Efficacy and safety of avatrombopag in the treatment of thrombocytopenia after umbilical cord blood transplantation

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Abstract

Background: Delayed platelet engraftment is a common complication after umbilical cord blood transplantation (UCBT), and there is no standard therapy. Avatrombopag (AVA) is a second-generation thrombopoietin (TPO) receptor agonist (TPO-RA) that has shown efficacy in immune thrombocytopenia (ITP). However, few reports have focused on its efficacy in patients diagnosed with thrombocytopenia after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods: We conducted a retrospective study at the First Affiliated Hospital of the University of Science and Technology of China to evaluate the efficacy of AVA as a first-line TPO-RA in 65 patients after UCBT; these patients were compared with 118 historical controls. Response rates, platelet counts, megakaryocyte counts in bone marrow, bleeding events, adverse events and survival rates were evaluated in this study. Platelet reconstitution differences were compared between different medication groups. Multivariable analysis was used to explore the independent beneficial factors for platelet implantation.

Results: Fifty-two patients were given AVA within 30 days post-UCBT, and the treatment was continued for more than 7 days to promote platelet engraftment (AVA group); the other 13 patients were given AVA for secondary failure of platelet recovery (SFPR group). The median time to platelet engraftment was shorter in the AVA group than in the historical control group (32.5 days *vs*. 38.0 days, $Z = 2.095$, $P = 0.036$). Among the 52 patients in the AVA group, 46 achieved an overall response (OR) (88.5%), and the cumulative incidence of OR was 91.9%. Patients treated with AVA only had a greater 60-day cumulative incidence of platelet engraftment than patients treated with recombinant human thrombopoietin (rhTPO) only or rhTPO combined with AVA (95.2% *vs*. 84.5% *vs*. 80.6%, $P < 0.001$). Patients suffering from SFPR had a slightly better cumulative incidence of OR (100%, $P = 0.104$). Patients who initiated AVA treatment within 14 days post-UCBT had a better 60-day cumulative incidence of platelet engraftment than did those who received AVA after 14 days post-UCBT (96.6% *vs*. 73.9%, $P = 0.003$).

Conclusion: Compared with those in the historical control group, our results indicate that AVA could effectively promote platelet engraftment and recovery after UCBT, especially when used in the early period (≤14 days post-UCBT).

Keywords: Avatrombopag; Umbilical cord blood transplantation; Thrombopoietin receptor agonist; Secondary failure of platelet recovery; Historical control; Thrombocytopenia

Introduction

Thrombocytopenia is one of the complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is correlated with increased transplant-related mortality (TRM) and inferior overall survival (OS).[1–3] Prolonged isolated thrombocytopenia (PIT) and secondary failure of platelet recovery (SFPR) are the main types of thrombocytopenia after allo-HSCT. PIT has been described in 5–37% of allo-HSCT patients,[1,4] and the cumulative incidence of SFPR ranged from 10% to 20%.[2] Umbilical cord blood transplantation (UCBT) is an effective alternative to other transplant types. So it is widely used for various hematologic diseases. The platelet engraftment time is longer in these patients than in patients receiving other allo-HSCT types, and 20.1% of patients suffer from PIT after UCBT.[1,5]

The mechanisms of thrombocytopenia after allo-HSCT are complex. The factors associated with it include disease recurrence, stem cell source, lower infused $CD34^+$ cells, cytomegalovirus (CMV) infection, grade II–IV acute

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graft-versus-host disease (aGVHD), and iron overload before transplantation.[1–3,6,7]

There is no consensus on therapeutic strategies for thrombocytopenia after allo-HSCT. Treatment is generally based on platelet transfusion.[8] Currently, CD34-selected stem cell boosts,[9] mesenchymal stem cells (MSCs),[10] hypomethylating agents,[11] recombinant human thrombopoietin (rhTPO), and thrombopoietin receptor agonists (TPO-RAs)[12] are used for patients with poor engraftment, including those with thrombocytopenia. RhTPO[13] and TPO-RAs (such as eltrombopag, romiplostim, and hetrombopag) can enhance platelet recovery after hematopoietic stem cell transplantation (HSCT).[14–17]

Avatrombopag (AVA) is a second-generation TPO-RA approved for treating immune thrombocytopenia (ITP) and chronic liver disease-related thrombocytopenia.[18] It can bind to the transmembrane domain of the TPO receptor (TPO-R) and activate signaling pathways related to platelet production. However, few studies have analyzed the efficacy of AVA in the treatment of thrombocytopenia after HSCT. Thus, we conducted this study to evaluate the safety and efficacy of AVA post-HSCT.

Methods

Patients

From May 2021 to September 2023, a total of 174 patients who underwent allo-HSCT and were treated with AVA at the First Affiliated Hospital of the University of Science and Technology of China were reviewed retrospectively. Patients who received peripheral blood stem cell transplantation (PBSCT) (n = 37), treated with AVA followed by hetrombopag treatment (n = 4), or treated with AVA after platelet engraftment, but not for the treatment of SFPR (n = 3), were excluded. We identified 130 patients who underwent single-unit UCBT and who received AVA treatment as the first-line TPO-RA. Among them, 13 patients were diagnosed with SFPR, and the other 117 patients were treated with AVA to promote platelet engraftment. Patients who were enrolled in a previous report from our center served as the historical control group (ChiCTR-IPR-16009357, chictr.org);[13] among them, patients who withdrew consent before the transplant (n = 1) and died before treatment (n = 1) were excluded. The inclusion criteria for the historical control group (n = 118) and the AVA group (n = 117) were as follows: (1) had hematologic malignancies; (2) had a weight ≥30 kg; (3) were aged ≤60 years; (4) for the historical control group, treated without TPO-RAs; and for the AVA group, the administration of AVA was initiated within 30 days post-UCBT and continued for more than 7 days. A total of 170 patients were ultimately enrolled; 118 and 52 in the historical control group and AVA group, respectively. The flowchart of the selection process is shown in Figure 1. All participants signed an informed consent form before participating in the study. All procedures were performed in accordance with the ethical standards of the *Declaration of Helsinki*. This study was approved by the Ethics Committee of the

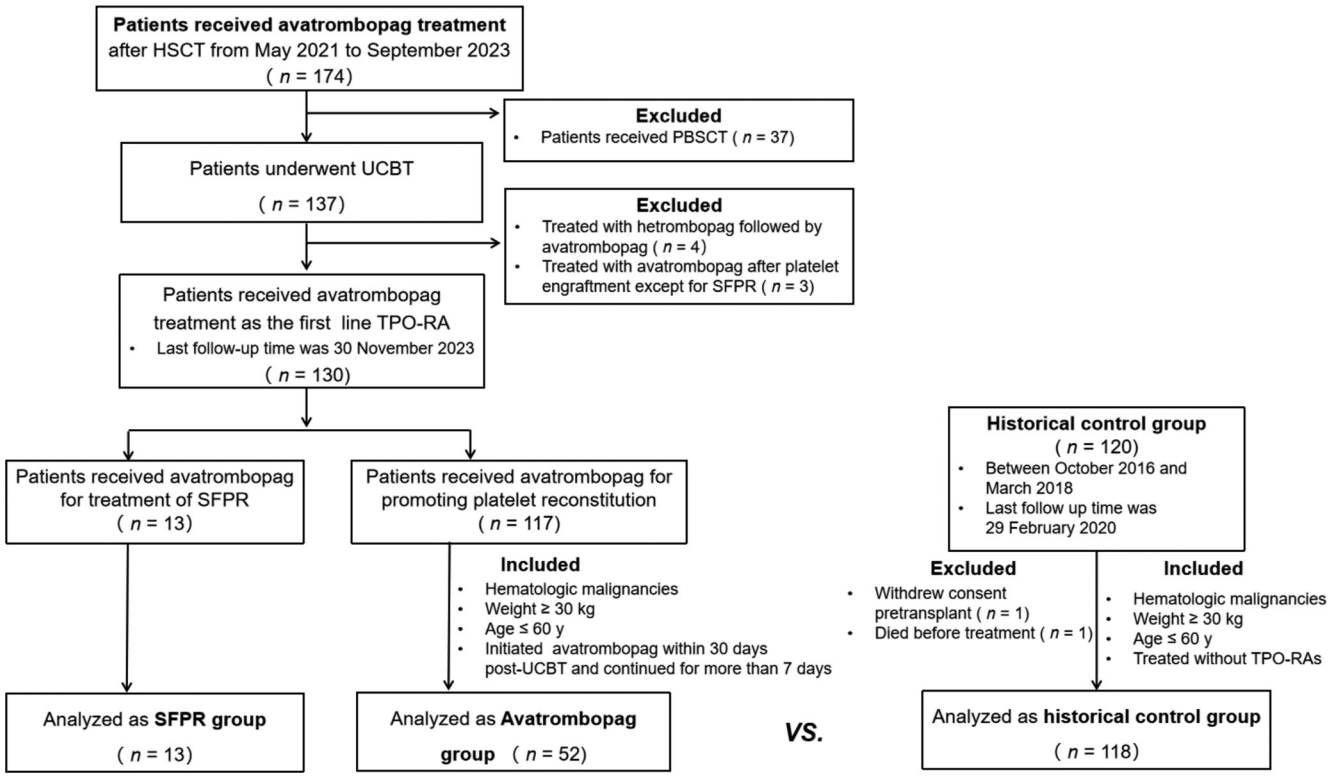

Figure 1: Flowchart illustrating selection of UCBT recipients receiving avatrombopag for either SFPR treatment or platelet reconstitution, and historical controls without TPO-RA exposure. HSCT: Hematopoietic stem cell transplantation; OR: Overall response; PBSCT: Peripheral blood stem cell transplantation; SFPR: Secondary failure of platelet recovery; TPO-RA: Thrombopoietin receptor agonist; UCBT: Umbilical cord blood transplantation.

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Transplantations

The strategies for cord blood selection and human leukocyte antigen (HLA) typing were performed, as previously described.[19,20] A total of 21 patients received a reduced-intensity conditioning (RIC) regimen consisting of FLAG (fludarabine 30 mg/m^2, cytarabine 2 g/m^2, granulocyte colony stimulating factor (G-CSF) 300 μg/day; all for 5 days), cyclophosphamide (60 mg/kg daily for 2 days) and total body irradiation (TBI, 4 Gy). The other 149 patients received a myeloablative conditioning (MAC) regimen comprising busulfan (0.8 mg/kg q6h for 4 days) and cyclophosphamide (60 mg/kg daily for 2 days). All patients received a combination of cyclosporine and mycophenolate mofetil as a GVHD prophylaxis regimen.

Definitions

Platelet engraftment was defined as a platelet count ≥20 × 10^9/L for 7 consecutive days without transfusion dependence. Platelet recovery was defined as the first day of platelet count ≥50 × 10^9/L for 7 consecutive days without transfusion dependence. SFPR was defined as a platelet count <20 × 10^9/L or ≥20 × 10^9/L with transfusion for more than 7 consecutive days after primary platelet recovery. OS was calculated from the date of UCBT until death or the last follow-up. GVHD-free, relapse-free survival (GRFS) was defined as survival without grade III–IV aGVHD or chronic GVHD requiring systemic immune suppression treatment or disease recurrence or relapse.[1]

Response criteria

An overall response (OR) was defined as a platelet count increase >20 × 10^9/L for 7 consecutive days and independence of platelet transfusion after the administration of AVA.[21] A complete response (CR) was defined as a platelet count >50 × 10^9/L without platelet transfusion for 7 consecutive days after the administration of AVA.

Statistical analysis

OS and GRFS were calculated by using the Kaplan–Meier method and compared by using the log-rank test. Competing-risk analysis was performed to calculate the cumulative incidence of OR and CR and to consider relapse and death as completing events. The Gray test was used to compare the differences between groups during competing-risk analysis. Univariable and multivariable analyses were performed by using Fine-Gray proportional hazard regression (considering death and relapse as completing events) or the Cox proportional hazards regression model (not completing events). Factors with a P value <0.1 in the univariable analysis were included in the multivariable analysis. GVHD was considered a time-dependent factor. All the data were analyzed using IBM SPSS Statistics software (version 22.0, SPSS, Inc., Chicago, IL, USA) and EZR (version 1.61, Saitama Medical Center, Jichi Medical University, Japan).[22] Line graphs were drawn using EZR, and bar graphs were drawn using GraphPad Prism 9 software (Graphpad Software, Inc., San Diego, CA, USA). P <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of patients

As shown in Figure 1, the efficacy population consisted of 118 patients in the historical control group, and 52 patients were treated with AVA to promote platelet reconstruction. Table 1 summarizes the clinical characteristics of the 170 evaluable patients: 81 had acute myeloid leukemia (AML), 47 had acute lymphoblastic leukemia (ALL), 18 had myelodysplastic syndrome (MDS), 8 had chronic granulocytic leukemia, and 16 had other hematological malignancies. Eighty (47.1%) patients were female. The median age was 28 years (range, 8–59 years). The median infused total nucleated cell (TNC) and CD34$^+$ cell counts were 2.59 × 10^7/kg (range, 1.14–6.60 × 10^7/kg) and 1.77 × 10^5/kg (range, 0.17–8.57 × 10^5/kg), respectively. The median neutrophil engraftment time was 17 days (range, 11–32 days). The occurrence rates of CMV, pre-engraftment syndrome (PES), and hemorrhagic cystitis (HC) were 80.0% (136/170), 74.1% (126/170), and 30.6% (52/170), respectively. Sixty-four (37.6%) patients developed grade II–IV aGVHD. A total of 48 (28.2%) patients suffered other hemorrhage events. The median age was 21 years (range, 2–46 years) in the SFPR group. Six of them were male. The median time to onset of SFPR was 95 days (range, 53–152 days) post-UCBT.

Among those in the historic control group, all surviving patients were followed up until February 29, 2020, for a median follow-up time of 943 days (range, 705–1227 days).[13] All surviving patients in the AVA group and SFPR group were followed up until November 30, 2023, with median follow-up times of 265 days (range, 84–516 days) and 476 days (range, 245–776 days), respectively. The probability of 1-year OS was 77.6% (95% confidence interval [CI], 63.2–86.9%) in the AVA group, 72.7% (95% CI, 62.0–80.8%) in the historical control group, and 92.3% (95% CI, 56.6–98.9%) in the SFPR group. The probabilities of 1-year GRFS were 65.8% (95% CI, 50.8–77.2%), 50.0% (95% CI, 37.5–61.3%), and 57.7% (95% CI, 24.9–80.4%) in the above three groups, respectively. The probabilities of 1-year OS and GRFS were similar between the AVA group and the historical control group (OS: P = 0.671; GRFS: P = 0.379).

AVA treatment

The details of the AVA treatment are presented in Table 2. The median time to start treatment with AVA was 14 days (range, 0–30 days) after UCBT to prompt platelet engraftment. The initial dose was 40 mg/day in the majority of patients (44/52, 84.6%) and 20 mg/day (n = 6) or 60 mg/day (n = 2) in the others. The median duration of AVA treatment in the AVA group was 38 days (range, 7–131 days). For patients with SFPR, 53.8% (7/13) were

Table 1: Clinical characteristics of patients between AVA group and historical control group.

Characteristics	AVA group ($N = 52$)	Historical control group ($N = 118$)	$\chi^2/Z/t$	P values
Gender			0.679	0.410*
Male	30 (57.7)	60 (50.8)		
Female	22 (42.3)	58 (49.2)		
Age, years	33 (10, 59)	27 (8, 59)	–2.248	0.025†
Diagnosis			9.629	0.041‡
AML	29 (55.8)	52 (44.1)		
ALL	11 (21.1)	36 (30.5)		
MDS	9 (17.3)	9 (7.6)		
CML	0	8 (6.8)		
Other hematological malignancies	3 (5.8)	13 (11.0)		
DRI-R			7.587	0.047‡
Low	4 (7.7)	7 (5.9)		
Intermediate	40 (76.9)	71 (60.2)		
High	6 (11.5)	36 (30.5)		
Very high	2 (3.8)	4 (3.4)		
ABO compatibility			4.196	0.241*
Identical	14 (26.9)	33 (28.0)		
Major incompatibility	16 (30.8)	28 (23.7)		
Minor incompatibility	11 (21.2)	41 (34.7)		
Bidirectional incompatibility	11 (21.2)	16 (13.6)		
HLA compatibility			6.034	0.093‡
3/6	1 (1.9)	2 (1.7)		
4/6	25 (48.1)	75 (63.6)		
5/6	21 (40.4)	38 (32.2)		
6/6	5 (9.6)	3 (2.5)		
Donor to recipient sex			0.009	0.926*
Female to male	12 (23.1)	28 (23.7)		
Others	40 (76.9)	90 (76.3)		
Conditioning regimen			2.187	0.139§
RIC	3 (5.8)	18 (15.3)		
MAC	49 (94.2)	100 (84.7)		
Infused TNCs, $\times10^7$/kg			3.492	0.062*
<2.59	31 (59.6)	52 (44.1)		
≥2.59	21 (40.4)	66 (55.9)		
Infused $CD34^+$ cells, $\times10^5$/kg			13.544	<0.001*
<2.60	30 (57.7)	99 (83.9)		
≥2.60	22 (42.3)	19 (16.1)		
Treatment for prompting platelet engraftment			–	–
Control	0	60 (50.8)		
rhTPO-only	0	58 (49.2)		
AVA-only	21 (40.4)	0		
rhTPO + AVA	31 (59.6)	0		
Hematopoietic reconstitution, days post-UCBT				
Neutrophil engraftment	15 (12, 32)	17 (11, 32)	–3.136	0.002†
Platelet engraftment	32.5 (22.0, 144.0)	38.0 (18.0, 170.0)	–2.095	0.036†
Platelet count before conditioning, $\times10^9$/L	151 (8, 363)	141 (4, 845)	0.610	0.543‖
Grade II–IV aGVHD	23 (44.2)	41 (34.7)	1.383	0.240*
CMV infection	43 (82.7)	93 (78.8)	0.339	0.560*
PES	41 (78.8)	85 (72.0)	0.873	0.350*
HC	17 (32.7)	35 (29.7)	0.156	0.693*
Other hemorrhage events	6 (11.5)	42 (35.6)	10.307	0.001*

Data are expressed as n (%) or median (range). *Pearson χ^2 test. †Mann–Whitney U test. ‡Fisher's exact test. §Continuity correction test. ‖Student's t-test. aGVHD: Acute graft-versus-host disease; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AVA: Avatrombopag; CML: Chronic granulocytic leukemia; CMV: Cytomegalovirus; DRI-R: Disease risk index; HC: Hemorrhagic cystitis; HLA: Human leukocyte antigen; MAC: Myeloablative conditioning; MDS: Myelodysplastic syndrome; PES: Pre-engraftment syndrome; rhTPO: Recombinant human thrombopoietin; RIC: Reduced-intensity conditioning; TNCs: Total nucleated cells; UCBT: Umbilical cord blood transplantation; –: Not applicable.

Table 2: Details of hematopoietic reconstruction and AVA treatment in 65 patients.

Characteristics	Treated for platelet engraftment post-UCBT			For SFPR (*N* = 13)
	Total (*N* = 52)	Early (≤14 days, *N* = 29)	Late (>14 days, *N* = 23)	
Time from UCBT to AVA treatment (days)	14 (0, 30)	4 (0, 14)	24 (15, 30)	98 (65, 200)
Achievement of OR	46 (88.5)	28 (96.6)	18 (78.3)	12 (92.3)
Achievement of CR	39 (75.0)	23 (79.3)	16 (69.6)	12 (92.3)
Duration of application (days)	38 (7, 131)	38 (15, 131)	34 (7, 91)	36 (7, 153)
MK counts before AVA initiation (per cm^2)	0.5 (0, 22)	0.6 (0, 22.0)	0.2 (0, 8.3)	1.5 (0, 10.4)
MK counts after AVA treatment (per cm^2)	6.4 (0, 33.4)	6.3 (0, 33.4)	6.4 (0.4, 29.1)	18.6 (2.4, 114.3)
Initial dose of AVA				
20 mg, daily	6 (11.5)	4 (13.8)	2 (8.7)	7 (53.8)
40 mg, daily	44 (84.6)	24 (82.8)	20 (87.0)	6 (46.2)
60 mg, daily	2 (3.8)	1 (3.4)	1 (4.3)	0
Maximum dose of AVA				
20 mg, daily	4 (7.7)	3 (10.3)	1 (4.3)	5 (38.5)
40 mg, daily	45 (86.5)	25 (86.2)	20 (87.0)	5 (38.5)
60 mg, daily	3 (5.8)	1 (3.4)	2 (8.7)	3 (23.1)

Data are expressed as *n* (%) or median (range). AVA: Avatrombopag; CR: Complete response; MK: Megakaryocyte; OR: Overall response; SFPR: Secondary failure of platelet recovery; UCBT: Umbilical cord blood transplantation.

treated with an initial dose of 20 mg/day, and the duration of drug treatment was 36 days (range, 7–153 days).

AVA efficacy

AVA treatment for promoting platelet engraftment post-UCBT

A total of 46 patients (88.5%) responded to AVA therapy, and the cumulative incidence of OR was 91.9% (95% CI, 79.8–96.9%) [Figure 2A]. The cumulative incidence of CR was 89.2% (95% CI, 74.4–95.7%) [Figure 2B]. The median platelet engraftment time was 32.5 days (range, 22–144 days) in the AVA group compared with 38 days (range, 18–170 days) in the historical control group ($P = 0.036$).

Considering concomitant medication, patients were further divided into four subgroups, namely, the control group ($n = 60$), the rhTPO-only group ($n = 58$), the AVA-only group ($n = 21$), and the rhTPO + AVA group ($n = 31$), according to whether rhTPO or AVA was used. The platelet engraftment rate was greater in patients who received TPO/TPO-RA than in untreated patients. The median of platelet engraftment was 43 days (range, 19–170 days) post-UCBT in the control group, which was significantly longer than that in the other three treatment groups (rhTPO group: 35 days [range, 18–144 days], $P = 0.365$; AVA group: 31 days [range, 24–144 days], $P = 0.027$; rhTPO + AVA group: 33 days [range, 22–98 days], $P = 0.039$). The differences among the three treatment groups were not significant ($P > 0.05$). The 60-day cumulative incidence of platelet engraftment was 84.5% (95% CI, 72.3–91.6%) in the rhTPO-only group, 95.2% (95% CI, 70.7–99.3%) in the AVA-only group, and 80.6% (95% CI, 61.9–90.8%) in the rhTPO + AVA group; these percentages were significantly greater than those in the control group (66.7% [95% CI, 53.0–77.2%], $P = 0.012$, $P < 0.001$, and $P = 0.030$, respectively) [Figure 2C]. Patients in AVA-only group had higher 60-day cumulative incidence of platelet engraftment than rhTPO group ($P = 0.028$), and slightly advantage than rhTPO + AVA group ($P = 0.107$).

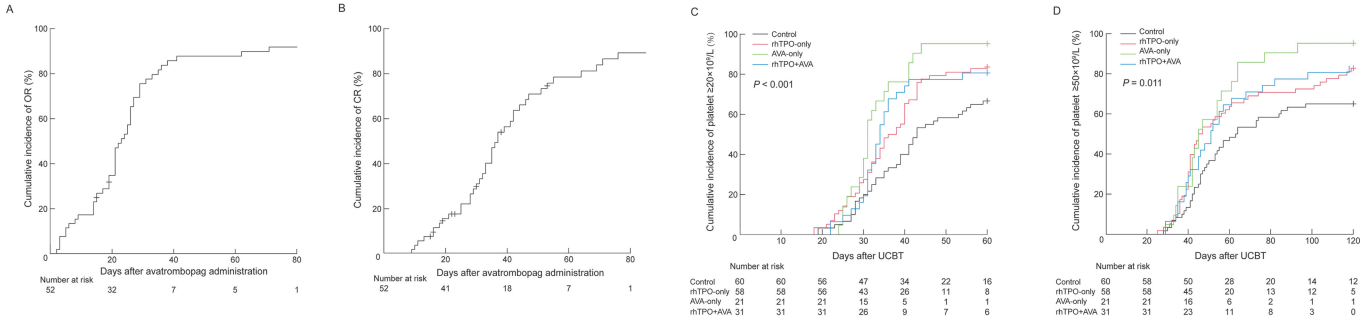

Figure 2: Platelet response following avatrombopag administration in patients receiving UCBT for promotion of platelet engraftment. The cumulative incidences of (A) OR and (B) CR in patients treated with AVA ($n = 52$). (C) The 60-day cumulative incidence of platelets ≥20 × 10^9/L. (D) The 60-day cumulative incidence of platelets ≥50 × 10^9/L in control group ($n = 60$), rhTPO-only group ($n = 58$), AVA-only group ($n = 21$), and rhTPO + AVA group ($n = 31$). AVA: Avatrombopag; CR: Complete response; OR: Overall response; rhTPO: Recombinant human thrombopoietin; UCBT: Umbilical cord blood transplantation.

The 120-day cumulative incidences for platelet recovery were 82.8% (95% CI, 70.3–90.3%), 95.2% (95% CI, 70.7–99.3%), 83.9% (95% CI, 65.5–92.9%), and 65.0% (95% CI, 51.3–75.7%) in the rhTPO group, AVA group, rhTPO + AVA group, and control group, respectively ($P = 0.011$) [Figure 2D]. Compared with patients in the control group, patients who received treatment for thrombocytopenia had greater 120-day cumulative incidences of platelet recovery (rhTPO group: $P = 0.021$; AVA group: $P = 0.001$; rhTPO + AVA group: $P = 0.049$). Patients treated with AVA only had slight advantages compared with patients in the rhTPO-only group ($P = 0.203$) and rhTPO + AVA group ($P = 0.218$).

Table 3: Univariate and multivariate analyses of the factors related with the 60-day platelet engraftment.

	Univariable analysis			Multivariable analysis		
Factors	**HR**	**95% CI**	***P* values**	**HR**	**95% CI**	***P* values**
Age (years)	0.996	0.983–1.008	0.490	–	–	–
Gender						
Male	1	–	–	–	–	–
Female	1.137	0.818–1.580	0.440	–	–	–
Diagnosis						
AML	1	–	–	–	–	–
ALL	1.100	0.746–1.621	0.630	–	–	–
MDS	0.877	0.487–1.580	0.660	–	–	–
CML	1.090	0.606–1.959	0.770	–	–	–
Other hematological malignancies	1.178	0.602–2.306	0.630	–	–	–
DRI-R						
Low	1	–	–	–	–	–
Intermediate	1.426	0.742–2.741	0.290	–	–	–
High	1.153	0.570–2.333	0.690	–	–	–
Very high	0.810	0.288–2.279	0.690	–	–	–
ABO compatibility						
Identical	1	–	–	–	–	–
Major incompatibility	1.044	0.672–1.622	0.850	–	–	–
Minor incompatibility	1.016	0.664–1.556	0.940	–	–	–
Bidirectional incompatibility	1.180	0.713–1.953	0.520	–	–	–
HLA compatibility						
3/6	1	–	–	–	–	–
4/6	0.893	0.535–1.490	0.660	–	–	–
5/6	1.086	0.626–1.885	0.770	–	–	–
7/6	1.353	0.717–2.552	0.350	–	–	–
Donor to recipient sex						
Female to male	1	–	–	–	–	–
Other	1.011	0.697–1.466	0.960	–	–	–
Conditioning regimen						
RIC	1	–	–	–	–	–
MAC	4.392	2.019–9.554	<0.001	4.446	2.158–9.158	<0.001
Infused TNCs ($\times 10^7$/kg)						
<2.59	1	–	–	–	–	–
≥2.59	1.533	1.103–2.131	0.011	1.322	0.951–1.837	0.097
Infused $CD34^+$ cells ($\times 10^5$/kg)						
<2.60	1	–	–	1	–	–
≥2.60	2.426	1.606–3.667	<0.001	1.881	1.162–3.043	0.010
Treatment for prompting platelet engraftment						
Control	1	–	–	1	–	–
rhTPO-only	1.674	1.121–2.501	0.012	1.744	1.133–2.683	0.011
AVA-only	2.802	1.670–4.702	<0.001	2.403	1.359–4.249	0.003
rhTPO + AVA	1.729	1.032–2.897	0.038	1.672	1.021–2.736	0.041
Platelet count before conditioning ($\times 10^9$/L)	1.002	1.001–1.003	<0.001	1.001	1.000–1.002	0.061

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AVA: Avatrombopag; CML: Chronic granulocytic leukemia; DRI-R: Disease risk index; HLA: Human leukocyte antigen; HR: Hazard ratio; MAC: Myeloablative conditioning; MDS: Myelodysplastic syndrome; rhTPO: Recombinant human thrombopoietin; RIC: Reduced-intensity conditioning; TNCs: Total nucleated cells; –: Not applicable.

To further explore the factors related to platelet engraftment, univariable analysis and multivariable analysis were performed [Table 3]. The results of univariable analysis indicated that five factors including treatment for promoting platelet engraftment (control, rhTPO-only, AVA-only or rhTPO + AVA group; P <0.05), conditioning regimen (RIC or MAC, P <0.001), infused TNCs (P = 0.011), infused CD34$^+$ cells (P <0.001), and platelet count before conditioning (P <0.001), were related to 60-day platelet engraftment. In the multivariable analysis, the MAC regimen (hazard ratio [HR], 4.446; 95% CI, 2.158–9.158; P <0.001), higher CD34$^+$ cells (≥2.60 × 10^5/kg) (HR, 1.881; 95% CI, 1.162–3.043; P = 0.010), treatment with either rhTPO (HR, 1.744; 95% CI, 1.133–2.683; P = 0.011), AVA (HR, 2.403; 95% CI, 1.359–4.249; P = 0.003), or rhTPO combined with AVA (HR, 1.672; 95% CI, 1.021–2.736; P = 0.041) were significantly independently associated with platelet engraftment.

Patients in the AVA group had faster neutrophil engraftment than did those in the historical control group (median time: 15 days [range, 12–32 days] *vs*. 17 days [range, 11–32 days], P = 0.002). The percentage of HCs was similar between the AVA group and the historical control group. In addition, compared with those in the historical control group, the occurrence of other hemorrhagic events, such as hemorrhage of the digestive tract, mucocutaneous, pulmonary, and cerebral systems, were lower (11.5% *vs*. 35.6%, P = 0.001). However, the number of platelet transfusions was 10 units (range, 3–29 units) and 7 units (range, 2–28 units) after UCBT in the AVA group and historical control group, respectively (P = 0.001).

Factors predicting platelet engraftment in the AVA group

To determine the predictive factors correlated with platelet reconstruction, we performed univariable and multivariable analyses of the 52 patients [Table 4]. Univariable analysis revealed that a greater number of transfused CD34$^+$ cells and early initiation of AVA (≤14 days post-UCBT) were statistically significant beneficial factors for 60-day platelet engraftment (HR, 2.014; 95% CI, 1.110–3.653, P = 0.021; HR, 2.548; 95% CI, 1.356–4.787, P = 0.004). The platelet count preconditioning and megakaryocyte (MK) count among bone marrow (BM) cells before AVA therapy did not have an impact on 60-day platelet engraftment. Three factors with a P value <0.1 were included in the multivariable analysis, and the data showed that patients who received the MAC regimen (HR, 9.101; 95% CI, 1.204–68.810; P = 0.032), more CD34$^+$ cells (HR, 2.379; 95% CI, 1.262–4.482; P = 0.007), or who started AVA treatment within 14 days post-UCBT (HR, 2.247; 95% CI, 1.182–4.271; P = 0.013) had superior platelet engraftment.

To explore the optimal medication duration, patients in the AVA group were divided into two subgroups according to the median initial usage time of AVA: the early subgroup (≤14 days, n = 29) and the late subgroup (>14 days, n = 23). The data showed that patients in the early subgroup had slightly better survival than patients in the subgroup that received AVA later (1-year OS, 85.7% [95% CI, 66.2–94.4%] *vs*. 68.3% [95% CI, 44.8–83.5%], P = 0.123; 1-year GRFS, 75.3% [95% CI, 54.9–87.4%] *vs*. 55.4% [95% CI, 33.0–73.1%], P = 0.126, respectively) [Figure 3A, B]. Moreover, there was no significant difference between the two groups. Patients treated with AVA earlier had faster platelet engraftment (median time: 31 days [range, 22–62 days] *vs*. 35 days [range, 22–144 days], P = 0.042; Figure 3C) and platelet recovery (median time: 45 days [range, 29–93 days] *vs*. 51 days [range, 29–154 days], P = 0.165; Figure 3D) than did those patients who received AVA later post-UCBT [Table 5]. The 60-day cumulative incidences of platelet engraftment and the 120-day cumulative incidences of platelet recovery were significantly higher in the early subgroup (platelet engraftment: 96.6% [95% CI, 85.1–99.7%] *vs*. 73.9% [95% CI, 55.3–89.4%], P = 0.003; Figure 3E; platelet recovery: 96.6% [95% CI, 77.9–99.5%] *vs*. 78.3% [95% CI, 55.4–90.3%], P = 0.044; Figure 3F).

The number of MKs increased significantly after AVA treatment in 52 patients in both subgroups (total: from 0.5/cm^2 [range, 0–22.0/cm^2] to 6.40/cm^2 [range, 0–33.4/cm^2], P <0.001; early subgroup: from 0.6/cm^2 [range, 0–22.0/cm^2] to 6.3/cm^2 [range, 0–33.4/cm^2], P <0.001; late subgroup: from 0.2/cm^2 [range, 0–8.3/cm^2] to 6.4/cm^2 [range, 0.4–29.1/cm^2, P <0.001]; Figure 4).

AVA in the treatment of SFPR post-UCBT

SFPR was present in 10.0% (13/130) of patients. Of the 13 patients with SFPRs, 12 (92.4%) responded to AVA therapy after a median of 11 days (range, 5–54 days) after administration. The cumulative incidence of the OR was 100% (95% CI, NA) [Figure 5A]. Twelve patients (92.4%) achieved CR within a median time of 37 days (range, 5–197 days), and the cumulative incidence of CR was also 100% (95% CI, NA) [Figure 5B].

Next, we compared the cumulative incidences of the ORs between the AVA group and the SFPR group, and the results suggested that the cumulative incidences of the ORs in patients with SFPRs were slightly greater than those in the AVA group (P = 0.108). Similarly, the median number of MKs in the BM increased significantly after AVA treatment compared with before administration (1.5/cm^2 [range, 0–10.4/cm^2] *vs*. 18.6/cm^2 [range, 2.4–114.3/cm^2], P = 0.006) [Figure 4B]. The MK counts pre-AVA were similar (P = 0.668), but patients in the SFPR had obviously increased MK counts after the administration of AVA (P = 0.156).

Adverse events associated with AVA treatment

In all patients, AVA was well tolerated, and no patients developed abnormalities related to the medication.

Discussion

Over the last decade, TPO-RAs have undergone rapid development and have been used in various clinical areas.[23] TPO-RAs increase platelet production by binding to TPO-Rs on MKs and hematopoietic stem cells (HSCs), activating downstream factors signaling pathways,

Table 4: Univariate and multivariate analyses of factors related with 60-day platelet engraftment in 52 patients received AVA.

	Univariable analysis			Multivariable analysis		
Factors	**HR**	**95% CI**	***P* values**	**HR**	**95% CI**	***P* values**
Gender						
Male	1	–	–	–	–	–
Female	1.549	0.855–2.804	0.149	–	–	–
Age (year)	1.012	0.990–1.036	0.291	–	–	–
Diagnosis						
AML	1	–	–	–	–	–
ALL	1.756	0.847–3.638	0.130	–	–	–
MDS	1.386	0.635–3.027	0.413	–	–	–
Other hematological malignancies	2.119	0.625–7.184	0.228	–	–	–
DRI-R						
Low	1	–	–	–	–	–
Intermediate	2.969	0.712–12.390	0.135	–	–	–
High	2.976	0.596–14.86	0.184	–	–	–
Very high	3.533	0.488–25.56	0.211	–	–	–
ABO compatibility						
Identical	1	–	–	–	–	–
Major incompatibility	1.286	0.599–2.761	0.518	–	–	–
Minor incompatibility	0.636	0.262–1.547	0.319	–	–	–
Bidirectional incompatibility	0.877	0.383–2.011	0.757	–	–	–
HLA compatibility						
3/6	1	–	–	–	–	–
4/6	1.100	0.146–8.270	0.926	–	–	–
5/6	1.613	0.214–12.170	0.643	–	–	–
6/6	1.402	0.163–12.060	0.758	–	–	–
Donor to recipient sex						
Female to male	1	–	–	–	–	–
Other	1.079	0.534–2.180	0.833	–	–	–
AHA MFI						
0	1	–	–	–	–	–
>0 and <5000	1.060	0.535–2.098	0.868	–	–	–
≥5000	0.538	0.207–1.399	0.204	–	–	–
Conditioning regimen						
RIC	1	–	–	1	–	–
MAC	6.007	0.822–43.92	0.077	9.101	1.204–68.810	0.032
Infused TNCs, $\times10^7$/kg						
<2.59	1	–	–	–	–	–
≥2.59	1.342	0.740–2.434	0.333	–	–	–
Infused $CD34^+$ cells, $\times10^5$/kg						
<2.60	1	–	–	1	–	–
≥2.60	2.014	1.110–3.653	0.021	2.379	1.262–4.482	0.007
MK counts before AVA initiation, per cm^2	1.044	0.970–1.124	0.249	–	–	–
Platelet counts before conditioning, 10^9/L	1.000	0.996–1.004	0.955	–	–	–
Beginning time of AVA treatment, days						
>14	1	–	–	1	–	–
≤14	2.548	1.356–4.787	0.004	2.247	1.182–4.271	0.013
History of rhTPO administration, with *vs*. without	0.639	0.353–1.156	0.139	–	–	–
CMV infection, with *vs*. without	1.028	0.492–2.149	0.942	–	–	–
PES, with *vs*. without	1.010	0.499–2.046	0.977	–	–	–
Grade II–IV aGVHD within 100 days post-UCBT with *vs*. without	0.730	0.373–1.426	0.356	–	–	–

aGVHD: Acute graft-versus-host disease; AHA: Anti-HLA antibodies; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BMFD: Bone marrow failure disease; CMV: Cytomegalovirus; DRI-R: Disease risk index; HLA: Human leukocyte antigen; HR: Hazard ratio; MAC: Myeloablative conditioning; MDS: Myelodysplastic syndrome; MFI: Mean fluorescence intensity; MK: Megakaryocyte; PES: Pre-engraftment syndrome; rhTPO: Recombinant human thrombopoietin; RIC: Reduced-intensity conditioning; TNCs: Total nucleated cells; UCBT: Umbilical cord blood transplantation; –: Not applicable.

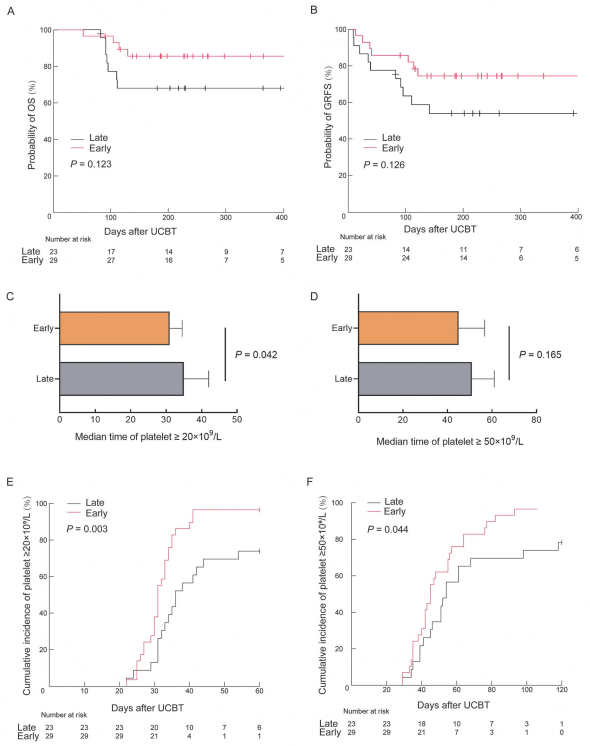

Figure 3: Survival, platelet engraftment, and platelet recovery for patients who started AVA treatment within 14 days post-UCBT (early, $n = 29$) and for patients who were given AVA after 14 days post-UCBT (late, $n = 23$). (A) OS, (B) GRFS, (C) median platelet count $\geq 20 \times 10^9$/L, (D) median platelet count $\geq 50 \times 10^9$/L, (E) 60-day cumulative incidence of platelet count $\geq 20 \times 10^9$/L, and (F) 60-day cumulative incidence of platelet count $\geq 50 \times 10^9$/L between the early and late subgroups. (C) and (D) are shown as medians with interquartile ranges. AVA: Avatrombopag; GRFS: graft-versus-host disease-free, relapse-free survival; OS: Overall survival; UCBT: Umbilical cord blood transplantation.

and promoting the proliferation and differentiation of MKs.[3,12,24] TPO-RAs seem to improve platelet counts safely and effectively in patients with thrombocytopenia after HSCT.[14,15,21,25,26] Compared with those of other TPO-RAs, fewer studies have analyzed the potential benefits of AVA in the post-HSCT setting, but all the studies have shown good response rates. To date, four (ongoing) prospective studies have evaluated the efficacy of AVA at promoting platelet engraftment after allo-HSCT (www.clinicaltrials.gov, accessed on April 21, 2025). Here, we report the results of the first retrospective analysis of AVA administration in the setting of thrombocytopenia after UCBT in comparison with historical controls from a previous study.[13]

To minimize the impact of differences in the initial duration and duration of AVA treatment, 52 patients who started treatment with AVA within 30 days and continued for more than 7 consecutive days were enrolled. Our study indicated that AVA was effective and tolerable at promoting platelet engraftment in patients who underwent UCBT. The cumulative incidences of OR and CR after AVA treatment were 91.9% and 89.2%, respectively, for prompting platelet engraftment, and both were 100% for the SFPR. To eliminate the effect of using rhTPO, we further divided patients into four subgroups according to drug usage. The results showed that patients treated with rhTPO, AVA, or a combination of drugs had greater 60-day platelet engraftment and recovery rates than did patients in the control group. No improvement in efficacy was shown in patients who received the combination of rhTPO and AVA, which may be caused by the small sample size and the distinct usage time of AVA.

Previous reports of the use of AVA in allo-HSCT patients have shown good clinical efficacy and safety. Zhou *et al*[21] performed a retrospective study that enrolled 61 patients diagnosed with thrombocytopenia after HSCT, including 25 delayed platelet engraftment patients and 17 SFPR patients, and the results suggested that the cumulative incidences of OR and CR were both 39.3%. The median durations from initial AVA administration to OR or CR were 21 days (range, 6–33 days) and 25 days (range, 9–40 days), respectively. In another retrospective study, Ruan *et al*[25] reported that the cumulative incidences of OR were 86.7% and 100% after AVA treatment in children from the poor graft function (PGF)/SFPR ($n = 20$) and engraftment-promotion ($n = 12$) groups, respectively. No severe adverse events were reported in these retrospective studies, including ours.

The difference in response rates between our study and previous reports might be due to the initial time, dosage, purpose, and duration of medication. To estimate the best time point for AVA treatment for platelet engraftment, we divided 52 patients into early (≤14 days posttransplant) and late (>14 days posttransplant) subgroups according to the median duration of AVA administration, which was validated by the receiver operating characteristic (ROC) curve analysis with the calculation of area under curve (AUC, 0.740, $P = 0.043$). Through univariate and multivariate analyses, we found that early use of AVA promoted better implantation outcomes, with a shorter median time of platelet engraftment (31 days *vs*. 35 days), a greater OR of 96.6% (28/29), and a 60-day cumulative incidence of platelet engraftment of 100%; moreover, these patients had better survival. In our previous report, the median duration of platelet engraftment was 38.5 days (range, 17–210 days) in 113 UCBT recipients[5] and 88 days (range, 62–211 days) in 49 UCBT recipients who underwent PIT after transplantation,[1] which suggested delayed platelet engraftment in the UCBT setting. Thus, preventive TPO/TPO-RA usage seems necessary. We previously reported that early rhTPO usage (300 U/kg once daily) from day +14 to day +28 after UCBT could effectively promote platelet reconstitution.[13] In another pilot study of 17 patients who underwent allo-HSCT, hetrombopag was administered from day +1 after HSCT until the platelet count reached $\geq 50 \times 10^9$/L,[17] and the cumulative incidence of platelet implantation on day +21 increased from 65% to 88% compared with that of the historical control. Due to the limitations of retrospective studies and the lack of a validation set, a multicenter prospective clinical trial is needed.

SFPR patients showed a similar cumulative incidence for OR and CR (both 100%) as did engraftment-promotion patients ($P > 0.05$), and they showed a higher cumulative incidence for OR and CR than did patients who received AVA 30 days after UCBT ($n = 66$; CI of OR: 88.0% [95% CI, 76.5–94.1%], $P = 0.004$; CI of CR: 87.1% [95% CI,

Table 5: Characteristics of patients between patients received AVA within 14 days post-UCBT and after 14 days post-UCBT.

	Treated with AVA post-UCBT			
	Early	Late		
Characteristics	(≤14 days, *N* = 29)	(>14 days, *N* = 23)	$\chi^2/Z/t$	*P* values
Gender			0.515	0.473*
Male	18 (62.1)	12 (52.2)		
Female	11 (37.9)	11 (47.8)		
Age (years)	35 (10, 59)	26 (10, 53)	–1.847	0.071†
Diagnosis			4.719	0.193‡
AML	18 (62.1)	11 (47.8)		
ALL	5 (17.2)	6 (26.1)		
MDS	3 (10.3)	6 (26.1)		
Other hematological malignancies	3 (10.3)	0 (0)		
DRI-R			2.653	0.513‡
Low	2 (6.9)	2 (8.7)		
Intermediate	23 (79.3)	17 (73.9)		
High	4 (13.8)	2 (8.7)		
Very high	0 (0)	2 (8.7)		
ABO compatibility			3.181	0.366‡
Identical	7 (24.1)	7 (30.4)		
Major incompatibility	11 (37.9)	5 (21.7)		
Minor incompatibility	4 (13.8)	7 (30.4)		
Bidirectional incompatibility	7 (24.1)	4 (17.4)		
HLA compatibility			2.064	0.623‡
3/6	1 (3.4)	0 (0)		
4/6	13 (44.8)	12 (52.2)		
5/6	11 (37.9)	10 (43.5)		
6/6	4 (13.8)	1 (4.3)		
Donor to recipient sex			0.287	0.592§
Female to male	8 (27.6)	4 (17.4)		
Others	21 (72.4)	19 (82.6)		
AHA MFI			4.036	0.261‡
0	16 (55.2)	14 (60.9)		
>0 and <5000	9 (31.0)	3 (13.0)		
≥5000	2 (6.9)	5 (21.7)		
NA	2 (6.9)	1 (4.3)		
Conditioning regimen			0.043	0.836§
RIC	1 (3.4)	2 (8.7)		
MAC	28 (96.6)	21 (91.3)		
Infused TNCs, $\times10^7$/kg			0.027	0.870*
<2.59	17 (58.6)	14 (60.9)		
≥2.59	12 (41.4)	9 (39.1)		
Infused $CD34^+$ cells, $\times10^5$/kg			0.957	0.328*
<2.60	15 (51.7)	15 (65.2)		
≥2.60	14 (48.3)	8 (34.8)		
Hematopoietic reconstitution, median (range) days post-UCBT				
Neutrophil engraftment	15 (12, 24)	14 (12, 32)	0.776	0.443†
Platelet engraftment	31 (22, 62)	35 (22, 144)	–2.031	0.042†
Platelet recovery	45 (29, 93)	51 (29, 154)	1.412	0.165†
MK counts before AVA treatment (per cm^2)	0.55 (0, 22.0)	0.23 (0,8.25)	–0.895	0.376†
MK counts after AVA treatment (per cm^2)	6.31 (0, 33.40)	6.40 (0.38, 29.12)	0.117	0.908†
Platelet counts before conditioning, $\times10^9$/L	154 (8, 363)	140 (30, 248)	–0.724	0.473†
Transplantation-related complications				
CMV infection	23 (79.3)	20 (87.0)	0.126	0.723§
PES	21 (72.4)	20 (87.0)	0.871	0.351§
Grade II–IV aGVHD	12 (41.4)	11 (47.8)	0.216	0.642*
HC	10 (34.5)	7 (30.4)	0.096	0.757*
Other hemorrhage events	3 (10.3)	3 (13.0)	0	1.000§
Counts of infused platelet, unit	9 (3, 19)	10 (3, 23)	0.822	0.415†

Data are expressed as *n* (%) or median (range). *Pearson χ^2 test. †Student's *t*-test. ‡Fisher's exact test. §Continuity correction test. ‖Mann–Whitney *U* test. aGVHD: Acute graft-versus-host disease; AHA: Anti-HLA antibodies; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AVA: Avatrombopag; BMFD: Bone marrow failure disease; CMV: Cytomegalovirus; DRI-R: Disease risk index; HC: Hemorrhagic cystitis; HCT: Hematopoietic cell transplantation; HLA: Human leukocyte antigen; MAC: Myeloablative conditioning; MDS: Myelodysplastic syndrome; MFI: Mean fluorescence intensity; MK: Megakaryocyte; NA: not available; PES: Pre-engraftment syndrome; RIC: Reduced-intensity conditioning; TNCs: Total nucleated cells; UCBT: Umbilical cord blood transplantation.

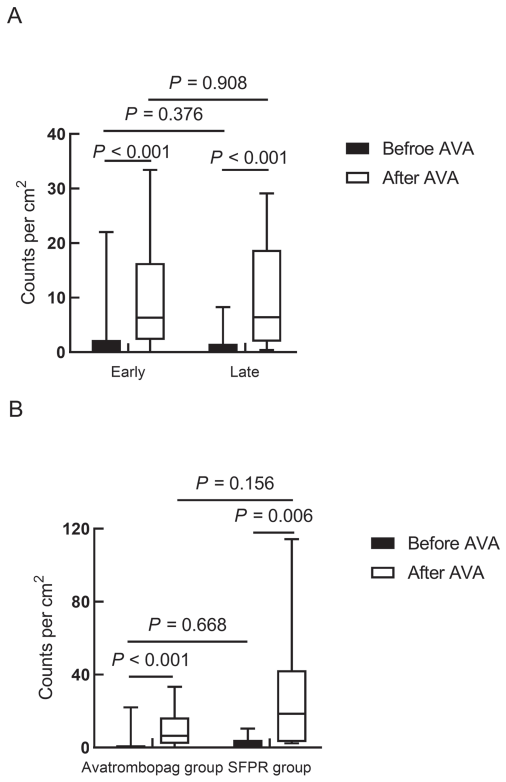

Figure 4: The MK count in the BM increased after AVA treatment in (A) patients initially treated with AVA early ($n = 29$) or late ($n = 23$), (B) 52 patients in the AVA group and 13 patients in the SFPR group. The results are shown as the box-and-whisker-plot diagrams. AVA: Avatrombopag; BM: Bone marrow; MK: Megakaryocyte; SFPR: Secondary failure of platelet recovery.

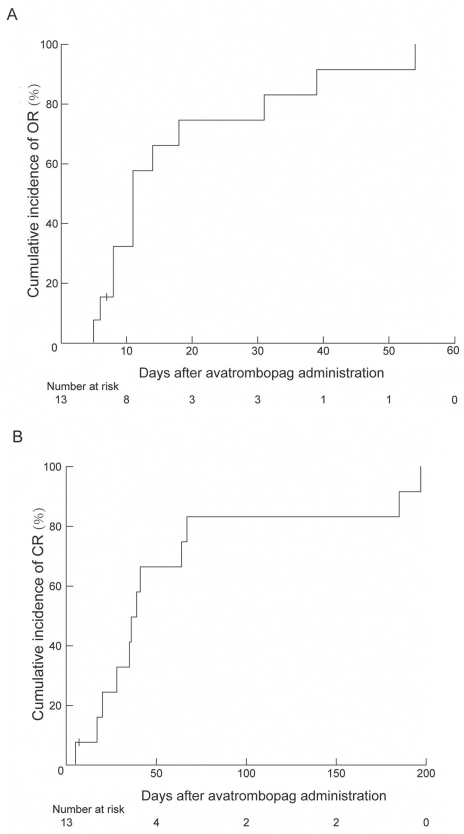

Figure 5: The cumulative incidences of (A) OR and (B) CR in patients with SFPR treated with AVA ($n = 13$). AVA: Avatrombopag; CR: Complete response; OR: Overall response; SFPR: Secondary failure of platelet recovery.

74.7–93.7%], $P = 0.058$). By comparing baseline MK counts in the BM between these three medication groups, we found a slightly greater MK before AVA administration and an obviously greater MK in patients with SFPR, which suggested that the function of MK was better in patients with SFPR and may be the reason for the greater response rates.

Several studies have shown that MK counts in BM before TPO-RA initiation are correlated with a good respo nse.[15,21,26,27] Due to the expression of c-MPL receptors on MKs, TPO-RAs can induce the production of platelets from MKs in the BM. We also found a greater level of MKs before AVA therapy in patients who had a better response. However, this cellular index was not confirmed to be a predictive factor for the OR by univariate analysis, possibly due to the limited available data on BM morphology before therapy in this study. Recently, Fu *et al*[28] reported that lower baseline TPO levels (≤1714 pg/mL) predicted a better response to AVA treatment. The endogenous TPO concentration may reflect the count and function of MKs, MK precursor cells, HSCs and hematopoietic progenitor cells HPCs), and increased TPO levels are associated with the inhibition of MK maturation and poor hematopoietic function.[28,29] Our study and previous reports need to be validated in a large cohort and basic experimental exploration.

The median number of units of platelet transfusion in the AVA group was greater than that in the historical control group. This seems opposite to the improved platelet engraftment. Considering patient data from different periods and changes in blood donation policy, we further compared platelet counts between patients who initially received AVA within 30 days post-UCBT and patients treated with AVA after 30 days post-UCBT to promote platelet engraftment. The number of units of platelet transfusion was significantly lower in patients who received AVA earlier (median: 10 units *vs*. 16 units, $P < 0.001$).

Our findings could provide a basis for clinical application and improve the survival of these patients. One limitation of this study was the small sample size, as was the retrospective design. However, additional patients and prospective studies are needed to validate our results. Thus, we are currently recruiting for a prospective clinical trial (ID: NCT05823376) to explore the early use of AVA for platelet engraftment post-UCBT.

In summary, AVA was well tolerated and an effective therapy for platelet recovery, and early initial administration of AVA within 14 days post-UCBT led to increased platelet engraftment rates. AVA treatment is a potential therapy for thrombocytopenia after UCBT.

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Conflicts of interest

None.

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