The efficacy and safety of endostar combined gemcitabine and cisplatin in the treatment of non-small cell lung cancer: a meta-analysis

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Abstract

To determine the efficacy and safety of Endostar combined with gemcitabine and cisplatin in the treatment of NSCLC, and provide evidence-based reference for clinical drug use. Retrieved from Cochrane Library, PubMed, Embase, ClinicalTrials, CNKI, Wanfang and VIP database, randomized controlled trials (RCT) were collected. Pooled standard mean differences (SMD) and 95% confidence intervals (CI) were analyzed using R software with a random-effects model. Data from a total of 27 RCTs were included, involving 1646 patients were analyzed. Results of meta-analysis showed that response rate and clinical benefit rate of trial group were significantly higher than those of control group. There was no statistical significance in the incidence of leucopenia, thrombocytopenia and gastrointestinal reaction between 2 groups. The results showed that Endostar combined with gemcitabine and cisplatin may generally improve therapeutic efficacy of NSCLC patients, without increasing the incidence of adverse reactions.

Keywords: endostar; gemcitabine; cisplatin; non-small cell lung cancer; meta-analysis.

Practical Application: Therapeutic efficacy of Endostar combined with gemcitabine and cisplatin on NSCLC patients.

1 Introduction

Lung cancer is one of the most common malignant tumors in the world, and it is a serious threat to human life and health (Mao et al., 2016; Khan et al., 2020). Moreover, non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of lung cancer (Siegel et al., 2016; Zhou et al., 2020). Because the early clinical symptoms of NSCLC are not that obvious, most patients are at the advanced stage when they seek medical consultations, and miss the opportunity of taking surgical resection (Sathiakumar et al., 2013). At present, the treatment of NSCLC is mainly chemotherapy, but the efficacy of chemotherapy is not good enough and various complications are prone (Hanna et al., 2014). However, targeted anti-tumor drugs have become one of the research hot spots in recent years. Among these targeted anti-tumor drugs, endostar is recognized as the best targeted drug for inhibiting tumor angiogenesis (Xu et al., 2014). Endostar is an endogenous angiogenesis inhibitor which was first isolated and purified from cultured mouse endothelial cell tumor supernatant by O'reilly MS at the end of the last century (O'Reilly et al., 1997). Endostar is able to inhibit tumor spread, prolong the survival time and improve the quality of life of cancer patients6. Researchers believe that endostar combined with chemotherapy may become an effective measure in treating tumors (Fu et al., 2009). In China, independently developed endostar has been approved for marketing by the former State Food and Drug Administration (SFDA) in 2005, combining with chemotherapy for clinical use in NSCLC. What's more, endostar is the first category of new anti-tumor drugs in biological products (Moschos et al., 2007;

Navarro-Peraza et al., 2020). Nevertheless, Studies have shown that the effectiveness, tolerability and adverse reactions of endostar combined with chemotherapy still remain controversial (Zhou et al., 2020; Sathiakumar et al., 2013; Hanna et al., 2014; Xu et al., 2014). Therefore, in this study, we systematically evaluated the efficacy and safety of Endostar combined with gemcitabine and cisplatin in the treatment of NSCLC by meta-analysis, providing evidence-based references for clinical use.

2 Methods

2.1 Selection criteria

Study type

Researchers will include all the RCTs of endostar combined gemcitabine and cisplatin in the treatment of non-small cell lung cancer. While others, such as non-RCTs, animal studies, case reports, will be excluded.

Participants

Regardless of gender, ages, nationalities and educational status, the patients with NSCLC will be included. The included participants should be diagnosed with NSCLC from cytological diagnosis, pathological diagnosis or clinical diagnosis based on the past or current diagnosis standards or guidelines of NSCLC, such as New Standard for Diagnosis and Treatment of Malignant Tumors, which is formulated by China Cancer Association.

2.2 Exclusion criteria

Those who meet with the criteria given below will be excluded: 1) Jadad scale rated 0 or non-RCT literature; 2) duplicate publications; 3) purely descriptive research; 4) documents in the literature that cannot be extracted; 5) animal experiment.

2.3 Interventions

Experimental interventions

Based on routine treatment, patients in the control group were given gemcitabine and cisplatin. While patients in the trial group were given endostar on the basis of treatment in the control group.

Outcome measures

The primary outcome measure will be the efficacy of endostar combined gemcitabine and cisplatin in treating NSCLC. The secondary outcome measures will be 1) clinical benefit rate; 2) incidence of leukopenia; 3) incidence of thrombocytopenia; 4) incidence of gastrointestinal reactions. Efficacy criteria are divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009).

2.4 Information sources

Search strategy and identification of studies

Related literatures published from inception to October 2019, will be retrieved from the following databases: Cochrane Library, Embase, PubMed, four Chinese databases (Chinese National Knowledge Infrastructure, Chinese Science and Technology Periodicals Database, Chinese BioMedical Database and Wanfang Database). The search terms will be 'Rh-endostatin', 'Endostatin', 'Recombinant human endostatin injection', 'GP Regimen', 'Gemcitabine', 'Cisplatin', 'NSCLC', 'Non-small cell lung cancer', 'Endu', 'Chongzurenxueuguanneipiyizhisu', 'GP fangan', 'Jixitabin', 'Shunbo', 'Feixiaoxibaofeiai'. In Chinese databases, we will use the corresponding translations of these search terms to perform electronic searches. Detailed search strategy is shown as Table 1.

Other resources including references list of anteriorly published reviews and relevant conference proceedings will be searched for potential eligible studies.

The reviewers (H.S.C) will scan full articles independently. When divarication generates during the course and cannot be solved through discussion between two reviewers, the third reviewer (W.Y.X) will be consulted for arbitration.

Selection of studies

The articles with repeated results, unclear outcome data or unavailable related information, will be excluded. The reviewers (W.L.) will review titles and abstracts to select potential eligible literature and scan full articles to select the literature which can conform to the inclusion criteria, independently. A third reviewer

(W.Y.X) will solve the disagreement between two reviewers. Endnote V.X7 will be utilized for literature managements and duplication removals.

Data extraction and management

The reviewers (G.J) will independently extract data by using a data extraction sheet. The data will include the following items: general information (first author and publication year), study design, randomization methods, allocation concealment, blind method, inclusion and exclusion criteria of participants, participant's characteristics (sex, age, and duration of disease), sample size, interventions, primary and secondary outcomes, outcome assessment methods, side effects, and follow-up. Any disagreements will be discussed by the reviewers to reach consensus, and if necessary, it will be consulted with the third reviewer.

Addressing missing data

Researchers will contact with the original authors by telephone or email to request incomplete or missing data when necessary. If the information cannot be supplemented sufficiently in this way, researchers will abandon it. The potential impact of missing data will be considered in the discussion section.

Risk of bias in included studies

For assessing the risk of bias, researchers will utilize Cochrane collaboration's tool, which contains the following domains: generation of random sequence, allocation concealment, blinding method of participants, blinding method of outcome assessors, selective outcome reporting, incomplete result and other bias. In order to describe the risk of bias in each study clearly, researchers will categorize the risk into unclear, low or high (Zhu et al., 2016). The Jadad scale was used to evaluate the quality of the included studies, including the generation of random sequences (2 points appropriate, 1 point unclear, and 0 point inappropriate), randomized hiding (2 points appropriate, 1 point unclear, and 0 points inappropriate), blind method (2 points appropriate, 1 point unclear, 0 points inappropriate), withdrawal and withdrawal (1 point described, 0 points not described). 0 to 3 are regarded as low quality studies, 4 to 7 are regarded as high quality studies (Haynes et al., 2006).

2.5 Statistical analysis

Data synthesis and analysis

Rev Man 5.3 software will be performed to analyze the data we obtained. We will calculate standard mean difference with 95% CIs for continuous outcomes and risk ratios (RRs) with 95% CIs for dichotomous outcomes.

For assessing the heterogeneity, a fixed effect model is used for analysis. otherwise, a random effect model is used for analysis. Sensitivity analysis is applied for assessing the stability of the results. Post-funnel plots, Begg's and Egger's tests (the latter two using Stata 12.0 software) are used for publication bias analysis. $P < 0.05$ is considered statistically significant.

Table 1. Basic characteristics and quality evaluation of included literatures.

Included trails	Pathological staging	Course, d	Intervention Control group	Intervention Trial group	Sample size Control group	Sample size Trial group	Age mean (SD) (years) Control group	Age mean (SD) (years) Trial group	Outcome measures	Jadad 评分
Tan et al. (2013)	IIIb~IV	21	Gemcitabine(G) 1000 mg/m², intravenous injection (ij), qd, d1-8+Cisplatin (C) 25 mg/m², ij, qd, d_{1-3}	The same chemotherapy as control group+ Endostar (E) 7.5 mg/m² with 0.9% sodium chloride injection (SCI) 500 mL, intravenous injection (ij), qd, d_{1-14}	38	38	61.7 ± 9.8		①②③④⑤	3
Xie & Huang (2009)	III~IV	21	G1000 mg/m², d_1 and d_8 + C75 mg/m², ij, qd, d_{1-3}	The same chemotherapy as control group+E 15 mg with 0.9% SCI 500 mL, d_{1-14}, ij	26	22	56.5	59	①②③④⑤	2
Chen et al. (2010)	IIIb~IV	21	G 1000 mg/m², ij, d_1 and d_8+C 25 mg/m², ij, d_{1-3}	The same chemotherapy as control group+E 15 mg with 0.9% SCI 500 mL, d_{1-14}, ij	25	30	49 ± 3	50 ± 2	①②③④⑤	1
Gu et al. (2010)	IIIb~IV	21	G 1000 mg/m², d_1 and d_8+C 25 mg/m², ij, d_{1-3}	The same chemotherapy as control group+E 15 mg with 0.9% SCI 500 mL, d_{1-14}, ij	33	27	53.6		①②③④⑤	1
Guo (2010)	III~IV	21	G 1000 mg/m², ij, d_1 and d_8+C 30 mg/m², ij, d_{1-3}	The same chemotherapy as control group+E15 mg, ij, d_{1-14}	38	38	55 ± 12	53 ± 14	① ②④	2
Wei et al. (2010)	IIIb~IV	21	G1g/m², ij, d_1 and d_8+ C 30 mg/m², ij, d_{2-4}	The same chemotherapy as control group+E15 mg, qd, d_{1-14}, ij	16	16	59.8		①②③④⑤	2
Xu (2010)	IIIb~IV	36	G1000 mg/m²+C 30 mg/m²,Tumor target artery perfusion, d_1; G1000 mg/m², ij, d_8+0.9% SCI 500 mL, ij, d_{2-12}	G 1000 m g/m²+C 30 mg/m²,Tumor target artery perfusion, d_1;G 1000 mg/m², ij, d_8,E 15 mg/d+0.9% SCI 500 mL, ij, d_{2-12}	20	20	64		①②③④⑤	2
Chen et al. (2011)	III~IV	21	G1000 mg/m², ij, d_1、 d_8+C80 mg/m², ij, d_1	The same chemotherapy as control group+E 15 mg with 0.9% SCI 500 mL, d_{1-14}, ij	35	33	65	63	①②③④⑤	1
Ruan & Sun (2011)	IIIb~IV	21	G1000 mg/m², d_1 and d_8+C75 mg/m², ij, d_{1-3}	The same chemotherapy as control group+E 15 mg with 0.9% SCI 500 mL, d_{1-14}, ij	19	17	58.5		①②③⑤	1
Wang (2011)	IIIb~IV	21	G 1000 mg/m², ij, d_1 and d_8+C 75 mg/m², ij, d_1	The same chemotherapy as control group+E 15 mg with 0.9% SCI500 mL, d_{1-14}, ij	29	31	55	56	① ②	1
Zheng et al. (2011)	IV	21-28	G 1000 mg/m², ij, d_1 and d_8+d+Cisplatin 20 mg/m², intravenous injection, d_{1-5}	The same chemotherapy as control group+Endostar 15 mg/d, d_{1-14}	18	17	54.5	50.1	①②⑤	1
Chen & Yang (2012)	Not mentioned	14	Gemcitabine 1000 mg/m² wiht 0.9% Sodium chloride injection 100 mL, intravenous injection, d_1 and d_8+Cisplatin 25 mg/m² with 0.9%Sodium chloride injection 500 mL, intravenous injection, d_{2-4}	The same chemotherapy as control group+Endostar 15 mg, intravenous injection, qd, d_{1-14}	26	27	56.5 ± 7.3	55.7 ± 8.6	①②③④⑤	1
He (2012)	III~IV	21	Gemcitabine 1000 mg/m², d_1 and d_8+Cisplatin 30 mg/m², d_{2-4}	The same chemotherapy as control group+Endostar 7.5 mg/m², d_{1-14}	32	40	69.8 ± 5.5	70.5 ± 5.3	①②⑤	1

1) the efficacy of endostar combined gemcitabine and cisplatin in treating NSCLC; 2) clinical benefit rate; 3) incidence of leukopenia; 4) incidence of thrombocytopenia; 5) incidence of gastrointestinal reactions.

Table 1. Continued...

Included trails	Pathological staging	Course, d	Intervention		Sample size		Age mean (SD) (years)		Outcome measures	Jadad 评分
			Control group	Trial group	Control group	Trial group	Control group	Trial group		
Liu et al. (2012)	IIIb~IV	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 75 mg/m², intravenous injection	The same chemotherapy as control group+Endostar 15 mg, d_{1-7}, intravenous injection	30	30	56	58	①②③④⑤	2
Luan (2012)	III~IV	21	Gemcitabine 1250 mg/m², intravenous injection, d_1 and d_8+Cisplatin 75 mg/m², intravenous injection, d_1	The same chemotherapy as control group+Endostar 75 mg/m² with 0.9% Sodium chloride injection 500 mL, d_{1-14}, intravenous injection	27	25	40-67	42-68	① ②	1
Yin et al. (2012)	Not mentioned	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 30 mg/m², intravenous injection, d_{2-4}	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 500 mL, intravenous injection, qd, d_{1-4}	90	94	49.3 ± 4.5	48.3 ± 5.2	①②⑤	1
Alimujiang et al. (2013)	IIIb~IV	21	Gemcitabine 1.0 g/m² with 250 mL 0.9% Sodium chloride injection, d_1 and d_{14}, intravenous injection +Cisplatin with 500 mL 0.9% Sodium chloride injection, intravenous injection, d_{1-3}	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 500 mL, d_{1-14}, intravenous injection	40	40	59.2 ± 9.5	58.3 ± 9.6	①②③④⑤	2
Zhang (2014)	IIIb~IV	21	Gemcitabine 1000 mg/m², d_1 and d_8+Cisplatin 75 mg/m², dosing in 3 days	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 250 mL, Intravenous pumping, d_{1-9}	28	31	54	53	①②③④⑤	2
Fu et al. (2015)	IIIb~IV	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 25 mg/m², intravenous injection, d_{1-3}	The same chemotherapy as control group+Endostar15 mg with 0.9% Sodium chloride injection 500 mL, d_{1-14}, intravenous injection	28	32	55.81	56.21	①②③④⑤	2
Liu (2015)	III~IV	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 80 mg/m², intravenous injection, d_{1-2}	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 500 mL, d_{1-14}, intravenous injection	32	32		无	① ②	2
Li et al. (2016)	IIIb~IV	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 30 mg/m², intravenous injection, d_{1-3}	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 500 mL, d_{1-14}, intravenous injection	23	23	52.3 ± 10.6		①②③④⑤	3
Fang (2017)	Not mentioned	21	Gemcitabine 1000 mg/m², intravenous injection, d_1 and d_8+Cisplatin 75 mg/m², intravenous injection,used 3 days continuously	The same chemotherapy as control group+Endostar 7.5 mg/m² with 0.9% Sodium chloride injection 500 mL, qd, d_{1-14}	23	23	52	60	① ②	2
Jia et al. (2017)	IIIb~IV	21	Gemcitabine 1.0 mg/m² with 0.9% Sodium chloride injection 150 mL, intravenous injection, d_1 and d_8+Cisplatin 25 mg/m² with 0.9% Sodium chloride injection 500 mL, intravenous injection, d_{1-3}	The same chemotherapy as control group+Endostar 30 mgwith 0.9% Sodium chloride injection 110 mL, d_{1-7}	20	20	50 ± 2		①②③④⑤	2

1) the efficacy of endostar combined gemcitabine and cisplatin in treating NSCLC; 2) clinical benefit rate; 3) incidence of leukopenia; 4) incidence of thrombocytopenia; 5) incidence of gastrointestinal reactions.

Table 1. Continued...

Included trails	Pathological staging	Course, d	Intervention		Sample size		Age mean (SD) (years)		Outcome measures	Jadad 评分
			Control group	Trial group	Control group	Trial group	Control group	Trial group		
Xu & Wu (2017)	Not mentioned	21	Gemcitabine 1.0 g/m² wiht 0.9% Sodium chloride injection 250 mL, intravenous injection, d₁ and d₈+Cisplatin 30 mg/m² with 0.9% Sodium chloride injection 500 mL, intravenous injection, d₁₋₃	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 500 mL, intravenous injection, d₁₋₁₄	35	35	54.1 ± 11.3		①②③⑤	3
Song et al. (2018)	III~ IV	21	Gemcitabine 1250 mg/m², intravenous injection, d₁ and d₈+Cisplatin 25 mg/m², intravenous injection, d₁₋₃	The same chemotherapy as control group+Endostar 15 mg/m², d₁₋₇? intravenous injection	30	30	61.7	57.4	①②③④⑤	1
Wang (2018)	IIIb~IV	21	Gemcitabine 1000 mg/m² with 0.9% Sodium chloride injection 100 mL, intravenous injection, d₁ and d₂ applied Cisplatin 75 mg/m² with 0.9% Sodium chloride injection 500 mL, intravenous injection, dosing in 3 days	The same chemotherapy as control group+Endostar 15 mg with 0.9% Sodium chloride injection 250 mL, intravenous pumping, d₁₋₉	30	34	55.45	55.97	①②③④⑤	1
Zhong & Chen (2018)	Not mentioned	21	Gemcitabine 1000 mg/m² with 0.9% Sodium chloride injection 150 mL, intravenous injection, d₁ and d₈ applied Cisplatin 30 mg/m² with 0.9% Sodium chloride injection 500 mL, intravenous injection, d₁₋₃	The same chemotherapy as control group+Endostar 7.5 mg/m² with 0.9% Sodium chloride injection 100 mL, d₁₋₁₄	25	25	70.34	70.21	①②③④⑤	2

1) the efficacy of endostar combined gemcitabine and cisplatin in treating NSCLC; 2) clinical benefit rate; 3) incidence of leukopenia; 4) incidence of thrombocytopenia; 5) incidence of gastrointestinal reactions.
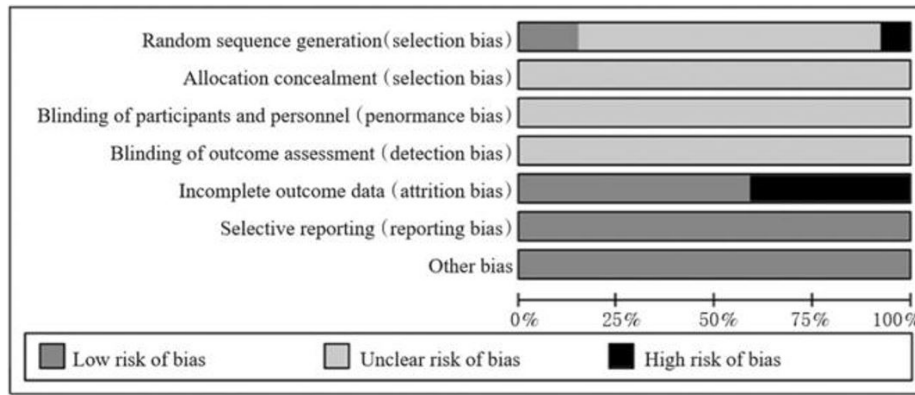
Figure 1. Bar graph of bias risk.

3 Results

3.1 Description of studies

We identified 360 potentially relevant articles, in which 317 were in Chinese and 43 were in English. After screening titles and abstracts, 81 articles were excluded owing that they were nonclinical studies, expert experience, or case reports. We reviewed the remaining 81 studies, 54 were excluded because they did not meet with our inclusion criteria. Therefore, 27 articles (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fang, 2017; Fu et al., 2015; Gu et al., 2010; Guo, 2010; He, 2012; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Liu, 2015; Luan, 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2011, 2018; Wei et al., 2010; Xie & Huang, 2009; Xu & Wu, 2017; Xu, 2010; Yin et al., 2012; Zhang, 2014; Zheng et al., 2011; Zhong et al., 2019) involving 1646 participants met our inclusion criteria, in which 830 participants were in the trial group and 816 participants were in the control group.

3.2 Study characteristics

All studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fang, 2017; Fu et al., 2015; Gu et al., 2010; Guo, 2010; He, 2012; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Liu, 2015; Luan, 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2011, 2018; Wei et al., 2010; Xie & Huang, 2009; Xu & Wu, 2017; Xu, 2010; Yin et al., 2012; Zhang, 2014; Zheng et al., 2011; Zhong et al., 2019) included are RCTs. 6 studies (Fu et al., 2015; Li et al., 2016; Song et al., 2018; Tan et al., 2013; Xu & Wu, 2017; Zheng et al., 2011) reported random methods. 8 studies (Chen et al., 2010; Chen & Yang, 2012; Fu et al., 2015; Gu et al., 2010; Luan, 2012; Wang, 2011, 2018; Zheng et al., 2011) results data are incomplete; all studies did not mention allocation concealment, blindness, and whether there are other sources of bias. Detailed characteristics of included studies are listed in Figures 1 and 2.

3.3 Assessment by meta-analysis

Efficacy assessment

Twenty-seven studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fang, 2017; Fu et al., 2015;

Figure 2. Risk of bias summary.

Gu et al., 2010; Guo, 2010; He, 2012; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Liu, 2015; Luan, 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2011, 2018; Wei et al., 2010; Xie & Huang (2009); Xu & Wu, 2017; Xu, 2010; Yin et al., 2012; Zhang, 2014; Zheng et al., 2011; Zhong & Chen, 2018) reported efficiency, and there was no statistical heterogeneity between the studies (P = 0.99, I2 = 0). Meta-analysis was performed using a fixed-effects model. Details are showed in Figure 3. Meta analysis results showed that the efficacy of patients in the trial group is significantly higher than that in the control group, and the difference is statistically significant [RR = 1.67, 95% CI (1.48, 1.89), P <0.000 01].

Clinical benefit rate

Twenty-seven studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fang, 2017; Fu et al., 2015; Gu et al., 2010; Guo, 2010; He, 2012; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Liu, 2015; Luan, 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2011, 2018; Wei et al., 2010; Xie & Huang (2009); Xu & Wu, 2017; Xu, 2010; Yin et al., 2012; Zhang, 2014; Zheng et al., 2011; Zhong & Chen, 2018) reported clinical benefit rates, and there was no statistical heterogeneity between the studies (P = 0.49, I2 = 0). Meta-analysis was performed using a fixed-effects model. Details are shown in Figure 4. Meta analysis results showed that the clinical benefit

rate of patients in the trial group was significantly higher than that in the control group, and the difference was statistically significant [RR = 1.26, 95% CI (1.20, 1.33), P <0.000 01].

Incidence of leukopenia

19 studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fu et al., 2015; Gu et al., 2010; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2018; Wei et al., 2010; Xie & Huang (2009); Xu & Wu, 2017; Xu, 2010; Zhang, 2014; Zhong & Chen, 2018) reported the incidence of leukopenia, and there was no statistical heterogeneity between the studies (P = 1.00, I2 = 0). We applied a fixed-effects model for meta-analysis. Details are shown in Figure 5. Meta analysis results showed that there was no significant difference in the incidence of leukopenia between the two groups of patients [RR = 0.98, 95% CI (0.88, 1.11), P = 0.79].

Incidence of thrombocytopenia

Eighteen studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fu et al., 2015; Gu et al., 2010; Guo, 2010; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Song et al., 2018; Tan et al., 2013; Wang, 2018; Wei et al., 2010; Xie & Huang (2009); Xu, 2010; Zhang, 2014; Zhong & Chen, 2018) reported the incidence of thrombocytopenia without statistical heterogeneity among the studies (P = 0.97, I2 = 0). Meta-analysis
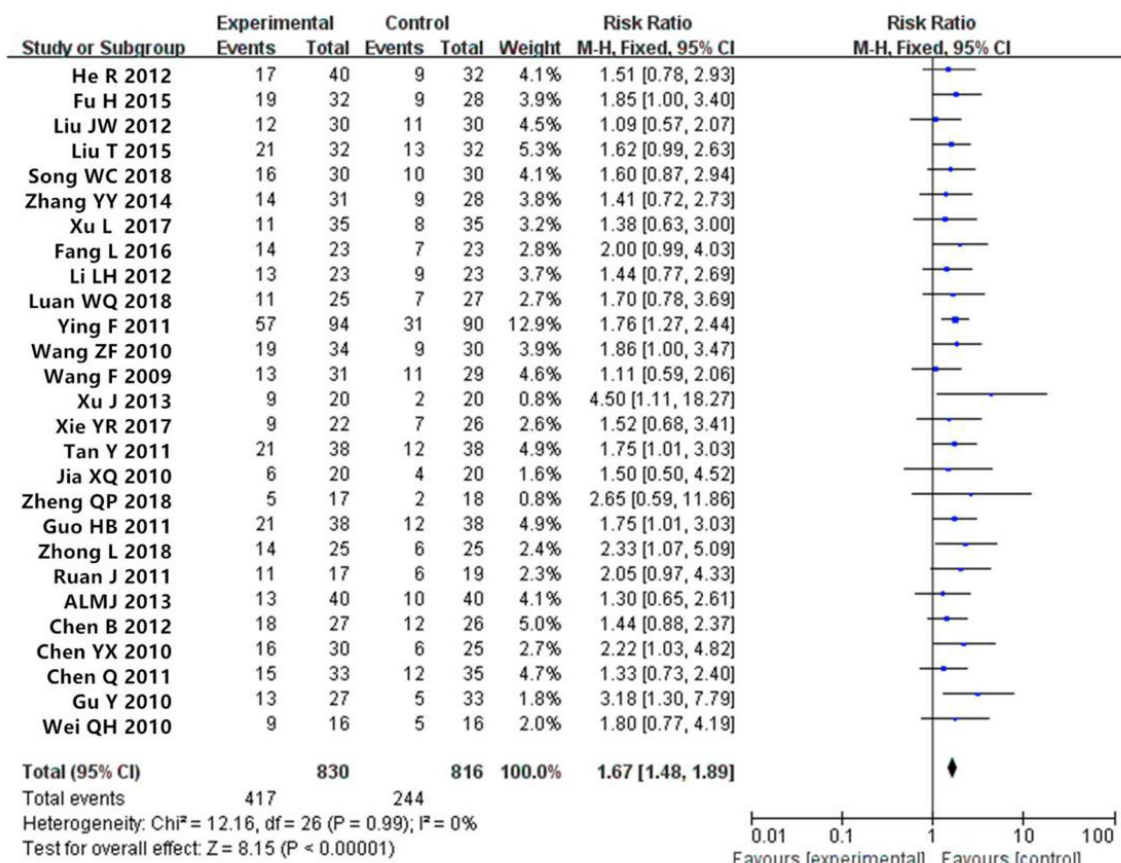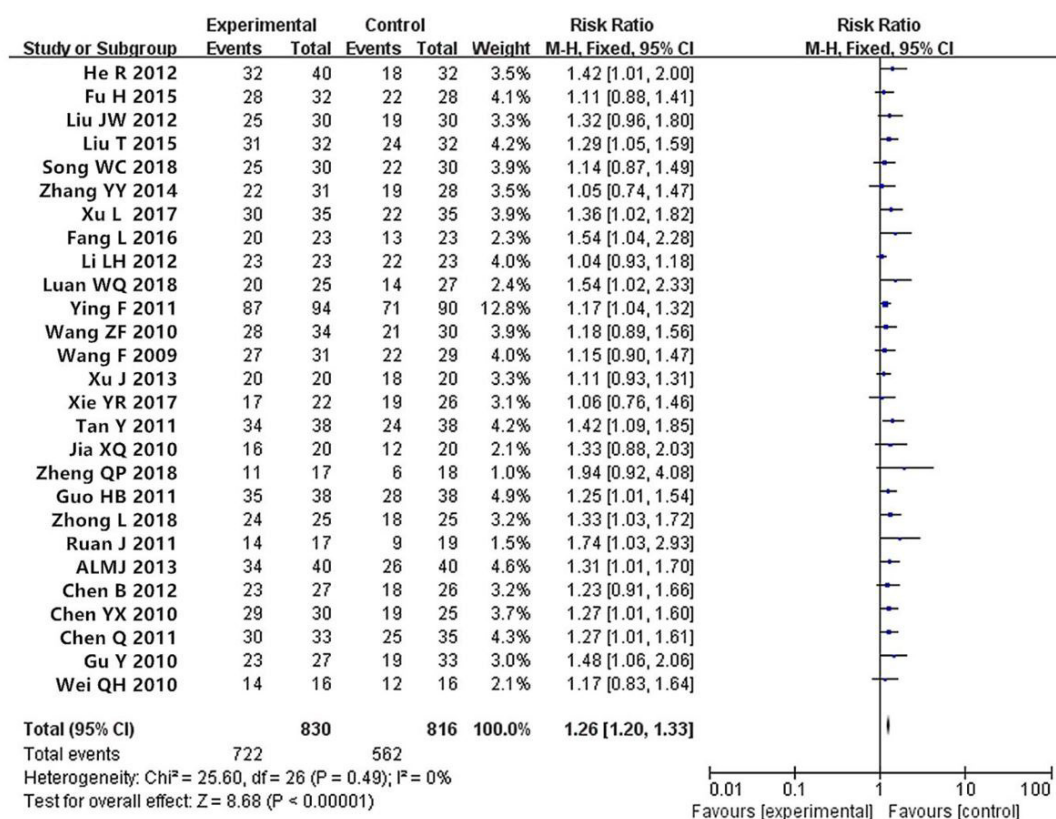

Figure 3. Forest plot of efficiency.

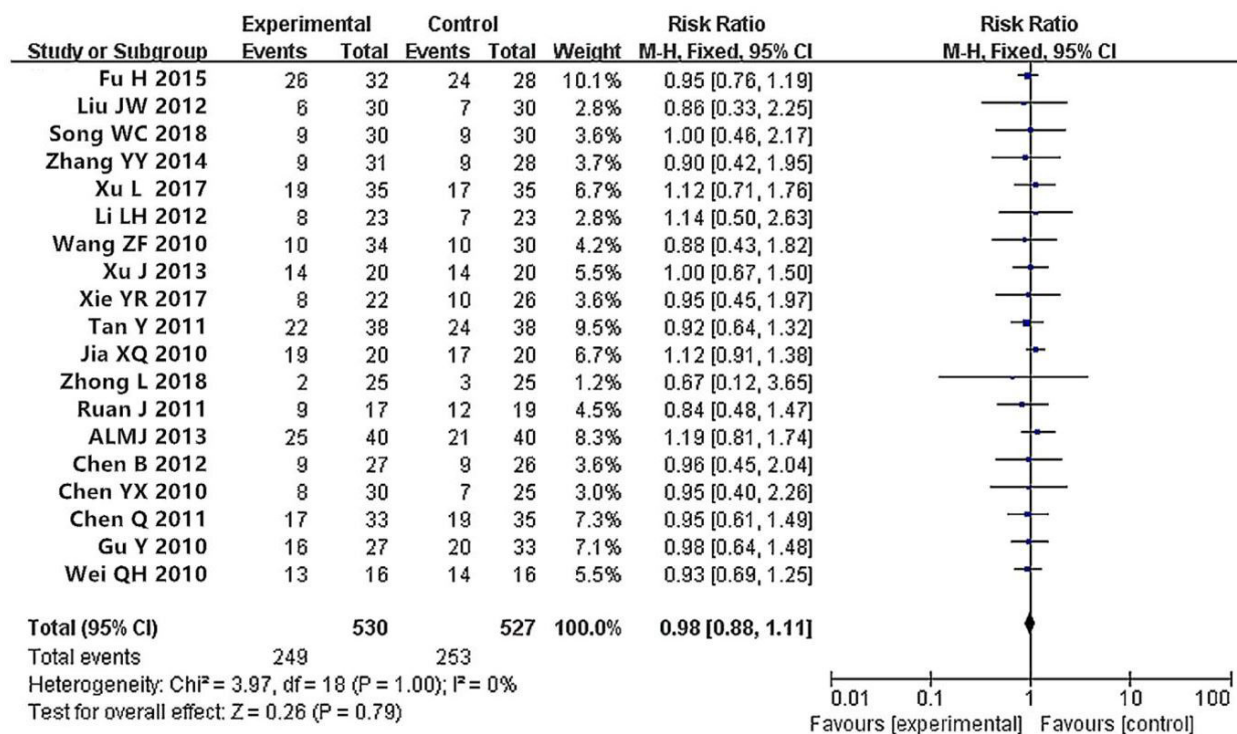**Figure 4**. Forest plot of clinical benefit rate.

Figure 5. Forest plot of the incidence of leukopenia.

was performed using a fixed-effect model. Details were shown in Figure 6. Meta analysis showed that there was no significant difference in the incidence of thrombocytopenia between the two groups of patients [RR = 1.07, 95% CI (0.91, 1.26), P = 0.39].

Incidence of gastrointestinal reactions

Twenty-two studies (Alimujiang et al., 2013; Chen et al., 2010, 2011; Chen & Yang, 2012; Fu et al., 2015; Gu et al., 2010;

He, 2012; Jia et al., 2017; Li et al., 2016; Liu et al., 2012; Ruan & Sun, 2011; Song et al., 2018; Tan et al., 2013; Wang, 2018; Wei et al., 2010; Xie & Huang (2009); Xu & Wu, 2017; Xu, 2010; Yin et al., 2012; Zhang, 2014; Zheng et al., 2011; Zhong & Chen, 2018) reported the incidence of gastrointestinal reactions, with no statistical heterogeneity between the studies (P = 1.00, I2 = 0). Meta-analysis was performed using a fixed-effects model. Details were shown in Figure 7. Meta analysis showed that there was no significant difference in the incidence of gastrointestinal
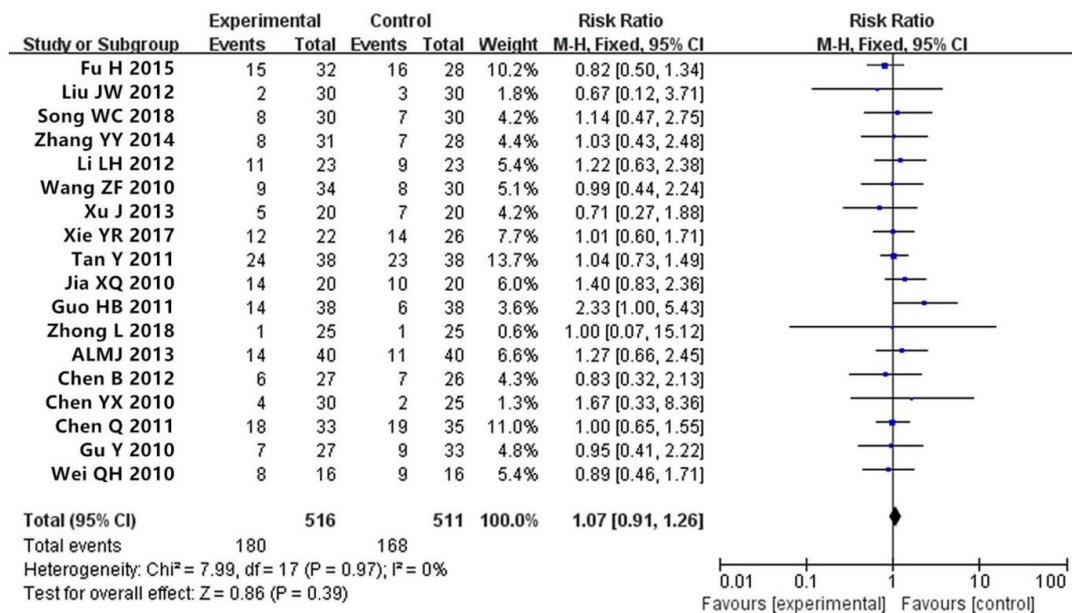

Figure 6. Forest plot of the incidence of thrombocytopenia.
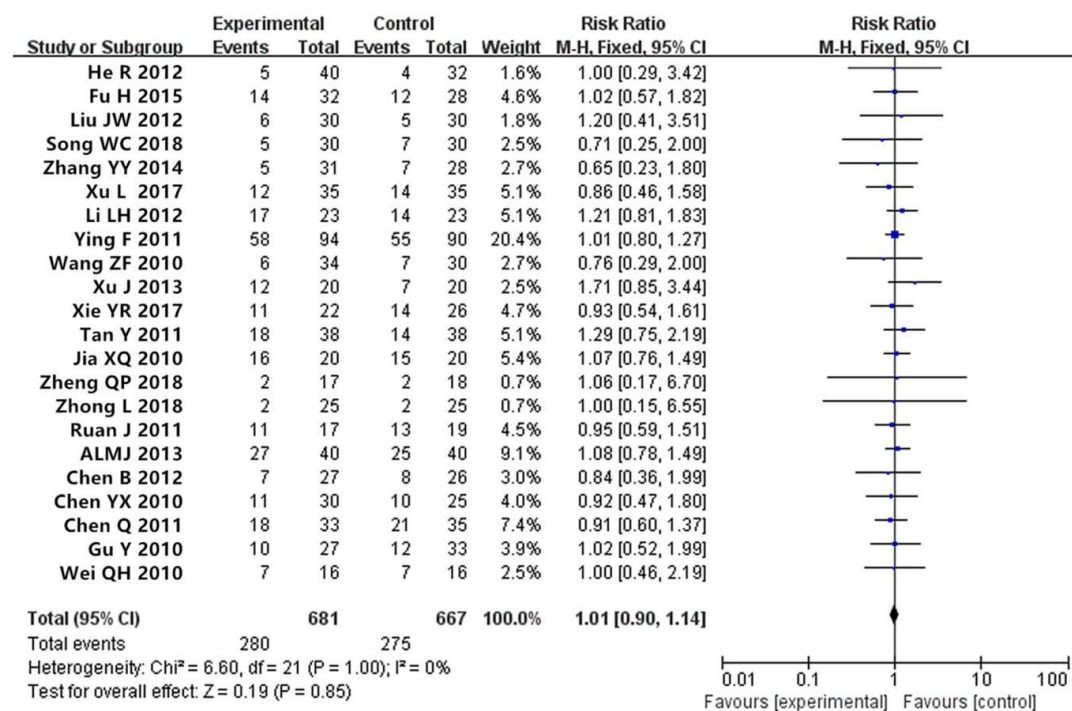

Figure 7. Forest plot of the incidence of gastrointestinal reactions.

reactions between the two groups of patients [RR = 1.01, 95% CI (0.90, 1.14), P = 0.85].

Influence analysis

We conducted the influence analysis for the included studies of efficacy. No single study affected the overall result by influence analysis (see Table 2).

Publication bias

To evaluate publication bias, we conducted the funnel plot for the included studies of efficacy (see Figures 8 to 10). Owing to insufficient details of other outcomes, we did not conduct the funnel plot. The asymmetrical figure reflected that potential publication bias might have an influence on results of meta-analysis. And no publication bias was detected by Begg's and Egger's test. (*P* value: 0.084 and 0.135, resp.) (see Figure 9 and 10).

4 Discussion

Platinum drugs are cell cycle non-specific anti-tumor drugs. Its anti-cancer mechanism is that after the drug enters tumor cells, it can combine with the DNA of the tumor cells to form a Pt-DNA adduct, which then mediates tumor cell necrosis or apoptosis (Wang & Lippard, 2005; Tao et al., 2019). Cisplatin is

the first-generation platinum-based anti-tumor drug (Aixue et al., 2018). It has a broad anticancer spectrum and ideal effect, and is the first-line drug for several solid tumors (Ferry et al., 2017). Gemcitabine is not only a cytidine derivative, but also a cycle-specific anti-tumor drug. Its metabolites in the body can bind to DNA and act in the G1/S phase of the cell cycle, blocking the synthesis and repair of tumor cells' DNA (Stukov et al., 2020). Gemcitabine combined with Cisplatin is currently the first-line treatment for the clinical use of NSCLC (Holmsten et al., 2020). However, some studies have suggested that the efficacy of gemcitabine combined with cisplatin is limited, and some patients showed no significant improvement after treatment (Scagliotti et al., 2002). This suggested that the chemotherapy effect of gemcitabine and cisplatin in treating NSCLC may have reached to a bottleneck (Wu et al., 2014). Therefore, there is an urgent need to find a new treatment to control the progress of tumors.

Endostar is an anti-tumor drug with anti-angiogenic activity, which can inhibit the synthesis and proliferation of vascular endothelial cells, and play an inhibitory role in all aspects of tumor angiogenesis (Ge et al., 2011). Studies have found that nucleolar protein on the surface of cell membranes are receptors of Endostar. The drug can inhibit the growth of new blood vessels and tumors by inhibiting the phosphorylation of nucleolar protein (Shi et al., 2007). It has been reported that Endostar

Table 2. The results of sensitivity analysis.

Excluded trails	Heterogeneity		95% CI	P
Tan et al. (2013)	P=0.99	I²=0	1.67(1.47, 1.89)	P<0.000 01
Xie & Huang (2009)	P=0.99	I²=0	1.68(1.48, 1.90)	P<0.000 01
Chen et al. (2010)	P=0.99	I²=0	1.66(1.46, 1.88)	P<0.000 01
Gu et al. (2010)	P=1.00	I²=0	1.65(1.45, 1.86)	P<0.000 01
Guo (2010)	P=0.99	I²=0	1.67(1.47, 1.90)	P<0.000 01
Wei et al. (2010)	P=0.99	I²=0	1.67(1.47, 1.89)	P<0.000 01
Xu (2010)	P=1.00	I²=0	1.65(1.46, 1.87)	P<0.000 01
Chen et al. (2011)	P=0.99	I²=0	1.69(1.49, 1.92)	P<0.000 01
Ruan & Sun (2011)	P=0.99	I²=0	1.66(1.47, 1.89)	P<0.000 01
Wang (2011)	P=1.00	I²=0	1.70(1.50, 1.93)	P<0.000 01
Zheng et al. (2011)	P=0.99	I²=0	1.67(1.47, 1.89)	P<0.000 01
Chen & Yang (2012)	P=0.99	I²=0	1.69(1.48, 1.91)	P<0.000 01
He (2012)	P=0.99	I²=0	1.68(1.48, 1.91)	P<0.000 01
Liu et al. (2012)	P=1.00	I²=0	1.70(1.50, 1.93)	P<0.000 01
Luan (2012)	P=0.99	I²=0	1.67(1.48, 1.90)	P<0.000 01
Yin et al. (2012)	P=0.99	I²=0	1.66(1.45, 1.90)	P<0.000 01
Alimujiang et al. (2013)	P=0.99	I²=0	1.69(1.49, 1.92)	P<0.000 01
Zhang (2014)	P=0.99	I²=0	1.68(1.48, 1.91)	P<0.000 01
Fu et al. (2015)	P=0.99	I²=0	1.67(1.47, 1.89)	P<0.000 01
Liu (2015)	P=0.99	I²=0	1.68(1.48, 1.90)	P<0.000 01
Li et al. (2016)	P=0.99	I²=0	1.68(1.48, 1.91)	P<0.000 01
Fang (2017)	P=0.99	I²=0	1.66(1.47, 1.89)	P<0.000 01
Jia et al. (2017)	P=0.99	I²=0	1.68(1.48, 1.90)	P<0.000 01
Xu & Wu (2017)	P=0.99	I²=0	1.68(1.48, 1.91)	P<0.000 01
Song et al. (2018)	P=0.99	I²=0	1.68(1.48, 1.90)	P<0.000 01
Wang (2018)	P=0.99	I²=0	1.67(1.47, 1.89)	P<0.000 01
Zhong & Chen (2018)	P=0.99	I²=0	1.66(1.46, 1.88)	P<0.000 01

The 95% confidence interval (CI) is the probability that the population parameters are in this range, which is about 95%.
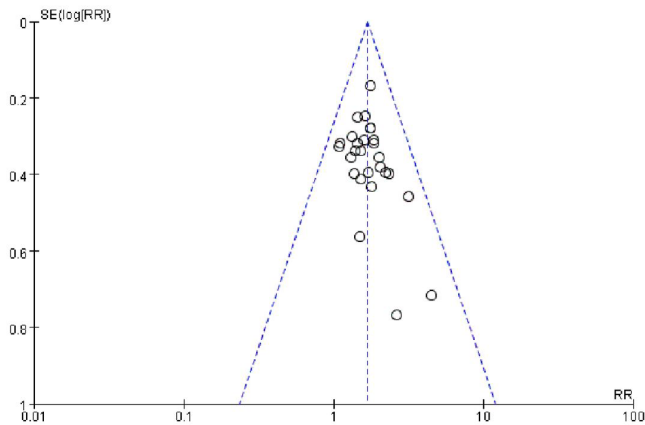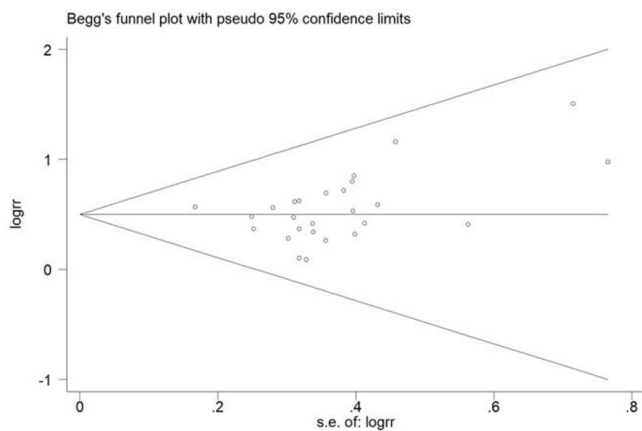
Figure 8. Funnel plot of efficiency.

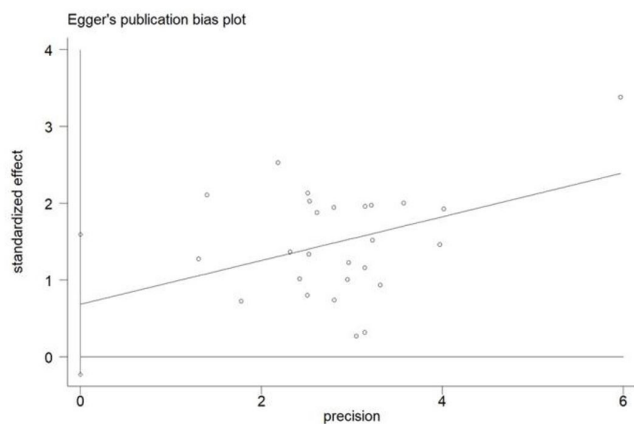**Figure 9**. Begg analysis plot.

Figure 10. Egger analysis plot.

combined chemotherapy can work together to kill tumor cells and improve the efficacy in different ways (Xie & Huang (2009).

According to this study, the results showed that the efficacy and clinical benefit rate of patients in the trial group are significantly higher than those in the control group. These results suggested that Endostar combined with gemcitabine and cisplatin can improve the efficacy in treating NSCLC. There was no significant

difference in the incidence of leukopenia, thrombocytopenia, and gastrointestinal reactions in the two groups of patients. It meant that Endostar combined with gemcitabine and cisplatin will not increase the incidence of adverse reactions. What's more, inverted funnel plots, Begg's and Egger's tests all indicated that no publication bias was found in this study. However, there were stiil some limitations in this study: 1) The documents retrieved were those included in each database. Unpublished documents had not been search; 2) The included literatures are mainly Chinese literatures; the results may not reflect the whole world conditions; 3) None of the included literature evaluated patients' quality of life. Therefore, the conclusions of this study need to be further confirmed by high-quality, multi-center RCT. In summary, Endostar combined with gemcitabine and cisplatin can improve the efficacy of advanced NSCLC without increasing the incidence of side effects.

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