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Commentary

Is traditional Chinese herbal medicine effective in prolonging survival times in extensive-stage small-cell lung cancer patients?

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1. Focal article

Rui Liu, Shu Lin He, Yuan Chen Zhao, Hong Gang Zheng, Cong Huang Li, Yan Ju Bao, Ying Gang Qin, Wei Hou, Bao Jin Hua. Chinese herbal decoction based on syndrome differentiation as maintenance therapy in patients with extensive-stage small-cell lung cancer: an exploratory and small prospective cohort study. *Evid Based Complement Alternat Med* 2015;2015:601067. doi:10.1155/2015/601067. Epub 2015 Mar 1.

2. Aim

The aim of this study is to evaluate the effect of traditional Chinese herbal medicine (TCHM) and the impact of treatment duration on both progression-free survival (PFS) and postprogression survival (PPS) in patients with extensive-stage small-cell lung cancer (ES-SCLC). Additionally, this study attempts to reflect clinical practice by prescribing individualized TCHM on the basis of syndrome differentiation.

3. Design

This was an exploratory and small prospective cohort study using TCHM as the maintenance therapy alongside standard comprehensive treatments for ES-SCLC.

4. Setting

The study included 28 patients with ES-SCLC who underwent TCHM treatment at the Oncology Department of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China from January 2010 to March 2012.

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5. Participants

A total of 28 patients [22 men, 6 women; median age, 61 years (42–75)] were enrolled. The median number of metastatic sites was 2 (range, 1–6). All participants had undergone first-line chemotherapy, consisting of four to six cycles of either cisplatin or carboplatin combined with etoposide, and were considered responsive to therapy. The major symptoms of the participants were fatigue (75%) and cough (64%).

The participants were divided into two groups: (1) Group A: 16 participants undergoing TCHM during and after chemotherapy and (2) Group B: 12 participants undergoing TCHM only after, but not during, chemotherapy.

The inclusion criteria were as follows:[1] (1) The patients should have a histologically or cytologically confirmed diagnosis of ES-SCLC according to Veterans Administration Lung Study Group staging criteria. This included patients with pleural or pericardial effusions and/or supraclavicular lymphadenopathy. (2) They should have an effective response after first-line chemotherapy, including complete response, partial response, or stable disease. (3) They should have a combination of platinum and etoposide as first-line chemotherapy. (4) They should have a life expectancy of at least 3 months. (5) They should have the ability to swallow and retain oral medication. (6) They should have a World Health Organization performance status of 0–2, aged > 18 years and < 80 years. (7) They should have adequate hematologic, hepatic, and renal function and coagulation parameters.

6. Intervention

(1) Individualized TCHM was prescribed based on syndrome differentiation. The median total duration of treatment was 12.2 months (3.2–27 months).
(2) The period encompassing both treatment and follow-up was divided into two phases, as shown below. The treatment period is detailed in Table 1. (i) First phase: From the beginning of TCHM treatment until cancer progression. (ii) Second phase: From cancer progression until either death or the end of the study (September 2013)
(3) The basic syndromes and the respective prescriptions for these syndromes are as follows:
Qi deficiency: radix Astragali 45 g/d, radix Pseudostellariae 15 g/d, Atractylodes 15 g/d, Wolfiporia extensa 20 g/d, and pericarpium Citri reticulatae 6 g/d.
Yin deficiency: *Adenophora elata* 30 g/d, *radix Ophiopogonis* 12 g/d, mulberry leaf 12 g/d, *Scrophularia ningpoensis* 12 g/d, and gypsum 45 g/d.
Phlegm syndrome: *fructus Trichosanthis* 20 g/d, *Allium macrostemon* 15 g/d, almond 10 g/d, *Platycodon grandiflorus* 30 g/d, and *Pinellia ternata* 10 g/d—this prescription was modified depending on the individual's symptoms, signs, and status.
(4) Comprehensive treatment consisted of TCHM, chemotherapy, and radiotherapy.
(5) At least 1 year of TCHM treatment was recommended; however, the duration of treatment was decided by the participants.

Table 1 – TCHM treatment duration and participants number in each phase

Number of TCHM treatment	Median months(range)	Number of patients
Taking TCHM during and after chemotherapy	4.7 (2.6-11.1)	16
Taking TCHM after chemotherapy	2.4 (1-10.7)	12
Total treatment time	12.2 (3.2-27)	28
≥ 12 mo	17.2 (12.4-27)	15
< 12 mo	5.3 (3.2-10.5)	13
First phase treatment time	3.4 (1-11.1)	28
≥ 3 mo	6.7 (3.4-11.1)	15
< 3 mo	1.8 (1-3)	13
Second phase treatment time	7.0 (1-22.5)	27
≥ 7 mo	12.7 (7.3-16.7)	13
< 7 mo	2.6 (1-7.0)	14

TCHM, traditional Chinese herbal medicine.

7. Main outcome measures

The primary endpoint was PFS, defined as the "time from the beginning of CHD treatment until disease progression or death from any cause and confirmed on the last CT before progressive disease."[1]

The secondary endpoints were as follows: (1) PPS; (2) 24-week PFS rate; (3) overall survival (OS); (4) 1-year survival rate; and (5) functional assessment. PPS was defined as "the time from disease progression to death or study conclusion (September 2013)."[1] OS was defined as "the time from the date of first-line treatment until death or the study deadline."[1] Adverse events were also recorded.

8. Main results

(1) The median total follow-up period was 14 months (range: 8–27 months). All patients survived the first phase. The median follow-up period during the first phase was 3.4 months (range, 1–11.1 months). During the second phase, 21 patients died due to cancer progression, while one died due to infection and one due to heart failure. The 24-week PFS rate was 60.7%.
(2) The median PFS periods were 7 months in Group A and 6.2 months in Group B; this difference was not significant [hazard ratio = 0.88; 95% confidence interval (CI) = 0.41–1.36].
(3) During the first phase, the median PFS period was significantly longer in patients who had received TCHM for ≥ 3 months than in those who received TCHM for < 3 months (8.7 months vs. 4.5 months; hazard ratio = 0.52; 95% CI 0.41–0.99).
(4) During the second phase, the median PPS period was significantly longer in patients who had received TCHM for ≥ 7 months than in those who received this treatment for < 7 months (11.7 months vs. 5.1 months; hazard ratio = 2.32; 95% CI = 1.90–2.74).

(5) During the entire follow-up period, the median PPS period was significantly longer in patients who had received TCHM for ≥ 12 months than in those who had done so for < 12 months (13.1 months vs. 5.6 months; hazard ratio = 2.34; 95% CI = 1.91–2.77).
(6) Adverse events: During chemotherapy, bone marrow suppression was lower in Group A (TCHM and chemotherapy) than in Group B (chemotherapy alone), as evidenced by the differing rates of leukopenia (44% vs. 75%) and anemia (19% vs. 50%). Fatigue was also less common in Group A (19% vs. 91%).

9. Authors' conclusions

The authors argued that, in cases where first-line chemotherapy is effective, TCHM may prolong PPS and PFS of ES-SCLC patients. Furthermore, they contended that concurrent treatment with TCHM and first-line chemotherapy was particularly effective, as it protected against bone marrow suppression and fatigue. They also claimed that the effect of TCHM is related to the duration of treatment and recommended implementation of TCHM as soon as possible, in order to lengthen the treatment duration. They also suggested the minimum duration of TCHM treatment before progression to exceed 3 months and the total duration to exceed 12 months. This study may provide a basis for future TCHM clinical trials that employ syndrome differentiation.

10. Comment/critique

Lung cancer is a major cause of cancer-related death.[1] It is of two main types: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC);[2] approximately 15% of lung cancers are of the SCLC kind.[1] The 5-year survival rate in NSCLC is about 25%,[2] whereas in SCLC it is 1–5%, mainly because 60–70% of SCLC patients have metastases in multiple sites; common loci include the bone marrow, brain, bone, and liver.[2] Both survival time and quality of life (QOL) are important factors in lung cancer treatment,[2] while the cancer stage is the most important factor in cancer prognosis.

In recent years, the number of studies addressing cancer treatment using traditional East Asian medicine has increased.[3] These investigations have addressed several pressing problems, such as improving treatment response rate, reducing the toxicity and side effects of standard cancer therapy, and elucidating unpredicted interactions between conventional therapy and herbal medicines.[3] In addition, several studies have investigated the effect of traditional East Asian medicine on QOL in cancer patients. For example, in a systematic review of the use of TCHM to treat cancer-related fatigue, the Jianpi Yiqi Huatan decoction or *Ganoderma lucidum* was found to reduce cancer-related fatigue significantly.[4] In a pragmatic acupuncture trial conducted on 302 breast cancer patients, those receiving acupuncture treatment experienced a better QOL than the usual-care group, as evaluated using the Functional Assessment of Cancer Therapy—Breast Cancer.[5] The general fatigue score, evaluated using the Multidimensional Fatigue Inventory, was also lower in the acupuncture group.[5]

In a randomized clinical trial addressing the use of herbal medicine in 118 NSCLC patients, those receiving the Feiji decoction, for soothing the liver, as well as both psychotherapy and chemotherapy experienced an improved QOL as compared to those receiving chemotherapy alone. QOL was assessed using the European Organization for Research and Treatment of Cancer QOL Questionnaire LC-43.[6]

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)-targeted treatment is the standard therapy for advanced SCLC.[7] In a systematic review, it was found that the use of TCHM in combination with EGFR-TKI resulted in higher 1- and 2-year survival rates than did the use of EGFR-TKI alone. Moreover, TCHM improved or stabilized Karnofsky performance status and reduced treatment toxicity.[7] In another systematic review involving 15 trials and 862 patients, oral TCHM was found to improve QOL, as well as diminish anemia and neutropenia, in Stage III/IV NSCLC patients.[8]

However, fewer studies have investigated the use of traditional East Asian medicine as treatment for SCLC, which has a mean expected OS of 6–8 weeks in the absence of treatment. With combination chemotherapy using platinum and etoposide, the OS increases to a mere 7–11 months, due to a relatively short PFS of 4–6 months.[1] The cancer recurs in almost all ES-SCLC patients, causing death in 95% of cases.[1] As chemotherapy in SCLC does little to improve survival rates and has debilitating side effects,[9,10] the major goals for clinicians treating this type of cancer are (1) prolonging life expectancy and (2) easing side effects.[1] In a randomized clinical trial conducted in China, patients treated using Xidan soup combined with chemoradiotherapy had significantly improved OS compared to those treated with chemoradiotherapy alone;[11] the median OSs were 11.1 months and 7.6 months, respectively. Additionally, the 1-, 2-, and 3-year survival rates were 38.6% versus 18.2%, 18.1% versus 4.5%, and 13.6 versus 2.3%, respectively.[11] Although TCHM has been shown to improve QOL in a systematic review, the authors of the focal article claimed that higher-quality studies are needed to draw objective conclusions regarding the efficacy of TCHM in ES-SCLC.[1]

This was the first paper on TCHM that mentioned syndrome differentiation and treatment duration in the context of ES-SCLC.[1] The authors claimed that the overall 24-week PFS rate was higher in their study than in a historical control (60.7% vs. 41%), and believe that this suggests that individualized TCHM therapy improves prognosis in ES-SCLC patients who have responded to first-line chemotherapy. Thus, this article suggests that TCHM can form a part of cancer treatment and advocates adopting a new clinical research model that employs a personalized prescription method. The overall median PPS was 7.6 months; this was also longer than the previously reported postrecurrence median survival of 4–5 months.[1] Moreover, they found that TCHM treatment duration is a key factor in cancer treatment, because TCHM therapy in excess of 3 months increased PFS, implying improved sensitivity to second-line therapy.

By contrast, this study also had several limitations. First, the stage of chemotherapy during which TCHM treatment was administered did not have a significant effect on PFS compared to chemotherapy alone. Therefore, although a longer

treatment duration improved clinical outcome, the efficacy of TCHM should be investigated further. Moreover, this was an exploratory study that contained many statistical analyses, and hence, the possibility of a type-1 error cannot be excluded. For this reason, a future study should include PFS or PPS as the primary outcome. Additionally, the authors did not explain why they selected 3 months, 7 months, and 12 months as cutoff points; it is also possible that the participants did not die earlier because of shorter TCHM treatment, but might in fact have stopped TCHM treatment due to death or disease progression. In such a case, this study does not prove that individualized TCHM treatment is superior to conventional treatment for cancer patients.

In summary, the results of this cohort study should be interpreted with care, and future clinical research should focus on the causal relationship between treatment duration and clinical outcome in SCLC.

Conflicts of interest

The author has no conflicts of interest to declare.

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