietin (rhTPO) and thrombopoietin receptor agonists have been used to treat PTT.
- We analyzed the efficacy of hetrombopag in 21 patients with rhTPO-resistant PTT.
- Hetrombopag was effective for PTT, even in patients who were unresponsive to rhTPO.

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents an important curative approach for a wide range of hematological disorders [1]. Posttransplant thrombocytopenia, including prolonged isolated thrombocytopenia (PIT) and secondary failure of platelet recovery (SFPR), is a frequent complication, with a reported incidence of up to 37% [2]. Complex factors, such as deficiency of hematopoietic stem cells, mesenchymal stem cell or endothelial cell damage in bone marrow (BM) microenvironment, and abnormal immunity, were reported to be involved in the occurrence of posttransplant thrombocytopenia [3–5]. These factors result in impaired platelet production, increased platelet destruction, or both. Thrombopoietin (TPO) is the principal cytokine influencing megakaryopoiesis and platelet production [6]. Published data show that reduced megakaryocyte ploidy, low numbers of mature megakaryocytes, and relative insufficiency of endogenous TPO were identified in patients with posttransplant thrombocytopenia [7,8]. Therefore, TPO mimetics, including recombinant human TPO (rhTPO) and TPO receptor agonists (TPO-RAs), are expected to be important therapeutic options for posttransplant thrombocytopenia.

rhTPO is a full-length glycosylated TPO produced in Chinese hamster ovary cells, with biological functions similar to those of endogenous TPO [9]. It is an important treatment for thrombocytopenia caused by various settings, including allo-HSCT [10–12]. Sun et al. [12] reported that the response rate to rhTPO was 45.8% in patients with posttransplant thrombocytopenia. A significant proportion of patients were still resistant to rhTPO. TPO-RAs, such as eltrombopag and avatrombopag, were more widely used to treat posttransplant thrombocytopenia. These studies reported a high response rate to TPO-RAs in the treatment of posttransplant thrombocytopenia [13–15]. However, the sample sizes of these studies were relatively small, and there was heterogeneity in the patient population. Whether TPO-RAs are effective for patients with rhTPO-resistant posttransplant thrombocytopenia remains unanswered.

Hetrombopag, a novel small-molecule TPO-RA developed in China, has shown encouraging efficacy in treating immune thrombocytopenia (ITP) or severe aplastic anemia (SAA) [16,17]. However, there are currently no reports on the clinical efficacy of hetrombopag in the treatment of posttransplant thrombocytopenia. It is worthwhile to explore the efficacy of hetrombopag in patients with posttransplant thrombocytopenia, especially in rhTPO-resistant patients. In this study, we retrospectively analyzed the efficacy and safety of hetrombopag in 21 patients with rhTPO-resistant posttransplant thrombocytopenia.

2 | METHODS

2.1 | Patients

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University and was conducted according to the Declaration of Helsinki. From August 1, 2021, to July 31, 2022, a total of 21 patients were included in this study. Written informed consent was obtained from all patients. All the patients met the following criteria: (1) diagnosed as posttransplant thrombocytopenia; (2) usage of rhTPO before hetrombopag administration and no response to rhTPO; (3) treated with hetrombopag for at least 2 weeks; (4) complete donor engraftment; (5) the disease in complete remission; (6) without active graft versus host disease (GVHD), concurrent virus infection, and sepsis at the first day of hetrombopag treatment.

Posttransplant thrombocytopenia was categorized into PIT and SFPR. PIT includes delayed platelet engraftment (DPE) and poor graft function [13]. Poor graft function was not included in this study. DPE was defined as platelet counts $<20 \times 10^9$/L beyond 35 days after allo-HSCT despite neutrophil engraftment [18]. SFPR was defined as a drop of platelet counts below 20×10^9/L for at least 7 consecutive days after achieving platelet counts $\geq 20 \times 10^9$/L without platelet transfusion for 7 consecutive days after allo-HSCT [19]. All patients received rhTPO treatment for 2 weeks prior to hetrombopag administration. No response to rhTPO meant that platelet count was still $<20 \times 10^9$/L after 2 weeks of treatment.

2.2 | Conditioning regimen

For hematologic malignant diseases, including leukemia and myelodysplastic syndrome, the patients received a myeloablative conditioning regimen. Busulfan (Bu)/cyclophosphamide (Cy) regimen (3.2 mg/kg/d of Bu for 4 days; 60 mg/kg/d of Cy for 2 days) was administered for human leukocyte antigen (HLA)-matched sibling donor hematopoietic stem cell transplantation (MSD-HSCT). Modified Bu/Cy/anti-thymocyte globulin (ATG) regimen (4 g/m^2/d of cytarabine for 2 days; 3.2 mg/kg/d of Bu for 4 days; 50 mg/kg/d of Cy for 2 days; 250 mg/m^2/d of semustine for 1 day; 2.5 mg/kg/d of ATG for 3 days) was administered for haploidentical donor hematopoietic stem cell transplantation (HID-HSCT). For patients with aplastic anemia, Cy/ATG regimen (50 mg/kg/d of Cy for 4 days; 2.5 mg/kg/d of ATG for 4 days) was administered for MSD-HSCT, and Bu/Cy/ATG regimen (3.2 mg/kg/d of Bu for 1 day; 50 mg/kg/d of Cy for 4 days; 2.5 mg/kg/d of ATG for 4 days) was administered for HID-HSCT.

2.3 | GVHD prophylaxis

For MSD-HSCT, GVHD prophylaxis consisted of cyclosporine and a short course of methotrexate. Cyclosporine was started as a continuous intravenous infusion for 24 hours from day −2 before hematopoietic stem cell transplantation at a daily dose of 2.5 mg/kg/d. When patients were able to tolerate oral medications, cyclosporine was given orally and adjusted according to target trough levels. Methotrexate (15 mg/m^2) was administered intravenously on day 1 and 10 mg/m^2 on day 3, day 6, and day 11. For HID-HSCT, GVHD prophylaxis included cyclosporine, a short course of methotrexate, mycophenolate mofetil, and low-dose posttransplant Cy. The usage of cyclosporine and methotrexate was consistent with that in MSD-HSCT. Mycophenolate mofetil was administered from day −2 before hematopoietic stem cell transplantation, with a dosage of 1 g/d. The drug was discontinued on day 31. Low-dose Cy (14.5 mg/kg/d) was administered on day 3 and day 4 after transplantation.

2.4 | Stem cell harvesting, growth factor, and platelet transfusion support

Fifteen patients underwent peripheral blood stem cell transplantation. Six patients underwent BM transplantation combined with peripheral blood stem cell transplantation. The median number of mononuclear cells transfused was 9.83 (4.77-13.63) $\times 10^8$/kg, and the median number of CD34$^+$ cells was 4.03 (2.16-5.84) $\times 10^6$/kg. Recombinant human granulocyte colony-stimulating factor was started from day 5 after transplantation at a dose of 5 to 10 μg/kg/d until neutrophil recovery. rhTPO was administrated on day 7 after transplantation at a dose of 300 IU/kg/d until platelet counts were $\geq 50 \times 10^9$/L without platelet transfusion for 3 consecutive days. Platelet transfusions were given for any platelet count $<20 \times 10^9$/L or clinical bleeding with a platelet count $<50 \times 10^9$/L.

2.5 | Hetrombopag treatment

Hetrombopag was initiated at the dose of 5 mg once daily in 18 patients. The remaining 3 patients were administered hetrombopag with an initial dose of 2.5 mg once daily. If platelet count did not reach the threshold of 20×10^9/L, the dose of hetrombopag was increased every 2 weeks up to the maximal dose of 7.5 mg/d. When the platelet counts exceeded 100×10^9/L, hetrombopag was gradually tapered or stopped. If platelet levels dropped below 30×10^9/L again, hetrombopag was resumed.

2.6 | Endpoints and BM evaluation

The primary endpoint was the overall response rate (ORR), including complete response (CR) and partial response (PR). CR was defined as platelet recovery to $\geq 50 \times 10^9$/L for 7 consecutive days without platelet transfusion. PR was defined as a recovery of a platelet count of 20 to 50×10^9/L for 7 consecutive days without platelet transfusion [15,20]. No response was defined as a lack of CR/PR after the application of 7.5 mg/d hetrombopag for 8 weeks. The secondary endpoints included achievement of transfusion independence, the time to reach response and CR, the factors influencing the response to hetrombopag, and safety evaluation.

BM aspirate smears were evaluated for the number of megakaryocytes. The number of megakaryocytes between 7 and 35 in an area of 1.5 × 3 cm^2 was regarded as normal.

2.7 | Statistical analysis

Categorical variables were analyzed by chi-squared tests, and continuous variables were analyzed by Mann–Whitney U-tests. The overall survival was analyzed using the Kaplan–Meier method. All *P* values were 2-tailed, and $P < .05$ was considered statistically significant. Statistical analysis was performed using SPSS v20.0 (IBM).

3 | RESULTS

3.1 | Patient characteristics

Patients' clinical characteristics are shown in Table 1. Twenty-one patients were enrolled in this retrospective study. Nine patients were females, and 12 were males. The median age at transplantation was 32 (14-51) years. There were 10 cases of acute myeloid leukemia (AML), 7 cases of acute lymphoblastic leukemia (ALL), 2 cases of aplastic anemia (AA), 1 case of myelodysplastic syndromes (MDS), and 1 case of extranodal natural killer (NK)/T-cell lymphoma (ENKTL). Three patients underwent MSD-HSCT, and 18 underwent HID-HSCT. The median time to neutrophil engraftment was 11 days (10-16 days) after transplantation. Twelve patients (57%) experienced cytomegalovirus (CMV) reactivation. Ganciclovir or sodium phosphonate was used for antiviral therapy. Six patients (29%) experienced acute GVHD, including 4 cases of grade II GVHD and 2 cases of grade III GVHD. Two patients were diagnosed with DPE on the 35th day after transplantation. They received hetrombopag treatment at 31 and 35 days after transplantation, respectively. SFPR occurred in 19 patients with a median time of 67 (45-161) days after transplantation. The median time to the initiation of hetrombopag treatment was 78 (53-177) days after transplantation.

3.2 | Efficacy of hetrombopag

The median platelet count was 11 × 10^9/L when starting hetrombopag treatment. The efficacy of hetrombopag is presented in

TABLE 1 Patients' clinical characteristics (*N* = 21).

Age at transplantation (y)	Sex	Disease	Ethnicity	Disease status	Donor type	MNC (10^8/kg)	CD34 (10^6/kg)	Neutrophil implantation (d)	Type of thrombocytopenia	STR (%)
20	Female	AA	Han Chinese	Severe	HID	10.76	4.03	13	SFPR	99.5
31	Male	AA	Han Chinese	Severe	HID	10.16	4.75	10	SFPR	99.8
29	Female	AML	Han Chinese	CR	HID	9.83	4.59	11	SFPR	100
51	Male	AML	Han Chinese	R/R	HID	13.50	5.84	11	SFPR	100
44	Male	B-ALL	Han Chinese	CR	HID	5.17	3.20	10	SFPR	99.6
21	Male	B-ALL	Han Chinese	CR	HID	7.41	3.15	14	SFPR	99.0
14	Male	AML	Han Chinese	R/R	HID	11.17	3.61	12	SFPR	98.8
42	Male	ENKTL	Han Chinese	R/R	HID	8.67	3.79	14	DPE	99.5
32	Male	AML	Han Chinese	CR	MSD	7.35	2.73	11	SFPR	100
30	Female	AML	Han Chinese	CR	HID	13.63	5.54	16	DPE	99.5
47	Female	B-ALL	Han Chinese	CR	HID	4.77	2.16	14	SFPR	99.4
49	Female	B-ALL	Han Chinese	CR	HID	13.57	4.17	11	SFPR	99.7
16	Male	B-ALL	Han Chinese	CR	HID	9.17	4.05	10	SFPR	100
50	Female	MDS	Han Chinese	CR	HID	10.26	3.86	13	SFPR	99.2
16	Female	AML	Han Chinese	CR	HID	5.56	2.94	15	SFPR	100
18	Male	T-ALL	Han Chinese	CR	HID	11.68	5.62	11	SFPR	100
26	Female	B-ALL	Han Chinese	CR	HID	8.96	3.07	11	SFPR	99.8
39	Male	AML	Han Chinese	CR	MSD	9.54	3.82	10	SFPR	100
47	Male	AML	Han Chinese	CR	HID	11.27	4.39	12	SFPR	99.7
38	Female	AML	Han Chinese	CR	HID	10.68	5.08	11	SFPR	100
41	Male	AML	Han Chinese	CR	MSD	8.83	4.21	11	SFPR	99.5

AA, aplastic anemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukaemia; CR, complete response; DPE, delayed platelet engraftment; ENKTL, natural killer (NK)/T-cell lymphomas; HID, haplo-identical donor; MDS, myelodysplastic syndromes; MNC, mononuclear cell; MSD, matched sibling donor; R/R relapsed/refractory; SFPR, secondary failure of platelet recovery; STR, short tandem repeat; T-ALL, T cell acute lymphoblastic leukemia.

TABLE 2 Efficacy of hetrombopag treatment.

Characteristic	PIT (*n* = 2)	SFPR (*n* = 19)	All (*N* = 21)
Response to hetrombopag, *n* (%)			
Yes	1 (50%)	16 (84%)	17 (81%)
No	1 (50%)	3 (16%)	4 (19%)
Complete response to hetrombopag, *n* (%)			
Yes	0 (0%)	13 (68%)	13 (62%)
No	2 (100%)	6 (32%)	8 (38%)
Initial dose of treatment, *n* (%)			
2.5 mg	0 (0%)	3 (16%)	3 (14%)
5.0 mg	2 (100%)	16 (84%)	18 (86%)
7.5 mg	0 (0%)	0 (0%)	0 (0%)
Maximum dose of treatment, *n* (%)			
2.5 mg	0 (0%)	0 (0%)	0 (0%)
5.0 mg	0 (0%)	15 (79%)	15 (71%)
7.5 mg	2 (100%)	4 (21%)	6 (29%)
Time from transplantation to hetrombopag treatment (d), median (range)	35 (35-35)	78 (53-177)	72 (31-177)
Time from initiation of hetrombopag to platelet response (d), median (range)	23[a]	16 (7-31)	16 (7-31)
Time from initiation of hetrombopag to platelet complete response (d), median (range)	[b]	31 (11-87)	31 (11-87)
State of thrombocytopenia at last follow-up, *n* (%)			
Transfusion independence without hetrombopag	0 (0%)	14 (74%)	14 (67%)
Transfusion independence with hetrombopag	0 (0%)	2 (10%)	2 (9%)
Transfusion dependence	0 (0%)	0 (0%)	0 (0%)
Died	2 (100%)	3 (16%)	5 (24%)

PIT, prolonged isolated thrombocytopenia; SFPR, secondary failure of platelet recovery.
[a]Only 1 patient with PIT achieved response.
[b]No patient with PIT achieved complete response.

Table 2. Seventeen patients (81%) responded to the treatment in the whole cohort, including 13 patients with CR (62%) and 4 with PR (19%). The CI of ORR was 82% (Figure 1A), and the CI of CR was 67% (Figure 1B). Among 2 patients with DPE, 1 patient achieved PR after 23 days of hetrombopag treatment and the other had no response. Among 19 patients with SFPR, 13 patients (68%) achieved CR, and 3 patients (16%) achieved PR. After 1 month of hetrombopag treatment, 16 patients (76%) had achieved platelet transfusion independence. The median time to reach response and CR was 16 (7-31) and 31 (11-87) days after hetrombopag, respectively. The initial dose was 2.5 mg once daily in 3 patients (14%) and 5 mg in 18 patients (86%). The final dose was 5 mg once daily in 15 patients (71%) and 7.5 mg in 6 patients (29%). The median maximum dose was 5 mg daily (ranging from 5 to 7.5 mg daily). Of note, 78% (14/18) of patients responded at the initial dose of 5 mg once daily, and no patient responded at the initial dose of 2.5 mg once daily (P = .03). Moreover, 2 patients with an initial dose of 2.5 mg/d responded after dose adjustment to 5 mg/d.

3.3 | Predictors of hetrombopag efficacy

Before starting hetrombopag, the number of megakaryocytes in the BM was tested. A total of 9 patients (43%) showed a reduction in megakaryocytes, including 2 patients with DPE and 7 patients with SFPR. Based on univariate analysis, decreased megakaryocytes in the BM predicted a low probability of achieving CR to hetrombopag (77% vs 25%; P = .03). Other variables, including age, sex, donor source, infused mononuclear cell dose, infused $CD34^+$ cell dose, type of thrombocytopenia, acute GVHD, and CMV reactivation, were not associated with response or CR (Table 3). Further multivariate analysis also showed that adequate megakaryocytes (hazard ratio,

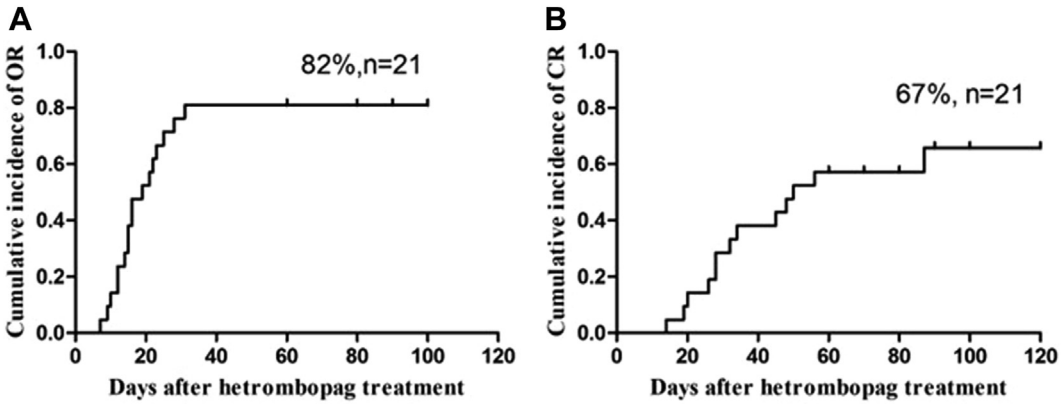

FIGURE 1 (A) The cumulative incidence of overall response (OR). (B) The cumulative incidence of complete response (CR).

4.372; 95% CI, 1.74-13.81; P = .03) were independent predictors for CR.

3.4 | Safety analysis

No patients withdrew from hetrombopag treatment as a result of adverse effects or intolerance. When hetrombopag was initiated, no patients had an active infection (bacterial, fungal, CMV, Epstein-Barr virus, and tuberculosis) or GVHD. During hetrombopag treatment, 6 patients developed cytomegalovirus viremia, 4 patients had skin hemorrhage, 2 patients had hemorrhagic cystitis, 4 patients exhibited GVHD, and 3 patients developed pyrexia due to bacterial or fungal infection. Based on clinical evaluation, none of the above events was deemed treatment-related. Notably, TPO-RA, such as eltrombopag, presents some risk of hepatotoxicity. We thus focused on hepatotoxicity specifically. The safety data in this study suggested that no patient had an elevation in liver function tests and bilirubin related to hetrombopag.

3.5 | Follow-up

The follow-up time was until December 30, 2022. At the last follow-up, 12 of 17 responders (71%) had discontinued hetrombopag

TABLE 3 Factors associated with response to hetrombopag.

Variables	Overall cohort	Response to hetrombopag			CR to hetrombopag		
		Yes (n = 17)	No (n = 4)	P value	Yes (n = 13)	No (n = 8)	P value
Sex, male, n (%)	12 (57%)	10 (59%)	2 (50%)	>.99	7 (54%)	5 (62%)	>.99
Age (y), median (range)	32 (14-51)	31 (14-51)	40.5 (30-50)	.62	31 (16-51)	40.5 (14-50)	>.99
Donor type				.49			>.99
Matched sibling donor, n (%)	3 (14%)	2 (12%)	1 (25%)		2 (15%)	1 (13%)	
Haploidentical donor, n (%)	18 (86%)	15 (88%)	3 (75%)		11 (85%)	7 (87%)	
MNC × 10^8/kg, median (range)	9.83 (4.77-13.63)	9.99 (4.77-13.50)	9.90 (8.67-13.63)	.97	9.83 (4.77-13.57)	9.90 (5.17-13.63)	>.99
CD34 × 10^6/kg, median (range)	4.03 (2.16-5.84)	4.05 (2.16-5.84)	3.84 (3.79-5.54)	>.99	4.17 (2.16-5.84)	3.81 (3.07-5.54)	.87
Time of neutrophil engraftment (d), median (range)	11 (10-16)	11 (10-15)	13.5 (10-16)	.19	11 (10-14)	11.5 (10-16)	>.99
Types of thrombocytopenia				.35			.13
DPE, n (%)	2 (10%)	1 (6%)	1 (25%)		0 (0%)	2 (25%)	
SFPR, n (%)	19 (90%)	16 (94%)	3 (75%)		13 (100%)	6 (75%)	
CMV reactivation, n (%)	12 (57%)	9 (53%)	3 (75%)	.60	7 (54%)	5 (63%)	>.99
Grade II-IV acute GVHD, n (%)	6 (29%)	4 (24%)	2 (50%)	.54	3 (23%)	3 (38%)	.63
Megakaryocyte counts before hetrombopag				.27			.03
Decreased, n (%)	9 (43%)	6 (35%)	3 (75%)		3 (23%)	6 (75%)	
Normal or increased, n (%)	12 (57%)	11 (65%)	1 (25%)		10 (77%)	2 (25%)	

CMV, cytomegalovirus; CR, complete response; DPE, delayed platelet engraftment; GVHD, graft-versus-host disease; MNC, mononuclear cell; SFPR, secondary failure of platelet recovery.

without transfusion support and sustained their best response. Specifically, 10 of 13 patients with CR and 2 of 4 patients with PR tapered off the medication. The median time from starting hetrombopag treatment to discontinuing treatment was 94 (34-286) days. The median platelet level was 84×10^9/L (41-283 $\times 10^9$/L) and 79×10^9/L (32-266 $\times 10^9$/L) on the day of hetrombopag discontinuation and 1 month of hetrombopag withdrawal, respectively. Thrombocytopenia recurred after treatment interruption in 2 patients with initial CR. Fortunately, the platelet count recovered again after restarting hetrombopag treatment. One patient with CR died of disease relapse, and 2 patients with PR died of GVHD and infection.

Among 4 patients with NR, 2 patients died of disease relapse and transplant-associated thrombotic microangiopathy, respectively. Two patients who did not respond after more than 2 months of hetrombopag treatment received low-dose decitabine (3 mg/m^2 for 5 days) in combination with hetrombopag. These 2 patients achieved platelet recovery $\geq 20 \times 10^9$/L on days 33 and 38 after initiation of decitabine treatment.

4 | DISCUSSION

In this study, we reported the results of hetrombopag treatment for patients with rhTPO-resistant posttransplant thrombocytopenia. The ORR was 81%, and the CR rate was 62%. Reduced megakaryocyte counts in the BM were negatively correlated with the achievement of CR. Furthermore, hetrombopag was well tolerated by all patients without any significant increase in adverse events. Our data suggested that hetrombopag was effective and safe for patients with posttransplant thrombocytopenia, even for rhTPO-resistant patients. To our knowledge, this is the first study to report the application of hetrombopag in posttransplant thrombocytopenia. Hetrombopag has the same action mechanism as eltrombopag by stimulating the TPO-R signaling pathway to elevate platelet counts [21]. Furthermore, a preclinical study demonstrated that hetrombopag has better pharmacologic performance than eltrombopag both *in vitro* and *in vivo* (nude mice) [22]. In clinical settings, previous studies have shown that hetrombopag has a similar response rate to that of eltrombopag in elevating platelet counts when treating ITP or SAA [16,17]. In this study, the ORR and CR rates of hetrombopag treatment for posttransplant thrombocytopenia were 81% and 62%, respectively. The response rates were generally similar to several real-world studies of eltrombopag (the CR rate was 57% in a Spanish study, 60.7% in a Chinese study, and 62% in an American study) [20,23,24]. Although the comparison should be cautiously interpreted due to the different patient populations enrolled, our results suggested that hetrombopag is noninferior to eltrombopag in treating posttransplant thrombocytopenia.

The optimal dose of hetrombopag in the treatment of posttransplant thrombocytopenia is an important concern. The initial dose of hetrombopag in a multicenter phase II study in SAA is 7.5 mg once daily, and the maximum dose is 15 mg once daily [17]. However, when treating ITP, a dose of 2.5 mg once daily has shown good efficacy in elevating platelets [16]. In this study, we used an initial dose of 5 mg/d in 18 patients and 2.5 mg/d in 3 patients to treat posttransplant thrombocytopenia. The results showed that 78% (14/18) of patients responded at the initial dose of 5 mg once daily, and no patients responded at the dose of 2.5 mg once daily. Therefore, we recommend using hetrombopag at an initial dose of at least 5 mg/d when treating posttransplant thrombocytopenia.

Previous studies showed that the response time after TPO-RA administration varied in different diseases. For instance, the median response time from hetrombopag initiation to response was 2.1 weeks in ITP patients and 7.9 weeks in SAA patients [16,17]. It was seen that the response of TPO-RA therapy is not the same in immune-mediated or impaired production settings. In the present study, the median time to reach response and CR was 16 (7-31) and 31 (11-87) days after hetrombopag initiation in patients with posttransplant thrombocytopenia, respectively. The interpatient variation in response time was large, which may be related to the complex factors involved in the mechanism of posttransplant thrombocytopenia.

We also explored the timing of hetrombopag withdrawal and its long-term efficacy. Our data suggested that 71% of responders discontinued the medication and sustained their best response. The median time from initiation to discontinuation of hetrombopag treatment was 94 (34-286) days. The results indicated a durable efficacy of hetrombopag in the treatment of posttransplant thrombocytopenia.

The important features of our patients were the usage of rhTPO before hetrombopag administration and resistance to rhTPO. Comparing the efficacy of rhTPO and TPO-RAs, Wen et al. [25] found that rhTPO was comparable with eltrombopag in promoting platelet engraftment in a randomized controlled study. However, a meta-analysis showed that TPO-RAs have a significantly higher response rate than rhTPO in the treatment of posttransplant thrombocytopenia [26]. Two real-world retrospective studies also indicated whether or not the usage of rhTPO before TPO-RA initiation had a similar response rate to eltrombopag or avatrombopag [15,20]. Consistent with the 2 studies, our study suggested that hetrombopag was effective in patients with rhTPO-resistant posttransplant thrombocytopenia. Mechanistically, although both rhTPO and TPO-RAs promote megakaryocyte proliferation and maturation through interaction with the c-mpl receptor, they have been shown to bind to distinct sites of c-mpl receptor. rhTPO binds to the extracellular domain of c-mpl, and TPO-RAs bind to the transmembrane domain of the c-mpl [27]. Furthermore, the development of neutralizing TPO antibodies after rhTPO treatment might attenuate the drug efficacy [28]. In contrast, a previous study in a mouse model found that TPO-RAs inhibited the production of antiplatelet antibodies [29]. In addition, TPO-RAs were reported to have an immunomodulatory role, including improving regulatory T cells and shifting the balance of Fcγ receptors toward the inhibitory receptor IIb on monocytes [30,31].

In this study, decreased megakaryocytes in the BM before hetrombopag was a predictor factor for CR. The results were consistent with several studies, which showed that adequate megakaryocytes were positively correlated with response [15,20]. However, Yuan et al. [24] reported that eltrombopag improved platelet

counts regardless of megakaryocytes. Of note, all these conflicting conclusions were based on studies with relatively small sample sizes. Additional studies with a larger sample size may be useful for confirming the present data.

Safety is also an important concern. Hetrombopag was well tolerated by all 21 patients. There was no treatment-related mortality and no evidence of any other grade 3/4 toxicities. In particular, no patients developed an increased risk of hepatotoxicity.

This study has several limitations. First, it is a single-center, retrospective study with a relatively small sample size. Second, there is a lack of a control group, which limits our ability to perform comparative analysis. Of note, in a previous randomized controlled trial, none of the 18 patients with posttransplant thrombocytopenia who received placebo treatment achieved complete remission [32]. Drawing on the data from the placebo group, it has been further confirmed that hetrombopag is effective in treating posttransplant thrombocytopenia. However, given the limitations mentioned above, our results should still be regarded as preliminary. Randomized controlled trials with larger samples are required to confirm our results.

In summary, our study demonstrates that hetrombopag offers a novel treatment for posttransplant thrombocytopenia. Based on our limited data, it also seems that resistance to rhTPO in posttransplant thrombocytopenia does not affect the response to TPO-RAs.

ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in the study.

FUNDING

This work was supported by the Research Foundation of Anhui Medical University (grant number 2021xkj154), Natural Science Foundation of Anhui Province (grant number 2208085QH243), Clinical Research Project of First Affiliated Hospital of Anhui Medical University (grant number LCYJ2021Y8007), and Beijing Natural Science Foundation (number 7242072).

AUTHOR CONTRIBUTIONS

J.N., Q.L., and M.Y. designed the study. J.H. and Z.L. collected the data. X.L., J.D., and X.L. managed the patients. J.N. and Q.L. analyzed the data and wrote the paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

All the data and materials are available if necessary.

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