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Monotherapy with Romiplostim Is Comparable to Combination with Short-Acting Platelet- Elevating Therapy in Platelet Recovery for Chemotherapy-Induced Thrombocytopenia (CTIT): A Retrospective Clinical Study

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Abstract

Objective

To compare the efficacy and safety of romiplostim monotherapy versus romiplostim combined with short-acting platelet-elevating agents in the treatment of chemotherapy-induced thrombocytopenia (CTIT), and to provide evidence for optimizing clinical regimens.

Methods

A total of 79 CTIT patients admitted to our hospital from May 2024 to January 2026 were enrolled and divided into a monotherapy group (romiplostim) and a combination group (romiplostim plus short-acting platelet-elevating agents) based on their treatment regimen. Treatment was discontinued when the platelet count recovered to greater than 75×10^9/L or increased by 30×10^9/L from baseline. The main outcome measures included time to platelet recovery, objective response rate of platelet recovery, and related adverse events.

Results

In the romiplostim monotherapy group, there were 19 complete responses (CR), 5 partial responses (PR), 2 minimal responses (MR), and 13 no responses (NR), with an objective response rate (ORR) of 61.5% and a median time to platelet recovery of 10.5 days. In the combination group, there were 22 CR, 4 PR, 4 MR, and 10 NR, with an ORR of 65% and a median time to platelet recovery of 15.5 days. No statistically significant differences were observed between the two groups in ORR (61.5% vs. 65%, P = 0.750), time to platelet recovery (10.5 days vs. 15.5 days, P = 0.299), chemotherapy modification rate (34.2% vs. 41.4%, P = 0.507), incidence of bleeding (21.1% vs. 7.3%, P = 0.143), incidence of thromboembolism (0% vs. 2.4%, P = 0.333), or platelet transfusion rate (50% vs. 63.4%, P = 0.229).

Conclusion

In the treatment of CTIT, adding short-acting platelet-elevating agents to romiplostim does not significantly improve platelet recovery compared with romiplostim monotherapy, and the safety profiles are comparable. Romiplostim monotherapy can be considered an effective and convenient treatment option for CTIT.

Introduction

Cancer therapy-induced thrombocytopenia (CTIT) refers to the suppression of bone marrow megakaryocytes by antineoplastic treatments, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, resulting in decreased platelet production, increased platelet destruction, and

abnormal distribution. CTIT not only results in reduced chemotherapy drug dosages, delayed or even interrupted treatment cycles, poor prognosis, and increased medical costs, but also significantly elevates the patient's risk of bleeding, which can be life-threatening [1].

Previously, the treatment of CTIT was mainly based on platelet transfusion and supportive care, with limited drug options. Although exogenous platelet transfusion can rapidly increase platelet counts in the short term and prevent potential bleeding emergencies, it is difficult to serve as a long-term stable treatment due to its rapid consumption, short duration of effect, potential for transfusion refractoriness following repeated infusions, and associated economic burden. Although recombinant human thrombopoietin (rhTPO) and interleukin-11 (IL-11) are used clinically, both require daily injections and have limitations such as unstable efficacy, potential for antibody induction, or poor tolerability.

Thrombopoietin (TPO) is the primary growth factor for megakaryocyte proliferation, differentiation, and platelet production. The TPO receptor (MPL), present on hematopoietic stem cells, megakaryocytes, and platelets, is a homodimeric receptor encoded by the human myeloproliferative leukemia virus (mpl) gene [2]. Thrombopoietin receptor agonists (TPO-RAs) are a class of drugs that bind to and activate the TPO receptor but do not contain the peptide sequence of TPO itself. Currently, FDA-approved TPO-RAs include romiplostim (indicated for immune thrombocytopenia), eltrombopag, hetrombopag (for ITP, hepatitis C-associated thrombocytopenia, and severe aplastic anemia), avatrombopag (for ITP and perioperative thrombocytopenia in chronic liver disease), and lusutrombopag (for perioperative thrombocytopenia in chronic liver disease) [3]. Romiplostim is the first long-acting TPO-RA globally. It is an Fc-peptide fusion protein that stimulates megakaryocyte proliferation and differentiation and promotes platelet production by binding to and activating the thrombopoietin receptor [4]. The once-weekly administration is highly effective and convenient. Several small, single-center studies in CTIT have preliminarily confirmed its ability to increase platelet counts effectively [5,6]. According to the current NCCN guidelines for hematopoietic growth factors, romiplostim is recommended as a Category 2A option, with the rationale that the use of TPO-RAs for CIT is considered when the benefits outweigh the potential risks, in order to maintain chemotherapy dose regimens and intensity [7]. Currently, combination therapy with short-acting and long-acting platelet-elevating agents is commonly used in clinical practice, with the expectation of achieving "faster and higher" increases in platelet counts in patients with CTIT. However, whether combination therapy is superior remains unclear due to a lack of definitive evidence. Therefore, this study aims to investigate the efficacy and safety of romiplostim monotherapy versus romiplostim combined with short-acting platelet-elevating agents in patients with solid tumors or non-myeloid hematologic malignancies complicated by CTIT.

Materials and Methods

1.1 Patients and Data Collection

A retrospective analysis was conducted on patients aged ≥ 18 years with malignant solid tumors or non-myeloid hematologic malignancies (myeloma, lymphoma) who developed thrombocytopenia after

antitumor therapy and received romiplostim treatment at the Department of Oncology, Nanjing Second Hospital, from May 2024 to January 2026. Patient information is detailed in Table 1.

Table 1
Baseline Clinical Characteristics of All Patients

Clinical Characteristics	
Median age(years),range	63(31–92)
Sex,n	
Male	42
Female	37
Tumor type,n	
Gastric cancer	18
Colorectal cancer	14
Lung cancer	7
Uterine cancer	5
Ovarian cancer	4
Pancreatic cancer	3
Nasopharyngeal carcinoma	1
Breast cancer	4
Liver cancer	4
Cholangiocarcinoma	1
Myeloma	5
Lymphoma	10
Mediastinal tumor	1
Tongue cancer	1
Thyroid cancer	1
ECOG performance status, n	
0–2	23
3–4	56
Baseline platelet count, ×10⁹/L, n	
≤ 20	21
20–50	49

Clinical Characteristics	
≥ 50	9
Concomitant therapy,n	
Radiotherapy	1
Targeted therapy	27
Immunotherapy	12
Comprehensive therapy	29
Chemotherapy alone	10
Platelet transfusion,n	
Yes	45
No	34
Treatment response, n	
Complete response (CR)	41
Partial response (PR)	9
Minor response (MR)	4
No response (NR)	5
Median time to platelet recovery in CR/PR patients, days	14.5

Inclusion criteria

(1) Treated with romiplostim; (2) Age ≥ 18 years; (3) Histopathologically or cytologically confirmed solid tumor, myeloma, or lymphoma; (4) Thrombocytopenia induced by antitumor therapy, with baseline platelet count < 50×10^9/L before treatment.

Exclusion criteria

(1) Concurrent immune thrombocytopenia (ITP); (2) Significant impairment of major organ function; (3) Bone marrow infiltration by tumor.

1.2 Methods

Group 1 (Monotherapy): Patients received romiplostim (specification: 250 μg/vial) alone via subcutaneous injection at a starting dose of 3 μg/kg once weekly. The dose was subsequently adjusted based on platelet count and clinical symptoms, with a maximum of 10 μg/kg once weekly. No short-acting platelet-elevating agents were combined. Treatment was discontinued when platelet count

recovered to > 75×10⁹/L or increased by 30×10⁹/L from baseline. If the patient received romiplostim at 10 μg/kg once weekly for two consecutive weeks without response, treatment was stopped.

Group 2 (Combination therapy)

Patients received romiplostim concurrently with short-acting platelet-elevating agents, including IL-11, rhTPO, and short-acting TPO-RAs. IL-11 was administered at 25–50 μg/kg/day for 7–14 days. rhTPO was given at an initial dose of 300 U/kg/day once daily for 14 days. Romiplostim was used in Group 1. The short-acting TPO-RAs used were eltrombopag (5 cases) and hetrombopag (1 case). Eltrombopag was initiated at an oral dose of 25 mg/day, with a maximum dose of 75 mg/day; hetrombopag was initiated at 2.5 mg/day orally, with a maximum dose of 7.5 mg/day. For the above agents, treatment was discontinued if platelet count recovered to > 75×10⁹/L or increased by 30×10⁹/L from baseline during the course of therapy. For patients with platelet count ≤ 20×10⁹/L or with obvious bleeding tendency, platelet transfusion via apheresis and enhanced hemostatic treatment were administered.

1.3 Efficacy Evaluation Criteria and Definitions

The first day of romiplostim injection was defined as Day 1. Platelet recovery and bleeding status within 30 days of romiplostim injection, or until recovery, were recorded. **Complete response (CR)**: Platelet count ≥ 100×10⁹/L with no bleeding. **Partial response (PR)**: Platelet count ≥ 75×10⁹/L or an increase of ≥ 30×10⁹/L from baseline (before romiplostim NO1 administration), with no or essentially no bleeding. **Minimal response (MR)**: Platelet count increased from baseline but did not reach PR level, with reduced bleeding symptoms. **No response (NR)**: No increase in platelet count from baseline.CR and PR were considered effective responses. **Objective response rate (ORR) = (CR + PR) / total number of cases × 100%**

1.4 Safety Assessment

Other clinical outcomes included: the rate of chemotherapy modification (dose reduction or treatment delay) due to thrombocytopenia, platelet transfusion rate, bleeding incidence, and incidence of arterial or venous thromboembolic events.

1.5 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Descriptive statistics were used to describe clinical characteristics. Normally distributed continuous data were expressed as mean ± standard deviation (x ± s), while non-normally distributed continuous data were expressed as median and interquartile range [M (Q1, Q3)]. Comparisons between groups were performed using the t-test or the Wilcoxon signed-rank test. Categorical data were expressed as frequency and percentage (n, %), and comparisons between groups were performed using the chi-square test. A P-value < 0.05 was considered statistically significant.

Results

2.1 Patient Clinical Characteristics

A total of 79 patients were enrolled, including 42 males and 37 females, with a median age of 63 years. Tumor types included: gastric cancer (18 cases), colorectal cancer (14 cases), lung cancer (7 cases), uterine cancer (5 cases), ovarian cancer (4 cases), pancreatic cancer (3 cases), nasopharyngeal carcinoma (1 case), breast cancer (4 cases), liver cancer (4 cases), cholangiocarcinoma (1 case), mediastinal tumor (1 case), tongue cancer (1 case), thyroid cancer (1 case), myeloma (5 cases), and lymphoma (10 cases). ECOG performance status was 0–2 in 23 patients and 3–4 in 56 patients. Baseline platelet count was ≤ 20×10^9/L in 21 patients, 20–50×10^9/L in 49 patients, and ≥ 50×10^9/L in 9 patients. Treatment regimens were as follows: chemotherapy alone (10 cases), chemotherapy combined with radiotherapy (1 case), combined with targeted therapy (27 cases), combined with immunotherapy (12 cases), and a combination of three or more modalities (29 cases). A total of 45 patients received platelet transfusions. Among all patients, 41 achieved CR, 9 achieved PR, 4 achieved MR, and 5 had NR. The median time to platelet recovery in CR/PR patients was 12.5 days (Table 1).

According to the platelet-elevating treatment regimen, Group 1 received romiplostim monotherapy, and Group 2 received romiplostim combined with short-acting platelet-elevating agents. The median age was the same in both groups (63 years), and the sex distribution was comparable (P = 0.207). Group 1 included 38 patients, of whom 12 had hematologic malignancies (31.6%), and 26 had solid tumors (68.4%). Group 2 included 41 patients, of whom 3 had hematologic malignancies (7.3%), and 38 had solid tumors (92.7%) (P = 0.006). Regarding the ECOG score 3–4, there were 27 patients in Group 1 and 29 patients in Group 2. Baseline platelet count (P = 0.085) and treatment regimen (P = 0.198) showed no statistically significant differences between the two groups.

The objective response rate (61.5% vs. 65%, P = 0.750), time to platelet recovery (10.5 days vs. 15.5 days, P = 0.299), chemotherapy modification rate (34.2% vs. 41.4%, P = 0.507), incidence of bleeding (21.1% vs. 7.3%, P = 0.143), incidence of thromboembolism (0% vs. 2.4%, P = 0.333), and platelet transfusion rate (50% vs. 63.4%, P = 0.229) were similar between the two groups, with no statistically significant differences (Table 2).

Table 2
Clinical Characteristics and Outcomes Between Two Treatment Groups

Clinical Characteristics	Romiplostim Monotherapy	Combined with Short-acting Thrombopoietic Agents	P-value
Median age (years), range	63 (36–92)	63 (31–77)	0.506
Sex, n			0.207
Male	23	19	
Female	15	22	
Tumor type, n			0.033
Gastric cancer	4	14	
Colorectal cancer	8	6	
Lung cancer	1	6	
Uterine cancer	2	3	
Ovarian cancer	0	4	
Pancreatic cancer	3	0	
Nasopharyngeal carcinoma	1	0	
Breast cancer	2	2	
Liver cancer	1	2	
Cholangiocarcinoma	1	0	
Myeloma	4	1	
Lymphoma	8	2	
Mediastinal tumor	1	0	
Tongue cancer	0	1	
Thyroid cancer	1	0	
Hematologic neoplasms	12	3	0.006
Solid tumors	26	38	
ECOG performance status, n			0.975
0–2	11	12	
3–4	27	29	
Baseline platelet count, $\times 10^9$/L, n			0.085

Clinical Characteristics	Romiplostim Monotherapy	Combined with Short-acting Thrombopoietic Agents	P-value
≤ 20	6	15	
20–50	26	23	
≥ 50	6	3	
Concomitant therapy, n			0.198
Radiotherapy	0	1	
Targeted therapy	17	10	
Immunotherapy	4	8	
Comprehensive therapy	12	17	
Chemotherapy alone	5	5	
Treatment response, n			0.711
Complete response (CR)	19	22	
Partial response (PR)	5	4	
Minor response (MR)	2	4	
No response (NR)	13	10	
Objective response rate (ORR, CR + PR), %	61.5	65.0	0.750
Median time to platelet recovery in CR/PR patients, days	10.5	15.5	0.299
Chemotherapy adjustment rate, n/N (%)	13/38 (34.2)	17/41 (41.4)	0.507
Bleeding rate, n/N (%)	8/38 (21.1)	3/41 (7.3)	0.143
Embolism rate, n/N (%)	0/38 (0.0)	1/41 (2.4)	0.333
Platelet transfusion rate, n/N (%)	19/38 (50.0)	26/41 (63.4)	0.229

2.2 Efficacy Evaluation

The median platelet count before treatment in all patients was 30×10⁹/L, and the median platelet count after treatment was 95×10⁹/L, with a statistically significant difference between the two groups ($P < 0.001$). Among different subgroups, in patients with hematologic malignancies receiving romiplostim monotherapy, the pre-treatment platelet count was 34.5×10⁹/L, and the post-treatment count was 86.5×10⁹/L, showing a statistically significant difference ($P = 0.002$). In patients with solid tumors receiving romiplostim monotherapy, the pre-treatment platelet count was 30×10⁹/L, and the post-

treatment count was 69×10⁹/L, with a statistically significant difference (P < 0.001) (Table 3a). In the combination therapy group for patients with hematologic malignancies, the pre-treatment platelet count was 18×10⁹/L, and the post-treatment count was 141×10⁹/L, with a statistically significant difference (P = 0.014). In the combination therapy group for patients with solid tumors, the pre-treatment platelet count was 25×10⁹/L, and the post-treatment count was 95×10⁹/L, with a statistically significant difference (P < 0.001) (Table 3b). That is, whether using romiplostim monotherapy or romiplostim combined with short-acting platelet-elevating agents, the platelet-elevating efficacy was significant in both hematologic and solid tumor patients.

Table 3
a: Romiplostim Monotherapy Group

Item	Hematologic Neoplasms	Solid Tumors	P-value
Objective response rate	8/12 (66.7%)	16/27 (59.3%)	0.661
Median time to platelet recovery (d)	10.5	12	0.610
Median platelet count before treatment	34.5	30.0	—
Median platelet count after treatment	86.5	69.0	*P* = 0.002; *P* < 0.001

Table 3
b: Romiplostim Combined with Short-acting Thrombopoietic Agents Group

Item	Hematologic Neoplasms	Solid Tumors	P-value
Objective response rate	3/3 (100%)	23/37 (62.2%)	0.186
Median time to platelet recovery (d)	15.5	15.0	0.135
Median platelet count before treatment	18	25	—
Median platelet count after treatment	141	95	*P* = 0.014; *P* < 0.001

The combination with short-acting platelet-elevating agents could be further subdivided. In the IL-11 combination group (23 patients), the ORR was 65.2%, and the median time to platelet recovery in responders was 16 days. In the TPO combination group (3 patients), the ORR was 100%, and the median time to platelet recovery in responders was 10 days. In the TPO-RA combination group (6 patients), including 1 patient receiving hetrombopag and 5 receiving eltrombopag, the ORR was 50%, and the median time to platelet recovery in responders was 22.5 days. In the group receiving three or more platelet-elevating agents (8 patients: 4 receiving TPO + IL-11 + romiplostim, 2 receiving IL-11 +

eltrombopag + romiplostim, and 2 receiving IL-11 + hetrombopag + romiplostim), the ORR was 62.5%, and the median time to platelet recovery in responders was 10 days. There were no statistically significant differences among the groups in terms of ORR (P = 0.683) or time to platelet recovery (P = 0.804) (Table 4).

Table 4
Efficacy outcomes of Romiplostim monotherapy versus different combination thrombopoietic regimens

Characteristics	Romiplostim monotherapy	Combined with IL-11	Combined with TPO	Combined with TPO-RA	Three or more thrombopoietic agents	P-value
CR	19	14	3	2	3	—
PR	5	1	0	1	2	—
MR	2	3	0	1	0	—
NR	13	5	0	2	3	0.632
ORR (CR + PR), %	61.5	65.2	100.0	50.0	62.5	0.683
Median time to platelet recovery in CR/PR patients, d	11	16	10	22.5	10	0.804

2.3 Clinical Efficacy and Safety Analysis

Overall, romiplostim was associated with relatively mild adverse events. In the monotherapy group, the main adverse events were musculoskeletal pain in 5 cases (12.8%), dizziness in 3 cases (7.7%), and diarrhea in 2 cases (5.1%). In the romiplostim monotherapy group, the chemotherapy modification rate (including treatment delay or dose reduction) was 34.2%, the bleeding rate was 21.1%, no thromboembolic events occurred, and the platelet transfusion rate was 50%. In the combination therapy group, the chemotherapy modification rate was 41.4%, the bleeding rate was 7.3%, the thromboembolism rate was 2.4%, and the platelet transfusion rate was 63.4%. None of these differences were statistically significant (P for chemotherapy modification rate = 0.507, P for bleeding rate = 0.143, P for thromboembolism rate = 0.333, P for platelet transfusion rate = 0.229). No significant changes in liver or kidney function were observed before and after treatment (Table 5).

Table 5
Changes in liver and renal function parameters before and after treatment

Item	Romiplostim Monotherapy	*P*-value	Combined with Short-acting Thrombopoietic Agents	*P*-value
ALT before treatment	26.2 ± 26.5	0.803	26.0 ± 30.0	0.069
ALT after treatment	25.6 ± 25.1	—	18.8 ± 16.5	—
AST before treatment	40.4 ± 40.5	0.681	31.4 ± 22.2	0.578
AST after treatment	38.6 ± 37.0	—	33.4 ± 27.4	—
Creatinine before treatment	88.7 ± 64.0	0.604	65.2 ± 33.9	0.212
Creatinine after treatment	87.0 ± 54.4	—	60.5 ± 24.6	—

Discussion

Patients with solid tumors and non-myeloid hematologic malignancies are currently treated predominantly with chemoradiotherapy combined with targeted therapy and immunotherapy. Chemoradiotherapy can lead to varying degrees of myelosuppression, including neutropenia and thrombocytopenia. When these events occur, chemotherapy intervals often need to be extended and doses reduced, adversely affecting progression-free survival and overall survival. Severe CTIT may also cause bleeding in vital organs and can be life-threatening in serious cases [8]. One study showed that the overall incidence of chemotherapy dose delays due to CIT across treatment cycles was 5.39%, with oxaliplatin and capecitabine being significantly associated with CIT [9]. CIT occurs more frequently in patients treated with cisplatin or gemcitabine for bladder cancer, or with carboplatin, gemcitabine, or cisplatin/ etoposide for lung cancer [10]. Among patients receiving gemcitabine plus platinum regimens, the incidence of grade 3 and 4 CIT is even higher [11]. Therefore, rapidly and effectively increasing the platelet count, maintaining platelet homeostasis, and ensuring the smooth delivery of chemotherapy are the core goals of CTIT clinical management.

The present study found that romiplostim monotherapy was comparable to romiplostim combined with short-acting platelet-elevating agents in terms of platelet recovery in CTIT, with both regimens effectively increasing platelet counts. There were no significant differences between the two groups in ORR or median time to platelet recovery. However, there was a difference in the proportion of patients with hematologic malignancies between the monotherapy group and the combination group (31.6% vs. 7.3%). This, to some extent, reflects real-world prescribing preferences: for patients with hematologic malignancies, given the complex mechanisms of thrombocytopenia and frequent coexistence of immune abnormalities, clinicians tend to prefer romiplostim monotherapy to avoid potential immune cross-

reactions or additive adverse effects from combination therapy. For patients with solid tumors, on the other hand, they are more inclined to try combination regimens in pursuit of faster platelet elevation. Such non-random allocation is an inherent selection bias in retrospective studies. Nevertheless, we believe this bias has limited impact on the primary conclusion (comparable efficacy between the two groups), for the following reasons: Subgroup analysis supports consistency — in both hematologic malignancy patients and solid tumor patients, platelet counts increased significantly from pre- to post-treatment in both the monotherapy and combination groups (all subgroups $P < 0.05$), and there were no statistically significant differences in ORR or time to platelet recovery between the two regimens. This suggests that the efficacy trend of monotherapy versus combination therapy is consistent across different tumor types. There were no differences in primary endpoints in the overall population — the two groups showed no statistically significant differences in key endpoints such as time to platelet recovery, chemotherapy modification rate, bleeding rate, or thromboembolic events, indicating that even with differences in patient composition, no significant deviation in efficacy was observed. Admittedly, we acknowledge that the retrospective design cannot eliminate residual confounding. Due to the limited sample size (n = 79), propensity score matching (PSM) was not performed. However, this bias has been clearly noted in the limitations. Subgroup analyses were conducted, and we recommend that future studies expand the sample size, perform matched analyses, and preferably conduct prospective, randomized controlled trials to further validate the findings.

Romiplostim, as a long-acting thrombopoietin receptor agonist (TPO-RA), leverages its unique molecular structure to specifically bind to the c-Mpl receptor on the surface of megakaryocytes, continuously activating megakaryocyte proliferation, differentiation, and maturation, thereby promoting platelet production. It offers the advantages of durable efficacy and low dosing frequency (once-weekly subcutaneous injection) and has been recommended by authoritative domestic and international guidelines for the treatment of CTIT. Its clinical efficacy and safety have been confirmed by multiple studies [9]. Romiplostim also possesses immunomodulatory functions, reducing platelet antibody levels, thereby improving regulatory T-cell function and decreasing the release of inflammatory cytokines [12].

A global phase III, double-blind, randomized, placebo-controlled trial (the RECITE study) published in *The New England Journal of Medicine (NEJM)* enrolled 165 patients with persistent CIT undergoing oxaliplatin-based multi-agent combination chemotherapy for gastrointestinal tumors. The results showed that the proportion of patients without CIT-induced chemotherapy dose modifications (reduction, delay, omission, or discontinuation) was 84% (92/109) in the romiplostim group, compared with only 36% (20/56) in the placebo group, yielding an odds ratio of 10.16 (95% CI: 4.44–23.72, $P < 0.001$). In terms of safety, the incidence of treatment-related adverse events in the romiplostim group was 12%, with thromboembolic events occurring in only 2% (2/109), and no serious treatment-related adverse events led to discontinuation of the study drug or chemotherapy [13]. Regarding platelet response speed, the median time to platelet response (PLT ≥ 100×10^9/L or an increase from baseline to a level safe for chemotherapy) in the romiplostim group was 1.1 weeks, significantly shorter than 2.1 weeks in the placebo group ($P < 0.001$). The overall response rate (97%) in the romiplostim group in that study reached

a level rarely seen with short-acting agents or placebo, suggesting that romiplostim monotherapy for CTIT has approached a "ceiling effect" in terms of both speed and efficacy of platelet elevation [14].

A comprehensive retrospective study of 173 CIT patients (including 153 with solid tumors and 20 with lymphoma or myeloma) showed that once-weekly romiplostim administration was superior to intermittent dosing, achieving a higher median platelet count (143×10^9/L vs. 106×10^9/L, $P < 0.001$) and a higher response rate (81% vs. 63%, $P < 0.001$), with fewer chemotherapy dose reductions/delays (82 vs. 224 per 100 patient-years, $P = 0.010$), fewer bleeding events (11 vs. 34 per 100 patient-years, $P = 0.029$), and fewer venous thromboembolic events (7.1 vs. 20 per 100 patient-years) [15].

Additional research has indicated that TPO levels are associated with the therapeutic efficacy of romiplostim. In that study, 54/63 (86%) patients achieved a platelet count response (platelet count ≥ 75×10^9/L and an increase of ≥ 30×10^9/L from baseline). A higher predicted response was associated with lower baseline TPO levels ($P = 0.036$). A TPO level < 100 pg/mL predicted a response in > 90% of evaluated patients with a platelet count ≥ 60% [16].

Short-acting platelet-elevating agents, such as recombinant human thrombopoietin (rhTPO) and recombinant human interleukin-11 (rhIL-11), have been widely used conventionally in the treatment of CTIT. They exert their platelet-elevating effects by directly supplementing exogenous thrombopoiesis-promoting factors. Owing to their rapid onset of action and short half-life, they are often used in patients with CTIT to achieve a rapid short-term increase in platelet count, thereby managing acute bleeding risk or ensuring that chemotherapy is delivered on schedule. In studies of another class of short-acting oral TPO-RAs in CTIT patients, a meta-analysis showed that eltrombopag ranked first in reducing chemotherapy dose reductions or delays and in increasing platelet nadir. In reducing the incidence of grade 3/4 thrombocytopenia, recombinant human thrombopoietin (rhTPO) ranked highest, followed by eltrombopag. Recombinant human interleukin-11 (rhIL-11) had the lowest platelet transfusion rate but the highest incidence of adverse events, while avatrombopag had the lowest incidence of adverse events and thromboembolism. Taken together, eltrombopag may suggest the best balance of efficacy and safety [17]. In clinical practice, for patients with very low platelet counts, a combination regimen of romiplostim plus short-acting platelet-elevating agents is often attempted, with the expectation of achieving a synergistic effect of "rapid response plus sustained stability." However, the present study suggests that the combination regimen does not demonstrate a clear incremental efficacy advantage over monotherapy. At present, clinical research on this combination strategy in CTIT remains very limited, lacking uniform regimens and comparative standards, leaving the evidence base for combination therapy relatively weak. A real-world, single-center prospective observational study published in *Blood* showed that in CTIT patients, the 7-day response rate with romiplostim monotherapy was 61.9%, the median time to platelet recovery to ≥ 100×10^9/L or an increase of ≥ 50×10^9/L from baseline was 6 days, and only 4 patients (9.5%) received combination with other TPO-RAs, suggesting that both romiplostim monotherapy and combination with short-acting platelet-elevating agents are effective for CTIT. Although the article did not directly compare the monotherapy and combination groups, this finding suggests that combination therapy may not be necessary in routine clinical practice [18]. A randomized controlled trial

published in *Annals of Hematology* in 2025 compared romiplostim with recombinant human thrombopoietin (rhTPO) for platelet engraftment after umbilical cord blood transplantation. The results showed no statistically significant difference in median time to platelet engraftment between the romiplostim group and the rhTPO group (P = 0.269), and platelet transfusion volumes were also similar between the two groups (P = 0.694). The incidence of acute graft-versus-host disease was lower in the romiplostim group [19].

From the perspective of pharmacological mechanisms, the targets of romiplostim and rhTPO exhibit substantial overlap; both exert their platelet-elevating effects by activating the thrombopoietin receptor (c-Mpl) and its downstream signaling pathways. This may be one of the core reasons why the combination regimen did not produce a synergistic effect. Such mechanistic overlap may lead to a "receptor saturation" phenomenon when the agents are used together [20]. In clinical practice for CTIT, when the receptors on megakaryocyte surfaces are continuously occupied by romiplostim, subsequently administered rhTPO has difficulty binding further and exerting its effect, thereby failing to effectively enhance megakaryocyte proliferative capacity and failing to produce the expected additive or synergistic effect. Consequently, the efficacy of the combination regimen does not surpass that of monotherapy. Romiplostim and short-acting TPO-RAs have different binding sites on the receptor; theoretically, there should be no competitive inhibition. So why is the efficacy of monotherapy comparable to that of combination therapy? A 2021 review article explained that when TPO concentration exceeds a certain threshold, receptor saturation leads to the formation of non-signaling complexes, resulting in signal attenuation. This provides a molecular basis for the theoretical upper limit of TPO-RA efficacy [21].

From the perspective of clinical practice value in CTIT, the findings of this study have important guiding implications, particularly in optimizing CTIT treatment regimens, improving treatment cost-effectiveness and safety, and ensuring the smooth delivery of chemotherapy. Given comparable efficacy, the romiplostim monotherapy regimen offers significant advantages over combination therapy. First, it is more economical: the cost of combination therapy is substantially higher than that of monotherapy, and CTIT patients often require long-term treatment across multiple cycles of chemotherapy. Long-term use of combination regimens imposes a greater financial burden on patients, making monotherapy more accessible. Second, it offers greater convenience: romiplostim is administered as a once-weekly subcutaneous injection, whereas short-acting platelet-elevating agents typically require daily injections. Especially for patients with malignancies who are physically weak and have limited mobility after chemotherapy, monotherapy is more acceptable and can reduce the number of hospital visits, indirectly improving treatment adherence. Third, it provides better safety: combination therapy may lead to additive adverse effects. For example, when TPO-RAs are used together with IL-11, the incidence of adverse events such as thrombosis, fever, fatigue, and nausea may increase [4]. In contrast, romiplostim monotherapy for CTIT is associated with mild adverse effects, good tolerability, and no significant thromboembolic complications, offering a more favorable safety profile. Our study found no differences between the romiplostim monotherapy group and the combination group in the incidence of thromboembolism, bleeding, or chemotherapy modification rates, suggesting comparable safety between the two regimens.

It should be noted that the conclusions of this study do not exclude the possibility that combination therapy may still hold value in specific clinical situations. For example, in patients with refractory CTIT (those who have failed two or more platelet-elevating agents and whose platelet count remains persistently below the safety threshold), combination or sequential therapy strategies may warrant re-evaluation. A multicenter randomized controlled trial comparing romiplostim N01 versus rhTPO for refractory CTIT is currently underway in China (NCT06440824), which will provide higher-level evidence to guide treatment decisions in this subgroup. At the same time, we must objectively acknowledge the limitations of this study, which may have some impact on the generalizability of the findings. First, this was a single-center retrospective analysis with a limited sample size and a short follow-up period, which may have failed to capture potential long-term benefits of combination regimens in CTIT or in special subgroups (e.g., elderly CTIT patients, those with concomitant hepatic or renal impairment, or those with refractory CTIT). Second, as a retrospective study, there is inherent selection bias, and unmeasured confounding factors (e.g., medication adherence, lifestyle, chemotherapy tolerance) may still influence the efficacy assessment. Finally, this study did not measure biological markers such as serum TPO levels or c-Mpl receptor expression during treatment, preventing a molecular-level explanation of why the combination regimen failed to produce a synergistic effect.

In summary, based on existing evidence from pivotal phase III clinical trials and real-world studies, romiplostim monotherapy has demonstrated highly effective and rapid platelet-elevating effects in the treatment of CTIT, showing no significant advantage over combination with short-acting platelet-elevating agents in core clinical endpoints such as time to platelet recovery, response rate, and objective response rate. For the vast majority of CTIT patients whose primary goal is to rapidly raise platelet counts to a safe threshold to ensure the smooth completion of chemotherapy cycles, romiplostim monotherapy can serve as a simple and preferred option. The necessity of combination therapy is not yet strongly supported by high-level evidence-based medicine, and clinical decisions should be made prudently based on individualized patient circumstances.

Declarations

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Data availability statement: The data in this study are available from the corresponding author.

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