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Efficacy and safety of different treatments in chemotherapy-induced thrombocytopenia : a systematic review and network meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2024 and was last updated on 24 November 2024.

INTRODUCTION

Review question / Objective P: cancer patients who developed CIT I: treated with rhTPO, rhIL-11, mIL-11, and TPO-RAS (romiplostim, eltrombopag and avatrombopag) C: placebo O: platelet transfusion, incidence of grade 3/4 thrombocytopenia and platelet recovery to ≥100×109/L, bleeding events, dose delays/dose reductions/missed doses due to thrombocytopenia, incidence of neutropenia and anemia, time of platelet recovery to ≥100×109/L, nadir platelet count, thromboembolic events, adverse events. S: randomized controlled trials.

Condition being studied Chemotherapy-Induced Thrombocytopenia (CIT) is a common hematologic adverse effect of chemotherapy, typically occurring when chemotherapeutic agents suppress the generation and function of bone marrow megakaryocytes, leading to a significant decrease in platelet count1. Platelet count below 100×109/L is diagnostic of thrombocytopenia, which, if severe, can cause bleeding tendencies, increased infection risk, and interfere with the overall treatment plan. Platelet transfusions are commonly used to treat severe thrombocytopenia but are associated with adverse reactions related to blood product transfusion and may result in transfusion refractoriness2.

Thrombopoietic drugs are effective in reducing bleeding risk and decreasing the need for platelet transfusions in CIT management. Research indicates that thrombopoietic agents help maintain Relative Dose Intensity (RDI) and extend overall survival3. These agents include recombinant human interleukin-11 (rhIL-11), recombinant human thrombopoietin (rhTPO), and thrombopoietin receptor agonists (TPO-RAs), which promote platelet production by stimulating megakaryocyte progenitor cells or specifically binding to the thrombopoietin (TPO) receptor, regulating megakaryocyte proliferation, differentiation, and maturation. rhTPO binds to the extracellular domain of the TPO receptor, inducing a conformational change and activating

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downstream signaling pathways, including JAK/STAT, RAS/MAPK, and PI3K/AKT, to stimulate the development and maturation of hematopoietic stem cells, megakaryocyte progenitors, and polyploid megakaryocytes, thereby promoting platelet production4. TPO-RAs interacts with the transmembrane domain of the human TPO receptor to initiate a signaling cascade that induces the proliferation and differentiation of myeloid progenitors and megakaryocytes5. IL-11 is used to treat grade III and IV thrombocytopenia after chemotherapy for solid tumors and non-myeloid leukemia. However, its clinical use is limited due to side effects, including fluid retention, arrhythmias, and pulmonary edema, and its efficacy is restricted6. rhTPO is approved for CIT treatment only in China, while TPO-RAs has not been approved for CIT in any country or region due to a lack of sufficient evidence. The NCCN guidelines recommend romiplostim for CIT management7. In terms of adverse events, thrombosis or embolism is a concern, as studies have shown that TPO-RAs may promote platelet activation in ITP patients by increasing platelet microparticle formation and upregulating platelet glycoprotein VI (GPVI) and P-selectin expression8. Due to the differences in the target sites, in vivo metabolism, and platelet-raising efficacy of various thrombopoietic drugs, and the challenge of conducting head-to-head randomized controlled trials (RCTs) to determine the optimal choice among multiple treatment options, we conducted a systematic review and network meta-analysis. By directly and indirectly comparing data from eligible RCTs, we performed pairwise comparisons. Our analysis revealed the differences in efficacy and safety across different treatment methods, as well as their ranking probabilities, providing evidence for selecting a superior treatment approach for CIT.

METHODS

Participant or population The enrolled patients were cancer patients who developed CIT, and among these patients, treatments with rhTPO, rhIL-11, mIL-11, and TPO-RAS (romiplostim, eltrombopag and avatrombopag) were utilized.

Intervention The intervention groups we evaluated were efficacy and safety of different treatments in CIT, including rhTPO, rhIL-11, mIL-11, and TPO-RAS (romiplostim, eltrombopag and avatrombopag).

Comparator Placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria Randomized controlled trials, both published and unpublished, were included if they fulfilled the following inclusion criteria regarding the efficacy and safety of treatments for preventing or managing CIT: cancer patients who developed CIT were enrolled, and among these patients, treatments with rhTPO, rhIL-11, mIL-11, and TPO-RAS (romiplostim, eltrombopag, and avatrombopag) were administered. All included literature was in English. To enhance the diversity of treatment options, the study also considered the latest conference abstracts. Non-English articles were excluded.

Information sources PubMed, Web of science, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases.

Main outcome(s) Platelet transfusion rates were compared in 11 studies, showing significantly lower rates for rhIL-11 and mIL-11 compared to placebo (placebo vs. rhIL-11 [OR=3.50, 95% CI: 1.75-6.98]; placebo vs. mIL-11 [OR=7.37, 95% CI: 1.50-36.18]). The mIL-11 group had a significantly lower transfusion rate than the avatrombopag group (avatrombopag vs. mIL-11 [OR=9.82, 95% CI: 1.19-80.96]), while other groups (eltrombopag, avatrombopag, rhTPO, romiplostim, and placebo) showed no statistically significant differences. For grade 3/4 thrombocytopenia, eltrombopag and rhTPO significantly reduced the incidence compared to placebo (placebo vs. eltrombopag [OR=2.24, 95% CI: 1.13-4.44]; placebo vs. rhTPO [OR=3.87, 95% CI: 1.09-13.68]). Bayesian ranking probability analysis indicated that rhTPO was most likely to rank lowest (SUCRA =11.5), followed by eltrombopag (SUCRA =37.8) and rhIL-11 (SUCRA =39.9), with romiplostim ranking highest (SUCRA =73.4). Eltrombopag showed a clear advantage over placebo in reducing chemotherapy delays/reductions and increasing nadir platelet count (eltrombopag vs. placebo [OR=0.37, 95% CI: 0.20-0.68]; placebo vs. eltrombopag [SMD = -37.80, 95% CI: -63.68 to -11.92]). Bayesian ranking probability analysis further showed eltrombopag as most likely to rank lowest for chemotherapy dose reduction/delay (SUCRA=11.1), followed by romiplostim (SUCRA=52.7). For increasing nadir platelet count, eltrombopag was ranked highest (SUCRA=85.2), followed by avatrombopag (SUCRA=58.8), mIL-11 (SUCRA=52.6), and rhTPO (SUCRA=49.2), with rhIL-11 ranked lowest (SUCRA=47.6).

Quality assessment / Risk of bias analysis Each trial's risk of bias was assessed using the Cochrane Risk of Bias Tool, evaluating domains such as random sequence generation, allocation

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concealment, blinding of participants and personnel, blinding for outcome assessment, incomplete outcome data, selected outcome reporting, and other bias. Trials were classified as low, high, or unclear risk of bias based on the above criteria. Two investigators independently performed the inclusion of trials, data collection and evaluation of bias risk. In cases of disagreement, the study team made the final decision through joint deliberation.

Strategy of data synthesis We aimed to compare the efficacy and safety of treatments in chemotherapy-induced thrombocytopenia patients by combining all available direct and indirect evidence which was reported as odds ratio (OR), mean difference (MD) and corresponding 95% credible intervals (Crl). Final evaluation of treatment modality ranking in combination with the surface under the cumulative ranking curve (SUCRA) and the probability of being the best (Prbest) results.
Network plots were generated to indicate direct or indirect comparison of different treatments using Stata (version 17.0). Paired meta-analyses were performed for two and more head-to-head comparisons, applying I2 in visual forest plots to assess heterogeneity between studies, all of which were performed by R software (4.3.2). I2 values 50% were considered indicative of low, medium, and high heterogeneity, respectively.
A Bayesian network meta-analysis of treatments for CIT patients was conducted using a Markov chain Monte Carlo simulation with the Gemtc package in R software. We used a fixed-effects consistency model and non-informative uniform and normal prior distributions. 20000 iterations were generated for each outcome, including 5,000 burn-ins and a thinning interval of 1. Trace plots and the Brooks-Gelman-Rubin statistic were used to assess convergence (Figure S1), and was considered reached once a stable equilibrium distribution was achieved. After confirming convergence, the model parameters' posterior distributions were obtained.
Within a Bayesian framework, the network meta-analysis ranks the treatments by Computing the surface under the cumulative ranking curve (SUCRA), with scores ranging from 0 to 1, where 1 indicates the best treatment.
We employed the OR and MD with 95% CI, using a fixed-effects model as a conservative estimate. To evaluate global inconsistency, We compared the fit between the consistency and inconsistency models. Publication bias was assessed using a comparison-adjusted funnel plot.

Subgroup analysis In terms of adverse events, data from 6 studies indicated similar rates between the TPO-RA and placebo groups (OR =1.44; 95% CI: 0.79-2.62; p >0.05), though rhIL-11 was associated with a significantly higher rate of adverse events than placebo (OR =4.26; 95% CI: 3.07-5.91; p >0.05).

Sensitivity analysis Method: Sensitivity analysis was performed to test the robustness and reliability of the results. This analysis involved excluding trials identified as sources of heterogeneity, based on a decrease in I^2 following their exclusion. We also tested heterogeneity by changing the model.
Result: To evaluate the robustness and reliability of the results, a sensitivity analysis was conducted by excluding the studies by Amgen Inc. (2009) and Winer (2017) on bleeding events. The results showed that Eltrombopag was ranked as the best treatment for bleeding, with a SUCRA value of 54.4, followed by avatrombopag (49.8) and romiplostim (24.4) . Sensitivity analysis using an inconsistency model showed that eltrombopag still had a significant advantage over placebo in terms of platelet nadir (SMD=-37.82, 95% CI: -62.93 to -12.71). Bayesian ranking probability analysis indicated that eltrombopag was most likely to rank first in increasing the platelet nadir (SUCRA = 80.8), followed by mIL-11 (SUCRA=64.5), rhIL-11 (SUCRA=61.0), and avatrombopag (SUCRA=54.7), with rhTPO ranked last (SUCRA=32.4).

Country(ies) involved China.

Keywords chemotherapy-induced thrombocytopenia, meta-analysis, eltrombopag, romiplostim,interleukin-11, Avatrombopag, mIL-11, rhTP.

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