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Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours (Review)

Zhang X, Chuai Y, Nie W, Wang A, Dai G

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[Intervention Review]

Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours

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ABSTRACT

Background

Chemotherapy-induced thrombocytopenia (CIT) is defined as a peripheral platelet count less than $100 \times 10^9/L$, with or without bleeding in cancer patients receiving myelosuppressive chemotherapy. CIT is a significant medical problem during chemotherapy, and it carries the risk of sub-optimal overall survival and bleeding. Alternative interventions to platelet transfusion are limited. Different stages of preclinical and clinical studies have examined the thrombopoietin receptor agonists (TPO-RAs) for CIT in patients with solid tumours.

Objectives

To assess the effects of TPO-RAs to prevent and treat CIT in patients with solid tumours:

(1) to prevent CIT in patients without thrombocytopenia before chemotherapy, (2) to prevent recurrence of CIT, and (3) to treat CIT in patients with thrombocytopenia during chemotherapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, to 28 September 2017), MEDLINE (from 1950 to 28 September 2017), as well as online registers of ongoing trials (Clinical Trials, Chinese Clinical Trial Register, Australian New Zealand Clinical Trial Registry, WHO ICTRP Search Portal, International Standard Randomised Controlled Trial Number registry, GlaxoSmithKline Clinical Study Register, and Amgen Clinical Trials) and conference proceedings (American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, European Society of Medical Oncology, and Conference Proceedings Citation Index-Science, from 2002 up to September 2017) for studies.

Selection criteria

Randomised controlled trials (RCTs) comparing TPO-RAs alone, or in combination with other drugs, to placebo, no treatment, other drugs, or another TPO-RAs for CIT in patients with solid tumours.

Data collection and analysis

Two review authors independently screened the results of the search strategies, extracted data, assessed risk of bias, and analysed data according to standard methodological methods expected by Cochrane.

Main results

We identified six trials eligible for inclusion, of which two are ongoing, and one awaiting classification study. The three included trials were conducted at many different sites in Europe, America, and Asia. All of the three studies recruited adult and elder participants (no children were included) with solid tumours, and compared TPO-RAs with placebo. No studies compared TPO-RAs alone, or in combination with other drugs, to no treatment, or other drugs, or another TPO-RAs.

We judged the overall risk of bias as high as we found a high risk for detection bias. We assessed the risk of bias arising from inadequate blinding of outcome assessors as high for number and severity of bleeding episodes (one of the primary outcomes).

To prevent CIT: We included two trials (206 participants) comparing TPO-RAs (eltrombopag, multiple-dose oral administration with chemotherapy) with placebo. The use of TPO-RAs may make little or no difference to the all-cause mortality at 33 weeks of follow-up (RR 1.35, 95% CI 0.53 to 3.45; one trial, 26 participants; low quality of evidence). There is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one bleeding episode of any severity (RR 0.62, 95% CI 0.22 to 1.78; two trials, 206 participants; very low quality of evidence). There is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one severe/life-threatening bleeding episode (RR 0.36, 95% CI 0.06 to 2.06; two trials, 206 participants; very low quality of evidence). No studies were found that looked at overall survival (one of the primary outcomes), the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, the amount of bleeding, or quality of life.

To prevent recurrence of CIT: We included one trial (62 participants) comparing TPO-RAs (romiplostim, single-dose subcutaneous administration with chemotherapy) with placebo. There is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one bleeding episode of any severity (RR 2.80, 95% CI 0.17 to 47.53; one trial, 62 participants; very low quality of evidence). There is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one severe/life-threatening bleeding episode (no severe/life-threatening bleeding episodes; one trial, 62 participants; very low quality of evidence). No studies were found that looked at overall survival (one of the primary outcomes), the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, the amount of bleeding, or quality of life. We found one ongoing study (expected recruitment 74 participants), it is planned to give TPO-RAs (romiplostim, subcutaneous administration with chemotherapy) to participants, but to date this trial has not reported any outcomes.

To treat CIT: We found one ongoing study (expected recruitment 83 participants), which is planned to give TPO-RAs (eltrombopag, seven days orally) to participants when their platelet counts are less than $75 \times 10^9/L$ during chemotherapy. This trial was originally planned to complete in March 2017, however, the completion date has passed and no results are reported.

The one awaiting classification study included patients without thrombocytopenia before chemotherapy (to prevent CIT), patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT), and other patients during chemotherapy (uncertain whether CIT had happened). There was no evidence for a difference in the number of patients with at least one bleeding episode of any severity (RR 0.27, 95% CI 0.07 to 1.02; one trial, 75 participants). There was no evidence for a difference in the number of patients with at least one severe/life-threatening bleeding episode (RR 0.44, 95% CI 0.03 to 6.77; one trial, 75 participants). This study did not address overall survival or quality of life.

Authors' conclusions

No certain conclusions can be drawn due to the lack of strong evidence in the review. The available weak evidence did not support the use of TPO-RAs for preventing CIT or preventing recurrence of CIT in patients with solid tumours. There was no evidence to support the use of TPO-RAs for treating CIT in patients with solid tumours.

PLAIN LANGUAGE SUMMARY

Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours

Background

Chemotherapy-induced thrombocytopenia (CIT) is a platelet count less than $100 \times 10^9/L$ with or without bleeding in cancer patients receiving chemotherapy. CIT carries the risk of sub-optimal overall survival and bleeding.

Thrombopoietin receptor agonists (TPO-RAs) may be used to:

(1) prevent CIT in patients with normal platelet count before chemotherapy, (2) prevent recurrence of CIT, and (3) treat CIT in patients with low platelet count during chemotherapy.

Review questions

With this review we aimed to find out whether TPO-RAs (i.e. eltrombopag and romiplostim) can prevent or treat CIT in patients with solid tumours.

Study characteristics

We searched Cochrane Central Register of Controlled Trials, MEDLINE, online registries of ongoing trials, and conference proceedings. The evidence is current to September 2017. We found six trials eligible for inclusion, of which two are still ongoing, and one awaiting classification study. We included 268 adult and elder participants (no children were included).

Two studies compared eltrombopag with placebo for patients with normal platelet counts before chemotherapy (to prevent CIT). One study compared romiplostim with placebo for patients with low platelet counts during chemotherapy (to prevent recurrence of CIT). All of the studies were funded by the drug manufacturers.

Key results

To prevent CIT, the review shows that when patients (206 participants) with normal platelet count before chemotherapy are given eltrombopag (multiple-dose oral administration with chemotherapy), compared to placebo:

- the use of TPO-RAs may make little or no difference to the all-cause mortality (low quality of evidence);
- there is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one bleeding episode of any severity (very low quality of evidence);
- there is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one severe/life-threatening bleeding episode (very low quality of evidence);
- no studies were found that looked at overall survival, the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, the amount of bleeding, or quality of life.

To prevent recurrence of CIT, the review shows that when patients (62 participants) with low platelet counts during a chemotherapy cycle are given romiplostim (single-dose subcutaneous administration with chemotherapy), compared to placebo:

- there is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one bleeding episode of any severity (very low quality of evidence);
- there is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one severe/life-threatening bleeding episode (very low quality of evidence);
- no studies were found that looked at overall survival, the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, the amount of bleeding, or quality of life.

We found one ongoing study (expected recruitment 74 participants), planning to give romiplostim (subcutaneous administration with chemotherapy) to participants. As yet, there are no reported outcomes.

To treat CIT, one ongoing study (expected recruitment 83 participants) planned to give eltrombopag (seven days orally) to participants when their platelet counts are less than $75 \times 10^9/L$ during chemotherapy. Its completion date (March 2017) has passed and no results have been reported.

One study awaiting classification included patients with normal platelet counts before chemotherapy (to prevent CIT), patients with low platelet counts during chemotherapy (to prevent recurrence of CIT), and others (uncertain whether CIT had happened). There was no evidence for a difference in the number and severity of bleeding episodes. This study did not address overall survival or quality of life.

Quality of the evidence

There is low and very low quality evidence for the use of TPO-RAs to prevent CIT or prevent recurrence of CIT in patients with solid tumours.

Conclusion

No certain conclusions can be drawn due to the lack of strong evidence in the review. The available weak evidence did not support the use of TPO-RAs for preventing CIT or preventing recurrence of CIT in patients with solid tumours. No completed studies looked at the use of TPO-RAs for treating CIT in patients with solid tumours.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

TPO-RAs compared to placebo for prevention of CIT in patients with solid tumours

Patient or population: patients with solid tumours without thrombocytopenia before chemotherapy

Setting: hospital

Intervention: eltrombopag

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with TPO- RAs				
All-cause mortality follow-up: 33 weeks	429 per 1,000	579 per 1,000 (227 to 1,000)	RR 1.35 (0.53 to 3.45)	26 (1 RCT)	⊕⊕⊕⊕ LOW ¹	As overall survival has not been reported, we calculated all-cause mortality at 33 weeks in the study of Winer 2015 .
Number of patients with at least one bleeding episode of any severity follow-up: 30 days	94 per 1,000	58 per 1,000 (21 to 168)	RR 0.62 (0.22 to 1.78)	206 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 3}	At least four patients (a maximum of five) with seven bleeding events in the placebo group in the study of Kellum 2010 .
Number of patients with at least one severe/life-threatening bleeding episode follow-up: 30 days	38 per 1,000	14 per 1,000 (2 to 78)	RR 0.36 (0.06 to 2.06)	206 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{2 3}	
Number of treatment cycles with at least one bleeding episode - not measured	-	-	-	-	-	
Number of days on which bleeding occurred - not measured	-	-	-	-	-	
The amount of bleeding - not measured	-	-	-	-	-	
Quality of life score - not measured	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded by two for very serious imprecision. The included study was a small study and the 95% confidence interval of the risk ratio includes the possibility of significant harm or significant benefit.

² Downgraded by one for serious risk of bias. There was a high risk of performance bias and detection bias.

³ Downgraded by two for very serious imprecision. There were few events and the 95% confidence interval of the risk ratio includes the possibility of significant harm or significant benefit.

Summary of findings 2.

TPO-RAs compared to placebo for relapse prevention of CIT in patients with solid tumours

Patient or population: patients with solid tumours with thrombocytopenia during chemotherapy

Setting: hospital

Intervention: romiplostim

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with TPO- RAs				
Overall survival - not measured	-	-	-	-	-	
Number of patients with at least one bleeding episode of any severity follow-up: 30 days	83 per 1,000	233 per 1,000 (14 to 1,000)	RR 2.80 (0.17 to 47.53)	62 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}	No patients bled in the placebo group. Assuming a control group risk of 8.3% (equivalent to one in this group). At least five patients (a maximum of eight) with eight bleeding

						events in the romiplostim group.
Number of patients with at least one severe/life-threatening bleeding episode follow-up: 30 days	See comment	See comment	Not estimable	62 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 3}	There were no severe/life-threatening bleeding events in either of the study groups.
Number of treatment cycles with at least one bleeding episode - not measured	-	-	-	-	-	
Number of days on which bleeding occurred - not measured	-	-	-	-	-	
The amount of bleeding - not measured	-	-	-	-	-	
Quality of life score - not measured	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded by one for serious risk of bias. There was a high risk of detection bias.

² Downgraded by two for very serious imprecision. The included study was a small study and the 95% confidence interval of the risk ratio includes the possibility of significant harm or significant benefit.

³ Downgraded by two for very serious imprecision. The included study was a small study and this is a rare outcome with no events in either study arm.

BACKGROUND

Description of the condition

Chemotherapy-induced thrombocytopenia (CIT) is defined as a peripheral platelet count less than $100 \times 10^9/L$, with or without bleeding in cancer patients receiving myelosuppressive chemotherapy, excluding other causes including idiopathic thrombocytopenic purpura (ITP), myelodysplastic syndrome, aplastic anaemia, radiation sickness, hepatitis C virus infection, MYH9-related diseases (a congenital thrombocytopenia) and megalosplenism (enlarged spleen) (CSCO 2014). Platelets are released by their progenitor cells in the bone marrow, megakaryocytes, into sinusoidal blood vessels (Machlus 2014). Chemotherapeutic drugs suppress megakaryocyte development and platelet production (Machlus 2014). CIT carries the risk of sub-optimal overall survival and bleeding, and increases the need for chemotherapy dose reduction, treatment delay, platelet transfusion, and incremental cost (Elting 2001; Elting 2003).

Under the influence of tumour types, chemotherapy plans and individual differences, CIT does not always follow a consistent pattern (Levy 2008). A large observational study of 43,995 patients (62,072 chemotherapy regimens) showed the overall incidence of CIT was 52% in patients with solid tumours treated with four main regimens (platinum-based, anthracycline-based, gemcitabine-based, and taxane-based). The incidence ranged from 21.9% in patients treated with taxane-based regimens to 64.2% in patients treated with gemcitabine-based regimens, and the highest incidence rate of CIT by tumour type was 61.7% in colorectal cancer, followed by 50.5% in non-small cell lung cancer, 45.6% in ovarian cancer, and the lowest 37.6% in breast cancer (Wu 2009). Most patients (17.6% to 41%) with CIT had grade 1 thrombocytopenia, while grade 3 to 4 thrombocytopenia was observed in 10.6% of patients with platinum-based and gemcitabine-based regimens, 5.2% of patients with anthracycline-based regimens, and 1.9% of patients with taxane-based regimens (Wu 2009). In an observational study including 320 patients with CIT, the incidence of CIT increased significantly with the accumulation of cycles (0.6% in cycle one, 17.8% in cycle two, 37.8% in cycle three, and 43.8% in cycle four) (Hassan 2011). CIT often occurs at day three to seven after many treatment cycles, reaches its lowest point at about day 14, and gradually recovers its baseline by day 28 to 35 (Wu 2010). The platelet lowest points were earlier observed in some regimens such as ICE (ifosfamide, carboplatin, etoposide), AI (mesna, doxorubicin, ifosfamide), or MAID (mesna, doxorubicin, ifosfamide, dacarbazine), than in others such as carboplatin, melphalan, or nitrosourea (Vadhan-Raj 2009a). With multiple cycles of chemotherapy, the lowest points showed a downward and prolonged trend. In patients treated with high-dose doxorubicin plus cyclophosphamide, the median lowest points reduced from $60 \times 10^9/L$ in cycle one to $9 \times 10^9/L$ in cycle six, and the median durations (less than $100 \times 10^9/L$) increased from two days in cycle one to 18 days in cycle six (Hoekman 1991).

Some established risk factors make cancer patients more prone to bleeding in a new treatment cycle. In a cohort that included 609 patients with solid tumours and lymphoma who developed CIT, the single most significant risk factor associated with bleeding was a previous bleeding episode, with an odds ratio of 5.4 and 95% confidence interval of 2.9 to 10.2, and the next key predictor of bleeding was a low baseline platelet count, less than $75 \times 10^9/L$,

with an odds ratio of 3.1 and 95% confidence interval of 1.9 to 5.1 (Elting 2001). When we leave all other considerations aside, the risk of bleeding is often related to the platelet count (Kaufman 2015). The probability of all bleeding ranges from 0% to 9.6% when the count falls below $50 \times 10^9/L$, doubles (from 10.1% to 17.7%) when the count falls below $20 \times 10^9/L$, and doubles again (from 18.4% to 40.1%) when the count falls below $10 \times 10^9/L$ (Kaufman 2015; Kuter 2015; Schiffer 2001). The causes of poor bone marrow function, such as bone marrow metastases, poor performance status, and previous radiotherapy (especially in the long bone, sternum, and pelvis), are also important risk factors of bleeding (Hashiguchi 2015). Special regimen administration (cisplatin, carboplatin, gemcitabine, carmustine, or lomustine) is also associated with a significantly increased risk of bleeding in patients with solid tumours (Elting 2001; Ten 2011).

CIT is a common problem, but there is no guideline that codifies its diagnosis and treatment. Oncologists should consider the causes of the thrombocytopenia, and provide cancer treatments cautiously, being aware of the possibility of worsening the thrombocytopenia and increasing the risk of bleeding, when the platelet counts are less than $100 \times 10^9/L$ (Kuter 2013). Management of CIT is still difficult, it often involves platelet transfusion or weakened chemotherapy, or both. The main emphasis of current research has shifted to the second-generation thrombopoietic agents (i.e. romiplostim and eltrombopag).

Description of the intervention

The most frequently used interventions for CIT are to reduce the drug dose or to delay the next treatment cycle, or both (Hassan 2011). In a large observational study with 43,995 patients, delays were examined in 26,317 patients (113,175 cycles) with complete doses, and delays occurred in 22.7% of patients and 8.2% of cycles (Wu 2009). The cohort study of 609 patients with CIT showed dose reductions occurred during 15% of cycles (1262 cycles), and delays occurred during 8% of cycles (Elting 2001). The compromised strategies, sub-therapeutic dose and delay, carry the risk of sub-optimal overall survival and progression-free survival (Kuter 2015).

Platelet transfusions are currently the most effective and rapid therapies for patients with severe CIT, and about 30% of patients with solid tumours with CIT require platelet transfusions (Hassan 2011). Prophylactic transfusions should be given when the first signs of bleeding appear or the platelet counts are below $10 \times 10^9/L$ without bleeding; however the traditional threshold, less than $10 \times 10^9/L$, may not be present for all patients with their own specific risk factors for bleeding (such as infection, coagulopathy, medication, and chemotherapy regimen) (Kuter 2015; Rioux-Massé 2013). CIT often causes extra expenses, mainly due to the use of prophylactic platelet transfusions (Kuter 2015). There are many side effects of the transfusions including febrile, allergic transfusion reactions, and transmission of bacterial and viral infections (Estcourt 2012). Refractoriness to platelet transfusion is one of the major long-term complications of repeated transfusions, yet patients undergoing intensive treatments often require several transfusions due to the long recovery time of bone marrow and the short life span of platelets (Fletcher 2015; Vadhan-Raj 2010a; Wandt 2014).

The process of megakaryocytopoiesis is controlled by a number of cytokines. Recombinant human interleukin-11 (rhIL-11) is

the only platelet growth factor approved by the United States (US) Food and Drug Administration for CIT (CSCO 2010). Based on a series of phase I/II clinical trials including patients with solid tumours and lymphoma, rhIL-11 could provide an effective strategy for preventing CIT, accelerating platelet recovery, and reducing platelet transfusions (Cairo 2005; Lei 2006; Wang 2005; Wu 2012). However, the use of rhIL-11 is severely limited by its narrow therapeutic index and significant side effects (Bhatia 2007). Oedema (20%) and arrhythmia (15%) are the most common adverse events, so rhIL-11 must be used cautiously for cancer patients with renal dysfunction or cardiac disease, especially the elderly (CSCO 2010). More than half of patients who receive anthracycline-based chemotherapy are likely to develop myocardial damage, and the use of rhIL-11 is not recommended for these patients (CSCO 2010). A pharmaco-economic analysis showed that prophylactic rhIL-11 was more expensive than routine platelet transfusion for patients with solid tumours with CIT (Cantor 2003). Over a three-week period, the total expected cost of rhIL-11 in this study was 5328 US dollars, compared with 3495 US dollars for platelet transfusion (Cantor 2003).

Thrombopoietin (TPO) is the primary regulator of megakaryocyte development and platelet production (Hitchcock 2014). Endogenous TPO is the ligand of c-mpl receptor, which is expressed on pluripotential stem cells, progenitor cells, megakaryocytes, and platelets (Deutsch 2013). Thrombopoietic agents were designed to stimulate the c-mpl receptor to promote megakaryocyte maturation and platelet production. The first-generation thrombopoietic agents include two recombinant versions of TPO: pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) from *Escherichia coli*, and recombinant human thrombopoietin (rhTPO) from ovarian cells of Chinese hamsters. They both have been shown to increase platelet counts and reduce platelet transfusions in patients with thrombocytopenia (Busse 2014). However, phase I/II clinical trials of PEG-rHuMGDF demonstrated that patients and healthy participants developed neutralising antibodies against PEG-rHuMGDF and endogenous TPO (Basser 2002; Li 2001). The USA has stopped the trials of PEG-rHuMGDF and rhTPO (Kuter 2007). Endogenous TPO and rhTPO have similar structures, and rhTPO may have a very low immunogenicity. Phase II/III clinical trials of rhTPO have been completed in China, and showed that rhTPO was an effective agent for CIT without finding neutralising antibodies (Bai 2004; Li 2012; Zhao 2001). The rhTPO has been approved by the China Food and Drug Administration for CIT. After rhTPO went on sale in China, its safety was evaluated in 1153 patients. The overall incidence of adverse effects was 3.9%, primarily fatigue (0.78%), fever (0.61%), and elevation of transaminase (0.52%). There was one case each of oedema, rash, itching and dizziness, and most of adverse effects were grade 1 or grade 2 (CSCO 2014). The second-generation thrombopoietic agents, thrombopoietin receptor agonists (TPO-RAs) or thrombopoietin mimetics, are in different stages of preclinical and clinical studies (Sekeres 2011; Zeng 2011). Phase III clinical trials of two TPO-RAs (romiplostim and eltrombopag) have been completed in patients with ITP, and the two have been approved by the US Food and Drug Administration for ITP (Sekeres 2011; Zeng 2011). Some randomised and non-randomised studies have examined the TPO-RAs for CIT in patients with solid tumours, however, romiplostim and eltrombopag are not approved for use in preventing or treating CIT outside of clinical trials in

the USA, Europe or China (Chawla 2013; Kellum 2010; Kuter 2015; Parameswaran 2014; Winer 2015).

How the intervention might work

TPO-RAs were developed to overcome the antigenicity of recombinant versions of TPO, and they can be divided into three categories: peptide molecules (romiplostim, Fab59, Peg-TPOmp), non-peptide molecules (eltrombopag, AKR-501), and TPO agonist antibodies (VB22B, MA01G4G344) (Levy 2008). These TPO-RAs are being examined in preclinical and clinical studies. Only romiplostim (weekly subcutaneous injection) and eltrombopag (daily oral administration) have completed extensive phase III trials in patients with ITP (Kuter 2008). Platelet counts started to rise at day five and peak at days 12 to 15 with romiplostim, and rise at day seven and peak at day 16 with eltrombopag (Kuter 2007). A Cochrane review of TPO-RAs for chronic ITP found that TPO-RAs significantly increased platelet response, and were generally well-tolerated. TPO-RAs did not improve significant bleeding events, however, nor was there a randomised trial studying overall survival (Zeng 2011).

Romiplostim (AMG 531) is a TPO peptide mimetic with a c-mpl receptor binding domain and an Fc domain (Wang 2004). Romiplostim stimulates the megakaryocytopoiesis and increases the platelet count using the same method as TPO (Wang 2004). In a case series of persistent CIT including 20 patients with solid tumours and lymphoma, weekly romiplostim (mean 2.9 µg/kg, range 1 µg/kg to 5.1 µg/kg) achieved adequate platelet recovery in most patients by two weeks, and allowed resumption of chemotherapy without recurrence of CIT (Parameswaran 2014). Adverse events such as osteonecrosis, thrombosis, rebound thrombocytopenia (after stopping the drug), and bone marrow fibrosis were reported in some small trials (AMGEN 2011; Kantarjian 2009; Sekeres 2011).

Eltrombopag (SB-497115) is a non-peptide hydrazone small molecule which activates TPO-specific signal pathway by interacting with the transmembranous domain of c-mpl receptor (Erickson-Miller 2005). In a phase I clinical trial in patients with soft tissue sarcoma who had developed CIT during previous chemotherapy, daily oral eltrombopag 75 mg (N = 7), 100 mg (N = 4), and 150 mg (N = 1) for 10 days in AI chemotherapy (21-day cycle), most patients had increased pre-chemotherapy platelet counts, no dose-limiting toxicities were found, and the most common adverse events were fatigue (53%), elevated alanine aminotransferase, constipation, and nausea (Chawla 2013). In a phase II study in patients with solid tumours who received first-line carboplatin/paclitaxel (21-day cycle), daily oral eltrombopag 50 mg (N = 45), 75 mg (N = 45), and 100 mg (N = 46) for 10 days, platelet counts increased after their lowest points during cycles one and two in eltrombopag treatment group compared with placebo (N = 47), and the most common adverse events were nausea and alopecia (Kellum 2010).

Why it is important to do this review

CIT is a significant medical problem during chemotherapy, and alternative interventions to platelet transfusion are limited (Webert 2012). Current clinical studies mainly focus on the TPO-RAs (i.e. romiplostim and eltrombopag) (Levy 2008; Vadhan-Raj 2009a). These drugs have been tested in ITP and myelodysplastic syndrome (Desborough 2016; Dodillet 2017; Sekeres 2011; Zeng 2011). A

Cochrane review is needed to evaluate the safety and effectiveness of TPO-RAs for CIT in patients with solid tumours.

OBJECTIVES

To assess the effects of thrombopoietin receptor agonists (TPO-RAs) to prevent and treat chemotherapy-induced thrombocytopenia (CIT) in patients with solid tumours.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs). We included full-text, abstracts, and unpublished data if sufficient information on study design, participant characteristics, interventions and outcomes was available. Quasi-randomised trials, cluster-randomised trials, and cross-over trials were not eligible for inclusion.

Types of participants

Two populations were considered:

- Part 1 population: patients without thrombocytopenia before chemotherapy (to prevent CIT).
- Part 2 population: patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT, or to treat CIT).

Thrombocytopenia was defined as a platelet count less than $100 \times 10^9/L$.

We included patients of all age groups, including children, adults, and older adults aged over 65 years. We included only patients diagnosed with solid tumours, using histological and cytological criteria, regardless of the type or stage of the disease, or previous therapy. We excluded other causes of thrombocytopenia, such as ITP, non-anticancer drugs, aplastic anaemia, hepatitis C, megalosplenia, MYH9-related diseases, radiation sickness, myelodysplastic syndrome and leukaemia.

We investigated both populations in separate analyses.

Types of interventions

- TPO-RAs versus placebo or no treatment.
- TPO-RAs versus other drugs.
- TPO-RAs plus other drugs versus the other drugs only.
- TPO-RAs 1 versus TPO-RAs 2 (different types, dosages or time schedules).

Types of outcome measures

Primary outcomes

- Overall survival (OS), defined as the time interval from random treatment assignment to death from any cause, or to last follow-up.
- Number and severity of bleeding episodes, including the number of patients with at least one: a) bleeding episode of any severity; and b) severe/life-threatening bleeding episode (as defined in the individual trials).

Secondary outcomes

- Number and severity of bleeding episodes (per patient), including the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, and the amount of bleeding.
- Quality of life (QoL) score, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
- Platelet responses, including the number of patients with at least one platelet count less than $100 \times 10^9/L$, the number of days on which a platelet count less than $100 \times 10^9/L$ occurred, the increase of platelet counts, the lowest point of platelet counts, and the number of treatment cycles with one platelet count less than $100 \times 10^9/L$.
- Transfusion requirements, including the number of patients with at least one platelet transfusion, the number of platelet transfusions, and the number of treatment cycles with at least one platelet transfusion.
- Progression-free survival (PFS).
- Time in hospital.
- Healthcare cost.
- Adverse events, according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 2009). Four adverse events were studied as separate outcomes, including thrombosis, rebound thrombocytopenia, bone marrow fibrosis, and hepatotoxicity.

Search methods for identification of studies

Electronic searches

Search strategies were adapted from those suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). To reduce the language bias, we did not apply a language restriction.

We searched the following databases.

- MEDLINE (1950 to September 2017) (Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL), (the Cochrane Library, September 2017) (Appendix 2).

Searching other resources

We searched the following database (to 28 September 2017) of ongoing trials and unpublished trials.

- Clinical Trials (<http://www.clinicaltrials.gov>).
- Chinese Clinical Trial Register (<http://www.chictr.org>).
- Australian New Zealand Clinical Trial Registry (<http://www.anzctr.org.au/>).
- WHO ICTRP Search Portal (<http://www.who.int/ictrp/network/en/index.html>).
- International Standard Randomised Controlled Trial Number registry (<http://www.isrctn.com/>).
- GlaxoSmithKline (GSK) Clinical Study Register (<https://www.gsk-clinicalstudyregister.com/>).
- Amgen Clinical Trials (<http://www.amgentrials.com/amgen/study.aspx>).

We handsearched the reference lists of all identified studies, relevant review articles and current treatment guidelines, and made contact experts in the field to identify further reports of trials. We also searched the reports of conferences (from 2002 up to September 2017) in the following sources.

- American Society of Hematology (ASH).
- American Society of Clinical Oncology (ASCO).
- European Hematology Association (EHA).
- European Society of Medical Oncology (ESMO).
- Conference Proceedings Citation Index-Science (CPCI-S).

Data collection and analysis

Selection of studies

We selected studies according to the recommendations in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two review authors (WN and AW) downloaded all titles and abstracts retrieved by electronic searching to a reference management database, removed duplicates, and examined the remaining references independently. The same two authors excluded those studies which clearly do not meet the inclusion criteria, obtained copies of the full text of potentially relevant references, and read them in full. The two authors (WN and AW) assessed the eligibility of retrieved papers independently, and resolved disagreements by discussion with a third author (GD). We documented the reasons for exclusion.

Data extraction and management

We collected data according to the recommendations in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two authors (XZ and YC) extracted data independently onto a data extraction form specially designed for the review. We resolved differences between review authors by discussion or by appeal to a third review author (GD), if necessary.

The form contained the following items:

- general information: author, title, source, publication date, country, language, duplicate publications;
- 'Risk of bias' assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias;
- study characteristics: trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, compliance with assigned treatment, length of follow-up, time point of randomisation;
- participant characteristics: age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of solid tumour, stages of disease, lost to follow-up with reasons, protocol violations, previous treatments, current treatments, prognostic factors;
- treatment details according to study protocol: primary intervention (medication, dosage, administration);
- outcomes: outcomes as specified above (see [Types of outcome measures](#)).

We contacted the manufacturers and original investigators to clarify data and obtain additional information about the extracted data.

One review author (YC) entered data into [Review Manager 2014](#) software and a second author (WN) checked the data for accuracy.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using the following criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

Two review authors (XZ and YC) independently applied the 'Risk of bias' tool and resolved differences by discussion or by appeal to a third review author (GD). We summarised results in both a 'Risk of bias' graph and a 'Risk of bias' summary.

Measures of treatment effect

According to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), we used the following measures of the effects of treatment.

- For time-to-event data, such as OS, we planned to extract and report the hazard ratio (HR), and we planned to estimate the HR from published data according to the procedure recommended by Parmar (Parmar 1998) and Tierney (Tierney 2007) in case there were only survival curves without HRs available.
- For dichotomous outcomes, we planned to calculate the risk ratio (RR), and we planned to use the generic inverse variance method to pool log-transformed RRs which were then back-transformed.
- For continuous outcomes, such as QoL scores, we planned to calculate the mean differences (MDs) when different studies measured the same outcome on the same scale, or standardised mean differences (SMDs) when different studies measured the same outcome on different scales.

Unit of analysis issues

We did not anticipate unit of analysis issues, and there were no unit of analysis issues within the included studies.

Dealing with missing data

We dealt with missing data according to the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We contacted the manufacturers and original investigators to request missing data, but no data were provided. Our requests for eltrombopag (Kellum 2010; Winer 2015; Winer 2017) are under review by ClinicalStudyDataRequest.com (<https://clinicalstudydatarequest.com/>), which is authorised by study sponsors such as GSK and Novartis (eltrombopag has been transferred from GSK to Novartis). Our request for romiplostim (Natale 2009) was temporarily rejected by Amgen (datasharing@amgen.com). We did not impute missing outcome

data for the primary outcomes (OS, number and severity of bleeding episodes). From GSK Clinical Study Register and Amgen Clinical Trials, we received the data about the number of patients with at least one: a) bleeding episode of any severity; and b) severe/life-threatening bleeding episode. The lack of OS data, which were not measured or reported, might have caused biases in the review.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials by using the χ^2 test and the I^2 statistic, according to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias as the review included only two trials (Part 1 population, to prevent CIT) and one trial (Part 2 population, to prevent recurrence of CIT). We had specified in the protocol that we planned to address reporting biases according to the recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

When data were sufficiently similar to be combined, we carried out meta-analyses (fixed-effect model) using Review Manager software (Review Manager 2014) according to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), and using the random-effects model with inverse variance weighting for all meta-analyses (DerSimonian 1986).

We created 'Summary of findings' tables using the GRADEpro software (<https://gradepro.org/>), as suggested in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We included the following outcomes for each type of comparison listed below.

- OS or mortality
- Number of patients with at least one bleeding episode of any severity
- Number of patients with at least one severe/life-threatening bleeding episode
- Number of treatment cycles with at least one bleeding episode
- Number of days on which bleeding occurred
- The amount of bleeding
- QoL score

Subgroup analysis and investigation of heterogeneity

We had considered performing subgroup analyses using the following characteristics:

- different ages of the patients (children, adults, older adults aged over 65 years);
- different initial platelet counts (less than $50 \times 10^9/L$ versus between $50 \times 10^9/L$ to $100 \times 10^9/L$);
- different types of treatments (more than 70% of patients receiving platinum-based, gemcitabine-based, and anthracycline-based chemotherapy versus less than 70% of patients receiving platinum-based, gemcitabine-based, and anthracycline-based chemotherapy versus chemotherapy without platinum, gemcitabine, and anthracycline);
- different types of treatments (chemotherapy alone versus combination therapy);
- patients receiving initial chemotherapy versus salvage chemotherapy.

However, as only two trials (Part 1 population, to prevent CIT) and one trial (Part 2 population, to prevent recurrence of CIT) were included and none of the three studies provided data concerning those subgroups, we did not perform the intended subgroup analyses.

Sensitivity analysis

We re-analysed data using a random-effects model instead of a fixed-effect model. We planned to re-analyse data by including/excluding studies on the basis of differences in risk of bias, quality components (full-text publications versus abstracts and preliminary results versus mature results), participant dropout, and missing data. However, only two RCTs (Part 1 population, to prevent CIT) were finally meta-analysed, sensitivity analysis was limited.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); and [Characteristics of ongoing studies](#).

Results of the search

The literature search was designed to find all relevant references about thrombopoietin receptor agonists (TPO-RAs) for prevention and treatment of chemotherapy-induced thrombocytopenia (CIT) in patients with solid tumours. After removing duplicates, we screened 1891 unique records for eligibility, and excluded 1863 records during the initial screening process, and assessed the full text or abstract of the remaining 28 records. Finally, 13 references of three trials (two trials for Part 1 population, to prevent CIT; one trial for Part 2 population, to prevent recurrence of CIT) that fulfilled the methods criteria were formally included in this systematic review. The study flow diagram in [Figure 1](#) provides an overview of the searching process.

Figure 1. Study flow diagram.

Included studies

Three studies fulfilled the inclusion criteria of this review, two trials ([Kellum 2010](#); [Winer 2015](#)) for Part 1 population (to prevent CIT) and one trial ([Natale 2009](#)) for Part 2 population (to prevent recurrence of CIT). See [Characteristics of included studies](#) for full details of each study.

Design

The two trials ([Kellum 2010](#); [Winer 2015](#)) for Part 1 population were published as full-text articles in English. [Kellum 2010](#) reported that participants were randomly assigned 1:1:1:1 to receive 50 mg, 75 mg, 100 mg of eltrombopag or placebo, it was double-blinded in the first four chemotherapy cycles and open-label after the first four cycles. [Winer 2015](#) was a double-blind study and reported that participants were randomly assigned 3:1 to receive 100 mg of eltrombopag or placebo.

The one trial ([Natale 2009](#)) for Part 2 population was published as a meeting abstract. [Natale 2009](#) reported that participants were randomly assigned 4:1 to receive 250 µg, 500 µg, 750 µg of romiplostim or placebo. Blinding of outcome assessors was not reported in the study.

Sample sizes

[Kellum 2010](#) included 183 participants, 180 randomised and received at least one dose of TPO-RAs or placebo (134 in the TPO-RAs group, 46 in the placebo group). [Winer 2015](#) included 33 participants, 26 randomised and received at least one dose of TPO-RAs or placebo (19 in the TPO-RAs group, seven in the placebo group).

[Natale 2009](#) included 63 participants, 62 randomised and received at least one dose of TPO-RAs or placebo (50 in the TPO-RAs group, 12 in the placebo group).

Setting

[Kellum 2010](#) was conducted at 22 sites in the USA, 49 sites in Europe, 16 sites in South America and Asia. [Winer 2015](#) was conducted at 90 sites in the USA, Belgium, Czech, Finland, Greece, India, Israel, Poland, Canada, Germany, Hungary, Ireland, and Italy.

[Natale 2009](#) was conducted at 58 sites in the USA, Austria, Canada, Germany, Hungary, Ireland, Italy and Portugal.

Participants

Part 1 population: patients without thrombocytopenia before chemotherapy.

[Kellum 2010](#) included chemotherapy-naïve participants with non-small cell lung cancer (N = 112), ovarian cancer (N = 46), breast cancer (N = 7), and other (N = 15), who were scheduled to receive carboplatin and paclitaxel (a maximum of eight cycles). [Winer 2015](#) included participants with non-small cell lung cancer (N = 8), breast cancer (N = 4), pancreatic cancer (N = 4), bile duct cancer (N = 3), colorectal cancer (N = 3), and other (N = 4), who were scheduled to receive gemcitabine monotherapy or gemcitabine and platinum (a minimum of two cycles, a maximum of six cycles). These participants were recovered from previous chemotherapy-related toxicity except for alopecia (N = 18), or chemotherapy-naïve (N = 8). The two studies recruited adult and elder participants (18 years and older), and no children were included.

Part 2 population: patients with thrombocytopenia during chemotherapy.

[Natale 2009](#) included participants with CIT with locally advanced or metastatic stage IIIB or stage IV non-small cell lung cancer (N = 62), who were receiving gemcitabine/carboplatin or gemcitabine/cisplatin (a maximum of five cycles). No participants received a prior systemic chemotherapy. The study recruited adult and elder participants (18 years and older), and no children were included.

Interventions

In [Kellum 2010](#), participants were randomised to eltrombopag 50 mg, 75 mg, 100 mg or placebo given orally once daily on day two to day 11 for each 21-day chemotherapy cycle for up to a maximum of eight cycles. In [Winer 2015](#), participants were randomised to eltrombopag 100 mg or placebo given orally once daily for five days before and five days after day one of cycle two and up to a maximum of six cycles (21-day cycle, gemcitabine and platinum; 28-day cycle, gemcitabine monotherapy).

In [Natale 2009](#), chemotherapy regimens (gemcitabine and platinum) were delayed until the platelet counts returned to more than $100 \times 10^9/L$ on day one of the first study cycle, and participants were randomised to romiplostim 250 µg, 500 µg, 750 µg or placebo given subcutaneously on day two of each 21-day chemotherapy cycle for up to a maximum of five cycles.

Outcomes

[Kellum 2010](#) reported deaths during the study, number and severity of bleeding episodes, platelet responses, and adverse events. [Winer 2015](#) reported all-cause mortality at 33 weeks of follow-up, number and severity of bleeding episodes, platelet responses, and adverse events. [Natale 2009](#) reported deaths during the study, number and severity of bleeding episodes, platelet responses, transfusion requirements, and adverse events. None of the trials evaluated OS, PFS, QoL, time in hospital, and healthcare costs.

Excluded studies

We excluded 10 studies ([Al-Samkari 2016](#); [Chawla 2013](#); [Dardis 2016](#); [Iuliano 2016a](#); [Iuliano 2016b](#); [Miao 2016](#); [NCT02052882](#); [Urena 2016](#); [Vadhan-Raj 2009b](#); [Vadhan-Raj 2010b](#)). The studies ([Al-Samkari 2016](#); [Chawla 2013](#); [Dardis 2016](#); [Iuliano 2016a](#); [Iuliano 2016b](#); [Miao 2016](#); [NCT02052882](#); [Urena 2016](#); [Vadhan-Raj 2009b](#)) were not RCTs. The study [Vadhan-Raj 2010b](#) included participants with non-Hodgkin lymphoma. See [Characteristics of excluded studies](#).

Studies awaiting classification

The trial [Winer 2017](#) included patients without thrombocytopenia before chemotherapy (to prevent CIT), patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT), and other patients during chemotherapy (uncertain whether CIT had happened during the preceding cycle). We did not exclude the study this time, however, we did not get sufficient data (from [Winer 2017](#) and GSK Clinical Study Register) to report these populations separately. Our requests for eltrombopag are under review by ClinicalStudyDataRequest.com (<https://clinicalstudydatarequest.com/>). [Winer 2017](#) reported three bleeding events 3/52 in the eltrombopag group and five bleeding events 5/23 in the placebo group (RR 0.27, 95% CI 0.07 to 1.02; one trial, 75 participants), and one severe/life-threatening

bleeding events 1/52 in the eltrombopag group and one severe/life-threatening bleeding events 1/23 in the placebo group (RR 0.44, 95% CI 0.03 to 6.77; one trial, 75 participants). This study did not address OS or QoL. See [Characteristics of studies awaiting classification](#).

Ongoing studies

Two trials for Part 2 population are ongoing and no results are reported (EUCTR2013-002564-69-DE; NCT02093325). In the study EUCTR2013-002564-69-DE (to prevent recurrence of CIT), salvage chemotherapy regimens will be delayed until the platelet counts return to more than $100 \times 10^9/L$ on day one of the first study cycle,

and participants will be randomised to romiplostim or placebo given subcutaneously. In the study NCT02093325 (to treat CIT), participants will be randomised to eltrombopag 50 mg or placebo at 2:1 ratio once a day for seven days when platelet count less than $75 \times 10^9/L$ during chemotherapy. See [Characteristics of ongoing studies](#).

Risk of bias in included studies

The risk of bias of the included studies (Kellum 2010; Winer 2015; Natale 2009) is summarized in Figure 2 and Figure 3. See the 'Risk of bias' tables within [Characteristics of included studies](#) for details of the assessment.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Objective outcomes	Blinding of outcome assessment (detection bias): Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kellum 2010	+	+	-	+	-	+	+	?
Natale 2009	?	?	+	+	-	+	+	?
Winer 2015	+	+	+	+	+	+	+	?

Allocation

The studies on eltrombopag (Kellum 2010; Winer 2015) were judged as having adequate allocation concealment. Participants were randomly assigned by an in-house validated randomisation system.

The study on romiplostim (Natale 2009) was as being unclear. There was no information in clinical trials registers.

Blinding

Performance bias

Kellum 2010 broke the blind after the first four chemotherapy cycles, we assessed the study to be at high risk of performance bias. In Winer 2015 and Natale 2009, both participants and investigators were blinded, we assessed the both studies to be at low risk of performance bias.

Detection bias

Kellum 2010 was open-label after the first four cycles, we assessed the risk of bias arising from lack of blinding of outcome assessors

as low for objective outcomes (i.e. mortality), and as high for subjective outcomes (i.e. number and severity of bleeding episodes, QoL score). In [Winer 2015](#), outcomes assessors were blinded, we assessed the study to be at low risk of detection bias for both objective and subjective outcomes. In [Natale 2009](#), only participants and investigators were blinded, we assessed the risk of bias arising from lack of blinding of outcome assessors as low for objective outcomes, and as high for subjective outcomes.

Although bleeding events were objective, there was subjectivity involved in assessing the number and severity of bleeding episodes.

Incomplete outcome data

All studies ([Kellum 2010](#); [Winer 2015](#); [Natale 2009](#)) included all participants who were randomised and received at least one dose of study medications for the analyses of bleeding episodes, maximum toxicities in haematology data, and adverse events. We assessed these studies to be at low risk of attrition bias.

Selective reporting

All study protocols were available and all studies ([Kellum 2010](#); [Winer 2015](#); [Natale 2009](#)) reported a primary outcome measure. The outcomes in the study protocols were the same as finally reported in the publications. We assessed these studies to be at low risk of selective reporting bias.

Other potential sources of bias

The studies on eltrombopag ([Kellum 2010](#); [Winer 2015](#)) were sponsored by GSK, the manufacturer of eltrombopag. Eltrombopag has been transferred from GSK to Novartis. The study on romiplostim ([Natale 2009](#)) was sponsored by Amgen, the manufacturer of romiplostim. We assessed these studies to be at unclear risk of other bias.

Effects of interventions

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

Part 1 population: patients without thrombocytopenia before chemotherapy (to prevent CIT).

Overall survival

No hazard ratios (HRs) for overall survival were measured. [Winer 2015](#) provided data on the all-cause mortality at 33 weeks of follow-up; there was no statistical significance between TPO-RAs and placebo (risk ratio (RR) 1.35, 95% confidence interval (CI) 0.53 to 3.45; one trial, 26 participants; low quality of evidence) (see [Analysis 1.1](#)). [Kellum 2010](#) reported seven deaths 7/134 in the TPO-RAs group and three deaths 3/46 in the placebo group during the study (RR 0.8, 95% CI 0.22 to 2.97; one trial, 180 participants).

Number and severity of bleeding episodes, including the number of patients with at least one: a) bleeding episode of any severity; and b) severe/life-threatening bleeding episode (as defined in the individual trials)

[Kellum 2010](#) and [Winer 2015](#) provided data on the number and severity of bleeding episodes. Treatment with TPO-RAs (eltrombopag) results in a similar incidence of any bleeding events compared to placebo (RR 0.62, 95% CI 0.22 to 1.78; two trials, 206

participants; very low quality of evidence) (see [Analysis 1.2](#)), and in a similar incidence of severe/life-threatening bleeding events compared to placebo (RR 0.36, 95% CI 0.06 to 2.06; two trials, 206 participants; very low quality of evidence) (see [Analysis 1.3](#)).

Including the awaiting classification study [Winer 2017](#) in the number and severity of bleeding episodes for reference, there was no evidence for a difference in the number and severity of bleeding episodes: a) any severity (RR 0.45, 95% CI 0.2 to 1.01; $P = 0.05$; $I^2 = 0\%$; fixed-effect model; three trials, 281 participants); b) severe/life-threatening episodes (RR 0.38, 95% CI 0.09 to 1.66; $P = 0.2$; $I^2 = 0\%$; fixed-effect model; three trials, 281 participants).

Number and severity of bleeding episodes, including the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, and the amount of bleeding

Not measured.

Quality of life

Not measured.

Platelet responses, including the number of patients with at least one platelet count less than $100 \times 10^9/L$, the number of days on which a platelet count less than $100 \times 10^9/L$ occurred, the increase of platelet counts, the lowest point of platelet counts, and the number of treatment cycles with one platelet count less than $100 \times 10^9/L$

[Kellum 2010](#) and [Winer 2015](#) reported the platelet count less than $100 \times 10^9/L$ in 64/153 participants receiving TPO-RAs (eltrombopag) and in 28/53 participants receiving placebo, there was no statistical significance between the two groups (RR 0.81, 95% CI 0.60 to 1.09; two trial, 206 participants) (see [Analysis 1.4](#)).

[Winer 2015](#) reported the number of days on which a platelet count less than $100 \times 10^9/L$ occurred (across cycles two to six, without cycle one), there was no statistical significance between TPO-RAs and placebo (mean difference (MD) -1.31, 95% CI -7.41 to 4.79; one trial, 20 participants) (see [Analysis 1.5](#)).

[Kellum 2010](#) reported the increase of platelet counts (change from day one to peak) in each chemotherapy cycle (from cycle one to eight). The increase of platelet counts was significantly higher with the use of TPO-RAs (eltrombopag) compared with placebo in the first chemotherapy cycle (MD 147.91, 95% CI 105.77 to 190.05; one trial, 166 participants), however, there were no statistical differences between the two groups in the following seven cycles (see [Analysis 1.6](#)).

[Kellum 2010](#) reported the lowest point of platelet counts in each chemotherapy cycle (from cycle one to eight). There were no statistical differences between the two groups in most cycles, except for cycle two; the lowest point of platelet counts were significantly higher with the use of TPO-RAs (eltrombopag) compared with placebo in cycle two (MD 36.61, 95% CI 13.33 to 59.89; one trial, 139 participants) (see [Analysis 1.7](#)). [Winer 2015](#) also reported the lowest point of platelet counts in each chemotherapy cycle (from cycle one to six). The lowest point of platelet count was significantly higher with the use of TPO-RAs (eltrombopag) compared with placebo in the first chemotherapy cycle (MD 54.86, 95% CI 9.11 to 100.61; one trial, 26 participants); however, there

were no statistical differences between the two groups in the following five cycles (see [Analysis 1.8](#)).

[Kellum 2010](#) and [Winer 2015](#) studied the number of treatment cycles with one platelet count less than $100 \times 10^9/L$, however, we did not receive the data.

Transfusion requirements, including the number of patients with at least one platelet transfusion, the number of platelet transfusions, and the number of treatment cycles with at least one platelet transfusion

These outcomes were not measured.

Progression-free survival

Not measured.

Time in hospital

Not measured.

Healthcare cost

Not measured.

Adverse events

[Kellum 2010](#) and [Winer 2015](#) reported the total adverse events in 137/153 participants receiving TPO-RAs (eltrombopag) and in 45/53 participants receiving placebo without statistical significance (RR 1.06, 95% CI 0.93 to 1.21; two trials, 206 participants) (see [Analysis 1.9](#)), and the total serious adverse events in 28/153 participants receiving TPO-RAs (eltrombopag) and in 11/53 participants receiving placebo without statistical significance (RR 0.89, 95% CI 0.48 to 1.65; two trials, 206 participants) (see [Analysis 1.10](#)).

Four adverse events were reported as separate outcomes: [Kellum 2010](#) and [Winer 2015](#) reported the thrombosis in 13/153 participants receiving TPO-RAs (eltrombopag) and in 3/53 participants receiving placebo without statistical significance (RR 1.37, 95% CI 0.44 to 4.25; two trials, 206 participants) (see [Analysis 1.11](#)); [Kellum 2010](#) studied the thrombocytopenia (after discontinuation of study medication regardless of cycle), and reported no events in either of the study groups; bone marrow fibrosis was not measured; [Kellum 2010](#) reported the hepatotoxicity in 7/134 (at least seven, a maximum of eight) participants receiving TPO-RAs (eltrombopag) and in 8/46 participants receiving placebo (RR 0.30, 95% CI 0.12 to 0.78; one trial, 180 participants), and [Winer 2015](#) reported the hepatotoxicity in 4/19 participants receiving TPO-RAs (eltrombopag) and in 0/7 participants receiving placebo (RR 3.60; 95% CI 0.22 to 59.46; one trial, 26 participants) (see [Analysis 1.12](#)). Due to the high heterogeneity ($I^2 = 66\%$), we did not pool the data.

Part 2 population: patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT).

Overall survival

No HR for overall survival was measured. [Natale 2009](#) reported two deaths 2/50 in the TPO-RAs (romiplostim) group and no deaths 0/12 in the placebo group during the study (RR 1.27, 95% CI 0.07 to 24.96; one trial, 62 participants).

Number and severity of bleeding episodes, including the number of patients with at least one: a) bleeding episode of any severity; and b) severe/life-threatening bleeding episode (as defined in the individual trials)

[Natale 2009](#) provided data on the number and severity of bleeding episodes. There were at least five participants (a maximum of eight) with eight bleeding events in the TPO-RAs (romiplostim) group and no participants bled in the placebo group, without statistical significance between the two groups (RR 2.80, 95% CI 0.17 to 47.53; one trial, 62 participants; very low quality of evidence) (see [Analysis 2.1](#)). There were no severe/life-threatening bleeding events in either of the study groups (very low quality of evidence).

Including the awaiting classification study [Winer 2017](#) in the number of patients with at least one bleeding episode of any severity for reference, there was no statistical significance between the two groups (RR 0.63, 95% CI 0.06 to 6.31; $P = 0.69$; $I^2 = 57\%$; random-effects model; two trials, 137 participants).

Number and severity of bleeding episodes, including the number of treatment cycles with at least one bleeding episode, the number of days on which bleeding occurred, and the amount of bleeding

Not measured.

Quality of life

Not measured.

Platelet responses, including the number of patients with at least one platelet count less than $100 \times 10^9/L$, the number of days on which a platelet count less than $100 \times 10^9/L$ occurred, the increase of platelet counts, the lowest point of platelet counts, and the number of treatment cycles with one platelet count less than $100 \times 10^9/L$

[Natale 2009](#) reported the platelet count less than $100 \times 10^9/L$ in 29/50 participants receiving TPO-RAs (romiplostim) and in 5/12 participants receiving placebo, there was no significant difference between the two groups (RR 1.39, 95% CI 0.68 to 2.83; one trial, 62 participants) (see [Analysis 2.2](#)). Other outcomes were not measured or reported.

[Natale 2009](#) provided data on the number of days on which a platelet count less than $50 \times 10^9/L$ occurred in the first chemotherapy cycle, there was no statistical significance between TPO-RAs and placebo (MD 0.60, 95% CI -1.54 to 2.74; one trial, 61 participants) (see [Analysis 2.3](#)).

Transfusion requirements, including the number of patients with at least one platelet transfusion, the number of platelet transfusions, and the number of treatment cycles with at least one platelet transfusion

These outcomes were not measured or reported.

[Natale 2009](#) provided data on the number of patients with at least one platelet transfusion in the first chemotherapy cycle, there was no statistical significance between TPO-RAs and placebo (RR 1.47, 95% CI 0.19 to 11.08; one trial, 61 participants) (see [Analysis 2.4](#)).

Progression-free survival

Not measured.

Time in hospital

Not measured.

Healthcare cost

Not measured.

Adverse events

Natale 2009 reported the total adverse events in 48/50 participants receiving TPO-RAs (romiplostim) and in 12/12 participants receiving placebo without statistical significance (RR 0.99, 95% CI 0.87 to 1.12; one trial, 62 participants) (see [Analysis 2.5](#)), and the total serious adverse events in 17/50 participants receiving TPO-RAs (romiplostim) and in 1/12 participants receiving placebo without statistical significance (RR 4.08, 95% CI 0.60 to 27.71; one trial, 62 participants) (see [Analysis 2.6](#)).

Four adverse events were reported as separate outcomes: thrombosis occurred in three participants who received romiplostim, but not in any of the participants who received placebo (RR 1.78, 95% CI 0.1 to 32.43; one trial, 62 participants) (see [Analysis 2.7](#)); rebound thrombocytopenia and bone marrow fibrosis were not measured; and hepatotoxicity did not occur in any participants who received romiplostim, but did in one participant who received placebo (RR 0.08, 95% CI 0.00 to 1.97; one trial, 62 participants) (see [Analysis 2.8](#)).

DISCUSSION

Summary of main results

This Cochrane review included two trials with 206 adult and elder participants (no children were included) for Part 1 population (to prevent chemotherapy-induced thrombocytopenia (CIT)), both trials compared eltrombopag with placebo and were sponsored by GSK.

- There was no evidence for a difference in the all-cause mortality (at 33 weeks of follow-up from one small trial with 26 participants).
- There was no evidence for a difference in the number and severity of bleeding episodes (any severity or severe/life-threatening episodes).
- There was no evidence for a difference in the platelet responses (the number of patients with at least one platelet count less than $100 \times 10^9/L$, the number of days on which a platelet count less than $100 \times 10^9/L$ occurred, the increase of platelet counts, or the lowest point of platelet counts).
- There was no evidence for a difference in the adverse events (total or severe events).
- Data regarding overall survival (OS), number of treatment cycles with at least one bleeding episode, number of days on which bleeding occurred, the amount of bleeding, quality of life (QoL), transfusion requirements, progression-free survival (PFS), time in hospital, and healthcare costs were not measured.

This Cochrane review included one trial with 62 adult and elder participants (no children were included) for Part 2 population (to prevent recurrence of CIT), the trial compared romiplostim with placebo and was sponsored by Amgen. The review also found one ongoing trial (expected recruitment 74 participants) for Part 2

population (to prevent recurrence of CIT), which has not to date reported any outcomes.

- There was no evidence for a difference in the number and severity of bleeding episodes (any severity or severe/life-threatening episodes).
- There was no evidence for a difference in the platelet responses (the number of patients with at least one platelet count less than $100 \times 10^9/L$, or the number of days on which a platelet count less than $50 \times 10^9/L$ occurred in the first chemotherapy cycle).
- There was no evidence for a difference in the platelet transfusion requirements (the number of patients with at least one platelet transfusion in the first chemotherapy cycle).
- There was no evidence for a difference in the adverse events (total or severe events).
- Data regarding OS, number of treatment cycles with at least one bleeding episode, number of days on which bleeding occurred, the amount of bleeding, QoL, PFS, time in hospital, and healthcare costs were not measured.

The review also found one trial awaiting classification trial with 75 patients for Part 1 population (to prevent CIT), Part 2 population (to prevent recurrence of CIT), and other. We did not receive sufficient data to report the these populations separately. There was no evidence for a difference in the number and severity of bleeding episodes (any severity or severe/life-threatening episodes). Data regarding OS and QoL were not measured.

The review also found one ongoing trial (expected recruitment 83 participants) for Part 2 population (to treat CIT), which has not to date reported any outcomes.

Overall completeness and applicability of evidence

Overall completeness and applicability of evidence was low due to the poor findings. The following aspects should be taken into consideration when interpreting the data of this systematic review.

- This review did not report many patient-related outcomes, such as OS (one of the primary outcomes), PFS, QoL, and long-term adverse events. The three included studies ([Kellum 2010](#); [Winer 2015](#); [Natale 2009](#)), the one awaiting classification study [Winer 2017](#), and the two ongoing studies ([EUCTR2013-002564-69-DE](#); [NCT02093325](#)) mainly focused on platelet responses rather than clinically relevant outcomes. OS was the most important missing data; this outcome was not measured or reported in all these trials.
- This review was not powered for finding small differences in the outcomes with few events, such as bleeding episodes (one of the primary outcomes), thrombosis, and hepatotoxicity.
 - * For Part 1 population (to prevent CIT), only two published trials involving 206 participants were included. In order to detect an increase in overall mortality from 43 in 100 to 58 in 100, a study would need to recruit 348 participants (80% power, 5% significance). In order to demonstrate a reduction in any bleeding episodes from 9 in 100 to 6 in 100, a study would need to recruit 2418 participants (80% power, 5% significance). See [Summary of findings for the main comparison](#).
 - * For Part 2 population (to prevent recurrence of CIT), only one published trial involving 62 participants was included, and one ongoing trial evaluating 74 participants with no results.

In order to detect an increase in any bleeding episodes from 8 in 100 to 23 in 100, a study would need to recruit 182 participants (80% power, 5% significance). See [Summary of findings 2](#).

- * For Part 1 population (to prevent CIT) and Part 2 population (to prevent recurrence of CIT) and other, one awaiting classification trial involving 75 participants was found. In order to demonstrate a reduction in any bleeding episodes from 22 in 100 to 6 in 100, a study would need to recruit 146 participants (80% power, 5% significance).
- * For Part 2 population (to treat CIT), only one ongoing trial evaluating 83 participants with no results.
- The one study awaiting classification ([Winer 2017](#)) might not be able to answer all main questions, because it was a small trial and did not address OS.
- The two ongoing randomised controlled trials (RCTs) have not to date reported any outcomes, and we are waiting for their results. However, they might not be able to answer all main questions, because they are small trials: [EUCTR2013-002564-69-DE](#) does not address OS, and [NCT02093325](#) does not address OS or bleeding episodes.
- This review did not perform the subgroup analyses planned in the protocol. The results of this systematic review should not be extended to all risk patients, because CIT often varied greatly from individual to individual.
- The intervention of eltrombopag, multiple-dose oral administration, might not be performed very well even under the condition of a randomised trial. This review analysed all participants who were randomised and received at least one dose of eltrombopag. However, 34% (two cycles) and 89% (eight cycles) of participants withdrew in [Kellum 2010](#), 35% (six cycles) participants withdrew in [Winer 2015](#), and 64% (six cycles) participants withdrew in [Winer 2017](#).

Quality of the evidence

The risk of selection bias in [Kellum 2010](#) and [Winer 2015](#) was low as they were reported as randomised trials. The risk of selection bias in [Natale 2009](#) was unclear as no information was reported. The risk of performance bias in [Natale 2009](#) and [Winer 2015](#) was low as participants and investigators were blinded. The risk of performance bias in [Kellum 2010](#) was high as the study was open-label after the first four cycles. The risk of detection bias in [Winer 2015](#) was low as outcomes assessors were blinded. The risk of detection bias (subjective outcomes) in [Kellum 2010](#) and [Natale 2009](#) was high as outcomes assessors were blinded for the first four cycles but the study ([Kellum 2010](#)) was open-label for the next four cycles and blinding of outcome assessors was not reported in [Natale 2009](#). We rated the risk of attrition and reporting bias as low for all three trials. We rated the risk of other bias as unclear for the three trials as they were supported and sponsored by manufacturers.

The quality of evidence for preventing CIT with TPO-RAs (Part 1 population) is low and very low. We downgraded all-cause mortality two points for imprecision, as the study ([Winer 2015](#)) was a small trial and the 95% confidence intervals were wide. We downgraded 'number of patients with at least one bleeding episode of any severity' one point for risk of performance bias and detection bias, and two points for imprecision as there were few events and the 95% confidence intervals were wide. We

downgraded 'number of patients with at least one severe/life-threatening bleeding episode' one point for risk of performance bias and detection bias, and two points for imprecision as there were few events and the 95% confidence intervals were wide.

The quality of evidence for preventing recurrence of CIT with TPO-RAs (Part 2 population) is very low. We downgraded 'number of patients with at least one bleeding episode of any severity' one point for risk of detection bias, and two points for imprecision as the study ([Natale 2009](#)) was a small trial and the 95% confidence intervals were wide. We downgraded 'number of patients with at least one severe/life-threatening bleeding episode' one point for risk of detection bias, and two points for imprecision as [Natale 2009](#) was a small trial and there were no events.

Potential biases in the review process

To prevent bias within the review, we performed a thorough search of multiple databases, online registers of clinical trials, and conference proceedings to capture all relevant RCTs, and we performed all relevant processes (searching, data collection, and analysis) in duplicate. One awaiting classification study [Winer 2017](#) was a small trial (N = 75) and did not address OS. The study included patients without thrombocytopenia before chemotherapy (to prevent CIT), patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT), and other patients during chemotherapy (uncertain whether CIT had happened during the preceding cycle). We did not exclude [Winer 2017](#) this time, our requests for eltrombopag are under review, and we did not get sufficient data to report these populations separately. Two ongoing studies ([EUCTR2013-002564-69-DE](#); [NCT02093325](#)) are not completed and no results have been reported; we await their results. The trial [EUCTR2013-002564-69-DE](#) (to prevent recurrence of CIT, expected recruitment 74 participants) does not address OS, and the trial [NCT02093325](#) (to treat CIT, expected recruitment 83 participants) does not address OS or bleeding episodes. Although the three studies might not be able to answer all main questions, it is not known what effect the results will have on the conclusions for this review. We were unable to assess publication bias as the review included only two trials (Part 1 population, to prevent CIT) and one trial (Part 2 population, to prevent recurrence of CIT).

Agreements and disagreements with other studies or reviews

There are no other systematic reviews of RCTs to assess the effects of TPO-RAs to prevent and treat CIT in patients with solid tumours. We excluded some phase I and phase II trials without control groups. Results of these studies are summarised below.

A phase I study [Chawla 2013](#), AI (mesna, doxorubicin, ifosfamide) alone (N = 15) in cycle one and AI plus 75 mg (N = 7), 100 mg (N = 4), and 150 mg (N = 1) eltrombopag daily for 10 days in cycle two, was conducted in patients with soft tissue sarcoma. These patients had developed CIT (platelet count less than $75 \times 10^9/L$) in a previous chemotherapy treatment setting or in a previous chemotherapy cycle, and their platelet counts recovered from less than $75 \times 10^9/L$ to more than $100 \times 10^9/L$ before the study. This trial closed prior to meeting its protocol objectives due to the difficulty of enrolment. Both safety and efficacy analyses were limited. No dose-limiting toxicities were reported. The most common adverse events were thrombocytopenia (80%), neutropenia (73%),

anaemia (67%), fatigue (53%), alanine aminotransferase increased (47%), constipation (47%), and nausea (47%). Participants receiving eltrombopag found an increase in pre-chemotherapy platelet counts during cycle two (AI plus eltrombopag) compared to cycle one (AI alone). There were no definite improvements in the lowest point of platelet counts.

A phase I/II study [Vadhan-Raj 2009b](#) (an abstract), carboplatin or AI alone in cycle one and carboplatin or AI plus romiplostim in subsequent cycles, was conducted in 27 patients with cancer. At least six participants were enrolled at each dose level of romiplostim (1 µg/kg, 3 µg/kg, and 10 µg/kg), which was administered subcutaneously as two doses given two days apart from day two of each chemotherapy cycle, and an additional six participants received romiplostim (10 µg/kg) two doses administered at day five before and day five after day one of each cycle. This study showed that romiplostim was well-tolerated in most patients. One participant developed pulmonary embolism in cycle six. This study suggested the biological activity of romiplostim in patients receiving chemotherapy. There was a reduction in the duration of thrombocytopenia during cycle two (chemotherapy plus romiplostim) compared to cycle one (chemotherapy alone). There was a trend for increase in the lowest point of platelet counts in cycle two as compared to cycle one.

A phase II study [NCT02052882](#) (recruiting), 2 µg/kg romiplostim weekly, will be conducted in 64 patients with solid tumour with CIT. The main outcomes are platelet responses (more than $100 \times 10^9/L$ within three weeks of treatment) and adverse events.

This review excluded the following uncontrolled observational studies or case series studies ([Al-Samkari 2016](#); [Dardis 2016](#); [Iuliano 2016a](#); [Iuliano 2016b](#); [Miao 2016](#); [Parameswaran 2014](#); [Urena 2016](#)). These studies showed efficacy in improving platelet responses, or in allowing resumption of chemotherapy, or both.

AUTHORS' CONCLUSIONS

Implications for practice

No certain conclusions can be drawn due to the lack of strong evidence in the review.

The available weak evidence did not support the use of thrombopoietin receptor agonists (TPO-RAs) for preventing chemotherapy-induced thrombocytopenia (CIT) (Part 1 population, two trials, 206 participants) or preventing recurrence of CIT (Part 2 population, one trial, 62 participants) in patients with solid tumours. For Part 1 population (patients without thrombocytopenia before chemotherapy), there were no data about overall survival (OS) or quality of life (QoL), and there was no evidence for differences in all-cause mortality, bleeding events, or platelet responses between TPO-RAs and placebo. For Part 2 population (patients with thrombocytopenia during chemotherapy), there were no data about OS or QoL, and there was no evidence for differences in bleeding events, platelet responses, or platelet transfusion requirements between TPO-RAs and placebo.

There was no evidence (only one ongoing trial, [NCT02093325](#), for Part 2 population) to support the use of TPO-RAs for treating CIT in patients with solid tumours.

Implications for research

Our search strategy found three preliminary trials of TPO-RAs in phase I or phase II. There were not many bleeding events in these studies, to detect the difference between TPO-RAs and others, future trials should include participants in high-risk situations of bleeding or thrombocytopenia. The optimal dose and schedule of TPO-RAs need continued research. The three studies compared TPO-RAs with placebo, future trials should consider alternative agents (e.g. rhIL-11) as positive control groups to weigh the use of TPO-RAs. The included studies mainly focused on platelet responses and short-term adverse events, future trials should report patient-relevant outcomes, such as OS, PFS, QoL, and long-term adverse events.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [author-defined order]

Kellum 2010

Methods	<p>Part 1 population, to prevent CIT</p> <p>Phase II, Clinical Trial</p> <p>Randomisation</p> <ul style="list-style-type: none"> • 1:1:1:1 ratio • Intervention arm: eltrombopag 50 mg, 75 mg, 100 mg once daily on day 2 to day 11 for each 21-day chemotherapy cycle for up to a maximum of eight cycles. • Control arm: placebo once daily on days 2 to day 11 for each 21-day chemotherapy cycle for up to a maximum of eight cycles. <p>Recruitment period</p> <ul style="list-style-type: none"> • 7 February 2005 to 28 February 2007 <p>Follow-up time</p> <ul style="list-style-type: none"> • on-therapy and up to 30 days following last dose of study drug <p>Multicentre</p> <ul style="list-style-type: none"> • 22 sites in the USA, 49 sites in Europe, 16 sites in South America and Asia
Participants	<p>180 participants randomised and received at least one dose of study medication</p> <ul style="list-style-type: none"> • 134 participants in intervention arms • 46 participants in control arm <p>Age (median, range): 58, 23 to 81years</p> <p>Female (N = 101), Male (N = 79)</p> <p>White 78%</p> <p>Non-small cell lung cancer (N = 112), ovarian cancer (N = 46), breast cancer (N = 7), and other (N = 15)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants with histologically- or cytologically-confirmed advanced solid tumour who were chemotherapy-naïve but scheduled to receive carboplatin and paclitaxel. • No history of platelet disorders or dysfunction, or bleeding disorders. • Life expectancy more than six months. • Eastern Cooperative Oncology Group performance status of 0 to 2. • Adequate baseline organ function. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of central nervous system metastases. • Clotting disorder associated with hypercoagulability. • History of drug-induced thrombocytopenia. • Surgery within two weeks. • Radiotherapy within four weeks of study entry. • Use of aspirin, nonsteroidal anti-inflammatory drugs, or quinine for more than three consecutive days during the two weeks prior to the study, and rosuvastatin or pravastatin within one week of the first dose of study medication.
Interventions	<p>Intervention arm</p> <ul style="list-style-type: none"> • Eltrombopag 50 mg, 75 mg, 100 mg once daily on day 2 to day 11 for each 21-day chemotherapy cycle for up to a maximum of eight cycles.

Kellum 2010 (Continued)

Control arm

- Placebo once daily on day 2 to day 11 for each 21-day chemotherapy cycle for up to a maximum of eight cycles.

Additional cycles (to a maximum of eight) of study medication were permitted if chemotherapy was continued, the patient appeared to benefit from the study drug, and the patient had not encountered greater than grade 2 toxicity associated with the study drug.

Outcomes	<p>Primary</p> <ul style="list-style-type: none"> • Change in baseline platelet count from the first day of the second cycle of chemotherapy to the lowest count observed during the cycle. <p>Secondary</p> <ul style="list-style-type: none"> • Safety and tolerability. • Pharmacodynamic parameters including platelet count, grade of thrombocytopenia, serum thrombopoietin, and platelet aggregation and activation during the first and second cycles of carboplatin and paclitaxel. • Change in platelet count from day 1 (baseline) to nadir during the first cycle and beyond the second cycle of carboplatin and paclitaxel. • Population pharmacokinetic of eltrombopag. • Dose intensity (per cent of intended dose) of carboplatin and paclitaxel. • Carboplatin and paclitaxel-associated thrombocytopenia-related adverse events.
Notes	The study was supported and sponsored by GSK. Eltrombopag has been transferred from GSK to Novartis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by an in-house validated randomisation system.
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned by an in-house validated randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was double-blind (participants, investigators, outcomes assessors) in the first four chemotherapy cycles and open-label after the first four cycles.
Blinding of outcome assessment (detection bias): Objective outcomes All outcomes	Low risk	Assessment of this outcome was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias): Subjective outcomes All outcomes	High risk	The study was double-blind (participants, investigators, outcomes assessors) in the first four chemotherapy cycles and open-label after the first four cycles.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% patients (10% eltrombopag group, 13% placebo group) completed the trial. All participants who were randomised and received at least one dose of study medication were included in the analysis.

Kellum 2010 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes have been reported.
Other bias	Unclear risk	Funded by drug manufacturers. There is evidence that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004).

Winer 2015

Methods	Part 1 population, to prevent CIT Phase I, Clinical Trial Randomisation <ul style="list-style-type: none"> • 3:1 ratio • Intervention arm: eltrombopag 100 mg once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles for up to a maximum of six cycles. • Control arm: placebo once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles for up to a maximum of six cycles. Recruitment period <ul style="list-style-type: none"> • 15 January 2010 to 16 March 2015 Follow-up time <ul style="list-style-type: none"> • on-therapy and up to 30 days following last dose of study drug (total 168 days) Multicentre <ul style="list-style-type: none"> • 90 sites in the USA, Belgium, Czech, Finland, Greece, India, Israel, Poland, Canada, Germany, Hungary, Ireland, and Italy.
Participants	26 participants randomised and received at least one dose of study medication <ul style="list-style-type: none"> • 19 participants in intervention arm • 7 participants in control arm Age (median, range): 53 to 69, 31 to 81 years Female (N = 14), Male (N = 12) White 81% Non-small cell lung cancer (N = 8), breast cancer (N = 4), pancreatic cancer (N = 4), bile duct cancer (N = 3), colorectal cancer (N = 3), and other (N = 4). Inclusion criteria <ul style="list-style-type: none"> • Confirmed solid tumours scheduled to receive more than two cycles of gemcitabine monotherapy or gemcitabine and platinum. • Life expectancy more than three months. • Recovered from previous chemotherapy-related toxicity except alopecia. • Platelet counts less than $300 \times 10^9/L$. • Eastern Cooperative Oncology Group performance status of 0 to 2. • Adequate baseline organ function. Exclusion criteria <ul style="list-style-type: none"> • Pre-existing cardiovascular disease.

Winer 2015 (Continued)

	<ul style="list-style-type: none"> Known factor V Leiden, antiphospholipid antibody syndrome, prothrombin gene mutations, low antithrombin III levels, protein C or protein S deficiency. Recent history (within six months) of arterial or venous thrombosis. A history of radiotherapy to more than 20% of bone marrow-bearing sites. A history of platelet agglutination abnormality, platelet disorders or dysfunction, or bleeding disorders. Central nervous system metastases treated by neurosurgical resection or brain biopsy performed within three months. Hepatitis B, hepatitis C, or human immunodeficiency virus.
Interventions	<p>Intervention arms</p> <ul style="list-style-type: none"> Participants receiving gemcitabine on day 1 and day 8 plus carboplatin or cisplatin on day one as a part of the 21-day chemotherapy cycle, were administered eltrombopag 100 mg once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles. Participants receiving gemcitabine on day 1, day 8 and day 15 as a part of the 28-day chemotherapy cycle, were administered eltrombopag 100 mg once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles. <p>Control arms</p> <ul style="list-style-type: none"> Participants receiving gemcitabine on day 1 and day 8 plus carboplatin or cisplatin on day one as a part of the 21-day chemotherapy cycle, were administered placebo 100 mg once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles. Participants receiving gemcitabine on day 1, day 8 and day 15 as a part of the 28-day chemotherapy cycle, were administered placebo 100 mg once daily for five days before and five days after day one of cycle two and subsequent chemotherapy cycles.
Outcomes	<p>Primary</p> <ul style="list-style-type: none"> Number of participants with any adverse event or serious adverse event. Number of participants with indicated maximum toxicity grades for the indicated haematology parameters. Number of participants with indicated maximum toxicity grades for the indicated clinical chemistry laboratory parameters. Number of participants with a change from baseline in creatinine more than 26.5 µmol/L. Eastern Cooperative Oncology Group performance status scores. Number of participants with electrocardiogram findings. <p>Secondary</p> <ul style="list-style-type: none"> Average pre-chemotherapy platelet count. Average within-participant central laboratory platelet count prior to scheduled chemotherapy across cycles 2 to 6. Platelet count nadir for each chemotherapy cycle. Central laboratory average daily area under the curve platelet-time course across cycles 2 to 6. Number of participants with thrombocytopenia of grade 1, 2, 3 or 4 across all the chemotherapy cycles. Maximum duration of thrombocytopenia across cycles 2 to 6. Central laboratory platelet count for time taken to reach platelet nadir for each chemotherapy cycle. Time to recovery from platelet nadir for each chemotherapy cycle. Dose intensity of gemcitabine plus cisplatin and gemcitabine plus carboplatin and gemcitabine across chemotherapy cycles 1 to 6. Number of participants with at least one delay in their scheduled dose of chemotherapy in any cycle.
Notes	<p>The study was supported and sponsored by GSK. Eltrombopag has been transferred from GSK to Novartis.</p>

Winer 2015 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by an in-house validated randomisation system.
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned by an in-house validated randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded.
Blinding of outcome assessment (detection bias): Objective outcomes All outcomes	Low risk	Outcomes assessors were blinded to treatment.
Blinding of outcome assessment (detection bias): Subjective outcomes All outcomes	Low risk	Outcomes assessors were blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	65% patients (68% eltrombopag group, 57% placebo group) completed the trial. All participants who were randomised and received at least one dose of study medication were included in the analysis.
Selective reporting (reporting bias)	Low risk	All outcomes have been reported.
Other bias	Unclear risk	Funded by drug manufacturers. There is evidence that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004).

Natale 2009

Methods	Part 2 population, to prevent recurrence of CIT Phase II, Clinical Trial Randomisation <ul style="list-style-type: none"> • 4:1 ratio • Intervention arm: romiplostim 250 µg, 500 µg, 750 µg on day two of each chemotherapy cycle for up to a maximum of five cycles. • Control arm: placebo 250 µg, 500 µg, 750 µg on day two of each chemotherapy cycle for up to a maximum of five cycles. Recruitment period <ul style="list-style-type: none"> • 28 December 2006 to 11 August 2008 Follow-up time <ul style="list-style-type: none"> • on-therapy and up to 30 days following last dose of study drug Multicentre
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Natale 2009 (Continued)

- 58 sites in the USA, Austria, Canada, Germany, Hungary, Ireland, Italy and Portugal.

Participants

63 participants randomised

- 51 participants in intervention arm (one did not received a study medication)
- 12 participants in control arm

Age (mean, standard): 63.1, 8.5 years

Female (N = 18), Male (N = 45)

White 98%

Inclusion criteria

- Histologically- or cytologically-confirmed locally advanced or metastatic stage IIIB or stage IV non-small cell lung cancer receiving 21 days gemcitabine/carboplatin or gemcitabine/cisplatin.
- Life expectancy more than 12 weeks.
- Thrombocytopenia as evidenced by a platelet count less than $50 \times 10^9/L$ during the qualifying cycle of chemotherapy, or platelet count less than $100 \times 10^9/L$ on day 22 of the qualifying cycle, this criteria ensured that the participant must be dose delayed for platelet recovery.
- Platelet count more than $100 \times 10^9/L$ on day one of the first on study chemotherapy treatment cycle.
- Eastern Cooperative Oncology Group performance status of 0 to 2.
- Adequate baseline organ function.

Exclusion criteria

- Receipt of more than one prior systemic chemotherapy regimen.
- Sepsis, disseminated coagulation or any other condition that might exacerbate thrombocytopenia.
- History of unstable angina, uncontrolled hypertension, or uncontrolled cardiac arrhythmia.
- History of arterial thrombosis within one year of screening.
- History of pulmonary embolism or other venous thrombosis within one year of screening.
- Use of any nitrosourea or mitomycin-C within six weeks of screening.
- Have received any thrombopoietic growth factor or related substance.
- Have received granulocyte macrophage colony stimulating factor within the last four weeks prior to screening.
- Have received any experimental therapy within four weeks prior to screening.
- Have ever received a bone marrow or peripheral blood stem cell infusion within one year of screening.
- Known hypersensitivity to any recombinant *Escherichia coli* derived product.

Interventions
Intervention arms

- Participants received romiplostim 250 µg, 500 µg, 750 µg administered subcutaneously on day two of each chemotherapy cycle. Chemotherapy consisted of 21-day cycles of gemcitabine and carboplatin (gemcitabine and carboplatin on day one and gemcitabine again on day eight) or 21-day cycles of gemcitabine and cisplatin (gemcitabine and cisplatin on day one and gemcitabine again on day eight), up to a maximum of five cycles administered according to standard institutional practice.

Control arm

- Participants received a placebo subcutaneous injection on day two of each chemotherapy cycle. Chemotherapy consisted of 21-day cycles of gemcitabine and carboplatin (gemcitabine and carboplatin on day one and gemcitabine again on day eight) or 21-day cycles of gemcitabine and cisplatin (gemcitabine and cisplatin on day one and gemcitabine again on day eight), up to a maximum of five cycles administered according to standard institutional practice.

Outcomes
Primary

- Number of participants with adverse events.

Natale 2009 (Continued)

Secondary (during the first treatment cycle)

- Duration of grade 3 or 4 thrombocytopenia.
- Number of participants experiencing grade 3 or 4 thrombocytopenia.
- Number of participants with platelet transfusions.
- Platelet count on day 22.
- Gemcitabine dose reduction on day eight.

Notes The study was supported and sponsored by Amgen.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated in clinical trials registers.
Allocation concealment (selection bias)	Unclear risk	Not stated in clinical trials registers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded.
Blinding of outcome assessment (detection bias): Objective outcomes All outcomes	Low risk	Assessment of this outcome was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias): Subjective outcomes All outcomes	High risk	Blinding of outcome assessors was not reported in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	84% patients (82% romiplostim group, 92% placebo group) completed the trial. All participants who were randomised and received at least one dose of study medication were included in the analysis.
Selective reporting (reporting bias)	Low risk	All outcomes have been reported.
Other bias	Unclear risk	Funded by drug manufacturers. There is evidence that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004).

CIT: chemotherapy-induced thrombocytopenia

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Samkari 2016	The study was a case series of patients with solid tumour who received romiplostim.
Chawla 2013	The study was a non-randomised trial with a single eltrombopag group.

Study	Reason for exclusion
Dardis 2016	The study was a case series of patients with solid tumour who received eltrombopag or romiplostim.
Iuliano 2016a	The study was a case series of patients with cancer who received eltrombopag.
Iuliano 2016b	The study was a case series of patients with cancer who received eltrombopag.
Miao 2016	The study was a case series of patients with cancer who received romiplostim.
NCT02052882	This study is registered as a non-randomised trial and currently recruiting participants. The first 21 patients were stated as random, 2:1 to romiplostim (N = 14) or watchful waiting (N = 7), five watchful waiting patients were crossed over to romiplostim (romiplostim N = 19, watchful waiting N = 2), because they did not response to the expectant management.
Urena 2016	The study was a case series of patients with cancer who received romiplostim.
Vadhan-Raj 2009b	The study was a non-randomised trial.
Vadhan-Raj 2010b	The RCT included patients with non-Hodgkin lymphoma.

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Winer 2017](#)

Methods	<p>Phase II, Clinical Trial</p> <p>Randomisation</p> <ul style="list-style-type: none"> • 2:1 ratio • Intervention arms: eltrombopag 100 mg once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles for up to a maximum of six cycles. • Control arms: placebo once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles for up to a maximum of six cycles. <p>Recruitment period</p> <ul style="list-style-type: none"> • 15 January 2010 to 16 March 2015 <p>Follow-up time</p> <ul style="list-style-type: none"> • on-therapy and up to 30 days following last dose of study drug (total 168 days) <p>Multicentre</p> <ul style="list-style-type: none"> • 90 sites in the USA, Belgium, Czech, Finland, Greece, India, Israel, Poland, Canada, Germany, Hungary, Ireland, and Italy.
Participants	<p>75 participants with solid tumours randomised and received at least one dose of study medication</p> <ul style="list-style-type: none"> • 52 participants in intervention arms • 23 participants in control arms <p>Age (median, range): 64 to 67.5 (in four groups), 36 to 83 years</p> <p>Female (N = 36), Male (N = 39)</p> <p>White 98.7%</p>

Winer 2017 (Continued)

Inclusion criteria

- Confirmed solid tumours scheduled to receive more than two cycles of gemcitabine monotherapy or gemcitabine and platinum.
- Life expectancy more than three months.
- Recovered from previous chemotherapy-related toxicity except alopecia.
- Platelet counts entry criteria
 - * Participants have not started the first cycle in this disease setting and have a platelet count less than $150 \times 10^9/L$ in the screening period as measured within three days before entry into the study.
 - * Participants started chemotherapy for this disease setting and had platelet count less than $150 \times 10^9/L$ on day one in the preceding cycle before entry into the study.
 - * Platelet count less than $100 \times 10^9/L$ at day eight in the preceding cycle before entry into the study.
 - * For participants receiving gemcitabine monotherapy, platelet count less than $100 \times 10^9/L$ at day 15 in the preceding cycle before entry into the study.
- Eastern Cooperative Oncology Group performance status of 0 to 2.
- Adequate baseline organ function.

Exclusion criteria

- Pre-existing cardiovascular disease.
- Known factor V Leiden, antiphospholipid antibody syndrome, prothrombin gene mutations, low antithrombin III levels, protein C or protein S deficiency.
- Recent history (within six months) of arterial or venous thrombosis.
- A history of radiotherapy to more than 20% of bone marrow-bearing sites.
- A history of platelet agglutination abnormality, platelet disorders or dysfunction, or bleeding disorders.
- Central nervous system metastases treated by neurosurgical resection or brain biopsy performed within three months.
- Hepatitis B, hepatitis C, or human immunodeficiency virus.

Interventions

Intervention arms

- Participants receiving gemcitabine on day 1 and day 8 plus carboplatin or cisplatin on day one as a part of the 21-day chemotherapy cycle, were administered eltrombopag 100 mg once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles.
- Participants receiving gemcitabine on day 1, day 8 and day 15 as a part of the 28-day chemotherapy cycle, were administered eltrombopag 100 mg once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles.

Control arms

- Participants receiving gemcitabine on day 1 and day 8 plus carboplatin or cisplatin on day one as a part of the 21-day chemotherapy cycle, were administered placebo 100 mg once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles.
- Participants receiving gemcitabine on day 1, day 8 and day 15 as a part of the 28-day chemotherapy cycle, were administered placebo 100 mg once daily for five days before and five days after day one of cycle one and subsequent chemotherapy cycles.

Outcomes

Primary

- Mean day one scheduled pre-chemotherapy platelet count evaluated across cycles 1 to 6.

Secondary

- Number of participants with any adverse event or serious adverse event.
- Number of participants with any bleeding event and significant bleeding event.
- Number of participants with platelet transfusions.

Winer 2017 (Continued)

- Number of participants with at least one delay in their scheduled dose.
- Number of participants with any dose reduction in their scheduled dose.
- Dose intensity of gemcitabine plus cisplatin and gemcitabine plus carboplatin and gemcitabine across chemotherapy cycles 1 to 6.
- Number of participants with indicated maximum toxicity grades for the indicated haematology parameters.
- Number of participants with a change from baseline in creatinine more than 26.5 µmol/L.
- Eastern Cooperative Oncology Group performance status scores.
- Number of participants with electrocardiogram findings.
- Mean day eight scheduled pre-chemotherapy platelet counts evaluated across cycles 1 to 6.
- Mean day 15 scheduled pre-chemotherapy platelet counts evaluated across cycles 1 to 6.
- Average within-participant central laboratory platelet count prior to scheduled chemotherapy across cycles 1 to 6.
- Platelet count nadir for each chemotherapy cycle.
- Number of participants with thrombocytopenia of grade 1, 2, 3 or 4 across all the chemotherapy cycles.
- Maximum duration of thrombocytopenia across cycles 1 to 6.
- Central laboratory platelet count for time taken to reach platelet nadir for each chemotherapy cycle.
- Time to recovery from platelet nadir for each chemotherapy cycle.

Notes

The study was supported and sponsored by GSK. Eltrombopag has been transferred from GSK to Novartis.

This trial included patients without thrombocytopenia before chemotherapy (to prevent CIT), patients with thrombocytopenia during chemotherapy (to prevent recurrence of CIT), and other patients during chemotherapy (uncertain whether CIT had happened during the preceding cycle). We did not get sufficient data (from Winer 2017 and GSK Clinical Study Register) to report these populations separately. Our requests for eltrombopag are under review by ClinicalStudyDataRequest.com (<https://clinicalstudydatarequest.com/>).

The main outcomes were as follows for reference:

- Deaths during the study (RR 0.64, 95% CI 0.32 to 1.28; N = 75, 13/52 TPO-RAs versus 9/23 placebo)
- Number of patients with at least one bleeding episode of any severity (RR 0.27, 95% CI 0.07 to 1.02; N = 75, 3/52 TPO-RAs versus 5/23 placebo)
- Number of patients with at least one severe/life-threatening bleeding episode (RR 0.44, 95% CI 0.03 to 6.77; N = 75, 1/52 TPO-RAs versus 1/23 placebo)
- Number of patients with at least one platelet count less than $100 \times 10^9/L$ (RR 0.88, 95% CI 0.77 to 0.99; N = 75, 45/52 TPO-RAs versus 23/23 placebo)
- Number of days on which a platelet count less than $100 \times 10^9/L$ occurred (MD -9.1, 95% CI -19.03 to 0.83; N = 68, mean 23.5 and standard 18.68 in 45 TPO-RAs patients versus mean 32.6 and standard 20.31 in 23 placebo patients)
- Number of patients with at least one platelet transfusion (RR 1.33, 95% CI 0.4 to 4.45; N = 75, 9/52 TPO-RAs versus 3/23 placebo)
- Total adverse events (RR 0.93, 95% CI 0.85 to 1.03; N = 75, 48/52 TPO-RAs versus 23/23 placebo)
- Total serious adverse events (RR 0.59, 95% CI 0.34 to 1.04; N = 75, 16/52 TPO-RAs versus 12/23 placebo)
- Thrombosis (RR 1.11, 95% CI 0.23 to 5.29; N = 75, 5/52 TPO-RAs versus 2/23 placebo)
- Hepatotoxicity (RR 1.44, 95% CI 0.52 to 3.94; N = 75, 13/52 TPO-RAs versus 4/23 placebo)

CI: confidence interval; **CIT:** chemotherapy-induced thrombocytopenia; **MD:** mean difference; **RR:** risk ratio; **TPO-RAs:** thrombopoietin receptor agonists

Characteristics of ongoing studies [ordered by study ID]

[EUCTR2013-002564-69-DE](#)

Trial name or title	Double-blind, placebo-controlled multicenter phase II trial to evaluate the efficacy and safety of romiplostim for the treatment of chemotherapy-induced thrombocytopenia in subjects with relapsed ovarian cancer (second or further line).
Methods	Multicentre, double-blind, parallel assignment, randomised, placebo-controlled trial.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Women more than 18 years of age • Platelet count more than $100 \times 10^9/L$ on day one of the first on study cycle of the chemotherapy treatment. • Thrombocytopenia have to be defined during a "qualifying cycle", qualifying cycle could be the first or the second cycle of the palliative chemotherapy, thrombocytopenia as evidenced by a platelet count less than $50 \times 10^9/L$ during the qualifying cycle of chemotherapy or platelet count less than $100 \times 10^9/L$ on the planned starting day of the next cycle of chemotherapy (or 1 day to 3 days before), requiring dose delay for platelet recovery. • Participants with histologically-confirmed advanced or metastatic ovarian cancer who are receiving second- or third-line chemotherapy. • Life expectancy more than 12 weeks. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Previous treatment with PEG-rHuMGDF, rhTPO, romiplostim, eltrombopag, or another thrombopoietic protein. • Participants who have had a larger surgery within the last two weeks before entering this study. • Participants with an active infection; sepsis, disseminated intravascular coagulation, or any other condition that may have exacerbated thrombocytopenia. • History of arterial thrombosis, pulmonary embolism or other venous thrombosis within one year of screening.
Interventions	Romiplostim subcutaneous injection versus placebo subcutaneous injection.
Outcomes	<p>Primary</p> <ul style="list-style-type: none"> • The rate of grade 3 to 4 thrombocytopenia in the first treatment cycle. <p>Secondary</p> <ul style="list-style-type: none"> • The rate of adverse events of grade 3 and 4 in the first four on-study cycles. • The average platelet nadir per cycle. • Number of participants with platelet transfusions. • Platelet count on day 22.
Starting date	11 April 2014
Contact information	GMIHO Gesellschaft für Medizinische Innovation - Hämatologie und Onkologie mbH, Berlin, Germany. Tel: 004930450564417. E-mail: info@gmiho.de
Notes	<p>Trial registration: EUCTR2013-002564-69 on 28 January 2014</p> <p>Planned recruitment: 74 adults</p>

NCT02093325

Trial name or title	A randomised, double blind, placebo-controlled study to assess the efficacy and safety of eltrombopag as a rescue of isolated chemotherapy-induced thrombocytopenia in patients with gynaecologic cancer.
Methods	Two-centre, double-blind, parallel assignment, randomised, placebo-controlled trial.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Female participants more than 18 years of age. • Diagnosed with malignancy of female genital tract cancers. • On active chemotherapy with combined regimen. • A baseline platelet count less than $75 \times 10^9/L$ within two days of screening. • Eastern Cooperative Oncology Group performance status of 0 to 2. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants with haemoglobinopathies. • Any prior history of arterial or venous thrombosis. • Any disease condition associated with active bleeding or requiring anticoagulation, heparin or warfarin. • Pre-existing cardiac disease, or arrhythmias known to involve the risk of thromboembolic events. • History of prior radiotherapy to more than 20% bone marrow bearing sites.
Interventions	Participants will be randomly assigned to receive either eltrombopag 50 mg or placebo at 2:1 ratio once a day for seven days.
Outcomes	<p>Primary</p> <ul style="list-style-type: none"> • Platelet response. <p>Secondary</p> <ul style="list-style-type: none"> • Safety and feasibility, change from baseline in use eltrombopag at seven days.
Starting date	March 2014
Contact information	Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Kaohsiung, Chinese Taiwan; Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, Linkou, Chinese Taiwan. E-mail: irb1@cgmh.org.tw and yuga0122@cgmh.org.tw
Notes	<p>Trial registration: NCT02093325 on 21 March 2014</p> <p>Planned recruitment: 83 adults</p> <p>The recruitment status of this study is unknown. The completion date has passed (March 2017), and the status has not been verified in more than two years.</p>

PEG-rHuMGDF: pegylated recombinant human megakaryocyte growth and development factor; **rhTPO:** recombinant human thrombopoietin

DATA AND ANALYSES

Comparison 1. TPO-RAs versus placebo for prevention of CIT in patients with solid tumours

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of patients with at least one bleeding episode of any severity	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.22, 1.78]
3 Number of patients with at least one severe/life-threatening bleeding episode	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.06, 2.06]
4 Number of patients with at least one platelet count less than $100 \times 10^9/L$	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.60, 1.09]
5 Number of days on which a platelet count less than $100 \times 10^9/L$ occurred	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 The increase of platelet counts	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Cycle one	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Cycle two	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Cycle three	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Cycle four	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 Cycle five	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.6 Cycle six	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.7 Cycle seven	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 Cycle eight	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 The lowest point of platelet counts for each chemotherapy cycle a	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Cycle one	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Cycle two	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Cycle three	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Cycle four	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Cycle five	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.6 Cycle six	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.7 Cycle seven	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.8 Cycle eight	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 The lowest point of platelet counts for each chemotherapy cycle b	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Cycle one	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Cycle two	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Cycle three	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Cycle four	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.5 Cycle five	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 Cycle six	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Total adverse events	2	206	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.93, 1.21]
10 Total severe adverse events	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.65]
11 Thrombosis	2	206	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.44, 4.25]
12 Hepatotoxicity	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 2 Number of patients with at least one bleeding episode of any severity.

Analysis 1.3. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 3 Number of patients with at least one severe/life-threatening bleeding episode.

Analysis 1.4. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 4 Number of patients with at least one platelet count less than $100 \times 10^9/L$.

Analysis 1.5. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 5 Number of days on which a platelet count less than $100 \times 10^9/L$ occurred.

Analysis 1.6. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 6 The increase of platelet counts.

Analysis 1.7. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 7 The lowest point of platelet counts for each chemotherapy cycle a.

Analysis 1.8. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 8 The lowest point of platelet counts for each chemotherapy cycle b.

Analysis 1.9. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 9 Total adverse events.

Analysis 1.10. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 10 Total severe adverse events.

Analysis 1.11. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 11 Thrombosis.

Analysis 1.12. Comparison 1 TPO-RAs versus placebo for prevention of CIT in patients with solid tumours, Outcome 12 Hepatotoxicity.

Comparison 2. TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with at least one bleeding episode of any severity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of patients with at least one platelet count less than 100×10 ⁹ /L	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Number of days on which a platelet count less than $50 \times 10^9/L$ occurred in the first chemotherapy cycle	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Number of patients with at least one platelet transfusion in the first chemotherapy cycle	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Total adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Total severe adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Hepatotoxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 1 Number of patients with at least one bleeding episode of any severity.

Study or subgroup	[TPO-RAs] n/N	[placebo] n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Natale 2009	5/50	0/12		2.8[0.17,47.53]
		[placebo]	0.02 0.1 1 10 50	[TPO-RAs]

Analysis 2.2. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 2 Number of patients with at least one platelet count less than $100 \times 10^9/L$.

Study or subgroup	[TPO-RAs] n/N	[placebo] n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Natale 2009	29/50	5/12		1.39[0.68,2.83]
		[placebo]	0.2 0.5 1 2 5	[TPO-RAs]

Analysis 2.3. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 3 Number of days on which a platelet count less than $50 \times 10^9/L$ occurred in the first chemotherapy cycle.

Study or subgroup	[TPO-RAs]		[placebo]		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Natale 2009	49	2.7 (3.7)	12	2.1 (3.3)		0.6[-1.54,2.74]
					[placebo]	[TPO-RAs]

Analysis 2.4. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 4 Number of patients with at least one platelet transfusion in the first chemotherapy cycle.

Analysis 2.5. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 5 Total adverse events.

Analysis 2.6. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 6 Total severe adverse events.

Analysis 2.7. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 7 Thrombosis.

Analysis 2.8. Comparison 2 TPO-RAs versus placebo for relapse prevention of CIT in patients with solid tumours, Outcome 8 Hepatotoxicity.

APPENDICES

Appendix 1. MEDLINE search strategy

1. THROMBOPOIESIS/
2. thrombopoie\$.tw,kf,ot.
3. thrombocytopoie\$.tw,kf,ot.
4. megakaryocytopoies\$.tw,kf,ot.
5. megakaryocyte\$.tw,kf,ot.
6. MEGAKARYOCYTES/
7. THROMBOPOIETIN RECEPTOR/
8. (eltrombopag\$ or promacta\$ or revolade\$).tw,kf,ot,nm.
9. mpl ligand*.tw,kf,ot.
10. mgdf factor*.tw,kf,ot.
11. c-mpl ligand*.tw,kf,ot.
12. (cd110 or cd-110).tw,kf,ot.
13. (romiplostin\$ or romiplostim\$ or nplate\$).tw,kf,ot,nm.
14. (amg531 or amg 531 or amg-531).tw,kf,ot,nm.
15. sb497115.tw,kf,ot,nm.
16. ((TPO or thrombopoie\$) adj2 (mimetic* or receptor agonist* or agonist* or agent*)).tw,kf,ot.
17. (fab59 or fab 59 or fab-59).tw,kf,ot.
18. (AKR501 or AKR 501 or AKR-501).tw,kf,ot.
19. (YM477 or YM 477 or YM-477).tw,kf,ot.
20. Peg-TPOmp\$.tw,kf,ot.
21. TPO.tw,kf,ot.
22. (thrombopoie\$ and agent\$).tw,kf,ot.
23. or/1-22
24. exp NEOPLASMS BY HISTOLOGIC TYPE/
25. exp NEOPLASMS BY SITE/
26. neoplas\$.tw,kf,ot.
27. tumo?r\$.tw,kf,ot.
28. (Krebs or cancer\$).tw,kf,ot.
29. malignan\$.tw,kf,ot.
30. (carcino\$ or karzino\$).tw,kf,ot.
31. karzinom\$.tw,kf,ot.
32. sarcom\$.tw,kf,ot.
33. leuk#?m\$.tw,kf,ot.
34. lymphom\$.tw,kf,ot.
35. melano\$.tw,kf,ot.
36. metastas\$.tw,kf,ot.
37. (mesothelio\$ or mesotelio\$).tw,kf,ot.
38. carcinomatos\$.tw,kf,ot.
39. (gliom\$ or glioblastom\$).tw,kf,ot.
40. osteo?sarcom\$.tw,kf,ot.
41. (blastom\$ or neuroblastom\$).tw,kf,ot.
42. adenocarcinoma\$.tw,kf,ot.
43. (choriocarcinoma\$ or teratoma\$).tw,kf,ot.
44. or/24-43
45. exp ANTINEOPLASTIC AGENTS/
46. REMISSION INDUCTION/
47. exp ANTINEOPLASTIC PROTOCOLS/
48. ((consolidat\$ or induct\$ or maintenance or conditioning\$) and (therap\$ or treat\$ or regimen\$ or patient\$)).tw,kf,ot.
49. ((anticancer\$ or cancer\$) adj2 (therap\$ or treat\$)).tw,kf,ot.

50.(remission\$ adj2 therap\$).tw,kf,ot.
51.(remission\$ adj2 induction\$).tw,kf,ot.
52.(chemotherap\$ or chemo-therap\$).tw,kf,ot.
53.(Antineoplast\$ or anti-neoplast\$).tw,kf,ot.
54.((cytosta\$ or cytotox\$) adj2 (therap\$ or treat\$ or regimen\$)).tw,kf,ot.
55.or/45-54
56.23 and (44 or 55)
57.randomized controlled trial.pt.
58.controlled clinical trial.pt.
59.randomi?ed.ab.
60.placebo.ab.
61.drug therapy.fs.
62.randomly.ab.
63.trial.ab.
64.groups.ab.
65.or/57-64
66.exp ANIMALS/ not HUMANS/
67.65 not 66
68.56 and 67

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Thrombopoiesis] explode all trees
#2 thrombopoie*
#3 thrombocytopoie*
#4 megakaryocytopoies*
#5 megakaryocyte*
#6 MeSH descriptor: [Megakaryocytes] explode all trees
#7 MeSH descriptor: [Receptors, Thrombopoietin] explode all trees
#8 mpl ligand*
#9 mgdf factor*
#10 c-mpl ligand*
#11 (cd110 or cd-110)
#12 eltrombopag* or promacta* or revolade*
#13 romiplostin* or romiplostim* or nplate*
#14 (amg531 or amg 531 or amg-531)
#15 (sb497115 or sb 497115 or sb-497115)
#16 ((TPO or thrombopoie*) near/2 (mimetic* or receptor agonist* or agonist* or agent* or receptor*))
#17 (fab59 or fab 59 or fab-59)
#18 (AKR501 or AKR 501 or AKR-501)
#19 (YM477 or YM 477 or YM-477)
#20 Peg-TPOmp*
#21 TPO*

#22 (thrombopoie* and agent*)

#23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees

#25 MeSH descriptor: [Neoplasms by Site] explode all trees

#26 neoplas*

#27 tumor* or tumour*

#28 (Krebs or cancer*)

#29 malignan*

#30 (carcino* or karzino*)

#31 karzinom*

#32 sarcom*

#33 leukaem* or leukam* or leuc*

#34 lymphom*

#35 melano*

#36 metastas*

#37 (mesothelio* or mesotelio*)

#38 carcinomatos*

#39 (gliom* or glioblastom*)

#40 osteo*sarcom*

#41 (blastom* or neuroblastom*)

#42 adenocarcinoma*

#43 (choriocarcinoma* or teratoma*)

#44 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43

#45 MeSH descriptor: [Antineoplastic Agents] explode all trees

#46 MeSH descriptor: [Remission Induction] explode all trees

#47 MeSH descriptor: [Antineoplastic Protocols] explode all trees

#48 ((consolidat* or induct* or maintenance or conditioning*) and (therap* or treat* or regimen* or patient*))

#49 ((anticancer* or cancer* or antineoplastic* or antitumor* or chemotherapeutic anticancer*) near/2 (therap* or treat* or agent* or drug*))

#50 (remission* near/2 therap*)

#51 (remission* near/2 induction*)

#52 (chemotherap* or chemo-therap*)

#53 (antineoplast* or anti-neoplast*)

#54 ((cytosta* or cytotox*) near/2 (therap* or treat* or regimen*))

#55 #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54

#56 #23 and (#44 or #55) in Trials

HISTORY

Protocol first published: Issue 1, 2016

Review first published: Issue 11, 2017

Date	Event	Description
7 April 2016	Amended	<p>There is a clerical error in our "search strategy of Central":</p> <p>#19: "#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #10 or #11 or #13 or #14 or #15 or #16 or #17 or #18"</p> <p>The #9 and #12 are orphan lines.</p> <p>The right one is: "#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18"</p>

CONTRIBUTIONS OF AUTHORS

Xia Zhang (XZ): drafted the protocol

Wei Nie (WN) and Aiming Wang (AW): developed and ran the search strategy

Guanghai Dai (GD): obtained copies of studies

WN and AW: selected which studies to include

WN and AW: extracted data from studies

Yunhai Chuai (YC): entered data into RevMan

AW: carried out the analysis

YC: interpreted the analysis

XZ: drafted the final review

XZ and YC: will update the review

DECLARATIONS OF INTEREST

Xia Zhang (XZ): none known

Yunhai Chuai (YC): none known

Wei Nie (WN): none known

Aiming Wang (AW): none known

Guanghai Dai (GD): none known

SOURCES OF SUPPORT

Internal sources

- Salary, China.

Chinese PLA General Hospital, Beijing, China. Salary of Xia Zhang (XZ).

Chinese PLA General Hospital, Beijing, China. Salary of Guanghai Dai (GD).

Navy General Hospital, Beijing, China. Salary of Yunhai Chuai (YC).

Navy General Hospital, Beijing, China. Salary of Aiming Wang (AW).

No.425 Hospital of Chinese PLA, Sanya, China. Salary of Wei Nie (WN).

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Objectives and types of participants

In the protocol, objectives were described as "To assess the effects of TPO-RAs to prevent (Part 1) and treat (Part 2) CIT in patients with solid tumours". The two populations were: Part 1 population, patients without thrombocytopenia before chemotherapy; and Part 2 population, patients with thrombocytopenia during chemotherapy. In the review, we found the studies of Part 2 population included two trials (included study (Natale 2009); ongoing study (EUCTR2013-002564-69-DE)) for preventing recurrence of CIT, and another ongoing study (NCT02093325) for treating CIT. Objectives were modified as the followings:

"To assess the effects of TPO-RAs to prevent and treat CIT in patients with solid tumours:

(1) to prevent CIT in patients without thrombocytopenia before chemotherapy,

(2) to prevent recurrence of CIT, and (3) to treat CIT in patients with thrombocytopenia during chemotherapy."

Electronic searches

- MEDLINE search strategy was modified, we added four items: "9. mpl ligand*.tw,kf,ot.", "10. mgdf factor*.tw,kf,ot.", "11. c-mpl ligand*.tw,kf,ot.", and "(cd110 or cd-110).tw,kf,ot.".
- CENTRAL search strategy was modified, we added four items: "#8 mpl ligand*", "#9 mgdf factor*", "#10 c-mpl ligand*", and "#11 (cd110 or cd-110)".

Searching other resources

- The service of MetaRegister of Controlled Trials was under review. We searched International Standard Randomised Controlled Trial Number registry, GlaxoSmithKline (GSK) Clinical Study Register, and Amgen Clinical Trials instead.
- In addition,, we searched the reports of conferences in Conference Proceedings Citation Index-Science (CPCI-S).

The search strategy of ongoing trials and CPCI-S was "eltrombopag* or promacta* or revolade* or romiplostin* or romiplostim* or nplate* or amg531 or amg 531 or amg-531 or sb497115 or sb 497115 or sb-497115 or fab59 or fab 59 or fab-59 or AKR501 or AKR 501 or AKR-501 or YM477 or YM 477 or YM-477 or Peg-TPOmp or thrombopoie* or TPO or TPO* or mpl ligand or mgdf factor or c-mpl ligand or cd110 OR cd-110", and this search strategy was adapted when necessary.

Subgroup analysis and investigation of heterogeneity

We did not perform the subgroup analysis as described in the protocol. As only two trials (Part 1 population, to prevent CIT) and one trial (Part 2 population, to prevent recurrence of CIT) were included and none of the three studies provided data concerning those subgroups, we did not perform the intended subgroup analyses.

Sensitivity analysis

We did not perform the sensitivity analysis as described in the protocol. We re-analysed data using a random-effects model instead of a fixed-effect model. We planned to re-analyse data by including/excluding studies on the basis of differences in risk of bias, quality components (full-text publications versus abstracts and preliminary results versus mature results), participant dropout, and missing data. However, only two RCTs (Part 1 population, to prevent CIT) were finally meta-analysed, sensitivity analysis was limited.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*adverse effects]; Benzoates [*administration & dosage]; Hydrazines [*administration & dosage]; Neoplasms [drug therapy]; Pyrazoles [*administration & dosage]; Randomized Controlled Trials as Topic; Receptors, Fc [*administration & dosage]; Receptors, Thrombopoietin [*agonists]; Recombinant Fusion Proteins [*administration & dosage]; Thrombocytopenia [chemically induced] [*drug therapy] [mortality] [*prevention & control]; Thrombopoietin [*administration & dosage]

MeSH check words

Adult; Aged; Humans; Middle Aged