

Cinobufotalin injection combined with chemotherapy for the treatment of advanced NSCLC in China

A PRISMA-compliant meta-analysis of 29 randomized controlled trials

Fan Zhang, MD^a, Yantong Yin, MD^b, Tiantian Xu, MD^{a,*}

Abstract

Background and objective: Cinobufotalin injection (CFI), a kind of Chinese medicine, has been considered as a promising complementary therapy option for advanced non-small cell lung cancer (NSCLC), but their efficacy and safety remain controversial. This study aimed to systematically evaluate the efficacy and safety of CFI and chemotherapy-combined therapy for advanced NSCLC.

Methods: Clinical trials were searched from Web of Science, Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Chinese Medical Citation Index (CMCI), Wanfang database and Chinese Scientific Journal Database (VIP). Main measurements, including therapeutic efficacy, quality of life (QoL) and adverse events, were extracted from the retrieved publications and were systematically evaluated.

Results: The 29 trials including 2300 advanced NSCLC patients were involved in this study. Compared with chemotherapy alone, its combination with CFI significantly prolonged the patients' 1-, 2- and 3-year overall survival rate (OS) (1-year OS, OR=1.94, 95% CI=1.42–2.65, P < .0001; 2-year OS, OR=2.31, 95% CI=1.55–3.45, P < .0001; 3-year OS, OR=4.69, 95% CI=1.78–12.39, P = .002) and improved patients' overall response (ORR, OR=1.84, CI=1.54–2.18, P < .00001), disease control rate (DCR, OR= 2.09, 95% CI=1.68–2.60, P < .00001) and QoL (quality of life improved rate, QIR, OR=2.64, 95% CI=1.98–3.52, P < .00001; karnofsky performance score, KPS, OR=10.97, 95% CI=5.48–16.47, P < .0001). Most adverse events caused by chemotherapy were obviously alleviated (P < .05) when CFI was also applied to patients.

Conclusion: The combination of CFI and chemotherapy is safe, and is more effective in treating NSCLC than chemotherapy alone. Therefore, CFI mediated therapy could be recommended as an adjuvant treatment method for NSCLC.

Abbreviations: CBM = Chinese Biological Medicine Database, CFI = Cinobufotalin injection, CMCI = Chinese Medical Citation Index, CNKI = China National Knowledge Infrastructure, CR = complete response rates, DCR = disease control rate, KPS = karnofsky performance score, NSCLC = advanced non-small cell lung cancer, OR = odds ratio, ORR = overall response rate, OS = overall survival, PD = progressive disease rates, PR = partial response rates, QIR = quality of life improved rate, QoL = quality of life, RCT = randomized controlled trials, ROS = reactive oxygen species, SD = stable disease rates, VIP = Chinese Scientific Journal Database, CI = confidence interval.

Keywords: chemotherapy, cinobufotalin injection, meta-analysis, non-small cell lung cancer, traditional Chinese medicine

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1. Introduction

Lung cancer represents the first leading cause of death among all cancer types and caused 1,600,000 deaths every year in the whole world.^[1,2] China is a high risk area for lung cancer, and has the most new lung cancer cases (733,300 per year) accounting for about 40% in the world.^[3,4] Non-small cell lung cancer (NSCLC) is constitutes for approximately 85% of all lung cancer cases.^[4,5] Approximately 2/3 of NSCLC patients are diagnosed at advanced stages, under which condition they were not able to be applied with radical treatment such as surgery,^[4] leaving traditional chemotherapy as their primary treatment option. However, chemotherapy's therapeutic efficacy was unsatisfied for advanced NSCLC, and patients also endured its toxicity and a compromised quality of life (QoL).^[6]

In recent years, traditional Chinese medicine has been more widely used as compounds for chemotherapy, and showed promising therapeutic effects in cancer treatment.^[7–9] Cinobu-

fotalin contains bufadienolides and cardiotonic steroids extracted from the skin secretions of bufo gargarizans.^[10–12] Evidences emerged from *in vitro* studies have demonstrate cinobufotalin's anti-tumor activity, accompanied with enhanced chemotherapeutic effects.^[7,13] Sheng et al^[10] found that cinobufotalin can kill lung cancer cells by inducing non-apoptotic death possibly depending on Cyp-D involved pathway. Emam et al^[11] showed that cinobufotalin induced lymphoma cells apoptosis through Caspase- mediated Fas apoptotic pathway. In addition, cinobufotalin was also able to induce tumor cell apoptosis by increasing reactive oxygen species (ROS) production and interfering their DNA structure.^[11,14]

Several clinic trials have revealed the prominent therapeutic effects of cinobufotalin injection (CFI) and chemotherapy combined therapy for advanced NSCLC, which was also proved more effective than chemotherapy alone.^[15–17] Despite the intensive clinical studies using CFI and chemo-combined therapy in treating NSCLC, its clinical efficacy and safety has not been systematically evaluated. In this study, we performed a meta-analysis to evaluate the efficacy and safety for NSCLC treatment, with a comparison between CFI and chemo-combined therapy and chemotherapy alone, in order to provide scientific reference for the design of future clinical trials.

2. Materials and methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The ethical approval and patient consent are not required because this study was a meta-analysis.

2.1. Search strategy and selection criteria

Literatures were searched across Web of Science, Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Chinese Medical Citation Index (CMCI), Wanfang database and Chinese Scientific Journal Database (VIP) from January 2000 to June 2018, with key terms "cinobufotalin" or "cinobufotalin" or "cinobufacini" or "cinobufagin" or "huachansu" combined with "lung cancer" or "lung carcinoma" or "lung neoplasm" or "non-small cell lung cancer" or "NSCLC" without restriction on the language (Supplementary Table 1, http://links.lww.com/MD/D201).

Selection standards: trials brought into this analysis were randomized controlled trials (RCT) with reference to advanced NSCLC, in which patients in the experimental groups were treated by CFI (intravenous infusion) and chemo-combined therapy, and patients in the control groups were treated by solely chemotherapy.

2.2. Data extraction and quality assessment

Two investigators respectively collected and summarized the following information from the involved studies: names of first authors, years of publication, study locations, tumor stages, number of cases, patient ages, study parameter types, treatment regimens and periods, administration route and expected survival time. Quality of the involved clinical trials was assessed as instructed by Cochrane Handbook.^[18]

2.3. Outcome definition

The following clinical responses were taken into analysis in this study: therapeutic effects, QoL and adverse events. Therapeutic

effects were evaluated by overall survival rate (OS), complete response rates (CR), partial response rates (PR), stable disease rates (SD), progressive disease rates (PD), overall response rate (ORR, ORR=CR+PR), and disease-control rate (DCR, DCR =CR+PR+SD). QoL improved rate (QIR) and karnofsky performance score (KPS) was used to reflect patients QoL. Adverse events taken into assessment included leukopenia, thrombocytopenia, nausea and vomiting, hepatotoxicity, nephrotoxicity, gastrointestinal side effects, diarrhea, peripheral neurotoxicity, granulopenia, phlebitis, alopecia, myelosuppression, constipation, hemoglobin reduction, allergy, and anemia.

2.4. Statistical analysis

Review Manager 5.3 (Cochrane Collaboration) was the main statistical analysis tool in this study. P < .05 indicates difference with statistical significance. Analysis model was determined by heterogeneity among studies assessed by Cochran's Q test, and publication bias was analyzed by Begg and Egger regression asymmetry tests and presented by funnel plots.^[19] $I^2 < 50\%$ or P > .1 indicated the studies were homogenous. Therapeutic effects were mainly represented by odds ratio (OR) presented with a 95% confidence interval (CI).

Pooled analysis with publication bias determined that trimand-fill method would be applied to coordinate the estimates of unpublished studies, and the adjusted results were compared with the original pooled OR.^[20] Sensitivity analysis was conducted to evaluate the impact of different therapeutic regimens and sample sizes.

3. Results

3.1. Search results

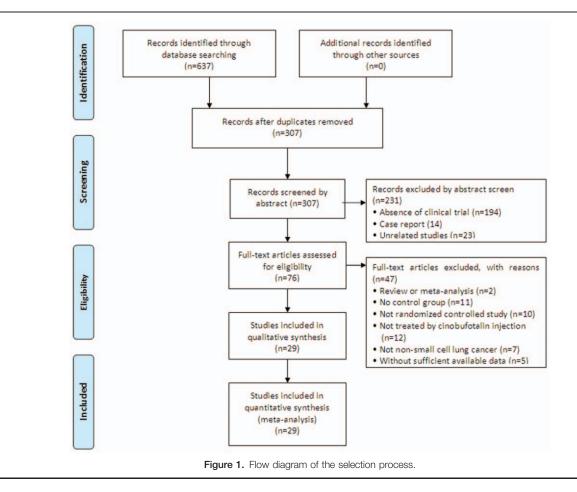
Our retrieve gathered a total of 637 articles initially, and 561 articles were ruled out because they did not including clinical trials (n=194) or were case report (n=14), unrelated studies (n=23) or repetition (n=330), leaving 76 studies as potentially relevant. Further detailed assessment of full texts screened out reviews or meta-analysis (n=2), articles without control groups (n=11), trials that were not randomized controlled (n=10) or did not included CFI and chemo-combined therapy (n=12), patients were not NSCLC (n=7) and studies with insufficient data (n=5). Finally, 29 trials^[15–17,21–46] involving 2300 advanced NSCLC patients were included in this meta-analysis (Fig. 1).

3.2. Patient characteristics

All studies involved in this analysis contained RCT carried out in China since 2000. These trials include 2300 patients with advanced NSCLC, among which 1164 were treated by CFI and chemo-combined therapy, and 1136 were treated by chemotherapy alone. Tables 1 and 2 represent details of the involved trials and patients.

3.3. Quality assessment

All involved trials were subjected to risk assessment of bias. It turns out all trials were randomly controlled with low selection risk, but performance and detection risks were not able to be



assessed as relevant information were not shown in the publications (Fig. 2). Among all the included clinical studies, 3 trials^[21,28,35] were regarded as high attrition risk owing to absent of follow-up data and 9 studies^[22,24–26,32,37,39,40,44] were considered as unclear reporting risk due to lack of efficacy and safety assessment (Fig. 2).

3.4. Therapeutic efficacy assessments

Pooled analysis on treatment effects showed 1-, 2- and 3-year OS of combined therapy treated patients were greatly improved (1-year OS, OR = 1.94, 95% CI=1.42-2.65, P<.0001; 2- year OS, OR=2.31, 95% CI=1.55-3.45, P<.0001; 3-year OS, OR = 4.69, 95% CI = 1.78 - 12.39, P = .002), CR (OR = 2.01, CR)95% CI=1.47-2.75, P<.0001), PR (OR=1.51, 95% CI=1.26-1.80, P < .00001), ORR (OR = 1.84, 95% CI = 1.54-2.18, P < .00001) and DCR (OR = 2.09, 95% CI = 1.68-2.60, P < .00001) and significantly decreased PD (OR=0.47, 95%) CI = 0.38 - 0.59, P < .00001), whereas the 0.5-year OS (OR = 1.70, 95% CI=0.98-2.94, P=.06) and SD (OR=0.87, 95% CI = 0.73 - 1.03, P = .11) did not show significant difference from patients who received chemotherapy alone (Figs. 3 and 4, Supplementary Figure 1, http://links.lww.com/MD/D201 and Table 3). The analysis of OR rate was conducted with fixed-effect models because of low heterogeneity.

3.5. QoL assessment

The QoL evaluation demonstrated that CFI and chemocombined therapy-treated patients had improved QoL than those treated solely by chemotherapy, according to QIR (Fig. 5A, OR = 2.64, 95% CI = 1.98–3.52, P < .00001) and KPS (Fig. 5B, OR = 10.97, 95% CI = 5.48–16.47, P < .0001).

3.6. Adverse events assessment

As shown in Table 4 and Supplementary Figure 2, http://links. lww.com/MD/D201, patients treated by CFI and chemocombined therapy displayed lower incidences of leukopenia, thrombocytopenia, nausea and vomiting, hepatotoxicity, nephrotoxicity, gastrointestinal side effects, diarrhea, peripheral neurotoxicity, granulopenia, alopecia, myelosuppression, constipation, hemoglobin reduction and anemia (leukopenia: OR= 0.33, 95% CI=0.20-0.54, P<.0001; thrombocytopenia: OR= 0.33, 95% CI=0.20-0.57, P < .0001; nausea and vomiting: OR=0.23, 95% CI=0.11-0.49, P=.0001; hepatotoxicity: OR =0.41, 95% CI=0.27-0.62, P < .0001; nephrotoxicity: OR = 0.36, 95% CI=0.24-0.56, P<.00001; gastrointestinal side effects: OR=0.52, 95% CI=0.33-0.80, P=.003; diarrhea: OR = 0.21, 95% CI = 0.05–0.89, P = .03; peripheral neurotoxicity: OR = 0.47, 95% CI = 0.23–0.94, P = .03; granulopenia: OR =0.30, 95% CI=0.21-0.44, P<.00001; alopecia: OR=0.46,

Clinical information from the eligible trials in the meta-analysis.

				Age	(yr)	
Included studies	Country	Tumor stage	Patients Con/Exp	Con	Exp	Parameter types
Bao, 2011	China	III—IV	48/45	52 (Median)	56 (Median)	ORR, DCR, QoL, AE
Bian, 2015	China	$KPS \ge 60$	31/32	ND	ND	ORR, DCR, QoL, AE
Cao, 2009	China	III—IV	25/25	ND	ND	ORR, DCR
Cao, 2016	China	IV	40/40	57.2 ± 9.2 (mean)	57.4 ± 9.0 (mean)	ORR, DCR, AE
Chen, 2016	China	III—IV	45/45	59.4 ± 10.7 (mean)	60.1 ± 11.5 (mean)	OS, ORR, DCR, AE
Deng, 2018	China	ND	34/34	52.7 ± 7.1 (mean)	53.8 ± 7.0 (mean)	ORR, DCR
Ding, 2011	China	III—IV	39/39	ND	ND	ORR, DCR, QoL
Dong, 2013	China	IV	40/46	48-69	46-66	ORR, DCR, QoL
Duan, 2018	China	$KPS \ge 60$	30/30	67.2±6.3 (mean)	66.9±6.1 (mean)	ORR, DCR, AE
Hu, 2012	China	III—IV	38/36	≥70 (17)	≥70 (15)	OS, ORR, DCR, QoL, AE
Li, 2007	China	III—IV	32/32	ND	ND	OS, ORR, DCR, QoL, AE
Li, 2010	China	III—IV	30/30	ND	ND	ORR, DCR, QoL, AE
Liu, 2017	China	ND	24/24	76.1 ± 6.0 (mean)	76.5±5.6 (mean)	ORR, DCR, AE
Liu, 2007	China	III—IV	30/32	ND	ND	ORR, DCR, AE
Lu, 2015	China	III—IV	31/31	ND	ND	ORR, DCR
Ma, 2011	China	II—IV	108/109	47.1 ± 6.8 (mean)	44.5±6.4 (mean)	OS, ORR, DCR, QoL, AE
Miao, 2007	China	III—IV	44/43	53.0±19.0 (mean)	54.0 ± 20.0 (mean)	ORR, DCR, QOL, AE
Qi, 2011	China	III—IV	30/30	ND	ND	ORR, DCR, AE
Qiao, 2006	China	II—IV	60/60	ND	ND	OS, ORR, DCR, QoL, AE
Sun, 2004	China	ND	37/45	ND	ND	ORR, DCR, AE
Wang, 2006	China	III—IV	30/30	60.2 (mean)	58.8 (mean)	AE
Wang, 2013	China	III—IV	45/45	68.5±7.6 (mean)	68.2±7.5 (mean)	ORR, DCR, QoL, AE
Wang, 2005	China	IV	40/40	ND	ND	OS, ORR, DCR
Wang, 2009	China	III—IV	60/60	61 (Median)	56 (Median)	ORR, DCR, QoL
Yang, 2006	China	III—IV	30/30	ND	ND	ORR, DCR, QoL, AE
Yu, 2012	China	III—IV	32/32	62 (Median)	64 (Median)	ORR, DCR, AE
Zhang, 2001	China	II—IV	35/37	50 (mean)	51 (mean)	OS, ORR, QoL, DCR
Zhang, 2011	China	III—IV	30/46	75.1 (mean)	75.5 (mean)	ORR, DCR, QoL, AE
Zhou, 2014	China	III—IV	47/47	60-82	59-82	ORR, DCR, AE

Con = control group (chemotherapy alone group), Exp = experimental group (Cinobufotalin injection plus chemotherapy).

AE=adverse events, DCR=disease control rate, KPS=karnofsky performance score, ND=non determined, ORR=overall response rate, OS=overall survival rate, QoL=quality of life.

95% CI=0.28-0.75, P=.002; myelosuppression: OR=0.38, 95% CI=0.21-0.67, P=.0010; constipation: OR=0.51, 95% CI=0.34-0.77, P=.002; hemoglobin reduction: OR=0.53, 95% CI=0.32-0.90, P=.02; anemia: OR=.06, 95% CI= 0.01-0.34, P=.001), and higher incidence of phlebitis (OR= 2.85, 95% CI=1.33-6.11, P=.007), whereas no difference was found in the occurrence of allergy (OR=0.78, 95% CI=0.28-2.17, P=.64).

3.7. Publication bias

Publication bias of primary outcomes (CR, PR, SD, PD, ORR, DCR, QIR, and adverse events) were evaluated and presented by funnel plots. All plots were approximately symmetrical, indicating well controlled publication bias and satisfied reliability (Fig. 6 and Supplementary Fig. 3, http://links.lww. com/MD/D201).

We also assessed publication bias by Begg and Egger regression asymmetry tests, and nausea and vomiting was found with bias (Table 5, Egger: P=.024; Begg: P=.007, P<.05 indicating that there have publication bias in the included studies). To determine if the bias affect the pooled risk, we conducted trim and filled analysis. The adjusted OR indicated same trend with the result of the primary analysis (before: P=0.00001, after: P=0.0001), reflecting the reliability of our primary conclusions, except those based on few numbers of trials.

3.8. Sensitivity analysis

Subgroup analysis was performed for ORR and DCR heterogeneity assessment concerning therapeutic regimens and sample sizes of involved trials. No difference with statistical significance was observed on sample sizes of different studies (Table 6). Moreover, CFI combined with TP/GP/DP chemotherapy regimens was found more effective for NSCLC treatment.

We also conducted meta-regression analysis for detecting the impact of independent variables: therapeutic regimens and sample sizes, and the primary results were consistent with the subgroup analysis (Supplement Table 2, http://links.lww.com/MD/D201).

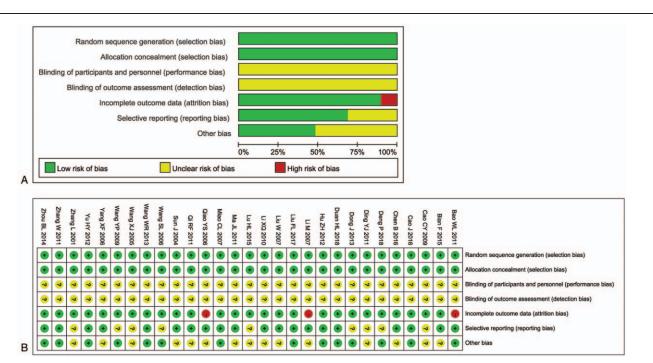
4. Discussion

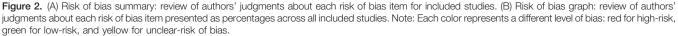
In the common treatment of NSCLC, chemotherapy bears serious side effects such as myelosuppression, hepatotoxicity, nephrotoxicity and gastrointestinal side effects, which severely affected the normal life of NSCLC patients.^[47,48] Clinicians have been exploring complementary and alternative medicine treatments

	Therapeutic regim	ien			
Included studies	Experimental group	Control group	Enrollment Period	Administration route	Expected survival time (week)
Bao, 2011	GP+Cinobufotalin injection	GP	2015.6-2016.6	Intravenous infusion	>3
Bian, 2015	GP+Cinobufotalin injection	GP	2010.9-2012.8	Intravenous infusion	>3
Cao, 2009	NP+Cinobufotalin injection	NP	2006-2008	Intravenous infusion	>3
Cao, 2016	DP+Cinobufotalin injection	DP	2013.1-2015.1	Intravenous infusion	>3
Chen, 2016	GP+Cinobufotalin injection	GP	ND	Intravenous infusion	>4
Deng, 2018	PC+Cinobufotalin injection	PC	2016.3-2017.3	Intravenous infusion	>6
Ding, 2011	NI+Cinobufotalin injection	NI	2008.1-2010.1	Intravenous infusion	>3
Dong, 2013	PD+Cinobufotalin injection	PD	2009.2-2011.12	Intravenous infusion	>3
Duan, 2018	Docetaxel+Cinobufotalin injection	Docetaxel	2015.1-2017.1	Intravenous infusion	≥3
Hu, 2012	TP+Cinobufotalin injection	TP	2005.3-2009.5	Intravenous infusion	>3
Li, 2007	NP/GP+Cinobufotalin injection	NP/GP	2002.6-2006.6	Intravenous infusion	>3
Li, 2010	NP/EP+Cinobufotalin injection	NP/EP	2006.8-2008.6	Intravenous infusion	>3
Liu, 2017	Docetaxel+Cinobufotalin injection	Docetaxel	2014.3-2016.8	Intravenous infusion	ND
Liu, 2007	NP+Cinobufotalin injection	NP	2000.11-2004.9	Intravenous infusion	>3
Lu, 2015	NP+Cinobufotalin injection	NP	2008.1-2013.12	Intravenous infusion	>3
Ma, 2011	GP+Cinobufotalin injection	GP	2005-2010	Intravenous infusion	>3
Miao, 2007	NP+Cinobufotalin injection	NP	2002.6-2005.2	Intravenous infusion	>3
Qi, 2011	TP/GP/NP+Cinobufotalin injection	TP/GP/NP	2008.6-2010.6	Intravenous infusion	>3
Qiao, 2006	NP+Cinobufotalin injection	NP	1999.1-2004.1	Intravenous infusion	≥3
Sun, 2004	VP+Cinobufotalin injection	VP	1998.2-2000.12	Intravenous infusion	ND
Wang, 2006	TP+Cinobufotalin injection	TP	2003.5-2004.6	Intravenous infusion	>3
Wang, 2013	TP+Cinobufotalin injection	TP	2010.6-2011.12	Intravenous infusion	≥3
Wang, 2005	TP+Cinobufotalin injection	TP	1998.7-2003.7	Intravenous infusion	ND
Wang, 2009	TP+Cinobufotalin injection	TP	2007.9-2008.9	Intravenous infusion	>3
Yang, 2006	NP+Cinobufotalin injection	NP	2003.8-2005.8	Intravenous infusion	≥3
Yu, 2012	DP+Cinobufotalin injection	DP	2009.6-2010.12	Intravenous infusion	>3
Zhang, 2001	NP+Cinobufotalin injection	NP	ND	Intravenous infusion	>3
Zhang, 2011	Docetaxel+Cinobufotalin injection	Docetaxel	2009.12-2010.12	Intravenous infusion	>3
Zhou, 2014	TP+Cinobufotalin injection	TP	2011.12-2013.6	Intravenous infusion	ND

Con = control group (chemotherapy alone group), Exp = experimental group (Cinobufotalin injection plus chemotherapy).

DDP = Cisplatin, DP = Docetaxel+DDP, EP = Etoposide+DDP, GP = Gemcitabine+DDP, ND = non determined, NI = NVB+lfosfamide, NP = Navelbine+DDP, NVB = Navelbine, PC = Paclitaxel+Carboplatin, PD = Pemetrexed+DDP, TP = Paclitaxel+DDP, VP = Vindesine+DDP.





	Experim	ental	Conti	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.1.1 0.5-Year OS							A second provide a seco
Ma JL 2011	101	109	94	108	6.1%	1.88 [0.75, 4.69]	
Wang XJ 2005	30	40	23	40	5.1%	2.22 [0.86, 5.74]	
Zhang L 2001	27	37	25	35	6.1%	1.08 [0.38, 3.03]	
Subtotal (95% CI)		186		183	17.3%	1.70 [0.98, 2.94]	◆
Total events	158		142				
Heterogeneity: Chi ² =	1.09, df = 2	(P = 0.1)	58); l ² = 0	1%			
Test for overall effect:	Z = 1.88 (F	P = 0.06)	Section 4				
1.1.2 1-Year OS							
Chen B 2016	28	45	20	45	6.7%	2.06 [0.89, 4.78]	
Hu ZH 2012	13	36	9	38	4.9%	1.82 [0.66, 5.00]	
Li M 2007	26	32	22	32	3.6%	1.97 [0.62, 6.29]	
Ma JL 2011	59	109	30	108	12.2%	3.07 [1.74, 5.40]	
Qiao YS 2006	44	60	41	60	9.7%	1.27 [0.58, 2.81]	
Wang XJ 2005	13	40	10	40	6.0%	1.44 [0.55, 3.83]	
Zhang L 2001	19	37	16	35	7.1%	1.25 [0.50, 3.16]	
Subtotal (95% CI)	270	359		358	50.2%	1.94 [1.42, 2.65]	•
Total events	202		148				
Heterogeneity: Chi ² =	4.86, df = 6	(P = 0.1)	56); $I^2 = 0$	1%			
Test for overall effect:				823			
1.1.3 2-Year OS							
Chen B 2016	8	45	4	45	2.9%	2.22 [0.62, 7.97]	
Hu ZH 2012	4	36	2	38	1.5%	2.25 [0.39, 13.12]	
Li M 2007	11	32	3	32	1.5%		
Ma JL 2011	24	109	12	108	8.3%	5.06 [1.26, 20.42] 2.26 [1.06, 4.79]	
Qiao YS 2006	24	49	12	48	8.3%		
	25	49	3	40		1.59 [0.71, 3.56]	
Wang XJ 2005	18	37	8	35	2.3%	1.76 [0.39, 7.93]	
Zhang L 2001 Subtotal (95% CI)	10	348	0	35	28.8%	3.20 [1.15, 8.86] 2.31 [1.55, 3.45]	•
Total events	95	340	51	340	20.0 /0	2.51 [1.55, 5.45]	
and the second	A CONTRACT OF A CONTRACT	(D - 0)	Contraction of the local sectors of the local secto	0/			
Heterogeneity: Chi ² = Test for overall effect:				70			
1.1.4 3-Year OS			1000				
	0	00		00	0 40/	15 04 10 96 000 45	
Li M 2007	6 16	32 35	0	32 36		15.94 [0.86, 296.15]	
Qiao YS 2006	16	35 67	1	68	3.3% 3.7%	3.49 [1.21, 10.07]	
Subtotal (95% CI)	00	07	-	00	3.1%	4.69 [1.78, 12.39]	
Total events	22	(D - C	7	0/			
Heterogeneity: Chi ² =		•		70			
Test for overall effect:	Z = 3.12 (F	= 0.002	2)				
Total (95% CI)		960		955	100.0%	2.10 [1.69, 2.62]	•
Total events	477		348				
Heterogeneity: Chi ² =	12.26, df =	18 (P =	0.83); l ² :	= 0%			0.01 0.1 1 10 100
and the second se	Z = 6.69 (F	- 0 000	1001				

Figure 3. Forest plot of the comparison of overall survival (OS) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, Cinobufotalin injection plus chemotherapy. The fixed-effects meta-analysis model (Mantel-Haenszel method) was used.

for advanced NSCLC, and traditional Chinese medicine, particularly cinobufotalin, has been clinically applied as an adjuvant therapy for decades.^[8,9] CFI has been reported beneficial to patients with advanced NSCLC in several trials.^[15–17] Despite the published reviews on clinical trials using cinobufotalin, its therapeutic effects have not been systematically demonstrated. These trials had various sample sizes following different protocols, which compounded the difficulties of statistical analysis. To perform a reliable systematic analysis with statistical significance, in this research, we gathered large

amounts of data from online databases and conducted comparative analysis in various categorization.

Our meta-analysis revealed that CFI and chemo-combined therapy for NSCLC patients achieved more beneficial effects in comparison with those treated by solely chemotherapy. Combined therapy-treated patients exhibited broadly increased 1 to 3 years OS, CR, PR, ORR, and DCR (P < .05), and also significantly improved QoL. These results indicated that intravenous infusion of CFI improved the curative effects of chemotherapy.

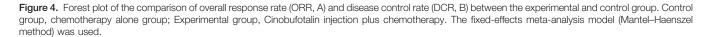
Study or Subgroup	Experim Events		Cont		Weight	Odds Ratio M-H. Fixed, 95% C	Odds Ratio M-H. Fixed, 95% CI
Bao WL 2011	24	45	21	48	4.9%	1.47 [0.65, 3.33]	
Bian F 2015	15	32	10	31	2.8%	1.85 [0.67, 5.16]	
Cao CY 2009	10	25	8	25	2.5%	1.42 [0.44, 4.52]	
Cao J 2016	14	40	12	40	4.1%	1.26 [0.49, 3.21]	
Chen B 2016	28	45	18	45	3.5%	2.47 [1.06, 5.77]	
Deng P 2018	11	34	10	34	3.5%		
	24	39				1.15 [0.41, 3.21]	
Ding YJ 2011			15	39	3.0%	2.56 [1.03, 6.37]	
Dong J 2013	33	46	23	40	3.6%	1.88 [0.76, 4.60]	
Duan HL 2018	24	30	14	30	1.5%	4.57 [1.45, 14.39]	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Hu ZH 2012	20	36	14	38	3.2%	2.14 [0.84, 5.44]	
Li M 2007	3	21	0	21	0.2%	8.14 [0.39, 167.98]	
Li XQ 2010	16	30	14	32	3.3%	1.47 [0.54, 4.00]	
Liu FL 2017	9	24	5	24	1.6%	2.28 [0.63, 8.25]	
Liu W 2007	19	32	13	30	2.8%	1.91 [0.70, 5.25]	
Lu HL 2015	18	31	15	31	3.3%	1.48 [0.54, 4.02]	
Ma JL 2011	61	109	41	108	9.5%	2.08 [1.21, 3.57]	100.5
Miao CL 2007	24	43	15	44	3.4%	2.44 [1.03, 5.81]	
Qi RF 2011	17	30	12	30	2.7%	1.96 [0.70, 5.48]	
Qiao YS 2006	27	60	24	60	6.9%	1.23 [0.59, 2.53]	
Sun J 2004	25	45	17	37	4.3%	1.47 [0.61, 3.52]	
Wang WR 2013	33	45	23	45	3.2%	2.63 [1.09, 6.36]	
Wang XJ 2005	21	40	18	40	4.5%	1.35 [0.56, 3.25]	
Wang YP 2009	31	60	18	60	4.5%	2.49 [1.18, 5.28]	
Yang XF 2006	11	30	7	30	2.3%	1.90 [0.62, 5.86]	
Yu HY 2012	17	32	13	32	3.2%	1.66 [0.62, 4.46]	
Zhang L 2001	14	37	12	35	4.0%	1.17 [0.45, 3.06]	
Zhang W 2011	14	46	10	30	4.4%	0.88 [0.33, 2.34]	
Zhou BL 2014	35	47	24	47	3.2%	2.80 [1.17, 6.67]	
Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect				1106 = 0%	100.0%	1.84 [1.54, 2.18]	0.01 0.1 1 10 100
							Favours [Control] Favours [Experimenta
	Experim	ental	Cont	n		Odds Ratio	Favours [Control] Favours [Experimenta
Study or Subgroup	Experim		Cont		Weight	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Odds Ratio
Bao WL 2011	Events 39	Total 45	Events 40	Total 48	4.5%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09]	Odds Ratio
Bao WL 2011 Bian F 2015	Events 39 23	Total 45 32	Events 40 17	Total 48 31	4.5% 4.3%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09] 2.10 [0.74, 5.99]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009	Events 39 23 18	Total 45 32 25	Events 40 17 18	Total 48 31 25	4.5% 4.3% 4.4%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016	Events 39 23 18 31	Total 45 32 25 40	Events 40 17 18 25	Total 48 31 25 40	4.5% 4.3% 4.4% 4.9%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016	Events 39 23 18 31 37	Total 45 32 25 40 45	Events 40 17 18 25 31	Total 48 31 25 40 45	4.5% 4.3% 4.4% 4.9% 4.8%	<u>M-H, Fixed, 95% Cl</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018	Events 39 23 18 31 37 32	Total 45 32 25 40 45 34	Events 40 17 18 25 31 25	Total 48 31 25 40 45 34	4.5% 4.3% 4.4% 4.9% 4.8% 1.3%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011	Events 39 23 18 31 37 32 34	Total 45 32 25 40 45 34 39	Events 40 17 18 25 31 25 31	Total 48 31 25 40 45 34 39	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013	Events 39 23 18 31 37 32 34 43	Total 45 32 25 40 45 34 39 46	Events 40 17 18 25 31 25 31 38	Total 48 31 25 40 45 34 39 40	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5% 2.3%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018	Events 39 23 18 31 37 32 34 43 27	Total 45 32 25 40 45 34 39 46 30	Events 40 17 18 25 31 25 31 25 31 38 19	Total 48 31 25 40 45 34 39 40 30	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5% 2.3% 1.7%	M-H, Fixed, 95% Cl 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding VJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012	Events 39 23 18 31 37 32 34 43 27 31	Total 45 32 25 40 45 34 39 46 30 30 36	Events 40 17 18 25 31 25 31 38 19 24	Total 48 31 25 40 45 34 39 40 30 30 38	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5% 2.3% 1.7% 2.8%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007	Events 39 23 18 31 37 32 34 43 27 31 17	Total 45 32 25 40 45 34 39 46 30 36 21	Events 40 17 18 25 31 25 31 38 19 24 6	Total 48 31 25 40 45 34 39 40 30 38 21	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5% 2.3% 1.7% 2.8% 1.0%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010	Events 39 33 18 31 37 32 34 43 27 31 17 26 26	Total 45 32 25 40 45 34 39 46 30 36 21 30	Events 40 17 18 25 31 25 31 38 19 24 6 27	Total 48 31 25 40 45 34 39 40 30 38 21 32	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 3.5% 2.3% 1.7% 2.8% 1.0% 3.0%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017	Events 39 23 18 31 37 32 34 43 27 31 17 26 15	Total 45 32 25 40 45 34 39 46 30 36 21 30 24	Events 40 17 18 25 31 25 31 38 19 24 6 27 10	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 2.3% 1.3% 2.3% 1.0% 3.0% 3.3%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.88] 2.33 [0.73, 7.43]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28	Total 45 32 25 40 45 34 39 46 30 36 21 30 24 32	Events 40 17 18 25 31 25 31 25 31 38 19 24 6 27 10 25	Total 48 31 25 40 45 34 39 40 30 38 21 32 24 30	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 2.3% 1.7% 2.8% 1.0% 3.0% 3.3% 2.8%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2013 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015	Events 39 23 18 31 37 32 34 43 43 43 17 26 15 28 28	Total 45 32 25 40 45 34 39 46 30 30 30 321 30 24 32 31	Events 40 17 18 25 31 25 31 38 19 24 6 27 10 25 28	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24 30 31	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 2.3% 1.7% 2.8% 1.0% 3.0% 3.3% 2.8% 2.4%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.61] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011	Events 39 33 18 31 37 32 34 433 27 311 17 26 15 28 98	Total 45 32 25 40 45 34 39 46 30 36 30 36 30 321 30 24 32 31 109	Events 40 17 18 25 31 25 31 25 31 38 19 24 6 27 10 25 28 86	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24 30 31 108	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 2.3% 1.7% 2.8% 1.0% 3.0% 3.0% 3.2% 2.8% 2.4% 7.6%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38	Total 45 32 25 40 45 34 39 46 30 36 21 30 24 30 24 31 109 43	Events 40 17 18 25 31 25 31 25 31 38 19 24 6 27 10 25 28 886 38	Total 48 31 25 40 45 34 39 40 30 38 21 32 24 30 31 108 44	4.5% 4.3% 4.9% 4.8% 1.3% 3.5% 2.3% 1.7% 2.8% 3.0% 3.3% 2.8% 2.4% 3.8%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.88] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011	Events 39 23 18 31 37 32 34 43 27 31 17 26 28 98 38 25	Total 45 32 25 40 45 34 30 46 30 36 21 30 24 32 31 109 43 30	Events 40 17 18 25 31 25 31 38 19 24 6 27 10 25 28 86 6 38 86 6 38	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24 30 31 108 44 30	4.5% 4.3% 4.9% 4.9% 3.5% 2.3% 1.7% 2.8% 1.0% 3.0% 3.3% 2.8% 2.4% 7.6% 3.8% 2.9%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2013 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48	Total 45 32 25 40 45 34 39 46 30 30 36 21 30 24 32 31 109 43 0 60	Events 40 17 18 255 31 38 19 24 6 27 10 25 28 86 86 38 20 0 42	Total 48 31 25 40 45 34 39 40 30 30 30 30 38 21 32 24 30 31 108 44 30 60	4.5% 4.3% 4.4% 4.8% 1.3% 3.5% 2.3% 1.7% 3.0% 3.0% 3.0% 3.8% 2.4% 7.6% 3.8% 2.9% 2.9%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.74, 8.50] 1.71 [0.74, 3.97]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48 42	Total 45 32 25 40 45 34 30 46 30 36 21 30 24 32 31 109 43 30	Events 40 17 18 255 31 25 31 25 31 38 19 24 6 27 10 25 28 86 86 38 820 422 34	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24 30 31 108 44 30 31 52 52 54 57 57 57 57 57 57 57 57 57 57 57 57 57	4.5% 4.3% 4.4% 4.9% 1.3% 3.5% 2.3% 1.0% 3.0% 3.0% 3.3% 2.8% 2.4% 7.6% 3.8% 2.9%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2013 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48	Total 45 32 25 40 45 34 39 46 30 30 36 21 30 24 32 31 109 43 0 60	Events 40 17 18 255 31 38 19 24 6 27 10 25 28 86 86 38 20 0 42	Total 48 31 25 40 45 34 39 40 30 30 30 30 38 21 32 24 30 31 108 44 30 60	4.5% 4.3% 4.4% 4.8% 1.3% 3.5% 2.3% 1.7% 3.0% 3.0% 3.0% 3.8% 2.4% 7.6% 3.8% 2.9% 2.9%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.88] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.00 [0.61, 6.52]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2013 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qia RF 2011 Qiao YS 2006 Sun J 2004	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48 42	Total 45 32 25 40 45 34 39 46 30 36 21 30 24 32 31 109 43 30 60 60	Events 40 17 18 255 31 25 31 25 31 38 19 24 6 27 10 25 28 86 86 38 820 422 34	Total 48 31 25 40 45 34 39 40 30 30 38 21 32 24 30 31 108 44 30 31 52 52 54 57 57 57 57 57 57 57 57 57 57 57 57 57	4.5% 4.3% 4.4% 4.9% 1.3% 3.5% 2.3% 1.0% 3.0% 3.0% 3.3% 2.8% 2.4% 7.6% 3.8% 2.9%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.61] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.87] 1.24 [0.23, 6.52]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006 Sun J 2004 Wang WR 2013	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48 42 40	Total 45 32 25 40 45 34 39 46 30 36 21 30 24 32 31 109 43 30 60 60 60 545	Events 40 17 18 25 31 25 31 38 19 24 6 27 10 25 28 86 38 20 42 34 36	Total 48 31 25 40 45 34 39 40 30 38 21 32 24 30 31 108 44 30 60 37 45	4.5% 4.3% 4.4% 4.9% 4.8% 1.3% 2.3% 1.0% 3.0% 3.0% 3.0% 3.3% 2.8% 2.4% 7.6% 3.8% 2.9% 7.4% 3.5%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.88] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.00 [0.61, 6.52]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006 Sun J 2004 Wang WR 2013 Wang XJ 2005	Events 39 23 18 31 37 32 34 43 27 31 17 26 28 98 98 38 25 48 42 40 36	Total 45 32 255 40 45 34 39 46 30 36 21 30 24 32 31 109 43 30 60 45 45 40	Events 40 17 18 25 31 25 31 38 19 24 6 27 10 25 28 8 86 38 20 42 23 4 36 32	Total 48 31 25 40 45 34 39 40 300 30 302 24 301 31 108 44 300 60 60 60 745 40	4.5% 4.3% 4.9% 4.8% 1.3% 2.3% 1.7% 2.8% 1.0% 3.0% 2.8% 2.4% 7.6% 3.8% 2.9% 7.4% 2.2% 3.5% 2.8%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.00 [0.61, 6.52] 2.25 [0.62, 8.18]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li W 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006 Sun J 2004 Wang WR 2013 Wang XJ 2005 Wang YP 2009	Events 39 23 18 31 37 32 34 43 27 31 17 26 28 98 38 25 48 42 40 36 52	Total 45 32 25 40 45 34 39 46 30 30 36 21 30 36 21 30 24 32 31 109 43 30 60 45 45 60 60	Events 40 17 18 255 31 38 19 24 6 27 10 25 28 86 36 320 42 34 32 34 32 34 32 34 44	Total 48 31 25 40 40 45 34 45 39 40 300 30 322 24 300 31 108 44 300 60 377 455 400 600	4.5% 4.3% 4.4% 4.8% 1.3% 2.3% 1.0% 3.0% 3.0% 3.0% 3.0% 3.0% 3.8% 2.4% 7.6% 3.8% 2.2% 3.5% 2.2% 3.5% 2.5%	<u>M-H, Fixed, 95% Ci</u> 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.51] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.00 [0.61, 6.52] 2.25 [0.62, 8.18] 2.36 [0.92, 6.04] 1.63 [0.41, 6.47]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Qiao YS 2006 Sun J 2004 Wang WR 2013 Wang XJ 2005 Wang YP 2009 Yang XF 2006	Events 39 23 18 31 37 32 34 43 27 31 17 26 15 28 98 38 25 48 42 40 36 52 26	Total 45 32 25 40 45 34 39 46 30 21 30 24 30 24 32 31 109 43 30 60 45 40 60 30	Events 40 17 18 255 31 25 31 38 19 24 6 27 10 25 28 86 38 20 25 28 86 38 20 42 42 34 34 32 34 42 42	Total 48 31 25 34 39 40 45 34 39 40 30 30 38 21 32 24 30 30 31 108 44 30 30 31 108 44 30 60 30 30	4.5% 4.3% 4.4% 4.9% 1.3% 3.5% 2.3% 1.0% 3.0% 3.0% 3.8% 2.4% 7.6% 3.8% 2.9% 3.5% 2.2% 3.5% 2.8%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.61] 2.09 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.98] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.00 [0.61, 6.52] 2.25 [0.62, 8.18] 2.35 [0.92, 6.04]	Odds Ratio
Bao WL 2011 Bian F 2015 Cao CY 2009 Cao J 2016 Chen B 2016 Deng P 2018 Ding YJ 2011 Dong J 2013 Duan HL 2018 Hu ZH 2012 Li M 2007 Li XQ 2010 Liu FL 2017 Liu W 2007 Lu HL 2015 Ma JL 2011 Miao CL 2007 Qi RF 2011 Miao CL 2007 Qi RF 2011 Miao CL 2007 Qi Wang WR 2013 Wang XJ 2005 Wang YP 2009 Yang XF 2006 Yu HY 2012	Events 39 23 18 31 37 32 34 27 31 17 26 15 28 28 38 25 48 40 36 52 26 28	Total 45 32 255 40 45 34 39 46 30 361 21 300 24 32 311 109 43 300 60 455 40 60 300 32	Events 40 17 18 25 31 38 19 24 6 27 10 25 28 86 86 88 83 8 20 42 34 32 34 32 32 44 22 22	Total 48 31 255 34 400 45 34 39 300 300 31 32 24 300 31 32 24 300 31 108 44 30 600 600 600 301 32	4.5% 4.3% 4.4% 4.9% 1.3% 3.5% 2.3% 1.0% 3.0% 3.0% 3.3% 2.8% 2.4% 7.6% 3.8% 2.2% 3.5% 2.8% 5.1% 2.8% 2.4%	M-H, Fixed, 95% Ci 1.30 [0.41, 4.09] 2.10 [0.74, 5.99] 1.00 [0.29, 3.44] 2.07 [0.78, 5.63] 5.76 [1.14, 29.08] 1.75 [0.52, 5.94] 0.75 [0.12, 4.76] 5.21 [1.28, 21.24] 3.62 [1.14, 11.44] 10.63 [2.51, 44.99] 1.20 [0.29, 4.88] 2.33 [0.73, 7.43] 1.40 [0.34, 5.80] 1.00 [0.19, 5.39] 2.28 [1.05, 4.97] 1.20 [0.34, 4.27] 2.50 [0.74, 8.50] 1.71 [0.74, 3.97] 1.24 [0.23, 6.52] 2.25 [0.62, 8.18] 2.36 [0.94, 6.47] 3.18 [0.88, 11.52]	Odds Ratio

Total (95% CI) 1106 100.0% 2.09 [1.68, 2.60] 1134 822 Total events 969 Heterogeneity: Chi² = 18.52, df = 27 (P = 0.89); l² = 0% 0.01 0.1 Test for overall effect: Z = 6.63 (P < 0.00001) B Favours [Control] Favours [Experimental]

37 47

42

47



3.4%

2.27 [0.71, 7.25]

In the evaluation of safety in CFI involved therapy for NSCLC, our analysis showed that most of adverse events caused by chemotherapy were obviously alleviated (P < .05). However,

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patients received CFI and chemo-combined therapy showed higher incidence of phlebitis, which should be considered before treatment for sensitive groups.

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100

	Experimental group	Control group		Hetero	ogeneity			
Parameter	No. of patients (n)	No. of patients (n)	Analysis method	l ² (%)	P value	Odds Ratio (OR)	95% CI	P value
CR	1134	1106	Fixed	0	1.00	2.01	1.47 to 2.75	<.0001
PR	1134	1106	Fixed	0	1.00	1.51	1.26 to 1.80	<.00001
SD	1134	1106	Fixed	10	.31	0.87	0.73 to 1.03	.11
PD	1134	1106	Fixed	0	.92	0.47	0.38 to 0.59	<.00001
ORR	1134	1106	Fixed	0	.97	1.84	1.54 to 2.18	<.00001
DCR	1134	1106	Fixed	0	.89	2.09	1.68 to 2.60	<.00001

Con = control group (chemotherapy alone group), Exp = experimental group (Cinobufotalin injection plus chemotherapy).

CR=complete response rates, DCR=disease control rate, ORR=overall response rate, PD=progressive disease rates, PR=partial response rates, SD=stable disease rates.

The analysis on therapeutic effects may be influenced by several factors. In our study, no difference was found between sample sizes of trials. Our sensitivity analysis showed that CFI combined with TP/GP/DP chemotherapy was more effective for NSCLC treatment. However, but recent studies on the impact of this factor on the curative effect of CFI mediated therapy remain insufficient and further investigations still should be performed.

There are some limitations in our analysis. Firstly, as a traditional medicine, cinobufotalin was mainly applied in China, which comes with unavoidable regional bias and subsequently has an effect on CFI's widely application out of China. Secondly, since researchers in different clinical studies reported various outcomes, categorization was complicated and making it difficult to summarize the results at the same scale. Moreover, the efficacy of CFI therapy might be related with NSCLC subtypes. However, our data were extracted from publications where this information was not sufficiently provided. Therefore, based on currently available literature, there are insufficient data to perform a statistical analysis to evaluate the correlation. We will keep paying close attention to this concern in our later studies. Finally, as the sources of our data were published articles instead of raw records of clinical trials, analytical bias would be possibly existed. Therefore,

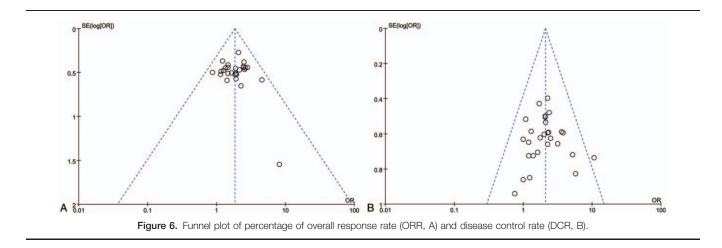
	Exp	erime	ntal	Con	trol			Odds Ratio		Odd	Is Ratio		
Study or Subgroup	Eve	ents	Total	Events	s Tota	I We	eight	M-H, Fixed, 95% Cl		M-H, Fi	xed, 95%	CI	
Bao WL 2011		24	45	8	3 48	3 (6.2%	5.71 [2.19, 14.91]			-		
Bian F 2015		15	32	12	2 31	1 1	1.1%	1.40 [0.51, 3.81]		_	-		
Ding YJ 2011		15	39	9	39	9 9	9.5%	2.08 [0.78, 5.58]			+		
Dong J 2013		20	46	18	3 40) 18	8.6%	0.94 [0.40, 2.21]			•		
Hu ZH 2012		11	36	e	38	3 (6.9%	2.35 [0.76, 7.22]			+	-	
Li M 2007		16	32	11	32	2 1	9.4%	1.91 [0.70, 5.22]					
Li XQ 2010		16	30	5	5 32	2 :	3.9%	6.17 [1.87, 20.36]				_	
Miao CL 2007		37	43	30) 44	4	7.1%	2.88 [0.99, 8.40]			-		
Wang YP 2009		52	60	38	60) (B.7%	3.76 [1.51, 9.36]					
Yang XF 2006		22	30	e	30) :	2.7%	11.00 [3.29, 36.75]			-		-
Zhang L 2001		9	37	e	35	5 8	8.0%	1.55 [0.49, 4.94]		1	-		
Zhang W 2011		21	46	7	30)	7.9%	2.76 [0.99, 7.70]			-	_	
Total (95% CI)			476		459	10	0.0%	2.64 [1.98, 3.52]			٠		
Total events		258		156	5								
Heterogeneity: Chi2 =	= 19.07	df = 1	1 (P =	0.06); 12	= 42%						<u> </u>	1	
Test for overall effec	t: Z = 6.	60 (P	< 0.000	001)					0.01	0.1 vours [Control		10	100
10000000000000000000000000000000000000				1999 B					га	vours [Control] Favours	s [Expe	nmenta
A		22	225		12.72			12 12 12		122			
01 1 0 1		eriment			ontrol			Mean Difference			Difference	100000	
Study or Subgroup	Mean			Mean			Weight			IV. Rai	ndom, 95%	CI	
Ma JL 2011 Qiao YS 2006	89.41 86.15	6.54 9.33	60	82.43 71.36	5.32 8.23	108 60	36.7% 33.7%		-		104		
Wang WR 2013	68.5			56.92		45	29.6%		-		1.		
Wally WR 2013	00.5	12.40	40	30.92	10.57	40	29.0%	11.00 [0.00, 10.31	1				
Total (95% CI)			214			213	100.0%	10.97 [5.48, 16.47]	1		•		
Heterogeneity: Tau ² = :	20.74; C	$hi^2 = 20$).29, df	= 2 (P <	0.0001	; ² =	90%	65 82 55	-	1	-	1	
B Test for overall effect:					100000000000000000000000000000000000000				-100	-50 Favours [Contr	0	50	100

Figure 5. Forest plot of the comparison of quality of life improved rate (QIR, A) and karnofsky performance score (KPS, B) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, Cinobufotalin injection plus chemotherapy.

Comparison of adverse	events between t	he experimental	and control groups.

	Experimental group	Control group		Hetero	ogeneity			
Adverse events	No. of patients (n)	No. of patients (n)	Analysis method	l ² (%)	P value	Odds Ratio (OR)	95% CI	P value
Leukopenia	590	586	Random	68	.0001	0.33	0.20 to 0.54	<.0001
Thrombocytopenia	515	496	Random	62	.002	0.33	0.20 to 0.57	<.0001
Nausea and vomiting	416	398	Random	62	.002	0.23	0.11 to 0.49	.0001
Hepatotoxicity	372	377	Fixed	0	.51	0.41	0.27 to 0.62	<.0001
Nephrotoxicity	372	377	Fixed	0	.99	0.36	0.24 to 0.56	<.00001
Gastrointestinal side effects	231	229	Fixed	12	.34	0.52	0.33 to 0.80	.003
Diarrhea	240	223	Random	72	.01	0.21	0.05 to 0.89	.03
Peripheral neurotoxicity	122	124	Fixed	0	.49	0.47	0.23 to 0.94	.03
Granulopenia	299	274	Fixed	48	.09	0.30	0.21 to 0.44	<.00001
Phlebitis	169	157	Fixed	0	.67	2.85	1.33 to 6.11	.007
Alopecia	216	219	Fixed	0	.75	0.46	0.28 to 0.75	.002
Myelosuppression	156	155	Fixed	0	.55	0.38	0.21 to 0.67	.0010
Constipation	214	217	Fixed	39	.18	0.51	0.34 to 0.77	.002
Hemoglobin reduction	120	124	Fixed	3	.36	0.53	0.32 to 0.90	.02
Allergy	128	130	Fixed	0	.90	0.78	0.28 to 2.17	.64
Anemia	82	68	Fixed	0	.57	0.06	0.01 to 0.34	.001

Con, control group (chemotherapy alone group); Exp, experimental group (Cinobufotalin injection plus chemotherapy).



more original data would be valuable to achieve a higher reliability of statistical analysis on CFI involved NSCLC treatment.

5. Conclusion

This meta-analysis indicated that CFI and chemo-combined therapy was effective in treating advanced NSCLC. Intravenous

infusion of CFI not only greatly improved the therapeutic effects of chemotherapy, but also effectively alleviates the toxicity and most of side effects caused by chemotherapy. Considering the possibility of causing phlebitis, clinician should weigh and consider balance of using CFI for sensitive NSCLC patients. On the other hand, fighting cancer war is a long term task. Therefore, it is necessary to further investigate the cancer mechanism and synthesis of anti-cancer natural medicines.^[49–52]

Table 5

Publication bias on therapeutic efficacy indexes (CR, PR, SD, PD, ORR, DCR, and QIR) and adverse events indexes (Leukopenia, Thrombocytopenia and Nausea and vomiting).

Therapeutic efficacy indexes								Adverse events indexes			
Publication Bias	CR	PR	SD	PD	ORR	DCR	QIR	Leukopenia	Thrombocytopenia	Nausea and vomiting	
Begg	0.492	1.000	0.514	0.890	0.984	0.594	0.244	0.584	0.631	0.024	
Egger	0.488	0.391	0.339	0.625	0.644	0.983	0.107	0.481	0.630	0.007	

Parameters discussed in over 10 papers were conducted bias analyses.

CR = complete response rates, DCR = disease control rate, ORR = overall response rate, PD = progressive disease rates, PR = partial response rates, QIR = quality of life improved rate, SD = stable disease rates.

Ta	blo	6	
I a	DIE		

Subgroup analyses of ORR and DCR between the experimental and co	control group.
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Parameter	Factors at study level	Exp group No. of patients (n)	Con group No. of patients (n)		Heterogeneity				
				Analysis method	l² (%)	P value	Odds Ratio	(OR)	P value
ORR	Therapeutic regimen								
	Cinobufotalin injection+NP	240	229	Fixed	0	.93	1.44	0.99 to 2.10	.05
	Cinobufotalin injection+TP	199	200	Fixed	0	.54	1.96	1.28 to 2.99	.002
	Cinobufotalin injection+GP	143	143	Fixed	31	.23	1.95	1.20 to 3.18	.007
	Cinobufotalin injection+DP	215	208	Fixed	0	.88	2.14	1.44 to 3.18	.0002
	Cinobufotalin injection+Docetaxel	90	82	Fixed	0	.40	1.92	1.05 to 3.52	.03
	Study sample size								
	≥80	625	614	Fixed	0	.87	1.89	1.51 to 2.38	<.00001
	<80	509	492	Fixed	0	.91	1.76	1.36 to 2.29	<.0001
DCR	Therapeutic regimen								
	Cinobufotalin injection+NP	240	229	Fixed	0	.86	1.54	0.99 to 2.41	.06
	Cinobufotalin injection+TP	199	200	Fixed	33	.20	2.13	1.29 to 3.52	.003
	Cinobufotalin injection+GP	143	143	Fixed	0	.48	2.85	1.55 to 5.23	.0007
	Cinobufotalin injection+DP	215	208	Fixed	0	.52	2.07	1.18 to 3.64	.01
	Cinobufotalin injection+Docetaxel	90	82	Fixed	0	.59	1.82	0.78 to 4.25	.16
	Study sample size								
	≥80	625	614	Fixed	0	.99	1.88	1.38 to 2.55	<.0001
	<80	509	492	Fixed	0	.46	2.33	1.71 to 3.16	<.00001

Con = control group (chemotherapy alone group), Exp = experimental group (Cinobufotalin injection plus chemotherapy).

DCR=disease control rate, DDP=Cisplatin, DP=Docetaxel+DDP, GP=Gemcitabine+DDP, NP=Navelbine+DDP, NVB=Navelbine, ORR=overall response rate, TP=Paclitaxel+DDP.

Author contributions

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Formal analysis: Fan Zhang, Yantong Yin.

Investigation: Fan Zhang, Yantong Yin.

Methodology: Fan Zhang, Yantong Yin.

Project administration: Tiantian Xu.

Software: Fan Zhang.

Supervision: Tiantian Xu.

Validation: Fan Zhang, Yantong Yin, Tiantian Xu.

Visualization: Fan Zhang, Yantong Yin.

Writing - original draft: Fan Zhang, Yantong Yin.

Writing - review & editing: Tiantian Xu.

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