• Study Protocol

Chemotherapy in conjunction with traditional Chinese medicine for survival of elderly patients with advanced non-small-cell lung cancer: protocol for a randomized double-blind controlled trial

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BACKGROUND: Traditional Chinese medicine (TCM) is considered an important complementary therapy with beneficial effects for cancer patients. Elderly patients with non-small-cell lung cancer (NSCLC) are a complex patient group with increasing co-morbidity and shrinking physiological reserve, and may derive substantial benefit from the supportive aspects of TCM. Researchers from Shanghai Longhua Hospital found that qi and yin deficiency is a common syndrome in patients with stage III or IV lung cancer. This project was designed to study the combination of single-agent chemotherapy with TCM methods of benefiting qi and yin in elderly patients with advanced NSCLC.

METHODS AND DESIGN: This is a double-blind controlled, multi-center, and prospective study with randomly selected participants from elderly NSCLC patients in China. Seventy-six patients who meet the inclusion criteria will be allocated into two groups, which will receive treatments of 3-week single-agent chemotherapy with TCM or placebo for four cycles. Progression-free survival (PFS) is the primary end point, and the secondary end points are overall survival, objective response rate, time-to-progression, and quality of life (EORTC QLQ-LC43, and TCM syndrome score). Meanwhile, other end points such as toxicity, side effects and safety of the treatments will be assessed.

DISCUSSION: Results from this study may provide evidence on the effectiveness, and parameters for the usage of single-agent chemotherapy combined with or without TCM on PFS of elderly patients with NSCLC.

TRIAL REGISTRATION: ClinicalTrials.gov. (Identifier: NCT01780181).

KEYWORDS: non-small-cell lung carcinomas; chemotherapy; traditional medicine, Chinese; progression-free survival; randomized controlled trials; study protocol

http://dx.doi.org/10.1016/S2095-4964(14)60028-5

Received April 9, 2014; accepted April 15, 2014.
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1 Introduction

Lung cancer is the top cause of cancer morbidity and mortality worldwide[1]. Non-small-cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer[2], and more than two thirds of NSCLC cases are diagnosed in persons aged 65 or older[3]. NSCLC can therefore be regarded as a disease of the elderly and the proportion of the elderly among NSCLC patients is expected to progressively increase due to the aging populations in many countries[3]. Like other solid tumors, most patients are diagnosed with advanced NSCLC that is unsuitable for surgery[3,6]. Thus, life prolongation and symptom palliation are the main treatment goals for these patients.

Systemic chemotherapy has been a mainstay of therapy for patients with advanced NSCLC. The standard first-line treatment for advanced NSCLC, in patients with good performance status, consists of platinum-based combinations. This therapy has been shown to provide a survival advantage over supportive care alone[7]. Nevertheless, in most population-based studies, a large majority of older patients are not offered chemotherapy, possibly due to negative preconceptions held by the doctors, patients and their relatives regarding treatment relevance and toxicity in older patients. For example, in the published Surveillance, Epidemiology, and End Results database[3], only 25.8% of the 21 285 patients over 66 years old, who were diagnosed with NSCLC between 1997 and 2002, received first-line chemotherapy. Elderly patients are typically excluded from large randomized clinical trials, thus there is a limited body of evidence-based data available to guide the treatment of these patients.

On the other hand, platinum-based doublets are often unsuitable for elderly patients who exhibit deficits in functional status and organ function. Older patients differ from their younger counterparts in many aspects. Ageing is associated with decreases in lean body mass, drug clearance, and marrow reserve. Furthermore, concomitant comorbidities that affect functional status, general health, and tumor symptoms are frequently present in this patient population[9].

In 1999, the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) trial demonstrated evidence of the clinical utility of chemotherapy in elderly patients with advanced NSCLC[10]. In this randomized phase III trial with 161 patients older than 70 years of age, single agent vinorelbine improved quality of life (QOL) and survival compared with supportive care alone (median survival 27 vs. 21 weeks, P<0.04). Toxicity of the therapy in this study was acceptable. Other studies have shown that gemcitabine monotherapy in elderly patients with NSCLC produced an overall response rate of 22.2% to 38.5% with minimal toxicities[11,12]. The response rate of 22.2% is comparable to that of 20.0% in the ELVIS trial. Another Italian trial of 698 patients aged 70 years was unable to demonstrate any benefit in survival for combination therapy over single agent therapy[9]. They found that the combination of vinorelbine and gemcitabine was not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (median survival time (MST) was 36 weeks for vinorelbine, 28 weeks for gemcitabine, and 30 weeks for the combination). In fact, the combination arm was slightly more toxic, although QOL was similar across the three treatment arms. Conclusions from the MILES study[9] recommended single-agent chemotherapy as standard treatment for the elderly with advanced NSCLC, until new studies can show a clear benefit for poly-chemotherapy. Based on the results of these studies, the recommendations for older patients with advanced NSCLC are to treat them with a single-agent therapy[13], the most frequently investigated being vinorelbine and gemcitabine. In comparison to vinorelbine, a randomized study demonstrated that docetaxel showed a statistically significant improvement in progression-free survival (PFS) (5.5 vs. 3.1 months) in the elderly patients[14]. But the overall survival time which favored docetaxel (10.3 vs. 6.4 months) did not reach statistical significance (hazard ratio, 0.78; 95% confidence interval, 0.56 to 1.09; P=0.65). This study represents the first phase III trial for taxane monotherapy in the elderly population with advanced NSCLC, and makes docetaxel an option in the standard treatment for these patients. In elderly patients, single-agent chemotherapy with a third-generation agent (vinorelbine, gemcitabine, or taxanes) is the recommended approach by the American Society of Clinical Oncology guidelines and international expert panels in unselected patients[15,16]. Oncologists increasingly recognize and accept the need for more aggressive treatments for elderly NSCLC patients.

Despite improvements in treatment over the past few decades, survival in patients with lung cancer remains poor, and the most appropriate regimen for elderly patients with NSCLC has not yet been established. The elderly are a complex patient group with increasing co-morbidity and shrinking physiological reserve. Careful selection of individual patients through optimal work up, and tailoring proposed treatments to accommodate co-morbidities and the likely prognosis can allow us to provide effective management of this challenging disease.

As an important complementary therapy for cancer, traditional Chinese medicine (TCM) has gradually shown its distinctive curative effect. The research team from Shanghai Longhua Hospital summarized that qi and yin deficiency syndrome is a common syndrome in lung cancer patients in stage III or IV. We designed this project in order to further study the effects of benefiting qi and yin when combined with single-agent chemotherapy on...
elderly patients with advanced NSCLC.

2 Methods and design

2.1 Study aims
The main purpose of this study is to observe whether chemotherapy combined with TCM has a better effect in prolonging PFS of elderly patients with advanced NSCLC than chemotherapy combined with placebo. This study will also compare overall survival, objective response rate (ORR), time-to-progression (TTP), QOL (EORTC QLQ-LC43, and TCM syndrome score), and safety of the intervention between the two groups.

2.2 Study design
This is a controlled, double-blind, multi-center, and prospective study with randomly selected participants among elderly NSCLC patients in China. Longhua Hospital affiliated to the Shanghai University of TCM, Shanghai Chest Hospital, and Fudan University Shanghai Cancer Center will engage into this clinical trial. Seventy-six patients who meet the inclusion criteria will be allocated into two groups, who will receive treatments of 3-week single-agent chemotherapy with TCM or placebo for four cycles (Figure 1).

2.3 Randomization and blinding
The random numbers referring to pre-configured stratified factors (stages, pathological types, ages and TCM syndromes) will be automatically generated by computer in the Shanghai Clinical Research Center. The block size and treatment assignment table will not be available to the investigators until the end of the study.

2.4 Target population and selection
Elderly patients (more than 65 years old) with stage IIIB-IV NSCLC, whose TCM syndromes are deficiency of yin, deficiency of qi and deficiency of both qi and yin.

2.4.1 Diagnostic criteria
The diagnostic criteria and TNM classification of NSCLC in this project are taken from the guidelines published by the National Institute for Clinical Excellence (NICE)[17] in April 2011.

2.4.2 Syndrome differentiation criteria
According to The Guiding Principles of Clinical Research of New Chinese Medicine (trial)[18] and Shanghai Diagnosis and Treatment Routine of TCM Syndrome[19], TCM syndrome differentiation types are as follows:

- Qi deficiency syndrome: main symptoms of weakness, poor appetite, coughing, phlegm, pale and plump tongue; secondary symptoms of spontaneous sweating, loose stools or soft slippery pulse.

- Yin deficiency syndrome: main symptoms of dry mouth, coughing, scanty phlegm, red tongue; secondary symptoms of night sweating, low-grade fever, insomnia and heartburn, thready and rapid pulse.

- Qi and yin deficiency syndrome: main symptoms of weakness, coughing, scanty phlegm, shortness of breath and thirst without desire to drink; secondary symptoms of spontaneous sweating, night sweating, reddish tongue with teeth marks, thready and weak pulse.

Figure 1 Flow diagram of the study
PFS: progression-free survival; OS: overall survival; ORR: objective response rate; TTP: time-to-progression; QOL: quality of life.
Syndrome differentiation and classification must be in accordance with at least two of the main symptoms and one of the secondary symptoms.

### 2.4.3 Inclusion criteria

Aged 65 years or older; conformed to the diagnostic criteria of stage IIIIB-IV NSCLC; TCM syndrome differentiation of qi deficiency, yin deficiency, or qi and yin deficiency; voluntary participation in this project and having signed the informed consent form; Eastern Cooperative Oncology Group performance status of two or less; life expectancy greater than 12 weeks; normal liver and kidney function; normal hematological function.

### 2.4.4 Exclusion criteria

Life expectancy fewer than 12 weeks; suffering from two or more primary malignant tumors; having received previous single-agent chemotherapy treatment; severe problems of the heart, liver or kidneys; allergic to the drugs in this study; mental or cognitive disorders that impair judgment on one’s QOL; participating in other drug trials.

#### 2.5 Sample size

Based on the current reports, for elderly patients with advanced NSCLC, the expected mean PFS (mPFS) by single-agent chemotherapy with TCM is 5.9 months. Treatment and follow-up time is 12 months, two groups for 1:1. Being lost to follow-up rate will be controlled at less than 10%. We calculated the sample size of this study for 1:1. Being lost to follow-up rate will be controlled at less than 10%. We calculated the sample size of this study by assuming validity of the previous clinical experience (α=0.05, 1-β=0.80). 76 cases (n=38 in each group) will be included to compare PFS of elderly patients with advanced NSCLC treated by single-agent chemotherapy combined with TCM or placebo.

### 2.6 Intervention

#### 2.6.1 Chemotherapy

Single-agent chemotherapy: vinorelbine 30 mg/m² on day 1 and day 8; or docetaxel 60 mg/m² on day 1; or gemcitabine 1 200 mg/m² on day 1 and day 8; every three weeks for four cycles.

#### 2.6.2 Chinese herbal medicine and placebo

There are three types of granules (Tian Jiang Ltd, Jiangyin, China) for the treatment group in this study: Benefiting-qi Recipe, including Huangqi (Radix Astragali Mongolici), Dangshen (Radix Salviae Miltiorrhizae), Baizhu (Rhizoma Atractylodis Macrocephalae), Fuling (Poria), Xianlingpi (Herba Euphorbiae Helioscopiae), and Buguzhi (Fructus Psoraleae); Benefiting-yin Recipe, including Nanshashen (Radix Adenophorae Tetraphyllae), Beishashen (Radix Glehnia), Tiandong (Radix Asparagi Cochinchinensis), Maidong (Radix Ophiopogonis), Baihe (Bulbus Lilii Viriduli), and Nüzhenzi (Herba Euphorbiae Helioscopiae), Sheliugu (Rhizoma Amorphophalli Rivieri), and Buguzhi (Fructus Psoraleae); Benefiting-qi Recipe, including Huangqi (Radix Astragali Mongolici), Dangshen (Radix Salviae Miltiorrhizae), Baizhu (Rhizoma Atractylodis Macrocephalae), Fuling (Poria), Xianlingpi (Herba Euphorbiae Helioscopiae), and Buguzhi (Fructus Psoraleae); Benefiting-yin Recipe, including Nanshashen (Radix Adenophorae Tetraphyllae), Beishashen (Radix Glehnia), Tiandong (Radix Asparagi Cochinchinensis), Maidong (Radix Ophiopogonis), Baihe (Bulbus Lilii Viriduli), and Nüzhenzi (Herba Euphorbiae Helioscopiae), Sheliugu (Rhizoma Amorphophalli Rivieri), and Buguzhi (Fructus Psoraleae).

#### 2.6.3 Syndrome differentiation-based treatment

Qi deficiency: 1 package of Benefiting-qi Recipe, 2 packages of Detoxification and Resolving Masses Recipe. Take all 3 packages twice a day, except the day of chemotherapy.

Yin deficiency: 2 packages of Benefiting-yin Recipe, 2 packages of Detoxification and Resolving Masses Recipe. Take all 4 packages twice a day, except the day of chemotherapy.

Qi and yin deficiency: 1 package of Benefiting-qi Recipe, 1 package of Benefiting-yin Recipe, 2 packages of Detoxification and Resolving Masses Recipe. Take all 4 packages twice a day, except the day of chemotherapy.

All patients allocated to the control group will be given placebo granules according to their respective syndrome classification.

#### 2.7 Outcome measures

##### 2.7.1 Primary outcome measure

PFS refers to the interval time either from the first date of medication to recurrence or metastasis being observed, or death for any reason (record according to the first event). The date of last evaluation will be recorded if patients have neither recurrence nor metastasis, unless when reaching censored data or if there is loss of follow-up.

##### 2.7.2 Secondary outcome measures

Overall survival refers to the interval time from the first date of medication to that of death for any reason. ORR is evaluated according to solid tumor curative effect evaluation standard (RECIST1.1).

TTP refers to the interval time from the first date of medication to that of recurrence and metastasis observed.

##### 2.7.3 QOL scale

EORTC QLQ-LC43 scales established by the European Organisation for Research and Treatment of Cancer will be used to evaluate the QOL prior and after intervention. Results will be assessed by a change in the score[20]. Meanwhile, the performance status of patients will be assessed.

##### 2.7.4 Assessment of TCM syndromes

According to the graded scale of lung cancer symptoms required in The Guiding Principles of Clinical Research of New Chinese Medicine treating Primary Bronchial...
Lung Cancer (2002)\textsuperscript{[23]} issued by the State Food and Drug Administration, the symptom scores will be assessed before and after each intervention.

2.7.5 Other outcome measures

2.7.5.1 Safety assessment

Based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) issued by the National Cancer Institute (NCI)\textsuperscript{[21]}, liver and kidney function, urination and stool samples, bloodwork, and electrocardiogram will be tested before and after intervention to evaluate the toxicity and side effects of each group.

2.7.5.2 Adverse events

Based on the CTCAE issued by NCI, all adverse events including toxicity and side effects must be reported. In case of serious adverse events occurring, experimental intervention should be ceased at once, and proper treatments must be provided.

2.8 Trial registration

This trial has been registered in ClinicalTrials.gov. The trial registration number is NCT01780181.

2.9 Statistical analysis

In this study, all of the data collected will be stored in a database using Microsoft Access 2007 software. Using SPSS 18.0 statistical package, statistical analysis will be conducted on an intention-to-treat basis with a 95% confidence interval. Either two-sample t tests or Wilcoxon rank sum tests for continuous data, and Chi-squared tests or Fisher’s exact tests for categorical data will be conducted for analysis of baseline characteristics. Kaplan-Meier survival analyses will be used with regard to the mPFS, and log-rank test will be used between the two groups. A significance level of 5% will be used throughout the analysis.

2.10 Ethics statement

This study has been approved by the Institutional Review Board of Shanghai Longhua Hospital (Approval Number: 2013LCSY06).

3 Discussion

The positive benefits of TCM’s usage in the treatment of lung cancer have been progressively demonstrated. The NSCLC research team from the Longhua Hospital affiliated to the Shanghai University of TCM has completed four prospective randomized clinical studies supported by China’s State Science and Technology in the past few decades. Results from these studies showed that the patients’ immune function and QOL were improved by the treatment of integrated Chinese and Western medicine as compared to the control group\textsuperscript{[22-29]}, and median survival was 417 d (13.9 months). A recent study by Guo et al\textsuperscript{[30]} enrolled 133 fully ambulant clinical outpatients treated with platinum-based chemotherapy (PBT) alone or PBT with/without second-line targeted therapy (TT), with/without TCM. They reported that 88% of TCM-treated patients (\(n=103\), PBT+TT+TCM, \(n=62\); PBT+TT-TCM, \(n=41\)) had 1-year overall survival rate with median survival time of 27 months, as compared to 27% 1-year overall survival and MST of 5.0 months for non-TCM-treated patients (\(n=30\)). Patients with chemotherapy/TT/TCM (PBT+TT+TCM, \(n=62\)), TCM without TT (PBT+TT TCN, \(n=41\)), or chemotherapy only (PBT+TT TCN, \(n=30\)), had 1-year survival rates of 94%, 78%, and 27% respectively.

Data from some studies have shown that elderly lung cancer patients in China obtain benefit from TCM. A randomized phase III trial with 91 patients demonstrated that TCM therapy can relieve the symptoms of elderly patients with advanced NSCLC, and it may extend PFS of the elderly patients\textsuperscript{[31]}. Liu et al\textsuperscript{[32]} performed a retrospective review of 103 elderly patients with advanced NSCLC receiving TCM intervention. They found that the MST of 103 elderly patients was 16.12 months and their 1-, 3-, and 5-year survival rates were 60%, 16%, and 3%, respectively. Univariate analysis showed that the significant prognostic factors were sex (\(P=0.035\)), clinical stage (\(P=0.029\)), co-morbidity (\(P=0.000\)), treatment strategies (\(P=0.018\)), and TCM intervention duration (\(P=0.000\)), and the COX regression multivariate analysis suggested that co-morbidity (\(P=0.000\)), treatment strategies (\(P=0.005\)), and TCM intervention duration (\(P=0.000\)) were the independent prognostic factors.

TCM theory and practice dictate that a positive therapeutic effect is dependent on proper syndrome differentiation. The research team from Longhua Hospital summarized that varying combinations of qi and yin deficiency syndrome are common in patients with stage III or IV lung cancer, and the methods of benefiting qi and yin should be the main treatment strategies for TCM therapy.

This paper outlines the methodology for a randomized-controlled clinical study of single-agent chemotherapy combined with Chinese medicine on the survival of elderly patients with lung cancer that adhere to the CONSORT Statement\textsuperscript{[33]}. Three types of quality-controlled granules are used according to syndrome differentiation: Benefiting-qi Recipe, Benefiting-yin Recipe, and Detoxification and Resolving Masses Recipe. Results of this study should help provide support and parameters for the use of integrative treatments in elderly patients with advanced NSCLC.

4 Authors’ contribution

Zhou, Xu, Li, and Tian were responsible for identifying the research questions, designing the study, obtaining ethics approval, the acquisition of funding and overseeing study implementation. All authors were responsible for the manuscript drafting and have read and approved the final version.
5 Acknowledgements

This work was supported by the Longhua Medical Project (D-11) and The Science and Technology Commission of Shanghai Municipality (No. 12401905700).

6 Competing interests

All the authors have no conflicts of interest.

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