Research Article

Clinical Efficacy and Safety of Aidi Injection Plus Docetaxel-Based Chemotherapy in Advanced Nonsmall Cell Lung Cancer: A Meta-Analysis of 36 Randomized Controlled Trials

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality around the world with only 15% of 5-years survival rate [1–3]. Approximately 80% of lung cancers are nonsmall cell lung cancer (NSCLC). Nevertheless, over 50% of patients with NSCLC have advanced local invasion and metastasis, when they were admitted to the hospital for diagnosis. They must...
receive the systemic chemotherapy, radiotherapy, or chemoradiotherapy because they missed the opportunity for operation [4–6]. As first- or second-line chemotherapy, taxane agents including paclitaxel (taxol) and docetaxel (taxotere) are widely used in NSCLC. But they have different acute/subacute toxicity, which results in poor prognosis with only 15% of 5-years survival rate and substandard quality of life (QOL) [7, 8]. Therefore, new effective strategies with attenuation and synergistic efficacy are urgently needed.

As Cantharis and Astragalus-based Chinese herbs, Aidi injection (Z52020236, China Food and Drug Administration) is composed of the extracts of Cantharis, Astragalus, Eleutherococcus senticosus, and Ginseng, which appear to have antitumor efficacy and reduce the toxicity [9–13]. Meta-analysis (Wang, Q. 2010) [14] reported that Aidi injection plus paclitaxel or docetaxel and cisplatin could significantly improve the clinical efficiency and QOL in NSCLC. The combination had low risk of neutropenia, thrombocytopenia, and nausea/vomiting, but unclear risk of anemia, hepatotoxicity, nephrotoxicity, neurotoxicity, and alopecia. However, many studies [15–18] showed that docetaxel and paclitaxel had different clinical manifestations, especially the acute/subacute toxicity. Docetaxel is one of the important first- or second-line chemotherapeutic agents for NSCLC [19–21]. And docetaxel-based chemotherapy refers to docetaxel alone or plus cisplatin, carboplatin, oxaliplatin, lobaplatin, or nedaplatin, which are important chemotherapy regimens in NSCLC. The application of Aidi injection plus docetaxel-based chemotherapy was clinically used in a wide range of treatment. Can Aidi injection plus docetaxel-based chemotherapy improve clinical efficacy with satisfying level of safety in NSCLC? Has Aidi injection attenuated and synergistic efficacy to docetaxel-based chemotherapy in NSCLC? Many studies [22–25] had shown that Aidi injection plus docetaxel-based chemotherapy might improve the clinical efficacy and QOL with low risk of acute/subacute toxicity in NSCLC. However, these conclusions vary in different studies with limited sample size. At present, there is a lack of strong evidence to prove the efficacy of the treatments. Therefore, to further reveal its real clinical efficacy and provide the best evidence for clinical strategies in NSCLC, we systematically evaluated all the related studies.

2. Materials and Methods

This article followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA guidelines). Ethical approval was not required, as materials of this study were published or unpublished studies.

2.1. Search Strategy. Two reviewers (Chengqiong Wang and Lianhong Li) independently searched articles in Chinese and English databases using the search strategy (Aidi OR Aidi injection OR Compound cantharis injection OR Compound disodium cantharidinate injection or Addie injection) and the search strategy (Taxoids OR Docetaxel OR Docetaxel OR Taxotere) and the search strategy (“Lung Neoplasms”[Mesh] OR Lung cancer OR Lung cancers OR Non small cell lung cancer OR NSCLC OR SCLC OR Pulmonary neoplasms OR Lung neoplasm OR Pulmonary neoplasm OR Pulmonary cancer OR Pulmonary cancers OR Lung carcinoma OR Pulmonary carcinoma). Published studies were retrieved in Medline, Embase, Web of Science (ISI), China National Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Full-Text Database (VIP), Wanfang Database, China Biological Medicine Database (CBM) (established to September 2017), and Cochrane Central Register of Controlled Trials (CENTRAL, Issue 8 of 12, August 2017). Ongoing studies were retrieved in Chinese clinical trial registry (Chi-CTR) and US-clinical trials (established to September 2017). All retrievals were implemented by using the Mesh and free word. Finally, all related systematic reviews (SRs) or meta-analysis was evaluated, and studies meeting inclusion criteria were selected from the references.

2.2. Inclusion and Exclusion Criteria. Included studies must meet the following criteria. (1) The patients had NSCLC with stages III to IV being diagnosed and confirmed with the histopathological and cytological diagnostic criteria and TNM staging system. (2) There was no severe damage in liver or kidney function in any of the patients. (3) There were randomized controlled trials (RCTs). (4) The experimental group undergone Aidi injection plus docetaxel-based chemotherapy, and the control group undergone docetaxel-based chemotherapy. Docetaxel-based chemotherapy refers to docetaxel alone or plus platinum such as cisplatin, carboplatin, oxaliplatin, lobaplatin, and nedaplatin (DP, DC, DO, DL, and DN). (5) Patients prior to being included in the study have not accepted the radiotherapy, other chemotherapy, or Chinese herbs. (6) Main outcomes included the clinical efficacy and acute/subacute toxicity. Clinical efficacy was evaluated using tumor responses and QOL. (7) No restrictions were set on the follow-up time or types of hospitals.

Excluded studies must meet the following criteria: (1) duplicates, (2) unrelated studies including studies concerning Aidi injection plus paclitaxel chemotherapy, radiotherapy, additional chemotherapeutic agents, other Chinese herbs and other themes, (3) non-RCTs including case control studies and series case reports, (4) abstracts and reviews without specific data and unrelated SRs, and (5) studies without the clinical efficacy, QOL, and acute/subacute toxicity.

2.3. Bias Risk Assessment. According to the Cochrane evaluation handbook of RCTs (5.1.0) [26], we evaluated the bias risk of all trials using the bias parameters such as the random sequence generation (selection bias), the allocation concealment (selection bias), the blinding of participants and personnel (performance bias), the blinding of outcome assessment (detection bias), the incomplete outcome data (attrition bias), the selective reporting (reporting bias), and the other bias (whether the baseline is comparable). We judged each parameter on three levels (“yes” for a low risk of bias, “no” for a high risk of bias, and “unclear”). Then, we assessed the trials and categorized them into three levels: low risk (all items were “yes”), high risk (at least one item was “no”), and unclear risk (at least one item was “unclear”).
2.4. Selection and Evaluation of Studies. Two reviewers (Xue-mei Tang and Nana Li) independently screened and assessed studies according to the above standards. Any disagreements were eliminated by discussing between themselves or with Zheng Xiao.

2.5. Main Outcomes. We measured the tumor response using objective response rate (ORR) and disease control rate (DCR). According to the World Health Organization (WHO) guidelines for solid tumor responses [27] or Response Evaluation Criteria in Solid Tumors (RECIST) [28], indicators were complete response (CR), partial response (PR), no change (NC), progressive disease (PD), ORR being equal to CR plus PR, and DCR being equal to CR plus PR and NC. According to Karnofsky Performance Status scale (KPS scale) [29, 30], QOL was considered to be improved if KPS score increased 10 points or higher after treatment. We measured the acute/subacute toxicity using hematotoxicity such as neutropenia (granulocytes < 2 × 10^9/L), thrombocytopenia (platelets < 100 × 10^9/L) and anemia (Hemoglobin < 110g/L), liver dysfunction (serum aminotransferase or alkaline phosphatase > 1.25 × N), renal dysfunction (serum urea nitrogen or creatinine > 1.25 × N), hepatorenal dysfunctions, and gastrointestinal toxicity including the gastrointestinal reactions and nausea/vomiting, neurotoxicity (peripheral neuritis), alopecia, rash, phlebitis, and oral mucositis.

2.6. Data Extraction. Two reviewers (Chengqiong Wang and Lianhong Li) independently extracted all the data in a predesigned data extraction form according to the PICO principle. All the data included the first author, the publishing time, the randomization methods, the demographic characteristics, the sample size, the usage of Aidi injection and the types of docetaxel chemotherapy, the evaluation criteria of clinical efficacy and acute or subacute toxicity and the follow-up information, and main outcomes including the ORR, DCR, QOL, and acute or subacute toxicity. The data were obtained directly from the articles. If insufficient details were reported, authors were contacted for further information.

2.7. Statistical Analysis. Meta-analysis was implemented by two reviewers (Chengqiong Wang and Jing Li) using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). The relative risk (RR) and 95% confidence intervals (CI) were calculated. Statistical heterogeneity of the results across trials was assessed by chi-square based Q-statistic test and the consistency was calculated by I^2. If the homogeneity (P ≥ 0.1, I^2 ≤ 50%) was not rejected, the fixed-effects model (FEM) was used to calculate the summary RR and the 95% CI. Otherwise, the results were calculated by random-effects model (REM). We performed the subgroup analysis according to different doses of Aidi injection, docetaxel-based chemotherapy and evaluation criteria, which revealed their influence on the tumor responses. Publication bias was evaluated using funnel plots if there were more than 10 included studies. The poor quality studies and studies with over- or underestimated results were important factors that damage the robustness of meta-analysis results. The studies were defined as poor quality studies when they had at least one domain considered as high risk of bias. The over- or underestimated studies were identified according to the result of funnel plots and heterogeneity analysis, in which results were statistically different and had positive effects on publication bias or heterogeneity. Therefore, the sensitivity was evaluated through excluding the poor quality studies and studies with overestimated efficacy and underestimated toxicity.

3. Results

3.1. Search Results. The initial database search identified 286 published studies without ongoing studies using our search strategies (Figure 1). Reading the title and excluding the duplicates, 114 records were included. After reading the abstract, 51 full texts and 2 SRs [14, 31] were included. And then reading the full text and 17 unqualified studies excluded, 36 RCTs [22–24, 32–64] were included. After further evaluating the 2 SRs [14, 31], 6 RCTs [22, 32–34, 36, 37] were included. Finally, we included 36 RCTs [22–24, 32–64] after excluding 6 RCTs from SRs.

3.2. Characteristics of Included Studies. In this meta-analysis, we included 36 RCTs [22–24, 32–64] with 2837 advanced NSCLC patients (Table 1). Docetaxel-based chemotherapy included docetaxel alone, DP, DC, DO, DL, and DN. Experimental group was Aidi injection plus docetaxel-based chemotherapy involving 1422 cases, and control group was docetaxel chemotherapy alone involving 1415 cases. The males and females were 1722 and 1044 cases, respectively, with age between 27 and 82 years. The dosage of Aidi injection was 40 100 ml/day, and treatment time was 1-6 weeks/cycle with 1-6 cycles by intravenous injection. Outcomes were evaluated at 6-12 w after treatment. According to the WHO guidelines [27] for solid tumor responses or RECIST [65], tumor responses were evaluated in 34 studies [22–24, 32–55, 57–61, 63, 64] involving 2714 patients. QOL was evaluated in 22 studies [22–24, 32–42, 44, 46–48, 56–59] involving 1676 patients. According to WHO standards [27] or National Cancer Institute Common Toxicity Criteria (NCI-CTC) [66], acute or subacute toxicity was evaluated in 31 studies [22, 23, 32–43, 45–47, 49–55, 59, 60] involving 2434 patients.

3.3. Methodological Bias Risk. In 36 studies, nine studies described the random sequence generation using randomized digital table in eight studies [33, 43, 45, 51, 55, 57, 59, 61] and lottery in one study [24]. The random allocation concealment was implemented using envelope in one study [34], and other studies did not provide the detailed information about it. None of the studies did provide the detailed information about blinding of participants, personnel, and outcome assessment. All studies had complete outcome data without loss to follow-up. Nine studies [23, 36, 38, 40, 47, 54, 56, 57, 60] had selective reporting about the acute/subacute toxicity. Except for two studies [37, 52], baseline was comparable in other studies. The methodological bias risk of all included studies is presented in Figure 2.
3.4. Tumor Response. Thirty-four studies with 2714 cases [22–24, 32–55, 57–61, 63, 64] were reported the ORR (Figure 3). Pearson's chi-square test and $I^2$ test showed that there was no statistical heterogeneity among studies ($I^2 = 0\%$). Meta-analysis showed that the ORR had statistical differences between Aidi injection plus docetaxel-based chemotherapy and docetaxel-based chemotherapy alone [RR = 1.30, 95% CI (1.19, 1.42), and $P < 0.00001$] by FEM. Thirty-three studies with 2664 cases reported the DCR (Figure 4). There was minimal heterogeneity among studies ($I^2 = 12\%$). Meta-analysis showed that the DCR had statistical differences between the two groups [RR = 1.17, 95% CI (1.12, 1.22), and $P < 0.00001$] by FEM.

3.5. QOL. The QOL was evaluated according to KPS scale [29, 30]. Twenty-two studies with 1676 cases reported the QOL (Figure 5). There was minimal heterogeneity among studies ($I^2 = 12\%$). Meta-analysis showed that the QOL had statistical differences between the two groups [RR = 1.73, 95% CI (1.54, 1.95), and $P < 0.00001$] by FEM.

3.6. Acute/Subacute Toxicity. Thirty-one studies [22, 23, 32–43, 45–47, 49–55, 57, 59–64] involving 2434 patients reported the acute or subacute toxicity. There was heterogeneity among studies in neutropenia ($I^2 = 73\%$), gastrointestinal toxicity ($I^2 = 88\%$) and neurotoxicity ($I^2 = 56\%$), minimal heterogeneity in rash ($I^2 = 2\%$), and no heterogeneity in others toxicity ($I^2 = 0\%$). Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had lower risk of neutropenia [RR = 0.70, 95% CI (0.61, 0.79), and $P < 0.00001$] and gastrointestinal toxicity [RR = 0.76, 95% CI (0.65, 0.89),
| First author | year | NSCLC(III-IV) | Randomized Method | Interventions | C | Scale(A) | Scale(B) | Follow-up | Outcomes |
|-------------|------|--------------|-------------------|---------------|---|----------|----------|-----------|----------|
| Bian, M. | 2006 [32] | 34/30 | 44/20 | 30-75 | Unclear | Aidi + DP | 50 ml/15d/2 | DP | WHO | WHO | 8 w | O1, O2, O3 |
| Zhu, Q. | 2006 [33] | 30/30 | 32/28 | 33-74 | Randomized digital table | Aidi + DP | 50 ml/10d/3 | DP | RECIST | WHO | 9 w | O1, O2, O3 |
| Chen, X. | 2007 [22] | 32/32 | 39/25 | 47-72 | Unclear | Aidi + DP | 50 ml/15-20d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Hou, E. | 2008 [34] | 35/35 | 41/29 | 34-70 | Unclear | Aidi + DP | 50 ml/10d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Jiang, L. | 2008 [35] | 50/50 | 69/31 | 39-76 | Unclear | Aidi + DP | 50 ml/21d/- | DP | WHO | WHO | 4 w | O1, O2, O3 |
| Lin, Q. | 2008 [36] | 30/30 | 41/19 | 35-73 | Unclear | Aidi + DP | 50 ml/14d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Wang, H. | 2008 [37] | 40/40 | 51/29 | 30-70 | Unclear | Aidi + DP | 80-100 ml/14d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Cui, H. | 2010 [38] | 30/30 | 39/21 | 38-76 | Unclear | Aidi + DP | 80-100 ml/8w/1 | DP | WHO | WHO | 8 w | O1, O2, O3 |
| Du, Z. | 2011 [23] | 60/60 | 94/26 | 42-71 | Unclear | Aidi + DP | 40 ml/20d/2 | DP | WHO | WHO | 8 w | O1, O2, O3 |
| Lin, S. | 2011 [39] | 42/40 | 52/30 | 32-79 | Unclear | Aidi + DP | 50 ml/14d/2 | DP | WHO | WHO | 4 w | O1, O2, O3 |
| Tang, L. | 2011 [40] | 25/25 | 28/22 | 37-74 | Unclear | Aidi + DP | 50 ml/14d/2 | DP | RECIST | WHO | 4 w | O1, O2, O3 |
| Wang, T. | 2011 [41] | 49/49 | 65/33 | 30-78 | Unclear | Aidi + DP | 80-100 ml/14d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Xing, H. | 2011 [42] | 35/35 | 42/28 | 60-82 | Unclear | Aidi + TXT | 50 ml/15d/2 | TXT | WHO | WHO | 10 w | O1, O2, O3 |
| Jiang, S. | 2012 [43] | 23/23 | 38/8 | 43-70 | Randomized digital table | Aidi + DP | 50 ml/14d/2 | DP | WHO | WHO | 6 w | O1, O3 |
| Shi, L. | 2012 [44] | 38/38 | 55/21 | 38-72 | Unclear | Aidi + DP | 100 ml/14d/2 | DP | WHO | No | 6 w | O1, O2 |
| Tang, X. | 2012 [45] | 36/40 | 42/34 | 38-73 | Randomized digital table | Aidi + DP | 50 ml/14d/2 | DP | RECIST | WHO | 6 w | O1, O3 |
| Chen, Z. | 2013 [24] | 52/54 | 72/34 | 57-78 | Lottery | Aidi + DP | 50 ml/12W/- | DP | RECIST | No | 12 w | O1, O2 |
| Ge, C. | 2013 [46] | 41/39 | 52/28 | 53-77 | Unclear | Aidi + DP | 50 ml/4W/- | DP | WHO | WHO | 4 w | O1, O3 |
| Wu, Y. | 2013 [47] | 19/19 | 21/17 | 31-68 | Unclear | Aidi + DP | 60 ml/10d/2 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Gao, E. | 2014 [48] | 36/35 | 37/34 | Unclear | Unclear | Aidi + DP | 50 ml/14d/3 | DP | Unclear | No | 9 w | O1, O2 |
| Li, J. | 2014 [49] | 25/26 | 19/17 | 42-75 | Unclear | Aidi + DO | 100 ml/10d/3 | DO | WHO | WHO | 12 w | O1, O3 |
| Song, L. | 2014 [50] | 32/32 | 41/23 | 27-75 | Unclear | Aidi + DC | 50 ml/21d/2 | DC | WHO | NCI-CTC 2.0 | 6 w | O1, O3 |
| Tang, Y. | 2014 [51] | 47/44 | 45/46 | 46-71 | Randomized digital table | Aidi + DO | 50 ml/14d/3 | DO | WHO | NCI-CTC 3.0 | 3 y | O1, O3 |
| First author, year | NSCLC (III-IV) | Randomized Method | Interventions | C | Scale(A) | Scale(B) | Follow-up | Outcomes |
|-------------------|----------------|-------------------|---------------|---|----------|----------|-----------|----------|
| Xing, G. 2014 [52] | 72/63 | 92/43 | Unclear | Aidi + DL | 100 ml/14d/1-6 | DL | WHO | WHO | 3 y | O1, O3 |
| Xu, H. 2014 [53] | 23/23 | 24/22 | 52-74 | Unclear | Aidi + DP | 50 ml/42d/2 | DP | WHO | WHO | 6 w | O1, O3 |
| Gao, Y. 2015 [54] | 40/48 | 59/29 | 32-78 | Unclear | Aidi + DP | 80 ml/14d/3 | DP | RECIST | WHO | 9 w | O1, O3 |
| Li, Z. 2015 [55] | 25/25 | 47/27 | 65-80 | Unclear | Aidi + TXT | 50 ml/10d/1 | TXT | No | Unclear | Unclear | O2 |
| Hu, Q. 2015 [56] | 35/35 | 41/29 | 34-76 | Randomized digital table | Aidi + DC | 50 ml/14d/2 | DC | WHO | WHO | 6 w | O1, O3 |
| Wang, J. 2015 [57] | 50/50 | 58/42 | 35-76 | Unclear | Aidi + DP | 80-100 ml/14d/2 | DP | WHO | No | 6 w | O1, O2 |
| Mo, Y. 2015 [58] | 43/43 | 49/37 | Unclear | Randomized digital table | Aidi + DP | 50 ml/14d/1 | DP | WHO | WHO | 6 w | O1, O2, O3 |
| Wang, L. 2015 [59] | 60/60 | 74/46 | 62-78 | Randomized digital table | Aidi + TXT | 50 ml/14d/1 | TXT | WHO | Unclear | O1, O2, O3 |
| Gao, Y. 2016 [60] | 50/50 | 54/36 | 32-78 | Unclear | Aidi + DN | 80 ml/14d/3 | DN | RECIST | WHO | 9 w | O1, O3 |
| He, Z. 2016 [61] | 39/39 | 27/51 | 46-70 | Randomized digital table | Aidi + DC | 50 ml/14d/1 | DC | WHO | WHO | Unclear | O1, O3 |
| Wang, Y. 2016 [62] | 23/23 | Unclear | 40-70 | Unclear | Aidi + DP | 50 ml/10d/2 | DP | RECIST | WHO | 6 w | O1, O3 |
| Wang, X. 2016 [63] | 37/37 | 53/20 | Unclear | Aidi + DP | 100 ml/7d/2 | DP | no | WHO | 6 w | O3 |
| Zhu, J. 2017 [64] | 60/60 | 74/46 | 31-75 | Unclear | Aidi + DC | 50 ml/14d/1 | DC | WHO | WHO | 6 w | O1, O3 |

Note: NSCLC: nonsmall cell lung cancer; E/C: experimental group (Aidi injection plus docetaxel-based chemotherapy) / control group (docetaxel-based chemotherapy); M/F: male/female; Aidi (D/T/C): dose/time/cycles; TXT: docetaxel; DP: docetaxel and cisplatin; DC: docetaxel and carboplatin; DO: docetaxel and oxaliplatin; DL: docetaxel and lobaplatin; DN: docetaxel and nedaplatin; scale. A: evaluation criteria of tumor response; scale. B: evaluation criteria of acute/chronic toxicity; RECIST: response evaluation criteria in solid tumors; NCI-CTC: National Cancer Institute Common Toxicity Criteria; O: outcomes; O1: ORR and DCR; O2: QOL; O3: acute/chronic toxicity.
and P = 0.0006] than that of docetaxel-based chemotherapy alone using REM and lower risk of thrombocytopenia [RR = 0.63, 95% CI (0.53, 0.75), and P < 0.00001], anemia [RR = 0.60, 95% CI (0.48, 0.75), and P < 0.00001], hepatorenal dysfunctions [RR = 0.56, 95% CI (0.36, 0.88), and P = 0.01], and alopecia [RR = 0.58, 95% CI (0.36, 0.93), and P = 0.02] than that of control group using FEM. And all differences were statistically significant (Table 2 and Figures S1, S2, S3, S4, S5, and S7). There were no statistical differences in liver dysfunction [RR = 0.69, 95% CI (0.47, 1.01), and P = 0.05], renal dysfunction [RR = 0.56, 95% CI (0.31, 1.00), and P = 0.05], neurotoxicity [RR = 0.65, 95% CI (0.35, 1.18), and P = 0.16], rash [RR = 0.75, 95% CI (0.38, 1.49), and P = 0.42], phlebitis [RR = 1.00, 95% CI (0.63, 1.59), and P = 1.00], and oral mucositis [RR = 0.64, 95% CI (0.38, 1.09), and P = 0.10] between the two groups (Table 2 and Figures S5, S6, and S7).

3.7. Subgroup Analysis of ORR and DCR. Subgroup analysis was performed to reveal the influence of different doses, docetaxel chemotherapy protocols, and evaluation criteria on the ORR and DCR. Drug doses included Aidi injection with 100 ml, 80-100 ml, 80 ml, 60 ml, 50 ml, and 40 ml/time. Subgroup analysis showed that, with 100 ml, 80-100 ml, and 50 ml, Aidi injection could increase the ORR and DCR (Table 3 and Figures S8-9). Docetaxel-based chemotherapy included docetaxel alone, DP, DC, DO, DL, and DN. Subgroup analysis showed that only Aidi injection plus DP, DC, and DO could increase the ORR and DCR (Table 3 and Figures S10-11). Tumor responses were evaluated using WHO or RECIST criteria. Subgroup analysis showed that Aidi injection plus docetaxel-based chemotherapy could increase the ORR and DCR using the WHO or RECIST criteria (Table 3 and Figures S8-13).

3.8. Publication Bias Analysis. The funnel plots were symmetric in ORR and thrombocytopenia (Figures 6(a) and 6(f)). And there was no publication bias in these studies which objectively reported the results. The funnel plots were asymmetric in DCR, QOL, neutropenia, and gastrointestinal toxicity (Figures 6(b), 6(c), 6(d), and 6(e)). These results indicated that there was publication bias in them. The DCR was underestimated in one study [33]. The QOL was overestimated in one study [49] and underestimated in two studies [52, 57]. The neutropenia was overestimated in four studies [33, 35, 54, 59] and the gastrointestinal toxicity was underestimated in four studies [35, 39, 52, 59] and underestimated in one study [41].

3.9. Sensitivity Analysis. Nine poor quality studies [23, 36, 38, 40, 47, 54, 56, 57, 60] had at least one domain considered as

![Figure 2: Risk of methodological bias.](image-url)
Figure 3: The analysis of ORR between two groups.

Figure 4: The analysis of DCR between two groups.
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**Figure 5:** The analysis of QOL between two groups.

### Table 2: Meta-analysis results of acute/chronic toxicity (Figures S1-7).

| Outcomes                           | Studies | Experimental group (Evans/totol) | Control groups (Evans/totol) | SM | RR (95% CI) | I²  | P     |
|------------------------------------|---------|---------------------------------|------------------------------|----|-------------|-----|-------|
| Neutropenia (Figure S1)            | 26      | 452/1007                        | 627/999                      | REM | 0.70 [0.61, 0.79] | 73% | P < 0.00001 |
| Thrombocytopenia (Figure S2)       | 17      | 153/715                         | 235/700                      | FEM | 0.63 [0.53, 0.75] | 0%  | P < 0.00001 |
| Anemia (Figure S3)                 | 9       | 85/353                          | 135/343                      | FEM | 0.60 [0.48, 0.75] | 0%  | P < 0.00001 |
| Gastrointestinal toxicity (Figure S4)| 26  | 504/1060                        | 634/1053                     | FEM | 0.76 [0.65, 0.89] | 88% | P = 0.0006 |
| Liver dysfunction (Figure S5)      | 7       | 37/308                          | 52/293                       | FEM | 0.69 [0.47, 1.01] | 0%  | P = 0.05 |
| Renal dysfunction (Figure S5)      | 5       | 15/181                          | 26/173                       | FEM | 0.56 [0.31, 1.00] | 0%  | P = 0.05 |
| Hepatorenal dysfunctions (Figure S5)| 5    | 23/147                          | 40/146                       | FEM | 0.56 [0.36, 0.88] | 0%  | P = 0.01 |
| Neurotoxicity (Figure S6)          | 5       | 42/192                          | 66/184                       | REM | 0.65 [0.35, 1.18] | 56% | P = 0.16 |
| Alopecia (Figure S7)               | 3       | 16/98                           | 27/92                        | FEM | 0.58 [0.36, 0.93] | 0%  | P = 0.02 |
| Rash (Figure S7)                   | 2       | 12/88                           | 15/83                        | FEM | 0.75 [0.38, 1.49] | 2%  | P = 0.42 |
| Phlebitis (Figure S7)              | 3       | 25/113                          | 25/113                       | FEM | 1.00 [0.63, 1.59] | 0%  | P = 1.00 |
| Oral mucositis (Figure S7)         | 3       | 18/110                          | 28/110                       | FEM | 0.64 [0.38, 1.09] | 0%  | P = 0.10 |

Note: SM: statistical method; REM: random-effects model; FEM: fixed-effects model; RR: risk ratios.

High risk of bias and selective reporting about acute/subacute toxicity (Table 4(a)). They had potential effect on robustness of neutropenia, thrombocytopenia, gastrointestinal toxicity, and oral mucositis. Therefore, the sensitivity was evaluated through excluding poor quality studies. After excluding poor quality studies, all results had good consistency. There was statistical heterogeneity in neutropenia, gastrointestinal toxicity and neurotoxicity, and minimal heterogeneity in QOL. There was publication bias in DCR, QOL, neutropenia, and thrombocytopenia. Therefore, the sensitivity was evaluated through excluding the studies with overestimated efficacy or underestimated toxicity. Before and after excluding these studies, results had good consistency (Table 4(b)). In all, this meta-analysis had good stability.

### 4. Discussion

Based on previous meta-analysis [14, 31], we eventually included 36 RCTs involving 2837 patients with advanced NSCLC. There were 1722 males and 1044 females, respectively, with ages between 27 and 82 years. The usage of Aidi injection was 50 ml-100 ml/day, 2-3 weeks/cycle with 2-3 cycles by intravenous injection. Docetaxel-based chemotherapy included docetaxel alone, DP, DC, DO, DL, and DN. The tumor responses, QOL, and acute or subacute toxicity were evaluated at 6-12 w after treatment.

Docetaxel-based chemotherapy is important first- or second-line chemotherapeutic agents for NSCLC. Can Aidi injection plus docetaxel-based chemotherapy improve the...
Table 3: Subgroup analysis results of ORR and DCR (Figures S8-13).

| Subgroups | Objective response rate (ORR) | Disease control rate (DCR) |
|-----------|-------------------------------|-----------------------------|
|           | Studies | Cases | SM | RR (95% CI) | I² | p | Studies | Cases | SM | RR (95% CI) | I² | p |
| Total     | 34      | 2714  | FEM | 1.30 [1.19, 1.42] | 0% | P < 0.00001 | 33 | 2664 | FEM | 1.17 [1.12, 1.22] | 3% | P < 0.00001 |
| Different drugs and doses (Figures S8-9) | | | | | | | | | | | |
| Aidi injection (100 ml) | 3 | 262 | FEM | 1.39 [1.08, 1.80] | 0% | P = 0.01 | 3 | 262 | FEM | 1.27 [1.07, 1.50] | 27% | P = 0.005 |
| Aidi injection (80-100 ml) | 4 | 338 | FEM | 1.37 [1.13, 1.67] | 0% | P = 0.002 | 4 | 338 | FEM | 1.19 [1.06, 1.33] | 0% | P = 0.002 |
| Aidi injection (80 ml) | 2 | 188 | FEM | 1.40 [1.00, 1.95] | 0% | P = 0.05 | 2 | 188 | FEM | 1.25 [1.00, 1.55] | 0% | P = 0.05 |
| Aidi injection (60 ml) | 1 | 38 | No | 1.25 [0.40, 3.95] | No | P = 0.70 | 1 | 38 | FEM | 1.17 [0.48, 2.83] | No | P = 0.73 |
| Aidi injection (50 ml) | 22 | 1690 | FEM | 1.27 [1.14, 1.42] | 4% | P < 0.0001 | 21 | 1640 | FEM | 1.16 [1.10, 1.21] | 0% | P < 0.00001 |
| Aidi injection (40 ml) | 1 | 120 | No | 1.18 [0.83, 1.68] | No | P = 0.36 | 1 | 120 | No | 1.06 [0.92, 1.23] | No | P = 0.43 |
| Aidi injection (Unclear) | 1 | 78 | No | 1.17 [0.62, 2.19] | No | P = 0.63 | 1 | 78 | FEM | 1.20 [0.99, 1.46] | No | P = 0.07 |
| Different chemotherapy regimens (Figures S10-11) | | | | | | | | | | | |
| Aidi injection plus DP | 24 | 1767 | FEM | 1.27 [1.15, 1.41] | 0% | P < 0.00001 | 23 | 1717 | FEM | 1.17 [1.12, 1.24] | 0% | P < 0.00001 |
| Aidi injection plus DC | 4 | 380 | FEM | 1.36 [1.05, 1.76] | 0% | P = 0.02 | 4 | 380 | FEM | 1.16 [1.07, 1.26] | 0% | P = 0.0004 |
| Aidi injection plus DO | 2 | 142 | FEM | 1.37 [1.02, 1.85] | 0% | P = 0.04 | 2 | 142 | FEM | 1.07 [0.93, 1.24] | 0% | P = 0.35 |
| Aidi injection plus DL | 1 | 135 | No | 1.41 [0.99, 2.01] | No | P = 0.05 | 1 | 135 | No | 1.47 [1.10, 1.96] | No | P = 0.009 |
| Aidi injection plus DN | 1 | 100 | No | 1.63 [1.00, 2.64] | No | P = 0.05 | 1 | 100 | No | 1.33 [0.98, 1.82] | No | P = 0.07 |
| Aidi injection plus docetaxel | 2 | 190 | FEM | 1.19 [0.82, 1.73] | 0% | P = 0.37 | 2 | 190 | FEM | 1.06 [0.89, 1.26] | 0% | P = 0.52 |
| Different evaluation criteria (Figures S12-13) | | | | | | | | | | | |
| WHO Criteria | 27 | 2188 | FEM | 1.30 [1.18, 1.43] | 0% | P < 0.00001 | 27 | 2188 | FEM | 1.17 [1.12, 1.22] | 0% | P < 0.00001 |
| RECIST | 7 | 526 | FEM | 1.30 [1.07, 1.57] | 0% | P = 0.008 | 6 | 476 | FEM | 1.18 [1.06, 1.32] | 41% | P = 0.003 |

Note: DP: docetaxel and cisplatin; DC: docetaxel and carboplatin; DO: docetaxel and oxaliplatin; DL: docetaxel and lobaplatin; DN: docetaxel and nedaplatin; SM: statistical method; RR: risk ratio; FEM: fixed-effects model.
Table 4: Sensitivity analysis.

(a) Sensitivity analysis by excluding the poor trials.

| Indicators            | Number | SM  | RR(95% CI)      | I² | Excluded studies | Number | SM  | RR(95% CI)      | I² |
|-----------------------|--------|-----|-----------------|----|-----------------|--------|-----|-----------------|----|
| Neutropenia           | 26     | REM | 0.70 [0.61, 0.79] | 73%| Poor* [36, 47, 54, 57] | 22     | REM | 0.70 [0.61, 0.80] | 75%|
| Thrombocytopenia      | 17     | FEM | 0.63 [0.53, 0.75] | 0% | Poor* [57]       | 16     | FEM | 0.65 [0.55, 0.76] | 0%|
| Gastrointestinal toxicity | 26    | REM | 0.76 [0.65, 0.89] | 88%| Poor* [36, 38, 54, 57] | 22     | REM | 0.75 [0.63, 0.89] | 90%|
| Oral mucositis        | 3      | FEM | 0.64 [0.38, 1.09] | 0% | Poor* [57]       | 3      | FEM | 0.64 [0.38, 1.09] | 0%|

(b) Sensitivity analysis excluding the under- or over-estimated trials.

| Indicators            | Number | SM  | RR(95% CI)      | I² | Excluded studies | Number | SM  | RR(95% CI)      | I² |
|-----------------------|--------|-----|-----------------|----|-----------------|--------|-----|-----------------|----|
| DCR                   | 33     | FEM | 1.17 [1.12, 1.22] | 0% | Over* [36, 52, 64] | 30     | FEM | 1.16 [1.11, 1.21] | 0%|
| QOL                   | 22     | FEM | 1.73 [1.54, 1.95] | 12%| Over* [22, 33–39, 41, 44, 48, 49, 59] | 9      | FEM | 1.41 [1.14, 1.74] | 38%|
| Neutropenia           | 26     | REM | 0.70 [0.61, 0.79] | 73%| Under* [22, 34, 36, 39, 43, 49, 52, 57, 62, 64], Over* [33, 35] | 14     | FEM | 0.72 [0.63, 0.81] | 29%|
| Thrombocytopenia      | 17     | FEM | 0.63 [0.53, 0.75] | 0% | Under* [52, 59]   | 15     | FEM | 0.66 [0.54, 0.79] | 0%|
| Gastrointestinal toxicity | 26   | REM | 0.76 [0.65, 0.89] | 88%| Under* [23, 33, 41, 42, 53, 63, 64], Over* [35] | 18     | FEM | 0.86 [0.79, 0.94] | 5%|
| Neurotoxicity         | 5      | REM | 0.65 [0.35, 1.18] | 56%| Under* [41, 42]   | 3      | FEM | 1.04 [0.65, 1.68] | 0%|

Note: DCR: disease control rate; QOL: quality of life; FEM: fixed-effects model; REM: random-effects model; RR: relative risk; SM: statistical method; CI: confidence interval; poor trials (Poor*) had at least one domain considered as high risk of bias; over* or under*: over- or underestimated trials of which results had statistical difference and positive effects on publication bias and heterogeneity.
clinical efficacy in NSCLC? Thirty-four studies [22–24, 32–55, 57–61, 63, 64] involving 2714 patients were included to evaluate the tumor responses. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy could significantly improve the ORR and DCR in NSCLC. But there was significant clinical heterogeneity in them. Further subgroup analysis showed that Aidi injection with 100 ml, 80-100 ml, and 50 ml could increase the ORR and DCR and 50 ml was the main dosage. Combined with DP, DC, and DO, Aidi injection could increase the tumor responses. This meta-analysis involved 34 studies with 2714 cases which ensured sufficient sample size for analysis. The DCR was underestimated and the meta-analysis results had good robustness. All these were beneficial to tumor responses. But most studies had unclear bias risk, which weakened the result’s reliability. Compared to the previous studies [14, 31], this meta-analysis revealed that Aidi injection plus docetaxel-based chemotherapy, especially plus DP, DC, and DO, might significantly improve the ORR and DCR and 50 ml was the main dosage. Our previous meta-analysis [67, 68] had shown that Aidi injection plus radiotherapy or gemcitabine and cisplatin (GP) could significantly improve the QOL in patients with lung cancer. Can Aidi injection plus docetaxel-based chemotherapy improve the QOL? To further analyze whether Aidi injection can improve the QOL, 22 studies with 1676 cases were included for analysis. Meta-analysis showed that Aidi injection could significantly improve the QOL. But, QOL was overestimated in one study [49] and underestimated in two studies [52, 57]. Sensitivity analysis revealed that QOL had good robustness. But most studies had unclear bias risk. Therefore, we believed that Aidi injection might also improve the QOL. Aidi injection is composed of extracts from Astragalus, Eleutherococcus senticosus, Ginseng, and Cantharis. In vitro studies [69–72] had shown that cantharidin could induce the tumor cells’ apoptosis and inhibit the proliferation, migration, and invasion. Animal studies [73–75] had shown that cantharidin or Ginseng could significantly inhibit the growth of malignant tumor cells. Our previous meta-analysis [76] had revealed that Aidi injection could significantly restore the cellular immunity damaged by platinum-based chemotherapy. In addition, many studies [77, 78] had shown that Astragalus, senticosus Eleutherococcus, and Ginseng also had antitumor activity and immune regulation functions. These results provided indirect evidence for the above conclusions. In all, we believe that Aidi injection plus docetaxel-based chemotherapy, especially plus DP, DC, and DO, may significantly improve clinical efficacy and QOL in patients with NSCLC. The main dose may be 50 ml/time. Results indirectly indicate that Aidi injection may have synergistic efficacy to docetaxel-based chemotherapy. Unfortunately, So far, there was no reliable evidence to confirm the long-term synergistic efficacy.

Docetaxel-based chemotherapy has varying degrees of blood, liver, kidney, and gastrointestinal toxicity due to docetaxel plus platinum [79–81]. However, can Aidi injection plus docetaxel-based chemotherapy increase the risk of acute/subacute toxicity? To answer this question, 31 studies [22, 23, 32–43, 45–47, 49–55, 57, 59–64] involving 2434 patients were included to reveal the risk of toxicity. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had lower risk of the neutropenia, thrombocytopenia, anemia and gastrointestinal toxicity, hepatorenal dysfunctions, and alopecia compared to that of docetaxel-based chemotherapy alone. And there were no significant differences in liver dysfunction, renal dysfunction, neurotoxicity, rash, phlebitis, and oral mucositis between the two
groups. The meta-analysis of neutropenia, thrombocytopenia, and gastrointestinal toxicity had sufficient studies and sample size. But there were limited studies and sample size in other meta-analysis, especially in the meta-analysis of liver and renal dysfunction, which might lead to insufficient assessment. Sensitivity analysis showed that the merged value of neutropenia, thrombocytopenia, and gastrointestinal toxicity had good robustness. Compared to the previous meta-analysis [14, 31], this study further revealed that Aidi injection plus docetaxel-based chemotherapy had low risk of the neutropenia, thrombocytopenia, and gastrointestinal toxicity. In addition, we found that it also had low risk of anemia, hepatorenal dysfunctions, and alopecia. Our previous study [67] had shown that Aidi injection plus GP had low risk of hematological and gastrointestinal toxicity and neurotoxicity in NSCLC. Furthermore, Aidi injection could alleviate the radiotherapy related toxicity, such as myelosuppression, radiation pneumonitis, and esophagitis [68]. These results provided indirect clinical evidence for the above conclusions. Zhu X and et al. [82, 83] had reported that Astragalus membranaceus injection (AMI) could promote myelopoiesis through improving the hematopoietic microenvironment and relieving the bone marrow cells apoptosis in mice. Hu, W et al. [84–87] had revealed that ginsenoside Rg1 also had antilymeloctocytoxic activity and promotion of myelopoiesis through enhancing the antioxidant and anti-inflammatory capacities of bone marrow mesenchymal stem cells (BMSCs) in vivo. Liu L and et.al [88] had shown that Astragalus injection ameliorated the cisplatin-induced nephrotoxicity through regulating the Bax and Bcl-2 expression in mice. Other study [89] had shown that ginsenoside Rg1 also had antioxidant activities which ameliorated the cisplatin-induced hepatic injury through Nrf2 signaling pathway in mice. All these revealed that Astragalus and Ginseng could ameliorate chemotherapy related toxicity through enhancing the antilymeloctocytoxic activity, antitumor, and antioxidant activities. These results provided the basic and mechanism evidence for the above conclusions. In summary, Aidi injection plus docetaxel-based chemotherapy may have low risk of hematotoxicity, gastrointestinal toxicity, and hepatorenal dysfunctions. Based on the optimization of efficacy and safety, results indicated that the optimal dose might be 50 ml/time. These results indirectly reveal that Aidi injection may have attenuation effect to docetaxel related toxicity.

There were some limitations in this study. Firstly, Chinese and English databases were retrieved but not Japanese and Korean databases. All included studies were published in China, which may lead to ethnic bias. Secondly, only 9 studies reported the random allocation method. No studies provided the detailed information about the random allocation concealment and the binding. Nine studies had selective reporting about the acute/subacute toxicity. Third, long-term efficacy had not been evaluated. Fourth, most studies reported the acute/subacute toxicity using WHO standards [27] or NCI-CTC [66]. And there were limited studies and sample size in liver and renal dysfunction, neurotoxicity, and alopecia. All these limitations might lead to an inadequate assessment of the clinical efficacy and safety.

5. Conclusions

The available evidence indicates that Aidi injection plus docetaxel-based chemotherapy, especially plus DP, DC, and DO, may significantly improve the clinical efficacy and QOL in patients with NSCLC. It may have low risk of hematotoxicity, gastrointestinal toxicity, and hepatorenal dysfunctions. Results indirectly indicate that Aidi injection may have attenuation and synergistic efficacy to docetaxel chemotherapy. Based on the optimization of efficacy and safety, the results indicated that the optimal dose may be 50 ml/time. Unfortunately, whether Aidi injection can improve long-term efficacy is still unclear. Furthermore, many limitations might lead to an inadequate assessment of the clinical efficacy and safety. Therefore, we look forward to larger scale RCTs or real-world studies for a more thorough review in future publications. Consequently, we hope that this study will provide valuable evidence for Aidi injection as an important supplementary therapy for malignant tumors.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AMI          | Astragalus membranaceus injection |
| BMSCs        | Bone marrow mesenchymal stem cells |
| CBM          | China Biological Medicine Database |
| CENTRAL      | Cochrane Central Register of Controlled Trials |
| CR           | Complete response |
| Chi-CTR      | Chinese clinical trial registry |
| CI           | Confidence interval |
| CNKI         | China National Knowledge Infrastructure Database |
| DC           | Docetaxel and carboplatin |
| DCR          | Disease control rate |
| DL           | Docetaxel and lobarlatin |
| DN           | Docetaxel and nedaplatin |
| DO           | Docetaxel and oxaliplatin |
| DP           | Docetaxel plus cisplatin |
| FEM          | Fixed effect model |
| GP           | Gemcitabine and cisplatin |
| ISI          | Web of Science |
| KPS scale    | Karnofsky Performance Status scale |
| NSCLC        | Nonsmall cell lung cancer |
| NCI-CTC      | National Cancer Institute Common Toxicity Criteria |
| NC           | No change |
| ORR          | Objective response rate |
| PD           | Progressive disease |
| PR           | Partial response |
| PRISMA       | Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines |
| QOL          | Quality of life |
| RR           | Relative risk |
| RCTs         | Randomized controlled trials |
| RECIST       | Response Evaluation Criteria in Solid Tumors |
| REM          | Random-effects model |

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SRs: Systematic reviews  
SM: Statistical Method  
TP: Paclitaxel  
VIP: Chinese Scientific Journals Full-Text Database  

Conflicts of Interest  
The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions  
Zheng Xiao and Xiaofei Li contributed equally to this work. Zheng Xiao and Chengqiong Wang performed conception and design. Chengqiong Wang developed methodology. Chengqiong Wang and Xuemei Tang did the literature search. Xuemei Tang and Nana Li did selection and evaluation of articles. Chengqiong Wang and Lianhong Li performed data extraction. Chengqiong Wang and Jing Li performed the statistical analysis. Chengqiong Wang, Zheng Xiao, Ling Chen, Qihai Gong, Fushan Tang, Jihong Feng, and Xiaofei Li wrote, reviewed, and/or revised the manuscript. Zheng Xiao was responsible for the study supervision. All authors reviewed the PRISMA criteria for authorship and agreed with manuscript results and conclusions.

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Supplementary Materials  
Meta-analysis results of acute or chronic toxicity (Figures S1-7). Figure S1: the analysis of neutropenia between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of neutropenia [RR = 0.70, 95% CI (0.61, 0.79), and P < 0.00001] using random-effects model. Figure S2: the analysis of thrombocytopenia between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of neutropenia [RR = 0.63, 95% CI (0.53, 0.75), and P < 0.00001] using fixed-effects model. Figure S3: the analysis of anemia between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of anemia [RR = 0.60, 95% CI (0.48, 0.75), and P < 0.00001] using fixed-effects model. Figure S4: the analysis of gastrointestinal toxicity between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of gastrointestinal toxicity [RR = 0.76, 95% CI (0.65, 0.89), and P = 0.0006] using random-effects model. Figure S5: the analysis of hepatorenal dysfunctions between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of hepatorenal dysfunctions [RR = 0.56, 95% CI (0.36, 0.88), and P = 0.01] using fixed-effects model. But there were no statistically significant differences in liver dysfunction [RR = 0.69, 95% CI (0.47, 1.01), and P = 0.30], renal dysfunction [RR = 0.56, 95% CI (0.31, 1.00), and P = 0.05] between two groups. Figure S6: the analysis of neurotoxicity between the two groups. There were no statistically significant differences in neurotoxicity [RR = 0.65, 95% CI (0.35, 1.18), and P = 0.16] between two groups. Figure S7: the analysis of other toxicity between the two groups. Meta-analysis showed that Aidi injection plus docetaxel-based chemotherapy had low risk of alopecia [RR = 0.58, 95% CI (0.36, 0.93), and P = 0.02] using fixed-effects model. But there were no statistically significant differences in rash [RR = 0.75, 95% CI (0.38, 1.49), and P = 0.42], phlebitis [RR = 1.00, 95% CI (0.63, 1.59), and P = 1.00], and oral mucositis [RR = 0.64, 95% CI (0.38, 1.09), and P = 0.10] between two groups. Subgroup analysis results of ORR and DCR (Figures S8-13). Figure S8: subgroup analysis of ORR via drug doses. Subgroup analysis showed that with 100 ml, 80-100 ml, and 50 ml, Aidi injection could all increase the ORR. Figure S9: subgroup analysis of DCR via drug doses. Subgroup analysis showed that with 100 ml, 80-100 ml and 50 ml, Aidi injection could all increase the DCR. Figure S10: subgroup analysis of ORR via docetaxel-based chemotherapy. Subgroup analysis showed that only Aidi injection plus DP, DC, and DO could increase the DCR. Figure S11: subgroup analysis of DCR via docetaxel-based chemotherapy. Subgroup analysis showed that only Aidi injection plus DP, DC, and DO could increase the DCR. Figure S12: subgroup analysis of ORR via evaluation criteria. Subgroup analysis showed that Aidi injection plus docetaxel-based chemotherapy could increase the ORR using the WHO or RECIST criteria. Figure S13: subgroup analysis of DCR via evaluation criteria. Subgroup analysis showed that Aidi injection plus docetaxel-based chemotherapy could increase the DCR using the WHO or RECIST criteria.

( Supplementary Materials )

References  
[1] W. Chen, R. Zheng, P. D. Baade et al., “Cancer statistics in China, 2015,” CA: A Cancer Journal for Clinicians, vol. 66, no. 2, pp. 115-132, 2016.
[2] R. L. Siegel, K. D. Miller, and A. Jemal, “Cancer statistics, 2017,” CA: A Cancer Journal for Clinicians, vol. 67, no. 1, pp. 7–30, 2017.
[3] L. A. Torre, R. L. Siegel, and A. Jemal, “Lung cancer statistics,” Advances in Experimental Medicine and Biology, vol. 893, pp. 1–19, 2016.
K. Khodadad, A. Khosravi, Z. Esfahani-Monfared, S. Karimi, H.-C. Wang, Y.-H. Tseng, H.-R. Wu, F.-H. Chu, Y.-H. Kuo, Q. Wang, X. He, J. Tian et al., “A meta analysis of aidi injection combination with docetaxel and cisplatin in the treatment of non-small cell lung cancer,” *Radiation Oncology*, vol. 15, no. 1, pp. 134–140, 2019.

[4] R. Grilli, A. D. Oxman, and J. A. Julian, “Chemotherapy for advanced non-small-cell lung cancer: How much benefit is enough?” *Journal of Clinical Oncology*, vol. 11, no. 10, pp. 1866–1872, 1993.

[5] T. C. Hsia, C. Y. Tu, H. Y. Fang, J. A. Liang, C. C. Li, and C. R. Chien, “Cost and effectiveness of image-guided radiotherapy for non-operated localized lung cancer: a population-based propensity score-matched analysis,” *Journal of Thoracic Disease*, vol. 7, no. 9, pp. 1643–1649, 2015.

[6] V. K. Anagnostou and J. R. Brahmer, “Cancer immunotherapy: A future paradigm shift in the treatment of non-small cell lung cancer,” *Clinical Cancer Research*, vol. 21, no. 5, pp. 976–984, 2015.

[7] K. Eckmann, L. B. Michaud, E. Rivera et al., “Pilot study to assess toxicity and pharmacokinetics of docetaxel in patients with metastatic breast cancer and impaired liver function secondary to hepatic metastases,” *Journal of Oncology Pharmacy Practice*, vol. 20, no. 2, pp. 120–129, 2014.

[8] J. Schwartz, S. M. Domchek, W.-T. Hwang, and K. Fox, “Evaluation of anemia, neutropenia and skin toxicities in standard or dose-dense doxorubicin/cyclophosphamide (AC)-paclitaxel or docetaxel adjuvant chemotherapy in breast cancer,” *Annals of Oncology*, vol. 16, no. 2, pp. 247–252, 2005.

[9] S. A. Cichello, Q. Aoa, A. Dowell, B. Leury, and X.-Q. He, “Proliferative and inhibitory activity of Siberian ginseng (Eleutherococcus senticosus) extract on cancer cell lines; A-549, XWLC-05, HCT-116, CNE and HeLa,” *Asian Journal of Cancer Prevention and Treatment*, vol. 16, no. 11, pp. 4781–4786, 2015.

[10] H.-C. Wang, Y.-H. Tseng, H.-R. Wu, E.-H. Chu, Y.-H. Kuo, and S.-Y. Wang, “Anti-proliferation effect on human breast cancer cells via inhibition of pRb phosphorylation by Taiwanese *Eleutherococcus trifoliatus*,” *Natural Product Communications (NPC)*, vol. 9, no. 9, pp. 1303–1306, 2014.

[11] X. Tang, “Aidi injection combined with docetaxel and cisplatin for non small cell lung cancer: A clinical observation of 36 cases,” *Cancer Research and Clinic*, vol. 24, no. 5, pp. 343–345.

[12] H. Wu, “Clinical observation of Aidi injection combined with paclitaxel plus cisplatin in the treatment of middle or advanced non small cell lung cancer,” *Journal of New Chinese Medicine*, vol. 44, no. 6, pp. 118-119.

[13] Z. Yang, C. Teng, and L. Zhang, “Clinical observation of Aidi injection combined with chemotherapy in the treatment of middle or advanced non small cell lung cancer,” *China Journal of Pharmaceutical Economics*, vol. 0, no. 9, pp. 200-201.

[14] Q. Wang, X. He, J. Tian et al., “An meta analysis of aidi injection and cisplatin in the treatment of non-small cell lung cancer,” *Chinese Journal of Lung Cancer*, vol. 13, no. 11, pp. 1027–1034, 2010.

[15] M. Yang, Y. Wang, and L. Wang, “Comparative analysis of serious adverse reactions caused by docetaxel and paclitaxel,” *Chinese Journal of Pharmacovigilance*, vol. 11, no. 5, pp. 295-296.

[16] K. Khodadad, A. Khosravi, Z. Esfahani-Monfared, S. Karimi, and S. Seifi, “Comparing docetaxel plus cisplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: A single institute study,” *Iranian Journal of Pharmaceutical Research*, vol. 13, no. 2, pp. 575–581, 2014.

[17] G. Feng, P. Hu, J. Gao, H. Zhang, J. Tang, and H. Chen, “The clinical study of paclitaxel or docetaxel with 5-fluorouracil and cisplatin as first-line treatment for advanced gastric cancer,” *Chinese Journal of Clinical Research*, vol. 12, pp. 1616–1618.

[18] Z. Yin, P. Wang, T. Zhang, and M. Song, “Efficacy of neoadjuvant chemotherapy with antracyclines plus paclitaxel or docetaxel regimen in stage III breast cancer patients,” *China Oncology*, vol. 06, pp. 459–462.

[19] H. Liu, Y. Wu, Z. Wang, and Y. Song, “Response to first-line chemotherapy of docetaxel combined with platinum predicting the prognosis and subsequent treatment of patients with non-small cell lung cancer,” *Thoracic Cancer*, vol. 5, no. 4, pp. 337–342, 2014.

[20] A. Matikas, V. Georgoulias, and A. Kotsakis, “The role of docetaxel in the treatment of non-small cell lung cancer lung cancer: an update,” *Expert Review of Respiratory Medicine*, vol. 10, no. 11, pp. 1229–1241, 2016.

[21] M. Maemondo, A. Inoue, S. Sugawara et al., “Randomized phase II trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: North Japan lung cancer group trial 0801,” *The Oncologist*, vol. 19, no. 4, pp. 352–353, 2014.

[22] X.-M. Chen, H.-T. Gong, and Z.-J. Song, “Randomized study of Aidi injection plus TP regimen combination in the treatment of advanced non-small cell lung cancer,” *Chinese Journal of Cancer Prevention and Treatment*, vol. 14, no. 18, pp. 1427–1428, 2007.

[23] “Combined radio-chemotherapy in the management of locally advanced non-small cell lung cancer (NSCLC),” *Lung Cancer*, vol. 11, pp. 146-147, 1994.

[24] Z. Chen and H. Lu, “Clinical research of combining traditional Chinese medicine with Western medicine to treat non-small cell lung cancer,” *Chinese Journal of Experimental Traditional Medical Formulae*, vol. 19, no. 11, pp. 322–324.

[25] H. Xu, “The efficacy and safety evaluation of aidi injection combined with docetaxel and cisplatin for advanced non-small cell lung cancer,” *Jilin Medical Journal*, vol. 35, pp. 7798-7799.

[26] “G.S. Higgins JPT, Cochrane Handbook for Systematic Reviews of Interventions Ver-sion 5. 1. 0,” http://training.cochrane.org/handbook.

[27] A. B. Miller, B. Hoogstraten, M. Staquet, and A. Winkler, “Reporting results of cancer treatment,” *Cancer*, vol. 47, no. 1, pp. 207–214, 1981.

[28] H. Watanabe, S. Yamamoto, H. Kunitoh et al., “Tumor response evaluation of Interventions Version 5. 1. 0,” http://training.cochrane.org/handbook.

[29] M. Maemondo, A. Inoue, S. Sugawara et al., “Randomized phase II trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: North Japan lung cancer group trial 0801,” *The Oncologist*, vol. 19, no. 4, pp. 352–353, 2014.

[30] A. Matikas, V. Georgoulias, and A. Kotsakis, “The role of docetaxel in the treatment of non-small cell lung cancer lung cancer: an update,” *Expert Review of Respiratory Medicine*, vol. 10, no. 11, pp. 1229–1241, 2016.

[31] M. Maemondo, A. Inoue, S. Sugawara et al., “Randomized phase II trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: North Japan lung cancer group trial 0801,” *The Oncologist*, vol. 19, no. 4, pp. 352–353, 2014.

[32] A. Matikas, V. Georgoulias, and A. Kotsakis, “The role of docetaxel in the treatment of non-small cell lung cancer lung cancer: an update,” *Expert Review of Respiratory Medicine*, vol. 10, no. 11, pp. 1229–1241, 2016.

[33] M. Maemondo, A. Inoue, S. Sugawara et al., “Randomized phase II trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: North Japan lung cancer group trial 0801,” *The Oncologist*, vol. 19, no. 4, pp. 352–353, 2014.

[34] A. Matikas, V. Georgoulias, and A. Kotsakis, “The role of docetaxel in the treatment of non-small cell lung cancer lung cancer: an update,” *Expert Review of Respiratory Medicine*, vol. 10, no. 11, pp. 1229–1241, 2016.
[35] L. Jiang and Q. Kong, “Short term efficacy of DC regimen combined with Aidi injection in the treatment of advanced non small cell lung cancer,” *Hubei Journal of Traditional Chinese Medicine*, vol. 30, no. 7, pp. 29–30.

[36] Q. Lin, “Aidi injection combined with TP regimen for advanced non small cell lung cancer: A clinical study of 60 cases,” *Zhejiang Clinical Medicine Journal*, vol. 10, no. 11, pp. 1464–1465.

[37] H. Wang, G. Liao, P. Liu, G. Jie, Y. Qu, and S. Liu, “Aidi injection combined with chemotherapy for treatment of the advanced non-small cell lung cancer,” *Chinese Journal of Clinical Oncology and Rehabilitation*, vol. 15, no. 1, pp. 53–54.

[38] W. Lam, “Chemotherapy for Advanced Non-Small Cell Lung Cancer,” *Clinical Pulmonary Medicine*, vol. 3, no. 5, pp. 288–292, 1996.

[39] S. Lin, X. Shi, Y. Zhang, and M. Wang, “Clinical study of Aidi injection combined with DP regimen for advanced non small cell lung cancer,” *Modern Journal of Integrated Traditional Chinese and Western Medicine*, vol. 20, no. 30, pp. 3826–3828.

[40] L. Tang, X. Wu, J. Tao, and L. Wang, “Clinical study of Aidi injection combined with chemotherapy for non small cell lung cancer,” *Journal of Clinical Pulmonary Medicine*, vol. 16, no. 5, pp. 790–791.

[41] T. Wang, “Aidi injection combined with chemotherapy for the treatment of advanced non-small cell lung cancer,” *Chinese Journal of Experimental Traditional Medicine Fooumlae*, vol. 17, no. 18, pp. 261–263.

[42] H. Xing, “Aidi injection combined with docetaxel in the treatment of recurrent non small cell lung cancer in elderly patients,” *Chinese Journal of Primary Medicine and Pharmacy*, vol. 18, no. 21, pp. 2949–2953.

[43] S. Jiang, “Observations and analysis of the application results of Aidi Injection in non-small cell lung cancer chemotherapy,” *Modern diagnosis and treatment*, vol. 23, no. 10, pp. 1628–1629.

[44] L. Shi, “Clinical study of Aidi Injection combined with chemotherapy for advanced non-small cell lung cancer,” *Strait Pharmaceutical Journal*, vol. 24, no. 4, pp. 198–199.

[45] X. Tang, “Aidi injection combined with docetaxel plus cisplatin for advanced non-small cell lung cancer: a clinical study of 36 cases,” *Cancer Research and Clinic*, vol. 24, no. 5, pp. 343–345.

[46] C. Ge and Z. Luo, “Aidi injection combined with DP regimen for non small cell lung cancer: A clinical study of 41 cases,” *Guiding Journal of Traditional Chinese Medicine and Pharmacy*, vol. 19, no. 10, pp. 47–48.

[47] Y. Wu, “Clinical study of aidi injection combined chemotherapy for non-small cell lung cancer,” *Medical Information*, vol. 26, no. 27, pp. 278–278.

[48] E. Gao and F. Zhang, “Application value and influence on quality of life of Aidi injection in middle-late stage lung cancer patients,” *China Modern Medicine*, vol. 21, no. 25, pp. 107–109.

[49] J. Li, J. Wang, and Y. Zhu, “Clinical research on Aidi injection combined with chemotherapy in the treatment of advanced NSCLC,” *Hainan Medical Journal*, vol. 25, no. 23, pp. 3444–3447.

[50] L. Song, N. Li, L. Duan, J. Zhou, and Y. Wang, “Clinical efficacy of Addie Injection combined with docetaxel and carboplatin for advanced non-small cell lung cancer,” *Oncology Progress*, vol. 12, no. 6, pp. 597–601.

[51] Y. Tang and L. Shi, “Effect of Aidi injection combined with oxaliplatin and docetaxel in treatment of advanced non-small cell lung cancer,” *Chinese Journal of Difficult and Complicated Cases*, vol. 13, no. 5, pp. 441–443.

[52] G. Xing, J. Hou, and Z. Zhang, “Aidi injection with lobaplatin and docetaxel for stage IIIB non small cell lung cancer: A clinical study of 72 cases,” *Journal of Chinese Medicinal Materials*, vol. 37, no. 4, pp. 722–725.

[53] H. Xu, “The efficacy and safety evaluation of aidi injection combined with docetaxel and cisplatin for advanced non-small cell lung cancer,” *Jilin Medical Journal*, vol. 35, no. 35, pp. 7798–7799.

[54] Y. Gao, Z. Li, X. Wei, H. Huo, M. Du, and X. Pan, “Clinical study of Aidi injection combined with TP chemotherapy for advanced non small cell lung cancer,” *Medical Information*, vol. 28, no. 16, pp. 192–192.

[55] Q. Hu and H. Qi, “Clinical Efficacy and Serum SIL-2 R/CEA/VEGF Level Changes of Addie Injection Combined with Docetaxel and Carboplatin for NSCLC,” *The Practical Journal of Cancer*, vol. 30, no. 10, pp. 1469–1472.

[56] Z. Li, “Clinical study of docetaxel combined with Aidi injection in the treatment of elderly patients with non small cell lung cancer,” *Journal of Mathematical Medicine*, vol. 28, no. 2, pp. 251–251.

[57] Y. Mo, “Addie Injection Combined with Docetaxel and Cisplatin Chemotherapy on Treatment of Non Small Cell Lung Cancer,” *Journal of Henan University of Science & Technology (Medical Science)*, vol. 33, no. 4, pp. 277–278.

[58] J. Wang, “The effect of Aidi injection combined with platinum chemotherapy for advanced non small cell lung cancer,” *Xiandaib Yangsheng*, vol. 7, no. 12, pp. 36–37.

[59] L. Wang and L. Wu, “Clinical study of Aidi injection combined with docetaxel in the treatment of elderly patients with recurrent non small cell lung cancer,” *Chinese Journal of Primary Medicine and Pharmacy*, vol. 22, no. 6, pp. 909–910.

[60] Y. Gao, Z. Li, W. Huo, X. Zhu, M. Du, and X. Pan, “Clinical study of Aidi injection combined with docetaxel and nedaplatin in the treatment of advanced non-small cell lung cancer,” *Chinese Journal of Modern Drug Application*, vol. 10, no. 4, pp. 148–149.

[61] Z. He, Y. Liu, and Y. Wu, “Effective and Safety of Addie Injection and Docetaxel and Carboplatin Chemotherapy for Non- Small Cell Lung Cancer,” *Chinese Archives of Traditional Chinese Medicine*, vol. 34, no. 4, pp. 1459–1461.

[62] X. Wang, “Clinical study of Aidi injection combined with TP regimen in the treatment of advanced NSCLC,” Hubei University of Chinese Medicine, 2016.

[63] Y. Wang, Z. Wen, G. Yu, Z. Hu, J. Wang, and S. Wu, “Analysis on Therapeutic Effect and Toxic end Side Effects of Aidi Injection combined with TP Regimen in the Treatment of Advanced Non-smell Cell Lung Cancer,” *Chinese Medicine Modern Distance Education of China*, vol. 14, no. 23, pp. 94–95.

[64] J. Zhu, “Efficacy of Aidi injection combined with docetaxel and carboplatin in the treatment of non-small cell lung cancer,” *Journal of Bethune Military Medical College*, vol. 15, no. 1, pp. 38–40.

[65] Y. Tsuchida and P. Therasse, “Response evaluation criteria in solid tumors (RECIST): New guidelines,” *Medical and Pediatric Oncology*, vol. 37, no. 1, pp. 1–3, 2001.

[66] A. Trotti, A. D. Colevas, A. Setser, and E. Basch, “Patient-reported outcomes and the evolution of adverse event reporting in oncology,” *Journal of Clinical Oncology*, vol. 25, no. 32, pp. 3121–3127, 2007.

[67] Z. Xiao, C. Wang, L. Chen et al., “Has aidi injection the attenuation and synergistic efficacy to gemcitabine and cisplatin in non-small cell lung cancer? A meta-analysis of 36 randomized controlled trials,” *Oncotarget*, vol. 8, no. 1, 2017.
[68] Z. Xiao, R. Liang, C.-Q. Wang et al., “Can Aidi injection alleviate the toxicity and improve the clinical efficacy of radiotherapy in lung cancer? A meta-analysis of 16 randomized controlled trials following the PRISMA guidelines,” *Medicine (United States)*, vol. 95, no. 35, Article ID e517, 2016.

[69] L. P. Deng, J. Dong, H. Cai, and W. Wang, “Cantharidin as an antitumor agent: a retrospective review,” *Current Medicinal Chemistry*, vol. 20, no. 2, pp. 159–166, 2013.

[70] T.-C. Hsia, J.-H. Lin, S.-C. Hsu et al., “Cantharidin induces DNA damage and inhibits DNA repair-associated protein levels in NCI-H460 human lung cancer cells,” *Environmental Toxicology*, vol. 30, no. 10, pp. 1135–1143, 2015.

[71] T.-C. Hsia, C.-C. Yu, S.-C. Hsu et al., “Cantharidin induces apoptosis of H460 human lung cancer cells through mitochondria-dependent pathways,” *International Journal of Oncology*, vol. 45, no. 1, pp. 245–254, 2014.

[72] K. M. Kern and J. R. Schroeder, “Comparison of Cantharidin Toxicity in Breast Cancer Cells to Two Common Chemotherapeutics,” *International Journal of Breast Cancer*, vol. 2014, pp. 1–7, 2014.

[73] X.-W. Li, N.-L. Li, L.-Y. Zhao, and Y.-Q. Li, “Experiment on expression of nm23-1 gene in lung cancer mice affected by cantharidin,” *Chinese Journal of Clinical Rehabilitation*, vol. 9, no. 47, pp. 96–98, 2005.

[74] J.-H. Kuo, T.-Y. Shih, J.-P. Lin et al., “Cantharidin induces DNA damage and inhibits DNA repair-associated protein expressions in TSGH8301 human bladder cancer cell,” *Anticancer Research*, vol. 35, no. 2, pp. 795–804, 2015.

[75] V. G. Bespalov, V. A. Alexandrov, A. L. Semenov, E. G. Kovan’Ko, and S. D. Ivanov, “Anticarcinogenic activity of alphadifluoromethylornithine, ginseng, eleutherococcus, and leuzea on radiation-induced carcinogenesis in female rats,” *International Journal of Radiation Biology*, vol. 90, no. 12, pp. 1191–1200, 2014.

[76] Z. Xiao, C. Wang, Y. Sun et al., “Can Aidi injection restore cellular immunity and improve clinical efficacy in non-small-cell lung cancer patients treated with platinum-based chemotherapy? A meta-analysis of 17 randomized controlled trials following the PRISMA guidelines,” *Medicine (United States)*, vol. 95, no. 44, Article ID e5210, 2016.

[77] S. Sun, K. Zheng, and H. Zhao, “Regulatory effect of astragalus polysaccharides on intestinal intraepithelial gamma delta T cells of tumor bearing mice,” *Molecules*, vol. 19, no. 9, pp. 15224–15236, 2014.

[78] K. I. Block and M. N. Mead, “Immune system effects of echinacea, ginseng, and astragalus: a review,” *Integrative Cancer Therapies*, vol. 2, no. 3, pp. 247–267, 2003.

[79] H. J. Stemmler, S. Kenngott, H. Diepolder, and V. Heinemann, “Gastrointestinal toxicity associated with weekly docetaxel treatment,” *Annals of Oncology*, vol. 13, no. 6, pp. 978–981, 2002.

[80] Y. Hsu, A. K. Sood, and J. I. Sorosky, “Docetaxel Versus Paclitaxel for Adjuvant Treatment of Ovarian Cancer: Case-Control Analysis of Toxicity,” *American Journal of Clinical Oncology*, vol. 27, no. 1, pp. 14–18, 2004.

[81] V. Pinzani, F. Bressolle, I. J. Haug, M. Galtier, J. P. Blayac, and P. Balmes, “Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review,” *Cancer Chemotherapy and Pharmacology*, vol. 35, no. 1, pp. 1–9, 1994.

[82] X.-L. Zhu and B.-D. Zhu, “Mechanisms by which Astragalus membranaceus injection regulates hematopoiesis in myelosuppressed mice,” *Phytotherapy Research*, vol. 21, no. 7, pp. 663–667, 2007.