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ARTICLE

Short-Term Efficacy of Different First-Line Chemotherapy Regimens for Advanced Non-Small Cell Lung Cancer: A Network Meta-Analysis

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This study intends to compare short-term efficacy of 12 chemotherapy regimens in treatment of advanced non-small cell lung cancer (NSCLC) by a network meta-analysis (NMA). PubMed, Cochrane Library, and Embase were searched from the inception of each database to June 2018. Randomized controlled trials (RCTs) of the 12 chemotherapy regimens for advanced NSCLC were included. Direct and indirect evidence were combined by NMA to evaluate the odds ratio and the surface under the cumulative ranking curves (SUCRA) of the 12 chemotherapy regimens. Nineteen RCTs that met our inclusion criteria were collected in this study. For partial response (PR), gemcitabine exhibited relatively poor efficacy compared with cisplatin + gemcitabine, carboplatin + gemcitabine, carboplatin + paclitaxel, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine. For overall response rate (ORR), gemcitabine had poorer efficacy than cisplatin + gemcitabine and paclitaxel + gemcitabine. For disease control rate (DCR), compared with carboplatin + gemcitabine and gemcitabine, paclitaxel + gemcitabine had a better efficacy. Gemcitabine had the lowest SUCRA values in terms of complete response, PR, ORR, stable disease, and DCR; whereas paclitaxel + gemcitabine ranked the highest in ORR, progressive disease, and DCR. The cluster analysis revealed that cisplatin + gemcitabine, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine had better short-term efficacy for advanced NSCLC. Collectively, short-term efficacy of multidrug combination chemotherapy regimens was superior to that of single-drug chemotherapy regimens for advanced NSCLC. Cisplatin + gemcitabine, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine may have particularly prominent short-term efficacy for advanced NSCLC.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Currently, patients with non-small cell lung cancer (NSCLC) are mainly treated by surgery, platinum-based chemotherapy, radiotherapy, molecular targeted therapy, and cell biological therapy. Although the molecular targeted therapy is better than chemotherapy with regard to progression-free survival and tolerability, targeted therapy does not surpass chemotherapy considering the overall survival time.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the optimal chemotherapy regimen for advanced NSCLC?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Cisplatin + gemcitabine, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine may have particularly prominent short-term efficacy for advanced NSCLC.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These findings will have important clinical implications for the treatment of NSCLC and provide doctors with the ability to better select treatment regimen for patients with NSCLC.

Non-small cell lung cancer (NCLSC) accounts for about 85% of lung cancers, with 5-year survival rates of 15.9%.[1] It was reported that nearly 75% of patients with NSCLC presented with the advanced-stage disease because obvious symptoms were absent from its early stage.[2] Environmental factors, like smoking, radon, and asbestos, as well as some internal genetic factors, have been suggested as possible etiological factors of NSCLC.[3] Currently, the main treatments for this disease include surgery, platinum-based chemotherapy, radiotherapy, molecular targeted therapy, and cell biological therapy.[4,5] Even though great advances have been achieved in lung cancer screening, diagnostics, and therapy since the last century, it is extremely significant to understand the application of NSCLC therapies and outcomes in clinical practice.[6]

Currently, platinum drugs are recognized as one of the accesses to prolong survival of patients with advanced NSCLC.[7] It interferes with the DNA replication by the electrophilic effect

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of Pt (II) and DNA to form DNA crosslinks.[8] In general, there are several kinds of platinum drugs, including cisplatin, carboplatin, oxaliplatin, nedaplatin, and lobaplatin.[9] However, the third-generation chemotherapy drugs, including gemcitabine, vinorelbine, paclitaxel, docetaxel, and irinotecan, have been developed to make up for the high toxicity and resistance deficiencies of platinum drugs since 1990.[10] Recently, some research had been done to identify the optimal treatment and improve patients' living quality by evaluating the efficacy of two or three chemotherapy regimens: a previous study showed that bevacizumab + cisplatin + gemcitabine was a more effective regimen than cisplatin + pemetrexed for patients with advanced NSCLC. [11] Another study suggested that regimen of a combination of cetuximab with taxane/carboplatin failed to significantly improve the primary end point compared with taxane/carboplatin for advanced NSCLC.[12] Nevertheless, the optimal chemotherapy regimen for advanced NSCLC remains elusive.[13]

The evaluation standard of solid tumor treatment efficacy has been developed for nearly 40 years. The Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) has become a new standard used in the international tumor field at present, in which overall response rate (ORR), progressive disease (PD), and other short-term indicators have irreplaceable guiding significance.[14] ORR is the sum of complete response (CR) and partial response (PR). CR refers to the disappearance of all target lesions, no existence of new lesions, and with the tumor markers being normal for at least 4 weeks. PR refers to the sum of all maximum diameters of lesions reduced by at least 30%, which maintained for at least 4 weeks. Stable disease (SD) is defined as a < 50% reduction and < 25% increase in total of the product of the two vertical diameters of all measured lesions with the appearance of no new lesions. PD is defined as an increase in the product of two perpendicular diameters of any measured lesion of > 25% with appearance of new lesions.[15] Moreover, a study showed that CR, PR, ORR, SD, PD, and disease control rate (DCR) was utilized to evaluate short-term efficacy in RECIST.[16] It is noted that ORR is the main therapeutic evaluation index of the phase II trial, which can provide preliminary evidence of biological activity of drugs and credible evidence for further phase III trials.[17] Sole drug therapy with ORR significantly higher than 30% has nearly 98% specificity and 89% positive predictive value in obtaining regulatory approval.[18] Therefore, in total, 19 randomized controlled trials (RCTs) were included in this study to evaluate the short-term efficacy of 12 chemotherapy regimens for patients with advanced NSCLC, and it is expected to provide effective regimens for the treatment of NSCLC.

MATERIALS AND METHODS

Literature search

The electronic retrieval of English databases, such as PubMed, Cochrane Library, and Embase, were searched from the inception of each database to June 2018. Search words, including chemotherapy, cisplatin, fluorouracil, irinotecan, vinorelbine, gemcitabine, non-small-cell lung cancer/lung cancer, and RCTs were retrieved based on the principle of combination of keywords and free words.

Inclusion and exclusion criteria

The inclusion criteria were defined as follows: (i) research type: RCT; (ii) sole chemotherapy regimens: cisplatin + gemcitabine, carboplatin + gemcitabine, gemcitabine, carboplatin + paclitaxel, paclitaxel + gemcitabine, vinorelbine, gemcitabine + vinorelbine, cisplatin + gemcitabine + vinorelbine, docetaxel, cisplatin + docetaxel, cisplatin + pemetrexed, and cisplatin + vinorelbine; (iii) research subjects: patients with advanced NSCLC (both squamous and nonsquamous) with at least one measurable lesion at stage III/IV confirmed by histology and diagnosed according to the standard of the RECIST[14]; (iv) outcomes: CR, PR, ORR, SD, PD, and DCR (ORR = CR + PR; DCR = CR + PR + SD) defined following the standard of the RECIST (considering the feasibility of the meta-analysis, the specific outcome indicators were not used as the initial criteria for inclusion and exclusion).[19] Exclusion criteria were defined as follows: (i) articles with incomplete data (e.g., the nonpaired study); (ii) non-RCTs; (iii) duplicate articles; (iv) conference reports, systematic reviews, or summary articles; (v) articles about second-line chemotherapy regimens for the treatment of NSCLC; (vi) non-English articles; (vii) non-human studies; (viii) no pharmacotherapy; (ix) articles not about NSCLC; (x) studies with patients who received chemoradiotherapy before experiment; and (xi) studies with pregnant or lactating patients.

Data extraction and quality assessment

Two researchers independently extracted the data from articles enrolled in this study using the unified data collection form. Disagreements between two reviewers were resolved by a discussion with other researchers until a consensus was achieved. Two or more researchers evaluated RCTs with the Cochrane risk bias assessment tool,[20] which contained six domains, such as random distribution, allocation concealment, blind method, outcome data loss, optional outcomes report, and other bias. For each domain, a judgment of "yes," "no," or "unclear," which was assigned by the assessment system represented a low, high, or unclear risk of bias, respectively. A study was determined as having a low risk of bias with no domain or one domain decided as "unclear" or "no." On parallel, if more than four domains were reported with "unclear" or "no," the study was considered as having a high risk of bias. Other circumstances were considered as having a moderate risk of bias.[21] Review Manager 5 (RevMan version 5.2.3; Cochrane Collaboration, Oxford, UK) was used for quality assessment and investigation of publication bias.

Statistical analysis

First, direct evidence under the fixed-effects model was analyzed using pair-wise meta-analyses with R version 3.2.1 and the meta-package. The pooled estimates of odds ratio (OR) with 95% confidence intervals (CIs) of six end-point outcomes were shown. The χ^2 test and I-square test were used for testing heterogeneity among the studies. For enumeration data, we chose the MantelHaenszel method, which was suitable for the fixed effect model. This method used the principle of hierarchical analysis to take each layer as an independent study and calculate the comprehensive OR value for examination.[22] Second, R version 3.2.1 software

was used to draw a network evidence plot of chemotherapy regimens. Every node represented one chemotherapy regimen; the node size represented the sample size of the corresponding chemotherapy regimen; the line thickness between two nodes represented the number of RCTs of two chemotherapy regimens. Then, a random-effect network meta-analysis (NMA) with the gemtc package was conducted, and it modeled the relative effects (e.g., log-OR) fitting a generalized linear model under the Bayesian framework by linking to JAGS, OpenBUGS, or WinBUGS as first described by Lu and Ades[23] and extended by others.[24,25] Additionally, the node-splitting method was utilized to evaluate the consistency between direct and indirect evidence. The consistency model would be applied if the node-splitting result showed $P > 0.01$.[26] In order to proof ORs, the surface under the cumulative ranking curves (SUCRA) of each chemotherapy regimen was calculated based on a Bayesian approach. The larger the SUCRA value, the better the efficacy of the chemotherapy regimen.[27,28] Heterogeneity test was carried out among outcomes using a cluster analysis.[27] All analyses were conducted with R version 3.2.1.

RESULTS

Baseline characteristics of included studies

A total of 4,066 articles were initially retrieved from electronic databases. A total of 336 duplicate articles, 236 letters or reviews, 152 non-English articles, and 1,204 non-human studies were excluded. After full and further assessment of the remaining 2,138 articles, 891 noncohort studies, 599 studies irrelevant to NSCLC, 628 studies irrelevant to chemotherapy, and 1 study without complete data were further excluded. Finally, 19 RCTs were considered eligible to be enrolled in the current NMA[19,22,29–45] (**Figure 1**). There were 4,322 patients with advanced NSCLC, the majority of who received the chemotherapy regimen of carboplatin + gemcitabine. The enrolled studies all were published from 2003–2015. Study subjects of 13 studies were white; and study subjects of 6 studies were Asians. Furthermore, 17 of the 19 studies were two-arm trials, and the other two were three-arm trials. The baseline characteristics of the included studies are shown in **Table S1**. The original data for some outcome indicators (ORR and DCR) are displayed in the **Table S2**, and the Cochrane bias assessment is shown in **Figure 2**.

Pairwise meta-analysis of 12 first-line chemotherapy regimens for advanced NSCLC

The traditional pairwise meta-analysis was carried out to assess short-term efficacies of 12 chemotherapy regimens for the treatment of advanced NSCLC. It turned out that in terms of PR, ORR, and SD, the efficacy of carboplatin + gemcitabine for patients with advanced NSCLC was relatively better than that of gemcitabine (OR = 3.00, 95% CI = 1.71–5.28; OR = 3.27, 95% CI = 1.90–5.62, respectively). As for PR, ORR, and DCR, gemcitabine + vinorelbine had a poorer efficacy for patients with advanced NSCLC when compared with cisplatin + gemcitabine + vinorelbine (OR = 0.48, 95% CI = 0.26–0.86; OR = 0.51, 95% CI = 0.28–0.91; and OR = 0.45, 95% CI = 0.22–0.94, respectively). For ORR and DCR, compared with paclitaxel + gemcitabine, carboplatin + paclitaxel showed a relatively poorer efficacy (OR = 0.40, 95% CI = 0.30–0.54; OR = 0.32, 95% CI = 0.23–0.46, respectively). In terms of PD, compared with cisplatin + gemcitabine + vinorelbine, gemcitabine + vinorelbine exhibited a higher rate of PD (OR = 2.39, 95% CI = 1.04–5.45), which indicated that the efficacy of gemcitabine + vinorelbine was relatively poorer

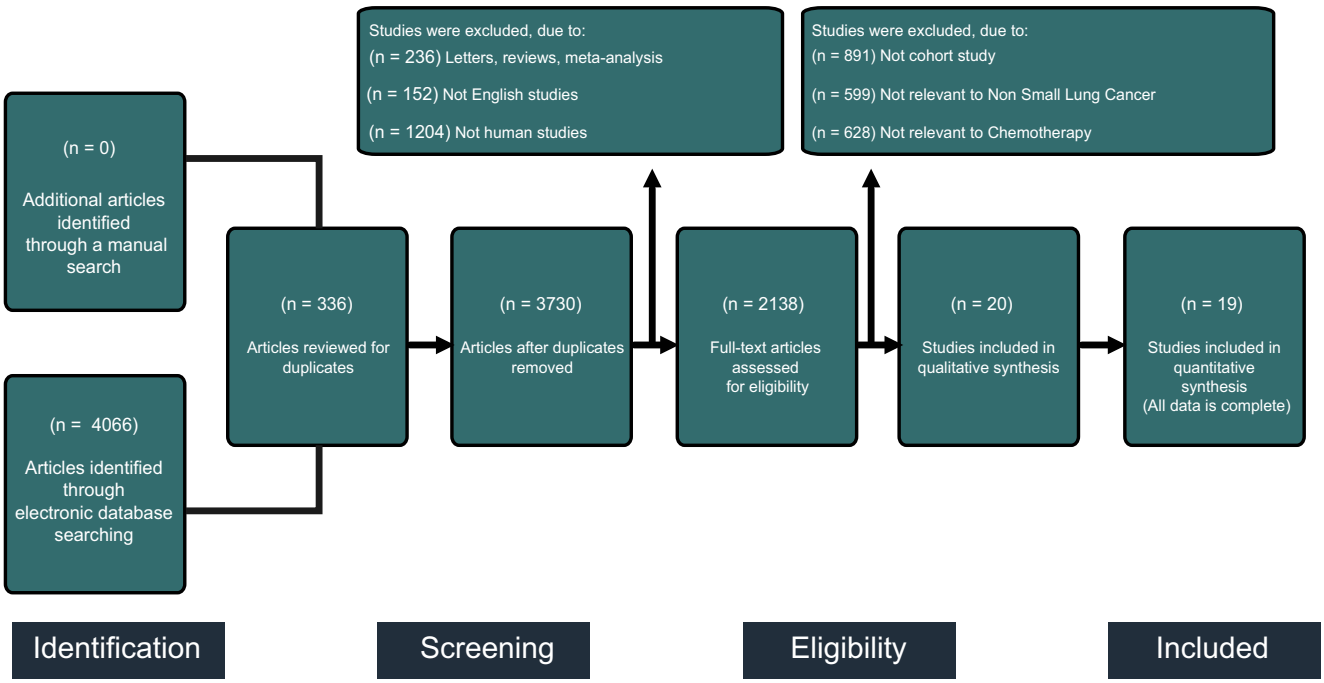

Figure 1 Flow chart of the literature selection.

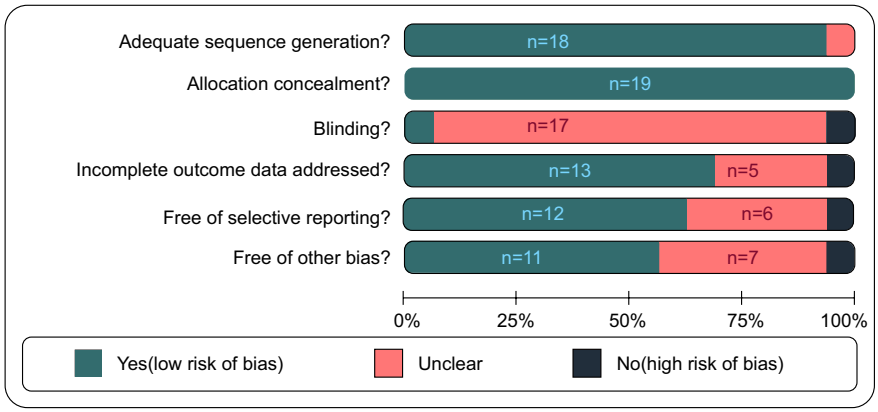

Figure 2 Cochrane risk of bias graph for included studies in current network meta-analysis.

than that of cisplatin + gemcitabine + vinorelbine. However, in terms of CR, there was no significant difference in efficacy among seven chemotherapy regimens for advanced NSCLC, including cisplatin + gemcitabine, carboplatin + gemcitabine, gemcitabine, carboplatin + paclitaxel, paclitaxel + gemcitabine, gemcitabine + vinorelbine, and cisplatin + gemcitabine + vinorelbine (**Table S3**). The first positive comparison, that is, B vs. C (carboplatin + gemcitabine vs. gemcitabine) was taken as an example. Direct comparison showed that for PR, carboplatin + gemcitabine regimen was more effective in patients with advanced NSCLC than gemcitabine chemotherapy alone (OR = 3.00). For B vs. C, there were two studies. The number of events and sample size of B were 7 and 31, the number of events and sample size of C were 3 and 30 in the study of Kusagaya *et al.*[32] The number of events and sample size of B in the study of Sederholm *et al.*[42] were 40 and 142, and those of C were 18 and 159. The primary calculation method was as follows: combining the two studies, the OR1 of intervention measure B = (7 + 40)/(24 + 102), and the OR2 of intervention measure C = (3 + 18)/(27 + 141), and then the OR (B vs. C) = OR1/OR2 = 3.00.

Network evidence of 12 first-line chemotherapy regimens for advanced NSCLC

In terms of CR, PR, ORR, SD, PD, and DCR, it was observed that the most patients received the treatment of carboplatin + gemcitabine, whereas patients receiving gemcitabine + vinorelbine and cisplatin + gemcitabine + vinorelbine were relatively few (**Figure 3**).

Inconsistency test

The node-splitting method was conducted for the inconsistency test of the six outcomes (CR, PR, ORR, SD, PD, and DCR). The results suggested that direct and indirect evidence of all outcomes were consistent, so the consistency model should be used (all $P > 0.01$; **Table S4**).

The main results of NMA

For PR, in comparison with cisplatin + gemcitabine, carboplatin + gemcitabine, carboplatin + paclitaxel, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine, the efficacy of gemcitabine for patients with advanced NSCLC was relatively poorer (OR = 0.19, 95% CI = 0.05–0.67; OR = 0.34, 95% CI = 0.14–0.76; OR = 0.31, 95% CI = 0.10–0.81; OR = 0.32, 95% CI = 0.11–0.81; and OR = 0.17, 95% CI = 0.03–0.83, respectively). In terms of ORR, compared with cisplatin + gemcitabine and paclitaxel + gemcitabine, gemcitabine presented comparatively poorer efficacy (OR = 0.21, 95% CI = 0.05–0.97; OR = 0.16, 95% CI = 0.04–0.73, respectively). However, in terms of CR, there was no significant difference in efficacy among cisplatin + gemcitabine, carboplatin + gemcitabine, gemcitabine, carboplatin + paclitaxel, paclitaxel + gemcitabine, gemcitabine + vinorelbine, and cisplatin + gemcitabine + vinorelbine (**Table S4**, **Figures 4** and **5**).

With regard to DCR, compared with carboplatin + gemcitabine and gemcitabine, paclitaxel + gemcitabine displayed a better efficacy for patients with advanced NSCLC (OR = 2.23, 95% CI = 1.03–4.82; and OR = 6.92, 95% CI = 1.21–41.61, respectively). There was no statistical significance in efficacy among 12 chemotherapy regimens in terms of SD or PD (**Table S5** and **Figure 5**).

SUCRA values

As shown in **Table S5**, SUCRA values of 12 chemotherapy regimens indicated that gemcitabine had the lowest SUCRA values in CR, PR, ORR, SD, and DCR (CR: 34.14%; PR: 19.33%; ORR: 18.92%; SD: 31.36%; and DCR: 19.00%), but gemcitabine + vinorelbine exhibited the lowest SUCRA value in PD (34.67%). In terms of ORR, PD, and DCR, SUCRA values of paclitaxel + gemcitabine were the highest (ORR: 81.50%; PD: 81.33%; and DCR: 86.00%); gemcitabine + vinorelbine had the highest SUCRA values in CR (69.89%); and cisplatin + gemcitabine + vinorelbine presented the highest SUCRA value in PR (88.89%). SUCRA value of carboplatin + paclitaxel ranked the highest as for SD (69.55%).

Cluster analysis

The cluster analysis on the basis of the SUCRA values of ORR, PR, and DCR suggested that paclitaxel + gemcitabine, cisplatin + gemcitabine + vinorelbine, and cisplatin + gemcitabine exhibited relatively better efficacy for the treatment of advanced NSCLC, but the efficacy of gemcitabine and vinorelbine were relatively poorer (**Figure 6**). It should be

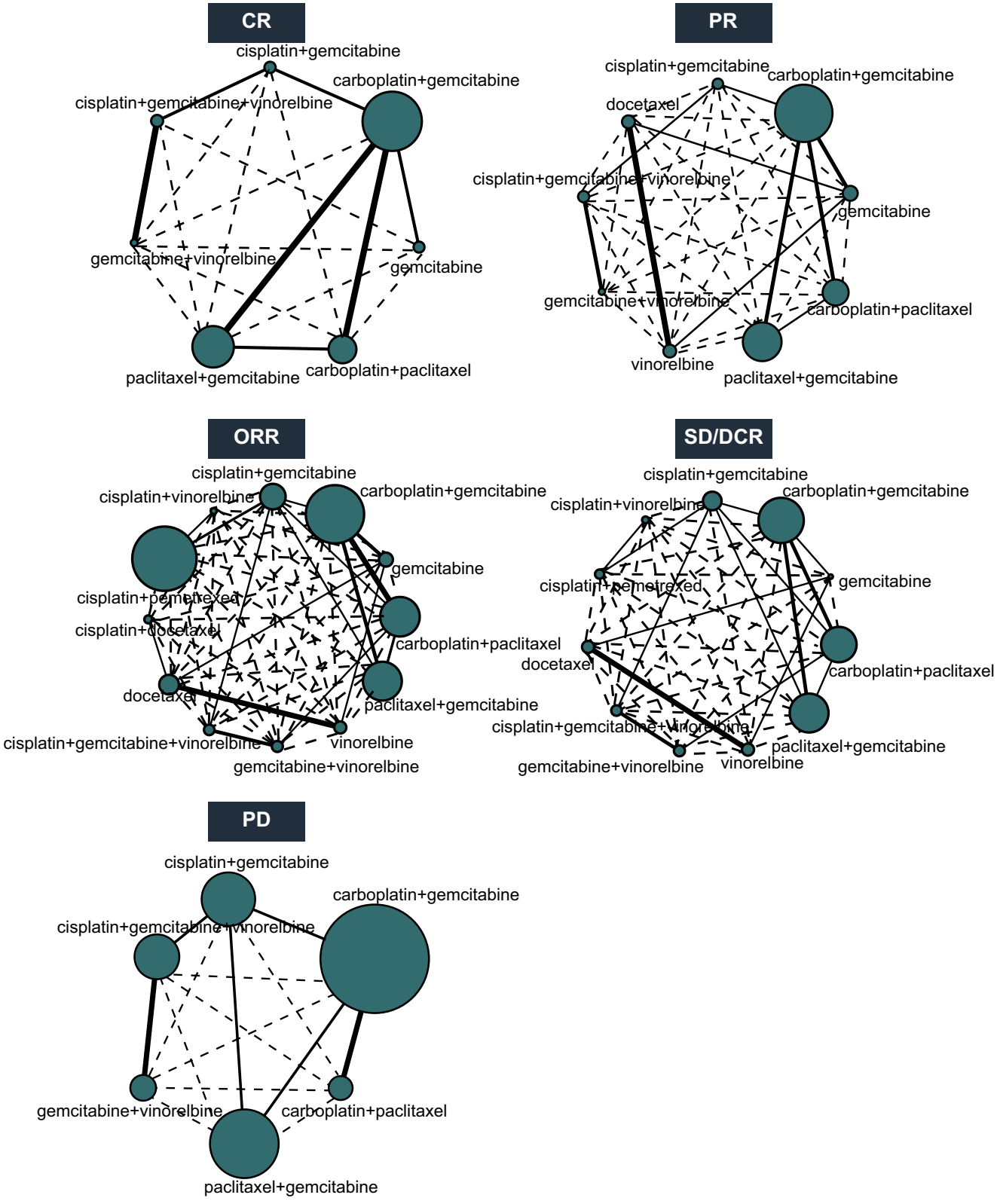

Figure 3 Network evidence plots of CR, PR, ORR, SD, DCR, and PD for the 12 chemotherapy regimens. Every node represented one chemotherapy regimen; the node size represented the sample size of the corresponding chemotherapy regimen; the line thickness between two nodes represented the number of randomized controlled trial of two chemotherapy regimens. CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

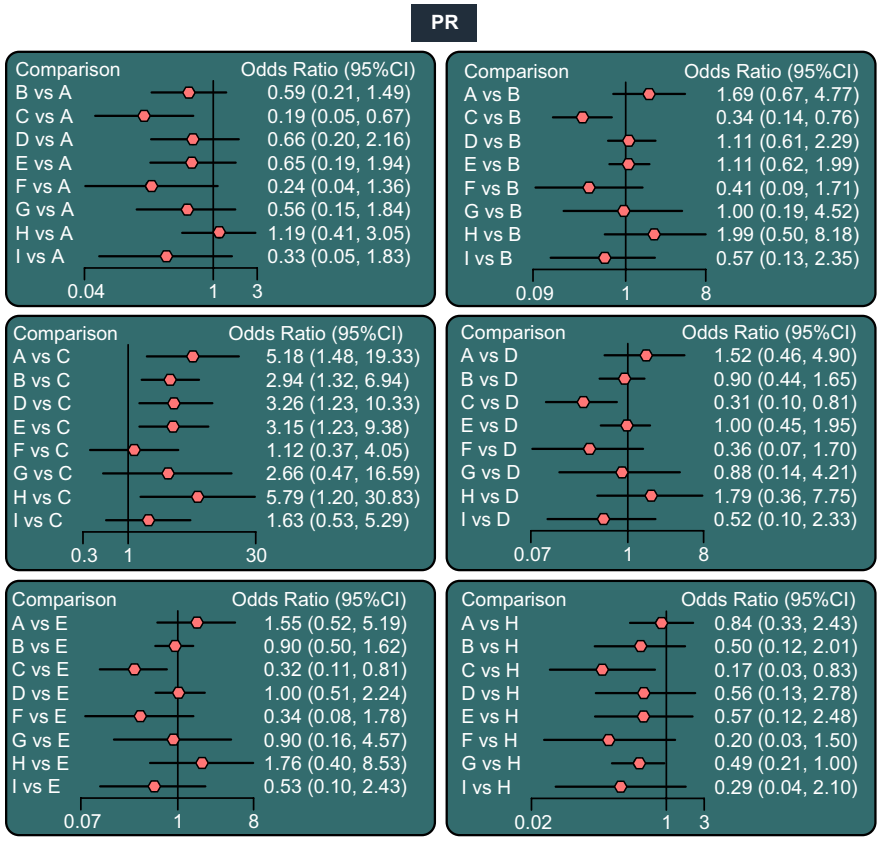

Figure 4 Relative relationship forest plots of PR for the 12 chemotherapy regimens. A, Cisplatin + gemcitabine; B, carboplatin + gemcitabine; C, gemcitabine; D, carboplatin + paclitaxel; E, paclitaxel + gemcitabine; F, vinorelbine; G, gemcitabine + vinorelbine; H, cisplatin + gemcitabine + vinorelbine; and I, docetaxel. CI, confidence interval; PR, partial response.

noted that the prerequisite for cluster analysis was that the outcome indicators included were obtained from the same intervention measures with as many interventions as possible included, which meant that some outcome indicators will be removed because of the lack of interventions. In this study, the key outcome indicators were not removed, and ORR, PR, and DCR were retained to compare the short-term efficacy of eight interventions, so the results of cluster analysis were valuable.

DISCUSSION

NSCLC is the most prevalent lung cancer, which is known to have diverse pathological features.[1] Therefore, a NMA was conducted to assess the short-term efficacy of 12 chemotherapy regimens for the treatment of NSCLC in this study. Based on the network analysis in addition to direct and indirect comparisons, results of the cluster analysis indicated that the efficacy of multidrug combination chemotherapy regimens was superior to that of single-drug chemotherapy regimens for advanced NSCLC. In addition, cisplatin + gemcitabine, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine might be better chemotherapy regimens for advanced NSCLC, whereas the efficacy of gemcitabine and vinorelbine was relatively poorer.

Cisplatin, belonging to the cell cycle nonspecific agents, is the earliest synthesized platinum-based chemotherapy and has cytotoxicity. Its mechanism is considered as platinum cross-linking two spots of DNA single-stranded or double-stranded to interfere with DNA replication so as to cause cell apoptosis.[46] Gemcitabine, a deoxycytidine analogue, mainly plays the role of preventing the cells from G1 to S phase. The specific characteristics of paclitaxel, a tricyclic diterpenoid extracted from the Pacific or Western yew tree Taxus brevifolia, make it one of the most beneficial and effective chemotherapeutic drugs against various tumors involving bladder, lung, prostate, breast, in addition to head and neck cancers.[47,48] Furthermore, it has been reported that gemcitabine has favorable antitumor efficacy for various solid tumors, especially prominent for NSCLC.[49] The combination of cisplatin and gemcitabine in particular has been widely used for the first-line treatment of advanced NSCLC by the synergistic activity.[45] Tamura *et al.* demonstrated that the short-term efficacy rate was 31.5%, median survival time was 10 months, and year survival rate was 43% with the combination of paclitaxel and gemcitabine for NSCLC.[50] Palmeri *et al.* emphasized that regimen of cisplatin + gemcitabine + vinorelbine had an efficiency of 48.5%, and it could effectively improve the survival of patients with unknown primary advanced cancer, with 13.6 months of 1-year median survival.[51] A previous study also demonstrated that median overall survival and progression-free survival of combination chemotherapy were significantly longer than those of gemcitabine and vinorelbine.[32] A study showed that

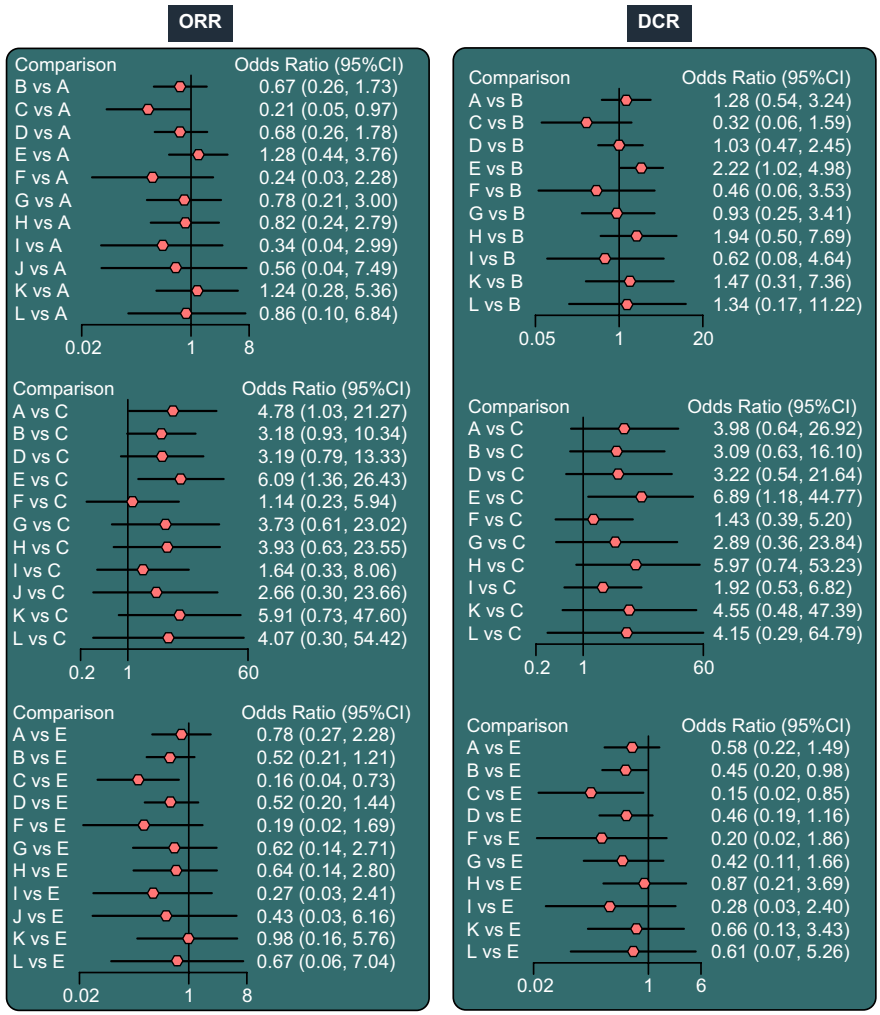

Figure 5 Relative relationship forest plots of ORR and DCR for the 12 chemotherapy regimens. A, Cisplatin + gemcitabine; B, carboplatin + gemcitabine; C, gemcitabine; D, carboplatin + paclitaxel; E, paclitaxel + gemcitabine; F, vinorelbine; G, gemcitabine + vinorelbine; H, cisplatin + gemcitabine + vinorelbine; I, docetaxel; J, cisplatin + docetaxel; K, cisplatin + pemetrexed; L, cisplatin + vinorelbine. CI, confidence interval; DCR, disease control rate; ORR, overall response rate.

paclitaxel + vinorelbine was worse than paclitaxel + gemcitabine in the aspect of toxicity in patients with advanced NSCLC.[52] Interestingly, carboplatin-based chemotherapeutic treatment (carboplatin, methotrexate, and vinblastine) has been reported to be less active than the cisplatin-based therapy (methotrexate, vinblastine, doxorubicin, and cisplatin) in advanced bladder carcinoma.[53] Another study showed no difference between cisplatin-based and carboplatin-based chemotherapies, but carboplatin-based regimen had higher hematologic toxicity, whereas cisplatin-based regimen had higher nonhematologic toxicity.[54] In this study, we found that cisplatin + gemcitabine and cisplatin + gemcitabine + vinorelbine showed better efficacy than carboplatin + gemcitabine and carboplatin + paclitaxel.

However, the efficacies of the gemcitabine/vinorelbine-based single-drug chemotherapy regimens for advanced NSCLC were relatively poorer. It was suspected that there were drug-resistance-related genes (hENT1, P-gp, and RRM1) of gemcitabine to decrease the reaction of drug and cancer cells, causing the efficacy to greatly reduce.[55] Additionally, patients with advanced NSCLC may also complicate with other diseases, as well as the myelosuppression and hepatotoxicity of gemcitabine, which may also contribute to the drug efficacy variable.[56]

Network meta-analysis method lies in the quantitative statistical analysis of 12 chemotherapy regimens for the same disease, so we selected better regimens for the treatment of advanced NSCLC by assessing different efficacies.[57] However, there were several limitations in this NMA. First, a limited number of enrolled studies in our study could have an impact on the universality of results. Moreover, except for ORR, we could not analyze the SUCRA values of other outcomes for there were no articles that involved gemcitabine, vinorelbine, docetaxel, cisplatin + docetaxel, cisplatin + pemetrexed, and cisplatin + vinorelbine chemotherapy regimens. Besides, the toxicity of the 12 chemotherapy regimens was not further analyzed for lack of tracking of chemotherapy toxicity indicators. More importantly, due to the lack of relevant literature containing progression-free survival and overall survival, the study focused on the short-term efficacy of the 12 chemotherapy

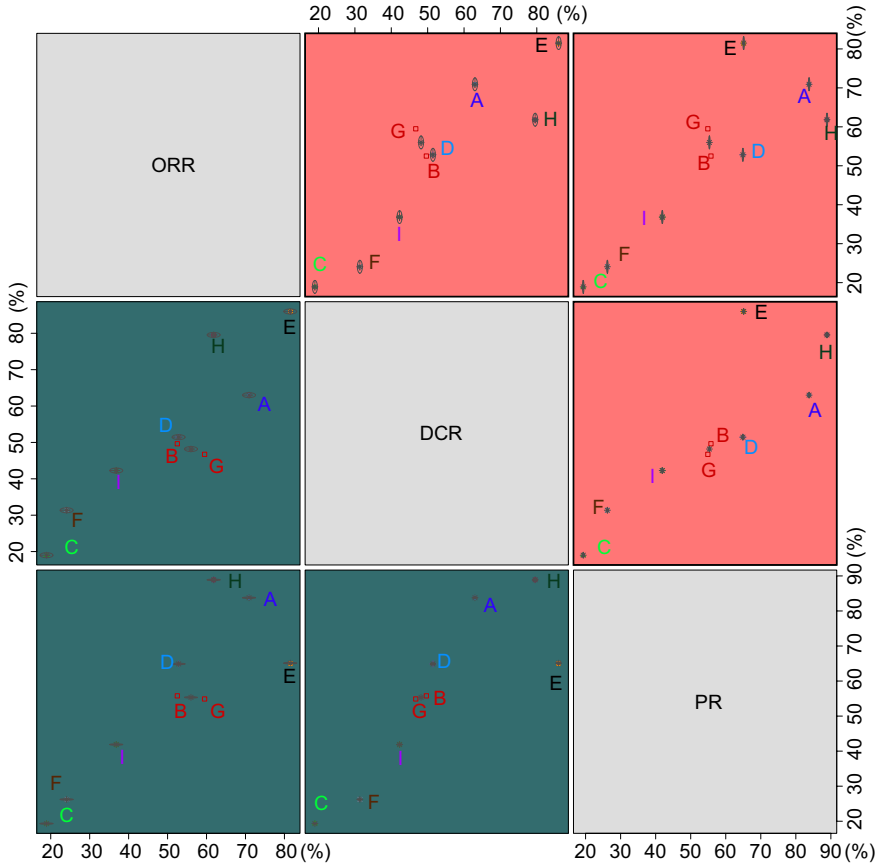

Figure 6 Cluster analysis of ORR, DCR, and PR for the 12 chemotherapy regimens. A, Cisplatin + gemcitabine; B, carboplatin + gemcitabine; C, gemcitabine; D, carboplatin + paclitaxel; E, paclitaxel + gemcitabine; F, vinorelbine; G, gemcitabine + vinorelbine; H, cisplatin + gemcitabine + vinorelbine; I, docetaxel. DCR, disease control rate; ORR, overall response rate; PR, partial response.

regimens for the treatment of NSCLC. Hence, we will continue to expand the scope of literature retrieval to further explore the long-term efficacy and safety of these first-line chemotherapy regimens. Last, considering that the main focus of the present study was chemotherapy, whereas modern clinical practice of cancers will take the role of immunotherapy and targeted therapy into account, further studies are warranted to probe the combined effect of immunotherapy and chemotherapy. In conclusion, the efficacy of multidrug combination chemotherapy regimens was superior to that of single-drug chemotherapy regimens for advanced NSCLC. Cisplatin + gemcitabine, paclitaxel + gemcitabine, and cisplatin + gemcitabine + vinorelbine might be better chemotherapy regimens in the treatment of advanced NSCLC, which provides important clinical guidance for the treatment of advanced NSCLC.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Table S1.
Table S2.
Table S3.
Table S4.
Table S5.

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