Efficacy and safety of anlotinib as a third-line treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials

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Abstract. Anlotinib is a novel multitarget tyrosine kinase inhibitor, which has been indicated to inhibit both tumor angiogenesis and signal transduction pathways associated with proliferation. The main proposed mechanism of anlotinib inhibiting tumor angiogenesis is that anlotinib inhibits the activation of VEGFR2, PDGFRβ and FGFR1, and downstream ERK signal transduction. The aim of the present study was to systematically evaluate the efficacy and safety of third-line treatment with anlotinib for advanced non-small cell lung cancer (NSCLC). To meet this aim, studies published up to February 2022 were searched in PubMed, Web of Science, the Cochrane Library and several Chinese databases. Only randomized controlled trials (RCTs) were included and a metaanalysis was performed using RevMan 5.3 software. A total of 18 RCTs were identified and included in the present study, comprising 1,658 patients. The anlotinib treatment group was indicated to be better than the control group at prolonging progression-free survival [hazard ratio (HR), 0.33; 95% confidence interval (95% CI), 0.28-0.37] and overall survival (HR, 0.70; 95% CI, 0.60-0.81). Anlotinib also provided a significant improvement in the disease control rate [risk ratio (RR), 1.51; 95% CI, 1.27-1.79], objective response rate (1.75, 95% CI, 1.51-2.03) and Karnofsky performance status (mean difference, 9.85; 95% CI, 6.26-13.43). Compared with the control group, the incidence of adverse events (AEs), such as hypertension and hemoptysis, was increased by anlotinib. Through subgroup analysis, it was determined that, compared with the placebo, the incidence of AEs was increased by anlotinib, although compared with other therapeutic drugs, no significant differences were observed. In conclusion, the findings of the present study suggested that the thirdline treatment of advanced NSCLC with anlotinib is more effective compared with other control measures and that the AEs are also controllable. However, given the limitations of the quantity and the quality of the included studies, further studies are required to gain a more complete understanding of the effects of anlotinib.

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Abbreviations: NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; HR, hazard ratio; RR, risk ratio; MD, mean difference; AE, adverse event; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; ORR, objective response rate; KPS, Karnofsky performance status

Introduction

According to the Global Cancer Observatory, >2,200,000 new cases of lung cancer were registered in 2020 and the number of deaths was ~1,800,000, showcasing that lung cancer is an important disease endangering health worldwide. Lung cancer is the leading cause of cancer morbidity and mortality in males. Among females, the incidence of lung cancer is third only to breast cancer and colorectal cancer, whereas the mortality rate is second after breast cancer (1). Non-small cell lung cancer (NSCLC) accounts for ~85% of all cases of lung cancer. Due to the inconspicuous symptoms of NSCLC, >55% of patients with NSCLC have already progressed to an advanced stage when they are diagnosed, with local spread or distant metastasis and poor prognosis (2,3).

For the treatment of NSCLC, radical surgery is the preferred option. However, drugs and radiotherapy become particularly important for patients with advanced NSCLC who cannot be treated with surgery (4). Previously, carboplatin or cisplatin combined with gemcitabine, vinorelbine or paclitaxel were commonly used in the clinic (5). However, in recent years, drastic changes have taken place in the treatment of advanced NSCLC. With the rapidly advancing knowledge of tumor pathogenesis and the increasing number of studies that have been dedicated to investigating this phenomenon, molecular targeted therapy has become a research 'hotspot' (6,7). At present, the drugs that have been indicated

to be effective as first-line therapies in targeted therapy research include erlotinib (8) and gefitinib (9); certain other drugs, such as osimertinib (10), have also been indicated to be efficient as secondline treatments. However, to the best of our knowledge, limited research has been performed to investigate drug selection after secondline treatment and docetaxel combined with cisplatin is frequently used in the clinic at present (11,12).

Anlotinib is a novel multitarget tyrosine kinase inhibitor (TKI), which is able to inhibit both tumor angiogenesis and signal transduction pathways associated with proliferation (13). The main mechanism may be inhibition of activation of VEGFR2, PDGFRβ and FGFR1 and downstream ERK signal transduction. In 2018, Han *et al* (14) demonstrated the effectiveness of anlotinib as a third-line treatment for advanced NSCLC through a multicenter randomized controlled study. However, this study only compared with a placebo and not with other drugs. After anlotinib became commercially available in China in May 2018, additional randomized controlled trials (RCTs) have compared the efficacy of anlotinib with that of other drugs. In order to explore the most suitable choice of drugs for the third-line treatment of patients with advanced NSCLC and to help formulate a better treatment strategy for NSCLC, the present study comprises a systematic review and metaanalysis to explore the efficacy and safety of third-line treatment with anlotinib for patients with advanced NSCLC. The findings in the present study were reported according to the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (15).

Materials and methods

Data sources and searches. Studies were searched from PubMed, Web of Science, the Cochrane Library (https://www.cochranelibrary.com/) and several Chinese databases, including Chinese National Knowledge Infrastructure (CNKI; https://www.cnki.net/), WangFang data (https://www.wanfangdata.com.cn/) and VIP (https://www.cqvip.com/), up to February 2022. Searches were based on combinations of the following index terms: 'anlotinib', 'tyrosine kinase inhibitor', 'advanced non-small cell lung cancer' and 'third line therapy'. At the same time, the references included within each individual study were searched to supplement the relevant information.

Retrieved articles were included in the present study as long as the following criteria were satisfied: i) The study was an RCT; ii) patients with refractory advanced NSCLC that had been confirmed by pathology or cytology had been treated previously with two or more chemotherapeutic drugs; iii) the patient was over 18 years of age; iv) there were no restrictions on the disclosure of other patient information, such as the sex of the patient; v) the anlotinib group had been treated with anlotinib; vi) the control group was treated with either a placebo or other drugs excluding anlotinib; and vii) the results included at least one outcome out of progression-free survival (PFS), overall survival (OS), disease control rate (DCR), objective response rate (ORR), Karnofsky performance status (KPS) or adverse events (AEs).

The exclusion criteria were as follows: i) Studies without original research data; ii) the study was published in a language other than English or Chinese; and iii) publications containing the same data as those published elsewhere.

Data extraction and quality assessment. A total of two researchers (BWZ and YXZ) independently screened the literature, extracted the data and cross-checked them. If any differences were identified, these were settled through discussion or by negotiation with a third party. When screening articles, the title was read first and after excluding obviously irrelevant articles, the abstract and full text were subsequently read to determine whether or not to include them. If deemed to be necessary, the author of the original research study was contacted by e-mail or telephone to obtain any information that was unclear but important for the present study. The data extraction contents included the following: Basic information included in the article, i.e., the research topic, first author, journal wherein the data had been published; baseline characteristics and intervention measures of research subjects; key elements of bias risk assessment; and the relevant outcome indicators and result measurement data.

Two researchers (BWZ and YXZ) also independently evaluated the bias risk of inclusion in the study and cross-checked the results. The bias risk assessment that was adopted was the RCT bias risk assessment tool recommended by the Cochrane Manual 5.1.0 (16).

Data analysis. RevMan 5.3 software (2014; Cochrane Cooperation Center) was used for the statistical analysis. The survival data were extracted from Kaplan-Meier curves using Engauge digitizer 4.1 software (17). The hazard ratio (HR) of PFS and OS, and the risk ratio (RR) of the DCR, ORR and AEs were calculated by RevMan5.3. The mean differences (MDs) of KPS were also calculated by RevMan5.3. Q-statistics were used to evaluate the statistical heterogeneity among experiments. If the P-value of the Q-statistics was indicated to be <0.1 or I^2 was >50%, this was considered to indicate that the heterogeneity among studies was statistically significant. If there was significant heterogeneity, the data were analyzed according to the random-effects model; otherwise, the fixed-effects model was adopted (18).

According to the intervention measures of the control group and the basic information of the patients, subgroup analysis was conducted to reduce the level of heterogeneity. For the outcomes of >10 articles, a funnel chart was used to test the publication bias. P<0.05 was considered to indicate a statistically significant difference. All P-values were bilateral and the bilateral coverage rate of the CI was 95%.

Results

Study selection. In the present study, a total of 955 articles were searched in various databases, as detailed above, and after screening, a total of 18 RCTs were included in the study (14,19-35). A flow chart of the study selection process is presented in Fig. 1.

Study characteristics and quality assessments. A total of 1,658 patients were included in the present study, comprising 913 patients in the anlotinib group (550 male and 363 female patients) and 745 patients in the control group (479 male and

266 female patients). The average age of the patients in each study ranged from 51.30 to 66.50 years. In the present study, the anlotinib groups of each study were treated with only anlotinib (12 mg daily for 21 days). Each study control group used different measures, such as a placebo or supportive treatment. The details are presented in Table I.

A total of 10 studies were based on the method of random grouping (14,19-24,29,31,34), whereas two studies had reported the methods of allocation concealment (14,24). Furthermore, five articles explicitly used doubleblinding (14,24,26,29,33), whereas only two articles had missing data (24,29). None of the studies featured selective reporting. The results are presented in Fig. 2.

Effectiveness analysis results
PFS. A total of five studies described the PFS (14,20,24,29,33). The interstudy heterogeneity was low with $I^2=27\%$, and analysis was thus performed using the fixed-effects model. The results indicated that there was a significant difference in PFS between the anlotinib group and the control group (HR=0.33; 95% CI: 0.28-0.37; P<0.00001; Fig. 3). In addition, two studies performed subgroup analyses according to the basic characteristics of patients (14,24) and the results indicated that the differences between the anlotinib group and the control group were not associated with basic demographic characteristics, such as age and sex. Significant differences in PFS comparing between the anlotinib group and the control group were identified when considering patients in the categories of <60 years or >60 years of age, having a history or no history of smoking, having a history or no history of receiving radiotherapy, benefiting or not benefiting from epidermal growth factor receptor (EGFR)-TKI treatment, and having or lacking the EGFR gene mutation.

OS. A total of five studies reported on OS (14,20,24,29,33). The interstudy heterogeneity was low $I^2=0\%$, so that analysis was performed using the fixed-effects model. The results suggested that there was a significant difference in OS between the anlotinib group and the control group (HR=0.70; 95% CI, 0.60-0.81; P<0.00001; Fig. 4). A study conducted subgroup analysis based on patients' age, gender, tissue type, smoking history and other information to determine whether different disease states have an impact on the efficacy of anlotinib (14). The results indicated an improvement of OS after treatment with anlotinib in all subgroups.

DCR. A total of 16 studies reported on the DCR (14,19-29,31,33-35). The heterogeneity between studies was $I^2=82\%$, so that analysis was performed using the random-effects model. The results suggested that the DCR in the anlotinib group was significantly higher compared with that in the control group (RR=1.51; 95% CI, 1.27-1.79; P<0.00001; Fig. 5). Subgroup analysis was performed according to the measures used in the control group. After grouping, the I^2 of the heterogeneity test in each group was 0, indicating that the control measure may be one of the factors leading to the heterogeneity among DCR studies. Subgroup analysis indicated that the anlotinib group was significantly different from the placebo, routine chemotherapy, gemcitabine + cisplatin, supportive treatment and gemcitabine + vinorelbine groups.

However, no significant difference was observed between the anlotinib group and the pemetrexed + cisplatin group. The results are presented in Table II.

ORR. A total of 17 studies reported the ORR (14,19-31,33-35). The heterogeneity among studies was $I^2=18\%$, and the fixed-effects model was used for analysis. The results indicated that the ORR of the anlotinib group was significantly higher compared with that of the control group (RR=1.75; 95% CI, 1.51-2.03; P<0.00001; Fig. 6). Subgroup analysis was performed according to the measures used by the control groups of each study. After grouping, the heterogeneity test results of each group were low ($I^2=0$), indicating that the control measures may be one of the factors leading to the heterogeneity of the ORR studies. Subgroup analysis suggested that there were significant differences between the anlotinib group and the placebo, conventional chemotherapy, gemcitabine + cisplatin and supportive treatment groups, although no statistically significant differences were obtained between the anlotinib group and the pemetrexed + cisplatin group or the gemcitabine + vinorelbine group. The results are presented in Table III.

KPS. A total of five studies reported the KPS (19,22,26,27,31). The heterogeneity among studies was $I^2=87\%$, and thus, data were analyzed using the random-effects model. The results suggested that the KPS of the anlotinib group was significantly higher compared with that of the control group (MD=9.85; 95% CI, 6.26-13.43; P<0.00001; Fig. 7). However, due to the small number of studies and the lack of subgroup information in each study, no further analysis was possible.

Sensitivity analysis. Sensitivity analysis was performed for PFS, OS, DCR, ORR and KPS. For this, the results of each of the 18 articles were excluded at a time and it was observed whether the pooled results had changed. It was found that exclusion of none of the individual studies affected the final result (data not shown).

Safety. A total of 13 articles reported the incidence of AEs in the anlotinib group and the control group in detail (14,19,21-25,27,29-33). The major AEs were included in the pooled analysis and there were eight studies on hypertension. The research on hypertension, hand-foot syndrome, fatigue, oral mucositis and hypertriglyceridemia had a high level of heterogeneity, so the random-effects model was used. For the other studies, the fixed-effects model was used. It was observed the anlotinib group was significantly higher than the control group in terms of seven AEs, namely hypertension, hand-foot syndrome, hemoptysis, proteinuria, cough, diarrhea and hypercholesterolemia, whereas no statistically significant differences were identified for the other AEs, as indicated in Table IV.

The AEs were analyzed in subgroups and divided into groups according to the control measures, with placebo or supportive treatment as one group and other drugs as the other group. It was determined that the anlotinib group had a significantly higher incidence of hypertension, hand-foot syndrome, hemoptysis, proteinuria, oral mucositis, diarrhea and hypertriglyceridemia than the placebo or supportive treatment group.

Table I. Basic characteristics of included studies.

Author and year (trial number)	Male cases		Age, years		Intervention measure		Outcomes	(Refs.)
	T (%)	C (%)	T	C	T	C		
Chen, *et al*, 2021	28 (62.2)	27 (60.0)	54.28±5.10	54.34±5.06	Anlotinib[a]	Gemcitabine + cisplatin[b]	DCR, ORR, KPS, AEs	(19)
Dai, *et al*, 2019	14 (70.0)	12 (60.0)	-	-	Anlotinib[a]	Support therapy[c]	PFS, OS, DCR, ORR	(20)
Feng, *et al*, 2020	38 (63.3)	40 (66.7)	65.73±5.23	64.36±4.84	Anlotinib[a]	Routine chemotherapy[d]	DCR, ORR, AEs	(21)
Gou, *et al*, 2020	14 (38.3)	13 (37.1)	62.72±14.23	65.68±16.86	Anlotinib[a]	Pemetrexed + cisplatin[e]	DCR, ORR, KPS, AEs	(22)
Han, *et al*, 2021	26 (57.8)	25 (55.6)	56.93±4.23	56.58±4.11	Anlotinib[a]	Gemcitabine + cisplatin[b]	DCR, ORR, AEs	(23)
Han, *et al*, 2018 (ALTER0302)	26 (43.3)	33 (57.9)	55.2±10.0	55.5±9.1	Anlotinib[a]	Placebo[f]	PFS, OS, DCR, ORR, AEs	(24)
Han, *et al*, 2018 (ALTER0303)	188 (64.0)	97 (67.8)	57.9±9.1	56.8±9.1	Anlotinib[a]	Placebo[f]	PFS, OS, DCR, ORR, AEs	(14)
Huang 2020	20 (57.1)	21 (60.0)	66.7±5.3	66.3±5.7	Anlotinib[a]	Routine chemotherapy[d]	DCR, ORR, AEs	(25)
Kong, *et al*, 2020	15 (68.2)	14 (63.6)	57.47±8.13	55.38±10.44	Anlotinib[a]	Placebo[f]	DCR, ORR, KPS	(26)
Liu, *et al*, 2020	33 (66.0)	31 (62.0)	60.94±10.74	60.74±10.98	Anlotinib[a]	Routine chemotherapy[d]	DCR, ORR, KPS, AEs	(27)
Luo and Yu, 2021	12 (52.2)	13 (56.5)	56.43±3.82	55.36±4.36	Anlotinib[a]	Gemcitabine+ cisplatin[b]	DCR, ORR	(28)
Si, *et al*, 2019	9 (56.3)	4 (50.0)	57.5	62.5	Anlotinib[a]	Placebo[f]	PFS, OS, DCR, ORR, AEs	(29)
Sun, 2021	13 (54.2)	14 (58.3)	51.48±1.78	51.51±1.84	Anlotinib[a]	Gemcitabine+ cisplatin[b]	ORR, AEs	(30)
Tian, 2021	30 (61.2)	28 (62.2)	50.64±10.36	52.00±11.06	Anlotinib[a]	Gemcitabine + vinorelbine[g]	DCR, ORR, KPS, AEs	(31)
Wang, 2020	15 (68.2)	16 (72.7)	66.3±1.7	66.5±1.5	Anlotinib[a]	Placebo[f]	AEs	(32)
Yang, 2019	23 (63.9)	9 (50.0)	-	-	Anlotinib[a]	Placebo[f]	PFS, OS, DCR, ORR, AEs	(33)
Yu and Liu, 2021	24 (60.0)	24 (60.0)	56.6±9.8	56.5±9.6	Anlotinib[a]	Support therapy[c]	DCR, ORR, AEs	(34)
Zhu, 2021	22 (64.7)	23 (67.6)	65.38±5.81	65.47±5.84	Anlotinib[a]	Routine chemotherapy[d]	DCR, ORR, AEs	(35)

Values are expressed as n (%) or the mean ± standard deviation. [a]Oral administration of anlotinib 12 mg once a day for 14 days continuously, with 21 days a cycle; [b]the injection dose of gemcitabine was 1,000 mg/m^2, the injection dose of cisplatin was 75 mg/m^2 and one cycle lasted 21 days; [c]best supportive treatment, including necessary nutritional support, thoracic puncture, blood transfusion and palliative radiotherapy to control symptoms such as cough, dyspnea and hemoptysis, with 21 days as a cycle; [d]according to the specific conditions of patients, they were treated with chemotherapy drugs, such as docetaxel and pemetrexed; [e]pemetrexed 500 mg/m^2 intravenous drip, cisplatin 20 mg/m^2 intravenous drip, 21 days as a treatment cycle; [f]oral placebo; [g]the injection dose of gemcitabine was 1,000 mg/m^2 and the injection dose of vinorelbine was 25 mg/m^2, with 21 days as one cycle. PFS, progressionfree survival; OS, overall survival; DCR, disease control rate; ORR, objective response rate; KPS, Karnofsky performance status; AE, adverse reaction; -, not available; T, test group; C, control group.

Table II. Subgroup analysis of the disease control rate of the third-line treatment of advanced non-small cell lung cancer in the anlotinib group and control group.

Control measure	Number of studies (Refs.)	Cases	Heterogeneity		Model	Meta-analysis results	
			P-value	I² value		RR (95% CI)	P-value
Placebo	5 (14,24,26,29,33)	428/248	0.63	0	Fixed	2.17 (1.83-2.56)	<0.001
Routine chemotherapy	4 (21,25,28,35)	179/179	0.78	0	Fixed	1.23 (1.10-1.36)	<0.001
Gemcitabine + cisplatin	3 (19,23,27)	113/113	0.55	0	Fixed	1.16 (1.04-1.30)	0.007
Support therapy	2 (20,34)	60/60	0.55	0	Fixed	2.39 (1.57-3.63)	<0.001
Pemetrexed + cisplatin	1 (22)	36/36	-	-	-	1.23 (0.97-1.55)	0.08
Gemcitabine + vinorelbine	1 (31)	49/45	-	-	-	2.57 (1.01-6.57)	0.05

RR, risk ratio; fixed, fixed-effects model.

Table III. Subgroup analysis of the objective response rate of the third-line treatment of advanced non-small cell lung cancer in anlotinib group and control group.

Control measure	Number of studies (Refs.)	Cases	Heterogeneity		Model	Meta analysis results	
			P-value	I² value		RR (95% CI)	P-value
Placebo	5 (14,24,26,29,33)	428/248	0.94	0	Fixed	8.98 (3.06-26.38)	<0.001
Routine chemotherapy	4 (21,25,28,35)	179/179	0.76	0	Fixed	1.54 (1.25-1.89)	<0.001
Gemcitabine + cisplatin	4 (19,23,27,30)	137/137	0.79	0	Fixed	1.49 (1.22-1.83)	<0.001
Support therapy	2 (20,34)	60/60	0.85	0	Fixed	5.67 (1.04-31.00)	<0.05
Pemetrexed + cisplatin	1 (22)	36/36	-	-	-	1.36 (0.73-2.55)	0.33
Gemcitabine + vinorelbine	1 (31)	49/45	-	-	-	1.84 (0.35-9.55)	0.47

RR, risk ratio; fixed, fixed-effects model.

However, no significant differences in each outcome index were identified between the anlotinib group and other drug groups, as indicated in Table IV.

In addition, four studies reported on the occurrence of AEs of grade 3 or above (14,24,29,31). The results indicated that there was no significant difference between the anlotinib group and control group in terms of hypertension (RR=4.68, 95% CI, 0.44-49.58; P=0.20), hemoptysis (RR=1.51, 95% CI, 0.46-4.91; P=0.49) and oral mucositis (RR=1.26, 95% CI, 0.29-5.41; P=0.76). However, the anlotinib group had a significantly higher incidence of hand-foot syndrome than the control group (RR=5.28, 95% CI, 1.18-23.59; P=0.03). Among the four studies on AEs, three were placebo studies and one used gemcitabine + vinorelbine. Subgroup analysis was conducted according to the control measures. The results indicated that the incidence of grade 3 or above AEs in the anlotinib group was significantly higher than compared with that in the placebo group with respect to hypertension and hand-foot syndrome, although no significant differences were observed when comparing between the anlotinib group and the gemcitabine + vinorelbine group, as indicated in Table V.

Publication bias. Drawing funnel graphs based on the DCR and ORR revealed that the two plots were left- and right-asymmetrical, as indicated in Figs. 8 and 9. This suggested that there may have been a certain amount of publication bias.

Discussion

At present, drugs available for the thirdline treatment of advanced NSCLC are limited. The first-line and second-line treatment schemes for patients with NSCLC with positive or negative driver gene mutations have been well-defined, but only a small number of drugs are in clinical use for the third-line treatment and the standardized treatment has not been perfected (36). Previous studies have used monoclonal antibodies or macromolecular vascular targeting drugs, such as bevacizumab, to treat advanced NSCLC, although their safety standards did not reach a satisfactory level (37). At present, pemetrexed or docetaxel is recommended for patients with the negative driver genes of non-squamous cell carcinoma. Anlotinib was approved for use in China in May 2018 (38).

Anlotinib is a novel type of multitarget small-molecule drug with antiangiogenesis and anti-tumor properties that is able to inhibit tumor angiogenesis and cell proliferation by selectively inhibiting vascular endothelial growth factor (VEGF) receptor, fibroblast growth factor receptor and plateletderived growth factor receptor (39). In addition to its usefulness for
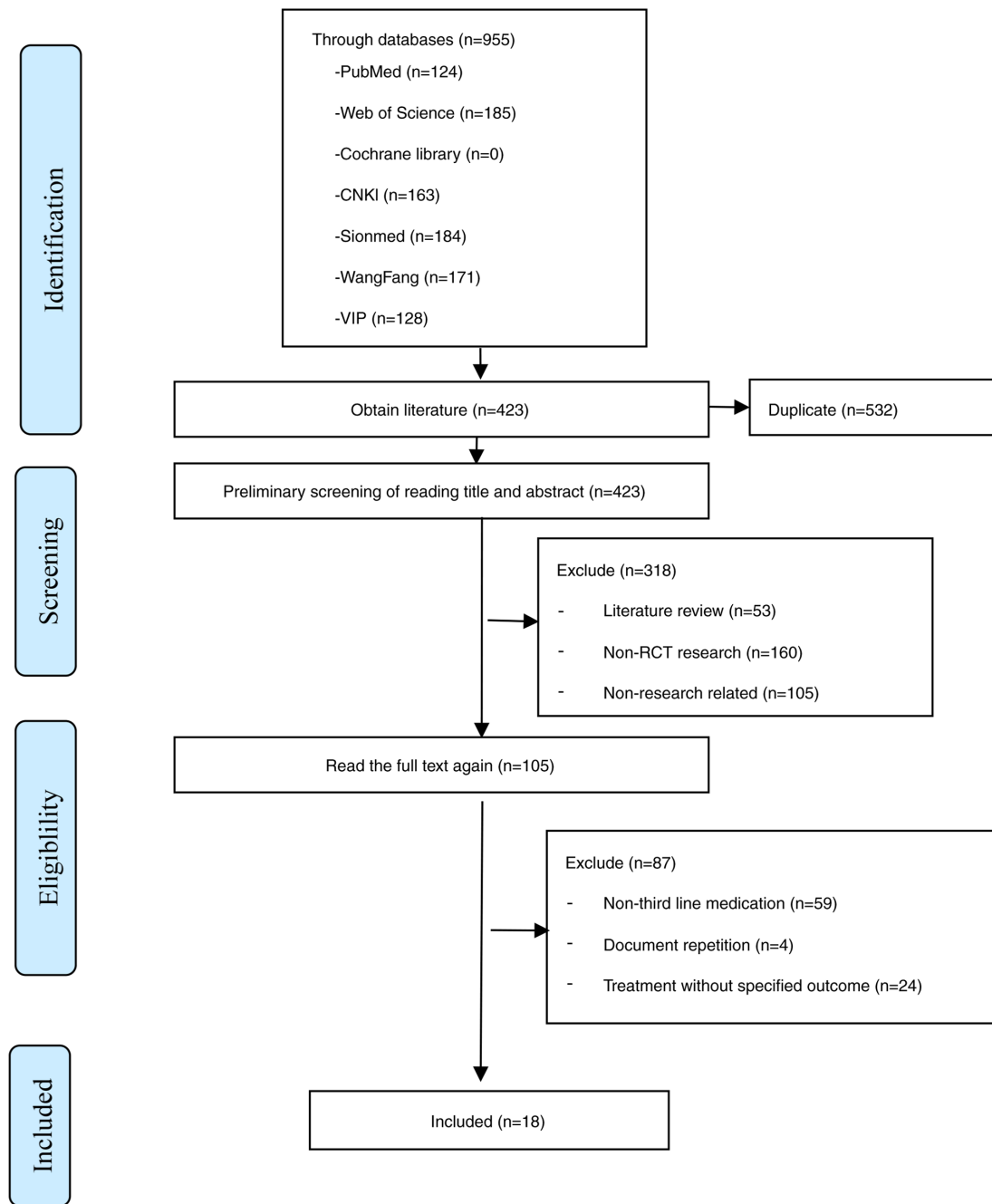
Figure 1. Flow diagram for the selection of studies. A total of 955 articles were initially retrieved and 532 articles were excluded as duplicate studies. The remaining studies were reviewed by reading titles and abstracts. Of these, 318 studies were excluded, 53 of which were reviews, 160 were non-RCTs and 105 were not research-related. After careful review of the full texts of the 105 articles remaining and excluding 87 studies (59 articles due to being on nonthird line medication, 4 articles due to being from the same study and 24 articles due to not specifying the outcomes), 18 articles were finally decided to be included. RCT, randomized controlled trial.

NSCLC, anlotinib monotherapy has also achieved good results for a variety of other solid tumors, including liver cancer (40).

Through systematic evaluation and meta-analysis, the present study indicated that, compared with the control group, the third-line treatment of advanced NSCLC with anlotinib was able to significantly improve the DCR, ORR and KPS, and significantly prolong PFS and OS. Subgroup analysis according to the treatment measures of the control group indicated that the DCR and ORR of the anlotinib group were significantly higher compared with those in the placebo, supportive treatment, conventional chemotherapy

and gemcitabine + cisplatin groups. However, compared with the pemetrexed + cisplatin and gemcitabine + vinorelbine groups, the DCR and ORR values failed to exhibit significant differences, although, given the relative sparsity of published studies in this area, it is not possible at present to draw any firm conclusions in relation to this. Subgroup analysis for PFS indicated that the difference between the anlotinib group and the control group was not associated with baseline characteristics, such as the age and sex of the patients. In conclusion, compared with the placebo or supportive treatment groups, the curative effect of anlotinib

Table IV. AEs in the anlotinib group and control group with third-line treatment of advanced non-small cell lung cancer.

AEs	Number of studies (Refs.)	Cases	Heterogeneity		Model	Meta-analysis results	
			P-value	I² value		RR (95% CI)	P-value
Hypertension	8	596/512	<0.001	80	Random	3.14 (1.43-6.90)	0.004
Placebo or support therapy	4 (14,24,29,33)	406/226	0.09	54	Random	5.74 (2.89-11.40)	<0.001
Other drugs	4 (19,21,24,31)	190/186	0.11	51	Random	1.42 (0.60-3.39)	0.43
Hand-foot syndrome	7	551/367	0.002	71	Random	3.07 (1.23-7.64)	0.02
Placebo or support therapy	4 (14,24,29,33)	406/226	0.60	0	Fixed	5.08 (3.19-8.08)	<0.001
Other drugs	3 (19,22,31)	145/141	0.02	76	Random	1.50 (0.21-10.50)	0.68
Hemoptysis	7	536/370	0.41	2	Fixed	1.81 (1.23-2.66)	0.003
Placebo or support therapy	4 (14,28,33,34)	392/230	0.73	0	Fixed	2.41 (1.46-3.96)	<0.001
Other drugs	3 (21,25,31)	144/140	0.77	0	Fixed	0.99 (0.52-1.88)	0.98
Proteinuria	6	502/322	0.85	0	Fixed	2.15 (1.48-3.11)	<0.001
Placebo or support therapy	4 (14,24,29,33)	406/226	0.78	0	Fixed	2.21 (1.47-3.30)	<0.001
Other drugs	2 (21,22)	96/96	0.59	0	Fixed	1.83 (0.71-4.76)	0.21
Nausea and vomiting	6	240/229	0.56	0	Fixed	0.76 (0.48-1.18)	0.22
Placebo or support therapy	2 (24,29)	76/65	0.60	0	Fixed	0.78 (0.42-1.42)	0.41
Other drugs	4 (19,23,27,30)	164/164	0.30	18	Fixed	0.74 (0.38-1.42)	0.36
Fatigue	5	466/304	0.002	76	Random	0.87 (0.56-1.37)	0.55
Placebo or support therapy	2 (14,24)	354/200	0.12	60	Random	1.44 (0.90-2.29)	0.13
Other drugs	3 (21,22,30)	112/104	0.51	0	Fixed	0.73 (0.52-1.04)	0.07
Oral Mucositis	5	479/313	0.004	74	Random	3.37 (0.94-12.17)	0.06
Placebo or support therapy	3 (14,24,29)	370/208	0.87	0	Fixed	8.64 (3.58-20.84)	<0.001
Other drugs	2 (21,31)	109/105	0.21	37	Fixed	1.13 (0.55-2.34)	0.74
Anaemia	4	150/132	0.75	0	Fixed	0.47 (0.22-1.02)	0.75
Placebo or support therapy	1 (33)	36/18	-	-	-	0.67 (0.27-1.63)	0.37
Other drugs	3 (19,23,30)	114/114	0.87	0	Fixed	0.29 (0.07-1.17)	0.08
Cough	4	411/257	0.23	30	Fixed	1.56 (1.19-2.04)	0.001
Placebo or support therapy	3 (14,24,32)	376/222	0.14	49	Fixed	1.61 (1.21-2.13)	0.001
Other drugs	1 (25)	35/35	-	-	-	1.14 (0.46-2.81)	0.77
Diarrhea	3	370/208	0.48	0	Fixed	2.52 (1.72-3.69)	<0.001
Placebo or support therapy	3 (14,24,29)	370/208	0.48	0	Fixed	2.52 (1.72-3.69)	<0.001
Hypercholesterolemia	3	370/208	0.75	0	Fixed	3.14 (2.12-4.66)	<0.001
Placebo or support therapy	3 (14,24,29)	370/208	0.75	0	Fixed	3.14 (2.12-4.66)	<0.001

Table IV. Continued.

AEs	Number of studies (Refs.)	Cases	Heterogeneity		Model	Meta-analysis results	
			P-value	I² value		RR (95% CI)	P-value
Hypertriglyceridemia	3	370/208	0.09	58	Random	1.95 (0.91-4.17)	0.09
Placebo or support therapy	3 (14,24,29)	370/208	0.09	58	Random	1.95 (0.91-4.17)	0.09

RR, risk ratio; AE, adverse event; fixed, fixed-effects model; random, random-effects model.

Table V. Grade 3 or above AEs in the anlotinib group and control group with third-line treatment of advanced non-small cell lung cancer.

AEs	Number of studies (Refs.)	Cases	Heterogeneity		Model	Meta-analysis results	
			P-value	I² value		RR (95% CI)	P-value
Hypertension	4	419/253	0.02	68	Random	4.68 (0.44-49.58)	0.20
Placebo	3 (14,24,29)	370/208	0.52	0	Fixed	19.59 (3.76-102.20)	<0.001
Gemcitabine + Vinorelbine	1 (31)	49/45	-	-	-	0.31 (0.03-2.84)	0.30
Hemoptysis	4	419/253	0.55	0	Fixed	1.51 (0.46-4.91)	0.49
Placebo	3 (14,24,29)	370/208	0.86	0	Fixed	2.17 (0.53-8.10)	0.30
Gemcitabine + Vinorelbine	1 (31)	49/45	-	-	-	0.31 (0.01-7.34)	0.47
Oral mucositis	4	419/253	0.56	0	Fixed	1.26 (0.29-5.41)	0.76
Placebo	3 (14,24,29)	370/208	0.72	0	Fixed	2.52 (0.30-21.10)	0.40
Gemcitabine + Vinorelbine	1 (31)	49/45	-	-	-	0.46 (0.04-4.89)	0.52
Hand-foot syndrome	4	419/253	0.80	0	Fixed	5.28 (1.18-23.59)	0.03
Placebo	3 (14,24,29)	370/208	0.63	0	Fixed	5.99 (1.10-32.70)	0.04
Gemcitabine + Vinorelbine	1 (31)	49/45	-	-	-	2.76 (0.12-66.07)	0.53

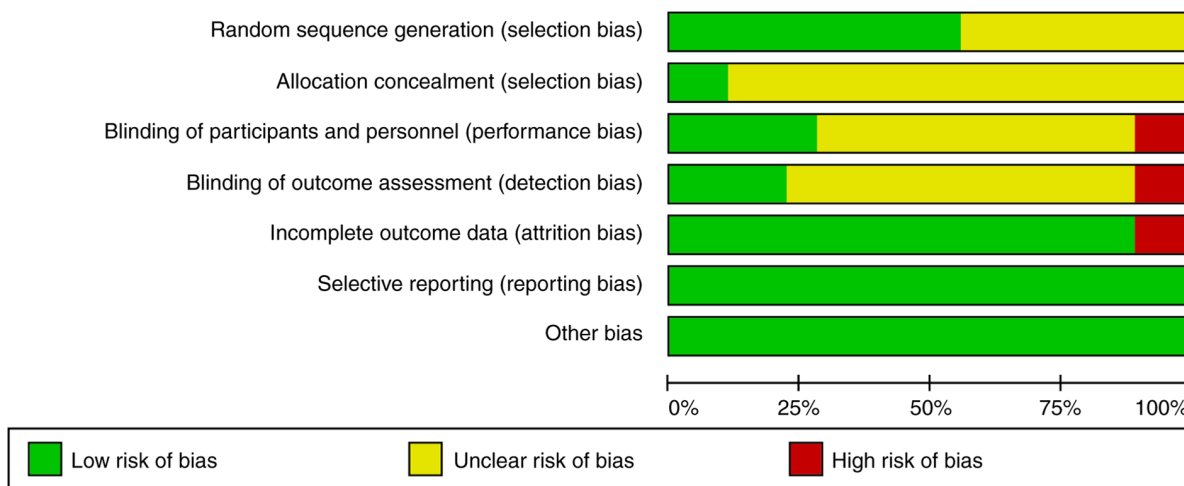RR, risk ratio; AE, adverse event; fixed, fixed-effects model; random, random-effects model.

Figure 2. Bias evaluation of included studies. Only two studies had low selection bias. Furthermore, 5 studies had low performance bias and 2 studies had high performance bias. Performance bias may generally be avoided by using standard treatment methods and blinding methods for patients and investigators. The detection bias of 4 studies was low and the detection bias of 2 studies was high. In general, detection bias may be avoided by using unified standard measurement methods and blinding of the investigators. A total of two studies had higher attrition bias, while the others had lower attrition bias. None of the studies had any reporting bias.
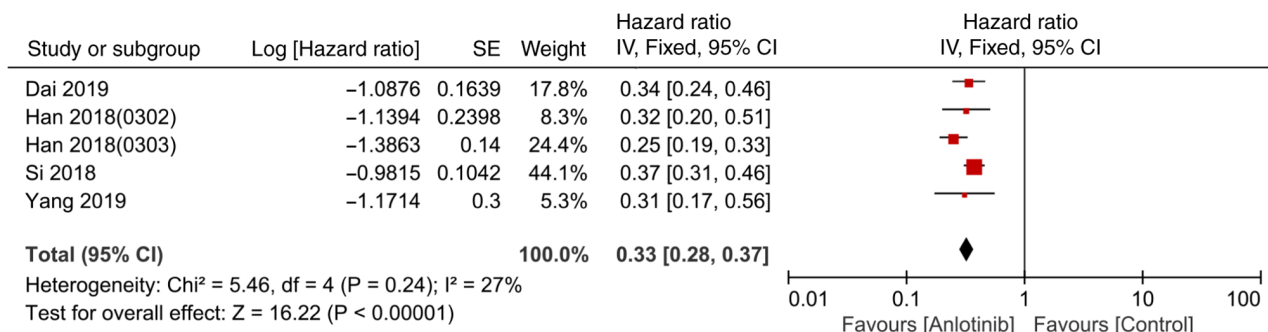

Figure 3. PFS for third-line treatment of advanced non-small cell lung cancer in the anlotinib group and control group. Vertical solid black line: Invalid line; horizontal black solid line: The width of the line represents the 95% CI of each study. The red squares represent the weight of each study. The results indicated that there was a significant difference in PFS between the anlotinib group and the control group (hazard ratio=0.33, 95% CI: 0.28-0.37, P<0.00001). PFS, progression-free survival; SE, standard error; IV, inverse variance; df, degrees of freedom.
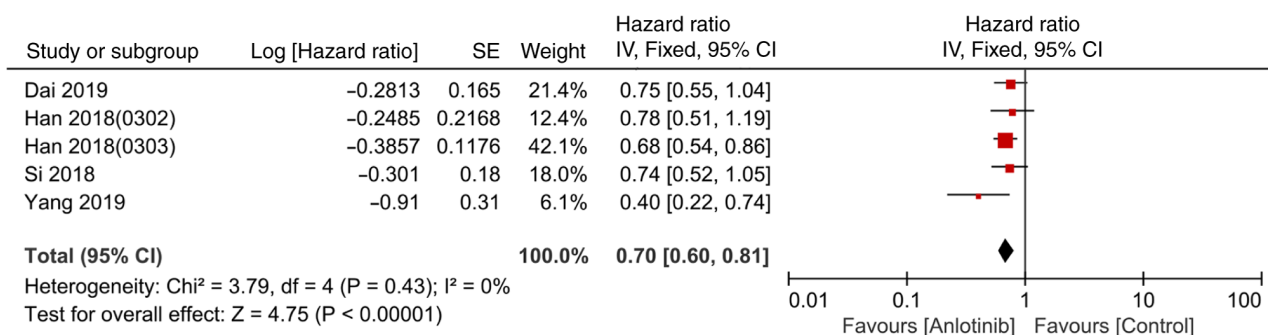

Figure 4. OS for third-line treatment of advanced non-small cell lung cancer in the anlotinib group and control group. Vertical solid black line: Invalid line; horizontal black solid line: The width of the line represents the 95% CI of each study; the red square represents the weight of each study. The results indicated that there was a significant difference in OS when comparing between the anlotinib group and the control group (hazard ratio=0.70, 95% CI, 0.60-0.81; P<0.00001). SE, standard error; IV, inverse variance; df, degrees of freedom; OS, overall survival.

on advanced NSCLC was appreciable. Compared with treatment with a combination of gemcitabine + cisplatin and therapy with other drugs currently used for third-line treatment, anlotinib also had advantages in terms of effectiveness.

In addition to the abovementioned studies included in the meta-analysis, several other studies have reported on other indicators with regard to evaluating their curative effects. Due to the different measurement methods and the small number of studies, however, it was not suitable for these
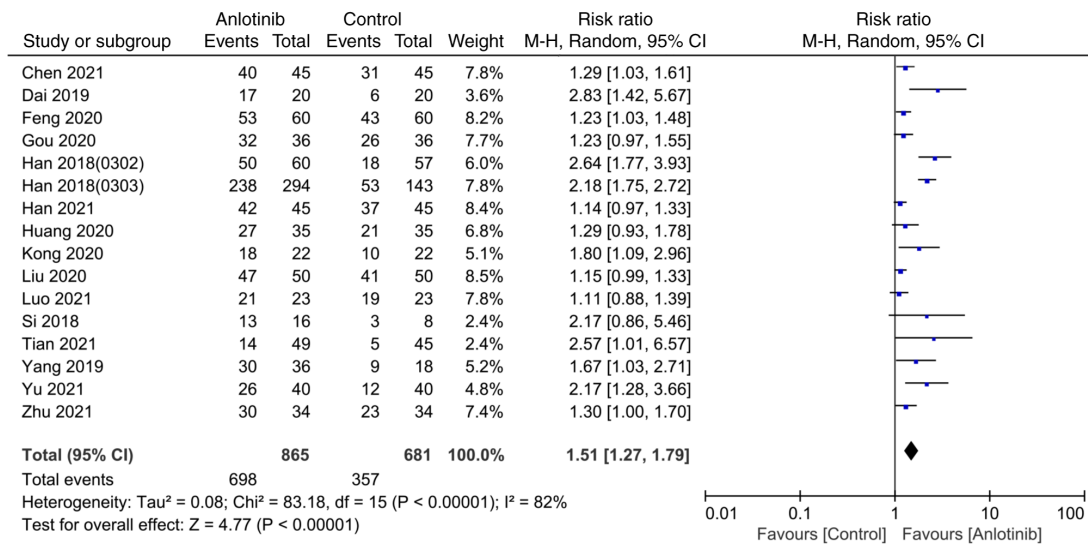
Figure 5. Disease control rate for third-line treatment of advanced non-small cell lung cancer in the anlotinib group and control group. Vertical solid black line: Invalid line; horizontal black solid line: The width of the line represents the 95% CI of each study; the blue square represents the weight of each study. The results suggested that the RR value of the anlotinib group was significantly higher compared with that of the control group (RR=1.51, 95% CI, 1.27-1.79; P<0.00001). RR, risk ratio; M-H, Mantel-Haenszel; df, degrees of freedom.
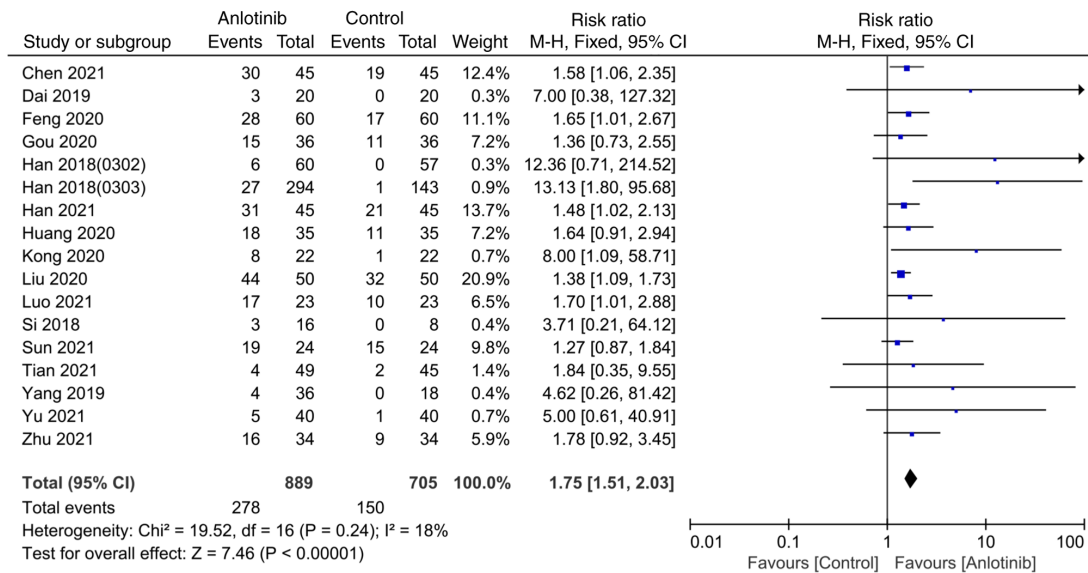

Figure 6. Objective response rate for third-line treatment of advanced non-small cell lung cancer in the anlotinib group and control group. Vertical solid black line: Invalid line; horizontal black solid line: The width of the line represents the 95% CI of each study; the blue square represents the weight of each study. The results indicated that the RR of the anlotinib group was significantly higher compared with that of the control group (RR=1.75, 95% CI, 1.51-2.03; P<0.00001). RR, risk ratio; M-H, Mantel-Haenszel; df, degrees of freedom.

studies to be included in the combined analysis, although several of these studies will now be briefly described. Two studies reported on the changes in tumor marker concentration in patients prior to and after intervention (21,27). The results suggested that, after treatment, the serum carcinoembryonic antigen and cytokeratin-19-fragment in the anlotinib group were significantly lower compared with those in the control group. Another study reported on the changes in lung function (27), which suggested that the forced expiratory volume in one second and 6-minute walking distance in the anlotinib group were significantly higher compared with those in the control group. A further study discussed the analysis of blood gas (28) and revealed that the partial

pressure of oxygen and oxygen saturation of the arterial blood in the anlotinib group were higher compared with those in the control group, whereas the partial pressure of CO_2 was lower than that in the control group, and this difference was statistically significant. The above findings also reflect different aspects of the effectiveness of anlotinib in improving the physical condition of patients with advanced NSCLC.

In terms of safety, the present study suggested that there were significant differences between the anlotinib group and the control group with respect to hypertension, hand-foot syndrome, hemoptysis, proteinuria, cough, diarrhea and hypercholesterolemia, but no statistical differences between the two

Study or subgroup	Anlotinib Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Chen 2021	82.23	9.23	45	76.89	9.78	45	19.0%	5.34 [1.41, 9.27]
Gou 2020	78.45	11.36	36	72.62	12.09	36	15.8%	5.83 [0.41, 11.25]
Kong 2020	62.37	5.17	22	53.32	4.38	22	21.4%	9.05 [6.22, 11.88]
Tian 2021	70.31	10.32	49	56.75	8	45	19.5%	13.56 [9.84, 17.28]
Liu 2020	78.96	2.36	50	65.26	2.28	50	24.3%	13.70 [12.79, 14.61]
Total (95% CI)			202			198	100.0%	9.85 [6.26, 13.43]

Heterogeneity: Tau² = 13.54; Chi² = 30.86, df = 4 (P < 0.00001); I² = 87%
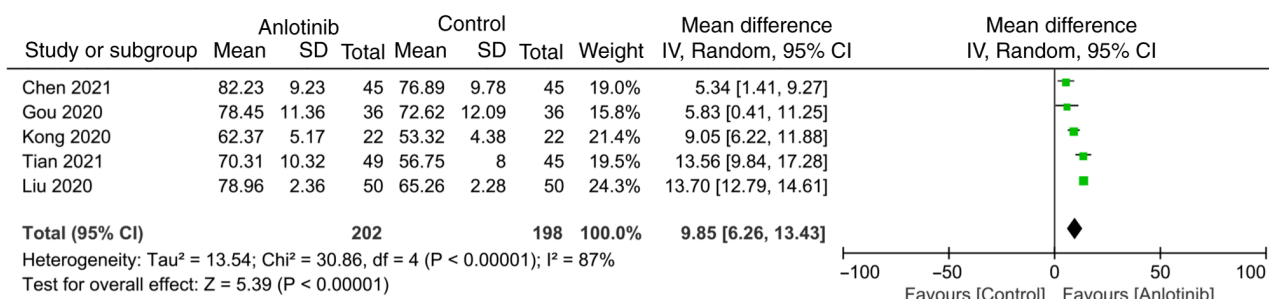Test for overall effect: Z = 5.39 (P < 0.00001)

Figure 7. KPS for third-line treatment of advanced non-small cell lung cancer in anlotinib group and control group. Vertical solid black line: Invalid line; horizontal black solid line: The width of the line represents the 95% CI of each study; the green square represents the weight of each study. The results suggested that the KPS of the anlotinib group was significantly higher compared with that of the control group (MD=9.85, 95% CI, 6.26-13.43; P<0.001). MD, mean difference; SD, standard deviation; IV, inverse variance; df, degrees of freedom; KPS, Karnofsky performance status.
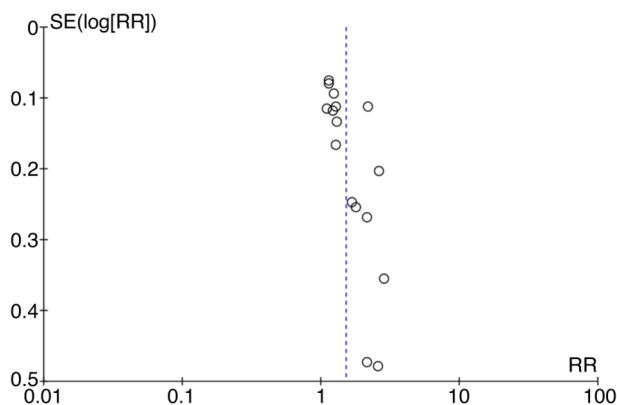

Figure 8. Funnel chart to assess the bias of studies included with regard to the disease control rate. The blue dotted line indicates the combined effect quantity. Each study is represented by a circle. Ideally, all studies should be evenly distributed on both sides. As the dots were distributed left- and right-asymmetrically, the study is asymmetric and there may be bias. SE, standard error; RR, risk ratio.
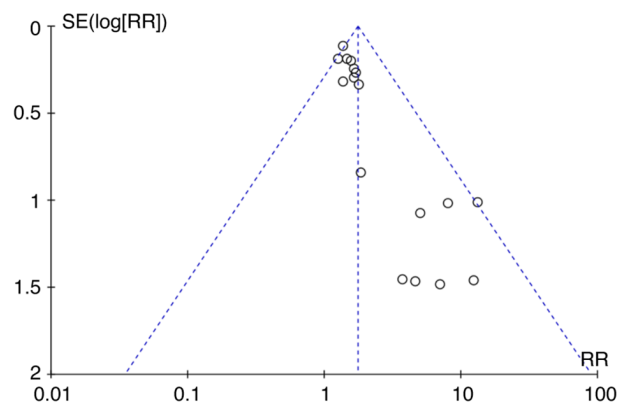

Figure 9. Funnel chart to assess the bias of studies included with regard to the objective response rate. The blue dotted line indicates the combined effect quantity. Each study is represented by a circle. Ideally, all studies should be evenly distributed on both sides. As the dots were distributed left- and right-asymmetrically, the study is asymmetric and there may be bias. SE, standard error; RR, risk ratio.

groups were identified for the remaining five adverse reactions, including nausea and vomiting, fatigue, mucositis, anaemia and hypertriglyceridemia. This finding was not consistent with those of a previous study by Yu *et al* (41), presumably because it included three trials in which the control group was either a placebo or supportive treatment. However, among the 18 studies included in the present study, a large proportion of the control groups used other drugs for treatment, and other therapeutic drugs also caused AEs. According to the above discussion, the present study suggests that, compared with other drugs currently used for thirdline treatment, anlotinib does not exhibit any safety deficiency.

Among the 18 articles included in the present study, the AEs of interest were hypertension, nausea and vomiting, hand-foot syndrome and hemoptysis. Nausea is a common gastrointestinal reaction, which may be caused by drugs directly stimulating the gastric mucosa or by metabolic factors. It is the cardiovascular AE that is most commonly associated with hypertension VEGF pathway inhibitors, a phenomenon that may be linked to the endothelial dysfunction and the reduction in nitric oxide release caused by drugs (42). Hemoptysis is an important AE of anlotinib, which may be associated with its inhibition of the VEGF receptor, thrombocytopenia and increased bleeding risk.

Hand-foot syndrome is mainly characterized by abnormal sensation, dullness or numbness of hands and feet, and blisters, ulcers or pain may also occur in severe cases. This may be associated with anlotinib acting on the signaling pathway of vascular repair in the compressed parts of hands and feet (43).

A total of four studies reported on the occurrence of high-level AEs and the results suggested that there was a significant difference between the anlotinib group and the control group in hypertension and handfoot syndrome. Si *et al* (29) reported in detail the treatment of AEs after they occurred; hand-foot syndrome and oral mucositis were obviously relieved after anlotinib was administered at a reduced dose of 10 mg, once a day, and other AEs were also well improved after symptomatic treatment. No treatment-associated deaths were reported in either study. It may be indicated that AEs associated with anlotinib are tolerable.

The advantages of the present study are as follows: i) There were 18 RCTs included in this study, and the results obtained are reliable; ii) subgroup analysis was carried out according to the measures of the control group, and the therapeutic effects and safety of anlotinib were compared with those of different control measures; and iii) the effectiveness of this study was evaluated by OS and four other indicators, with special

attention paid to high-level AEs when evaluating safety, and the evaluation was therefore more comprehensive. The limitations of this study were as follows: i) The time to market is short and the patients were all Chinese, so it is impossible to assess the influence of treatment with anlotinib on other populations; ii) since certain of the publications did not report on subgroups, the present study mainly comprised subgroup analysis according to control measures and sufficient subgroup analysis was not carried out on other factors; and iii) numerous studies featured small-sample analysis and there was lack of larger-sample studies.

According to the results of the present study, it is considered that for patients with NSCLC who have relapsed after receiving two types of systemic chemotherapy, it is possible to consider using anlotinib for treatment. At present, the drug is administered in a 3-week cycle, at a recommended dose of 12 mg once a day, with an interval for 1 week (i.e., the third week in the cycle) after 2 weeks of treatment. However, it is necessary to detect and prevent the occurrence of AEs. Blood pressure and blood lipid levels should be monitored regularly and oral mucosa and skin reactions should also be paid attention to. Anlotinib should also be used with caution in patients who are at high risk of bleeding and have hepatic renal insufficiency.

Acknowledgements

Not applicable.

Funding

Availability of data and materials

The datasets used or analyzed during the study are available from the corresponding author on reasonable request.

Authors' contributions

BWZ designed the review and meta-analysis. YXZ and RZY conceived and wrote the review. BWZ and YXZ acquired and analyzed the data. BWZ and RZY analyzed and confirmed the integrity of the data found in the literature. MDK was involved in designing the research and drafting the manuscript. All authors contributed to the analysis and reviewed the results and all authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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