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Thrombopoietin receptor agonists for thrombocytopenia in pediatric hematologic malignancies

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October 30, 2024

Abstract

Background: Thrombopoietin receptor agonists (TPO-RAs) have demonstrated efficacy in treating clinically significant thrombocytopenia, including chemotherapy-induced thrombocytopenia (CIT) in adults. However, data regarding their safety and efficacy in pediatric, adolescents, and young adult (AYA) patients with hematologic malignancies are limited. **Methods**: We retrospectively identified 15 pediatric and AYA patients aged 25 years or younger with hematologic malignancies treated with a TPO-RA at UCSF Benioff Children's Hospitals between 2015 and 2023. Platelet counts and transfusion requirements were compared before and after TPO-RA therapy. **Results**: The median age at TPO-RA initiation was 16 years (range: 7-25 years). Nine patients (60%) had a history of bleeding or comorbidity that predisposed to severe bleeding risk. Eleven patients received romiplostim and four patients received eltrombopag. The median platelet count significantly increased from 24 x 10 ^{9}/L at baseline to 54 x 10 ^{9}/L after 3 weeks of any TPO-RA therapy (p =0.029). Monthly platelet transfusion requirements significantly decreased from a median of 15 to two units after TPO-RA therapy (p=0.007). Fourteen of the 15 patients (93%) achieved a sustained platelet count >50,000/μL within eight weeks, with a median time to response of 3 weeks. No TPO-RA-related adverse events were observed. **Conclusion**: TPO-RAs were effective in managing refractory thrombocytopenia in pediatric and young adult patients being treated for hematologic malignancies, with a favorable safety profile, even among patients with multiple comorbidities. These findings warrant further investigation through prospective clinical trials to confirm efficacy and establish clinical guidelines for this population.

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Word Count:

a. Abstract: 248

b. Main Text: 2357

Number of Tables: 3

Number of Figures: 2

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Methods : We retrospectively identified 15 pediatric and AYA patients aged 25 years or younger with hematologic malignancies treated with a TPO-RA at UCSF Benioff Children's Hospitals between 2015 and 2023. Platelet counts and transfusion requirements were compared before and after TPO-RA therapy.

Results : The median age at TPO-RA initiation was 16 years (range: 7-25 years). Nine patients (60%) had a history of bleeding or comorbidity that predisposed to severe bleeding risk. Eleven patients received romiplostim and four patients received eltrombopag. The median platelet count significantly increased from 24 x 10^9/L at baseline to 54 x 10^9/L after 3 weeks of any TPO-RA therapy (p =0.029). Monthly platelet transfusion requirements significantly decreased from a median of 15 to two units after TPO-RA therapy (p=0.007). Fourteen of the 15 patients (93%) achieved a sustained platelet count >50,000/μL within eight weeks, with a median time to response of 3 weeks. No TPO-RA-related adverse events were observed.

Conclusion : TPO-RAs were effective in managing refractory thrombocytopenia in pediatric and young adult patients being treated for hematologic malignancies, with a favorable safety profile, even among patients with multiple comorbidities. These findings warrant further investigation through prospective clinical trials to confirm efficacy and establish clinical guidelines for this population.

Short running title: "TPO-RAs for pediatric hematologic malignancies"

Key words: Thrombopoietin receptor agonist, romiplostim, eltrombopag, pediatric, adolescent, and young adults, leukemia, hematologic malignancies

Abbreviations key:

Abbreviation	Full term
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
AYA	adolescent and young adult
CAR	chimeric antigen receptor
CIT	chemotherapy-induced thrombocytopenia
c-MPL	thrombopoietin receptor
HSCT	hematopoietic stem cell transplant
ITP	immune thrombocytopenia
MDS	myelodysplastic syndrome
MPAL	mixed phenotype acute leukemia

Abbreviation	Full term
TPO-RA	thrombopoietin receptor agonist

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Introduction

Thrombocytopenia in patients with hematologic malignancies often results from the disease itself or as a side effect of intensive chemotherapy. Persistent thrombocytopenia can lead to severe bleeding complications with associated morbidity and mortality.[1] Current standard-of-care strategies, including platelet transfusions, chemotherapy dose reductions, and delays to allow spontaneous platelet recovery, are problematic for several reasons. Platelet transfusions provide only transient increases in platelet count, can cause multiple side effects, and are not effective in all patients. Additionally, chemotherapy dose reductions and delays can compromise antitumor efficacy, potentially leading to poorer outcomes. [2-4]

Recombinant thrombopoietin receptor agonists (TPO-RAs) stimulate platelet production by binding to and activating the thrombopoietin receptor (c-MPL) on megakaryocyte progenitor cells, offering a pharmacologic approach to address thrombocytopenia in various clinical contexts. There are four currently available agents in the United States: the subcutaneous injectable drug romiplostim and the oral small-molecule agents eltrombopag, avatrombopag, and lusutrombopag. Romiplostim and eltrombopag are currently US Food and Drug Administration approved for pediatric and adult chronic immune thrombocytopenia (ITP)[5,6], while the oral TPO-RAs have additional approvals for aplastic anemia[7], periprocedural thrombocytopenia in patients with chronic liver disease[8], and hepatitis-associated thrombocytopenia in adults[9]. TPO-RAs have been shown to effectively increase and sustain platelet counts with a favorable long-term safety profile across these clinical contexts[5,10,11]. Although TPO-RAs are not approved for chemotherapy-induced thrombocytopenia (CIT), studies in adults with predominantly solid tumors have shown that romiplostim improves platelet counts, leading to fewer chemotherapy delays and dose reductions without significant toxicities.[3,12-15] Recent data also suggest eltrombopag is safe and effective for managing thrombocytopenia in adult patients with hematologic malignancies following chimeric antigen receptor (CAR)T-cell therapy. [16,17]

Despite these promising data supporting the use of TPO-RAs across multiple clinical contexts in adults with cancer, the role of TPO-RAs in pediatric oncology is underexplored. Data on their safety and efficacy in children and young adults are limited, and the few available studies are focused primarily on solid malignancies in small cohorts.[18-20] Although the National Comprehensive Cancer Network provides recommendations for managing thrombocytopenia in adults, including the use of TPO-RAs for CIT and ITP[21], these guidelines do not extend to pediatric or adolescent and young adult (AYA) populations.

In light of these gaps, we report on our institutional experience of 15 pediatric and AYA patients with hematologic malignancies who received a TPO-RA between 2015 and 2023.

Methods

Study Design and Patient Population

After IRB approval, a retrospective chart review identified eligible patients aged 25 years or younger. Patients were included if they were diagnosed with any hematologic malignancy and received treatment with a TPO-RA at any point in their clinical course from 2015 to 2023, including during treatment at initial diagnosis, relapse, following hematopoietic stem cell transplant (HCST) or CAR T-cell therapy.

Data were retrospectively extracted from electronic medical records, including patient demographics, diagnosis, treatment history, TPO-RA history, and clinical outcomes. Patients included in this case series were not on a clinical trial; therefore, the selection of TPO-RA, dose, and duration of treatment was based on clinician discretion.

Romiplostim was administered as a once weekly subcutaneous injection at doses ranging from 1 mcg/kg to 10 mcg/kg. Eltrombopag was administered as a daily tablet at doses ranging from 50mg to 150mg.

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Data and Statistical Analysis

Descriptive statistics were used to summarize patient demographics, diagnoses, and treatment characteristics. Platelet counts at baseline were compared with platelet counts at one, two, three, and four weeks after TPO-RA initiation using the exact Wilcoxon signed-rank test. Given the multiple comparisons across time points, a Benjamini-Hochberg correction was used to control the false discovery rate, with an adjusted p-value of <0.05 considered statistically significant. Platelet transfusion requirements before and after TPO-RA initiation were also compared using the exact Wilcoxon signed-rank test. Adverse events, including drug-related toxicities and bleeding events, were recorded and analyzed. All statistical analyses were conducted in R.

Results

Patient demographics and clinical characteristics

Fifteen pediatric and young adult patients with hematological malignancies who received a TPO-RA were included in this case series**(Table 1).** The cohort consisted of nine females and six males, with a median age of 16 years (range: 7-25 years). Diagnoses included a range of hematologic malignancies. Seven patients had undergone a prior HSCT. Patients received a TPO-RA during a variety of phases of therapy, including initial induction, consolidation, delayed intensification, re-induction following relapse, following CAR T-cell therapy and post-HSCT. Ten patients (67%) had disease in remission at the time of receiving a TPO-RA.

In 14 patients (93%), a TPO-RA was initiated due to thrombocytopenia refractory to platelet transfusions. Nine patients (60%) had an additional comorbidity that placed them at very high risk of bleeding or refractory thrombocytopenia, including angioinvasive fungal infections (n=3), history of retinal hemorrhages (n=2), brain abscess (n=1), transplant-associated thrombotic microangiopathy and respiratory infections with associated hemoptysis (n=2), and hemorrhagic cystitis secondary to BK viremia (n=1). One patient was a Jehovah's Witness who received romiplostim prophylactically to minimize transfusions. One patient had refractory thrombocytopenia secondary to human leukocyte antigen alloimmunization.

TPO-RA treatment and response

Data on TPO-RA treatment and response are summarized in **Table 3.** Ten patients (67%) received romiplostim and five (33%) received eltrombopag. The median starting dose for eltrombopag was 50 mg daily (range 50-200mg daily) and 2 mcg/kg (1-10 mcg/kg daily) for romiplostim. The median duration of treatment was four weeks for romiplostim (range: 1-32 weeks) and six weeks for eltrombopag (range: 3-20 weeks).

Platelet trends for each patient are shown in **Fig. 1** . The median baseline platelet count was 24 x 10^9/L(range: 2-119 x 10^9/L). There was no significant difference at one week after TPO-RA initiation ($p = 0.145$). Significant increases in platelet counts were observed at two weeks ($p = 0.031$), three weeks ($p = 0.031$), and four weeks ($p = 0.031$) of initiating a TPO-RA.

Fourteen patients (93%) achieved a sustained platelet count of 50 x 10^9/L or greater, with a median time to response of 3 weeks (range 1-8 weeks). Ten patients (67%) achieved a platelet count of 100 x10^9/L or greater following TPO-RA administration within eight weeks (range 2-8 weeks) , including 82% of patients who received romiplostim and 25% of patients who received eltrombopag. The peak platelet count recorded was 1,036 x 10^9/L in a patient receiving romiplostim at 10mcg/kg (patient 12). The median platelet count at three weeks was 66 x 10^9/L for patients who received romiplostim and 49 x 10^9/L for patients who received eltrombopag.

There was a statistically significant reduction in platelet transfusion requirements following TPO-RA initiation **(Fig. 2).** The median number of transfusions (platelet units) required in the month prior to treatment was 15 (range: 0-62), which decreased to two (range: 0-30) during the first four weeks post-treatment ($p = 0.004$).

Toxicities and reasons for discontinuing TPO-RA therapy

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No patients experienced adverse events related to TPO-RA therapy that were gradable by the Common Terminology Criteria for Adverse Events version 5[22]. Three patients experienced self-resolving thrombocytosis within 4 weeks of TPO-RA initiation (platelet count 527,000-1036,000/μL) without thromboembolic events. In eight patients (53%), the TPO-RA was discontinued due to a decreased platelet transfusion requirement or otherwise adequate clinical response defined by their provider. In six patients (40%), the TPO-RA was discontinued due to death that was unrelated to TPO-RA in all cases (**Table 2)** . For Patient 1, eltrombopag was discontinued in the setting of grade 4 hyperbilirubinemia, thought to be related to multiple infections, hemochromatosis secondary to transfusions, autoimmune hemolytic anemia, and possible graft versus host disease. While eltrombopag and its metabolites have been reported to positively interfere with spectrophotometric measurements of total bilirubin,[23,24] bilirubin continued to rise in this patient following discontinuation of eltrombopag, further supporting that the hyperbilirubinemia was unrelated to eltrombopag.

There were no new grade 3 or higher bleeding complications during TPO-RA therapy. However, four patients with pre-existing bleeding (bronchopulmonary hemorrhage, lower gastrointestinal hemorrhage, and epistaxis) experienced persistence or recurrence of these conditions while receiving a TPO-RA **(Table 3).**

Additional clinical outcomes

At a median follow-up of 37 months (range 11 to 69 months), eight patients had died due to disease progression or complications (**Table 3**). The median overall survival following TPO-RA initiation was 15 months (range: 1-48 months). Five patients relapsed following TPO-RA initiation: three patients with pre-B-ALL, one patient with myelodysplastic syndrome (MDS) that transformed to acute myeloid leukemia (AML) prior to TPO-RA initiation, and one patient with B/Myeloid mixed phenotypic acute leukemia (MPAL). The median relapse-free survival was 6 months (range: 0-46 months). No patients developed a new myeloid malignancy.

Discussion

To our knowledge, this is the first case series to report on the real-world use of TPO-RAs to treat thrombocytopenia in pediatric and AYA patients with hematologic malignancies. Our study demonstrated that treatment with TPO-RAs effectively increased platelet counts and reduced transfusion requirements in 93% (14/15) of patients. Platelet counts significantly increased within two weeks of initiating TPO-RA therapy, with sustained responses and an associated significant reduction in platelet transfusion requirements. These findings align with previous studies in adult populations and other pediatric contexts focused predominantly on their use in solid malignancies, suggesting that TPO-RAs can be valuable in managing thrombocytopenia in pediatric and AYA patients with hematologic malignancies.[5,6,9,10,25,26]

Refractory thrombocytopenia was the most common reason for TPO-RA administration. Nine patients (60%) had either an existing bleeding complication or a comorbidity that placed them at high risk of severe bleeding events and insufficient response to platelet transfusions. No patients experienced adverse events related to TPO-RA therapy. Three patients experienced self-resolving thrombocytosis without thromboembolic events, a known but manageable risk associated with TPO-RA use.

While more data are required to identify appropriate indications for TPO-RA therapy, our data suggest that both romiplostim and eltrombopag are safe across a range of doses, durations of therapy, diagnoses, and stages of treatment. Three representative patient courses are detailed in vignettes to highlight the broad range of potential contexts in which TPO-RAs may be useful (Supplemental Data). Despite the broad potential utility of TPO-RAs in managing thrombocytopenia, their use was limited in this cohort due to the high cost of these agents. The cost of 125mcg romiplostim is approximately $1390, and a two-week supply of 50 mg eltrombopag is approximately $6500. As such, in our cohort, use of TPO-RA therapy was limited to those patients with thrombocytopenia refractory to platelet transfusions and/or those with comorbidities that predisposed to high bleeding risk.

Notably, our study included a high proportion of patients (67%) with multiple life-threatening comorbidities

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and patients with relapsed disease, nearly half of whom had received prior HSCT. As such, more than half of the patients died of complications unrelated to TPO-RA use. In addition, about one third of patients in this cohort with high-risk hematologic malignancies experienced relapse after initiation of TPO-RA therapy.

Historically, concerns have been raised about the potential for TPO-RAs to stimulate the proliferation c-MPL-expressing myeloid blasts.[27] Subsequent preclinical studies[28] and clinical trials[25,26,29] of TPO-RAs in the context of AML and MDS have not supported these concerns. In our study, two of four patients with myeloid malignancies relapsed after receiving TPO-RA therapy: one patient with TCF3-ZN384-postive B/myeloid MPAL (patient 3) and one with GATA2-driven MDS transformed to AML (patient 4). Patient 7 with t(8;21) AML had a transiently rising RUNX1-RUNX1T1 fusion transcript by reverse transcription polymerase chain reaction but did not experience overt hematologic relapse. Patient 14 with inv(16) AML has been relapse-free for 48 months. While this study was neither designed nor powered to assess a causal relationship between TPO-RA use and leukemia relapse, the relapse rates both in the overall cohort and specifically among patients with myeloid malignancies are concordant with those reported in the literature for similar populations[30,31].

Although our cohort represents a highly pretreated group with multiple comorbidities, including severe infections, bleeding complications, and hyperinflammation, 14/15 (93%) of patients achieved a platelet count of 50 x 10^9/L or greater and had decreased platelet transfusion requirements within 8 weeks (range 1-8 weeks, median 3 weeks). Seven patients became transfusion independent during this time. We hypothesize that the magnitude of benefit may be even greater in populations with fewer comorbidities and prior cancer-directed therapies.

This study has several limitations that may restrict the external generalizability of our findings, including the retrospective design, single institution nature, and small sample size comprising a highly heterogeneous population enriched for patients with poor clinical outcomes. Further prospective studies with larger, more homogenous cohorts are needed to confirm these findings and establish standardized guidelines for the use of TPO-RAs in pediatric and AYA patients with hematologic malignancies. Moreover, our study did not include a matched control group of patients who did not receive TPO-RA therapy, raising the possibility that some patients could have experienced spontaneous platelet recovery. However, the close temporal association between TPO-RA administration and the significant increase in platelet counts in nearly all patients, most of whom had severe, transfusion-refractory thrombocytopenia, make it likely that platelet recovery was attributable to TPO-RA treatment. In addition, the rationale for selecting a specific TPO-RA among the four available agents was not available from our chart review. While we postulate that practical considerations, such as patient preferences around route of administration, dosing frequency, cost, and insurance coverage influenced the choice of therapy, we are unable to draw conclusions about the comparative efficacy and safety of these agents in this patient population. More detailed prospective data collection, including clinician rationale for therapy selection, would help to better understand these decision-making factors and optimize treatment strategies.

Despite these limitations, our findings suggest that romiplostim and eltrombopag are safe and effective agents that may be incorporated into supportive care regimens to manage thrombocytopenia in pediatric and AYA patients with hematologic malignancies and thrombocytopenia across a broad range of clinical contexts. However, neither eltrombopag nor romiplostim takes effect immediately, requiring a median of three weeks to improve platelet counts; therefore, these agents should not be a substitute for platelet transfusions during this period. Given the dearth of data on TPO-RA use in pediatric and young adult patients with hematologic malignancies, prospective clinical trials are warranted to validate our findings and explore the long-term outcomes of TPO-RA therapy. Additionally, future research should focus on identifying patient-specific factors that predict response to TPO-RAs, optimizing dosing strategies, and evaluating the cost-effectiveness of TPO-RA therapy in this population.

Conflict of Interest

The authors do not have any conflicts of interests to declare.

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Acknowledgements

This work was supported by Alex's Lemonade Stand Foundation Center of Excellence, the Campini Foundation, and Cancer Center Support Grant P30CA082103.

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Legends

Table 1: Patient demographics and cancer diagnosis at the time of TPO-RA initiation

Table 2: TPO-RA therapy and response

Table 2: Clinical course and survival outcomes

Table 3: TPO-RA Treatment and response

Figure 1 : TPO-RA treatment significantly increases platelet count

Figure 2: TPO-RA treatment significantly reduces monthly platelet transfusion requirement

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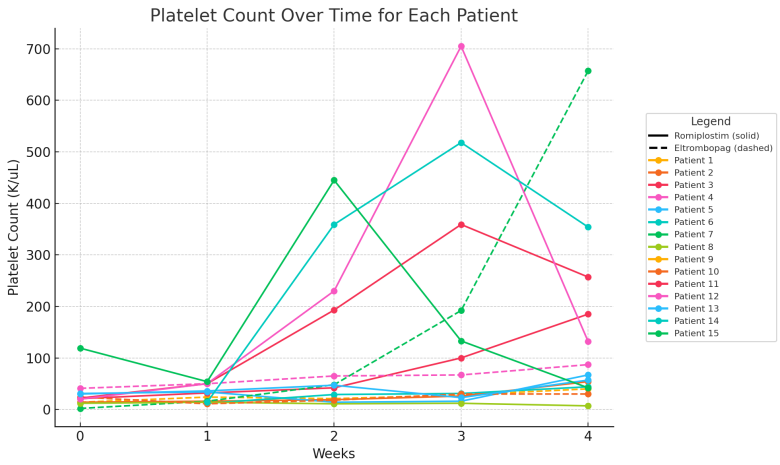

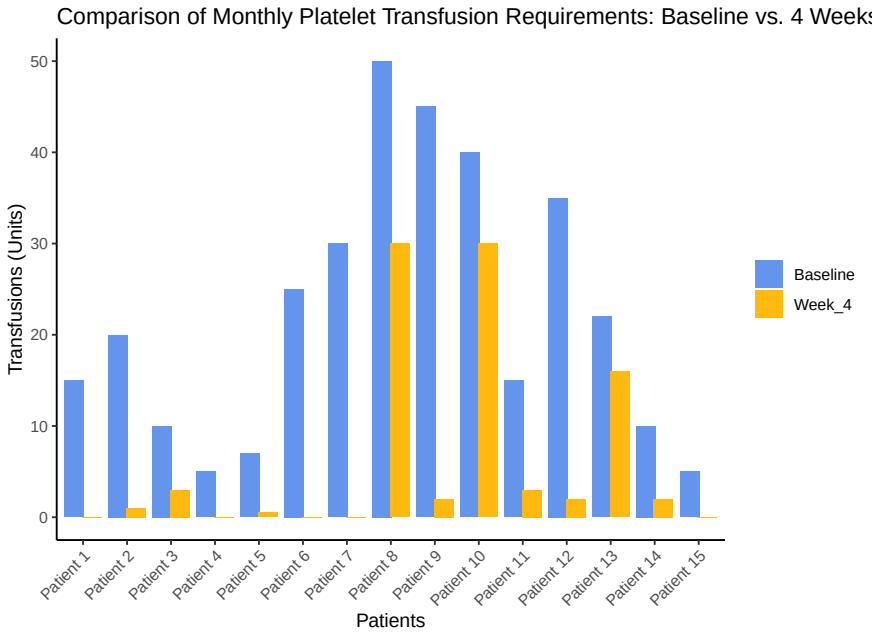

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