The efficacy of Endostar combined with platinum pleural infusion for malignant pleural effusion in tumor patients is significantly better than that of monotherapy, but the economy is lower: a systematic review, network meta-analysis and cost-effectiveness analysis

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Background: Endostar and platinum were widely used in the treatment of malignant pleural effusion (MPE), but there was no unified conclusion on which scheme is the best. The aim of this study was to systematically evaluate the efficacy and cost-effectiveness of Endostar, cisplatin, lobaplatin, Endostar combined with cisplatin, and Endostar combined with lobaplatin in the treatment of MPE so as to provide a reference for clinical treatment.

Methods: A comprehensive literature search was performed of sources on PubMed, Web of Science, and other databases published up to and including November 23, 2021, and screened out randomized controlled trial (RCT) concerning the efficacy of 5 interventions of pleural perfusion for MPE. The Cochrane Collaboration tool was used for assessing the risk of bias, and a network meta-analysis was performed with Addis software based on the Bayesian framework. A decision tree model was used to complete a cost-effectiveness analysis that was based on the direct medical costs and the probabilities were determined from the network meta-analysis. The one-way sensitivity analysis was presented with a tornado chart. In the probabilistic sensitivity analysis, the cost-effectiveness acceptability curve was obtained after Monte Carlo simulation.

Results: A total of 55 studies were included, comprising 3,379 total patients, excluding the unclear part, we evaluated as low risk of bias. According to the network meta-analysis, Endostar combined with lobaplatin had the highest effectiveness, followed by Endostar combined with cisplatin, Endostar, cisplatin, and lobaplatin. In the incremental cost-effectiveness ratio (ICER) analysis, lobaplatin and Endostar were excluded as inferior schemes. With cisplatin as the comparison, the ICER of Endostar combined with cisplatin was yuan renminbi ¥22,648.31. With Endostar combined with cisplatin as the comparison, the ICER of Endostar combined with lobaplatin was ¥236,502.67. The results of sensitivity analysis and cost-effectiveness analysis were basically consistent.

Conclusions: Endostar combined with lobaplatin had the highest effectiveness, but its ICER was relatively too high to be acceptable. Therefore, cisplatin alone and Endostar combined with cisplatin were more cost-effective, and clinicians can choose the optimal treatment scheme based on the willingness to pay (WTP) of different patients with comprehensive consideration of effectiveness and economy.

Keywords: Malignant pleural effusion (MPE); Endostar; cisplatin; lobaplatin; decision tree model

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Introduction

Malignant pleural effusion (MPE) is one of the typical complications of advanced malignant tumors; most commonly occurring in lung cancer (37%), breast cancer (16%), and hematologic malignancies (10%) (1,2), MPE is associated with a worse prognosis (3). Current guidelines do not indicate a strictly preferred treatment method for MPE (4). Pleural infusion after adequate drainage of pleural effusion is one of the feasible treatment methods presently available. Commonly used infusion drugs include Endostar, platinum, and other chemotherapy drugs, as well as multidrug combination therapy.

There had been several studies on the efficacy of pleural infusion of drugs in the treatment of MPE (5), but comparisons between multiple schemes were lacking and the results were inconsistent. Qin *et al.* reported an efficacy outcome of intra-pleural injection of Endostar and/or cisplatin in treatment of malignant hydrothorax and ascites, the objective response rate (ORR) of Endostar was similar to that of cisplatin (48.51% *vs.* 46.39%, P>0. 05), and there was no statistical significance difference in efficacy, while the combination of Endostar and cisplatin significantly improved the ORR (63.00%, P=0.0189) (6). However, other studies found that there was no statistical significant difference in the ORR between the single drug group and the combined group in the treatment of malignant hydrothorax and ascites (7,8). The differences between studies may be related to the small sample size. Studies had reported that pleural infusion medicine had achieved good efficacy in the treatment of MPE (9-11). However, most of them were direct comparisons, there was no evidence-based medicine for direct and indirect comparisons between different types of platinum and Endostar. In this study, we used a network meta-analysis through direct and indirect comparisons, the clinical efficacy, and safety of different schemes for the treatment of MPE were compared.

Lots of patients have financial burdens associated with cancer treatment (12). In a cross-sectional survey, 45% of study participants were nonadherent to medications as a result of cost (13). While another study found that cancer-related financial burden was associated with lower health-related quality of life (14). So, patients will also consider their financial factors when choosing treatment schemes. We compared different schemes' cost-effectiveness through a decision tree model so as to provide a health economics reference for the selection of schemes for MPE in patients with tumor. We present the following article in accordance with the CHEERS and PRISMA NMA reporting checklists (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2091/rc).

Methods

Network meta-analysis

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) as well as the PRISMA extension statement for network meta-analysis.

Search strategy

PubMed, Web of Science, Embase, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) were systematically searched from inception to November 23, 2021, using a combination of the main search terms "recombinant human endostatin", "rh-Endostatin", "Endostar", "cisplatin", "lobaplatin", and "pleural effusion".

Inclusion and exclusion criteria

The inclusion criteria applied for the literature were as follows: (I) the study participants were adult patients who had a clear histopathological and imaging diagnosis of malignant tumor with pleural effusion; (II) study participants in the experimental group or the control group received pleural perfusion of Endostar, cisplatin, lobaplatin, or the combination of the 2 drugs; and (III) the study design was a randomized controlled trial (RCT).

The following literature was excluded: (I) nonrandomized trials or trials with a faulty randomization method, (II) literature reviews, (III) duplicate publications, (IV) case reports, and (V) animal research papers.

Outcome indicators

Based on the change of pleural effusion, this study was evaluated in accordance with the response evaluation criteria in solid tumours (RECIST) (15) in the following fashion: complete response (CR), defined as the effusion completely disappearing lasting more than 4 weeks after completion of treatment; partial response (PR), defined as the effusion decreasing by more than 50% lasting more than 4 weeks after completion of treatment; stable disease (SD), defined as the effusion decreasing by less than 50% after treatment or increasing by less than 25%; progressive disease (PD), defined as the effusion increasing by more than 25% after treatment; and unknown, defined as the disease progression not being recorded.

The primary outcome was the ORR, which was calculated as follows: ORR = CR + PR; meanwhile, no response (NR) was calculated as follows: NR = SD + PD.

Data extraction and quality assessment

Two researchers screen the selected literature separately according to the above-mentioned inclusion and exclusion criteria. If the 2 researchers disagreed on whether the selected literature should be included, they arrived at a consensus via discussion. If the disagreement could not be resolved through discussion, a third researcher was invited to discuss and mediate an agreement. The data extracted from the included trials included the first author's name, year of publication, sample size, interventions, primary outcome, and, for safety profiles, counts of each specific adverse event.

The quality of the included studies was assessed using the Cochrane Collaboration tool for assessing the risk of bias. Two researchers assessed the risk of bias independently and in duplicate, and any disagreements were resolved via consultation with the third researcher.

Cost-effectiveness analysis

Modeling approach

In order to evaluate the short-term efficacy and economic feasibility, a decision tree model was used to complete a cost-effectiveness analysis of the 5 schemes. As there is no standard scheme or course of treatment of MPE, we assumed that the model course of treatment was 2 weeks according to the commonly used course of treatment and dose in the included literature; furthermore, each drug was administered twice a week with the following dosages: Endostar 45 mg, cisplatin 60 mg, and lobaplatin 50 mg.

Cost estimates

Pharmacoeconomic cost includes direct cost, indirect cost, and hidden cost. In this study, only direct medical costs were calculated from the perspective of the hospital, and mainly included drug costs, examination costs, hospitalization costs, and the cost of managing adverse events.

Pharmaceutical prices refer to the quotation of the medical institution where the author works. The price of Endostar (Shandong Xiandao Bio-pharmaceutical Co., Ltd.; specification: 15 mg per bottle) is yuan renminbi ¥490.00, cisplatin (Qilu Pharmaceutical Co., Ltd.; specification: 20 mg per bottle) is ¥13.17, and lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd.; specification: 50 mg per bottle) is ¥1,812.21. For other relevant fee data, we referred to the institution's 2021 fee standard. Due to the short treatment period, discounting was not performed. All costs are expressed in the 2021 values of Chinese yuan (¥). The costs were translated to US dollars at the rate of $1= ¥6.4512 (as of 2021).

Effectiveness estimates

The events examined in the decision tree model were the ORR of MPE within the model cycle. The probabilities used in the decision tree model were determined from the network meta-analysis of efficacy and safety. As the simple cost-effectiveness ratio could not fully reflect the economy of the 5 schemes, we added the incremental cost-effectiveness ratio (ICER) to evaluate it.

Statistical analysis

The statistical analyses of the network meta-analysis were performed using Addis software (version 1.16.6) based on the Bayesian framework. The parameters for the Addis software were as follows: number of chains, 4; tuning iterations, 20,000; simulation iterations, 50,000; thinning interval, 10; inference samples, 10,000; and variance scaling factor, 2.5. As only dichotomous outcomes were involved, odds ratios (ORs) and 95% CIs were calculated based on a random effects model. The convergence of the model was determined by the potential scale reduction factor (PSRF). If PSRF was in the range of 1 to 1.05, meanwhile inconsistency factors closed to 0 and 95% CI contained the neutral value (0), these indicated good convergence and that the consistency model could be used to calculate the pooled effect size; otherwise, the nonconsistency model was used.

Based on the results of the network meta-analysis, TreeAge Pro 2011 software was used to establish and

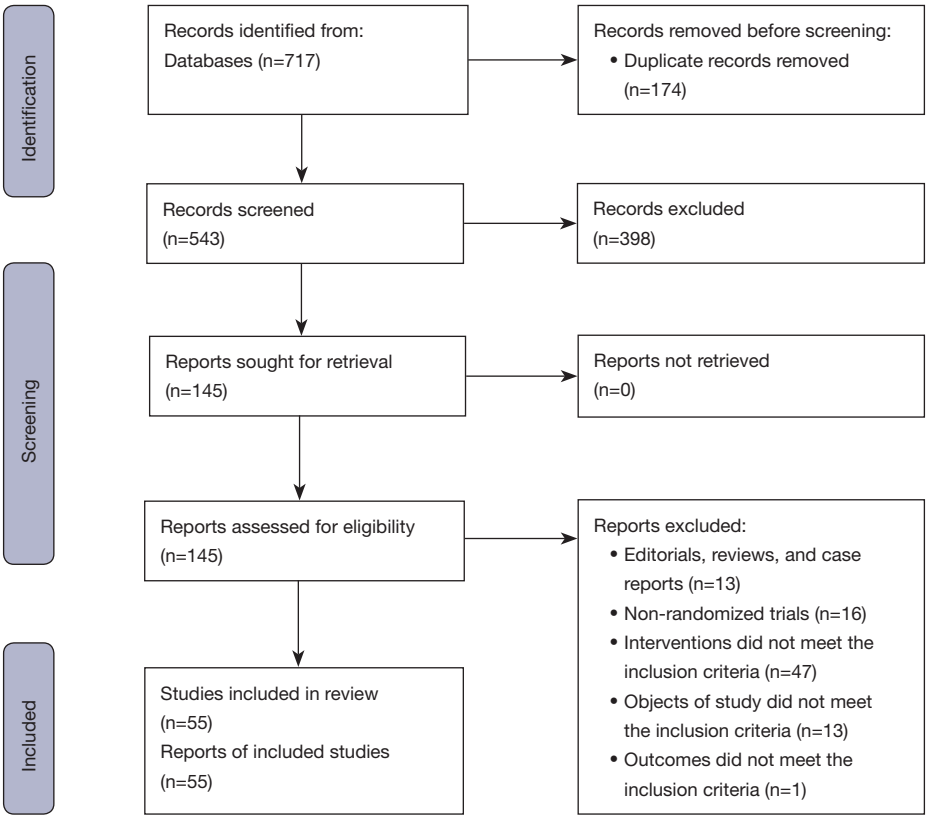

Figure 1 Screening process of the studies.

analyze the decision tree model, and the cost-effectiveness ratio and ICER were calculated. In the one-way sensitivity analyses, the influence of different indicators on the results was visualized by a tornado chart. In the probabilistic sensitivity analysis, the cost-effectiveness acceptability curve was obtained after Monte Carlo simulation by assuming efficiency and cost distribution.

Results

The results of the network meta-analysis

Study selection

A total of 717 relevant studies were initially retrieved using our established search strategy, and 572 were excluded as duplicate records or unrelated records. We subjected 145 studies to full-text screening, and 90 studies were excluded. Finally, a total of 55 studies met the eligibility criteria and were included for the meta-analysis. A schematic representation of the article searches and study selection process is presented in *Figure 1*.

Characteristics of the included studies

Among the 55 included studies, 3 were 3-arm studies and the remainder were 2-arm studies, with a total of 3,379 patients included. *Table 1* shows the summary of the basic characteristic information of the included studies while *Figure 2* presents the network diagrams drawn using RStudio software.

Quality assessment of the included studies

There were 26 RCTs among the 55 studies in the lowest categories of risk of bias for random sequence generation. None of the studies reported blindness, and the risk of bias was unclear. Outcome data of all studies were complete, and no other sources of bias were reported. The risk of bias assessment was summarized in *Figure 3*.

Effectiveness comparison of the different schemes

All of the PSRFs were less than 1.05, indicating good convergence with stable results. During the software calculation results, the inconsistency factors (median 0.33,

Table 1 Basic information of the included studies

Author (year)	N (T/C)	Age (mean/mean ± SD, year)	Interventions (T/C)	Course
Huang 2010 (9)	18/18	48	Endostar + cisplatin/cisplatin	3 weeks
Liu 2010 (10)	32/32/32	55	Endostar + cisplatin/Endostar/cisplatin	3 weeks
Mao 2011 (16)	45/45	51	Endostar + cisplatin/cisplatin	2 weeks
Li 2011 (17)	21/21	49±8.3	Endostar + cisplatin/cisplatin	3 weeks
Jia 2011 (18)	18/14	–	Endostar + cisplatin/cisplatin	1–2 weeks
Cao 2012 (11)	32/31	53.92±5.93/53.44±7.76	Endostar + lobaplatin/Endostar + cisplatin	2 weeks
Yang 2013 (19)	21/21	41.5±7.6	Endostar + cisplatin/cisplatin	3 weeks
Zheng 2013 (20)	60/60	53	Endostar + cisplatin/cisplatin	3–12 weeks
Han 2013 (21)	20/20	62	Endostar + cisplatin/cisplatin	1–3 weeks
Kang 2013 (22)	30/30	60.5±9.9	Endostar + cisplatin/cisplatin	24 days
Huang 2014 (23)	25/25	41.5±7.6	Endostar + cisplatin/cisplatin	2 weeks
Yue 2014 (24)	43/43	60.42±16.93	Endostar + cisplatin/cisplatin	2–3 weeks
Tu 2014 (25)	45/45	46.5±11.5/47.5±10.5	Endostar + cisplatin/cisplatin	3 weeks
Zhao 2015 (26)	18/18/18	–	Endostar + cisplatin/Endostar/cisplatin	42 days
Duan 2015 (27)	19/19	61.4	Endostar + cisplatin/Endostar	4 weeks
Pang 2015 (28)	21/25	61.2±5.3	Endostar + cisplatin/cisplatin	1–2 weeks
Chen 2015 (29)	21/24	56.7±5.7/55.1±4.9	Endostar + cisplatin/cisplatin	4 weeks
Zheng 2015 (30)	23/23	49.2/49.6	Endostar + cisplatin/cisplatin	6 weeks
Hu 2015 (31)	43/41	59/57	Endostar + cisplatin/cisplatin	1–2 weeks
Zhang 2015 (32)	24/22	61	Endostar + cisplatin/cisplatin	1–2 weeks
Shi 2016 (33)	21/21	42.3±5.6	Endostar + lobaplatin/lobaplatin	3 weeks
He 2016 (34)	27/25	60.28±6.17/61.31±6.05	Endostar + cisplatin/cisplatin	3 weeks
Dong 2016 (35)	23/23	48.5±4.3	Endostar + cisplatin/cisplatin	2 weeks
Bayalige 2016 (36)	16/20	55	Endostar + cisplatin/cisplatin	3 weeks
Zou 2016 (37)	36/36	56.8±5.9/57.3±6.2	Endostar + cisplatin/cisplatin	1 weeks
Qin 2016 (38)	21/21	59.6	Endostar + cisplatin/cisplatin	3 weeks
Lu 2016 (39)	30/30/30	63.2/65.1/62.6	Endostar + cisplatin/Endostar/cisplatin	5–11 days
Wang 2016 (40)	20/20	45.0±6.2/40.0±5.4	Endostar + cisplatin/Endostar	–
Zhang 2016 (41)	26/25	47	Endostar + cisplatin/cisplatin	–
Zheng 2016 (42)	46/46	60.35±2.18	Endostar + cisplatin/cisplatin	1–2 weeks
Li 2016 (43)	50/50	64.58±2.49/64.82±2.44	Endostar + lobaplatin/lobaplatin	3 weeks
Chen 2017 (44)	32/32	46.3±6.4/40.2±5.1	Endostar + cisplatin/cisplatin	2 weeks
Feng 2017 (45)	27/27	59.15±10.26/58.71±10.04	Endostar + cisplatin/cisplatin	3 weeks
Ruan 2017 (46)	45/45	58.53±4.26	Endostar + cisplatin/cisplatin	3 weeks

Table 1 (*continued*)

Table 1 (*continued*)

Author (year)	N (T/C)	Age (mean/mean ± SD, year)	Interventions (T/C)	Course
Zhao 2017 (47)	34/34	52.87±4.93/53.16±5.08	Endostar + cisplatin/cisplatin	4 weeks
Li 2017 (48)	25/21	–	Endostar/cisplatin	2 weeks
Jia 2017 (49)	22/18	62	Endostar + cisplatin/cisplatin	1–4 weeks
Wu 2017 (50)	35/20	54	Endostar + cisplatin/cisplatin	2–3 weeks
Deng 2018 (51)	53/53	65.08±3.08/66.10±3.10	Endostar + cisplatin/cisplatin	2 weeks
Sun 2018 (52)	18/22	–	Endostar + cisplatin/cisplatin	–
Wen 2018 (53)	30/30	52	Endostar + lobaplatin/Endostar + cisplatin	2–4 weeks
Qin 2018 (54)	42/42	56.84±7.03/57.19±8.25	Endostar + cisplatin/Endostar	4 weeks
Wang 2018 (55)	42/42	62.34±7.47/60.75±8.06	Endostar + cisplatin/cisplatin	1–3 weeks
Qing 2018 (56)	28/23	68.2±4.6	Endostar + cisplatin/cisplatin	3 weeks
Liu 2018 (57)	26/26	–	Endostar + cisplatin/cisplatin	2–3 weeks
Zheng 2019 (58)	24/24	53.2±2.5/52.3±2.4	Endostar + cisplatin/cisplatin	2 weeks
Jiang 2019 (59)	50/50	51.5±6.7/52.5±6.9	Endostar + cisplatin/Endostar	4 weeks
Li 2019 (60)	15/15	44.6±2/45.2±2	Endostar + cisplatin/cisplatin	42 days
Ji 2020 (61)	30/30	60.84±4.56/61.54±5.29	Endostar+lobaplatin/lobaplatin	4–8 weeks
Han 2020 (62)	30/30	58.95±10.45/59.46±10.37	Endostar + cisplatin/cisplatin	2 weeks
Xu 2020 (63)	20/20	66	Endostar + cisplatin/cisplatin	2 courses, 3–4 weeks between 2 courses
Su 2021 (64)	30/30	61.43±6.45/62.05±6.29	Endostar + cisplatin/cisplatin	2 courses, 3–4 weeks between 2 courses
Liu 2021 (65)	39/39	57.2±4.8/56.8±4.6	Endostar + cisplatin/cisplatin	3 weeks
Chen 2021 (66)	30/30	50.31±4.27/50.16±4.35	Endostar + lobaplatin/lobaplatin	4 weeks
Zhang 2021 (67)	40/40	55.36±3.25/55.84±3.16	Endostar + lobaplatin/lobaplatin	42 days

T, treatment group; C, control group; –, none reported.

95% CI: –0.14 to 0.88) closed to 0, and 95% CI: contained the neutral value (0). Thus, the network meta-analyses were performed based on the concordance model. Network meta-analysis showed that Endostar combined with lobaplatin (OR 5.70, 95% CI: 2.40–14.49), and Endostar combined with cisplatin (OR 3.84, 95% CI: 3.28–4.61) were significantly more effective than cisplatin. Nevertheless, Endostar (OR 1.27, 95% CI: 0.85–1.85), and lobaplatin (OR 1.16, 95% CI: 0.43–3.24) had no significant difference in effectiveness compared with cisplatin. The effectiveness was divided into five ranks from Rank 1 to Rank 5, Rank 1 is the best and Rank 5 is the worst. The probability of schemes ranking in each rank was calculated (*Figure 4*). Endostar combined with lobaplatin had the highest probability in Rank 1, so this scheme had the best effectiveness, followed by Endostar combined with cisplatin, Endostar, cisplatin, and lobaplatin.

Adverse drug reactions (ADRs)

There were 36 studies that detailed the specific occurrence and incidence of ADRs, with the common ADRs including nausea, vomiting, chest pain, and bone marrow suppression. There was no statistical significance between each treatment concerning the incidence of ADR (P>0.05) that were consistent with the results of ADR in the meta-analysis conducted by Liang *et al.* (68). Therefore, the follow-up pharmacoeconomic evaluation only included the treatment cost of the ADR with the highest incidence to nausea and

vomiting. Ondansetron was selected as the treatment for the ADR, and 1 box (12 tablets) per course of treatment cost ¥107.

Pharmacoeconomic evaluation

The decision tree model parameters

The effective index of each scheme was obtained from the included studies in the network meta-analysis, parameters were assigned, and the decision tree model was established (*Figure 5*), with a fluctuation within 20% being used as the variation range of parameters (*Table 2*).

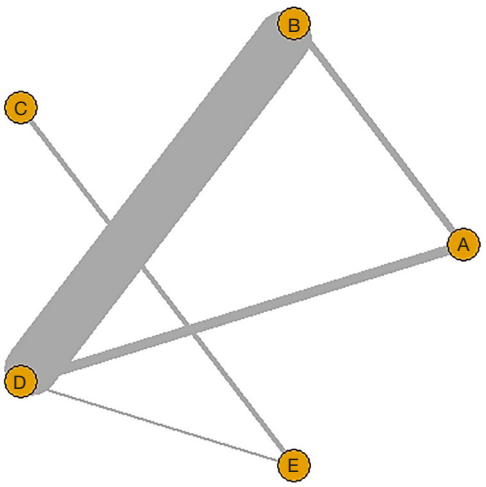

Figure 2 Network relationship among the different interventions of the included studies. A, Endostar; B, cisplatin; C, lobaplatin; D, Endostar combined with cisplatin; E, Endostar combined with lobaplatin.

Cost-effectiveness analysis

The cost-effectiveness analysis of the 5 schemes is shown in *Table 3*. In the ICER analysis, the scheme of lobaplatin was excluded as an absolutely inferior scheme due to its high cost and low effective rate, while the Endostar scheme was also excluded because of its higher ICER. Among the other 3 schemes, the ICER of Endostar and cisplatin combined, with the cisplatin alone scheme as the comparison, was ¥22,648.31, while the ICER of Endostar and lobaplatin combined, with the combined cisplatin scheme as comparison, was ¥236,502.67.

Different optimal schemes may exist according to the willingness to pay (WTP). When the WTP was <¥22,648.31, the optimal scheme was the cisplatin alone scheme. When the WTP was between ¥22,648.31 to ¥236,502.67, the optimal scheme was Endostar combined with cisplatin. When the WTP was >¥236,502.67, the optimal scheme was Endostar combined with lobaplatin.

Sensitivity analysis

Based on the upper and lower limits of model parameters in *Table 1*, the one-way sensitivity analysis was conducted for the ORR and the associated costs of the 5 schemes. As shown in *Figure 6*, the 5 most influential parameters were

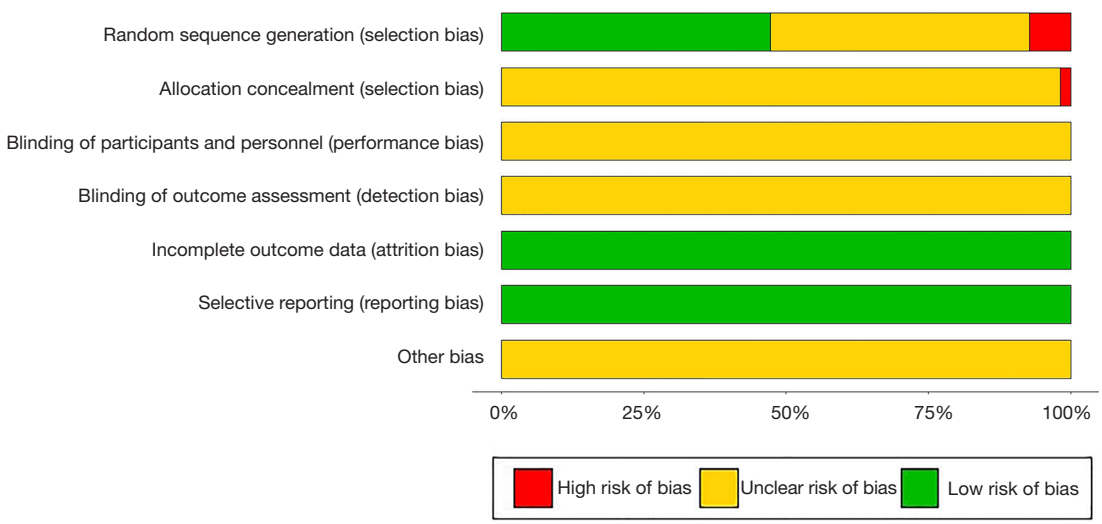

Figure 3 Percentages of included studies that produced risks of bias.

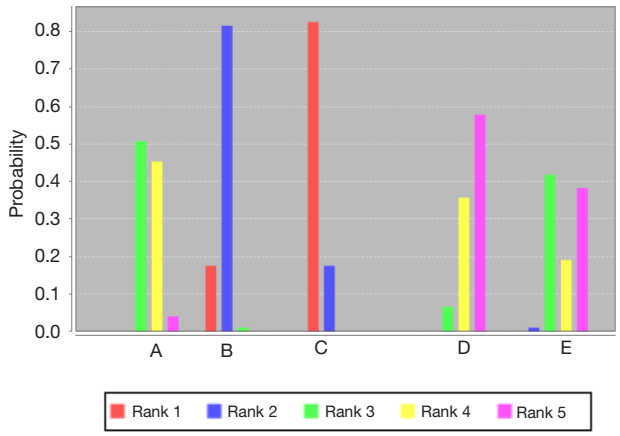

Figure 4 Ranking for the effectiveness of the different schemes. A, Endostar; B, Endostar combined with cisplatin; C, Endostar combined with lobaplatin; D, cisplatin; E, lobaplatin.

ORR of Endostar combined with cisplatin (pEac), ORR of Endostar combined with lobaplatin (pEal), treatment times (dTreatment), cost of Endostar (cEndostar), and hospitalization cost (chospitalization).

It was assumed that the change of ORR of the 5 schemes followed Beta distribution, the change of cost followed Gamma distribution, and the change of treatment times followed triangular distribution. The cost-effectiveness probabilistic sensitivity analysis of each parameter was conducted by Monte-Carlo simulation using TreeAge Pro 2011 software, and a cost-effectiveness acceptability curve based on 1,000 Monte-Carlo simulations was drawn (*Figure 7*).

According to the cost-effectiveness acceptability curve (*Figure 7*), when the WTP was 0, the probability of cisplatin alone scheme being the optimal solution was 100%. With the increase of WTP, the probability of cisplatin alone scheme being the optimal solution decreased continuously. With the change of WTP, the probability of Endostar both combined with cisplatin and combined with lobaplatin being the optimal scheme increased, while the other 2 schemes showed little change and were excluded as the inferior scheme.

Discussion

The occurrence of MPE is due to tumor metastasis to the pleura/pleural space either by direct invasion, hematogenous, or lymphangitic spread (69), which often leads to uncomfortable symptoms such as dyspnea and seriously affects the quality of life of tumor patients. Several studies have proven that the pleural infusion of drugs after adequate drainage of pleural effusion can effectively control effusion regeneration (70,71). Clinically common pleural infusion drugs, such as Endostar, lobaplatin, and cisplatin, are still controversial in terms of efficacy, safety, and economic viability.

A total of 55 RCTs were included in this study, and a network meta-analysis was applied to evaluate the efficacy and safety of 5 different schemes for MPE, with the included literature having a high evidence-based level and reliable results. Through a comparison of the efficiency of the 5 schemes, the probability and cost of all possible treatment events were determined, and a decision tree model was constructed for pharmacoeconomic evaluation, allowing for a more comprehensive and objective evaluation of possible treatment plans.

In the cost-effectiveness analysis, ICER was used to ascertain whether an advantage was present between a comparison of 2 schemes. A cost-effectiveness acceptability curve indicated that, cisplatin, Endostar combined with cisplatin, and Endostar combined with lobaplatin were the optimal schemes according to the level of WTP.

Currently, there is no uniform standard of WTP for the treatment of MPE. The efficacy of Endostar combined with lobaplatin is superior but may have low acceptability among Chinese patients due to its high cost. Moreover, the ICER of this scheme is relatively high according to the current per capita income of China. The cisplatin alone and cisplatin combined with Endostar schemes are more economical, and thus clinicians should make treatment choices based on patients' actual WTP.

Limitations

Although strict inclusion and exclusion criteria were established in this study and the model is robust, a few limitations should be noted. The effective rates of different schemes in this study were obtained from a meta-analysis while the included studies were all Chinese literature and may be of low quality; thus, a statistical bias might have been introduced into the effective rates. In addition, the pharmacoeconomic evaluation only analyzed the direct cost of treatment, while the indirect cost and hidden cost were not included and thus should be considered in future studies.

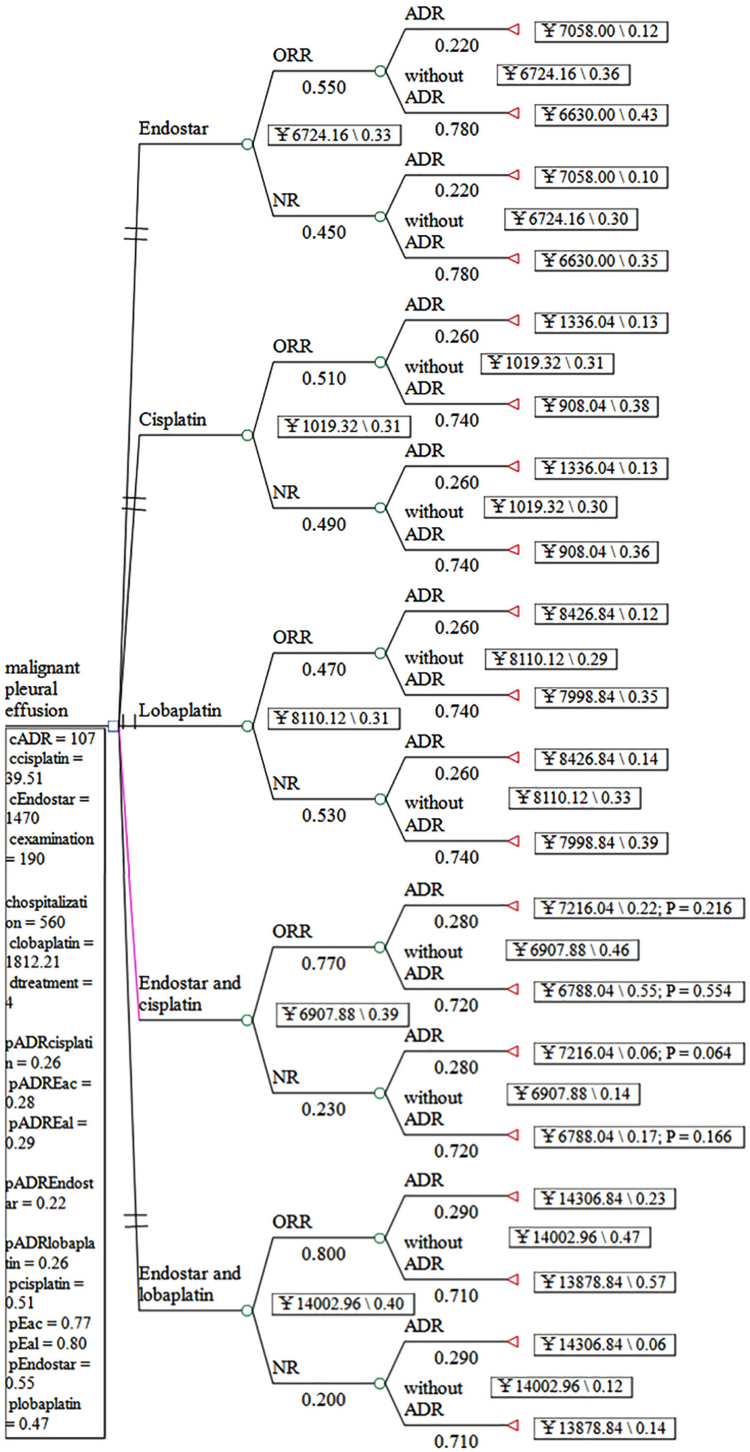

Figure 5 Decision tree model of the 5 schemes. ORR, objective response rate; ADR, adverse drug reactions; cADR, cost of ADR; ccisplatin, cost of cisplatin; cEndostar, cost of Endostar; cexamination, cost of examination; chospitalization, cost of hospitalization; clobaplatin, cost of lobaplatin; dtreatment, treatment times; pADRcisplatin, incidence of ADR to cisplatin; pADREac, incidence of ADR to Endostar combined with cisplatin; pADREal, incidence of ADR to Endostar combined with lobaplatin; pADREndostar, incidence of ADR to Endostar; pADRlobaplatin, incidence of ADR to lobaplatin; pcisplatin, ORR of cisplatin; pEac, ORR of Endostar combined with cisplatin; pEal, ORR of Endostar combined with lobaplatin; pEndostar, ORR of Endostar; plobaplatin, ORR of lobaplatin; NR, no response.

Table 2 The decision tree model parameters

Model parameter	Value	Range		Distribution
		Lower	Upper	
Cost, renminbi yuan				
Endostar 45 mg	1,470	1,176	1,764	Gamma
Cisplatin 60 mg	39.51	31.61	47.41	Gamma
Lobaplatin 50 mg	1,812.21	1,449.77	2,174.65	Gamma
ADR	107	85.6	128.4	Gamma
Examination	190	152	228	Gamma
Hospitalization	560	448	672	Gamma
Efficacy, %				
Endostar	55.02	44.02	66.02	Beta
Cisplatin	50.66	40.53	60.79	Beta
Lobaplatin	47.33	37.86	56.80	Beta
Endostar and cisplatin	77.15	61.72	92.58	Beta
Endostar and lobaplatin	79.79	63.83	95.75	Beta
Incidence of ADR (nausea and vomiting), %				
Endostar	21.70	17.36	26.04	Beta
Cisplatin	26.00	20.8	31.2	Beta
Lobaplatin	25.80	20.64	30.96	Beta
Endostar and cisplatin	27.90	22.32	33.48	Beta
Endostar and lobaplatin	28.70	22.96	34.44	Beta
Other				
Treatment times	4	3	5	Triangular

ADR, adverse drug reactions.

Table 3 Cost-effectiveness analysis results

Scheme	Effectiveness	Incremental effectiveness	Cost, yuan renminbi	Incremental cost, yuan renminbi	Cost-effectiveness ratio	ICER
Cisplatin	0.51	–	1,019.32	–	1,998.67	–
Lobaplatin	0.47	–0.04	8,110.12	7,090.80	17,255.57	–177,270.00
Endostar	0.55	0.04	6,724.16	5,704.84	12,225.75	142,621.00
Endostar and cisplatin	0.77	0.26	6,907.88	5,888.56	8,971.27	22,648.31
Endostar and lobaplatin	0.80	0.03	14,002.96	7,095.08	17,503.70	236,502.67

ICER, incremental cost-effectiveness ratio.

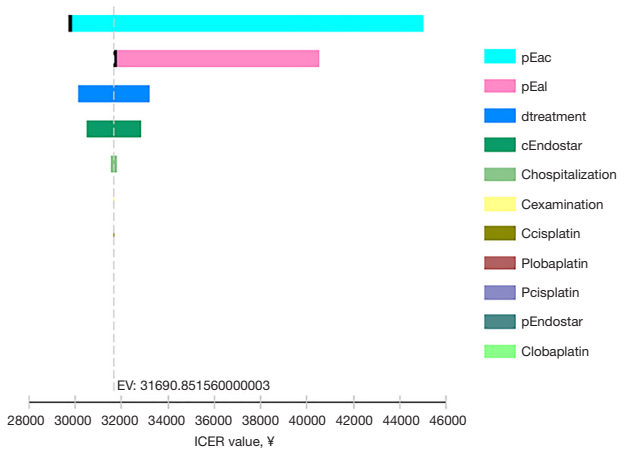

Figure 6 Tornado chart of sensitivity analysis. pEac, ORR of Endostar combined with cisplatin; ORR, objective response rate; pEal, ORR of Endostar combined with lobaplatin; dtreatment, treatment times; cEndostar, cost of Endostar; chospitalization, hospitalization cost; cexamination, cost of examination; ccisplatin, cost of cisplatin; plobaplatin, ORR of lobaplatin; pcisplatin, ORR of cisplatin; pEndostar, ORR of Endostar; clobaplatin, cost of lobaplatin; EV, expected value; ICER, incremental cost-effectiveness ratio; ¥, yuan renminbi.

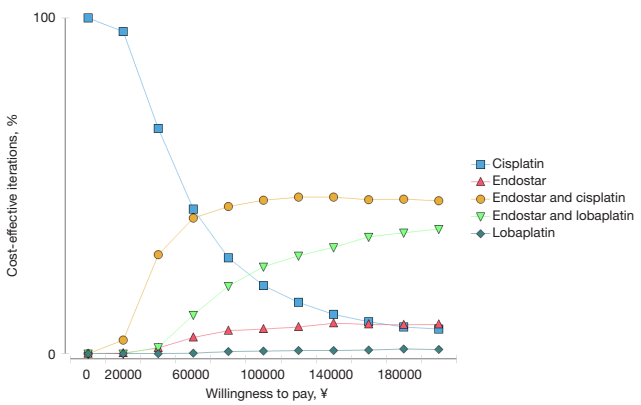

Figure 7 Cost-effectiveness acceptability curve. ¥, yuan renminbi.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2091/coif). The authors have no conflicts of interest to declare.

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