Secondary prevention of cancer therapy-induced thrombocytopenia with hetrombopag in breast cancer: a multicenter, randomized, exploratory phase II trial

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Abstract

Background: Cancer therapy-induced thrombocytopenia (CTIT) is a common complication of anti-tumor therapy, leading to treatment delays or interruptions, increased bleeding risk and compromised outcomes. In the present study, we aimed to evaluate the efficacy and safety of hetrombopag, an oral thrombopoietin receptor agonist, for managing and preventing CTIT in patients with breast cancer.

Methods: In this multi-center, randomized phase II clinical trial (NCT05394285), breast cancer patients with platelet counts <50×10□/L during anti-tumor treatment (Cycle 1) were enrolled. Those patients were randomly assigned (1:1)to receive either hetrombopag or subcutaneous recombinant human thrombopoietin (rhTPO) until their platelet counts >100×10□/L, which was defined as the thrombocytopenia treatment phase (TTP). During the secondary prevention phase (SPP), all cases as self-control received hetrombopag for 14 days starting on day 1 of the subsequent anti-tumor treatment cycle (Cycle 2). The primary endpoint was the response rate of the SPP. Secondary endpoints comprised the response rate of TTP (key secondary endpoint), other platelet-related parameters, and safety outcomes.

Results: Between September 2022 and May 2025, 67 patients with breast cancer were enrolled. After excluding one patient who withdrew informed consent, 66 patients were randomized. During the trial, 6 patients discontinued participation in the SPP, the remaining 60 patients constituted the per-protocol set (PPS). The majority of patients in the PPS (n=47) received antibody-drug conjugates (ADCs) treatment. For the primary endpoint, the response rate was 85.0% (51/60) in the PPS, and 89.4% (42/47) among patients receiving ADCs. Regarding the key secondary endpoint during the TTP, the response rates were 87.9% (29/33) in patients receiving hetrombopag and 81.8% (27/33) in those receiving rhTPO. No treatment-emergent severe adverse events were observed.

Conclusions: Hetrombopag represents a promising and well-tolerated strategy for the secondary prevention and management of CTIT in breast cancer patients, particularly in patients received ADCs.

Introduction

Cancer therapy-induced thrombocytopenia (CTIT) is a common complication of anti-tumor treatment and may lead to treatment delays or interruptions, increased bleeding risk, and compromised outcomes[1]. This concept encompasses thrombocytopenia induced by various treatments, such as chemotherapy (CIT), immune checkpoint inhibitors, targeted therapy including antibody-drug conjugates (ADCs), and radiotherapy[2].

In breast cancer, CTIT presents a major clinical challenge. With traditional chemotherapy, gemcitabine-based regimens are particularly associated with grade ≥ 3 thrombocytopenia, with an approximate incidence of 14% for monotherapy[3] and up to 32% for combination with cisplatin[4]. This challenge extends to certain ADCs, a transformative class of agents with rapidly expanding clinical utility in breast cancer. Trastuzumab Emtansine (T-DM1), a pioneering ADC targeting the human epidermal growth factor receptor 2 (HER2), was initially approved based on the results of the phase III EMILIA trial[5] and remains a cornerstone in adjuvant therapy for HER2-positive breast cancer following the KATHERINE trial[6]. However, its clinical utility is limited by high-grade thrombocytopenia, with a meta-analysis reporting a 32% incidence of grade ≥ 3 events, often requiring treatment modification or even discontinuation[7]. The subsequent development of trastuzumab deruxtecan (T-DXd), a later-generation ADC, is characterized by breakthrough efficacy across the spectrum of HER2 expression (low and positive) and disease stages (early and advanced) in breast cancer[8–11]. Nevertheless, thrombocytopenia

remains a relevant adverse event with T-DXd, occurring in approximately 20% of patients, including severe (grade ≥ 3) events in about 10%.

Although recombinant human thrombopoietin (rhTPO) is approved for the treatment of CTIT, there is currently no evidence supporting its use for prevention[12]. Thrombopoietin receptor agonists (TPO-RAs) represent a promising therapeutic strategy for CTIT by binding to the transmembrane domain of TPO receptor, which activates downstream signaling cascades to promote the proliferation and differentiation of megakaryocyte progenitor cells[13]. However, current evidence for TPO-RAs is limited to the treatment of established CIT[14–16], creating a critical gap in evidence for their use in preventing CTIT within the increasingly prevalent ADC-based regimens for breast cancer.

Hetrombopag, a novel oral TPO-RA developed in China, has demonstrated efficacy against CIT in a phase II trial involving patients with solid tumors[17]. Building on this evidence, this prospective study is the first to evaluate the efficacy and safety of hetrombopag as a secondary prevention strategy for CTIT in breast cancer patients.

Methods

Study design and participants

This multicenter, open-label, randomized, phase II study (NCT05394285) of hetrombopag for the treatment and prevention of CTIT in breast cancer patients was conducted at four qualified tertiary hospitals in China. The study protocol received approval from regulatory authorities and ethics committees at all anticipating centers. Written informed consents were received from all patients before enrollment.

Patients aged 18–75 years with pathologically confirmed breast cancer who received anti-tumor treatment and had severe thrombocytopenia were eligible for inclusion. Severe thrombocytopenia was defined as a platelet count (PLT) < 50×10□/L during the qualifying cycle (Cycle 1). PLT values were obtained in accordance with standard clinical practice prior to informed consent. Additionally, patients were required to be scheduled to receive the same anti-tumor regimen and dose in the subsequent cycle (Cycle 2). All participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy ≥ 12 weeks, and no serious complications.

Key exclusion criteria included a history of haematological malignancy or bone marrow metastasis; clinically active bleeding within 2 weeks; receipt of radiotherapy or any platelet-boosting therapy within 1 month; arterial or venous thrombosis within 6 months before enrollment; significant hepatic or renal dysfunction or other severe complications.

Randomization and interventions

Randomization was generated using a computer-generated randomization table by an interactive web response system. Both study participants and the research team were aware of the group assignments after randomization. Eligible patients were randomized in a 1:1 ratio to the hetrombopag group or the rhTPO group. The period from the start of thrombocytopenia treatment to PLT > 100×10□/L was defined as the thrombocytopenia treatment phase (TTP). In the TTP, patients in the hetrombopag group received hetrombopag (7.5 mg, orally, daily), and patients in the rhTPO group received rhTPO (15000 U, subcutaneously, daily). In the secondary prevention phase (SPP), all patients received hetrombopag at an

initial dose of 7.5 mg once daily for 14 consecutive days, starting on day 1 following the initiation of Cycle 2.

Regarding dose adjustment of hetrombopag, the daily dose was reduced to 5.0 mg when PLT were between 200×10⁹/L and 400×10⁹/L. If PLT reached ≥ 400×10⁹/L, hetrombopag was withheld until PLT dropped to < 200×10⁹/L, and then resumed at a daily dose of 5.0 mg. Any days of treatment interruption were counted toward the total 14-day treatment course.

Platelet counts were monitored every other day during both the TTP and SPP, with additional assessments performed at the investigator's discretion. Platelet transfusion might be considered when PLT < 10×10⁹/L or when there was a risk of bleeding. The detail study design is shown in Fig. 1.

Study endpoints

Patients who completed at least two consecutive cycles of anti-tumor therapy (Cycle 1 and Cycle 2) were included in the primary endpoint analysis. Efficacy endpoints were assessed during the defined observation period spanning from the time of randomization to the initiation of Cycle 3 therapy. The choice to extend hetrombopag prophylaxis beyond the core study period was guided by patient preferences, and data were systematically collected to enable subsequent post hoc analysis.

Response rate was defined as the proportion of patients who met the following criteria until the start of the subsequent cycle: 1. received the standard anti-tumor treatment without dose modification (defined as a dose reduction of ≥ 20% or a delay of ≥ 5 days) due to thrombocytopenia, 2. no platelet transfusion, and 3. no severe thrombocytopenia (defined as a PLT < 25×10⁹/L, or a PLT < 50×10⁹/L persisting for ≥ 7 consecutive days). The primary endpoint was the response rate during the SPP, defined as the proportion of responders until the start of Cycle 3. Subgroup analysis based on different anti-tumor treatment regimens was performed in post hoc analysis.

The key secondary endpoint was the response rate during the TTP, defined as the proportion of responders until the start of Cycle 2. Other secondary endpoints included the nadir and peak PLT, as well as the incidence and duration of PLT < 25×10^9/L and PLT < 50×10^9/L during the TTP and the SPP, respectively. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0. Bleeds were classified according to the WHO bleeding assessment scale (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; and grade 4, debilitating blood loss).

Statistical analyses

Full analysis set (FAS) included all randomly assigned patients. The per-protocol set (PPS) included all subjects who completed protocol-specified treatments without serious protocol violations. The proportion of responders was present as binary categories. For patients lacking efficacy data due to treatment interruption, additional patients were incorporate to complete the study. Descriptive statistical analyses were used to summarize other secondary outcomes. Results were presented as the number (percentage), mean±standard (deviation), or median (Min, Max). Data analyses were performed using SAS software (version 9.4). A comprehensive description of the study protocol is available in Supplementary Appendix 1.

Results

Patient characteristics

Between September 2022 and May 2025, a total of 67 female breast cancer patients were initially enrolled in the study. After excluding 1 patient who withdrew informed consent, 66 patients comprised the FAS. They were randomly assigned to receive either hetrombopag (n = 33) or rhTPO (n = 33).

Patients in the FAS had a median age of 54.4 years (range, 29–73) and an ECOG performance status of 0 or 1. The cohort comprised 19 patients with early-stage breast cancer and 47 with metastatic disease. Among those with metastatic disease, 38 had visceral metastases and 16 had ≥ 3 metastatic lesions. The median number of prior therapy lines was 3 (range, 0–10), and 23 patients had received more than 3 lines of systemic therapy. The average baseline PLT was 37.5 (15–49) ×10□/L, with 39.0 (23–49) ×10□/L in the hetrombopag group and 36.0 (15–49) ×10□/L in the rhTPO group, respectively. Furthermore, 9 patients (13.6%) had baseline PLT ≤ 25×10□/L, including 2 (6.1%) in the hetrombopag group and 7 (21.2%) in the rhTPO group.

A total of 51 patients (77.3%) received ADCs, comprising 23 patients in the hetrombopag group and 28 patients in the rhTPO group. Fourteen patients (21.2%) were treated with chemotherapy-based regimens (CBRs), while one patient (1.5%) received a combination of abemaciclib (a CDK4/6 inhibitor) and fulvestrant (an endocrine agent) along with inetetamab (a macromolecular monoclonal antibody). Detailed patient characteristics are presented in Table 1.

Table 1
Baseline characteristics

Characteristics	Hetrombopag group (n = 33)	rhTPO, group (n = 33)	All patients (N = 66)
Age, years	55.6 (32, 69)	52.5 (29, 73)	54.4 (29, 73)
Sex, n (%)			
Female	33 (100.0)	33 (100.0)	66 (100.0)
Stage, n (%)			
Early-stage	8 (24.2)	11 (33.3)	19 (28.8)
Metastatic	25 (75.8)	22 (66.7)	47 (71.2)
Visceral metastases			
Yes	19 (57.6)	19 (57.6)	38 (57.6)
No	6 (18.2)	3 (9.1)	9 (13.6)
Number of metastatic lesions			
1	7 (21.2)	6 (18.2)	13 (19.7)
2	8 (24.2)	10 (30.3)	18 (54.5)
≥ 3	10 (30.3)	6 (18.2)	16 (24.2)
Number of previous therapy lines, n (%)			
≤ 3	13 (39.4)	11 (33.3)	24 (36.4)
> 3	12 (36.4)	11 (33.3)	23 (34.8)
Baseline platelet count×10□/L (median, range)	39.0 (23, 49)	36.0 (15, 49)	37.5 (15, 49)
Baseline platelet count×10□/L, n (%)			
PLT ≤ 25	2 (6.1)	7 (21.2)	9 (13.6)
25 < PLT < 50	31 (93.9)	26 (78.8)	57 (86.4)
Regimen, n (%)			
ADCs	23 (69.7)	28 (84.8)	51 (77.3)
T-DM1	21 (63.6)	26 (78.8)	47 (71.2)
T-DXd	2 (6.1)	2 (6.1)	4 (6.1)
CBRs	10 (30.3)	4 (12.1)	14 (21.2)
Monotherapy chemotherapy	1 (3.0)	1 (3.0)	2 (3.0)
Combination chemotherapy	9 (27.3)	3 (9.1)	12 (18.2)
Abemaciclib, fulvestrant and inetetamab	0	1 (3.0)	1 (1.5)

ADCs: antibody-drug conjugates; CBRs: chemotherapy-based regimens; T-DM1: trastuzumab emtansine; T-DXd: trastuzumab deruxtecan

Primary endpoint: the response rate during the SPP

After excluding 6 patients who failed to complete cycle 2 anti-tumor therapy in accordance with the study protocol (2 due to disease progression, 4 due to withdrawal of informed consent), the remaining 60 patients constituted the PPS for primary analysis. Among them, 47 patients were treated with ADCs, while 12 patients were treated with CBRs. The response rate during the SPP was 85.0% (51/60). Post hoc analysis showed that the response rate in patients treated with ADCs (89.4%, 42/47) was numerically higher than that among patients treated with CBRs (75.0%, 9/12) (Table 2).

After receiving prophylactic hetrombopag during the SPP, the median nadir PLT was 56.5×10^9/L, with only one patient requiring platelet transfusion. Treatment adjustments due to thrombocytopenia occurred in 10% of patients and were numerically lower in the ADC group than in the CBR group (4.3% vs 25.0%). The detailed response items and other PLT parameters are shown in Table 3.

Table 2
The response rate during the SPP.

Primary endpoint	Response (n)	Non-response (n)	Response rate (%)
PPS (N = 60)	51	9	85.0
Regimen			
ADC (n = 47)	42	5	89.4
CBR (n = 12)	9	3	75.0

PPS: protocol set; ADC: antibody-drug conjugate; CBR: chemotherapy-based regimen

Table 3
The response items and other PLT parameters during the SPP

Other endpoints	ADC (N = 47)	CBR (N = 12)	PPS (N = 60)
Response items			
Treatment modification due to thrombocytopenia (n, %)	2 (4.3%)	3 (25%)	6 (10.0%)
Platelet transfusion requirement (n, %)	0	1 (8.3%)	1 (1.7%)
Grade 4 thrombocytopenia (PLT < 25×10⁹/L; n, %)	4 (8.5%)	2 (16.7%)	6 (10.0%)
Persistent thrombocytopenia (PLT < 50×10⁹/L for ≥ 7 consecutive days; n, %)	2 (4.3%)	1 (8.3%)	3 (5.0%)
Other PLT parameters			
PLT nadir (×10⁹/L; median, range)	55 (19, 236)	70.5 (20, 188)	56.5 (19, 331)
PLT maxmium (×10⁹/L; median, range)	179 (70, 445)	185 (87, 651)	179.5 (51, 445)
Median duration of grade 4 thrombocytopenia (PLT < 25×10⁹/L; days)	2.0	3.0	2.0
Grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; n, %)	18 (38.3%)	5 (41.7%)	23 (38.3%)
Median duration of grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; days)	2.5	3.0	3.0
PPS: protocol set; ADC: antibody-drug conjugate; CBR: chemotherapy-based regimen			

Secondary endpoints: the response rate during the TTP

In the FAS, the response rate was 84.8% (56/66), with similar rates in the hetrombopag and rhTPO groups (87.9% [29/33] vs. 81.8% [27/33]). Post hoc analysis showed a response rate of 90.2% (46/51) in ADC-treated patients, with rates of 95.7% (22/23) and 85.7% (24/28) in the hetrombopag and rhTPO groups, respectively. In the CBR subgroup, the response rate was 71.4% (10/14), with 70.0% (7/10) in the hetrombopag group and 75.0% (3/4) in the rhTPO group. Detailed data are showed in Fig. 2.

The median duration of the TTP was 6 days in the hetrombopag group and 7 days in the rhTPO group. Moreover, the median nadir and peak PLT, the incidence and the duration of grade 3/4 thrombocytopenia were comparable between the two groups (Table 4).

Table 4
Platelet parameters and thrombocytopenia occurrence in FAS during the TTP

Secondary endpoints during the TTP	Hetrombopag group (n = 33)	rhTPO group (n = 33)	FAS (N = 66)
PLT nadir (×10⁹/L; median, range)	53.0 (12, 164)	47.0 (10, 90)	49.5 (10, 164)
PLT maxmium (×10⁹/L; median, range)	125.0 (81, 552)	135.0 (96, 212)	126.5 (81, 552)
Grade 4 thrombocytopenia (PLT < 25×10⁹/L; n, %)	3 (9.1)	4 (12.1)	7 (10.6)
Median duration of grade 4 thrombocytopenia (PLT < 25×10⁹/L; days)	3.0	3.5	3.0
Grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; n, %)	14 (42.4)	19 (57.6)	33 (50.0)
Median duration of grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; days)	2.0	2.0	2.0
Median duration of the TTP (days)	6.0	7.0	7.0

Post hoc analysis of platelet parameters and the incidence of thrombocytopenia were performed in the ADC and CBR subgroups. In patients treated with ADC, the nadir PLT was significantly higher in the hetrombopag group compared to the rhTPO group (67 vs. 44×10^9/L), accompanied by a reduced incidence of grade 3/4 thrombocytopenia (Table 5). This favorable trend was not evident in patients treated with CBR (Supplementary Appendix 2). These findings indicated that hetrombopag may be more effective in managing ADC-induced thrombocytopenia compared to that induced by other medications.

Table 5
Platelet parameters and thrombocytopenia occurrence in ADC-treated patients during the TTP

Secondary endpoints	Hetrombopag group (n = 23)	rhTPO group (n = 28)	ADC (N = 51)
PLT nadir (×10⁹/L; median, range)	67.0 (21, 118)	44.0 (10, 90)	52.0 (10, 118)
PLT maxmium (×10⁹/L; median, range)	120.0 (89, 552)	135.5 (96, 212)	125.0 (89, 552)
Grade 4 thrombocytopenia (PLT < 25×10⁹/L; n, %)	1 (4.3)	3 (10.7)	4 (7.8)
Median duration of grade 4 thrombocytopenia (PLT < 25×10⁹/L; days)	3.0	3.0	3.0
Grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; n, %)	6 (26.1)	17 (60.7)	23 (45.1)
Median duration of grade 3/4 thrombocytopenia (PLT < 50×10⁹/L; days)	2.0	2.0	2.0
Median duration of TTP (days)	6.0	7.0	6.0

Safety

During the SPP, 12 patients underwent dose adjustments of hetrombopag. Of these, 9 patients reduced their dose to 5.0 mg for PLT ranging from 200 to 400×10⁹/L. The remaining 3 patients temporarily

discontinued treatment (2 days for two patients each; 3 days for one patient) when their PLT reached ≥ 400×10⁹/L and resumed hetrombopag at 5 mg once PLT dropped to < 200×10⁹/L.

In the FAS population, the most common treatment-emergent adverse events (TEAEs) of any grade were leukopenia (34, 51.5%) and anemia (34, 51.5%), followed by elevated aspartate aminotransferase (31, 47.0%), elevated glutamyltransferase (31, 47.0%), neutropenia (29, 43.9%) and elevated blood lactate dehydrogenase (22, 33.3%). The most common grade 3 or higher TEAEs were leukopenia (4, 6.1%) and elevated aspartate aminotransferase (4, 6.1%), followed by neutropenia (3, 4.5%), elevated alanine aminotransferase (3, 4.5%), elevated glutamyltransferase (3, 4.5%), and anemia (2, 3.0%). All TEAEs were predominantly associated with the anti-tumor agents and were considered unrelated to the thrombopoietic agents.

Six patients (9.1%) experienced bleeding, all classified as WHO grade 1, including hemoptysis, epistaxis, skin petechiae and ecchymosis. There were no arterial or venous thrombosis events during the study. Detailed data are presented in Table 6.

Table 6
Adverse events among FAS population.

Adverse events	Hetrombopag (n = 33)		rhTPO (n = 33)		FAS (N = 66)	
	Ang grades	≧ 3 grade	Ang grades	≧ 3 grade	Ang grades	≧ 3 grade
Leukopenia	17 (51.5%)	3 (9.1%)	17 (51.5%)	1 (3.0%)	34 (51.5%)	4 (6.1%)
Neutropenia	15 (45.5%)	3 (9.1%)	14 (42.4%)	0	29 (43.9%)	3 (4.5%)
Anemia	16 (48.5%)	2 (6.1%)	18 (54.5%)	0	34 (51.5%)	2 (3.0%)
Elevated alanine aminotransferase	9 (27.3%)	0	11 (33.3%)	3 (9.1%)	20 (30.3%)	3 (4.5%)
Elevated aspartate aminotransferase	16 (48.5%)	1(3.0%)	15 (45.5%)	3 (9.1%)	31 (47.0%)	4 (6.1%)
Elevated bilirubin	1 (3.0%)	0	1 (3.0%)	0	2 (3.0%)	0
Elevated glutamyltransferase	14 (42.4%)	2 (6.1%)	17 (51.5%)	1 (3.0%)	31 (47.0%)	3 (4.5%)
Elevated blood lactate dehydrogenase	12 (36.4%)	0	10 (30.3%)	0	22 (33.3%)	0
Elevated blood creatinine	2 (6.1%)	0	5 (15.2%)	0	7 (10.6%)	0
Hypokalaemia	3 (9.1%)	0	0	0	3 (4.5%)	0
Hyponatremia	1 (3.0%)	0	0	0	1 (1.5%)	0
Hypocalcaemia	1 (3.0%)	0	1 (3.0%)	0	2 (3.0%)	0
AEs of special interest	0	0	0	0	0	0
Bleeding	4 (12.1%)	0	2 (6.1%)	0	6 (9.1%)	0
Thrombosis	0	0	0	0	0	0

Follow-up: additional cycles

Among the 51 responders who completed the protocol-defined prevention phase, 12 patients chose to continue hetrombopag prophylaxis. Of these, six patients with early-stage breast cancer successfully completed the planned adjuvant T-DM1 treatment course (an additional 12 cycles). The remaining six patients (five on T-DM1 and one on chemotherapy) with advanced breast cancer received secondary prevention for variable durations: three for only 2 additional cycles, two for 6 cycles (both discontinued due to financial pressure), and one for 20 cycles until disease progression. Follow-up data about the remaining patients are showed in Supplementary Appendix 3.

Discussion

This phase II study is the first clinical trial to assess hetrombopag for the secondary prevention of CTIT in patients with breast cancer, demonstrating an 85.0% response rate in the PPS population. Furthermore, hetrombopag was well tolerated in this cohort, with no increased incidence of thromboembolic events or other serious adverse events.

Proactive prevention of thrombocytopenia, rather than reactive correction, better optimizes patient safety and facilitates timely completion of scheduled therapy, yet relevant research remains limited. A phase II randomized controlled trial (RCT) evaluated dose-ranging eltrombopag (50, 75, 100 mg) for CIT prevention in advanced solid tumor patients receiving carboplatin/paclitaxel, but failed to show significant pre-chemotherapy platelet elevation versus placebo[14]. Subsequently, a phase I study of once-daily eltrombopag (100 mg) in gemcitabine-treated advanced solid tumors demonstrated potential for preventing thrombocytopenia, with a significantly higher median PLT nadir than placebo[18]. A phase II study further confirmed that eltrombopag reduced chemotherapy modifications (delays, dose reductions, or discontinuation) due to thrombocytopenia (87% vs. 69%) compared with placebo[15]. A recent phase II study of hetrombopag demonstrated that a continuous oral dose of 7.5 mg is an effective and well-tolerated option for managing CIT in patients with solid tumors[17]. Therefore, the present study designed a SPP involving daily oral administration of hetrombopag at 7.5 mg for 14 consecutive days to prevent CTIT in breast cancer patients. Under this protocol, hetrombopag secondary prophylaxis allowed 90% of patients to complete their planned treatment without modifications due to thrombocytopenia. Notably, the post hoc analysis showed a significantly higher completion rate in the ADC group compared to the CBR group (95.7% vs. 75.0%). Moreover, with hetrombopag support, six patients completed 14 cycles of adjuvant T-DM1. These findings suggest hetrombopag may be an effective option for preventing CTIT in breast cancer patients, especially among patients receiving ADC treatment.

The precise mechanism underlying ADC-induced thrombocytopenia remains unclear. T-DM1 may potentially impede the maturation and function of megakaryocytes (MK) through a cytotoxic impact following the intracellular liberation of DM[19]. Although both T-DXd and T-DM1 target HER2, T-DXd elicits lower incidence of thrombocytopenia, which may be attributed to the markedly reduced cytotoxicity of its payload DXd on MK relative to DM[20]. As the progenitor cells responsible for platelet production, the MK undergo differentiation, maturation, proliferation, and ultimately fragmentation to release platelets[21]. Hetrombopag may facilitate megakaryopoiesis by activating TPO receptors, offering a plausible mechanistic basis for the clinical activity observed in this study.

Current management options for correcting thrombocytopenia remain limited. Platelet transfusion, a common intervention for severe thrombocytopenia, is constrained by supply shortages, infection risks, and transient efficacy[22]. Despite approval for this condition, platelet growth factors (rhTPO, interleukin-11) are often limited clinically by parenteral administration and associated adverse effects (fluid retention, allergic reactions)[23]. Consequently, an unmet clinical need persists for more convenient, well-tolerated,

and effective agents. TPO-RAs, originally approved for hematologic disorders, have emerged as a promising alternative and are under investigation for CIT.

Romiplostim, a peptide-based TPO-RA, has been evaluated for treating CIT in solid tumor patients. Previous retrospective studies have indicated its efficacy in elevating platelet counts[24–26], with the findings of prospective trials likewise demonstrating its superiority over placebo in normalizing platelet levels[27–29]. However, concerns regarding romiplostim-associated bone marrow fibrosis have limited its clinical adoption, spurring the development of small-molecule, non-peptide TPO-RAs. A phase II trial showed eltrombopag may improve platelet counts in chronic myeloid leukemia[30], and another phase II trial confirmed its efficacy for thrombocytopenia in hematological malignancies versus placebo[31]. An international phase III trial demonstrated that avatrombopag significantly increased the nadir PLT in solid tumor patients with CIT compared with control (51.5×10□/L vs. 29.1×10□/L).[16]. Additionally, a phase II study of hetrombopag for CIT revealed a superior response rate versus placebo (85.7% vs. 48.4%) during the correction phase in patients with advanced solid tumors[17], this finding was supported by preliminary results from an expanded phase III trial[32]. However, there remains a paucity of positive-controlled studies evaluating the efficacy of TPO-RAs. Our study represented the first RCT to directly compare hetrombopag with rhTPO, demonstrating the non-inferiority of hetrombopag to rhTPO for correction of thrombocytopenia (87.9% vs. 81.8%). Furthermore, post hoc analysis showed a higher response rate in the hetrombopag group compared with the rhTPO group in ADC-induced thrombocytopenia (95.7% vs. 85.7%). In contrast, no apparent advantage of hetrombopag over rhTPO was observed in the CBR population (70.0% vs. 75.0%), likely due to the limited sample size and the pan-hematopoietic bone marrow suppression effects of CIT in this cohort.

Hematological suppression and elevated transaminases, well-recognized adverse events of anti-tumor therapy, occurred at comparable rates in the hetrombopag and rhTPO groups, further confirming that such toxicities are not uniquely attributable to hetrombopag. A total of six participants experienced minor bleeding events in this study, which were associated with thrombocytopenia and clinically manifested as mild epistaxis or cutaneous petechiae. In addition, thrombotic risk may be influenced by patient age, comorbidities, and concomitant medications. Research on romiplostim indicated a thrombosis incidence of around 10%[28]. Subsequent investigations on other TPO-RAs demonstrated a significant decrease in thrombotic events, with a rate of 5% reported for eltrombopag[15] and no events observed in a hetrombopag trial[17]. A meta-analysis further confirmed that TPO-RAs are not associated with an increased risk of thrombotic events[33], which aligns with the safety profile observed in the present study.

Our findings should be interpreted with several limitations in mind. First, the two-cycle study duration and moderate sample size restrict robust assessment of sustained efficacy and long-term safety profiles. While follow-up data provided valuable reference, further validation in large-scale prospective trials with extended follow-up is warranted. Additionally, the absence of stratification by anti-tumor regimens prior to randomization may have resulted in imbalances in key prognostic factors across the study arms. To mitigate this limitation, a dedicated single-arm, multicenter trial evaluating hetrombopag for the prevention of T-DM1-associated thrombocytopenia is currently ongoing at our center (NCT07198672), designed to validate and strengthen the translational significance of our findings.

Conclusion

As the first prospective trial to evaluate hetrombopag for preventing CTIT in breast cancer patients, this multicenter, exploratory study demonstrated that hetrombopag may be a promising and well-tolerated option for the secondary prevention and management of CTIT. Moreover, encouraging efficacy was

observed in patients receiving ADCs, which prompts the need for large-scale, prospective studies with extended cycles and longer follow-up to confirm these findings.

Declarations

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Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest Statement

The authors declare no financial or non-financial conflicts of interest in relation to the work described in this manuscript.

Ethics Statement

- Approval of the research protocol by an Institutional Reviewer Board: The study protocol was approved by the Ethics Committee of Henan Cancer Hospital (approval number: 2022-214-012) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

- Informed Consent: Written informed consent was obtained from all participants before enrollment.

- Registry and the Registration No. of the study/trial: This clinical trial was registered at clinicaltrial.gov (NCT05394285).

Author Contributions

Huihui Sun and Huimin Lv contributed equally to this work. Min Yan, Huihui Sun, and Huimin Lv conceived and designed the study. Huihui Sun, Huimin Lv, Wenyan Chen, Yanxia Zhao, Mengwei Zhang, and Limin Niu collected and interpreted the data. Huihui Sun and Huimin Lv drafted the original draft. Min Yan supervised the study and critically revised the manuscript. All authors participated in the enrollment and management of patients. All authors had full access to the data, reviewed and edited the manuscript, and had final responsibility for the decision to submit for publication

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Figures

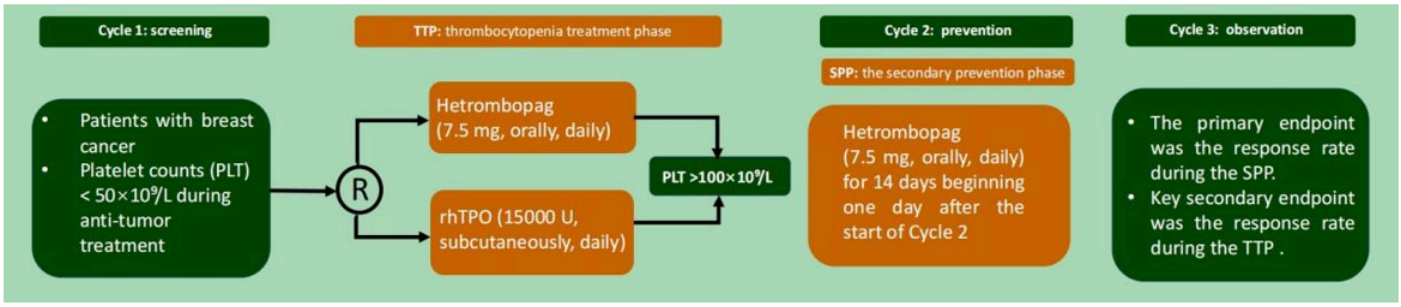

Figure 1

Study design

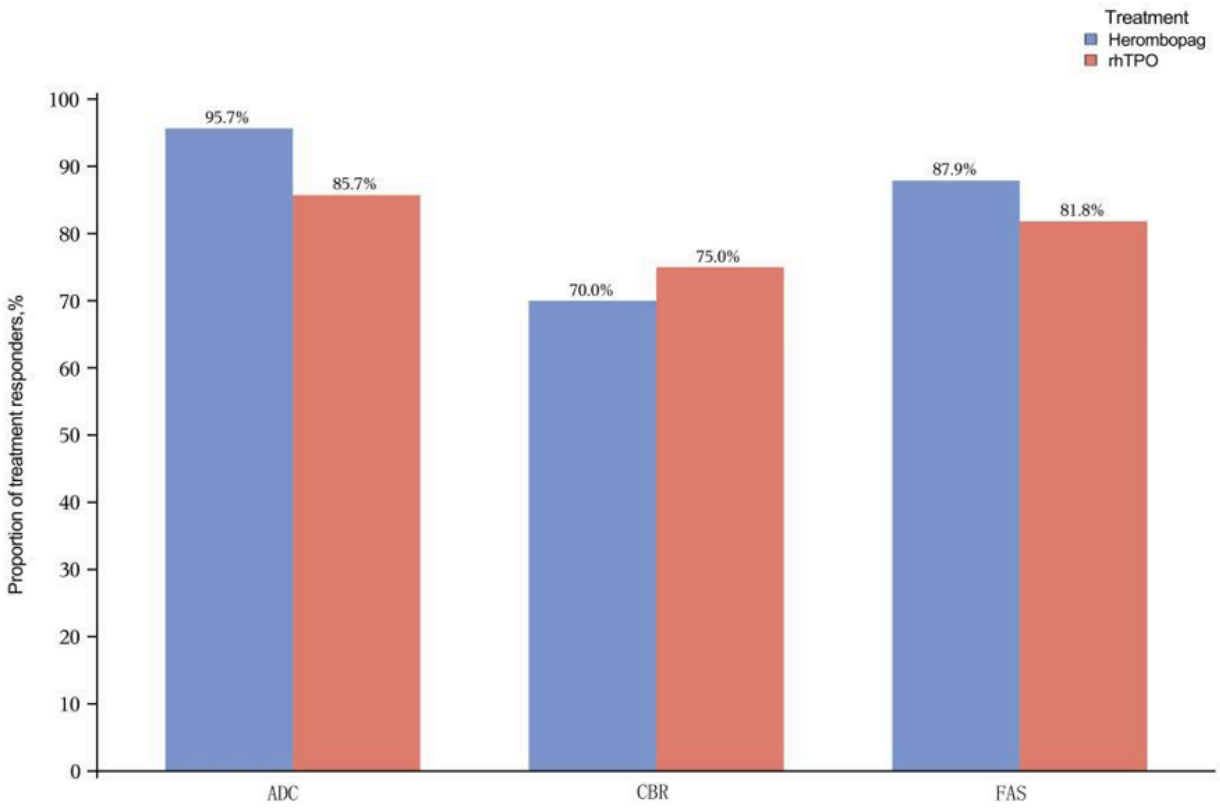

Figure 2

Response rates during the TTP.

Supplementary Files

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