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Chinese herbal medicine as maintenance therapy for improving the quality of life for advanced non-small cell lung cancer patients

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ABSTRACT

Objective: The purpose of the study was to assess the efficacy and safety of using Chinese herbal medicine (CHM) as maintenance therapy considering the survival of advanced non-small-cell lung cancer (NSCLC) patients after first-line conventional platinum-based chemotherapy.
Design: An open-label, randomized, controlled trial.
Setting: Four hospitals in China.
Interventions and main outcome measures: A total of 106 patients were eligible and randomly divided into two groups from four hospitals in China. Both groups received the best supporting care (BSC). Additionally, patients in the trial group were given CHM every day until the disease became aggravated or the patients resigned. The study took both progression-free survival (PFS) and quality of life (QOL) as the primary outcomes to comprehensively evaluate the effect of the treatment. QOL was measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) 4.0 questionnaire. Side effects and safety were evaluated at the same time.
Results: Of the 106 patients, 99 completed the study. After treatment and follow-up for PFS, there were no significant differences in the median PFS time and the 6-month PFS probability between the two groups. However, the 3-month PFS probability in the trial group was significantly higher than that in the control group (FAS, PPS: $P < 0.01$). For QOL, there were significant differences between the two groups in the following: physical well-being, emotional well-being, functional well-being, lung cancer symptom domain and total score of the FACT-L4.0 (FAS, PPS: $P < 0.05$). There was no significant difference in the social well-being domain. No serious adverse side effects to the treatment were observed.
Conclusions: CHM is well tolerated and may improve the QOL of advanced NSCLC patients. CHM is worth studying in future investigations.

1. Introduction

Lung cancer is the first leading cause of cancer-related death worldwide.[1,2] It is estimated that more than one hundred million people die from lung cancer each year.[3] Moreover, the morbidity and mortality of lung cancer are increasing annually in China,[4,5] indicating a major threat to health in this country. Non-small cell lung cancer (NSCLC) accounts for over 80% of newly diagnosed lung cancers.[6] The only way to cure patients with NSCLC is to completely remove the tumor in a surgical procedure. As typical symptoms are imperceptible during the early stages, approximately two-thirds of patients are unresectable because of metastatic or locally advanced disease at their initial diagnosis.[7] If untreated, the median survival time for NSCLC is only 4–5 months.[8] Currently, the standard first-line treatment for advanced NSCLC is platinum-based combination regimen chemotherapy, which ranges in efficiency from 20% to 40%,[9] adding approximately 3 months to the median progression-free survival (PFS) time[10] and 8–10 months to the

Abbreviations: CHM, Chinese herbal medicine; NSCLC, non-small-cell lung cancer; BSC, best supporting care; PFS, progression-free survival; QOL, quality of life; FACT-L, Functional Assessment of Cancer Therapy-Lung; FAS, full analysis set; PPS, per-protocol analysis set.

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median overall survival (OS) time.[11,12] In accordance with the previous standard treatment modalities, first-line chemotherapy should be administered for no more than six cycles in advanced NSCLC patients, and after documented disease control,[9] patients are kept waiting and under observation[13] to restore their performance status (PS) and immune system. If there is disease progression, patients are recommended a second-line treatment. However, the second-line chemotherapy has lower efficiency, short-term remission, and quicker disease progression.[14] In addition, approximately 20–80% of patients have no opportunity to receive second-line chemotherapy.[15]

Maintenance therapy has emerged in recent years as a novel therapeutic paradigm for advanced NSCLC that aims to sustain a clinically favorable state after first-line chemotherapy. It refers to continued use of the drug treatment until disease progression or the occurrence of intolerable adverse events (AEs) if there is a stable disease (SD) or better response after completion of the first-line chemotherapy. The theoretical foundation of the therapy originates from the Goldie–Coldman theory,[16] which states that resistant and slowly growing cancer cells remain after first-line chemotherapy, which has primarily killed the sensitive and rapidly proliferating cells. Use of different non-cross-resistant chemotherapy regimens is effective in eradicating the remaining resistant cancer cells. In recent years, there are a number of clinical studies on maintenance therapy, which has been shown to have a potential benefit in prolonging PFS.[17–21] The National Comprehensive Cancer Network (NCCN) version 2.2013 recommends several cytotoxic agents and target agents for use in maintenance therapy.[15] However, careful consideration of maintenance therapy is still required, and the following should be noted: one of the major goals of maintenance therapy is increasing the quality of life (QOL), but most studies have not evaluated the QOL; the selection of maintenance therapy depends on histologic type, PS, genetic alternations and other factors, indicating that only some patients can benefit from it; continuing cytotoxic agents will result in cumulative toxicity, damage immune function, lower QOL and increase the risk of drug resistance; and the prices of chemotherapy and targeted drugs are very high such that a proportion of patients cannot afford them, especially in a developing country. Therefore, the current maintenance therapy in advanced NSCLC still excites debates and requires for further research, which presents opportunities for Chinese herbal medicine (CHM) to treat the disease and act as maintenance therapy at the same time.

CHM, which has a long history in China and has accumulated rich experience in the treatment of malignant tumors, is widely used in the treatment of advanced NSCLC. Some studies have shown that CHM combined with chemotherapy, radiotherapy and targeted therapy can alleviate side effects of cancer treatment, enhance short-term therapeutic effects, stabilize the disease and improve the long-term efficacy of treatment.[22–24] In regards to patients who cannot accept conventional therapy, CHM can be used alone to ameliorate symptoms, improve QOL, and prolong the survival time with a tumor.[25] CHM shows an irreplaceable role in the comprehensive treatment of advanced NSCLC.[26] In fact, a majority of advanced NSCLC patients receive CHM as consolidation therapy after completion of first-line chemotherapy, which actually includes maintenance therapy. CHM has a definite advantage, including stabilizing tumor growth, relieving symptoms and mild adverse events, which can help patients to "survive with a tumor".[27,28] It also meets a criterion that the optimal maintenance therapy agent should be associated with an improvement in outcome, have good patient tolerance, and be devoid of cumulative toxicities. Furthermore, CHM is not limited to treating patients with histologic type, PS, or genetic alternations and is subsequently very suitable for maintenance therapy. In China, some studies have reported that CHM serving as maintenance therapy can prolong PFS and improve the QOL.[29,30] However, studies about CHM as maintenance therapy are limited, and almost all of the studies were small sample, non-randomized controlled trials (RCT), which lack strong evidence to prove that CHM can have an effective role as maintenance therapy. According to our previous pilot study, 28 cases of advanced NSCLC patients accepted CHM and best supported care (BSC) as maintenance therapy; the median PFS was 5.0 months, which showed a significant benefit compared with the literature reporting placebo and BSC as maintenance therapy (median PFS was 2.6 months).[31] Therefore, a multicenter randomized controlled study was carried out to evaluate the efficacy and safety of using CHM as maintenance therapy.

2. Patients and methods

2.1. Study design

This was a multicenter, randomized, open-label, controlled trial. The study was approved by the medical Ethics Committees of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, and written informed consent to participate in the study was received by all of the participating patients. The study was conducted following the principles of the Declaration of Helsinki, good clinical practices and local regulations.

2.2. Patients

2.2.1. Eligibility criteria included the following

No more than one week from completion of 4–6 cycles of platinum-based first-line induction therapy[32] with radiographic evidence of a complete response (CR) or partial response (PR) or SD; a histologic or cytological diagnosis of stage IIIB or stage IV NSCLC (using the seventh edition TNM staging system available at the time the study was conducted)[33]; between the ages of 18 and 75 years old; an estimated life expectancy of at least 3 months; an Eastern Cooperative Oncology Group (ECOG) PS of 0–2; at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)[34]; and adequate liver and kidney function.

2.2.2. Exclusion criteria included the following

Known brain metastasis (except for stable metastases being treated with stereotactic radiation or surgery); any serious concomitant systemic disorder, such as unstable angina pectoris, myocardial infarction, significant cardiac arrhythmia, stroke, or severe hypertension; pregnancy or breast-feeding; mental disease; allergies to any components of the study drug; unable to consent or comply with the protocol; concurrent or planned chemotherapy or targeted maintenance treatment or any other clinical and biochemical test; and unwilling or unable to complete QOL questionnaires and give written consent.

2.3. Treatment

Patients in the control group were treated with BSC recommended by the NCCN Cancer Palliative Care Guide (Version 1.2010)[35] at any time during the study if it was felt to be in the patient's best interest. This included, but was not restricted to, analgesics, paracentesis, psychosocial care, nutritional support, or blood transfusions. Localized radiotherapy to alleviate pain was allowed, provided that the radiation dose was in the palliative range. However, no other anticancer therapies were permitted during the study. Strict quality control measures for BSC were implemented and monitored.