BMJ Open

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: a network meta-analysis

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To cite: Xu Y, Cui Y, Jiang L, *et al*. Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: a network meta-analysis. *BMJ Open* 2024;**14**:e080703. doi:10.1136/bmjopen-2023-080703

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-080703).

Received 12 October 2023
Accepted 18 November 2024

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ABSTRACT

Objectives Different intrathoracic perfusion therapeutic regimens are available for non-small cell lung cancer with malignant pleural effusion (MPE). Antiangiogenic agents are often used to control MPE, and the results are satisfactory. Here, we performed a network meta-analysis to reveal optimal combinations of antiangiogenic agents and chemical agents and assess their effectiveness and safety.

Design Systematic review and network meta-analysis.

Data sources PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database and Chinese National Knowledge Infrastructure were searched from inception to May 2023. Eligible studies were randomised controlled trials that reported on curative effect of MPE.

Data extraction and synthesis The Cochrane Collaboration tool was used to assess risk of bias. The consistency was evaluated by examining the agreement between direct and indirect effects. Network meta-analysis was performed and the ranking probabilities of being at each possible rank for each intervention were estimated. Comparison-adjusted funnel plots were obtained to assess publication bias.

Results A total of 46 studies were included in the analysis. Among them, we included a total of seven interventions. A total of 3026 patients participated in this analysis. According to the results of the network meta-analysis, some antiangiogenic agents combined with chemotherapy regimens improved objective response rate (ORR) and disease control rate (DCR) and quality of life (QOL). The rank probabilities suggested that in terms of ORR, DCR and QOL, Endostar plus lobaplatin was the first-ranked intervention.

Conclusion Administration of antiangiogenic agents plus chemical agents significantly improved the clinical response and QOL. In addition, Endostar plus lobaplatin was the most effective combination.

PROSPERO registration number CRD42021284786.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The large number of studies and the considerable sample size enhanced the statistical power of our analysis.
⇒ The risk of bias tool recommended by Cochrane was used to assess the risk of bias of included randomised controlled trials.
⇒ Meta-regression analysis was performed to determine if potential effect modifiers influence the outcomes.
⇒ The absence of closed loops within the network prevented a formal assessment of inconsistency.

INTRODUCTION

Malignant pleural effusion (MPE) is the accumulation of exudative fluid in the pleural cavity as a result of malignancy; it is usually caused by malignant infiltration of the pleura and often results in dyspnoea, chest tightness and shortness of breat.[1] According to Global Cancer Statistics released by GLOBOCAN in 2020, lung cancer is the leading cause of cancer deaths worldwide and accounts for the most common cause (approximately 35.6%) of MPE.[2 3] Studies have revealed that lung cancer combined with MPE has a worse prognosis than other malignant tumours, with a median survival of 3.3 months.[4] Traditional treatments for MPE include pleurodesis, indwelling pleural catheters and thoracic perfusion of chemotherapeutic agents.[4] Currently, with various antiangiogenic agents being approved for cancer treatment, antiangiogenic therapy for MPE has attracted increasing attention.

Vascular endothelial growth factor (VEGF), a proangiogenic factor, has a prominent role in tumour angiogenesis, host vascular endothelial cell activation, malignant proliferation and metastasis.[5] High expression levels of VEGF have been confirmed in the serum of patients with cancer and in MPEs. Antiangiogenic agents (bevacizumab and Endostar) have been approved for MPE treatment, and the results are satisfactory.

Bevacizumab, a humanised monoclonal antibody with high binding affinity to VEGF, blocks VEGF signalling and decreases the formation of pleural effusion.[6] Endostar is a modified and recombinant human endostatin (Rh-endostatin). It is now a common angiogenesis antagonist and has been widely used in clinical practice to treat a wide range of tumours.[7]

There have been several studies on the efficacy of intrapleural perfusion with antiangiogenic agents combined with chemotherapy in the treatment of MPE,[8–11] but comparisons between multiple schemes are lacking, and the results are inconsistent. Network meta-analysis (NMA) allows for the comparison of multiple treatment regimens simultaneously, which is particularly valuable given the lack of direct head-to-head comparisons in the existing literature. Although some meta-analyses exist on individual treatments, our NMA provides a comprehensive comparative effectiveness analysis across multiple regimens, offering a broader perspective on the optimal treatment strategy for MPE in non-small cell lung cancer (NSCLC). Notably, there are no guidelines for the treatment of MPE; hence, we performed this systematic review and NMA to identify the optimal combination strategy to aid clinical decision-making.

MATERIALS AND METHODS

Registration and guidelines

The protocol of this systematic review and NMA has been registered in PROSPERO (CRD42021284786). The reporting of this NMA follows the Preferred Reporting Items for Systematic Reviews statement for NMAs checklist[12] (online supplemental table S1).

Differences between protocol and review

The initial protocol registered in PROSPERO (CRD42021284786) listed a broader range of outcomes, including dyspnoea, pain, functional status. However, post data extraction, it was observed that there were insufficient data for these planned outcomes across the included studies, preventing a robust meta-analysis. As a result, we focused on those outcomes for which sufficient data were available: objective response rate (ORR), disease control rate (DCR), quality of life (QOL) and treatment-related adverse events (TRAEs). This adjustment was necessary to maintain the integrity and validity of the analysis.

Search strategy and eligibility criteria

We searched electronic databases, including PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI), from inception to 25 May 2023, using the following keywords: “Endostar”, “recombinant human endostatin”, “Rh endostatin”, “yh-16”; “Bevacizumab”; “Lung Neoplasms”; “Pleural Effusion, Malignant” and “Drug Therapy” (online supplemental table S2). In this search, there were no restrictions on the language or publication date. In addition to searching electronic databases, we also reviewed relevant systematic reviews to identify primary studies that met our inclusion criteria. Publications were considered eligible based on the following criteria: (1) the study design was a randomised controlled trial (RCT); (2) the study participants were adult patients who had a clear histopathological diagnosis of NSCLC with pleural effusion and (3) the included studies must compare at least two of the following seven treatments, including pleural perfusion of bevacizumab plus chemical agents, Endostar plus chemical agents or chemical agents alone. Chemical agents include nedaplatin (NDP), lobaplatin (LBP) and cisplatin. During treatment, no patients received systematic chemotherapy, chemoradiotherapy, hyperthermia or other traditional Chinese medicine injections and (4) the studies included the ORR and DCR. Furthermore, non-clinical controlled trials, literature reviews, duplicate publications, case reports, animal research papers, conference abstracts, systematic reviews and meta-analyses, and studies with insufficient information for data extraction were excluded. Title and abstract screening and full-text screening were conducted independently and in duplicate by two reviewers. Discrepancies were resolved through discussion with a third reviewer.

Types of outcomes

Outcomes included the ORR, DCR, QOL and adverse reaction rate. The included articles were required to have ORR and DCR outcomes. Referring to previous evaluation criteria,[13] we defined the clinical response criteria as follows: (1) a complete response (CR) occurred when effusion disappeared for more than 4 weeks; (2) a partial response (PR) occurred when effusion was reduced >50% for more than 4 weeks; (3) stable disease (SD) was defined as reduced effusion <50% or increased effusion <25% and (4) progressive disease was effusion increased >25% along with other signs of progression or symptomatic reaccumulation of the fluid requiring repeat treatment. The ORR was defined as the ratio of the total number of patients experiencing CR and PR to the total number of patients. DCR was defined as the ratio of the total number of patients experiencing CR, PR and SD to the total number of patients. QOL was measured by the Karnofsky performance score (KPS). Improved (KPS increased by more than 10 points) and stable (KPS changed by less than 10 points) levels were considered to indicate efficacy. The safety outcomes included adverse reactions, such as myelosuppression, hypohepatia and gastrointestinal effects (regardless of the severity (any grade (AG) or grade 3 or more)).

Data extraction and quality evaluation

The required data were independently extracted by two reviewers, and the quality assessment of the studies was performed afterward. For eligible studies, the following data were extracted: the first author, study year, proportion of males, mean age, treatment plan, volume of MPE,

performance status, ORR, DCR, QOL, incidence of TRAEs and grade 3 or higher TRAEs (≥ grade 3 TRAEs) related to treatments. The risk of bias for each trial was assessed using the Cochrane risk of bias method,[14] which includes random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting and other concerns. A study is classified as low risk only if all evaluated items are deemed low risk. Conversely, if any item is judged high risk, the study is classified as high risk. Studies with any item rated as unclear are classified accordingly. Each study was independently evaluated by two reviewers, and any discrepancies were resolved through discussion with a third reviewer.

Statistical analysis

The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs (including AG-gastrointestinal effect, AG-hypohepatia, AG-myelosuppressive effects, grade 3 or higher (G3)-gastrointestinal effect, G3-hypohepatia and G3-myelosuppressive effects). The variations in dosing and scheduling across studies were minimal and consistent enough that we considered them unlikely to significantly influence the therapeutic effects. Thus, the same interventions with the different doses and schedules were grouped together.

Stata V.15.0 was used to graphically display the results. The NMA was performed using the 'rjags' and 'gemtc' packages in R V.4.2.3. We used non-informative uniform and normal prior distribution. Non-informative uniform priors were used for the heterogeneity parameter (τ), representing the SD of the random effects across studies. This choice was made to allow for a wide range of possible values and to minimise prior influence on the estimation process. Specifically, a uniform prior with a range of U (0, 5) was used for τ. Normal priors were applied to the treatment effects (log-odds ratios) for each intervention comparison. The treatment effects were modelled using N (0, 10^2) priors, indicating that we expected the treatment effects to be centred around zero with a wide range of possible values to capture any uncertainty in the effects.

The NMA model was estimated using the Monte Carlo Markov Chain (MCMC) method. We employed the MCMC method to run 4 MCMC chains simultaneously, setting the number of simulations to 5000 and the number of iterations to 20 000. The convergence of the model was assessed by the Brooks-Gelman-Rubin diagnostic and visual inspection of trace plots. The results are shown as ORs and 95% credible intervals (CrIs). Fixed and random effects models were considered and compared using the deviance information criterion. For each model, goodness-of-fit to data was evaluated using residual deviance.[15] Heterogeneity was assessed using the 'getmc' package. Between-study variance (τ^2), Cochran's Q and I^2 statistics were calculated to quantify heterogeneity. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. All treatments were ranked according to the surface under the cumulative ranking area curve (SUCRA). Higher SUCRA probabilities indicated better treatment effects.[16] To determine if potential effect modifiers influence the outcomes (ORR and DCR), we conducted a meta-regression analysis. This analysis considered variables such as sample size (categorised into <50, ≥50 and <100 and ≥100), mean age (<60 years and ≥60 years) and sex ratio (male/female <1, male/female ≥1) as potential covariates. Comparison-adjusted funnel plots were employed to assess publication bias. Statistical analyses of the pooled ORRs were performed using R V.2.3. We generated forest plots with the use of statistical software R V.4.2.3 to visualise the effect of treatment comparisons. The criteria for the selection of comparisons are considered in NMAs, including clinical relevance, data availability and heterogeneity assessment.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Literature search and study characteristics

We identified 5670 records from 7 electronic databases. After removing duplicates, 4442 titles and abstracts were reviewed, and 130 papers were selected for full-text screening. Finally, 46 studies were included in the NMA (figure 1 and online supplemental table S3).[17–62] Studies were published between 2012 and 2023 and included a total of 3026 patients. The intrapleural administration therapeutic regimens included Endostar+NDP (Endo+NDP), Endostar+DDP (Endo+DDP), Endostar+LBP (Endo+LBP), bevacizumab+DDP (Bev+DDP), DDP, NDP and LBP. In particular, 32 studies compared Endostar plus chemical agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical agents versus chemical agents alone and 7 studies compared the effects of different chemical agents. The general characteristics of the included studies are presented in online supplemental table S3.

Quality assessment

Figure 2 presents our risk of bias assessments for the studies. There were 41 RCTs among the 46 studies in the unclear risk of bias for random sequence generation. None of the studies reported the processes used for allocation concealment or blinding of outcome assessment; only one study mentioned the blinding of participants and personnel. The outcome data of all studies were complete, and no other sources of bias were reported.

Network meta-analysis

Objective response rate

All included studies with a total of 3026 patients who reported the data of ORR, ORR, with 1945 patients demonstrating an overall response. The network of

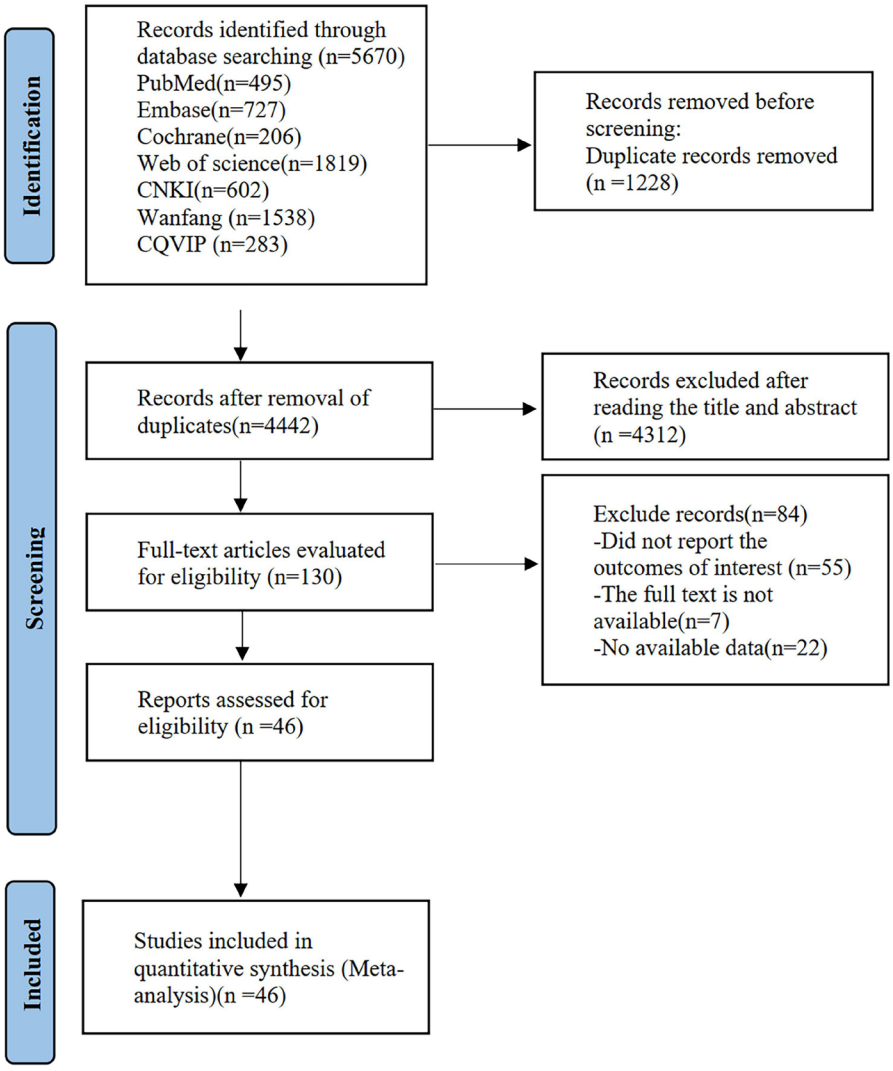

Figure 1 The flow diagram of the study selection process for the network meta-analysis.

studies is presented in online supplemental figure S1. Bev+DDP exhibited a significantly higher ORR than DDP alone, yet it was lower compared with the combinations of Endo+LBP and Endo+NDP. DDP alone showed a significantly lower ORR than all evaluated treatment regimens, including Endo+DDP, Endo+LBP, Endo+NDP, LBP and NDP. Furthermore, Endo+DDP had a lower ORR compared with both Endo+LBP and Endo+NDP, whereas Endo+LBP and Endo+NDP each displayed significantly higher ORRs than either LBP or NDP alone (online supplemental figure S2; table 1).

The SUCRA rank and probability value results indicated that Endo+LBP (95%) was the most likely to improve the ORR, followed by Endo+NDP (88%), NDP (48%), Endo+DDP (46%), LBP (40%), Bev+DDP (33%) and DDP (0.002%) (online supplemental figure S3; table 2).

Disease control rate

All included studies with a total of 3026 patients reported the data of DCR, with 2586 patients achieving disease control. The network of studies is presented in online supplemental figure S1. Bev+DDP demonstrated a

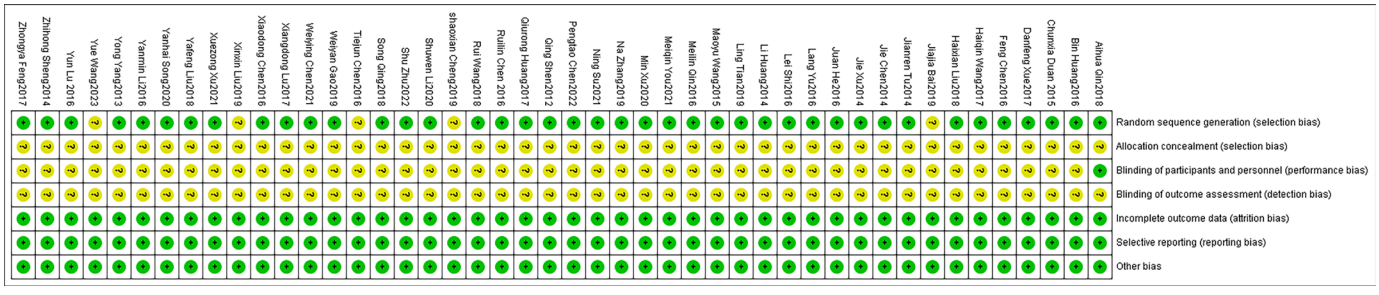

Figure 2 Assessment of risk of bias.

Table 1 The league table of network meta-analysis for ORR according to all interventions

OR 95% CrIs						
Bev_DDP						
3.19 (2.11, 4.92)*	DDP					
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP				
0.16 (0.05, 0.53)*	**0.05 (0.02, 0.15)***	**0.19 (0.06, 0.59)***	Endo_LBP			
0.25 (0.09, 0.68)*	**0.08 (0.03, 0.2)***	**0.29 (0.11, 0.75)***	**1.54 (0.35, 6.84)**	Endo_NDP		
0.92 (0.4, 2.03)	0.29 (0.14, 0.56)*	**1.08 (0.52, 2.18)**	5.69 (2.37, 14.65)*	**3.73 (1.17, 12.04)***	LBP	
0.81 (0.38, 1.71)	0.25 (0.13, 0.46)*	**0.95 (0.49, 1.81)**	**5.06 (1.39, 19.02)***	3.28 (1.65, 6.76)*	**0.88 (0.35, 2.24)**	NDP

ORs between the included interventions according to the results of network meta-analysis.
Data bolded in black indicate they are from an indirect comparison.
*p<0.05.
Bev_DDP, bevacizumab+cisplatin; CrIs, credible intervals; Endo_DDP, endostar+cisplatin; Endo_LBP, endostar+lobaplatin; Endo_NDP, endostar+nedaplatin; ORR, objective response rate.

significantly higher DCR compared with DDP alone. DDP, in turn, exhibited a lower DCR relative to Endo+DDP, Endo+LBP, Endo+NDP and NDP alone. Among these, Endo+DDP showed a significantly lower DCR than Endo+LBP, which itself recorded a higher DCR than Endo+NDP. Moreover, Endo+NDP achieved a significantly higher DCR compared with NDP alone (online supplemental figure S2 and table S4). The DCR was ranked for all treatments by estimating the SUCRA value. The results were as follows: Endo+LBP (95%), Endo+NDP (83%), Bev+DDP (51%), Endo+DDP (49%), NDP (41%), LBP (30%) and DDP (1%) (online supplemental figure S3; table 2).

Quality of life

19 studies, involving a total of 1173 patients reported the QOL, with 654 patients achieving high QOL. These studies constituted five pairs of direct comparisons involving six interventions (Endo+DDP, Endo+LBP, Bev+DDP, DDP, NDP and LBP). The network diagram is shown in online supplemental figure S1. DDP was associated with a lower QOL compared with Endo+DDP (OR=0.3, 95% CrI (0.22, 0.39)), Endo+LBP (OR=0.1, 95% CrI (0.02, 0.57)) and LBP (OR=0.31, 95% CrI (0.1, 0.93)) (online supplemental figure S2 and table S5).

After ranking the six interventions based on the SUCRA values, the results were as follows: Endo+LBP (95%), Endo+DDP (69%), LBP (63%), Bev+DDP (33%), NDP (29%) and DDP (10%), as shown in online supplemental figure S3 and table 2.

Safety and toxicity

35 studies included 582 patients reported the data of safety profiles. Including a total of 582 patients for any-grade gastrointestinal effect, and 37 patients for grade 3 or higher gastrointestinal effect. A total of 527 patients reported AG myelosuppressive effect, with 37 patients achieving grade greater than or equal to 3. A total of 122 patients reported AG hypohepatia, with 9 patients achieving grade greater than or equal to 3. The adverse reactions mainly included myelosuppression, headache, hypohepatia, renal insufficiency, gastrointestinal effects,

Table 2 Rank probabilities of each treatment for different outcome measures based on the network meta-analysis

	BEV_DDP	DDP	Endo_DDP	Endo_LBP	Endo_NDP	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19	0.59	0.47
Hypohepatia	0.55	0.46	0.35	0.57	0.30	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.45	0.57	0.74

The data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.
Bev_DDP, bevacizumab+cisplatin; DCR, disease control rate; Endo_DDP, endostar+cisplatin; Endo_LBP, endostar+lobaplatin; Endo_NDP, endostar+nedaplatin; G3, grade three or higher; ORR, objective response rate; QOL, quality of life; SUCRA, surface under the cumulative ranking area curve.

Table 3 Meta-regression analysis for the impact of potential factors on the outcomes

	Overall response rate		Disease control rate	
	β coefficient (95%CI)	P value	β coefficient (95%CI)	P value
Sample size	−0.65 (−1.91, 0.62)	0.316	−0.73 (−2.47, 1.00)	0.408
Mean age	0.36 (−0.59, 1.31)	0.459	0.18 (−1.28, 1.64)	0.810
Sex	0.12 (−0.84, 1.08)	0.811	−1.26 (−2.72, 0.20)	0.091

electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia and gastrointestinal effects. The NMA included seven therapeutic regimens for TRAEs of AG and six therapeutic regimens for TRAEs of grade greater than or equal to 3 (online supplemental figure S1). We did not find statistically significant differences in myelosuppression or hypohepatia. A single chemotherapeutic agent caused fewer gastrointestinal reactions (online supplemental tables S7–S11).

The probabilities of adverse events were ranked for all treatments by estimating the SUCRA value. A lower SUCRA value indicated a higher probability of AEs and a poorer treatment regimen. The corresponding ranking of incidences is shown in online supplemental figure S3 and table 2.

Meta-regression analysis

Table 3 shows the results of the meta-regression analysis for demographic and clinical variables (sample size, mean age and sex). Results indicated that none of these variables have significant impact on the ORR and DCR.

Publication bias

The comparison-adjusted funnel plots are presented in online supplemental figure S4. Overall, no distinct asymmetry was found in the comparison-adjusted funnel plot on the ORR, DCR, QOL, AG-gastrointestinal effects, AG-myelosuppression, G3-myelosuppression and G3-hypohepatia, indicating no evidence of publication bias. However, the comparison-adjusted funnel plot on AG-gastrointestinal effects, G3-gastrointestinal effects and AG-hypohepatia were not symmetric around the zero line, which revealed that there could be small-study effects.

DISCUSSION

Currently, to the best of our knowledge, intrapleural perfusion with antiangiogenic agents plus chemical agents in controlling MPE conferred satisfying clinical outcomes for patients with NSCLC. Although Endostar/bevacizumab combined with chemotherapy is widely used to treat MPE, there is a lack of head-to-head direct comparisons to determine the best regimen. Hence, we performed a NMA. In this analysis, two antiangiogenic agents and three chemical agents formed seven treatment regimens to identify which treatment was optimal in achieving higher clinical responses and QOL and fewer TRAEs. The results suggested the following:

1. Intrapleural administration of Endostar plus LBP was associated with the best ORR and DCR outcomes, followed by Endostar plus NDP.
2. For the ORR, Endo+LBP and Endo+NDP were significantly more favourable than Bev+DDP, while there were no significant differences in the efficacy of Endostar plus chemotherapy or bevacizumab plus chemotherapy with regard to DCR.

Endostar, an endogenous angiogenic inhibitor, can inhibit endothelial cell migration, repress the neovascularisation of tumours, block the nutrient supply of tumour cells, and thus prevent tumour proliferation and metastasis. In addition, Endostar reduces the permeability of tumour neovascularisation, thereby reducing the production of pleural effusion.[63] Xia *et al*[8] performed a meta-analysis that included 55 RCTs with a total of 3379 patients with lung cancer to investigate the efficacy, safety and cost-effectiveness of Endostar and platinum in controlling MPE. All the studies in the meta-analysis were published in Chinese. This supported the findings in the current NMA.

Bevacizumab is another frequently studied antiangiogenic agent and plays an important role in the treatment of several types of tumours.[7] It can prevent VEGF-induced vascular permeability and tumour cell migration, thereby reducing MPE.[64] Several studies have demonstrated the efficacy and safety of bevacizumab for the management of MPE. Du *et al*[65] compared the efficacy of combined intrapleural therapy with bevacizumab and cisplatin versus cisplatin alone in controlling MPE. The results revealed that bevacizumab plus cisplatin improved the ORR from 50% to 83.3%. However, in our meta-analysis, the pooled ORR of Bev+DDP was 73.8%, and the true efficacy of Bev might have been overestimated. After a literature search, we found no head-to-head comparison between Bev plus other chemical agents and the sole administration of chemical agents other than cisplatin. Therefore, more combination therapeutic regimens still need to be investigated in the future.

MPE is generally considered to be a manifestation of a malignancy in its preterminal stage. Hence, the interventions are palliative in nature. The main goal of treatment is to palliate symptoms and improve QOL.[66] In our study, we found that intrapleural injection of Endostar combined with DDP was the best in terms of improving QOL, while DDP was the worst.

With regard to the safety profile, although there was no significant difference in the incidence of

myelosuppression or hypohepatia between therapeutic regimens in our study, regardless of the severity, the incidence of AG-gastrointestinal effects was significantly more frequent with Endo+DDP and Bev+DDP than with LBP and NDP. Furthermore, in the gastrointestinal effect ranking of the six treatment groups, NDP was the safest, and Endostar plus DDP was the least safe (regardless of the severity (AG or grade 3 or more)). The results of these analyses suggest that safety considerations may be needed when Endostar plus DDP is administered.

The transitivity assumption, which underlies the validity of NMA, was assessed by comparing the distribution of key covariates across the included studies. These covariates—mean age, sex ratio and sample size—were relatively balanced across the different treatment comparisons, suggesting that the assumption of transitivity is plausible. However, it is important to note that unmeasured or inadequately reported effect modifiers could still potentially influence the results. Future studies should aim to collect more homogeneous data and consider additional covariates that may impact treatment effects.

This study had some limitations. First, we used only Chinese and English databases, which might have led to retrieval bias, and most of the trials did not report concealment or blinding, which might undermine the validity of the overall findings. Second, all the included RCTs were published in China, and the generalisability of the results is limited. Third, all of the included studies are at unclear risk of bias, and many comparisons rely solely on indirect evidence, as there are no closed loops within the network. This can lead to potentially misleading SUCRA rankings. Therefore, SUCRA rankings should be interpreted with caution. Fourth, although we did not impose restrictions based on the indexing status of journals during the literature search inclusion criteria, some of these journals are of low quality. The potential influence of journal quality on our results warrants cautious interpretation. Fifth, the absence of closed loops in the network precludes the formal assessment of inconsistency, which is a crucial aspect of NMA. Future studies should aim to include more diverse treatment comparisons to allow for a comprehensive inconsistency evaluation. Sixth, the results in online supplemental tables S9–S11 include analyses of all events and are intended to provide a comprehensive perspective. We believe that these results are important in the context of understanding whole NMAs, although the results for rare events may be subject to greater uncertainty. Because of the rarity of events, the use of informative priors may introduce additional bias, while non-informative priors, although leading to wider CrIs, can more objectively reflect the uncertainty of the data. Therefore, the potential influence on our results should be interpreted with caution.

Conclusions

This NMA comprehensively compared various treatments for thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity features. To the best of our knowledge, this is the first comprehensive NMA study of its kind. The results showed that antiangiogenic agents combined with chemotherapy regimens could improve clinical effectiveness and QOL. In our study, Endo+LBP was the most effective. However, high-quality RCTs with larger sample sizes are needed to further confirm the evidence.

Contributors YX conducted overall design, data collection, analysis and draft writing. YC and LJ were responsible for data collection, partial analysis and partial draft writing. YY, WS and XZ were responsible for data collection, YC and YX revised the manuscript. YX was responsible for the conduct of the study as a guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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