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www.elsevier.com/locate/issn/20954964

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• 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

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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

studies were of high quality and 6 studies were of low quality, according to the modified Jadad scale. When the TCMH plus EGFR-TKI treatment groups were compared with the EGFR-TKI control groups the meta-analysis demonstrated a statistically significant higher ORR (RR 1.34; 95% CI 1.15 to 1.57; $P=0.0002$), DCR (RR 1.18; 95% CI 1.09 to 1.27; $P<0.0001$), one-year survival rate (RR 1.21; 95% CI 1.01 to 1.44; $P=0.04$), 2-year survival rate (RR 1.91; 95% CI 1.26 to 2.89; $P=0.002$) and improved or stable KPS (RR 1.38; 95% CI 1.26 to 1.51; $P<0.0001$). Severe toxicity for rash was decreased (RR 0.55; 95% CI 0.32 to 0.94; $P=0.03$), as were nausea and vomiting (RR 0.17; 95% CI 0.04 to 0.72; $P=0.02$) and diarrhea (RR 0.46; 95% CI 0.24 to 0.89; $P=0.02$). Sensitivity analysis indicated that findings of the meta-analysis were robust to study quality. In the funnel plot analysis, asymmetry was observed, and publication bias was indicated by Egger's test ($P=0.03$).

CONCLUSION: TCMH intervention can increase efficacy and reduce toxicity when combined with EGFR-TKI for advanced NSCLC, although this result requires further verification by more well designed studies.

KEYWORDS: drugs, Chinese herbal; receptor, epidermal growth factor; protein-tyrosine kinases; non-small cell lung cancer; randomized controlled trials; review; meta-analysis

[http://dx.doi.org/10.1016/S2095-4964\(14\)60034-0](http://dx.doi.org/10.1016/S2095-4964(14)60034-0)

Liu ZL, Zhu WR, Zhou WC, Ying HF, Zheng L, Guo YB, Chen JX, Shen XH. 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. *J Integr Med*. 2014; 12(4): 346–358.

Received January 25, 2014; accepted April 15, 2014.

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1 Introduction

As one of the most common malignancies, lung cancer has become the leading cause of cancer-related mortality worldwide, of which non-small cell lung cancer (NSCLC) accounts for 80%–90%^[1]. Moreover, when diagnosed, the great majority of NSCLC cases have already reached inoperable stages of III and IV.

If the patients cannot tolerate chemotherapy or if it yields poor results, they can undergo treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib. Mutations in EGFR and never having smoked are effective predictors of treatment benefit for NSCLC patients whose progression-free survival can be significantly improved by first-line EGFR-TKI monotherapy^[2–5]. The use of EGFR-TKI in combination with chemotherapy fails to show a survival advantage, however, when used sequentially, progression-free survival can be prolonged^[6–9]. EGFR-TKI maintenance treatment can significantly prolong progression-free survival^[10,11]. Second-line treatment with EGFR-TKI showed a significant survival benefit compared with placebo, and it also had similar overall survival with the standard second-line treatment, but more safe^[12,13].

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^[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^[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.

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