Real-World Experience of Treatment With Thrombopoietin Receptor Agonists in Anti-thymocyte Globulin-Naïve Patients With Aplastic Anemia: An Observational Retrospective Analysis in a Single Institution

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Research Article

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Abstract

Thrombopoietin receptor agonists (TPO-RAs) are used to treat bone marrow failure in aplastic anemia (AA). Treatment with TPO-RAs, cyclosporine A (CsA) and anti-thymocyte globulin (ATG) induces remission and a sustained response. However, the efficacy of TPO-RAs without ATG remains unclear. We retrospectively assessed 45 patients with AA refractory to CsA and naïve for ATG treatment who received eltrombopag without ATG at our hospital during 2017-2021. Of these, 28 (62%) achieved a hematologic response in at least one lineage after six months of treatment, and 38 (84%) achieved best response at any point during the follow-up period. Four patients (25%) achieved trilineage responses during the follow-up period. Five patients switched from eltrombopag to romiplostim because of adverse events or lack of efficacy. Two developed hematologic malignancies. Eltrombopag was effective even in elderly ATG-ineligible patients with severe AA. The two-year overall survival rate was 84.3%, with a median follow-up of 26.3 months. Time from diagnosis to eltrombopag treatment initiation tended to affect the response ($p = 0.0727$), but no factors that significantly predicted hematologic response were identified. In conclusion, patients who are ineligible for ATG treatment because of age, complications, or even severe AA should nevertheless be considered for TPO-RA treatment.

1. Introduction

Aplastic anemia (AA) is a disease characterized by pancytopenia and hypoplastic bone marrow caused by an autoimmune mechanism [1]. Immunosuppressive treatment with anti-thymocyte globulin (ATG) and cyclosporine A (CsA) had been the standard therapy for mild to severe AA (SAA) as a first-line treatment for patients who are not candidates for hematopoietic stem cell transplantation [1].

Recently, the thrombopoietin receptor agonists (TPO-RAs) eltrombopag and romiplostim have become available for the treatment of refractory AA [2, 3]. The efficacy of eltrombopag with a combination of ATG and CsA for treating newly diagnosed AA has also been shown [4]. These TPO-RAs activate TPO receptors on not only megakaryocytes but also primitive hematopoietic stem and progenitor cells, and they enhance hematopoiesis [5]. In addition, recent studies have demonstrated that TPO-RAs effectively recover trilineage hematopoiesis, which in some patients is sustained even after TPO-RA discontinuation. Based on these findings, recent treatment guidelines suggest that a combination of TPO-RAs with immunosuppressive therapy should be considered as a standard of care for AA patients [6–8].

In real-world clinical practice, there are some patients for whom ATG is not appropriate treatment, for reasons such as age, comorbid infection, concomitant complications, the patients' preference, and allergic reaction to ATG. However, most data on the administration of TPO-RAs to AA patients has been limited to clinical trials, and limited evidence has been reported for TPO-RAs in CsA-refractory ATG-naïve patients [9–11]. As a result, the efficacy of TPO-RAs for such patients in the real world remains unclear and is of special interest. In the present study, we retrospectively evaluated the outcome of treatment with TPO-RAs, mainly eltrombopag, for patients who either did not require or were unable to receive ATG, and explored the factors that were predictive of TPO-RA treatment outcome to optimize the treatment.

2. Patients And Methods

2.1 Research participants and study design

We reviewed the medical records of consecutive patients who had been diagnosed with AA between September 2017 and April 2021 at Yamanashi Prefectural Central Hospital. We retrospectively evaluated 45 patients with AA aged ≥ 16 years who had been treated with TPO-RAs without ATG. We investigated the following patient characteristics: age, sex, severity of AA, complete blood count, duration from diagnosis to the initiation of TPO-RA treatment, bone marrow examination (including cytogenetic analysis at the initiation of TPO-RA treatment), positivity for paroxysmal nocturnal

hemoglobinuria (PNH) clone, transfusion dependency, number of prior treatments, type of prior treatments, type of TPO-RAs, maximal and maintenance dose of TPO-RAs, concomitant therapies during TPO-RA treatment, duration of TPO-RA treatment, hematologic response to TPO-RA treatment, adverse events during TPO-RA treatment, time to response, and overall survival. The TPO-RA eltrombopag was initially administered, in accordance with the approved indications for patients with AA in Japan [8, 11, 12].

If the eltrombopag was not effective or resulted in serious adverse events, it was changed to romiplostim at the discretion of the treating physicians. In brief, eltrombopag was orally administered at a starting dose of 25 mg/day; after two weeks of administration, dose adjustments in increments of 25 mg/day were considered, up to a maximum dose of 100 mg/day. Romiplostim was subcutaneously injected at a starting dose of 10 µg/kg once per week; this was adjusted in increments of 5 µg/kg up to a maximum of 20 µg/kg, according to hematopoietic recovery [13]. After a stable trilineage response had been achieved, the TPO-RA dosage was decreased gradually and then discontinued, while trilineage hematopoiesis was sustained. TPO-RA treatment was resumed when a loss of the response was observed, at the discretion of the treating physicians. Cytogenetic analysis (G-band staining and fluorescence *in situ* hybridization [FISH]) for chromosome 7q deletion was performed every 6-12 months or when a loss of treatment response was observed, using bone marrow or peripheral blood samples.

This study was approved by the ethics committee of Yamanashi Prefectural Central Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. All patients provided written informed consent.

2.2 Definitions

AA and the levels of disease severity have been defined previously [6–8]. Based on previous research [11], a platelet response was defined as an increase in platelet count of $\geq 20 \times 10^9/\text{L}$ above the baseline, or independence from platelet transfusions for at least eight weeks in patients who were previously transfusion dependent. An erythroid response in patients with a pretreatment hemoglobin level of $< 9 \text{ g/dL}$ was defined as an increase in the hemoglobin level by $\geq 1.5 \text{ g/dL}$ without transfusion, or a reduction of at least four transfusion units for eight weeks relative to transfusion requirements during the eight weeks immediately preceding the first administration of the TPO-RA. A neutrophil response was defined as an increase in the absolute neutrophil count (ANC) of $> 0.5 \times 10^9/\text{L}$, or at least a doubling of ANC from baseline in patients with a baseline ANC of $\leq 0.5 \times 10^9/\text{L}$. In patients who had an ANC $\geq 1.0 \times 10^9/\text{L}$ and/or a platelet count $\geq 100 \times 10^9/\text{L}$ at study entry, increases in ANC and/or platelet count were not considered for response assessment. Time to hematologic response was defined as the duration from the initiation of eltrombopag administration to any hematologic response. Overall survival was defined as the duration from the first day of eltrombopag administration to death from any cause. Adverse events during TPO-RA treatment were evaluated in accordance with the National Cancer Institute's Common Terminology Criteria, version 5.0 [14].

2.3 Statistical analysis

Categorical and continuous variables were analyzed using Fisher's exact tests and *t*-tests, respectively. Differences with a *p*-value of < 0.05 were considered statistically significant. Overall survival (OS) was estimated using the Kaplan-Meier method [15]. All statistical analyses were performed using EZR computer software [16].

3. Results

3.1 Patient characteristics

Forty-five patients with AA were treated with eltrombopag during the study period; their characteristics are summarized in Table 1. The median age was 76.5 years (range: 44–88 years). Of these 45 patients, 10 had SAA, while the remaining

35 had non-severe AA. The median reticulocyte count, hemoglobin level, ANC, and platelet count at the initiation of eltrombopag administration were $41,580 \times 10^6/L$ (range: $7,840-80,860 \times 10^6$); 8.6 g/dL (range: $5.0-14.8$); $925 \times 10^6/L$ (range: $120-6,622 \times 10^6$); and $16 \times 10^9/L$ (range: $2-109 \times 10^9$), respectively. The median time from the diagnosis of AA to the initiation of eltrombopag administration was 5.7 months (range: 2.2-18.3). Four patients had an abnormal karyotype (trisomy 8 [n = 1], 13q deletion [n = 1], and loss of Y chromosome [n = 2]), and 38 had a normal karyotype at the initiation of eltrombopag administration. PNH clone ($\geq 1\%$) was detected in eight patients (18%). The median number of prior treatments was one (range: 1-2). CsA was the most common prior medicine administered to all patients, with a median duration of 4.1 months. Thirty-eight patients had failed to respond to previous treatment with CsA with metenolone, five had failed to respond to CsA alone, and the remaining two had failed to respond to CsA with prednisolone. Of the 45 patients, 43 were eligible for response assessment using the platelet lineage (platelets $< 100 \times 10^3/\mu\text{L}$ or dependent on platelet transfusions), 29 were eligible for response assessment using the erythroid lineage (Hb $< 9 \text{ g/dL}$ or dependent on red blood cell transfusions), and 29 were eligible for response assessment using the neutrophil lineage (ANC $< 1.0 \times 10^9/L$). The reasons for avoiding treatment with ATG were as follows: advanced age (≥ 70 years), n = 22; not recommended according to the Japanese guidelines [8]¹⁰¹, n = 13; patient preference, n = 6; uncontrolled heart failure, n = 2; uncontrolled diabetes mellitus, n = 2; chronic renal failure, n = 2; invasive aspergillus infection, n = 1.

3.2 Clinical outcomes

Initially, all patients received eltrombopag when the TPO-RA treatment commenced, because eltrombopag is a convenient oral tablet and was approved earlier in Japan than romiplostim. However, five patients needed to switch to romiplostim because of adverse events (anorexia and nausea grade 2, n = 3) or lack of efficacy (n = 2). The median duration of TPO-RA administration was 23.4 months (range: 2.1-48.3). The median maximum dose of eltrombopag or romiplostim was 100 mg/day (range: 50-100) or 20 $\mu\text{g/kg}$ (range: 15-20), respectively. CsA was the main concomitant medicine administered to 43 patients, with a median duration of 6.3 months. Metenolone was the second most common concomitant medicine. The change in eltrombopag dose over time is shown in Figure 1. The median eltrombopag maintenance dose for responders (in at least one lineage) and non-responders was 75 mg/day (range: 12.5-100) and 50 mg/day (range: 25-100), respectively (p = 0.19). The median eltrombopag administration duration in responders and non-responders was 4.3 months (range: 2.1-8.4) and 26.5 months (range: 3.4-48.3), respectively (p = 0.028). Two patients received granulocyte colony-stimulating factor (G-CSF) for periods of infection; however, no neutrophil response was observed in these patients.

3.2 Hematologic improvements resulting from TPO-RA treatment in patients with AA

Of these 45 patients, a response was observed in at least one lineage in 38, with a median time to response of 84 days, and trilineage responses were observed in four patients, with median time to response of 397 days (Tables 2 and 3, Figure 2). Hematologic responses over time are shown in Figure 3. Of the 10 transfusion-dependent patients, two became transfusion-independent and the requirement for reduced transfusions reduced in two. However, one male patient became transfusion-dependent after the onset of acute myeloid leukemia (AML). All patients who had a hematologic response, except those who died or progressed to AML or myelodysplastic syndrome (MDS), were continuing to be administered with TPO-RAs at the time of analysis.

3.3 Adverse events and evolution to myeloid malignancy

Adverse events were observed in 18 of the 45 patients (40%, Table 4) during the TPO-RA treatment. Common adverse events were anorexia (n = 4), nausea (n = 4), lung infection (n = 3), oral submucosal hemorrhage (n = 2), blood liver transaminase elevation (n = 2), blood bilirubin elevation (n = 2), headache (n = 2), and febrile neutropenia (n = 2); however, most of these were not serious. Regarding serious adverse events, liver dysfunction was observed in a 44-year-

old patient who was receiving concomitant eltrombopag with CsA. He developed grade 2 upper abdominal pain and liver dysfunction, with elevation of serum transaminase and hyperbilirubinemia (grade 3 blood aspartate and alanine aminotransferase [ALT and AST] increase and grade 1 blood bilirubin increase) after two months of administration of eltrombopag at 75 mg/day. After discontinuation of eltrombopag for 22 days, his symptoms and liver function were resolved, and eltrombopag administration was then restarted at a dose of 25 mg/day, which was then increased to the maintenance dose (100 mg/day) and maintained until the time of analysis. A 52-year-old woman developed grade 2 anorexia, grade 2 nausea, grade 1 vomiting and liver dysfunction (grade 2 AST and ALT increase and grade 2 hyperbilirubinemia) after four months of administration with eltrombopag at 100 mg/day with concomitant CsA. After discontinuation of eltrombopag for 20 days, her appetite and liver function recovered, and eltrombopag treatment was resumed at a dose of 25 mg/day. However, when the dose was increased to 75 mg/day, the anorexia and nausea returned, and at that stage the eltrombopag was switched to romiplostim. Two other women, aged 77 and 76, both experienced grade 2 anorexia and grade 2 nausea, and their eltrombopag treatment was also switched to romiplostim. Eventually, these three women were receiving the maximum dose of romiplostim subcutaneously once a week, and this resulted in uni- to trilineage recovery. After switching to romiplostim, these three women had not again experienced the adverse events that they experienced prior to switching to romiplostim, as at the time of analysis.

The two-year OS rate was 84.3% (95% confidence interval: 67.9-92.7%), and five deaths were recorded, with a median follow-up period of 26.3 months (range: 2.1-45.3). The deaths were caused by infections (worsening invasive aspergillus pneumonia [n = 1], pyelonephritis [n = 1], and aspiration pneumonia [n=1]) and myeloid malignancy (n = 2).

None of the patients had cytogenetic abnormalities in chromosome 7 detected via FISH during the follow-up period. However, two patients who had a normal karyotype at the initiation of eltrombopag administration developed myeloid malignancies. A 67-year-old man achieved a unilineage response (platelets) after two months of eltrombopag administration. However, his platelet count started declining again after 11 months of treatment. Bone marrow examination revealed that he had hypoplastic AML with a blast percentage of 28%. Low-dose cytarabine and anthracycline were not effective, and he died 20 months after the initiation of eltrombopag treatment. The other patient, a 66-year-old man, achieved a trilineage response after a month of eltrombopag administration. However, he started to develop pancytopenia after six months of treatment. The eltrombopag was switched to romiplostim, but this did not improve the pancytopenia. Bone marrow examination revealed that he suffered from MDS with multilineage dysplasia. Azacytidine was administered, but it was not effective, and he died 12 months after the initiation of eltrombopag treatment.

3.4 Factors affecting hematologic improvements after initiation of TPO-RA administration in patients with ATG-naïve AA

In univariate analysis, we investigated the following factors that may affect the response at six months: age, sex, severity of AA, positivity for PNH clone, ANC, reticulocyte, platelet counts at the initiation of eltrombopag administration, maintenance dose of eltrombopag and time from diagnosis to eltrombopag treatment initiation (Table 5). The time from diagnosis to treatment initiation tended to influence the response in at least one lineage, but this was not significant ($p = 0.0727$, Table 3). Neither univariate nor multivariate analysis revealed any factors that were predictive of the response.

4. Discussion

In this study, we have demonstrated the efficacy of TPA-RAs without ATG for patients with AA in a real-world setting. The median age of the patients in this cohort was 76.5 years old, which is higher than that in previous prospective studies (32-53 years) [2–4, 11, 17–19], although in the one retrospective study we reviewed [9], the median age of patients naïve for ATG treatment was 74 years. The cohort in this study may therefore be more representative of the patients who

would typically be naïve for ATG treatment in daily clinical practice. Of the 45 patients included in this study, 32 were ineligible for ATG treatment because of their age (≥ 70 years) and/or comorbidities, and the other 13 had only mild symptoms and were not indicated for ATG treatment according to the Japanese guideline [8]. Hematologic response in at least one lineage was observed in 62% of patients at six months from the initiation of eltrombopag treatment, and an optimal response was observed in 84% of patients regardless of time. A trilineage response was observed in 25% of eligible patients at any point during the follow-up period. The median time to achieve hematological responses in at least one lineage and a trilineage response were 84 and 397 days, respectively.

Several prospective and retrospective studies have published data on the efficacy and safety of TPO-RA for newly diagnosed and refractory AA [2–4, 9, 11, 17–19]. In these studies, the response rates for at least unilineage and trilineage responses were approximately 40-80% and 20-40%, respectively.

In these studies, most patients had previously been treated with ATG, and one of these studies demonstrated that patients previously treated with ATG exhibited faster hematopoietic cell recovery (transfusion independence rate at three months: 44% versus 0%) and a slightly better hematological response rate than patients not treated with ATG (response rate in at least one lineage: 74% vs 64%; trilineage response rate: 34% vs 27%) [9]. Although the numbers of patients are small and there are obvious caveats concerning attempts to compare independent studies, the hematologic response rates and speed of hematopoietic recovery in our study do not seem to be inferior to the results of previous studies, including those involving younger patients and those previously treated with ATG.

This study cohort included 10 patients with SAA. Of these, six were over 75 years old, and the response rate for at least unilineage and trilineage responses in this group was 66% and 33%, respectively. Immunosuppressive therapy is effective regardless of the patient's age; however, the mortality rate is likely to be higher in older patients than younger patients [20, 21]. Therefore, clinicians should take extra care when administering ATG to elderly patients. However, previous case reports have demonstrated the efficacy of eltrombopag without ATG for treating SAA [22, 23], and findings in our study were consistent with these reports even in elderly patients who are ineligible for ATG treatment. These findings suggest that TPO-RA should be administered even to elderly SAA patients who are ineligible for ATG.

The safety profile of the eltrombopag treatment in this study was consistent with previous studies [2, 4, 11]. The most frequent adverse event was anorexia and nausea. These events were resolved within two to four weeks of discontinuation or reduction of eltrombopag administration. Although the adverse events did not recur in most of the patients when the eltrombopag was reinitiated, they did in three female patients, who were then switched to romiplostim. After the switch, their symptoms were completely resolved. Most of the adverse events were not serious and appear not to have been related to age. Instead, anorexia and nausea were more likely to be observed in female patients. Because the number of patients in this study was small, however, further data collection will be necessary to confirm these tendencies.

By the time of data analysis, five patients had been switched from eltrombopag to romiplostim. The reason for this in the other two patients (who were male) was lack of efficacy. After switching to romiplostim, the response was improved in one of these patients, but not in the other, due to the onset of MDS. Previous studies have shown that switching from one TPO-RA to another is effective in clinical practice in patients with not only immune thrombocytopenia [24, 25] but also AA [10, 26]. Our observational findings were consistent with their results. In this study, the eltrombopag dosage tended to affect the hematological response. An adequate TPO-RA dosage appears to be necessary for hematological recovery. If the first TPO-RA fails because an adequate dosage cannot be provided, switching to another TPO-RA should be considered to achieve treatment success.

Our study cohort included two patients who developed hematological malignancy. These patients eventually died as a result of AML and MDS, respectively. In previous studies on TPO-RA treatment for AA, clonal evolution and AML have

been observed at an incidence of 3-19% and 0-4%, respectively [2, 4, 17, 19, 27]. However, it is also reported that secondary MDS or AML occurs in 15–20% of patients with AA regardless of the use of TPO-RAs [28]. TPO-RAs can stimulate the expansion of hematopoietic stem cells via the c-MPL signaling pathway [5] and this could potentially affect the emergence of abnormal clones. Clonal evolution is of concern, and the precise mechanism underlying the development of hematologic malignancy remains controversial. Therefore, long-term follow-up and close surveillance of patients treated with TPO-RAs are essential.

We did not find any factors that significantly predicted hematological response to eltrombopag treatment. A shorter period from AA diagnosis to treatment initiation was likely to predict a hematopoietic response, but it was not significant. Previous studies have shown that higher reticulocyte counts and a shorter period from first immunosuppressive therapy to initiation of eltrombopag administration were likely to predict a hematological response to eltrombopag [2, 27]. While there are sufficient hematopoietic stem cells remaining in the bone marrow (i.e., before the hematopoietic stem cells are depleted), the introduction of a TPO-RA may be able to effectively stimulate a hematologic response.

This study has some limitations. First, it was a retrospective observational study with a small number of patients being treated at a single institution. The decisions to switch from pretreatment to TPO-RA when the TPO-RA was introduced and to switch the TPO-RA from eltrombopag to romiplostim were therefore left to the discretion of the treating physicians. To confirm our findings, we need to conduct a prospective study with a larger number of patients. Second, the reasons for not using ATG involved both cases in which the symptoms were mild and the use of ATG was unnecessary (i.e., not recommended according to the guidelines), and cases in which the symptoms were severe but ATG could not be used because of patient factors such as age and complications. There is thus a need for studies involving sufficient numbers of cases that the patients can be divided into separate cohorts according to these two sets of characteristics. Third, clonal evolution was not evaluated systematically, and it might occur more frequently than was documented here.

In conclusion, we investigated the efficacy of TPO-RAs in ATG-naïve patients with AA. Our findings reflect the nature of real-world TPO-RA treatment in patients with AA and suggest that TPO-RAs should be attempted in refractory patients with AA, even if they are elderly, have severe AA, and are ATG-ineligible. Further studies may identify factors that predict efficacy. Better understanding of TPO-RA action in AA and the proper use of TPO-RA in AA patients could improve AA treatment strategies and encourage successful long-term treatment of patients with ATG-naïve AA.

Declarations

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Authors' contributions: MI designed the study and wrote the initial draft of the manuscript. MI, TS, AJ and AN contributed to data collection and interpretation and critically reviewed the manuscript. MI, TS, AJ and AN approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1. Baseline patient characteristics

SAA Patients	n = 45
Patient age (years), median (range)	76.5 (44–88)
Sex (female/male), n (%)	27/18 (60/40)
Severity at initiation of Epag, n (%)	
SAA	10 (22)
NSAA	35 (78)
Reticulocyte count at initiation of Epag ($\times 10^6/L$), median (range)	41,580 (7,840–80,860)
Hemoglobin level at initiation of Epag (g/dL), median (range)	8.6 (5.0–14.8)
ANC at initiation of Epag ($\times 10^6/L$), median (range)	925 (120–6,622)
Platelet count at initiation of Epag ($\times 10^9/L$), median (range)	16 (2–109)
Time from diagnosis to initiation of Epag (months), median (range)	5.7 (2.2–18.3)
Karyotype	
Normal	38 (84)
Abnormal	4 (9)
Unknown	3 (7)
PNH clone	
Positive ($\geq 1\%$)	8 (18)
Negative ($< 1\%$)	34 (75)
Unknown	3 (7)
Transfusion dependency	
Platelet	5 (11)
Red blood cell	7 (16)
Number of prior treatments, median (range)	1 (1–2)
Prior treatments, n (%)	
Cyclosporine A	45 (100)
Metenolone acetate	38 (84)
Prednisolone	2 (4)
Eligible for platelet response assessment	43 (96)
(platelets $< 10 \times 10^9/L$ or transfusion dependent), n (%)	
Eligible for erythroid response assessment	29 (64)
(hemoglobin < 9 g/dL or transfusion dependent), n (%)	
Eligible for neutrophil response assessment ($< 1 \times 10^9/L$), n (%)	29 (64)

Abbreviations: ANC, absolute neutrophil count; Epag, eltrombopag; NSAA, non-severe aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; SAA, severe aplastic anemia.

Table 2. Outcomes of TPO-RA treatments

Patients	n = 45
Type of TPO-RA	
Epag alone, n (%)	40 (89)
Epag followed by Rom, n (%)	5 (11)
Maximum dose of TPO-RA	
Epag (mg), median (range)	100 (50–100)
Rom (µg/kg), median (range)	20 (15–20)
Maintenance dose of TPO-RA	
Epag (mg), median (range)	75 (12.5–100)
Rom (µg/kg), median (range)	20 (15–20)
Concomitant AA therapy	
Cyclosporine A	43 (96)
Metenolone acetate	29 (64)
None	6 (13)
Time to response	
Time to unilineage response (days), median (range)	84 (6–1,027)
Time to trilineage response (days), median (range)	397 (185–656)

Abbreviations: AA, aplastic anemia; Epag, eltrombopag; Rom, romiplostim; TPO-RA, thrombopoietin receptor agonist.

Table 3. Hematologic response to TPO-RAs by lineage

	Eligible, n	Response	
		At 6 months n (%)	Entire period n (%)
Any response	45	28 (62)	38 (84)
Platelet response	43	16 (37)	24 (56)
Erythroid response	29	8 (28)	11 (38)
Neutrophil response	29	15 (52)	22 (76)
Trilineage response	16	2 (13)	4 (25)

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Table 4. Adverse events during TPO-RA treatment

n = 45	Any grade	Grade 3–4	Grade 5
	No. of patients (%)		
All adverse events	18 (40)	3 (7)	5 (11)
Anorexia	4 (9)	0	0
Nausea	4 (9)	0	0
Lung infection	3 (7)	0	2 (4)
Oral submucosal hemorrhage	2 (4)	0	0
Blood AST increased	2 (4)	1 (2)	0
Blood ALT increased	2 (4)	1 (2)	0
Blood bilirubin increased	2 (4)	0	0
Headache	2 (4)	0	0
Febrile neutropenia	2 (4)	2 (4)	0
Urinary tract infection	1 (2)	0	1 (2)
Leukemia	1 (2)	0	1 (2)
Myelodysplastic syndrome	1 (2)	0	1 (2)
Hyperglycemia	1 (2)	0	0
Abdominal pain upper	1 (2)	0	0
Hemorrhoidal hemorrhage	1 (2)	0	0
Skin rash	1 (2)	0	0
Vomiting	1 (2)	0	0
Blood creatinine increased	1 (2)	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase;
TPO-RA, thrombopoietin receptor agonist.

Table 5. Univariate analysis of factors predicting response to eltrombopag

Factors		Patients, n	Unilineage response at 6 months (%)	p ^a
Age	< 75 vs ≥ 75 years old	19 vs 26	68 vs 58	0.543
Sex	female vs male	27 vs 18	56 vs 72	0.351
AA severitiy	non-severe vs severe	35 vs 10	60 vs 70	0.719
PNH clone	< 1 vs ≥ 1%	34 vs 8	71 vs 50	0.406
ANC	< 1.0 vs ≥ 1.0 x 10 ⁹ /L	27 vs 18	63 vs 61	1.000
Reticulocyte count	< 40 vs ≥ 40 x 10 ⁹ /L	21 vs 24	52 vs 71	0.233
Platelet count	< 20 vs ≥ 20 x 10 ⁹ /L	28 vs 17	64 vs 59	0.759
Maintenance dose of Epag	< 75 vs ≥ 75 mg/day	18 vs 27	50 vs 69	0.216
Time from AA diagnosis	< 6 vs ≥ 6 months	24 vs 21	75 vs 48	0.0727

Abbreviations: AA, aplastic anemia; ANC, absolute neutrophil count; Epag, eltrombopag; PNH, paroxysmal nocturnal hemoglobinuria.

^aFisher's exact test

Figures

Figure 1

Eltrombopag dose over time. The horizontal line in the center of each box indicates the median; the upper and lower edges of the box indicate the 25th and 75th percentiles, respectively; and the bars indicate the range from the 5th to the 95th percentile.

Figure 2

Response to TPO-RA by lineage. The Venn diagrams show the number of patients that had responses in each lineage at six months (A) and the best response during the entire follow-up period (B). The yellow, red, and blue circles indicate platelet, erythroid, and neutrophil responses, respectively.

Figure 3

Response to TPO-RA treatment over time by lineage: neutrophil response (A), erythroid response (B), and platelet response (C). The horizontal line in the center of each box indicates the median; the upper and lower edges of each box indicate the 25th and 75th percentiles, respectively; and the bars indicate the range from the 5th to the 95th percentile.