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

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

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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

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. 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. Non-small cell lung cancer (NSCLC) is constitutes for approximately 85% of all lung cancer cases. 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, 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).

In recent years, traditional Chinese medicine has been more widely used as compounds for chemotherapy, and showed promising therapeutic effects in cancer treatment. Cinobuf-
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. If 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 trim-and-fill method would be applied to coordinate the estimates of unpublished studies, and the adjusted results were compared with the original pooled OR. 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 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\(^\text{[21,28,35]}\) were regarded as high attrition risk owing to absent of follow-up data and 9 studies\(^\text{[22,24–26,32,37,39,40,44]}\) 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, 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,
95% CI = 0.28–0.75, \( P = .002 \); myelosuppression: OR = 0.38, 95% CI = 0.21–0.67, \( P = .001 \); 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 = 0.6, 95% CI = 0.03–0.94, \( P = .001 \), 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, QoL, 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 test and found no publication bias 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

### Table 1
Clinical information from the eligible trials in the meta-analysis.

| 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 |
| Biao, 2015       | China   | KPS ≥ 60    | 31/32           | ND  | ND  | ORR, DCR        |
| Can, 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 |
| Chen, 2016       | China   | III–IV      | 45/45           | 59.4 ± 10.7 (mean) | 60.1 ± 11.5 (mean) | QoL, 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           | 46–69 | 46–66 | ORR, DCR, QoL   |
| Duan, 2018       | China   | KPS ≥ 60    | 30/30           | 67.2 ± 6.3 (mean) | 66.9 ± 6.1 (mean) | ORR, DCR |
| Hu, 2012         | China   | III–IV      | 38/36           | ≥ 70 (17) | ≥ 70 (15) | ORR, DCR, AE |
| Li, 2007         | China   | III–IV      | 32/32           | ND  | ND  | ORR, DCR, QoL   |
| Li, 2010         | China   | III–IV      | 30/30           | ND  | ND  | ORR, DCR, QoL   |
| Liu, 2017        | China   | ND          | 24/24           | 76.1 ± 6.0 (mean) | 76.5 ± 5.6 (mean) | ORR, DCR |
| 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) | ORR, DCR, QoL, AE |
| Miao, 2007       | China   | III–IV      | 44/44           | 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, QoL   |
| Qian, 2006       | China   | II–IV       | 60/60           | ND  | ND  | ORR, DCR, QoL   |
| 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  | ORR, DCR, QoL   |
| 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   |
| 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) | 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.
Table 2
Information of cinobufotalin injection combined with chemotherapy.

| Included studies | Therapeutic regimen | 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 |
| Deng, 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 | 2003.3–2004.6 | 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 | ≥3 |
| Wang, 2009       | TP+Cinobufotalin injection | TP | 2007.9–2009.4 | 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+Ifosfamide, NP = Navelbine+DDP, NVB = Navelbine, PC = Paclitaxel+Carboplatin, PD = Pemetrexed+DDP, TP = Paclitaxel+DDP, VP = Vindesine+DDP.

Figure 2. (A) Risk of bias summary: review of authors’ judgments about each risk of bias item for included studies. (B) Risk of bias graph: review of authors’ judgments about each risk of bias item presented as percentages across all included studies. Note: Each color represents a different level of bias: red for high-risk, green for low-risk, and yellow for unclear-risk of bias.
for advanced NSCLC, and traditional Chinese medicine, particularly cinobufotalin, has been clinically applied as an adjuvant therapy for decades.\cite{8,9} CFI has been reported beneficial to patients with advanced NSCLC in several trials.\cite{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.

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

Figure 4. Forest plot of the comparison of overall response rate (ORR, A) and disease control rate (DCR, B) 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.
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, 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.

![Figure 5](image.png)

**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.
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 4 |
| --- |
| Comparison of adverse events between the experimental and control groups. |

| Adverse events                  | Experimental group | Control group | Analysis method | Heterogeneity | Odds Ratio (OR) | 95% CI | P value |
|--------------------------------|--------------------|---------------|----------------|---------------|----------------|--------|---------|
| Leukopenia                     | 590 (n)            | 586 (n)       | Random         | 68            | 0.33           | 0.20 to 0.54 | <.0001  |
| Thrombocytopenia               | 515 (n)            | 496 (n)       | Random         | 62            | 0.33           | 0.20 to 0.57 | <.0001  |
| Nausea and vomiting           | 416 (n)            | 398 (n)       | Random         | 62            | 0.23           | 0.11 to 0.49 | <.0001  |
| Hepatotoxicity                | 372 (n)            | 377 (n)       | Fixed          | 0             | 0.41           | 0.27 to 0.62 | <.0001  |
| Nephrotoxicity                | 372 (n)            | 377 (n)       | Fixed          | 0             | 0.36           | 0.24 to 0.56 | <.00001 |
| Gastrointestinal side effects | 231 (n)            | 229 (n)       | Fixed          | 12            | 0.52           | 0.33 to 0.80 | .003    |
| Diarrhea                      | 240 (n)            | 223 (n)       | Random         | 72            | 0.21           | 0.05 to 0.89 | .03     |
| Peripheral neurotoxicity      | 122 (n)            | 124 (n)       | Fixed          | 0             | 0.47           | 0.23 to 0.94 | .03     |
| Granulopenia                  | 299 (n)            | 274 (n)       | Fixed          | 48            | 0.30           | 0.21 to 0.44 | <.0001  |
| Pneumonitis                   | 169 (n)            | 157 (n)       | Fixed          | 0             | 2.85           | 1.33 to 6.11 | .007    |
| Alopecia                      | 216 (n)            | 219 (n)       | Fixed          | 0             | 0.46           | 0.28 to 0.75 | .002    |
| Myelosuppression              | 156 (n)            | 155 (n)       | Fixed          | 0             | 0.38           | 0.21 to 0.67 | .0010   |
| Constipation                  | 214 (n)            | 217 (n)       | Fixed          | 39            | 0.51           | 0.34 to 0.77 | .002    |
| Hemoglobin reduction          | 120 (n)            | 124 (n)       | Fixed          | 3             | 0.53           | 0.32 to 0.90 | .02     |
| Allergy                       | 128 (n)            | 130 (n)       | Fixed          | 0             | 0.78           | 0.28 to 2.17 | .64     |
| Anemia                        | 82 (n)             | 68 (n)        | Fixed          | 0             | 0.06           | 0.01 to 0.34 | .001    |

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

| Figure 6. Funnel plot of percentage of overall response rate (ORR, A) and disease control rate (DCR, B). |

| 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). |

| Publication Bias | Therapeutic efficacy indexes | Adverse events indexes |
|------------------|-----------------------------|------------------------|
|                  | CR  | PR  | SD  | PD  | ORR | DCR | QIR | Leukopenia | Thrombocytopenia | Nausea and vomiting |
| Begg             | 0.492 | 1.000 | 0.514 | 0.830 | 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.
Table 6
Subgroup analyses of ORR and DCR between the experimental and control group.

| Parameter                  | Factors at study level | Exp group | Con group | Analysis method | Heterogeneity | Odds Ratio (OR) | P value |
|----------------------------|------------------------|-----------|-----------|-----------------|---------------|----------------|---------|
| ORR Therapeutic regimen    | Cinobufotalin injection+NP | 240       | 229       | Fixed           | 0.93          | 1.44           | 0.099 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  |
| Study sample size          | ≥80                    | 625       | 614       | Fixed           | 0.87          | 1.89           | 1.51 to 2.38 | <.0001 |
|                            | <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    |
| 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 | <.0001 |

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.

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