ABSTRACT

Background  The concept of maintenance therapy in cancer treatment is currently under debate because of modest survival benefits, added toxicity, economic considerations, and quality-of-life concerns. Traditional Chinese Medicine (TCM) is widely used in China for cancer patients, offering the advantages of low toxicity and enhancement of quality of life. However, no systematic reviews or meta-analyses have assessed the role of TCM as maintenance treatment for non-small-cell lung carcinoma.

Methods  We searched the Chinese Biomedical Literature Database, the China National Knowledge Infrastructure, PubMed, Embase, and the Cochrane Library databases for all eligible studies. The endpoints were overall survival (OS), progression-free survival (PFS), the 1-year and 2-year survival rates, and performance status. Our meta-analysis used a fixed-effects model and a random-effects model for heterogeneity in the Stata software application (version 11.0: StataCorp LP, College Station, TX, U.S.A.), with the results expressed as hazard ratios (HRs) or risk ratios (RRs), with their corresponding 95% confidence intervals (95% CIs).

Results  Sixteen randomized studies representing 1150 patients met the inclusion criteria. Compared with best supportive care, observation, or placebo, TCM as maintenance treatment was associated with a significant increase in OS (HR: 0.49; 95% CI: 0.35 to 0.68; \( p < 0.001 \)), PFS (HR: 0.66; 95% CI: 0.51 to 0.84; \( p = 0.001 \)), and 2-year survival rate (RR: 0.63; 95% CI: 0.44 to 0.92, \( p = 0.017 \)), and a significant improvement in performance status (RR: 0.68; 95% CI: 0.61 to 0.75; \( p < 0.001 \)).

Conclusions  For patients who show non-progression—including stable disease, partial response, or complete response—after first-line chemotherapy, including those with poor quality of life, oral Chinese herbal medicine can be considered an efficient and safe maintenance therapy strategy.

Key Words  Traditional Chinese Medicine; non-small-cell lung cancer, advanced; maintenance therapy; integrative oncology

INTRODUCTION

Lung cancer remains one of the most common causes of cancer-related death all over the world. Non-small-cell lung cancer (NSCLC) represents nearly 85% of all lung cancers and is associated with an overall 5-year survival rate of 17.1%. The standard first-line treatment for advanced NSCLC has consisted of platinum-based doublet therapy. After 4–6 cycles of first-line therapy, patients who show no progressive disease might have a choice: watch-and-wait

a These authors contributed equally to the present work.
strategy (including best supportive care (bsc), treatment administered with the intent to maximize quality of life (qol) without a specific antineoplastic regimen, and follow-up) or maintenance therapy. However, primary data suggest that patients who receive the watch-and-wait strategy will experience progressive disease a few months later 5.

Maintenance therapy is one strategy that has been extensively investigated. Several randomized controlled trials (rct) have demonstrated that, compared with bsc or placebo, gemcitabine 6,7 or pemetrexed 8–10 is associated with improved progression-free survival (pfs), and that pemetrexed is associated with improved overall survival (os). Those well-tolerated agents are given to patients with a good performance status. However, in clinical practice, not all patients are suitable for maintenance chemotherapy or epidermal growth factor receptor tyrosine kinase inhibitor therapy. Drug-related grade 3 or greater toxic effects are reported more frequently in maintenance arms than in control arms 11–13. When patients experience unacceptable toxicity, treatments have to be stopped.

Traditional Chinese Medicine (tcm) has a long history in China and, with its advantages of low toxicity and enhancement of qol, has been widely used in the treatment of advanced nsclc 14. As a maintenance therapy, tcm is recommended for all kinds of patients because of good tolerance 15,16. Several meta-analyses have shown that, combined with chemotherapy, radiotherapy, and targeted therapy, tcm can alleviate side effects, enhance short-term therapeutic effects, stabilize disease, and improve the long-term efficacy of treatment 17–19. According to a previous study by our group 14, herbal formulas based on syndrome differentiation have been reported to make treatment more effective. However, no pooled data have demonstrated whether tcm as maintenance therapy might benefit patients with nonprogressing disease (including stable disease, partial response, or complete response) after first-line chemotherapy. In the present paper, we therefore undertook a systematic review and meta-analysis to assess the most up-to-date studies.

METHODS

Search Strategy

Eligibility Criteria
Relevant clinical trials were selected based on these criteria:

- Patients had to have locally advanced or metastatic nsclc (stages IIIA, IIIB, IV)
- After first-line treatment, patients had to have been evaluated for stable disease, partial response, or complete response
- Sequential maintenance treatment was limited to oral Chinese herbal medicine (chm) alone
- Rct, assessed for quality by the Jadad scale, had to score 1 or greater
- Trials had to include sufficient data, including survival data, for extraction
- Systematic reviews and meta-analyses were excluded
- Language of the selected articles was limited to English and Chinese

Data Extraction and Validity Assessment
Data extracted from eligible articles for analysis included os, pfs, 1- and 2-year survival rates, and Karnofsky performance status (kps). Basic study data extracted were the first author’s name, year of publication, stages of lung cancer treated, number of patients, and treatment strategies. The quantitative 5-point Jadad scale was used to assess the quality of the included trials 20. Two reviewers (QW, QW) searched the literature and extracted the data independently. Mismatches between the reviewers were resolved by discussion and consensus.

Ethics Approval
All analyses were based on previous published studies, and thus no ethics approval or patient consent was required.

Statistical Analysis
Risk ratio (rr) estimates were calculated using the Stata software application (version 11.0: StataCorp LP, College Station, TX, U.S.A.) 21. Heterogeneity between trials was estimated using the chi-square-based Q statistic and was considered statistically significant at a p value of less than 0.05 or an I2 exceeding 50%. If heterogeneity was detected, the data were analyzed in a random-effects model. Otherwise, a fixed-effects model was used. A statistical test resulting in p < 0.05 was considered to indicate a statistically significant difference. A rr less than 1 reflected a favourable outcome in the oral chm–based maintenance treatment arm. Publication bias was evaluated using Begg funnel plots, which examine the presence of an association between effect estimates and their variances (p > 0.05 means no correlation between studies), and the Egger test, which checks for asymmetry in the funnel plot 22,23. All p values are 2-sided. All cis have 2-sided probability coverage of 95%.

RESULTS

Study Selection
The initial literature search, performed in March 2016, found 103 articles. After titles and abstracts were screened, thirty-six articles were excluded because they did not meet the inclusion criteria. Sixty-seven full-text articles were further reviewed for inclusion. Subsequently, twenty-two articles were excluded because patients had not been evaluated after chemotherapy, and another five articles that were designed to compare tcm and chemotherapies as maintenance treatment were excluded. Further, twelve articles that were not rcts and twelve articles that were reviews were excluded. In the end, sixteen rcts that included 1150 patients and that were reported in full-text publication were eligible. Figure 1 and Table 1 show details of the study selection.
Publication Bias
The examination for publication bias revealed no obvious asymmetry in the Begg funnel plots ($p = 0.206$ for kps) or Egger test ($p = 0.206$ for kps, 0.09 and 0.667 for the 1- and 2-year survival rates, 0.08 for os, and 0.73 for PfS).

Survival Analysis
Maintenance treatments in the included studies were limited to oral chm, including herbal formulas prescribed based on syndrome differentiation (that is, the process of comprehensive analysis of clinical information obtained by the four main diagnostic tcm procedures: observation, listening, questioning, and pulse analyses) and oral patent formulations prescribed according to published specifications. Table 1 shows details of use and dose.

Four of the included trials 27,29,31,40 (276 patients) reported os data. In a fixed-effects model, the pooled rr for os favoured oral chm–based maintenance treatment over bsc, observation, or placebo [rr: 0.49; 95% ci: 0.35 to 0.68; $p < 0.001$; Figure 2(A)].

Six trials reported PfS data 25,28–30,38,39, but to avoid publication bias, one trial 29 was removed (355 patients analyzed). In a fixed-effects model, the pooled rr for PfS favoured oral chm–based maintenance treatment over bsc, observation, or placebo [rr: 0.66; 95% ci: 0.51 to 0.84; $p = 0.001$; Figure 2(B)].

Eight trials reported a 1-year survival rate 24,26,27,29,34,35,37,40, but to avoid publication bias, two trials 24,27 were removed (233 patients analyzed). In a random-effects model, the pooled rr for the 1-year survival rate showed no significant difference between oral chm–based maintenance treatment and bsc, observation, or placebo [rr: 0.84; 95% ci: 0.71 to 1.00; $p = 0.054$; Figure 2(C)].

Four trials 24,26,35,40 (158 patients) reported a 2-year survival rate. In a fixed-effects model, the pooled rr for oral chm–based maintenance treatment over bsc, observation, or placebo [rr: 0.63; 95% ci: 0.44 to 0.92; $p = 0.017$; Figure 2(D)].

Performance Status
Performance status improvement was defined as an increase in the kps score. Twelve trials 25,26,28–30,32–34,36–38,40 reported kps data. In a fixed-effects model, the pooled rr for performance status improvement favoured oral chm–based maintenance treatment over bsc, observation, or placebo (rr: 0.68; 95% ci: 0.61 to 0.75; $p < 0.001$; Figure 3).

Health-Related QOL Questionnaires and Adverse Events
The included studies used various evaluation scales for assessing health-related qol and adverse events (aes), and therefore those results are described rather than assessed in a statistically pooled analysis.

In the seven trials 25,29,30,34,35,37,39 that evaluated effects on qol, three 29,35,37 used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (QLQ-C30, QLQ-LC43), and four 25,29,30,39 used the Functional Assessment of Cancer Therapy–Lung. Three trials 25,29,37 that compared bsc, observation, or placebo with oral chm demonstrated a significant reduction in shortness of breath and cough with the use of oral chm. Using similar comparators, four trials 25,29,35,37 reported a significant improvement in physical and functional well-being with oral chm.

Three trials 32–34 reported a significant improvement in immune function (blood analysis of CD3+, CD4+, and CD4+/CD8+) in an oral chm treatment group compared with a bsc, observation, or placebo group. The studies were not pooled here because of varying data types.

In six trials 25,28,29,31,38,40, aes were graded using the toxicity criteria of the World Health Organization or the U.S. National Cancer Institute. Six trials 25,28,29,33,35,40 reported that patients experienced one or more of dry mouth, nausea, loss of appetite, sweating, dizziness, constipation, and diarrhea after taking oral chm and that such events might be associated with oral chm treatment. The grades of the aes were 1 and 2, and after temporary withdrawal of the oral chm or after symptomatic treatment, symptoms disappeared within a week. One study 33 reported a significant reduction in fatigue, nausea, vomiting, insomnia, loss of appetite, constipation, and diarrhea with the use of oral chm (compared with bsc, observation, or placebo). Overall, no treatment-related grade 3 or greater aes were reported.

DISCUSSION
In recent years, the concept of maintenance chemotherapy has come under scrutiny because of lack of survival benefit, added toxicity, economic considerations, and qol concerns. A review conducted by Jalal et al. 41 of trials evaluating platinum-based maintenance chemotherapy (carboplatin or cisplatin with paclitaxel, carboplatin–vinorelbine, cisplatin–docetaxel, cisplatin–gemcitabine) in patients with advanced nsclc demonstrated that maintenance improves pfs, but not os. However, a phase iii study 10 demonstrated that pemetrexed continuation as maintenance therapy was well tolerated and offered superior os and pfs compared with placebo and that, compared with platinum-based therapy, monotherapy is favourable for maintenance treatment. The study also demonstrated that compared with placebo, the treatment group still experienced a significantly greater incidence of drug-related grades 3 and 4 aes. Moreover, longer exposure to pemetrexed (>6 cycles)
<table>
<thead>
<tr>
<th>Reference</th>
<th>TNM stage</th>
<th>Pts (n)</th>
<th>First-line Therapy</th>
<th>Maintenance Therapy</th>
<th>Survival rate (%)</th>
<th>Median survival (months)</th>
<th>KPS</th>
<th>Jadad scale</th>
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<tr>
<td>Li et al., 2007</td>
<td>III, IV</td>
<td>81</td>
<td>First-line chemotherapy</td>
<td>Self-made Traditional Chinese Medicine</td>
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<td>Liu et al., 2009</td>
<td>III, IV</td>
<td>81</td>
<td>Cisplatin- or carboplatin-based</td>
<td>Fei Tai capsule</td>
<td>61.7</td>
<td>21.0</td>
<td>12</td>
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<td>Zhang et al., 2010</td>
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<td>31</td>
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<td>Qing Fei Xiao Yu decoction</td>
<td>62.5</td>
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<td>(1 dose daily until progression)</td>
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<td>Chai et al., 2011</td>
<td>IIIB, IV</td>
<td>32</td>
<td>First-line chemotherapy</td>
<td>Xiao Ji Yin decoction</td>
<td>40.1</td>
<td>6.4</td>
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<td>Xi et al., 2011</td>
<td>IIIB, IV</td>
<td>44</td>
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<td>Fu Zheng Kang Ai decoction</td>
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<td>15.1</td>
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<td>30</td>
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<td>(2 g, 3 times daily, days 1–21, 3 cycles)</td>
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<td>First-line chemotherapy</td>
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<tr>
<td>Yang et al., 2013</td>
<td>III, IV</td>
<td>40</td>
<td>Gemcitabine, vinorelbine, or</td>
<td>Fu Zheng Xiao Ji Yin</td>
<td>40</td>
<td>4.67</td>
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<td>paclitaxel plus cisplatin</td>
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<td>Zeng et al., 2013</td>
<td>IV</td>
<td>32</td>
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<td>ShenYi capsule</td>
<td>32.4</td>
<td>7.3</td>
<td>90.7</td>
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<td>(20 mg, 2 times daily until progression)</td>
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<td>Huang et al., 2014</td>
<td>III, IV</td>
<td>43</td>
<td>First-line chemotherapy</td>
<td>Fu Zheng Hua Du decoction</td>
<td>35.3</td>
<td>4.5</td>
<td>71.4</td>
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<td>(1 dose daily until progression)</td>
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<td>Shao et al., 2014</td>
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<td>50</td>
<td>First-line chemotherapy</td>
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<td>(0.75 g, 2 times daily until progression)</td>
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<td></td>
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<td>Best supportive care plus placebo</td>
<td>53.44</td>
<td>19.7</td>
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</table>
was reported to be associated with a numeric increase in grades 3 and 4 adverse events. In an RCT, RCT was also associated with improved patient QoL and a higher 1-year survival rate. In our study, compared with BSC group, the TCM group had higher survival rate, and in some studies, TCM group had better response rate and fewer adverse events.

FIGURE 2 Meta-analysis forest plot of sixteen studies assessing survival in patients with advanced non-small-cell lung cancer comparing oral Chinese herbal medicine–based maintenance treatment alone with best supportive care, observation, or placebo. (A) Overall survival. (B) Progression-free survival. (C) One-year survival. (D) Two-year survival. (E) Four-year survival. (F) Hazard ratio. (G) Confidence interval. (H) Traditional Chinese Medicine.
ORAL CHINESE HERBALS AS MAINTENANCE TREATMENT AFTER CTx FOR NSCLC, Wang et al.

chm–based maintenance treatment was associated with a significant increase in OS (p < 0.001), PFS (p = 0.001), 2-year survival rate (p = 0.017), and qol (p < 0.001). Looking at the 1-year survival rate (RR: 0.84; 95% CI: 0.71 to 1.00; p = 0.054), the improvement was nonsignificant, but the RR of less than 1 still showed an advantage for the maintenance group over the control group. Moreover, the p value is close to 0.05, which could reflect just a lack of available research.

Patients can benefit from maintenance chemotherapy or targeted therapy, but side effects and lesser qol might limit such approaches. Recent studies have reported that, combined with platinum-based chemotherapy, some chms show superiority in relieving symptoms for lung cancer patients, mitigating the severe AES of standard cancer therapy, enhancing short-term efficacy, and improving qol.43–45. In our study, performance status as evaluated by KPS was significantly improved in patients who received oral chm–based maintenance treatment (p < 0.001). Seven trials that evaluated effects on qol demonstrated a significant reduction in symptoms, including shortness of breath and cough, and an improvement in physical and functional well-being in patients receiving oral chm compared with those receiving bsc, placebo, or observation. Three trials31–33 reported a significant improvement in immune function and no treatment-related grade 3 or greater AES in oral chm groups. In the absence of toxicity requiring cessation of treatment, oral chm–based treatment could potentially be continued over longer periods of time. Therefore, although the molecular mechanisms are not fully understood, the immunostimulating effects, reductions in chemotherapy-induced toxicity, and improvements in qol might be major advantages for oral chm as adjuvant therapy in maintenance therapy for advanced nsclc.44

Several limitations have to be considered when interpreting our results. First, the patients in the included studies are solely of Asian ethnicity. Second, although the baseline studies in the meta-analysis have no heterogeneity, variation in the oral medicines used in the interventions means that heterogeneity of tcm treatment will be a possibility when we try to analyze more studies (for example, of injection chms) in the future. A third limitation is the low quality of several of the included studies, including one with a Jadad score of 1, and three with Jadad scores of 2.

Studies of tcm in diverse races are expected to be conducted in the future and would add to the strength of the literature reporting on the benefits of tcm during maintenance therapy. In addition, subgroup analyses based on the various treatments are needed. Particular attention should be paid to devising high-quality rcts to investigate these topics in the future.46,47

CONCLUSIONS

For patients whose evaluations after first-line chemotherapy indicated non-progression (including stable disease, partial response, or complete response), including those with poor qol, use of oral chms could be considered an efficient and safe maintenance therapy.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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