



Traditional Chinese Medicine treatment as maintenance therapy in advanced non-small-cell lung cancer: A randomized controlled trial[☆]



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ABSTRACT

Objectives: Maintenance therapy for patients with advanced non-small-cell lung cancer (NSCLC) is an increasingly hot topic in the field of clinical NSCLC research. This study aimed to evaluate the effects of Traditional Chinese Medicine (TCM) treatment as maintenance therapy on time to progression (TTP), quality of life (QOL), overall survival (OS) and 1-year survival rate in patients with advanced NSCLC.

Methods: This study was conducted as a randomized, controlled, open-label trial. 64 non-progressive patients who responded to initial therapy were randomized 1:1 to the TCM arm (treated with herbal injection (Cinobufacini, 20 ml/d, d1–d10), herbal decoction (d1–d21) and Chinese acupoint application (d1–d21), $n=32$) or to the chemotherapy arm (treated with pemetrexed (non-squamous NSCLC, 500 mg/m², d1), docetaxel (75 mg/m², d1) or gemcitabine (1250 mg/m², d1 and d8), $n=32$). Each therapy cycle was 21 days. They were repeated until disease progression, unacceptable toxicity, or until the patients requested therapy discontinuation. The primary end point was TTP; the secondary end points were QOL, OS and 1-year survival rate. “Intention-to-treat” analysis included all randomized participants.

Results: TCM treatment prolonged median TTP for 0.7 months compared with chemotherapy, but it was not statistically significant (3.0 months vs. 2.3 months, $P=0.114$). Median OS time for TCM treatment did not offer a significant advantage over for chemotherapy (21.5 months vs. 18.8 months, $P=0.601$). 1-year survival rate of TCM treatment significantly improved than that of chemotherapy (78.1% vs. 53.1%, $P=0.035$). TCM treatment can significantly improve QOL when compared to chemotherapy as assessed by EORTC QLQ-C30 and EORTC QLQ-LC13 QOL instruments.

Conclusions: TCM maintenance treatment had similar effects on TTP and OS compared with maintenance chemotherapy, but it improved patients' QOL and had higher 1-year survival rate. TCM Maintenance treatment is a promising option for advanced NSCLC patients without progression following first-line chemotherapy.

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Abbreviations: CR, complete response; CTLA-4, cytotoxic lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GAP, Good Agricultural Practice; GMP, Good Manufacturing Practice; NCCN, National Comprehensive Cancer Network; NSCLC, non-small-cell lung cancer; ORR, overall responsive rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; PS, performance status; QOL, quality of life; SD, stable disease; TCM, Traditional Chinese Medicine; TTP, time to progression; SAE, serious adverse events.

[☆] This study was registered with Chinese Clinical Trial Register and at www.chictr.org (ChiCTR-TRC-10001017).

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1. Introduction

Previous researches showed that four to six therapy cycles of first-line platinum-based chemotherapy in advanced non-small-cell lung cancer (NSCLC) had reached a therapeutic plateau, with a median overall survival (OS) of 8–10 months, a median time to progression (TTP) of 3–5 months, and an overall responsive rate (ORR) of approximately 30%.^{1,2} After first-line chemotherapy, non-progressive patients entered in the “watch and wait” period until disease progression, and then patients received second-line treatment. Nevertheless, a large number of patients might lose the opportunity to receive effective therapy after first-line treatment because of the declining performance status (PS) and symptom-atic deterioration.³ Patients may be more likely to proceed to additional therapy if it is offered immediately after first-line treatment.³

Maintenance therapy as a new therapy strategy which is a prolonged treatment through the “watch and wait” period has been investigated. Maintenance therapy is continued until disease progression, unacceptable toxicity, or until the patients request therapy discontinuation. The aim of maintenance therapy is to delay disease progression and prolong survival, without affecting patients’ quality of life (QOL). To maintain QOL and permit prolonged treatment administration, studies of maintenance therapy generally use well-tolerated, single-agent regimens.⁴

Maintenance chemotherapy consists of either a drug included in the induction regimen or another non-cross-resistant agent defining the “early second-line”.^{5–7} Recently, maintenance trials with gemcitabine, docetaxel and pemetrexed have shown promising outcomes in terms of progression-free survival (PFS) or TTP, and only pemetrexed has demonstrated an OS benefit.^{3,8–11} Based on these trials published so far, maintenance chemotherapy is a promising option for advanced NSCLC patients without progression following first-line chemotherapy, especially pemetrexed for non-squamous NSCLC. However, these clinical benefits must be weighed against cumulative toxicity, inconvenience of chemotherapy, and costs. A review of maintenance studies also suggested that no clinical trial had demonstrated significant improvement in global QOL with maintenance therapy compared with observation alone.⁴ According to these considerations, patients or doctors maybe choose to continue for a defined course of the treatment other than until disease progression in maintenance chemotherapy period.

In China, Traditional Chinese Medicine (TCM) is well accepted as a complementary and alternative therapy for NSCLC patients. Studies in China demonstrated that TCM treatment could control the tumor size, improve the clinical symptoms, promote patients’ QOL, and was effective in prolonging survival rate.^{12–17} In view of these results, we believe that TCM treatment may be a strong candidate for investigation in the maintenance setting. Thus, we designed the study to see whether maintenance therapy with TCM treatment versus chemotherapy would improve TTP, QOL, OS and 1-year survival rate in advanced NSCLC patients.

In consideration of cumulative toxicity, financial burden, and whether maintenance TCM has similarly effects or is better than maintenance chemotherapy, we compared TCM versus chemotherapy as maintenance and not TCM in combination with chemotherapy versus chemotherapy alone.

2. Methods

2.1. Study design

This study was conducted as a randomized, controlled, open-label trial. Subjects who responded to first-line platinum-doublet chemotherapy were randomized 1:1 to either TCM arm (treated

with herbal injection (Cinobufacini, 20 ml/d, d1–d10), herbal decoction (d1–d21) and Chinese acupoint application (d1–d21)) or chemotherapy arm (treated with pemetrexed (non-squamous NSCLC, 500 mg/m², d1), docetaxel (75 mg/m², d1) or gemcitabine (1250 mg/m², d1 and d8)). Each therapy cycle was 21 days. Therapy cycles were repeated until disease progression, unacceptable toxicity, or until the patients requested therapy discontinuation. Both TCM arm and chemotherapy arm patients with progression after maintenance therapy had option to receive subsequent anti-cancer treatments. The primary end point was TTP; the secondary end points were QOL, OS and 1-year survival rate.

2.2. Participants

Subjects with advanced (stage IIIB/IV) NSCLC were recruited from Longhua Hospital affiliated to Shanghai University of TCM and Shanghai Chest Hospital. TCM syndromes of them were Deficiency of Yin, Deficiency of Qi and Deficiency of both Qi and Yin.

2.3. Diagnostic criteria

The diagnostic criteria of NSCLC in this study was taken from the guidelines published by the National Institute for Clinical Excellence (NICE).¹⁸

TNM stage of NSCLC: According to the staging system of 2009 International Union against Cancer (UICC), version 7.

2.4. Syndrome differentiation criteria

Syndrome differentiation criteria based on “The Guiding Principles of Clinical Research of New Chinese Medicine (trial)”¹⁹ and “Shanghai diagnosis and treatment routine of TCM Syndrome”.²⁰ Three syndromes of TCM were as follows:

Qi deficiency syndrome contained main symptoms of coughing, phlegm, poor appetite, spiritlessness and weakness, light and plump tongue; secondary symptoms of spontaneous sweating, loose stool, soft slippery pulse.

Yin deficiency syndrome contained main symptoms of coughing, less phlegm, dry mouth, red tongue; secondary symptoms of night sweating, heartburn and insomnia, low fever, thread and rapid pulse.

Qi and Yin deficiency syndrome contained main symptoms of coughing, less phlegm, shortness of breath, spiritlessness and weakness, thirst without the desire to drink; secondary symptoms of spontaneous sweating, night sweating, reddish tongue or tongue with teeth marks, thread and weak pulse.

The diagnosis could be made with the conditions of at least two of the main symptoms and one of the secondary symptoms.

2.5. Inclusion criteria

The inclusion criteria were: diagnosis with primary bronchogenic carcinoma confirmed NSCLC via cytological or pathological examination; patients who were at TNM stage IIIB/IV, including patients with postoperative recurrence and metastasis; patients who were at an age equal or older than 18 years old but equal or less than 80 years old; TCM syndromes were Yin deficiency, Qi deficiency or Qi and Yin deficiency; patients who had completed four cycles of first-line chemotherapy; achieving a maximum tumor response, including complete response(CR)/partial response (PR)/stable disease(SD); Eastern Cooperative Oncology Group (ECOG) PS of two or less; life expectancy of at least 6 months; normal hematological function with total neutrophil count > 1.5 × 10⁹/L and platelets > 80 × 10⁹/L; normal liver function and kidney function.

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