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Avatrombopag for severe refractory thrombocytopenia in a pediatric patient with ALL following allogeneic hematopoietic stem cell transplantation: A case report

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ABSTRACT

Patients who receive allogeneic hematopoietic stem cell transplantation (alloHSCT) are at risk for developing persistent thrombocytopenia. Here, we describe treatment with avatrombopag, a thrombopoietin receptor agonist, in a pediatric patient with chronic, severe, transfusion-dependent thrombocytopenia ($<10 \times 10^3/\mu L$) post-alloHSCT that was persistent despite treatment with romiplostim, another thrombopoietin receptor agonist. Following the granting of a compassionate use investigational new drug authorization, avatrombopag treatment was initiated, and the patient's platelet count increased. To date, the patient has maintained a platelet count $>100 \times 10^3/\mu L$. No adverse events or medication toxicities have been reported, and he has resumed his pre-alloHSCT activities.

1. Introduction

Persistent thrombocytopenia following allogeneic hematopoietic stem cell transplantation (alloHSCT) leads to increased morbidity and mortality. Thrombocytopenia treatment may include immunomodulators, thrombopoietin receptor agonists (TPO-RAs), and stem cell boost.

TPO-RAs activate the thrombopoietin receptor, stimulating platelet production. Approved TPO-RAs include romiplostim, eltrombopag, lusutrombopag, and avatrombopag. While none are approved for treating persistent thrombocytopenia in the alloHSCT setting, several reports, mostly focused on adults, have provided evidence that they may be effective for these patients [1–8]. Findings from small retrospective studies and case series provide support for treatment with eltrombopag or romiplostim in the pediatric population [2–6]. Recently, evidence has emerged from small single-center studies in China supporting the safe and effective use of avatrombopag to treat thrombocytopenia following alloHSCT in adult and pediatric patients [7,8]. Despite these reports, there is an overall paucity of data describing the use of TPO-RAs in pediatric patients who develop thrombocytopenia following alloHSCT. This case study describes the use of avatrombopag in a pediatric patient with chronic, severe, transfusion-dependent thrombocytopenia ($<10 \times 10^3/\mu L$) post-alloHSCT.

2. Case presentation

A 14-year-old Hispanic male who presented with acute lymphoblastic leukemia (ALL) was initially treated as a non-registered participant of the Children's Oncology Group AALL1732 protocol (clinicaltrials.gov/study/NCT03959085) then transitioned to the AALL1631 protocol (clinicaltrials.gov/study/NCT03007147) on day 15 following a diagnosis of Philadelphia chromosome-positive ALL (Ph+ ALL). Details of the patient's chemotherapy regimen are provided in the Table 1.

He received bridging therapy with blinatumomab in the setting of refractory disease and was disease negative prior to undergoing maternal haploidentical peripheral alloHSCT (6.25×10^6 $CD34^+$/kg) with myeloablative conditioning. He received post-transplant cyclophosphamide with tacrolimus and mycophenolate mofetil as graft-versus-host disease (GVHD) prophylaxis. Platelet engraftment was observed on day +29 and neutrophil engraftment on day +21; platelet count remained $\leq 70 \times 10^3/\mu L$ after transplantation. Eltrombopag was initiated on day +171 (discontinued after 1 month due to lack of insurance), followed by romiplostim (2 months), high-dose intravenous immunoglobulin, rituximab, high-dose corticosteroids, and decitabine, but his severe thrombocytopenia persisted (Fig. 1). Post-alloHSCT, the patient experienced complications of hepatic variant GVHD,

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Table 1
Chemotherapy regimen for ALL.

Chemotherapy (Day 0 through Day 14)
Induction per AALL1732 (clinicaltrials.gov/study/NCT03959085):
• Intrathecal cytarabine: 70 mg; Day 1
• Vincristine: 1.5 mg/m^2; Days 1, 8
• Daunorubicin: 25 mg/m^2/dose; Days 1, 8
• Prednisone: 30 mg/m^2/dose; BID Days 1-14
• Pegaspargase: 2500 IU/m^2; Day 4
• Intrathecal methotrexate: 15 mg; Days 8
Chemotherapy (Day 6 through Day 30)
Induction IA per AALL1631 (clinicaltrials.gov/study/NCT03007147):
• Imatinib: 340 mg/m^2/day; Days 1-32
• Vincristine: 1.5 mg/m^2; Days 15 and 22
• Daunorubicin: 25 mg/m^2/dose; Days 15 and 22
• Prednisone: 30 mg/m^2/dose; BID Days 15-28
• Intrathecal methotrexate: 12 mg; Day 29
Chemotherapy (Day 36 through Day 101)
Induction IB:
• Cyclophosphamide: 1000 mg/m^2 IV; Days 1 and 28
• Cytarabine: 75 mg/m^2 IV; Days 1-4, 8-11, 15-18, and 22-25
• Mercaptopurine: 60 mg/m^2/day PO; Days 1-28
• Intrathecal methotrexate: 12 mg; Days 8 and 22
• Dasatinib 80 mg: PO daily Days 1-28
Chemotherapy (Day 119 through Day 147)
• Blinatumomab:
◦ 5 μg/m^2 IV; administered over 24 h on Days 1-7
◦ 15 μg/m^2 IV; Days 8-28
Chemotherapy (Day 167 through Day 195)
• Blinatumomab: 15 μg/m^2 IV; continuous infusion × 28 days

ALL: acute lymphocytic leukemia; BID: twice daily; IV: intravenous; PO: per oral

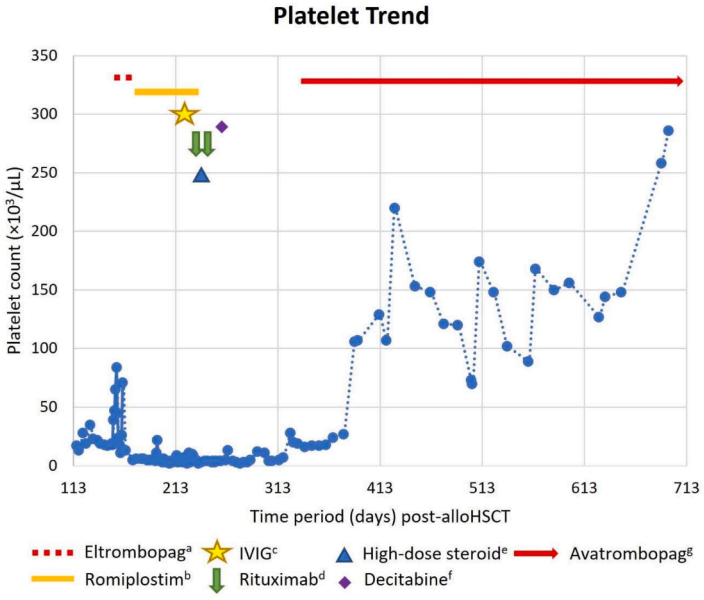

Fig. 1. Platelet trend and treatment over time.
alloHSCT: allogeneic hematopoietic stem cell transplantation; IV: intravenous; IVIG: intravenous immunoglobulin
[a]Eltrombopag dose, 75 mg daily (per oral)
[b]Romiplostim dose, 10 μg/kg once weekly subcutaneous
[c]IVIG dose, 1 mg/kg IV given over 12 h
[d]Rituximab dose, 375 mg/m^2 IV
[e]High-dose corticosteroid dose, 1 g IV given daily for 3 days
[f]Decitabine dose, 15 mg/m^2 IV given daily for 3 days
[g]Avatrombopag dose, titrated to the maximum dose of 40 mg daily; after 3 months, titrated down to 40 mg 3 times per week with 20 mg on alternating days; after 9 months, titrated down to 20 mg daily

adenoviremia, poor graft function, and *Enterobacter cloacae* bacteremia. He received a CD34$^+$ stem cell boost from his original donor for poor graft function on day +185. The patient had severe pancytopenia 7 months after receiving alloHSCT. Cellularity of 20–30 % with overall decreased megakaryocytes and no evidence of leukemia relapse or GVHD was found based on bone marrow morphology, and he did not have transplant-associated thrombotic microangiopathy. A stem cell boost was administered to treat presumed poor graft function. He had a partial response (anemia and neutropenia resolved), but his severe thrombocytopenia persisted. The patient was negative for disease and

had full donor chimerism and no evidence of T-cell receptor clonality. Immature platelet fraction and CXCL9 were elevated (8.8 % and 4270 pg/mL, respectively). He did not have hemophagocytic lymphohistiocytosis, and his maximum ferritin level was 2348 ng/mL. The patient continued to test negative for platelet antibodies, and his symptoms and laboratory data indicated persistent severe immune thrombocytopenia (ITP). Prior to initiating avatrombopag, he had been admitted to the hospital for symptomatic thrombocytopenia several times and had received 72 units of platelets.

A compassionate use investigational new drug authorization was granted for avatrombopag, given the disease severity. Treatment was initiated at 20 mg daily on day +332, followed by dose adjustment until platelet recovery to $>50 \times 10^3/\mu L$ without transfusion was achieved. Following the package insert, the avatrombopag dose was titrated to 40 mg daily (maximum dose); platelet count reached $>100 \times 10^3/\mu L$ in around 6 weeks. The dose was titrated to 40 mg 3 times per week after 3 months of treatment, with 20 mg on alternating days; following a platelet count increase to $>200 \times 10^3/\mu L$, the patient now receives 20 mg daily. To date, the patient has maintained a platelet count $>100 \times 10^3/\mu L$, and no adverse events or medication toxicities have been observed. The patient has returned to his pre-alloHSCT activities, has received re-immunizations, and is playing contact sports.

3. Discussion and conclusions

We presented a highly complex, multifactorial, and refractory case of post-alloHSCT thrombocytopenia in a pediatric patient with Ph+ ALL. The thrombocytopenia had no identifiable etiology and was highly refractory to treatment. In this patient, avatrombopag was well tolerated and effective in platelet recovery. The only other report of avatrombopag in pediatric patients with post-HSCT thrombocytopenia is a small, single-center, retrospective study that also found avatrombopag to be safe and effective [8]. That study reported that, of patients treated for thrombocytopenia due to poor graft function or secondary failure of platelet recovery, 65 % (13/20) achieved a complete response (defined as platelet count $\geq 50 \times 10^9/L$ for at least 7 consecutive days without transfusion) [8].

Treatment of thrombocytopenia is important for improving health-related quality of life (HRQoL) in pediatric patients, as it is negatively impacted by persistence of disease and low platelet counts [9]. Among pediatric patients with ITP, treatment with TPO-RAs to improve platelet counts has been reported to benefit mood and result in increased participation in activities/sports, suggesting an HRQoL benefit with treatment [10]. The sustained recovery of platelet counts in this pediatric patient with refractory thrombocytopenia following alloHSCT with avatrombopag treatment is encouraging and supports future clinical studies of avatrombopag for patients who experience post-HSCT thrombocytopenia.

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Informed consent

Verbal informed consent was obtained from the patient's parent.

CRediT authorship contribution statement

Emilie J. Lynch: Data curation, Project administration, Writing – original draft, Writing – review & editing. **Autumn Citta:** Project administration, Writing – review & editing. **Constance Alford:** Project administration, Writing – review & editing. **John A. Ligon:** Project administration, Writing – review & editing. **Mansi Dalal:** Project administration, Writing – review & editing. **Paul Castillo:** Project administration, Writing – review & editing. **Biljana Horn:** Project administration, Writing – review & editing. **Natalie Dotson:** Project administration, Writing – review & editing. **Giselle Moore-Higgs:** Project administration, Writing – review & editing. **Jordan Milner:** Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Avatrombopag was provided via compassionate use by Sobi, Inc. The authors have no conflicts of interest to declare related to the contents of this case study.

Data availability

The data are available from the corresponding author upon reasonable request.

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