Systematic Review

Traditional Chinese medicinal herbs combined with epidermal growth factor receptor tyrosine kinase inhibitor for advanced non-small cell lung cancer: a systematic review and meta-analysis

Zhong-liang Liu1*, Wei-rong Zhu2*, Wen-chao Zhou3, Hai-feng Ying2, Lan Zheng2, Yuan-biao Guo2, Jing-xian Chen2, Xiao-heng Shen2

1. Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
2. Department of Traditional Chinese Medicine, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 210000, China
3. Department of Science and Technology, Putuo District Central Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200062, China

BACKGROUND: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) targeted treatment has been a standard therapy for advanced non-small cell lung cancer (NSCLC), but it is not tolerated well by all patients. In China, some studies have reported that traditional Chinese medicinal herbs (TCMHs) may increase efficacy and reduce toxicity when combined with EGFR-TKI, but outside of China few studies of this kind have been attempted.

OBJECTIVE: This study is intended to systematically review the existing clinical evidence on TCMHs combined with EGFR-TKI for treatment of advanced NSCLC.

SEARCH STRATEGY: PubMed, the Cochrane Library, the Excerpta Medica Database (EMBASE), the China BioMedical Literature (CBM), and the China National Knowledge Infrastructure (CNKI) and web site of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the World Conference of Lung Cancer (WCLC) were searched; the search included all documents published in English or Chinese before October 2013.

INCLUSION CRITERIA: We selected randomized controlled trials based on specific criteria, the most important of which was that a TCMH plus EGFR-TKI treatment group was compared with an EGFR-TKI control group in patients with advanced NSCLC.

DATA EXTRACTION AND ANALYSIS: The modified Jadad scale was used to assess the quality of studies. For each included study, patient characteristics, treatment details, therapeutic approach and clinical outcomes were collected on a standardized form. When disagreements on study inclusion or data extracted from a study emerged, the consensus of all coauthors provided the resolution. The clinical outcome metrics consisted of objective response rate (ORR; complete response + partial response divided by the total number of patients), disease control rate (DCR; complete response + partial response + no change divided by the total number of patients), survival rate, improved or stabilized Karnofsky performance status (KPS), and severe toxicity. RevMan 5.0 software was used for data syntheses and analyses. Risk ratio (RR) and 95% confidence interval (CI) were calculated; if the hypothesis of homogeneity was not rejected ($P>0.1$, $I^2<50\%$), the fixed-effect model was used to calculate the summary RR and the 95% CI. Otherwise, a random-effect model was used.

RESULTS: In this review, 19 studies were included based on the selection criteria. Of them, 13
The benefits of treatment with EGFR-TKI have been shown by many randomized controlled trials (RCTs); however, many cases of adverse effects have also been reported\cite{14-16}. These side effects fall under three categories: the skin reaction, blood toxicity and gastrointestinal toxicity. Their clinical manifestations include symptoms such as rash, leukopenia, thrombopenia, and nausea and vomiting, which may severely affect the patient’s survival, quality of life and treatment outcomes. Therefore, how to best reduce the toxicity while enhancing the curative effect of EGFR-TKI is a lingering question to be resolved.

In China, many traditional Chinese medicinal herbs (TCMHs) have been widely used in combination with EGFR-TKI, in order to minimize the toxicity and maximize the curative effect of the therapy. These herbal treatments have included Chinese medicine decoction (CMD), Chinese medicine tablet (CMT) and Chinese medicine injection (CMI). Some researchers have found that TCMHs, when combined with EGFR-TKI, in the treatment of advanced NSCLC, are likely to improve survival, tumor response and performance status, as well as to reduce toxicity\cite{17-22}.

So far, awareness of the positive effects produced by TCMH in combination with EGFR-TKI for advanced NSCLC has not been raised outside of China. Similarly, there has been no systematic analysis of the reports based on Chinese studies. Based on systematic review and detailed analysis, this study aims to clarify whether the combination of TCMH with EGFR-TKI for NSCLC can result in enhanced efficacy and reduced toxicity.
2 Methods

2.1 Search principle

Complying with the guidelines from the Cochrane Collaboration,[23] PubMed (1966 to October 2013), the Cochrane Library (1988 to October 2013), the Excerpta Medica Database (EMBASE) (1974 to October 2013), the Cochrane Central Register of Controlled Trials (1966 to October 2013), the China BioMedical Literature (CBM) (1978 to October 2013), and the China National Knowledge Infrastructure (CNKI) (1984 to October 2013), and web site of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the World Conference of Lung Cancer (WCLC) were utilized for search, and the terms used were as follows: “gefitinib” or “erlotinib” or “icotinib” or “EGFR-TKI” and “traditional Chinese medicine herbs” or “plant medicine” or “animal medicine” or “natural medicine” and “lung cancer” or “NSCLC” or “carcinoma of the lungs” and “randomized controlled trials” or synonyms for RCTs. The deadline for trial inclusion was October 2013. Only articles published in Chinese and English were included in this review.

2.2 Study selection

RCTs were adopted when comparing a TCMH plus EGFR-TKI treatment group with an EGFR-TKI control group for patients with advanced NSCLC. In addition, the study had to report at least one of the following indicators: objective tumor response (adopting the 4-point WHO scale[24]), performance status ((the Karnofsky performance scale (KPS)[25] was used to divide performance status into 3 grades by the cutoff of a 10-point change) and toxicity (the 5-point WHO scale[26] was adopted); sufficient details had to be reported to allow the calculation of risk ratios (RR) and 95% confidence intervals (CI) for each outcome. The meta-analysis does not involve median survival time, and does not include duplicate cases.

2.3 Data extraction

Using a standardized form, two investigators independently collected data on patient characteristics, ethnicity, treatment details, therapeutic approach and clinical outcomes from each of the included studies. When discrepancies between the data collected on the two forms were found, the consensus of all coauthors was solicited to correct the data. The outcome measures extracted from each study consisted of objective response rate (ORR: complete response and partial response divided by the total number of patients), disease control rate (DCR: complete response and partial response and no change (NC) divided by the total number of patients), survival rate, stable or improved KPS, and severe toxicity.

2.4 Statistical analysis

Review Manager 5.0 (The Cochrane Collaboration, Oxford, UK)[27] was used to process data in the meta-analysis. RR and 95% CI were calculated for data from each study. When the data did not reject the hypothesis of homogeneity (P>0.1, I²<50%), a fixed-effect model was used to calculate the summary RR, and the 95% CI. Otherwise, a random-effect model was utilized.[28] In this meta-analysis, the following five outcomes were calculated and analyzed appropriately.

2.4.1 ORR

The ORR was calculated as the number of patients experiencing complete response (CR) and partial response (PR) divided by the total number of patients in each group. The RR of ORR was calculated as the ORR in the TCMH with EGFR-TKI treatment group divided by that in the EGFR-TKI control group. Thus, an RR of more than 1 suggests that patients in the TCMH combined with EGFR-TKI treatment group had a greater ORR. This method has been recommended by Sutton et al.[29]

2.4.2 DCR

The DCR was calculated as the sum of patients experiencing CR, PR and NC divided by the total number of patients in each group. The RR of DCR was calculated as the DCR in the TCMH with EGFR-TKI treatment group divided by that in the EGFR-TKI control group. Thus, an RR of more than 1 suggests that patients in the TCMH combined with EGFR-TKI treatment group had a greater DCR.

2.4.3 Survival rate

The survival rate was calculated as the number of patients surviving the study divided by the total number of patients that were admitted to the study. The RR of survival was calculated as the rate of survival in the TCMH with EGFR-TKI treatment group divided by that in the EGFR-TKI control group. Thus, an RR of more than 1 suggests that patients in the TCMH combined with EGFR-TKI treatment group had a greater survival rate.

2.4.4 Improved or stable KPS

The improved or stable KPS was calculated as the number of patients with stable or improved KPS (>10-point increase plus no change) divided by the total number of patients (>10-point increase, plus no change, plus >10-point decrease). This method was consistent with the approach of McCulloch et al.[29]. The RR for improved or stable KPS was calculated as the rate of improved or stable KPS in the TCMH combined with EGFR-TKI treatment group, divided by the proportion of patient with the same status in the EGFR-TKI control group. Thus, an RR of more than 1 suggests that the TCMH combined with EGFR-TKI treatment group had a greater improved or stable KPS.

2.4.5 Severe targeted treatment toxicity

The rate of targeted treatment toxicity was defined as the number of patients experiencing severe toxicity (WHO grades 3 and 4) divided by the total number of patients...
in each group. The RR of severe targeted treatment toxicity was analyzed as the proportion of severe toxicity in the TCMH combined with EGFR-TKI treatment group divided by this proportion in the EGFR-TKI control group. Thus, an RR of less than 1 suggests that the TCMH combined with EGFR-TKI treatment group had a lower rate of severe targeted treatment toxicity.

2.5 Study quality evaluation

Two reviewers independently graded each RCT by using the modified Jadad scale\(^{[29]}\), an eight-item scale designed to evaluate study quality based on randomization, blinding, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects and statistical analysis. The score for each article ranged from 0 to 8. Scores of 0 to 3 meant poor or low quality and 4 to 8 represented good to excellent (high quality).

2.6 Sensitivity analysis

We used sensitivity analysis to assess how robust the results were to measurement error, assumptions about study data and study methodologies\(^{[30]}\). In our sensitivity analysis, some studies of low quality (had a quality score of 3 or under 3) were excluded, which might to some extent weaken the conclusions.

2.7 Publication bias analysis

To test for publication bias in studies used in this analysis we used a funnel plot and the Egger’s regression test\(^{[31]}\) to evaluate the data on ORR. We chose this data parameter in particular because it included the most studies in the meta-analysis.

3 Results

3.1 Study characteristics and quality

As shown in the flow chart (Figure 1), our initial search yielded 64 potentially relevant published articles, all of which were published in Chinese. A review of the titles and abstracts of these articles resulted in the rejection of 33 articles. The remaining 31 articles were evaluated in detail by reviewing the full manuscript. Of these, 12 articles were excluded because they failed to meet inclusion criteria, or had missing data. Finally, 19 studies\(^{[32-50]}\), with a total of 1 274 patients, were included in the meta-analysis. Each of these studies was an RCT and clearly specified their grouping methods. These trials were also all published after 2004. Gefitinib (G) was the most common EGFR-TKI treatment regimen (15/19, 78.9%), with the remainder of studies using erlotinib (E). CMD was the most common TCMH treatment regimen (13/19, 68.4%), with the remainder of studies using CMI (5/19) and CMT (1/19). Of the 19 RCTs, only 5 clearly specified the randomization procedure (random digital table was adopted). The other 14 trials did not report their randomization procedures. Only 5 trials discussed withdrawal and dropout numbers, however 11 of the trials described inclusion/exclusion criteria. Only 17 trials described their statistical methods. According to the

![Figure 1](image_url)
modified Jadad scale, 13 studies were of high quality (with a quality score of 4 or more), and 6 studies were of low quality (with a quality score of 3 or less). Characteristics and quality of all included studies are shown in Table 1.

3.2 Meta-analysis for ORR
The ORR was reported in 19 trials, which involved 1,274 patients. Because the test for heterogeneity in different studies was negative ($P=1.00$), the fixed-effect model was used in this meta-analysis. Meta-analysis demonstrated a statistically significant higher ORR (RR 1.34; 95% CI 1.15 to 1.57; $P=0.0002$; Figure 2) in the TCMH combined with EGFR-TKI treatment group compared with the EGFR-TKI control group. Thus the 34% increase in RR was significant, indicating that the TCMH combined with EGFR-TKI treatment had better ORR.

3.3 Meta-analysis for DCR
The DCR was reported in 19 trials, which included 1,274 patients. There was no heterogeneity detected among data from the included studies ($P=0.28$), so the fixed-effect model was used for this meta-analysis. Meta-analysis revealed a statistically significant higher DCR in the TCMH combined with EGFR-TKI treatment group compared with the EGFR-TKI control group (RR 1.18; 95% CI 1.09 to 1.27; $P<0.0001$; Figure 3). Thus, the significant 18% increase in the RR for the DCR indicated that treatment with TCMH and EGFR-TKI resulted in better treatment outcomes.

3.4 Meta-analysis for survival rate
The one-year survival rates were reported in 5 trials, which included 353 patients. There was no heterogeneity detected among data from the included studies ($P=0.75$), so the fixed-effect model was used for the meta-analysis. The treatment group had a statistically higher rate of one-year survival rate when compared with the control group (RR 1.21; 95% CI 1.01 to 1.44; $P=0.04$; Figure 4). Therefore, the significant 21% increase in the RR for the one-year survival rate indicated that the addition of TCMH to EGFR-TKI treatment resulted in higher one-year survival rates.

The two-year survival rates were reported in 4 trials involving 277 patients. There was no heterogeneity detected among data from the included studies ($P=0.42$), so the fixed-effect model was used for the meta-analysis.

### Table 1: Characteristics and quality of all included studies

<table>
<thead>
<tr>
<th>Included study</th>
<th>Year</th>
<th>Patient number (T/C)</th>
<th>Intervention</th>
<th>Histological type: S/A (SA)</th>
<th>Gene mutation</th>
<th>Outcome</th>
<th>Modified Jadad score</th>
</tr>
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<tbody>
<tr>
<td>Liu H [32]</td>
<td>2012</td>
<td>49/48</td>
<td>CMD+G</td>
<td>G 40/9 38/10</td>
<td>Yes</td>
<td>a.b.c.d.e.f</td>
<td>4</td>
</tr>
<tr>
<td>Fu DZ [33]</td>
<td>2013</td>
<td>19/19</td>
<td>CMD+E</td>
<td>E 17/2 16/3</td>
<td>Not reported</td>
<td>a.b.d.e</td>
<td>3</td>
</tr>
<tr>
<td>Shi QH [34]</td>
<td>2013</td>
<td>25/20</td>
<td>CMD+G</td>
<td>G 22/3 18/2</td>
<td>Yes</td>
<td>a.b.c</td>
<td>3</td>
</tr>
<tr>
<td>Zhang JL [37]</td>
<td>2011</td>
<td>22/22</td>
<td>CMI+G</td>
<td>G 14/8 15/7</td>
<td>Yes</td>
<td>a.b.c</td>
<td>2</td>
</tr>
<tr>
<td>Fang F [38]</td>
<td>2012</td>
<td>46/42</td>
<td>CMD+G</td>
<td>G 38/8 36/6</td>
<td>Yes</td>
<td>a.b.c.d.e.f.g</td>
<td>4</td>
</tr>
<tr>
<td>Fang F [39]</td>
<td>2011</td>
<td>35/27</td>
<td>CMD+G</td>
<td>G 30/5 23/4</td>
<td>Yes</td>
<td>a.b.c.d.e.f.g</td>
<td>4</td>
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<tr>
<td>Fang F [40]</td>
<td>2011</td>
<td>36/35</td>
<td>CMD+G</td>
<td>G 23/13 21/14</td>
<td>Not reported</td>
<td>a.b.c.d.e.f.g</td>
<td>4</td>
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<tr>
<td>Fang H [41]</td>
<td>2011</td>
<td>22/22</td>
<td>CMI+G</td>
<td>G 13/9 14/8</td>
<td>Yes</td>
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<td>4</td>
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<tr>
<td>Yang XX [42]</td>
<td>2012</td>
<td>33/36</td>
<td>CMD+G</td>
<td>G 27/8 (1) 24/7 (2)</td>
<td>Yes</td>
<td>a.b.c.d.e</td>
<td>3</td>
</tr>
<tr>
<td>Liang H [43]</td>
<td>2012</td>
<td>30/26</td>
<td>CMD+G</td>
<td>G 24/6 22/4</td>
<td>Yes</td>
<td>a.b.c.d.e.g</td>
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<tr>
<td>Yuan GR [44]</td>
<td>2011</td>
<td>42/38</td>
<td>CMD+G</td>
<td>G 30/10 (2) 27/8 (3)</td>
<td>Yes</td>
<td>a.b.f</td>
<td>4</td>
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<tr>
<td>Jia YJ [45]</td>
<td>2009</td>
<td>30/28</td>
<td>CMD+E</td>
<td>E 17/13 15/13</td>
<td>Not reported</td>
<td>a.b.c.d</td>
<td>5</td>
</tr>
<tr>
<td>Guo J [46]</td>
<td>2013</td>
<td>32/31</td>
<td>CMI+E</td>
<td>E 9/23 (0) 6/23 (2)</td>
<td>Not reported</td>
<td>a.b.c.d.e.f</td>
<td>4</td>
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<tr>
<td>Qian J [47]</td>
<td>2004</td>
<td>12/13</td>
<td>CMI+G</td>
<td>G 10/2 11/1</td>
<td>Yes</td>
<td>a.b.</td>
<td>3</td>
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<tr>
<td>Huang Y [48]</td>
<td>2011</td>
<td>38/38</td>
<td>CMD+G</td>
<td>G 24/12 (2) 25/13 (0)</td>
<td>Yes</td>
<td>a.b.d.f.g</td>
<td>4</td>
</tr>
<tr>
<td>Lin YT [49]</td>
<td>2013</td>
<td>30/30</td>
<td>CMD+G</td>
<td>G 23/7 25/5</td>
<td>Yes</td>
<td>a.b.e</td>
<td>2</td>
</tr>
</tbody>
</table>

T: treatment group; C: control group; G: gefitinib; E: erlotinib; CMD: Chinese medicine decoction; CMI: Chinese medicine injection; CMT: Chinese medicine tablet; A: adenocarcinoma; S: lung squamous cell cancer; SA: adenocarcinoma and squamous tumor; a: objective tumor response; b: disease control rate; c: stabled/improved Karnofsky performance status; d: III-IV skin toxicity; e: III-IV diarrhea toxicity; f: III-IV nausea and vomiting toxicity; g: survival rate.
**Figure 2** Forest plot of the risk ratio for objective response rate
The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI.

**Figure 3** Forest plot of the risk ratio for disease control rate
The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI.
Meta-analysis showed the TCMH combined with EGFR-TKI treatment group had a statistically significant higher rate of two-year survival compared with the EGFR-TKI control group (RR 1.91; 95% CI 1.26 to 2.89; \( P = 0.002 \); Figure 4). Therefore, the significant 91% increase in the RR for the two-year survival rate indicated that addition of TCMH to treatment protocols improved two-year survival rates for study patients.

### 3.5 Meta-analysis for KPS

The rates of improved or stable KPS were reported in 11 trials\[^{32,34-36,38-40,42,43,45,46}\] involving 747 patients. These data were also found to be homogeneous, justifying the use of the fixed-effect model in this meta-analysis. The meta-analysis revealed a statistically significant higher rate of improved or stable KPS when the TCMH combined with EGFR-TKI treatment group was compared with the EGFR-TKI control group (RR 1.38; 95% CI 1.26 to 1.51; \( P = 0.000 \ 01 \); Figure 5). The significant 38% increase in the RR for patients with improved or stable KPS indicated that addition of TCMH to EGFR-TKI treatment resulted in better KPS.

### 3.6 Meta-analysis for grade 3 or 4 rash, diarrhea, and nausea and vomiting

Of the 19 included studies, 12 trials\[^{32,33,36,38-40,42,43,45,46,48,50}\] reported the number of patients with grade 3 or 4 rash; 3 trials\[^{32,33,47}\] reported the number of patients with grade 3 or 4 nausea and vomiting; 7 trials\[^{32,35,36,38-40,46}\] reported the number of patients with grade 3 or 4 diarrhea. The rate of severe toxicity was calculated for rash, diarrhea, and nausea and vomiting and then meta-analyses were performed. As indicated in Figures 6 and 7, there was statistically significant lower severe toxicity for rash (RR 0.55; 95% CI 0.32 to 0.94; \( P = 0.03 \); Figure 6), nausea and vomiting (RR 0.17; 95% CI 0.04 to 0.72; \( P = 0.02 \); Figure 7) and diarrhea (RR 0.46; 95% CI 0.24 to 0.89; \( P = 0.02 \); Figure 7) when the TCMH combined with EGFR-TKI treatment group was compared with the EGFR-TKI control group.

### 3.7 Sensitivity analysis

When low-quality studies were excluded, the sensitivity analysis showed that the summary RR and 95% CI for ORR, DCR, survival rate, KPS, and rash, diarrhea, and nausea and vomiting were only nominally different than values calculated for the entire dataset (Table 2). This indicated that the meta-analysis was not very sensitive to study quality, and suggested that the results of this study were reliable and verifiable.

### 3.8 Publication bias analysis

The funnel plot generated for studies with data on objective tumor response (Figure 8) was asymmetrical, indicating that there was evidence of publication bias in the included studies. Further, Egger’s test confirmed the presence of publication bias (\( P = 0.03 \)).

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![Figure 4](image-url)

**Figure 4**  Forest plot of the risk ratio for survival rate

The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI.
Discussion

To ensure that medical treatments are based on the best available data, systematic reviews and meta-analysis are often widely adopted in medicine. For example, meta-analysis can help the users to reach a more accurate and reliable conclusion by gathering empirical data from a range of studies and performing statistical synthesis\cite{51}. Thus, in order to systematically evaluate whether TCMH improves the efficacy and reduces the toxicity when combined with EGFR-TKI for advanced NSCLC, the authors carried out this systematic review. The results of this analysis demonstrate that addition of TCMH to EGFR-TKI targeted treatment can raise ORR and DCR, improve performance status and reduce toxicity (such as rash, diarrhea, and nausea and vomiting) when compared with EGFR-TKI targeted treatment alone. Addition of TCMH to EGFR-TKI treatment improved both one-year and two-year survival rates compared with EGFR-TKI alone, which means that TCMH intervention may improve survival rate in the long term. Patients receiving TKI therapy often develop resistance

Figure 5 Forest plot of improved or stable Karnofsky performance score
The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI.

Figure 6 Forest plot of grade 3 or 4 rash
The squares and horizontal lines correspond to the study-specific risk ratio and 95% CI. The area of the squares reflects the weight (Mantel-Haenszel). The diamond represents the summary risk ratio and 95% CI.
over time, resulting in treatment failure that progresses from unrestrained tumor growth, tumor metastasis and tumor progression. The results of this study show that the integrative medicine group had better treatment outcomes than the TKI group for ORR and DCR; this suggests that TCMH can delay acquired resistance. Experimental studies in vitro show that the Xiaoyanping injection can reverse gefitinib resistance caused by rock K-ras mutations, which also confirms the role of TCMH in reversal of acquired resistance to TKI[52]. Chinese medicine believes that the basic pathogenesis of tumors is a deficiency of healthy qi and an excess of evil pathogenic qi, so the method of strengthening healthy qi while eliminating pathogenic qi is widely applied to the treatment of cancer. Using Renshen (Radix Ginseng), Huangqi (Radix Astragali), Yiyiren (Semen Coicis), Jixueteng (Caulis spatholobi) and

### Table 2: Sensitivity analysis of this study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All studies</th>
<th>High-quality studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of studies</td>
<td>Number of patients</td>
</tr>
<tr>
<td>Tumor response rate</td>
<td>19</td>
<td>1,274</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>19</td>
<td>1,274</td>
</tr>
<tr>
<td>1-year survival</td>
<td>5</td>
<td>353</td>
</tr>
<tr>
<td>2-year survival</td>
<td>4</td>
<td>277</td>
</tr>
<tr>
<td>Karnofsky performance score</td>
<td>11</td>
<td>747</td>
</tr>
<tr>
<td>Rash</td>
<td>12</td>
<td>930</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
<td>211</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>479</td>
</tr>
</tbody>
</table>

RR: risk ratio; CI: confidence interval.
Danggui (*Radix Angelicae Sinensis*) to replenish qi, yin and blood, while using herbs with a direct antitumor effect to eliminate the pathogen, such as Banmao (*Mylabris*), Xiakucao (*Spica Prunellae Vulgaris*) or Baihuasheshecao (*Herba Hedyotidis Diffusae*). Modern pharmacological studies have shown that Renshen, Huangqi, Yiyiren and their extracts (such as ginsenosides, ginseng polysaccharide, ginseng alcohols, panaxtatriol, astragaloside, astragalus polysaccharides and Coix seed oil) can not only enhance the function of immune system, but may also have a direct inhibitory effect. TCMH’s antitumor effects include increasing immunity, reducing side effects of anticancer drugs, increasing sensitivity to anticancer drugs and other aspects. This is the first systematic review of TCMH for advanced NSCLC. The analysis finds compelling evidence for the application of TCMH to reduce toxicity and enhance the curative effect of EGFR-TKI-targeted treatment. While it is common in China to use TCMH combined with EGFR-TKI to treat advanced NSCLC and, accordingly, a great number of research articles have been produced, no relevant clinical research articles or evaluations have been published in English medical journals. This failure to publish reports of TCMH’s effectiveness in English language journals reduces the worldwide validity of the approach and hinders its widespread application. This study explores the use of TCMH in the treatment of advanced NSCLC, finding that it improves most treatment outcomes when combined with typical treatment approaches. Nevertheless, there are still large gaps in the understanding of TCMH such as, what are the essential effective components in TCMH and whether interplays exist between medicines and these herbal components? There are currently no clear answers for these questions and further in-depth investigation is needed.

There are some limitations to the present analysis. First, not all of the included trials specified how they handled concealment and blinding, which could result in bias and exaggeration of the efficacy of the treatment group. Second, a number of different factors may have affected the results, including the differences in various studies, the language limitation of the included studies, the variety of TCMH formulations and the heterogeneity. Furthermore, the funnel plot and Egger’s test indicated that publication bias may exist. Given the above factors, the evidence from this study may be inadequate, and should be carefully applied. Nevertheless, we believe that this study reflects the basic trends of the pharmaceutical efficacy of TCMH in combination with TKI. In spite of the above limitations, this study highlights the importance of TCMH as a complement to Western medicine and sheds light on methods for improving the treatment of advanced NSCLC.

5 Conclusion

In conclusion, in this systematic review evidence was found demonstrating that TCMH may increase efficacy and reduce toxicity when taken in combination with EGFR-TKI for advanced NSCLC. However, limitations exist and more high-quality RCTs will be needed to verify the results.

6 Acknowledgements

This study was supported by business proposals research and special topics of 2012 Annual National TCM Clinical Research Base (No. JDZX2012119). The authors are grateful to Prof. Xue-jun Cui in writing.

7 Author contributions

Conceived and designed the experiments: Liu ZL and Shen XH; performed the experiments: Liu ZL, Zhu WR, and Zhou WC; analyzed the data: Liu ZL, Zhu WR, Zhou WC, Ying HF, Guo YB, Zheng L, Chen JX, and Shen XH; contributed analysis tools: Ying HF, Guo YB, Zheng L, and Chen JX; wrote and approved the manuscript: Liu ZL, Zhu WR, Zhou WC, and Shen XH.

8 Competing interests

The authors declare that they have no competing interests.

REFERENCES


Submission Guide

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