ISSN: 2664-9640

Research on the Recombinant Human Thrombopoietin in the treatment of Thrombocytopenia Caused By Tumor Chemotherapy: A meta-analysis

REYILA ABUDUROUSULI [1], Tianxiang Luo [2], Rucheng Liu[1], Zihan Xu [1],

Xiaoxue Zhang [1], Xiaoyang Liu [1], Yundi Zhang [3]

[1] Shandong University, school of clinical medicine. Jinan, China

[2] Anzhen hospital, Peking, China

[3] National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China

Corresponding author: Yundi Zhang, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 641179040@qq.com.

Abstract

Background: Chemotherapy is one of the most basic and effective treatment methods for cancer. However, the huge adverse reactions caused by chemotherapy render patients who cannot tolerate it always put the treatment to an end. Recombinant human thrombopoietin (rhTPO) is a cytokine that stimulates the growth, differentiation and maturation of megakaryocytes. In recent years, the application of recombinant human thrombopoietin (rhTPO) has gradually developed. However, the efficacy and treatment-related adverse reactions of recombinant human platelets have not been determined. Thus we conducted this meta-analysis to observe the efficacy and side effects of rhTPO in the treatment of chemotherapy-induced thrombocytopenia. Methods: We systematically searched all available controlled trials in the following databases: EMBASE, PubMed, Web of Science , The Cochrane Library,Wanfang Library and Wei Pu to find potentially eligible studies.Primary outcomes were as follows:Duration of platelet count less than $50*10^9$,duration of platelet count less than $75*10^9$,duration of platelet count less than$100*10^9$,platelet count in day 3,day 7,day 11,day 15,day 19and day 23. Results: We searched 83 articles, removed 15 duplicate articles, 8 reviews, and finally selected 9 eligible articles. In our findings,the administration of rhTPO can yield better outcomes than placebo or IL-11.The days with platelet count < $50 * 10^9$ / L and days for platelet recovering ＞$75 * 10^9$ / L or ＞$100*10^9$ / L were shorter to a different degree.We analyzed platelet count in patients of both groups from day 3 to day 23.Moreover, the most commonly seen adverse events included diizziness and chill, but they were not severe.

Keywords

Recombinant human thrombopoietin (rhTPO), thrombocytopenia, chemotherapy, cancer.

1. Introduction

Cancer is an evolving problem and novel treatments are constantly being developed; however, patients with cancer still experience significant morbidity and mortality not only from the disease itself, but also from complications arising from our therapies. Chemotherapy is one of the most widely used regimens in clinic. According to recent studies, bone marrow suppression

ISSN: 2664-9640

is one of the most common side effects of anti-tumor chemotherapy drugs, among which thrombocytopenia lies in the second place ranking after neutropenia. Thrombocytopenia, an abnormally low blood platelet count, can potentially complicate surgical procedures and lead to chemotherapy dose delays, dose reductions, or discontinuation, which may result in suboptimal patient outcomes, and chemotherapy induced thrombocytopenia increases the likelihood of serious bleeding events, which may result in hospitalization. Hematologic complications of cancer have been well documented to impair quality of life, increase the rate and severity of medically significant complications, and even lead to death. While chemotherapy-related anemia and neutropenia are often adequately managed by judicious use of currently available hematopoietic growth factors, thrombocytopenia remains a significant contributor to morbidity and mortality in patients with this disease

Although platelet transfusions remain the "gold-standard" for the acute management of severe thrombocytopenia, there are many resource issues and possible complications associated with their use. Nowadays, molecular targeting of novel therapies has the promise of inducing very specific biologic effects. Over the past 2 decades, a number of hematopoietic growth factors with thrombopoietic activity have been identified, including recombinant granulocyte-macrophage colony-stimulating factor (GMCSF); stem cell factor (c-kit ligand or steel factor); interleukin 1(IL-1), IL-3, IL-6, and IL-11; and thrombopoietin (TPO).

The mature TPO protein consists of 332 amino acids, among which the 153 amino acids at the amino end of rhTPO can regulate the formation of megakaryocytes in all stages. It can obviously stimulate platelet production, increase peripheral platelet count, and has no effect on its morphology and function. Some investigators have alternatively suggested that local production of TPO by bone marrow stromal cells is increased during thrombocytopenia and stimulates megakaryocyte growth.

2. Methods

2.1. literature Search

This meta-analysis adheres to the guidelines provided by the PRISMA report and the EQUATOR Network. Relevant studies published between 2000and 2018 were selected by searching Embase, PubMed, Cochrane and Web of Science. The complete search used for PubMed was: ((Randomized Controlled Trials [Title/Abstract]) AND (((Thrombopenia[Title/Abstract]) OR Thrombopenias [Title/Abstract]) OR Thrombocytopenia [Title/Abstract])) AND (((((((Megakaryocyte Colony Stimulating Factor [Title/Abstract]) OR (Megakaryocyte Growth [Title/Abstract] AND Development Factor)) OR Thrombocytopoietin[Title/Abstract]) OR mpl Ligand[Title/Abstract]) OR Myeloproliferative Leukemia Virus Oncogene Ligand[Title/Abstract]) OR MGDF Factor[Title/Abstract]) OR Thrombocytopoiesis Stimulating Factor[Title/Abstract]).We considered all potentially eligible studies for review.

2.2. Study selection and data extraction

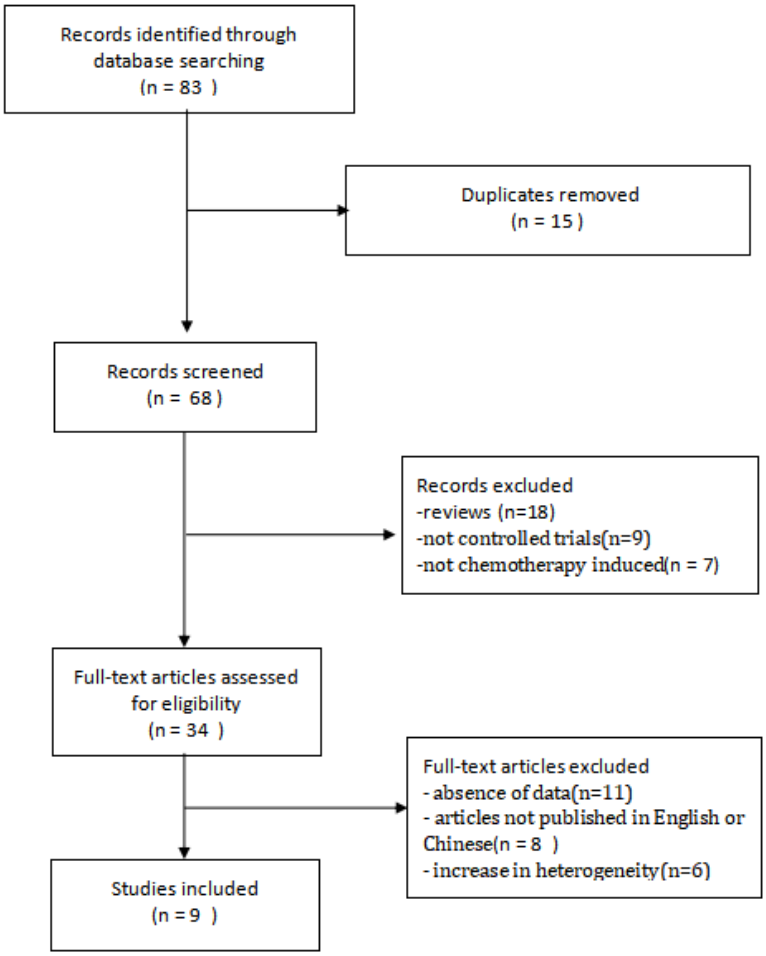
We regarded studies as eligible for inclusion which were prospective clinical trials in patients underwent chemotherapy, studies that used placebo or IL-11 as control groups. Moreover, eligible studies should include the following outcomes: Duration of platelet count less than $50*10^9$,duration of platelet count less than $75*10^9$, duration of platelet count less than$100*10^9$, platelet count in day 3,day 7,day 11,day 15,day 19and day 23 after the administration of rhTPO.

Exclusion criteria were as follows: not controlled trials, the absence of data and the increase in heterogeneity, articles not published in either English or Chinese. Any discrepancies were resolved by discussion.

Detailed reviews of full-text articles on research design, baseline characteristics, outcomes and toxicity were independently completed by ( ) and (.) The outcomes reported in the

ISSN: 2664-9640

articles, including publication year, author's name, study design, number of patients, median age, number of male patients, type of cancer, Duration of platelet count less than $50*10^9$, duration of platelet count less than $75*10^9$, duration of platelet count less than$100*10^9$, platelet count in day 3,day 7,day 11,day 15,day 19and day 23 after the administration of rhTPO, were obtained from each included study.



2.3. Statistical analysis

We assessed the clinical effect of rhTPO on the following outcomes: Duration of platelet count less than $50*10^9$,duration of platelet count less than $75*10^9$, duration of platelet count less than$100*10^9$, platelet count in day 3,day 7,day 11,day 15,day 19and day 23 after the administration of rhTPO.

We analyzed them as continuous variables and reported absolute differences on the therapeutic effect between rhTPO groups and control groups. Pooled estimates of mean differences was also calculated by using a random-effects model. Moreover, the possibility of publication bias was taken into consideration by constructing a funnel plot.$P<0.05$ was considered as statistically significant outcomes. We did I^2 testing to assess the heterogeneity between studies, with values greater than 50% considered as moderate-to-high heterogeneity.

ISSN: 2664-9640

TABLE 1 Baseline characteristics

Author	Year	No. patinets	Male,no.(%)	Median age	Type of cancer	Study design	Intervention	
							Control	Experimental
HUANG letian	2016	9	4 (44.4)	52.2	non small cell lung cancer	randomized controlled study	placebo	rhTPO administration
HUANG letian	2016	9	7 (77.8)	54.9	non small cell lung cancer	randomized controlled study	placebo	rhTPO administration
HUANG letian	2016	9	6 (66.7)	58.2	non small cell lung cancer	randomized controlled study	placebo	rhTPO administration
XUE Jun	2007	51	32 (62.7)	61	cancer	self controlled study	placebo	rhTPO administration
CHEN Xiequn	2004	10	10 (52.6)	43.3	cancer	self controlled study	placebo	rhTPO administration
Saroj Vadhan-Raj	2000	27	—	—	gynecologic cancer	self controlled study	—	rhTPO administration
Saroj Vadhan-Raj	2000	27	—	—	gynecologic cancer	self controlled study	—	rhTPO administration
SUN Shao-qin	2018	110	68 (61.8)	—	blood cancer	randomized controlled study	IL-11	rhTPO administration
XU Weiwei	2016	125	73 (58.4)	54.5	cancer	randomized controlled study	IL-11	rhTPO administration
WEI Yang	2017	76	40 (52.6)	55	cancer	randomized controlled study	IL-11	rhTPO administration
ZHOU Jianwei	2008	90	25 (55.6)	56	cancer	randomized controlled study	IL-11	rhTPO administration
LU Shiyun	2013	45	25 (55.6)	—	blood cancer	randomized controlled study	IL-11	rhTPO administration

3. Results

We searched 83 articles, removed 15 duplicate articles, 8 reviews, and finally selected 9 eligible articles. We included in the systematic review and meta-analysis a total of 12 clinical trials involving the group of patients treated with rhTPO and the group receiving placebo or IL-11,comprising 8 randomized controlled trial and 4 self-controlled study .Among the 8 RCTs,5 of them were regarding placebo as control group, the other 5 were IL-11. The characteristics of them were described in Table 1, and the summary of outcomes was presented in Table 2. All participants(n=588) in 12 studies were diagnosed with malignant cancer and underwent chemotherapy. The baseline characteristics were shown in table 1.

3.1. Duration of platelet count less than $50*10^9$

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
HUANG letian 2016	0.4	0.9	9	3.7	2.9	9	10.8%	-1.46 [-2.53, -0.39]
HUANG letian 2016'	1.7	2.6	9	3.7	2.9	9	10.9%	-0.69 [-1.65, 0.27]
HUANG letian 2016"	1.6	2.3	9	3.7	2.9	9	10.9%	-0.76 [-1.73, 0.20]
Saroj Vadhan-Raj 2000	6	1	11	8	1	16	10.9%	-1.94 [-2.89, -0.99]
Saroj Vadhan-Raj 2000'	3	1	11	5	1	16	10.9%	-1.94 [-2.89, -0.99]
WEI Yang 2017	2.21	1.12	38	3.97	1.75	38	11.5%	-1.19 [-1.68, -0.70]
XU Weiwei 2016	6.6	1.7	65	3.8	1.3	60	11.5%	1.83 [1.41, 2.25]
XUE Jun 2007	2.83	2.3	51	5.58	5.3	51	11.5%	-0.67 [-1.07, -0.27]
ZHOU Jianwei 2008	2.8	0.3	45	4.5	0.3	45	11.0%	-5.62 [-6.55, -4.68]
Total (95% CI)			**248**			**253**	**100.0%**	**-1.36 [-2.63, -0.09]**

Heterogeneity: Tau² = 3.63; Chi² = 262.47, df = 8 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.09 (P = 0.04)

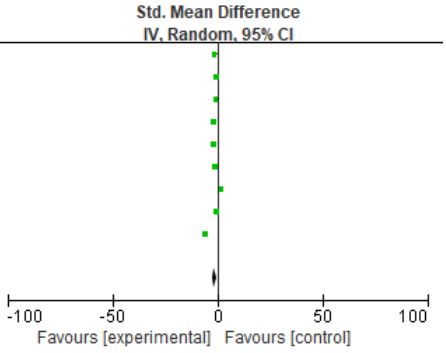


Figure 1 Forest plot of duration of platelet count less than $50*10^9$

TABLE 2 Comparison of platelet count after chemotherapy

Author	Duration of platelet count less than $50*10^9$				Duration of platelet count up to $75*10^9$				Duration of platelet count up to $100*10^9$			
	Experimental		Control		Experimental		Control		Experimental		Control	
	Average	SD	Average	SD	Average	SD	Average	SD	Average	SD	No.events	SD
HUANG letian	0.4	0.9	3.7	2.9	5.9	3.9	13.8	2.6	12.8	5.7	18.6	3
HUANG letian	1.7	2.6	3.7	2.9	9.5	3.3	13.8	2.6	14.6	3.2	18.6	3
HUANG letian	1.6	2.3	3.7	2.9	10.4	4.2	13.8	2.6	15.4	4.2	18.6	3
XUE Jun	2.83	2.3	5.58	5.3	10.66	4.55	19.33	8.72	13	4.22	23.41	8.3
Saroj Vadhan-Raj	6	1	8	1	—	—	—	—	23	1	25	1
Saroj Vadhan-Raj	3	1	5	1	—	—	—	—	20	2	20	2
SUN Shao-qin	—	—	—	—	—	—	—	—	—	—	—	—
XU Weiwei	6.6	1.7	3.8	1.3	—	—	—	—	9.5	2.4	6.5	1.8
WEI Yang	2.21	1.12	3.97	1.75	4.83	2.29	7.33	2.93	6.84	3.52	9.11	4.08
ZHOU Jianwei	2.8	0.3	4.5	0.3	—	—	—	—	13	4.2	18.4	4.3

Data were available from 9 of 12 studies, including 248 patients in the experimental group and 253 patients in the control group(table 2). Forest plots showed that the rhTPO group had a 55% lower duration of platelet count less than $50*10^9$. (SMD=-1.36 , 95% CI: [-2.63,-0.09], I^2=97%, P=0.04) (Figure 1).We also did funnel test to assess the publication bias .According to the funnel plot,)the publication bias was not obvious, and the difference in duration of platelet count less than $50*10^9$ was statistically significant(p=0.04).

ISSN: 2664-9640

3.2. Duration of platelet count less than $75*10^9$

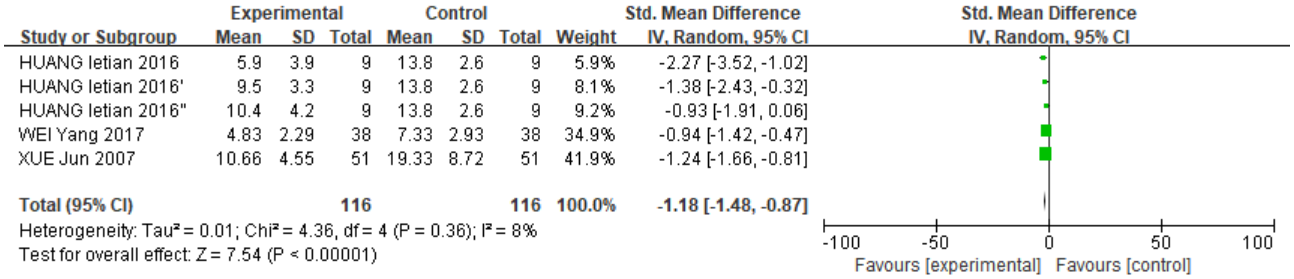


Figure 2 Forest plot of duration of platelet count less than $75*10^9$

We also obtained duration of platelet count less than $75*10^9$ from 5 of 12 studies, including 116 patients in the experimental group and 116 patients in the control group. Forest plots showed that the rhTPO group had a lower duration of platelet count less than $75*10^9$. (MD=-1.18 , 95% CI: [-1.48,-0.87], I^2=8%, P＜0.0001) (Figure 2).and the difference in duration of platelet count less than $75*10^9$ was statistically significant(p＜0.0001).

3.3. Duration of platelet count less than $100*10^9$

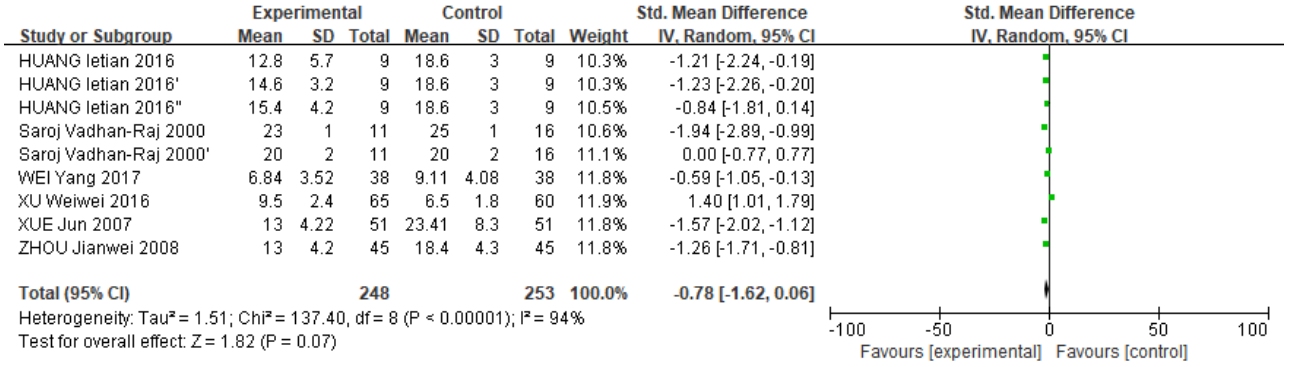


Figure 3 Forest plot of duration of platelet count less than $100*10^9$

The duration of platelet count less than $100*10^9$ was obtained from 9 studies with 248 patients from experimental groups and 253 patients from control group involved. Forest plots showed that the rhTPO group had a lower duration of platelet count less than $100*10^9$. (SMD=-0.78 , 95% CI: [-1.62,0.06], I^2=94%, P=0.07) (Figure 3).However, the difference in duration of platelet count less than $100*10^9$ was not statistically significant(p=0.07).

3.4. Comparison of recovery time of platelet count after chemotherapy

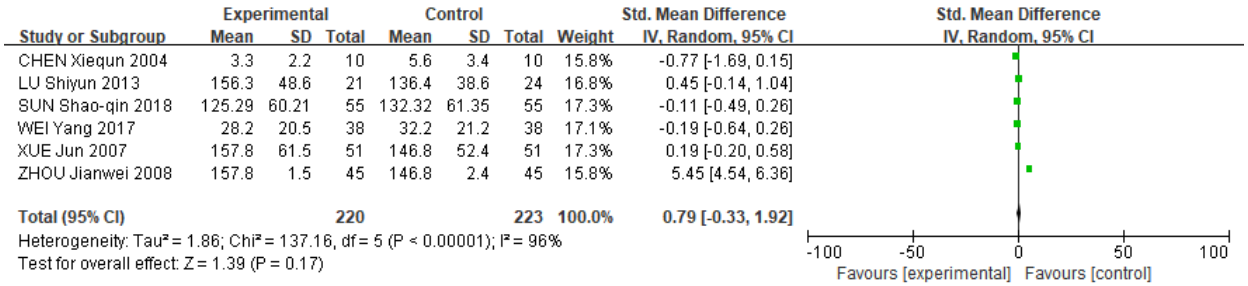


Figure 4 Forest plot of original platelet count

ISSN: 2664-9640

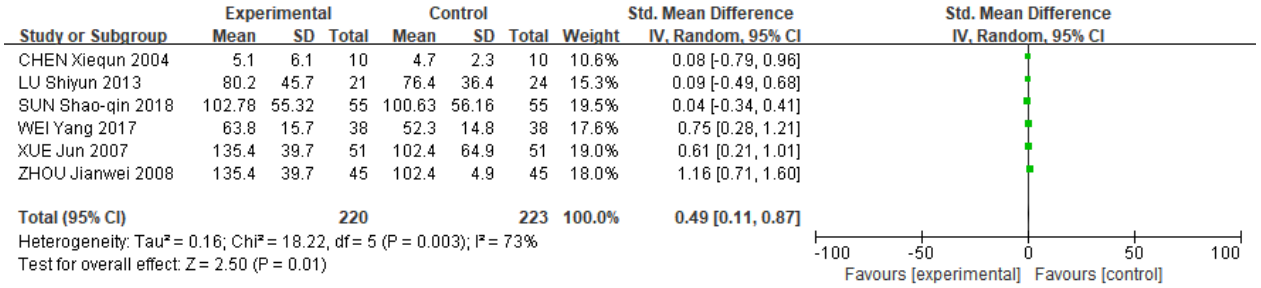


Figure 5 Forest plot of platelet count in day 3

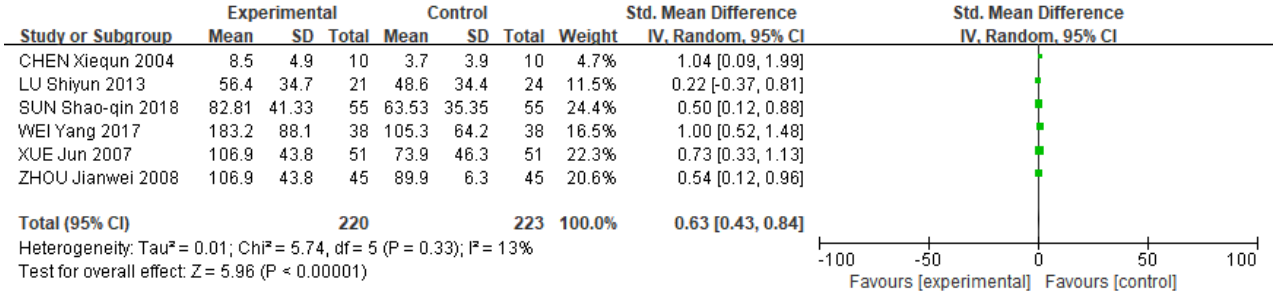


Figure 6 Forest plot of platelet count in day 7

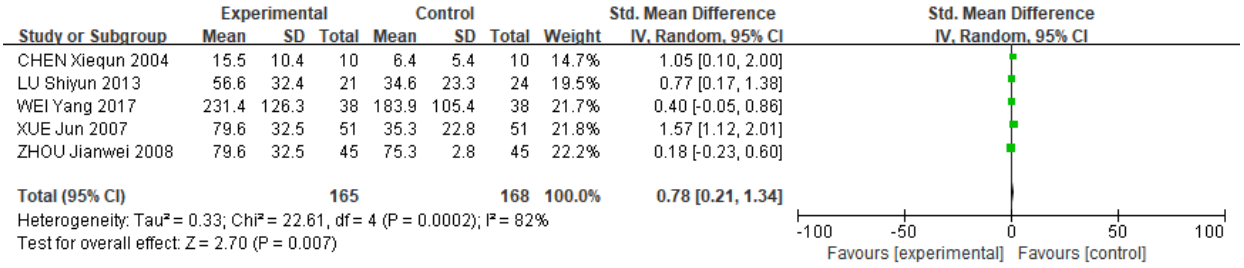


Figure 7 Forest plot of platelet count in day 11

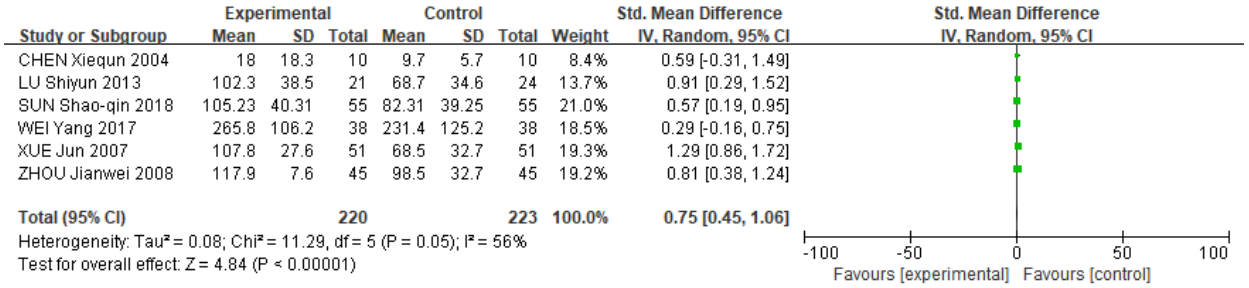


Figure 8 Forest plot of platelet count in day 15

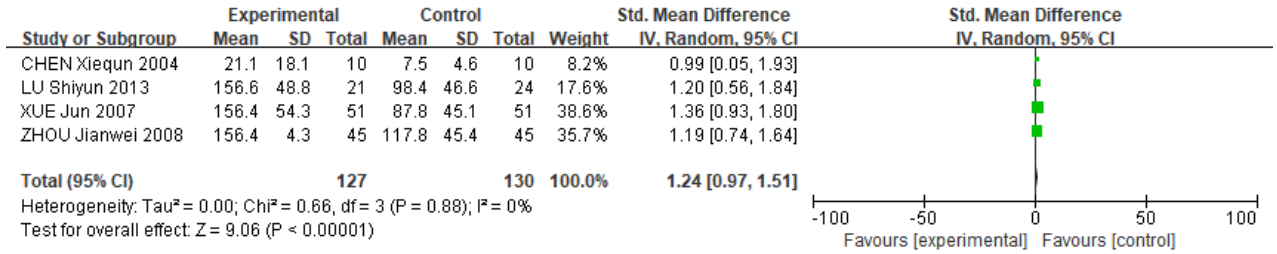


Figure 9 Forest plot of platelet count in day 19

ISSN: 2664-9640

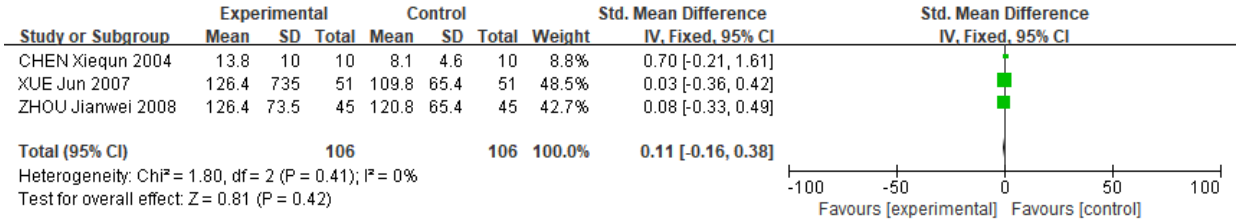


Figure 9 Forest plot of platelet count in day 23

In the pooled analysis of original platelet count in both groups, the difference was not statistically significant(p=0.17)(figure 4). The follow-up studies indicated that the administration of rhTPO increase the platelet count in patients underwent chemotherapy compared with those who were given placebo or IL-11.Forest plot showed platelet count in day 3 had an 49% increase in the experimental group(SMD=0.49 ,95%CI:[0.11,0.87], I^2=73%, P=0.01), in day 7 the platelet count had an 63% increase in the experimental group(SMD=0.63,95%CI:[0.43, 0.84],I^2=13%, P＜0.00001） ,in day 11 a clear trend of increase can also be observed(SMD=0.78,95%CI:[0.21,1.34],I^2=82%, P=0.007),in day 15 the platelet count had an 75% increase in the experimental group(SMD=0.75,95%CI:[0.45, 1.06],I^2=56%, P ＜ 0.00001),in day 19 the platelet count had an 124% increase in the experimental group(SMD=1.24,95%CI:[0.97, 1.51],I^2=0%, P＜0.00001),in day 23 the platelet count had an 11% increase in the experimental group(SMD=0.11,95%CI:[-0.16, 0.38],I^2=0%, P=0.42).Notwithstanding the platelet count in day 23 showed no statically significance difference in experimental group and control group, other data showed statistically significant difference. In total, the administration of rhTPO had protective effect to patients underwent chemotherapy and significantly increase the platelet count(figure 10)

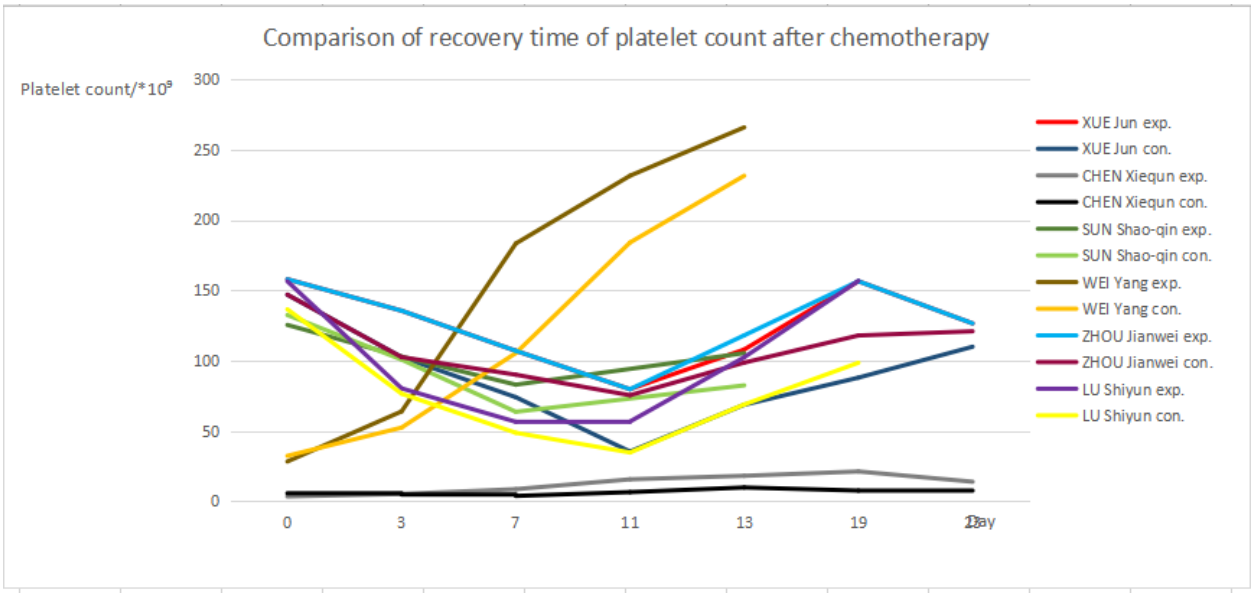


Figure 10 Comparison of recovery time of platelet count after chemotherapy

3.5. Publication bias

The publication bias was assessed by constructing funnel plots. For outcomes such as platelet count in day 23, publication bias was not assessed due to the small number of studies analyzed. In the results of Egger's test of other data, publication bias was not observed. Above all, this meta-analysis was at low risk for reporting bias.

ISSN: 2664-9640

3.6. Treatment related adverse events

According to all the eligible studies, the most commonly seen adverse events of rhTPO were chill, fatigue, muscle pain and loss of appetite. However, those adverse events were considered as mild reactions because after many patients received symptomatic treatment, the adverse reactions were relieved.

4. Discussion

Bone marrow suppression after chemotherapy is one of the main causes of cancer patients' death, and it is also an important factor of limited dose of chemotherapy. Thrombocytopenia caused by myelosuppression has been a problem that has not been solved well in clinical practice. PLT suspension infusion can decrease the occurrence of complications, but its effect is limited. Antibodies will be produces after repeated platelet infusion ,which reduces the effectiveness of platelet transfusion and increases the probability of platelet transfusion complications and blood borne diseases. Studies have found that rhTPO can reduce the degree of thrombocytopenia in cancer patients after chemotherapy, shorten the duration of thrombocytopenia, and accelerate the recovery of platelets to normal level. Therefore, the application of rhTPO is of great clinical significance to overcome the shortcomings of platelet transfusion and reduce the cost of treatment and mortality.

Our study found a positive effect of recombinant human thrombopoietin on thrombocytopenia caused by chemotherapy. From our findings, the application of rhTPO greatly shortens the duration of platelet number recovery, and significantly improves the number of platelets during treatment, which were statistically significant. The results suggested that rhTPO can make the patients with decreased platelet count return to normal or get better faster after chemotherapy.

Above all, our findings showed an overall benefit clinical effect of rhTPO and the use of rhTPO clinically could be expanded. Therefore, we conducted further study of treatment related adverse events in experimental and control group. We found that the most common adverse events were chill, fatigue, muscle pain and loss of appetite, however, the incidence of them was not obvious.

There were several limitations existing in this meta-analysis. First, a similar meta-analysis had been done and published in china. Second, the total number of patients and trials were not large enough. There were only 13 trials and 588 of patients were involved ,limiting the analysis in our study. Third, the heterogeneity was relatively high in some outcomes, which might be resulted from the different arrangement of control groups. Moreover, the exact incidence of adverse events was not obtained due to lack of data .

Although similar meta-analysis has been done in China and several limitations existed in our meta-analysis, this study is comprehensive in terms of patients and perspectives, and we have conducted data analysis for each outcome systematically. In conclusion, our study provides an effective scheme for clinical treatment of thrombocytopenia and can be an important way to reduce the adverse reactions caused by chemotherapy.

References

[1] Li Xiaoye. Clinical study of recombinant human thrombopoietin in the treatment of thrombocytopenia after chemotherapy [J]. Electronic Journal of clinical medicine, 2019,6 (57): 70.

[2] Zhou Liyun. Comparative observation on the therapeutic effect of recombinant human thrombopoietin and interleukin-11 on thrombocytopenia after chemotherapy in leukemia [J]. Electronic Journal of clinical medicine, 2019,6 (15): 56.

[3] Wan Yunyan. Efficacy and safety analysis of recombinant human thrombopoietin in the treatment of thrombocytopenia after chemotherapy in leukemia [J]. World composite medicine, 2019,5 (2): 151-153.

[4] Zhao horizontal, Jin Jie. Effect of rhTPO on thrombocytopenia after chemotherapy in acute leukemia [J].

Shenzhen Journal of integrated traditional Chinese and Western medicine, 2019,29 (1): 179-180.
[5] Wei Li. Clinical efficacy of recombinant human thrombopoietin in the treatment of thrombocytopenia after chemotherapy in acute leukemia [D]. Qingdao University, 2017:.
[6] Pan Jia, Miao Dong, Li Guojie. Effect of recombinant human thrombopoietin on leukocyte count and inflammatory factors in patients with thrombocytopenia after chemotherapy [J]. Sichuan Journal of Physiological Sciences, 2019,41 (2): 117-119.
[7] Liu Fangyuan, Guo Jianmin, Liu Manman, Sun Kai. Effect of recombinant human thrombopoietin on thrombocytopenia after chemotherapy in elderly patients with acute myeloid leukemia [J]. Chinese Journal of practical medicine, 2019,46 (9): 96-98.
[8] Chen Yanhong. Randomized controlled study of rhTPO and rhIL-11 in the treatment of thrombocytopenia after chemotherapy in acute leukemia [J]. Chinese and foreign medical research, 2019,17 (14): 47-48.
[9] Sun Shaoqin. Efficacy of recombinant human thrombopoietin in the treatment of thrombocytopenia caused by chemotherapy of blood tumor [J]. Clinical blood transfusion and test, 2018,20 (6): 632-635.
[10] Wu Yan, Liu Xiaojuan, Wang Hui. Efficacy and safety analysis of recombinant human thrombopoietin in the treatment of thrombocytopenia after chemotherapy in leukemia [J]. Inner Mongolia Medical Journal, 2017,49 (12): 1461-1462.
[11] Dong Zhigao, Chen Xuyan, Su junnan, Li Hua, Xiao Pingping, Fan Wei. Comparison of rhTPO and IL-11 in the treatment of severe thrombocytopenia after chemotherapy in elderly leukemia [J]. Xinjiang Medical Journal, 2018,48 (6): 643-644658.
[12] muhebai Abdur, Liu Hong. Clinical observation of recombinant human thrombopoietin in the treatment of thrombocytopenia after chemotherapy in acute leukemia [J]. Thrombosis and hemostasis, 2017,23 (4): 616-617620.
[13] Hu Xiaoliang. Research progress in the treatment of thrombocytopenia caused by chemotherapy-related drugs of leukemia [J]. Chinese new clinical medicine, 2017,10 (5): 488-490.