

Original article

Clinical outcomes of pediatric patients with severe acquired aplastic anemia treated at Siriraj Hospital

Nachapol Jatuten and Bunchoo Pongtanakul

Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University

Abstract:

Background: Severe acquired aplastic anemia (SAA) is a life-threatening condition. Thai treatment guidelines recommend matched sibling donor hematopoietic stem cell transplantation (MSD-HSCT) and immunosuppressive therapy (IST) combined with eltrombopag (EPAG). **Objective:** This study aimed to investigate the clinical outcomes of pediatric patients with SAA treated at Siriraj Hospital. **Method:** This retrospective study included pediatric patients with SAA treated at Siriraj Hospital from 1 January 2013 to 31 December 2023. **Result:** Twenty-seven patients were enrolled. Treatment modalities included IST in 13 patients (48.2%), IST+EPAG in 7 patients (25.9%) and MSD-HSCT in 7 patients (25.9%). At 3 and 6 months, overall response (OR) rates were 28.6% and 42.9% in the IST+EPAG group and 0% and 7.7% in the IST-only group, respectively. However, these differences were not statistically significant ($p = 0.111$ and 0.197 , respectively). Overall survival (OS) was similar between the IST+EPAG (62.5%, 95%CI: 0.14-0.89) and the IST group (63.3%, 95%CI: 0.29-0.84). The mean time to response and mean time to transfusion independence were shorter in the IST+EPAG group compared with the IST group, but the differences were not statically significance ($p = 0.085$ and 0.162 , respectively). The OS for the MSD-HSCT group was 42.9%. **Conclusion:** The combination of EPAG with IST was associated with a trend toward higher OR rates at 3 and 6 months. The IST+EPAG group also demonstrated shorter mean times to hematologic response and transfusion independence. OS was comparable between groups.

Keywords : ● Severe aplastic anemia ● Immunosuppressive ● Children ● Outcome
● Hematopoietic stem cell transplantation

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Correspondence should be addressed to Dr. Bunchoo Pongtanakul, MD, Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkok-noi, Bangkok 10700 E-mail: pongtanakul@yahoo.com

นิพนธ์ต้นฉบับ

ผลการรักษาผู้ป่วยเด็กโรคไขกระดูกฝ่อชนิดรุนแรงที่โรงพยาบาลศิริราช

ณัฏฐพล จตุเทิน และ บุญชู พงศ์ธนากุล

สาขาวิชาโลหิตวิทยาและอองโคโลยี ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

บทนำ โรคไขกระดูกฝ่อชนิดรุนแรงในเด็กมีความรุนแรงถึงชีวิตได้ การรักษาตามคำแนะนำของประเทศไทยประกอบด้วย การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากผู้บริจาคที่เป็นพี่น้องและมีลักษณะทางพันธุกรรมเข้ากันได้ การใช้ยากดภูมิต้านทานและอาจจะรวมกับการใช้ยากระตุ้นการสร้างเกล็ดเลือดเอลโทรมโบแพก **วัตถุประสงค์** เพื่อศึกษาผลการรักษาผู้ป่วยเด็กโรคไขกระดูกฝ่อที่รักษาที่โรงพยาบาลศิริราช **รูปแบบการวิจัย** การศึกษาย้อนหลังเชิงพรรณนา โดยการทบทวนเวชระเบียนผู้ป่วยเด็กที่วินิจฉัยด้วย โรคไขกระดูกฝ่อชนิดรุนแรง ที่รักษาในโรงพยาบาลศิริราช ในช่วงระหว่างวันที่ 1 มกราคม 2556 ถึง 31 ธันวาคม 2566 **ผลการวิจัย** ผู้ป่วยเข้าร่วมการศึกษา 27 คน ผู้ป่วย 13 คน (48.2%) 7 คน (25.9%) และ 7 คน (25.9%) ได้รับการรักษาด้วยยากดภูมิต้านทานอย่างเดียว ยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพก และการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากผู้บริจาคที่เป็นพี่น้องและมีลักษณะทางพันธุกรรมเข้ากันได้ ตามลำดับ ผลการตอบสนองโดยรวมที่ 3 และ 6 เดือน ร้อยละ 28.6 และ 42.9 ในกลุ่มที่ได้รับการรักษาด้วยยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพก ในขณะที่ร้อยละ 0 และ 7.7 ในกลุ่มการรักษาด้วยยากดภูมิต้านทานอย่างเดียวมีการตอบสนองตามลำดับ แต่อย่างไรก็ดีการตอบสนองนี้ไม่มีนัยสำคัญทางสถิติ ($p = 0.111$ และ 0.197). อัตรารอดชีวิตใกล้เคียงกันระหว่างกลุ่มที่ได้รับการรักษาด้วยยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพกและกลุ่มที่ได้ยากดภูมิอย่างเดียวใกล้เคียงกัน (62.5%, 95%CI: 0.14-0.89 และ 63.3%, 95%CI: 0.29-0.84 ตามลำดับ) ระยะเวลาเฉลี่ยที่ตอบสนองต่อการรักษาและระยะเวลาเฉลี่ยที่ผู้ป่วยไม่ต้องได้รับส่วนประกอบของเลือด ในกลุ่มที่ได้รับการรักษาด้วยยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพกจะสั้นกว่าในกลุ่มที่ได้ยากดภูมิอย่างเดียว แต่ไม่มีนัยสำคัญทางสถิติ ($p = 0.085$ และ 0.162 ตามลำดับ) อัตราการรอดชีวิตในผู้ป่วยที่ได้รับการรักษาด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากผู้บริจาคที่เป็นพี่น้องและมีลักษณะทางพันธุกรรมเข้ากันได้ คือ ร้อยละ 42.9% **สรุป** การรักษาผู้ป่วยเด็กโรคไขกระดูกฝ่อชนิดรุนแรง การใช้ยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพกมีแนวโน้มที่จะมีการตอบสนองโดยรวมที่ 3 และ 6 เดือนที่ดีกว่า กลุ่มที่ได้รับการรักษาด้วยยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพกจะสั้นกว่าในกลุ่มที่ได้ยากดภูมิอย่างเดียว อัตราการรอดชีวิตในผู้ป่วยที่ได้รับการรักษาด้วยยากดภูมิต้านทานร่วมกับยาเอลโทรมโบแพกและกลุ่มที่ได้รับการรักษาด้วยยากดภูมิอย่างเดียว ใกล้เคียงกัน

คำสำคัญ : ● โรคไขกระดูกฝ่อชนิดรุนแรง ● การใช้ยากดภูมิต้านทาน ● ผู้ป่วยเด็ก ● ผลการรักษา

● การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2569;36:189-99.

Introduction

Aplastic anemia is characterized by defective hematopoietic stem cell production, leading to pancytopenia and potentially life-threatening complications. While its exact cause remains uncertain, the main mechanism involves an immune-mediated attack by T lymphocytes.¹ The incidence of aplastic anemia varies widely by region, with rates in Asia being nearly ten times higher than those in Europe and the United States.² In Thailand, the incidence ranges from 3.9 to 5.0 cases per million people per year, with higher rates in the northeastern region than in the central region.³

Children with severe aplastic anemia (SAA) have several treatment options including matched sibling donor hematopoietic stem cell transplantation (MSD-HSCT) and immunosuppressive therapy (IST), which consists of antithymocyte globulin (ATG) and cyclosporine (CSA). Long-term survival rates reach approximately 88-92%.^{4,5} The introduction of eltrombopag (EPAG) into IST has been shown to enhance hematopoietic responses and improve complete response rates. The combination of IST and EPAG (IST+EPAG) has demonstrated a favorable safety profile and positive treatment outcomes, achieving response rate of 87%.⁶⁻⁸ Despite these promising results, data on treatment outcomes of IST+EPAG among children with SAA in Thailand remain limited. This gap highlights the need for further studies to evaluate safety and efficacy of this treatment in Thai children and to improve clinical outcomes. The objective of this study is to investigate the clinical outcomes of children with SAA who received treatment according to Thai aplastic anemia guidelines.⁹

Materials and methods

This retrospective study included pediatric patients aged < 18 years with very severe aplastic anemia (VSAA) and/or severe aplastic anemia (SAA) who were treated at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital from 1 January 2013 to 31 December 2023. The study was approved by the Ethics Com-

mittee of the Faculty of Medicine, Siriraj Hospital (Si 307/2024). All patients were diagnosed with VSAA and SAA based on diagnostic criteria previously described.¹⁰ Patients diagnosed with inherited bone marrow failure syndromes were excluded.

The treatment regimen consisted of rabbit anti-thymocyte globulin (rATG) at 3.75 mg/kg/day for 5 days, combined with CSA at 6-12 mg/kg/day, targeting a blood level of 200-400 µg/L and/or EPAG. The starting dose of EPAG was 25 mg/day for children ages 2-6 years and 50 mg/day for those aged 6-18 years. Inpatient dose escalation was permitted every 2 weeks starting on day 2 of week 3 until achieving the target platelet count ($50 \times 10^9/L$ to $200 \times 10^9/L$) or a maximum dose of 150 mg. Before administration of rATG, premedications included chlorpheniramine and dexamethasone. Additionally, oral prednisolone was prescribed and gradually tapered over 14 days to prevent serum sickness from ATG.⁹ Patients undergoing HLA-MSD HSCT received a conditioning regimen consisting of fludarabine (30 mg/m²/day) for 4 days, cyclophosphamide (100 mg/kg/course) for 2 days and rATG (3.75 mg/kg/day) for 3 days.

Efficacy parameters

The primary endpoints included complete response (CR; ANC $\geq 1,000/\mu L$, Hb ≥ 10 g/dL and platelet $\geq 100,000/\mu L$) and partial response (PR; ANC $\geq 500/\mu L$, Hb ≥ 8 g/dL, and platelet $\geq 20,000/\mu L$).¹¹ The overall response (OR) was defined as either CR or PR, while responses less than PR were categorized as non-responses (NR).¹² Outcomes were assessed at 3, 6, 12 and 24 months. Secondary endpoints included time to response (TTR) and duration of transfusion independence. Second-line treatment, either a second course IST± EPAG or HSCT, was initiated when patients were categorized as NR after 6 months of first-line treatment. Blood tests, including kidney and liver function tests, were monitored for EPAG-related adverse events.

Statistical analysis

Demographic and baseline characteristics were described using descriptive statistics. Continuous variables

were presented as mean or median as appropriate and categorical variables were expressed as frequencies and percentages. The Kaplan-Meier method was used to analyze overall survival (OS). Statistical analyses were performed using IBM SPSS software for Windows, version 25.0 (Armonk, NY: IBM Corp., USA), with a p -value < 0.05 considered statistically significant.

Results

A total of 27 pediatric patients were enrolled and divided into three treatment groups: 13 received IST, 7 underwent MSD-HSCT and 7 received IST+EPAG. The baseline characteristics (Table 1 and Figure 1) showed no statistically significant differences among age, sex and severity of aplastic anemia. When comparing treatment outcomes between the IST and IST+EPAG groups (Table 1), the time from diagnosis to initiation of treatment was significantly longer in the IST+EPAG group (126.4 ± 29.5 days) than in the IST group (48.5 ± 28.7 days; $p = 0.004$). The duration of treatment was 25.3 ± 11.8 months in the IST group and 16.1 ± 6.3 months in the IST+EPAG group. The median maximum dose of EPAG was 125 (range 100-150) mg/day.

Hematologic response to the first treatment in IST and IST+EPAG groups (Table 1)

At 3 months, the OR and PR rate was 28.6% in the EPAG+IST group, while no responses were observed in the IST group ($p = 0.111$); however, this difference was not statistically significant ($p = 0.111$). At 6 months, the responses were similar to those observed at three months. The OR and PR rate was 42.9% in the EPAG+IST, compared with 7.7% in the IST group, with no statistically significant difference ($p = 0.197$).

In the IST group, 12 patients (92.3%) were non-responsive; among them, 4 (30.8%) died, and 2 (15.4%) were lost to follow-up. In the IST+EPAG group, 4 patients (57.1%) did not respond to treatment, and 1 died from pulmonary hemorrhage with thrombocytopenia on Day 109. In the IST group, 6 non-responsive patients required further therapy: 5 received a second course

of IST, and 1 was treated with IST+EPAG. In the IST+EPAG group, 3 non-responsive patients required additional treatment: 1 underwent haploidentical HSCT, 1 received matched unrelated donor (MUD)-HSCT, and 1 was treated with androgen therapy (Figure 1).

At 12 months, an OR rate of 100% was observed in both groups. In the IST group, 1 patient achieved CR. In the EPAG+IST group, 1 and 2 patients achieved CR and PR, respectively. There were no statistically significant differences between the groups ($p = 1.000$ and $p = 0.248$, respectively). One patient in the IST group relapsed, while no relapses were observed in the IST+EPAG group; however, this difference was not statistically significant ($p = 0.333$).

The mean TTR was shorter in the IST+EPAG group (4.5 ± 1.8 months) compared with the IST group (6.7 ± 1.9 months; $p = 0.085$). Similarly, the mean time to achieve transfusion independence was shorter in the IST+EPAG group (4.5 ± 1.7 months) compared with the IST group (6.4 ± 2.1 months; $p = 0.162$). Patients in the IST group had a longer mean follow-up duration (54.5 ± 15.7 months) compared with the IST+EPAG group (23.7 ± 17.1 months), although this difference was not statistically significant ($p = 0.180$).

One patient in the IST group experienced relapse on day 607 after achieving CR at 12 months. He received a second course of IST 22 days after relapse, achieving PR and became transfusion-independent at 6 months. He ultimately achieved CR at 12 months, which has remained sustained to date.

Outcomes in the MSD-HSCT group (Figure 1)

Seven patients underwent MSD-HSCT. The mean time to initiation of treatment was 171.5 ± 47.9 days, while the mean duration of the transplantation process was 157.1 ± 100.6 days. Most patients had a fully HLA-matched donor, with only one patient (14.3%) having an 8/10 HLA match due to mismatches at DQR1 and DOB1. The mean time to myeloid engraftment was 20.4 ± 2.1 days, and the mean time to transfusion independence was 5.7 ± 1.7 months. Chimerism studies in 6 patients showed full donor chimerism in three (50%) and mixed

Table 1 Patients' characteristics and outcomes of first treatments

Characteristics	MSD-HSCT* (n = 7)	IST [#] (n = 13)	IST+EPAG [†] (n = 7)	p value
Age in years (mean ± SD)	9.1±2.8	8.7±4.7	7.9±4.7	0.184
Sex (%)				0.722
- Male	3 (42.9)	5 (38.5)	4 (57.1)	
- Female	4 (57.1)	8 (61.5)	3 (42.9)	
Diagnosis (%)				
- Severe AA	6 (85.7)	11 (84.6)	6 (85.7)	0.997
- Very Severe AA	1 (14.3)	2 (14.4)	1 (14.3)	
Time to initial treatment (days); mean ± SD		48.5±28.7	126.4±78.1	0.004
Time course of IST therapy (months); mean ± SD		25.3±11.8	16.1±6.3	0.237
Time course of EPAG (months); mean ± SD		-	7.8±4.9	-
Maximum dose of EPAG (mg); median (IOR)		-	125 (100-150)	-
3-month response				
OR [§] (%)		0	2 (28.6%)	0.111
CR ^{§§} (%)		0	0	
PR ^{§§§} (%)		0	2 (28.6%)	0.111
NR ^{§§§§} (%)		13 (100%)	5 (71.4%)	
6-month response				
OR (%)		1 (7.7%)	3 (42.9%)	0.197
CR (%)		0	0	
PR (%)		1 (7.7%)	3 (42.9%)	0.117
NR (%)		12 (92.3%)	4 (57.1%)	
12-month response				
		IST (n = 1)	IST+EPAG (n = 3)	
OR (%)		1 (100 %)	3 (100 %)	1.000
CR (%)		1 (100 %)	1 (33.3 %)	
PR (%)		0	2 (66.7 %)	0.248
NR (%)		0	0	
Relapse (%)		1 (100%)	0	0.333
Death (%)		4 (30.8%)	1 (14.3%)	0.732
Loss to follow up (%)		2 (15.4%)	0	0.179
Time to response, (months); mean ± SD		6.7±1.9	4.5±1.8	0.085
Time to transfusion free, (months) mean ± SD		6.4±2.1	4.5±1.7	0.162
Second treatment				
		IST (n = 6)	IST+EPAG (n = 3)	
● Haploidentical HSCT (%)		0	1 (14.3%)	-
● Matched unrelated donor HSCT (%)		0	1 (14.3%)	-
● IST (%)		5 (38.5%)	0	-
● IST+EPAG (%)		1 (7.7%)	0	-
● Androgen (%)		0	1 (14.3%)	-
Duration of FU (months); mean ± SD		54.5±15.7	23.7±17.1	0.180

*MSD-HSCT, matched sibling donor hematopoietic stem cell transplantation; [#]IST, cyclosporin A+ rabbit antithymoglobulin;

[†]EPAG, eltrombopag; [§]OR, overall response; ^{§§}CR, complete response; ^{§§§}PR, partial response; ^{§§§§}NR, non- response

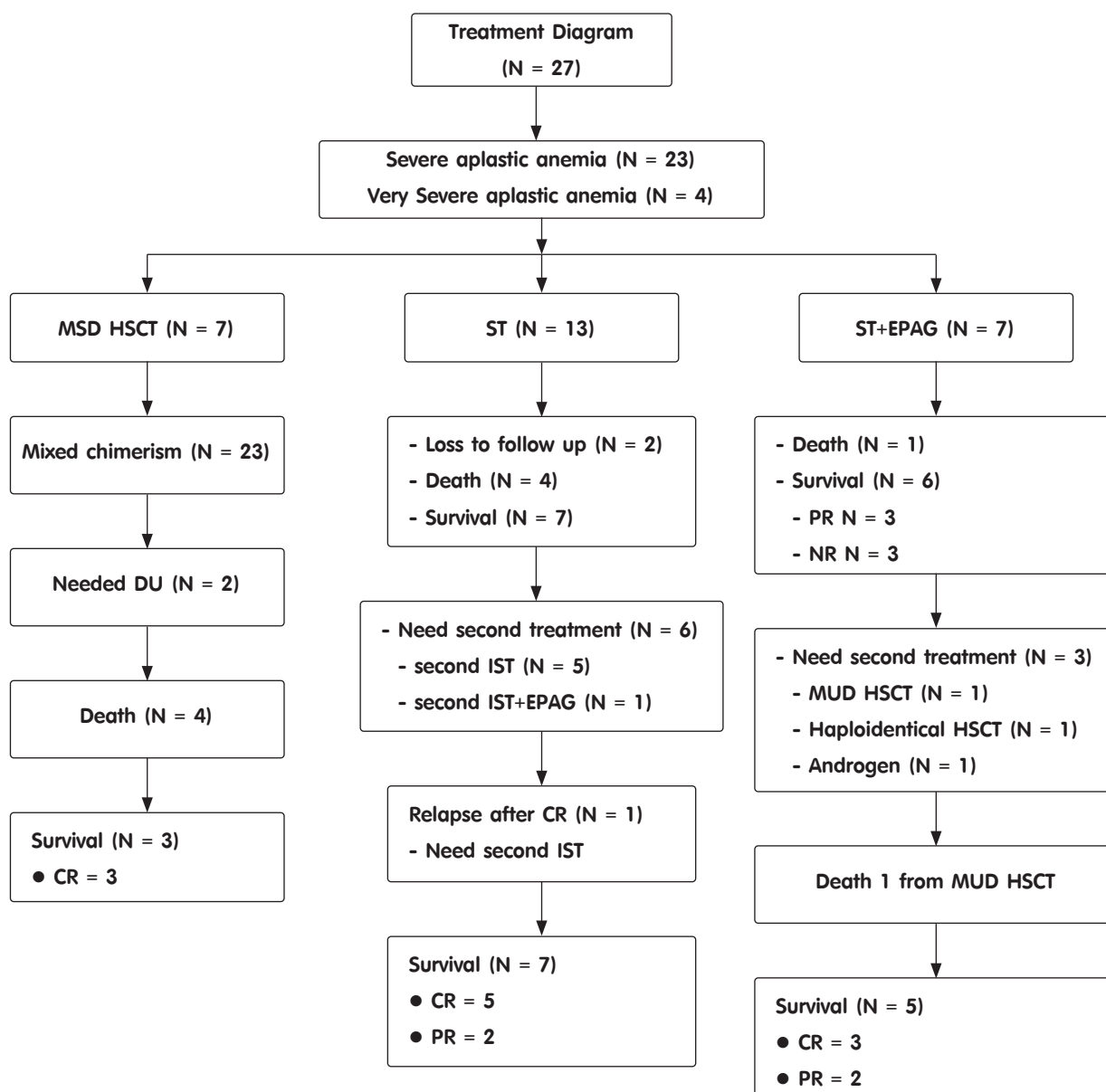


Figure 1 Treatment diagram

chimerism in three (50%). Two patients with mixed chimerism received donor lymphocyte infusion (DLI) to achieve full donor chimerism. No patients experienced relapsed or primary graft rejection; however, all 7 patients (100%) developed severe, life-threatening infections, resulting in death in 4 patients (57.1%).

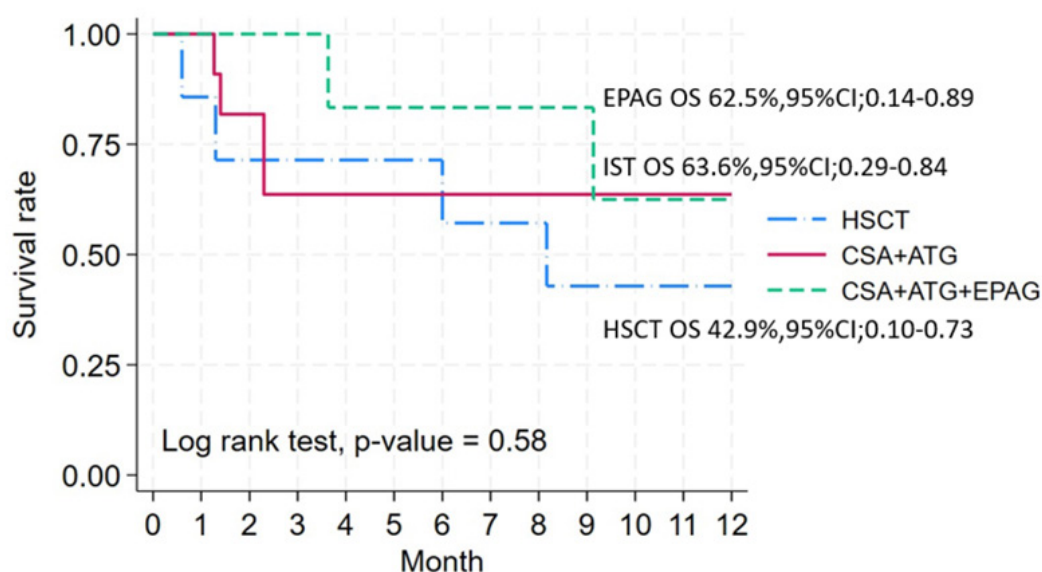
The first patient died on day 39 post-transplantation due to disseminated candidiasis and BK virus-associated hemorrhagic cystitis, which led to hemorrhagic shock.

The second patient experienced mixed chimerism and required DLI until full donor chimerism was achieved. However, she subsequently developed *Acinetobacter baumannii* pneumonia, *Stenotrophomonas maltophilia*

septicemia and lower gastrointestinal graft-versus-host disease (GVHD), resulting in death on day 180.

The third patient achieved engraftment on day 21 but developed mixed chimerism on day 28, requiring DLI. Full donor chimerism was successfully reestablished. However, on day 165, she developed disseminated candidiasis, which ultimately led to her death.

The fourth patient had an HLA mismatch at DRB1 and DOB1 and failed to achieve engraftment. On day 15, he developed veno-occlusive disease, followed by sepsis with disseminated intravascular coagulation caused by *Acinetobacter baumannii* and *Escherichia coli*, leading to death on day 18.



EPAG, Eltrombopag; IST, Immunosuppressive therapy; HSCT, Hematopoietic stem cell transplantation; CSA, Cyclosporin; ATG, Antithymocyte globulin

Figure 2 Overall survival rate

Another complication of MSD-HSCT was GVHD. Acute GVHD and chronic GVHD were observed in two patients (28.6%), both of whom had received DLI. The mean follow-up duration was 21.2 ± 16.5 months.

Overall survival rates (Figure 2)

Among all patients, the OS rate was 57.8% (95%CI: 0.36-0.75). Survival in the EPAG+IST group (62.5%, 95%CI: 0.14-0.89) did not significantly differ from the IST group (63.6%, 95%CI: 0.29-0.63) ($p = 0.58$). The OS rate for MSD-HSCT was 42.9% (95%CI: 0.10-0.73), showing a trend toward the lowest survival among all groups.

Outcomes of second treatment (Table 2, Figure 1)

At the 3-month evaluation, all patients showed no response, including 5 patients in the second IST group, 1 patient in the IST+EPAG group and 1 patient in the androgen therapy group. At 6 months, the IST group exhibited an OR rate of 80%, with 4 patients (80%) achieving a PR. Both the IST+EPAG and androgen groups achieved OR rates of 100%, with 1 patient in each group achieving a PR. The differences among the groups were not statistically significant ($p = 0.151$). At the 1-year follow-up, all patients across the three treatment groups achieved an OR rate of 100%. In the IST group, 4 patients (80%) achieved a PR, and 1

patient (20%) achieved a CR. Both the IST+EPAG and androgen groups also showed OR rates of 100%, with 1 patient (100%) in each group achieving a CR. The differences among the groups were not statistically significant ($p = 0.827$).

The median TTR was 5.6 months (range: 5.6-5.6) in the androgen group, 5.9 months (range: 4.9-8.7) in the IST group and 6.4 months (range: 6.4-6.4) in the IST+EPAG group. However, no significant difference was observed among the groups ($p = 0.191$). Similarly, the median time to transfusion independence was 5.6 months (range: 5.6-5.6) in the androgen group, 6.4 months (range: 6.4-6.4) in the IST+EPAG group and 8.8 months (range: 6.1-23.9) in the IST group ($p = 0.313$).

The median duration of follow-up was 8.7 months (range: 8.7-8.7) in the androgen group, 74.5 months (range: 74.5-74.5) in the IST+EPAG group and 101.1 months (range: 51.9-123.1) in the IST group. No significant differences were observed among the groups ($p = 0.314$) (Table 3).

Outcomes for second treatment in the HSCT group

The first patient underwent haploidentical HSCT as a second treatment. The time to transplantation was 198 days and the duration of hospitalization was 30 days. He received a conditioning regimen consisting

Table 2 Hematologic response to second treatment

Timing	IST* (N = 5)	IST+EPAG [#] (N = 1)	Androgen (N = 1)	p value
3 months				
OR ^{\$} (%)	0 (0)	0 (0)	0 (0)	0.120
CR ^{\$\$} (%)	0 (0)	0 (0)	0 (0)	
PR ^{\$\$\$} (%)	0 (0)	0 (0)	0 (0)	
NR ^{\$\$\$\$} (%)	5 (100%)	1 (100%)	1 (100%)	
6 months				
OR (%)	4 (80%)	1 (100%)	1 (100%)	0.151
CR (%)	0 (0)	0 (0)	0 (0)	
PR (%)	4 (80%)	1 (100%)	1 (100%)	
NR (%)	1 (20%)	0 (0)	0 (0)	
1 year				
OR (%)	5 (100%)	1 (100%)	1 (100%)	0.827
CR (%)	1 (20%)	1 (100%)	1 (100%)	
PR (%)	4 (80%)	0 (0)	0 (0)	
NR (%)	0 (0)	0 (0)	0 (0)	
Time to response, month median (IQR)	5.9 (4.9-8.7)	6.4 (6.4-6.4)	5.6 (5.6-5.6)	0.191
Time to transfusion free, month median (IQR)	8.8 (6.1-23.9)	6.4 (6.4-6.4)	5.6 (5.6-5.6)	0.313
Duration of FU (months), median (IQR)	101.1(51.9-123.1)	74.5 (74.5-74.5)	8.7 (8.7-8.7)	0.314

*IST, cyclosporin A+rabbit antithymoglobulin; ^{\$}OR, overall response; ^{\$\$}CR, complete response; ^{\$\$\$}PR, partial response;

^{\$\$\$\$}NR, non- response; [#]EPAG, elthrombopag

Table 3 Adverse events

Adverse events	IST* (N = 6)	IST + EPAG [#] (N = 7)	p-value
Liver test abnormalities: grade 1-2	3 (50)	2 (28.6)	0.413
Liver test abnormalities: grade 3-4	1 (16.7)	2 (33.3)	0.500
Hyperbilirubinemia	4 (66.7)	3 (42.9)	0.856
Infectious complications/febrile neutropenia	5 (83.3)	6 (85.7)	0.500
Skin hyperpigmentation	1 (16.7)	7 (100)	< 0.001
Renal insufficiency	2 (33.3)	6 (85.7)	0.086
Gastrointestinal (nausea/vomiting/abdominal pain)	2 (33.3)	5 (71.4)	0.209

*IST, cyclosporin A+ rabbit antithymoglobulin; [#]EPAG; elthrombopag

of fludarabine (40 mg/m²/day for 4 days), cyclophosphamide (30 mg/kg/course), rATG) (3.75 mg/kg/day for 3 days) and total body irradiation (TBI) (2 Gy, single fraction). He achieved engraftment on day 15 with full donor chimerism. The time to transfusion independence was 3 months. However, he developed complications, including febrile neutropenia with *Escherichia coli* septicemia on days 9 and 20, as well as grade 3 acute skin

GVHD. Six months later, he was re-hospitalized for BK virus-associated hemorrhagic cystitis and received adjusted immunosuppressive therapy along with continuous bladder irrigation, which led to improvement. The patient remains on a low dose of CSA, which is being tapered. He continues to maintain a CR and full donor chimerism, with improvement in acute skin GVHD. The follow-up period was 12 months.

The second patient received an MUD-HSCT, with a fully matched donor provided by the Thai Red Cross Society. The time to transplantation was 38 days. He received a conditioning regimen consisting of fludarabine (30 mg/m²/day for 4 days), cyclophosphamide (50 mg/kg/course), rabbit ATG (3.75 mg/kg/day for 3 days), and TBI (2 Gy, single fraction). The patient experienced primary graft failure, requiring a second stem cell infusion. However, engraftment was not achieved, leading to severe infections, including *Enterococcus faecium*, *Candida krusei*, *Stenotrophomonas maltophilia* and preseptal cellulitis. He required 17 granulocyte transfusions for infection control but failed to achieve treatment response or transfusion independence. He died on day 57 due to an upper gastrointestinal hemorrhage.

Adverse events (Table 3)

When assessing adverse events in the IST and IST+EPAG groups, only skin hyperpigmentation demonstrated a statistically significant difference in the IST+EPAG group (7 patients; 100%, $p < 0.001$). Other adverse events, including liver function test abnormalities, hyperbilirubinemia, infections, renal insufficiency and gastrointestinal side effects, did not differ significantly between the two treatment groups.

Discussion

Although significant outcomes have been reported in adults, the therapeutic advantage of adding EPAG to standard IST in children with SAA remains inconclusive. Groarke EM, et al.¹³ reported a prospective, non-randomized Phase I-II study evaluating the efficacy of EPAG in combination with standard IST in treatment-naïve children (< 18 years) with SAA. The study found no significant improvement in OR or CR at 6 months in the EPAG group compared with IST alone. Goronkova O, et al.⁸ conducted a multicenter, randomized, open-label trial assessing the addition of EPAG to standard IST in pediatric SAA. EPAG significantly enhanced early hematologic response and neutrophil recovery, with no new safety concerns. Long-term outcomes, such

as OS and EFS, were similar. These results suggest that EPAG may enhance treatment efficacy in pediatric patients with residual hematopoiesis. A recent phase II ESCALATE trial evaluating eltrombopag in combination with IST in pediatric SAA¹⁴ reported OS at 26 weeks was 71.4% and 48.6% in the relapsed/refractory (R/R) and treatment-naïve cohorts, respectively; most responders maintained sustained responses after discontinuing eltrombopag. Among baseline transfusion-dependent patients, 66.7% and 76.7% achieved red blood cell and platelet transfusion independence, respectively, with rates of 70% and 80% in the R/R cohort and 65.6% and 75.8% in the treatment-naïve cohort, respectively.

Our study showed that adding EPAG to IST may improve hematologic responses but does not improve OS compared with IST alone. The EPAG group demonstrated a trend toward higher OR rates at both 3 and 6 months compared with the IST alone group, although the differences were not statistically significant ($p = 0.111$ and $p = 0.197$, respectively). Additionally, patients in the EPAG group experienced a shorter TTR and achieved transfusion independence more rapidly than those in the IST group; however, these differences were also not statistically significant ($p = 0.085$ and $p = 0.162$, respectively).

These findings align with a randomized controlled trial conducted by Latour, et al.¹⁵ which confirmed that adding EPAG to IST (horse ATG/CSA) in patients older than 15 years significantly shortened the median time to first hematologic response and CR compared with horse ATG/CSA alone as well as with findings from the ESCALATE trial¹⁴ in pediatric patients. Although this study used rabbit ATG due to the unavailability of horse ATG in Thailand, prior research has demonstrated superior outcomes with horse ATG over rabbit ATG in adult aplastic anemia¹⁶. However, studies in pediatric patients have shown comparable efficacy between horse ATG and rabbit ATG.¹⁷ Zhao Y, et al.¹⁸ used propensity score matching to compare 15 children treated with IST plus EPAG with 45 children treated with IST

alone showing that EPAG led to a significantly shorter median time to hematologic response (105 vs. 184 days, $p = 0.008$). Subgroup analysis showed greater benefit in adolescents (≥ 14 years) and those with SAA, while younger children (< 14 years) and patients with VSAA showed less improvement.

EPAG promotes the generation and maturation of hematopoietic stem cells in the bone marrow, particularly megakaryocytes, thereby enhancing platelet production.⁶ These factors may contribute to improved hematologic responses. The differing therapeutic outcomes between pediatric and adult patients may, as suggested by Shimano KA, et al.,¹⁹ reflect the inherently better baseline response to IST in children.

Several studies have demonstrated no significant difference in OS between EPAG+IST and IST alone. Goronkova O, et al.⁸ reported a 3-year OS of 89% for EPAG+IST compared with 91% for IST. Townsley DM, et al.²⁰ observed a 2-year OS of 97% in patients receiving EPAG+IST. Lesmana H, et al.²¹ reported a 1-year OS of 100% in the EPAG+IST group, vs. 88% in the IST group. In our study, OS was similar between patients receiving IST+EPAG (62.5%) and IST alone (63.6%), with no statistically significant difference ($p = 0.58$).

Seven patients underwent MSD-HSCT; the average time to myeloid engraftment was 20.4 ± 2.1 days, and the mean time to transfusion independence was 5.7 ± 1.7 months. Mixed chimerism occurred in two patients (28.6%), both of whom successfully achieved full donor chimerism following DLI. No relapses were reported.

The OS of the MSD-HSCT group was 42.9% (95%CI: 0.10-0.73). This outcome was likely influenced by a prolonged waiting period for treatment after diagnosis, with a mean duration of 171.5 ± 47.9 days, as well as a high incidence of mixed chimerism requiring DLI. Additionally, some patients required blood component transfusions, increasing the risk of alloantibody development, par-

ticularly against platelets, which could lead to severe bleeding during transplantation. This is supported by the study of Chaudhry QUN, et al.²² which identified factors associated with poor outcomes in HSCT or high-risk aplastic anemia, including a transplant delay beyond 3 months, over 20 pre-transplant transfusions and active infection at the time of transplantation. Consequently, only three patients survived. The safety profile of adding EPAG to IST was acceptable, with the only mild adverse event observed being skin hyperpigmentation and no new safety concerns identified.

Compared with the Thai pediatric cohort study by Khattachan O. et al.,¹² which evaluated IST, androgen combined with low-dose prednisolone and MSD-HSCT, and reported 5-year OS of 69.4% overall and 72.9% with IST, our cohort demonstrated lower OS rates: 57.8% (95%CI: 0.36-0.75) overall, 63.6% (95%CI: 0.29-0.63) in the IST group and 62.5% (95%CI: 0.14-0.89) in the IST+EPAG group. These findings suggest that the addition of EPAG did not provide a survival benefit in our clinical context; however, EPAG showed a trend toward shortening the time to hematologic response and achieving transfusion independence.

The study's limitations, including its retrospective, single-center design, a relatively small cohort and inconsistent patient compliance with EPAG, which may have affected treatment outcomes.

Conclusion

The combination of EPAG with IST was associated with a trend toward higher OR rates at 3 and 6 months, although these differences were not statistically significant. The IST+EPAG group also demonstrated a shorter time to hematologic response and earlier achievement of transfusion independence. The OS was comparable between the two groups, and no new significant toxicity was observed in the IST+EPAG group.

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