CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Oral Chinese herbal medicine as maintenance treatment after chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis

Q. Wang MD,*†[a] Q. Wang MD,‡[a] S.F. Wang MD,§[a] L.J. Jiao MD,* R.X. Zhang PhD,‖ Y. Zhong MD,‖ J. Zhang MD,§ and L. Xu MD*

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

Curr Oncol. 2017 Aug;24(4):e269-e276 www.current-oncology.com

INTRODUCTION

Lung cancer remains one of the most common causes of cancer-related death all over the world [1]. Non-small-cell lung cancer (NSCLC) represents nearly 85% of all lung cancers and is associated with an overall l 5-year survival rate of 17.1% [2,3].

The standard first-line treatment for advanced NSCLC has consisted of platinum-based doublet therapy [4]. 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.

Correspondence to: Ling Xu, Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, 110 Ganhe Road, Shanghai 200437 P.R.C. or Jie Zhang, 270 Dong'an Road, Shanghai 200032 P.R.C.
E-mail: xulq77@163.com or zhangjie2299@hotmail.com ■ **DOI:** https://doi.org/10.3747/co.24.3561

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 (RCTs) 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 non-progressing 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

An online literature search strategy used PubMed (1966 to March 2016), EMBASE (1974 to March 2016), the Chinese Biomedical Literature Database (1978 to March 2016), the China National Knowledge Infrastructure (1979 to March 2016), and the Cochrane Library databases (1988 to March 2016) to locate relevant articles based on the keywords "non-small-cell lung cancer," "NSCLC," "Traditional Chinese Medicine," "maintenance," and "chemotherapy."

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
- RCTs, 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 I^2 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 I show details of the study selection.

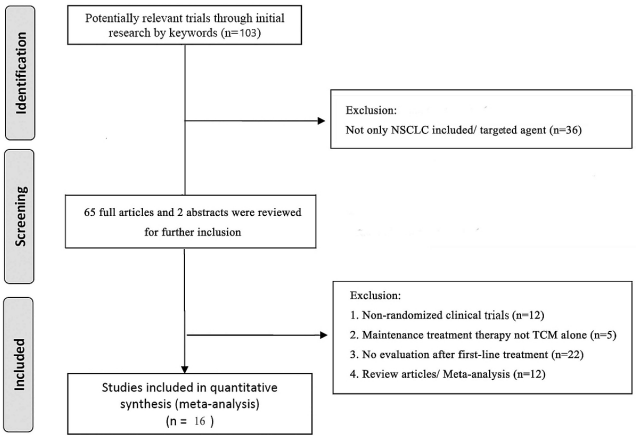

FIGURE 1 Article selection for the meta-analysis: sixteen studies involving 1150 patients were analyzed. NSCLC = non-small-cell lung cancer; TCM = Traditional Chinese Medicine.

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 I 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 HR for OS favoured oral CHM–based maintenance treatment over BSC, observation, or placebo [HR: 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 HR for PFS favoured oral CHM–based maintenance treatment over BSC, observation, or placebo [HR: 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 favoured 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 I Baseline characteristics of the sixteen trials used in the meta-analysis

Reference	TNM stage	Pts (*n*)	Therapy		Survival rate (%)		Median survival (months)		KPS	Jadad scale
			First line	Maintenance	1-Year	2-Year	Overall	Progression-free		
Li *et al.*, 2007 [24]	III, IV	81	First-line chemotherapy	Self-made Traditional Chinese Medicine (1 dose daily until progression)	70.4	37.0	18	NA	NA	1
		81		Follow-up	61.7	21.0	12	NA	NA	
Liu *et al.*, 2009 [25]	III, IV	31	Cisplatin- or carboplatin-based chemotherapy	Fei Tai capsule (2 g, 3 times daily, days 1–21, 3 cycles)	NA	NA	NA	6.23	51.6	3
		31		Follow-up	NA	NA	NA	4.67	25.8	
Zhang *et al.*, 2010 [26]	IIIB, IV	32	First-line chemotherapy	Qing Fei Xiao Yu decoction (1 dose daily until progression)	62.5	25	NA	NA	87.5	1
		32		Best supportive care	50	21.9	NA	NA	40.6	
Chai *et al.*, 2011 [27]	IIIB, IV	32	First-line chemotherapy	Xiao Ji Yin decoction (1 dose daily until progression)	40.1	NA	6.4	5	NA	3
		32		Best supportive care	8.9	NA	3.2	2.5	NA	
Xi *et al.*, 2011 [28]	IIIB, IV	44	First-line chemotherapy	He Chan tablet (0.25 g, 3 times daily, days 1–21, 3 cycles)	NA	NA	NA	5.67	90.9	2
		34		Follow-up	NA	NA	NA	4.12	58.8	
Zou *et al.*, 2011 [29]	IIIB, IV	32	First-line chemotherapy	Fu Zheng Kang Ai decoction (1 dose daily until progression)	50	NA	15.1	6.2	81.2	3
		32		Best supportive care	22	NA	8.1	4.1	43.8	
Yu *et al.*, 2012 [30]	III, IV	30	First-line chemotherapy	Fei Tai capsule (2 g, 3 times daily, days 1–21, 3 cycles)	NA	NA	NA	6.23	53.4	3
		30		Follow-up	NA	NA	NA	4.67	26.7	
Liang *et al.*, 2013 [31]	IIIB, IV	35	First-line chemotherapy	Rong Yan capsule (1.5 g, 3 times daily until progression)	49.8	NA	6.23	4.8	NA	3
		35		Best supportive care	14	NA	2.7	2.37	NA	
Yang *et al.*, 2013 [32]	III, IV	40	Gemcitabine, vinorelbine, or paclitaxel plus cisplatin	Fu Zheng Xiao Ji Yin (1 dose daily until progression)	NA	NA	NA	7.5	85	3
		40		Follow-up	NA	NA	NA	4.8	60	
Zeng *et al.*, 2013 [33]	IV	32	First-line chemotherapy	Shen Yi capsule (20 mg, 2 times daily until progression)	NA	NA	NA	6.5	65.6	3
		35		Follow-up	NA	NA	NA	6.2	51.4	
Huang *et al.*, 2014 [34]	III, IV	43	First-line chemotherapy	Fu Zheng Hua Du decoction (1 dose daily until progression)	32.4	NA	NA	7.3	90.7	2
		42		Best supportive care	35.3	NA	NA	4.5	71.4	
Shao *et al.*, 2014 [35]	IIIB, IV	50	First-line chemotherapy	Compound canth capsule (0.75 g, 2 times daily until progression)	56.43	24.2	NA	NA	NA	2
		50		Best supportive care plus placebo	53.44	19.7	NA	NA	NA	

TABLE I Continued

Reference	TNM stage	Pts (*n*)	Therapy		Survival rate (%)		Median survival (months)		KPS	Jadad scale
			First line	Maintenance	1-Year	2-Year	Overall	Progression-free		
Gao *et al.*, 2015 [36]	III, IV	31	First-line chemotherapy	Sha Shen Mai Dong decoction (1 dose daily until progression)	NA	NA	NA	7.29	83.8	2
		32		Follow-up	NA	NA	NA	4.9	50	
Liu *et al.*, 2015 [37]	IIIB, IV	36	First-line chemotherapy	Yangyin Qingfei Xiaoji decoction (1 dose daily until progression)	63.8	NA	NA	2.9	94.4	3
		36		Follow-up	61.1	NA	NA	2.2	75	
Tian *et al.*, 2015 [38]	III, IV	19	Cisplatin- or carboplatin-based chemotherapy	Yang Yin Yi Qi decoction (1 dose daily until progression)	NA	NA	NA	6.3	68.4	3
		18		Follow-up	NA	NA	NA	4.9	61.1	
Han *et al.*, 2016 [39]	IIIB, IV	53	First-line chemotherapy	Self-made TCHM (1 dose daily until progression)	NA	NA	NA	5.4	NA	3
		53		Best supportive care	NA	NA	NA	4.6	NA	
Wang *et al.*, 2016 [40]	III	40	Gemcitabine–cisplatin with synchronous RT	Zilongjin tablet (2.6 g, 3 times daily until progression)	72.2	55.6	NA	NA	82.5	3
		38		Placebo	54.5	32.7	NA	NA	68.4	

Pts = patients; KPS = Karnofsky performance status; NA = not available; RT = radiation therapy.

was reported to be associated with a numeric increase in grades 3 and 4 AEs.

In an RCT [42] in which TCM maintenance treatment alone was compared with maintenance chemotherapy (pemetrexed, docetaxel, or gemcitabine alone), effects on time to progression (3.0 months vs. 2.3 months) and OS (21.5 months vs. 18.8 months, $p = 0.601$) were similar with both strategies, but TCM was also associated with improved patient QOL and a higher 1-year survival rate. In our study, compared with BSC, placebo, or observation groups, oral

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 any of best supportive care, observation, or placebo. (A) Overall survival. (B) Progression-free survival. (C) One-year survival. (D) Two-year survival. hr = hazard ratio; CI = confidence interval; TCM = Traditional Chinese Medicine.

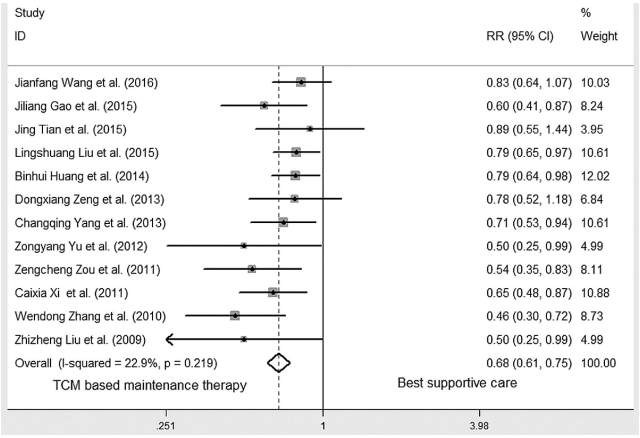

FIGURE 3 Forest plot of performance status improvement, comparing oral Chinese herbal medicine–based maintenance treatment alone with any of best supportive care, observation, or placebo. RR = risk ratio; CI = confidence interval; TCM = Traditional Chinese Medicine.

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 KPS ($p < 0.001$). 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 the KPS was significantly improved in patients who received oral CHM–based maintenance treatment ($p < 0.001$). Seven trials [25,29,30,34,35,37,39] 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 trials [31–33] 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

This study was funded by the Shanghai Minhang Municipal Planning Commission of Science and Research Fund (no. 2014MW24); the National Natural Science Fund (no. 81072740); the National Scientific Research Project of National Traditional Chinese Medicine (no. 201307006); the Science and Technology Commission of Shanghai Municipality (nos. 16401970700, 16401970701, 16401970704); and the Fund of Shanghai University of Traditional Chinese Medicine (no. 2015YSN37).

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.

AUTHOR AFFILIATIONS

*Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, †Department of Oncology, Shanghai Hospital of Integrated Traditional Chinese Medicine and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, ‡Department of Oncology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, and §Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, P.R.C.; and ‖Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD, U.S.A.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115–32.
3. Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:359–86.
4. Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T, Pignon JP. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. *JAMA* 2004;92:70–84.
5. Zarogoulidis K, Zarogoulidis P, Darwiche K, *et al.* Treatment of non–small cell lung cancer (NSCLC). *J Thorac Dis* 2013;5(suppl 4):389–96.
6. Brodowicz T, Krzakowski M, Zwitter M, *et al.* on behalf of the Central European Cooperative Oncology Group. Cisplatin and

gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non–small cell lung cancer: a phase III trial. *Lung Cancer* 2006;52:155–63.
7. Pérol M, Chouaid C, Pérol D, *et al.* Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3516–24.
8. Ciuleanu T, Brodowicz T, Zielinski C, *et al.* Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–40.
9. Paz-Ares L, de Marinis F, Dediu M, *et al.* Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247–55.
10. Paz-Ares LG, de Marinis F, Dediu M, *et al.* PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2013;31:2895–902.
11. Cappuzzo F, Ciuleanu T, Stelmakh L, *et al.* on behalf of the SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–9.
12. Westeel V, Quoix, E, Moro-Sibilot D, *et al.* Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2005;97:499–506.
13. Zhang L, Ma S, Song X, *et al.* Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet* 2012;13:466–75.
14. Wang SF, Wang Q, Jiao LJ, *et al. Astragalus*-containing Traditional Chinese Medicine, with and without prescription based on syndrome differentiation, combined with chemotherapy for advanced non-small-cell lung cancer: a systemic review and meta-analysis. *Curr Oncol* 2016;23:188–95.
15. Xu W, Yang G, Xu Y, *et al.* The possibility of Traditional Chinese Medicine as maintenance therapy for advanced non–small cell lung cancer. *Evid Based Complement Alternat Med* 2014;:278917.
16. Hsiao WL, Liu L. The role of traditional Chinese herbal medicines in cancer therapy—from TCM theory to mechanistic insights. *Planta Med* 2010;76:1118–31.
17. Lin HS, Zhang Y. Evidence-based medical study of Traditional Chinese Medicine on non-small-cell lung cancer [Chinese]. *Shi Jie Ke Xue Ji Shu: Zhong Yi Yao Xian Dai Hua* 2008;10:121–5. [DOI: https://doi.org/10.3969/j.issn.1674-3849.2008.04.026]
18. Ren SR, Liao DB, Zhou XQ, Wang J. Shen Qi Fu Zheng injection combined with radiotherapy in treating 34 elderly advanced non-small-cell lung cancer patients [Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2006;26:876. [DOI: https://doi.org/10.3321/j.issn:1003-5370.2006.10.028]
19. Cai HB, Dai FG, Min QF, Shi M, Liao JX, Luo RC. Clinical study of the effects of radiotherapy in combination with Traditional Chinese Medicine on non–small cell lung cancer [Chinese]. *Di Yi Jun Yi Da Xue Xue Bao* 2001;22:1112–14.
20. Jadad AR, Moore RA, Carroll D, *e0t al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
21. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
24. Li J. A clinical comparative study of Traditional Chinese Medicine serving as consolidation treatment in patients with advanced non-small-cell lung cancer [Chinese]. *Zhongguo Fei Ai Za Zhi* 2007;10:520–2. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=faiz200706016&dbname=CJFD&dbcode=CJFQ; cited 9 July 2017]
25. Liu Z, Yu Z, Ouyang X, *et al.* Effects of Feitai capsule on progression-free survival in patients with advanced non-small-cell lung cancer [Chinese]. *Chinese Journal of Clinical Oncology* 2009;4:344–6. [DOI: http://dx.chinadoi.cn/10.3969/j.issn.1009-0460.2009.04.014]
26. Zhang W, Tang W, Zhang B, *et al.* Qingfei Xiaoyu decoction in the consolidation treatment of advanced non-small-cell lung cancer: clinical observation of 32 cases [Chinese]. *Journal of New Chinese Medicine* 2010;12:70–1. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=rend201012039&dbname=CJFD&dbcode=CJFQ; cited 9 July 2017]
27. Chai X, Yang G, Li Z, *et al.* The effect on overall survival of Xiaojiyin maintenance treatment for advanced non-small-cell lung cancer [Chinese]. *Shizhen Guo Yi Guo Yao* 2011;10:2547–8.
28. Yang G, Li Z, Tao W. Clinical observation of Hebi tablets in maintenance therapy of advanced non-small cell lung cancer [Chinese]. *Zhong Liu Fang Zhi Yan Jiu* 2011;10:1170–2. [Available online at: http://d.wanfangdata.com.cn/Periodical/zlfzyj201110020; cited 7 July 2017]
29. Zou Z. Efficacy of Fuzheng Kangai decoction as a maintenance treatment in advanced non-small-cell lung cancer [thesis, Chinese]. Guangzhou, Guangdong Province, P.R.C.: Guangzhou University of Chinese Medicine; 2011: 60. [Available online at: http://cdmd.cnki.com.cn/article/cdmd-10572-1011136251.htm; cited 7 July 2017]
30. Yu ZY, Liu ZZ, Ouyou Xiu XN, *et al.* Effect of Feitai capsule on quality of life and progression-free survival of patients with unresectable non–small cell lung cancer. *Chin J Integr Med* 2012;18:106–11.
31. Liang J, Zhang L. Survival effect of Rongyan capsule, a maintenance treatment for advanced non-small-cell lung cancer [Chinese]. *Sichuan Zhong Yi* 2013;1:100–1. [Available online at: http://www.cqvip.com/QK/95258X/201301/44633521.html; cited 7 July 2017]
32. Yang C. Adjuvant chemotherapy and maintenance therapy with Fuzheng decoction in the treatment of advanced non-small-cell lung cancer [Chinese]. *China Journal of Chinese Medicine* 2013;28:1782–4. [Available online at: http://d.wanfangdata.com.cn/Periodical/henzyxyxb201312004; cited 7 July 2017]
33. Zeng DX, Bi YZ, Sheng GF, Dong YZ, Song HL. Effectiveness and safety of single-agent ginsenoside Rg3 maintenance therapy after response to first-line chemotherapy in patients with advanced non-small cell lung cancer. *Oncology Progress* 2013;6:554–7. [Available online at: http://en.cnki.com.cn/Article_en/CJFDTOTAL-AZJZ201306015.htm; cited 7 July 2017]
34. Huang B, Zha Q, Zhou Z. Fuzheng decoction as maintenance treatment after chemotherapy in 43 cases of advanced non-small-cell lung cancer [Chinese]. *Zhongguo Shi Yan Fang Ji Xue Za Zhi* 2014;8:210–13. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=zsfx201408062&dbname=CJFD&dbcode=CJFQ; cited 7 July 2017]
35. Shao H, Chen J. Prospective study on the therapeutic effect of compound cantharide capsules in the maintenance treatment of advanced lung cancer [Chinese]. *Chinese Journal of*

Traditional Chinese Medicine and Pharmacy 2014;3: 686–8. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=zyhs201403092&dbname=CJFD&dbcode=CJFQ; cited 7 July 2017]

36. Jiliang Gao. Observation of 31 cases of non-small-cell lung cancer receiving maintenance treatment with Shashen Maidong decoction after chemotherapy [Chinese]. *Zhejiang Journal of Traditional Chinese Medicine* 2016;50:90–1. [Available online at: http://d.wanfangdata.com.cn/Periodical/zjzyzz201502008; cited 7 July 2017]
37. Liu LS, Liu JX, Shen LP, Jiang Y, Gu AQ. Effect of TCM syndrome differentiation on consolidation treatment in advanced non-small-cell lung cancer [Chinese]. *Chinese Journal of Traditional Chinese Medicine* 2015;17:1473–8. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=zzyz201517015&dbname=CJFD&dbcode=CJFQ; cited 7 July 2017]
38. Tian J, Xiao J, Wu H. Supplementing *qi* and nourishing *yin* as a maintenance treatment in non-small-cell lung cancer. *Jilin Traditional Chinese Medicine* 2015;9:904–6. [Available online at: http://d.wanfangdata.com.cn/Periodical/jlzyy201509012; cited 7 July 2017]
39. Han Y, Wang H, Xu W, *et al.* Chinese herbal medicine as maintenance therapy for improving the quality of life for advanced non–small cell lung cancer patients. *Complement Ther Med* 2016;24:81–9.
40. Wang J, Chen YL, Ping C. Clinical observations on treating 40 cases of locally advanced non-small-cell lung cancer with the Zilongjin tablet. *Chinese Journal of Traditional Chinese Medicine* 2016;8:15–17. [Available online at: http://kns.cnki.net/KCMS/detail/detail.aspx?filename=zyly201601005&dbname=CJFD&dbcode=CJFQ; cited 7 July 2017]
41. Jalal SL, Ademuyiwa FO, Hanna NH. The role of maintenance chemotherapy in advanced nonsmall cell lung cancer. *Curr Opin Oncol* 2009;21:110–15.
42. Jiang Y, Liu LS, Shen LP, *et al.* Traditional Chinese Medicine treatment as maintenance therapy in advanced non-small-cell lung cancer: a randomized controlled trial. *Complement Ther Med* 2016;24:55–62.
43. Chen YZ, Li ZD, Gao F, Zhang Y, Sun H, Li PP. Effects of combined Chinese drugs and chemotherapy in treating advanced non–small cell lung cancer. *Chin J Integr Med* 2009;15:415–19.
44. Li SG, Chen HY, Ou-Yang CS, *et al.* The efficacy of Chinese herbal medicine as an adjunctive therapy for advanced non–small cell lung cancer: a systematic review and meta-analysis. *PLoS One* 2013;8:e57604.
45. Konkimalla VB, Efferth T. Evidence-based Chinese medicine for cancer therapy. *J Ethnopharmacol* 2008;116:207–10.
46. Flower A, Witt C, Liu JP, Ulrich-Merzenich G, Yu H, Lewith G. Guidelines for randomised controlled trials investigating Chinese herbal medicine. *J Ethnopharmacol* 2012;140:550–4.
47. Tang WR, Yang SH, Yu CT, *et al.* Long-term effectiveness of combined treatment with traditional Chinese medicine and Western medicine on the prognosis of patients with lung cancer. *J Altern Complement Med* 2016;22:212–22.