Eltrombopag for Treatment of Thrombocytopenia After Autologous Stem Cell Transplantation in Children: Single Center Experience

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Introduction: Thrombocytopenia is a common clinical problem in cancer patients undergoing high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). It can occur as prolonged isolated thrombocytopenia (PIT) or secondary failure of platelet recovery (SFPR) and may cause potentially fatal bleeding. However, data on the treatment of post-transplant thrombocytopenia is still lacking.

Methods: We reported our practices involving 15 pediatric patients who received eltrombopag (ELT) treatment for PIT and SFPR after autologous HSCT.

Results: The overall response was 78.5% (11/14), with 1 patient excluded due to noncompliance. The 12 surviving patients' median follow up was 699 days (range: 167 to 2250 d).

Conclusions: Our study indicates the efficacy and safety of ELT for treating PIT and SFPR after autologous HSCT in pediatric patients. However, more studies are needed to confirm these findings in children.

Key Words: autologous stem cell transplantation, thrombocytopenia, eltrombopag

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In cancer patients undergoing high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT), prolonged isolated thrombocytopenia (PIT), and secondary failure of platelet recovery (SFPR) are common clinical problems that can cause potentially fatal bleeding. PIT could be caused by an inadequate number of megakaryocytic progenitor cells in the autograft, insufficient megakaryocytic stimulatory growth factors, or the presence of inhibitory cytokines after high-dose chemotherapy.[1] Several studies have demonstrated an incidence of SFPR between 12% and 20%, and PIT around 20% to 40%.[2,3] There is currently no established guideline for treatment. Platelet transfusion remains the standard of care in patients with PIT or SFPR after HSCT. However, transfusion carries risks such as viral infections, infusion reactions, volume overload, acute lung injury, and platelet refractoriness.[4]

Thrombopoietin receptor agonists (TRAs), such as romiplostim and eltrombopag (ELT), bind to thrombopoietin c-MPL receptors to stimulate megakaryocyte maturation and platelet production.[5] Romiplostim's administration is subcutaneous, activating human TPO-R despite the absence of sequence homology with human thrombopoietin.[6] ELT is administered orally and is efficacious and safe in patients with immune thrombocytopenia (ITP) and aplastic anemia.[7,8] In addition, ELT leads to improvements in red blood cells and neutrophil counts.[9] Several studies have reported the efficacy of romiplostim and ELT for treating thrombocytopenia after mostly allogeneic HSCT in adults and pediatric cases. However, data on ELT treatment after autologous HSCT in children are lacking. Herein, we reported our practices involving 15 pediatric patients who received ELT treatment for PIT and SFPR after autologous HSCT.

PATIENTS AND METHODS

Patients

Inclusions

Our retrospective study included 15 consecutive patients who received ELT for persistent thrombocytopenia after autologous HSCT at Medipol University Hospital, Pediatric Stem Cell Transplantation Center between August 2016 and March 2023. This study was approved by our institute's ethics committee and involved off-label use. The following criteria were fulfilled by all patients: (a) underwent autologous HSCT, (b) improved total neutrophil count after myeloid engraftment, (c) developed PIT or SFPR.

PIT was defined as the engraftment of all peripheral blood cell lines but with platelet counts below 30,000/mm^3 or dependence on platelet transfusion for 30 days or longer after autologous HSCT. SFPR was defined as a decline in platelet counts below 30,000/mm^3 lasting at least 7 consecutive days after achieving primary platelet recovery.

Exclusions

None had a concurrent relapsed disease, liver enzymes >2.5 times normal values, or bilirubin >2 times normal values.

Treatment

Eltrombopag was started at a dosage of 12.5 mg/day in all patients below 12 kg in weight. The starting dose for

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TABLE 1. Summary of the Results

Parameters	Values, n (%)
Age, median (range) (y)	4.3 (1.4–19.75)
Sex	
Male	7 (46)
Female	8 (53)
Follow up, median (range) (d)	699 (67–2250)
Treatment duration, median (range) (d)	60 (15–198)
Disease	
Neuroblastoma	6 (40)
Ewing sarcoma	3 (20)
Brain tumor	3 (20)
Hodgkin lymphoma	3 (20)
Transfusion frequency	
>2 times per week	8 (53)
2 times per week	3 (20)
1 time per week	4 (26)
Type of thrombocytopenia	
Prolonged isolated thrombocytopenia	8 (53)
Secondary failure of platelet recovery	
After radiotherapy	5 (33)
Without radiotherapy	2 (13)
Bone marrow biopsy	
60%-80% cellularity	5 (33)
20%-30% cellularity	2 (13)
5% cellularity	2 (13)
Not performed	6 (40)
Outcome	
Alive	12 (80)
Dead	3 (20)
Response	
Good	11 (78.8)
No	3 (21.2)
Excluded*	1

*The patient who stopped the treatment, was excluded.

children between 12 and 20 kg was 25 mg/day, and for those above 20 kg, it was 50 mg/day. The dosage was increased by 12.5 mg every week until platelet counts exceeded 50,000/mm^3. We did not exceed 75 mg/day for patients below 11 years of age and 150 mg/day for older patients. When the platelet count exceeded 50,000/mm^3 without platelet transfusion for 7 consecutive days, the dose was tapered by 12.5 mg weekly.

Endpoints

The primary endpoints were platelet count recovery to 50,000/mm^3 for 7 consecutive days and transfusion independence. We defined partial response as platelet count recovery to 30,000/mm^3 for 7 consecutive days. Secondary endpoints were the safety and tolerability of ELT as assessed by evaluating adverse events.

We classified liver toxicity as follows:

- Grade 1 (mild): raised serum aminotransferase or alkaline phosphatase levels, or both, but total serum bilirubin <2.5 mg/dL and no coagulopathy (INR <1.5).
- Grade 2 (moderate): raised serum aminotransferase or alkaline phosphatase levels, or both, and total serum bilirubin level ≥ 2.5 mg/dL or coagulopathy (INR ≥ 1.5) without hyperbilirubinemia.
- Grade 3 (moderate to severe): raised serum aminotransferase or alkaline phosphatase levels and total serum bilirubin level ≥ 2.5 mg/dL, and hospitalization (or prolonged pre-existing hospitalization) because of drug-induced liver injury.
- Grade 4 (severe): raised serum aminotransferase or alkaline phosphatase levels and serum bilirubin ≥ 2.5 mg/dL, and at least one of the following: prolonged jaundice and symptoms beyond 3 months, signs of hepatic decompensation (INR ≥ 1.5, ascites, encephalopathy), or other organ failure believed to be related to drug-induced liver injury.
- Grade 5 (fatal): death or liver transplantation for drug-induced liver injury.

RESULTS

Fifteen patients were included in this study, comprising 8 females and 7 males. The median age was 4.3 years (range: 1.4 to 19.75). All patients underwent autologous HSCT

TABLE 2. The Details of the Eltrombopag Treatment

Number of the patient	PLT/mm^3 before ELT	Transfusion frequency per week before ELT	Time HSCT-start ELT (d)	Treatment duration (d)	ELT starting dose (mg)	ELT maximum dose (mg)	Time start ELT-PLT >30,000 (d)	Time start ELT-PLT >50,000 (d)
1	5000	2	30	170	12.5	25	96	96
2	12,000	3	28	52	25	25	24	29
3	14,000	1	86	15*	12.5	12.5	16	x
4	25,000	1	43	99	12.5	12.5	7	30
5	13,000	1	60	60	25	25	24	50
6	9000	4	28	60	50	50	11	19
7	9000	3	68	60	25	25	15	27
8	21,000	3	55	160	50	50	5	32
9	19,000	4	83	60	25	25	19	34
10	24,000	1	230	198	25	25	8	27
11	20,000	3	75	100	50	150	x	x
12	21,000	2	29	150	50	50	42	42
13	11,000	2	64	70	50	50	12	34
14	7000	4	44	19†	50	50	x	x
15	3000	4	76	28	50	150	x	x

*Refused the treatment.
†Relapsed under treatment.
ELT indicates eltrombopag; HSCT, hematopoietic stem cell transfusion; PLT, platelet.

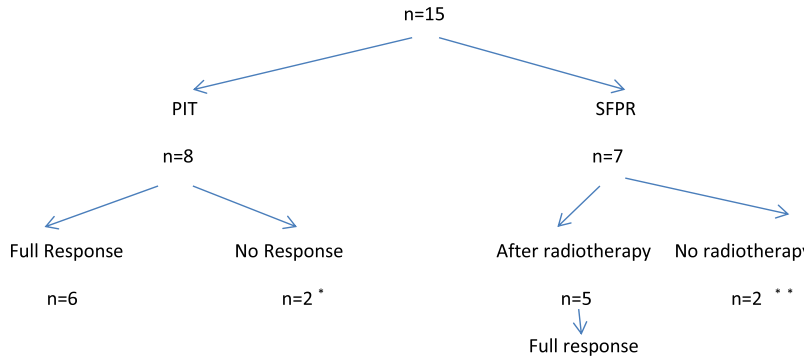

FIGURE 1. Summary of the responses. PIT indicates prolonged isolated thrombocytopenia; SFPR, secondary failure of platelet recovery. *One patient with 20% bone marrow cellularity and 1 patient with 5% bone marrow cellularity. **One patient stopped the treatment with a personal decision and 1 patient relapsed under ELT treatment. Both of them were excluded from the overall response.

(6 with neuroblastoma, 3 with Ewing sarcoma, 3 with brain neoplasm, and 3 with Hodgkin lymphoma). Eltrombopag was initiated in 8 patients with thrombocytopenia despite neutrophil engraftment on the 28th day of autologous HSCT (53.3%), defined as PIT. Seven patients (46.7%) had SFPR, with 5 of them experiencing thrombocytopenia after radiotherapy. None had concurrent relapsed disease, liver enzymes >2.5 times normal values, or bilirubin >2 times normal values.

Before ELT treatment, a bone marrow biopsy was performed on 9 patients. Bone marrow cellularity was 5% in 2 patients, 20% to 30% in 2 patients, and 60% to 80% in 5 patients. The overall response was 84% (11/13), with 2 patients excluded from the overall response, and 2 patients showing no response. The overall survival rate was 80% (12 /15). Three patients died due to relapsed disease. Demographic values and a summary of the results are shown in Table 1.

Details about ELT treatment are shown in Table 2. The median platelet count was 13,000/mm^3 (range: 3000 to 25,000/mm^3) before starting ELT. Patients who started ELT with platelet counts above 20,000/mm^3 were experiencing mucosal bleeding or epistaxis. Transfusion frequency before treatment was more than 2 times per week in 8 patients (53%), 2 times per week in 3 patients (20%), and 1 time per week in 4 patients (26%). Eltrombopag was initiated at a median time of 60 days (range: 28 to 230 d) and continued for a median period of 60 days (range: 15 to 198 d). In the patient with only 15 days of treatment (patient #3), treatment was refused by parents. In the patient with only 19 days of treatment (patient #14), the disease relapsed under treatment. These 2 patients were excluded from the overall response evaluation.

After excluding 2 patients, 11 of 13 patients (84%) reached a sustained platelet count of more than 30,000/mm^3 after a median time of 17 days (range: 5 to 96 d) and a sustained platelet count of more than 50,000/mm^3 after a median time of 32 days (range: 19 to 96 d) from starting ELT. Twelve of 15 platelet transfusion-dependent patients became independent from transfusions, with a median interval between starting treatment and the last transfusion of 22 days (range: 6 to 85 d). According to platelet monitoring, ELT dosage was increased in 3 patients starting from the second week. One of these 3 patients responded to the higher dose, while the other 2 did not. Except for these 2 nonresponding patients, 2 patients required platelet transfusions at the end of the first month, with their last transfusions on the 85th and 40th day of treatment, respectively. However, the need for transfusion was greatly reduced. All patients who had a full response to ELT tolerated tapering off ELT without recurrence of thrombocytopenia. There was no patient with a partial response.

None of our patients experienced grade 3 to 4 liver toxicity, thrombosis, or other grade 3 to 4 toxicities. Occasional elevations in liver enzymes were observed in 4 patients, but these were not dose limiting toxicities.

The median follow up of the 12 surviving patients is 699 days (range: 167 to 2250 d). Three patients died due to relapsed disease. One of them experienced a relapse under ELT treatment.

In 1 patient with 5% bone marrow cellularity and fewer megakaryocytes, the drug was fully effective. In the other patient with 5% bone marrow cellularity, the drug was not effective. In 2 patients with 20% to 30% bone marrow cellularity, the drug was also not effective. However, 1 of these 2 patients relapsed while under ELT treatment. Four patients with 60% to 80% bone marrow cellularity had a full response, and 1 patient was excluded from the statistics. Two patients had no response to ELT: 1 patient with Ewing sarcoma and 5% bone marrow cellularity had a full response to ELT but relapsed after stopping treatment and died. The second patient was diagnosed with Hodgkin lymphoma and

TABLE 3. Reports About Eltrombopag for Post-Transplant Thrombocytopenia in Adults

References	Patient (n)	PIT, n (%)	SFPR, n (%)	Response, n (%)	Median day to reach PLT $>50,000$/mm^3
Tanaka et al[12]	12	5 (41.6)	7 (58.4)	8 (66)	54
Gao et al[13]	32	15 (46.8)	17 (53.2)	21 (65.6)	41
Rivera et al[14]	14	3 (21.5)	11 (78.5)	8 (57)	91
Tang et al[15]	12	0	12	10 (83.3)	29

PIT indicates prolonged isolated thrombocytopenia; SFPR, secondary failure of platelet recovery.

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TABLE 4. Reports About Eltrombopag for Post-Transplant Thrombocytopenia in Children

References	Median age	Patient (n)	PIT, n (%)	SFPR, n (%)	Response, n (%)
Qiu et al[16]	6.6	43	33 (76.7)	10 (23.3)	38 (88.9)
Yaman et al[17]	15	18	12 (66.6)	6 (33.4)	14 (77.7)
Masetti et al[18]	14.1	9	0	9 (100)	8 (88.8)
Uria-Oficialdegui et al[19]	11	5	5 (100)	0	4 (80)
Li et al[20]	12	3	1 (33.4)	2 (66.6)	2 (66.6)

PIT indicates prolonged isolated thrombocytopenia; SFPR, secondary failure of platelet recovery.

had 20% bone marrow cellularity; he is disease free but is being followed up with thrombocytopenia. A summary of treatment results is shown in a diagram in Figure 1.

Bone marrow cellularity was correlated with days to reach PLT 30,000/mm^3 ($P<0.001$, $r=-0.981$) and 50,000/mm^3 ($P=0.045$, $r=-0.887$). However, stem cell dose was not correlated with days to reach PLT 30,000/mm^3 ($P=0.186$) and 50,000/mm^3 ($P=0.263$). There was no statistically significant difference between the response and bone marrow cellularity ($P=0.286$), stem cell dose ($P=0.753$), or age ($P=0.571$). There was no statistically significant difference between the days when PIT and SFPR groups reached 30,000/mm^3 ($P=0.937$) and 50,000/mm^3 ($P=0.662$) PLT values. There was no statistically significant correlation between the time to reach PLT 30,000/mm^3 ($P=0.425$) and 50,000/mm^3 ($P=0.968$) and the time to start ELT. There was no statistically significant correlation between the treatment time and the time between HSCT and ELT initiation ($P=0.222$).

DISCUSSION

We described our practices involving 15 pediatric patients who received ELT treatment for PIT and SFPR after autologous HSCT. There are 2 case reports of pediatric patients with poor graft function after autologous HSCT successfully managed with ELT. In the first report, a 4-year-old female patient with high-risk neuroblastoma was treated with ELT for thrombocytopenia after autologous HSCT. In 8 weeks, the platelet count increased to $>100{,}000/mm^3$, resulting in improvement in all 3 cell lines.[10] In the second report, a 5-year-old male patient with refractory Hodgkin lymphoma was treated with ELT for the same indication and had a good response.[11]

Several studies reported the use of ELT for post-HSCT thrombocytopenia, but they all involved allogeneic HSCT. Four studies in adults are summarized in Table 3,[12–15] and 5 studies in children are summarized in Table 4.[16–20] The median day to reach a 50,000/mm^3 platelet count in our study was similar to adult studies. In the studies by Tanaka et al[12] and Qui et al,[16] the number of megakaryocytes was found to correlate with the median day of reaching platelet recovery, supporting our finding that bone marrow cellularity was correlated with days to reach 50,000/mm^3.

In the study by Yaman et al,[17] grade 4 liver toxicity was seen in 2 patients. There were neither grade 3 to 4 toxicities nor thrombosis in other studies, like our study.

ELT also leads to an improvement in red blood cells and neutrophil counts.[9] Aydin and colleagues reported a single-center experience supporting this, with 12 patients, 6 of whom had trilineage cytopenia and 3 had bilineage cytopenia. Ten of the 12 patients became transfusion independent, confirming that ELT rescues multilineage hematopoiesis in patients with post-transplant cytopenias.[21]

Raut et al[22] reported an experience in adults with 12 patients using ELT for post-HSCT thrombocytopenia, and 10 of the 12 patients underwent autologous HSCT in that study. The median duration of treatment was 29 days, and the median platelet increment was 36,000/mm^3. This is the only report with a high number of patients who underwent autologous HSCT and were treated with ELT for post-HSCT thrombocytopenia.

Our study is the first report on the use of ELT for thrombocytopenia after autologous stem cell transplantation in pediatric patients. Our response rate was like the literature for postallogeneic HSCT thrombocytopenia in pediatric cases.

CONCLUSIONS

In summary, ELT appears to have significant outcomes for the treatment of PIT and SFPR after autologous HSCT in pediatric patients. However, our study is limited by its retrospective design and small patient number. Further studies with larger patient groups and randomized controlled trials are needed to validate these data.

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