Traditional Chinese Medicine Treatment as Adjuvant Therapy in Completely Resected Stage IB-IIIA Non–Small-Cell Lung Cancer: Study Protocol for a Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

Yi Jiang,[1] Ling-shuang Liu,[1] Li-ping Shen,[1] Jia-xiang Liu,[1] Ge-ning Jiang,[4] Ai-qin Gu,[5] He-cheng Li,[6] Qi Li,[2] He-gen Li,[1] Pin-xian Huang[3]

Abstract

Adjuvant chemotherapy (AC) has been proven to yield an approximately 5% improvement in 5-year survival for patients with early-stage non–small-cell lung cancer. With such small gains in survival, the optimal treatment regimen remains to be established. Traditional Chinese medicine (TCM) treatment in combination with AC is frequently used in China. The efficacy and safety of this integrated approach should be scientifically evaluated. We present the rationale and study design of the Combined Adjuvant Chemotherapy and Traditional Chinese Medicine (ACTCM) trial (ChiCTR-IPR-16009062). The ACTCM trial, a prospective multicenter double-blind randomized placebo-controlled study, will recruit 312 patients overall from 5 clinical research centers in China. Within 6 weeks of the thoracic surgery, eligible participants with stages IB-IIIA non–small-cell lung cancer will be randomly assigned in a 1:1 ratio to either the treatment or control group. Patients in the treatment group will receive AC combined with TCM herbal treatment for 4 cycles, then TCM herbal plus injection treatment for 4 cycles. Patients in the control group will receive AC combined with TCM placebo for 4 cycles and then TCM placebo for 4 cycles. Treatment will be discontinued if disease progression or unacceptable toxicity occurs. The primary end point is 2-year disease-free survival. Secondary end points include disease-free survival and quality of life. Other end points are TCM symptoms, performance status, and safety of the regimens. Recruitment started in October 2016 and is ongoing.

Clinical Lung Cancer, Vol. 20, No. 5, e541-7

Keywords: Adjuvant chemotherapy, Chinese herbal medicine, Disease-free survival, Quality of life, Radical surgery

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. An estimated 733,300 new lung cancer cases occurred in China in 2015.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 80% to 85% of all lung tumors. The most effective treatment for stage I, stage II, and some stage IIIA NSCLC is surgical resection with curative intent. Nevertheless, a substantial percentage of postoperative NSCLC patients subsequently experience relapse and death. The goal of adjuvant chemotherapy (AC) is to reduce the risk of disease recurrence by eliminating residual disease that may persist after surgical resection, thus prolonging survival time.[2]

A meta-analysis published in 1995 revealed that adjuvant cisplatin-based chemotherapy in resected NSCLC yielded an

[1]Department of Oncology, Longhua Hospital
[2]Department of Oncology, Shuguang Hospital
[3]Department of Health Statistics, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[4]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China
[5]Department of Respiratory Medicine, Shanghai Chest Hospital, Shanghai, China
[6]Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiaotong University, Shanghai, China

Submitted: Oct 2, 2017; Revised: Jan 13, 2019; Accepted: May 10, 2019; Epub: May 21, 2019

Address for correspondence: Ling-Shuang Liu, MD, Department of Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, No. 725, South Wanping Road, Shanghai 200032, China
Fax: (+86) 21-5152-7815; e-mail contact: liuls107@163.com

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.clc.2019.05.011

absolute 5-year survival benefit of 5%, although this did not reach statistical significance (hazard ratio [HR] = 0.87, $P = .08$).[3] Since then, many large randomized controlled trials (RCTs) have assessed the role of postoperative chemotherapy in NSCLC. The lung adjuvant cisplatin evaluation (LACE) meta-analysis[4] of individual patient data pooled 4584 patients who were accrued in 5 cisplatin-based AC trials.[5-9] The results of this previous study revealed a significant benefit (HR = 0.89, $P = .005$) on overall survival for chemotherapy compared to no chemotherapy, and an absolute 5-year benefit of 5.4%. Furthermore, disease-free survival (DFS) also favored chemotherapy (HR = 0.84, $P < .001$), with an absolute 5-year benefit of 5.8%. Simultaneously, it found a negative effect for AC for stage IA disease and a nonsignificant trend toward prolonged survival for stage IB disease. The Cancer and Leukemia Group B trial suggested that tumors > 4 cm in size had a survival advantage (HR = 0.69, $P = .043$) with the combination of carboplatin and paclitaxel for patients with resected stage IB disease.[10] Thus, survival benefits may be limited to NSCLC patients with stage II-IIIA disease, as well as stage IB disease with a high risk of recurrence.

However, these RCTs included patients with good performance status (PS) who were able to tolerate platinum-based chemotherapy. It is unclear whether this survival benefit extends to large population-based cohorts. A real-world study evaluating the outcomes of AC in patients with stage IB-IIIA NSCLC between 2001 and 2008 demonstrated a significant survival benefit associated with the use of AC comparable to that observed in RCTs.[2]

On the basis of evidence from large RCTs and meta-analyses, adjuvant platinum-based chemotherapy is the standard treatment for completely resected stage II-IIIA and IB NSCLC with a high risk of disease recurrence. Nevertheless, with such small gains in survival (approximately 5% 5-year improvement) and the inevitable toxicity of AC, such as bone marrow suppression, hepatotoxicity, nausea, and vomiting, there is a strong desire to offer patients and physicians innovative treatments in the adjuvant setting.

Worldwide, including in Western countries, traditional Chinese medicine (TCM) is increasingly becoming for its efficacy in the prevention and treatment of cancer.[11] Several studies have demonstrated that TCM treatment could increase chemotherapy efficacy, reduce toxicity, strengthen immune system functions, and prolong survival time.[11-15] Unfortunately, some studies of TCM in cancer care tend to be of poor methodologic quality.[16] However, a randomized controlled double-blind clinical study in China methodologically and rigorously confirmed that TCM combined with AC led to partial relief of symptoms in addition to a reduction of adverse effects and adverse events caused by the vinorelbine plus cisplatin/carboplatin (NP/NC) regimens in completely resected NSCLC patients with stage IB-IIIA disease.[17]

On the basis of these findings, we designed a prospective large double-blind RCT to study whether TCM treatment combined with and after chemotherapy in the adjuvant setting yields survival benefits for patients with completely resected stage IB-IIIA NSCLC.

Patients and Methods

Study Design and Treatment

This study is a multicenter double-blind randomized placebo-controlled trial. Patients are currently being enrolled at the following 5 clinical research centers in China: Longhua Hospital affiliated with Shanghai University of TCM, Shanghai Chest Hospital, Shanghai Pulmonary Hospital affiliated with Tongji University, Ruijin Hospital affiliated with Shanghai Jiaotong University, and Shuguang Hospital affiliated with Shanghai University of TCM. Within 6 weeks of thoracic surgery, eligible participants with stage IB-IIIA NSCLC will be randomly assigned in a 1:1 ratio to either the treatment group or the control group. The study design is shown in Figure 1.

Intervention will start within 2 weeks of randomization. Therefore, treatments will start no more than 8 weeks after surgery. Patients in the treatment group will receive AC combined with TCM herbal treatment for 4 cycles, then TCM herbal treatment plus injection treatment for 4 cycles. Patients in the control group will receive AC combined with TCM placebo for 4 cycles, then TCM placebo for 4 cycles. The interventions will be discontinued if patients experience unacceptable toxicity or progressive disease according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), or if they do not receive treatment for 6 weeks from the time of the last treatment. Postoperative radiotherapy for patients with stage IIIA-N2 disease is not mandatory; this decision is left to the researchers at the participating centers.

Adjuvant Chemotherapy. Patients will be administered platinum-based chemotherapy according to one of the following regimens, provided for 3 weeks per cycle of 4 cycles, as per the National Comprehensive Cancer Network guidelines: (1) NP regimen: vinorelbine, 25 mg/m^2 on days 1 and 8 and cisplatin, 75 mg/m^2 on day 1; (2) GP regimen: gemcitabine, 1250 mg/m^2 on days 1 and 8 and cisplatin, 75 mg/m^2 on day 1; (3) DP regimen: docetaxel, 75 mg/m^2 on day 1 and cisplatin, 75 mg/m^2 on day 1; (4) AP regimen: pemetrexed, 500 mg/m^2 on day 1 (for nonsquamous NSCLC) and cisplatin, 75 mg/m^2 on day 1; and (5) TC regimen: paclitaxel, 200 mg/m^2 on day 1 and carboplatin, area under the curve 6 on day 1.[18] Patients who cannot tolerate cisplatin will be administered carboplatin at area under the curve 5 to 6 on day 1. All chemotherapeutic agents will be administered intravenously in both groups.

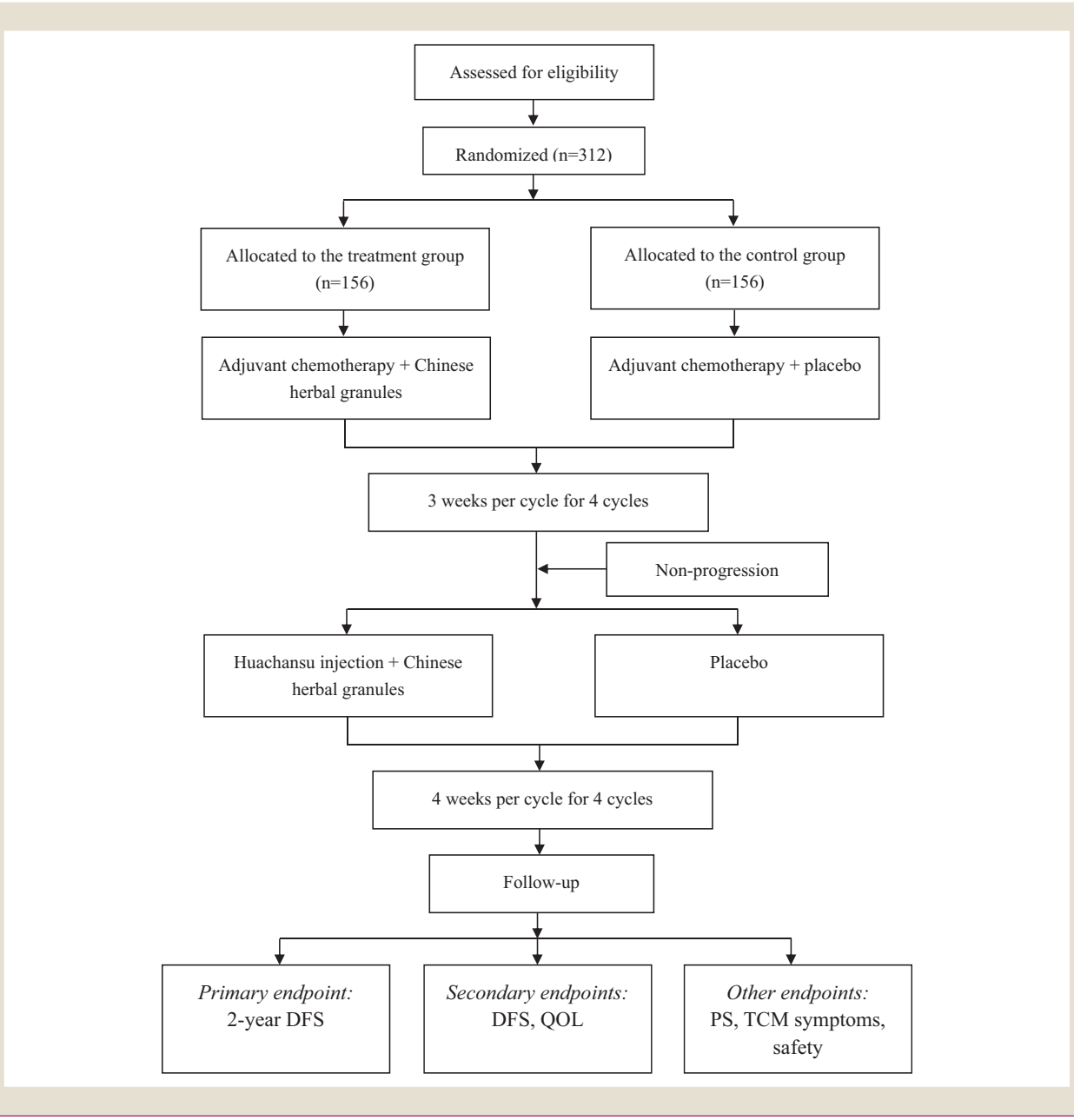
TCM Treatment. For the Chinese herbal medicine recipients, Jiaxiang Liu (Longhua Hospital, affiliated with Shanghai University of TCM) will prescribe Chinese herbal medicine prescriptions, which are classified into 4 recipes according to their function: benefiting qi recipe, benefiting yin recipe, benefiting qi and yin recipe, and detoxication and resolving masses recipe.

The ingredients in the benefiting qi recipe include Radix Astragali 15 g, Rhizoma Atractylodis Macrocephalae 12 g, Poria 15 g, Herba Epimedii 15 g, and Semen Trigonellae 15 g.

The ingredients in the benefiting yin recipe include Radix Adenophorae 30 g, Radix Glehniae 30 g, Radix Asparagi 15 g, Radix Ophiopogonis 15 g, Bulbus Lilii 12 g, Fructus Ligustri Lucidi 12 g, and Fructus Corni 12 g.

The ingredients in the benefiting qi and yin recipe include Radix Astragali 15 g, Radix Glehniae 30 g, Radix Asparagi 15 g, Radix Ophiopogonis 15 g, Fructus Ligustri Lucidi 12 g, Fructus Corni 12 g, Semen Trigonellae 12 g, and Herba Epimedii 15 g.

Figure 1 Study Flow Diagram



The ingredients in the detoxication and resolving masses recipe include *Selaginella doederleinii Hieron* 15 g, *Salvia chinensis* Benth 15 g, *Paris polyphylla* 7.5 g, Pseudobulbus Cremastrae Seu Pleiones 7.5 g, Herba Euphorbia-helioscopia 7.5 g, Spica Prunellae 7.5 g, Rhizoma Arisaematis 7.5 g, Rhizoma Amorphophalli 15 g, and Fructus Jujubae 6 g.

TCM herbal medications used in this study are in the form of granules. Dosages of Chinese herbal granules according to different TCM syndromes are shown in Table 1. The herbal granules are water soluble and are manufactured at a good manufacturing practice—standard facility in China (Jiangyin Tian Jiang Pharmaceutical). All crude herbs are harvested according to good agricultural practice for Chinese crude drugs. All herbal medicines used are sourced from the same production area and the same batch.

Chinese herbal granules will be administered daily during the intervention period. The granules will be dissolved in 150 mL of warm water for drinking, to be taken 30 minutes after a meal in the morning and evening. The placebo includes 0 Chinese herbal medicine and is also provided by Jiangyin Tian Jiang Pharmaceutical. On the basis of the 4 formulas of the Chinese herbal granules, there are 4 kinds of oral placebo that match the Chinese herbal granules by weight, color, smell, taste, and packaging. The therapeutic and placebo packages are stored in different cabinets; only the dispensing technician knows the contents of the packages. Participants will return any unused granules at each cycle visit.

Table 1 Dosages of Chinese Herbal Granules According to Different Traditional Chinese Medicine Syndromes

Syndrome Differentiation	Benefiting Qi Recipe[a]	Benefiting Yin Recipe[b]	Benefiting Qi and Yin Recipe[c]	Detoxication and Resolving Masses Recipe[d]
Qi deficiency	2	—	—	2
Yin deficiency	—	2	—	2
Qi and yin deficiency	—	—	3	2

Unit: package.
[a]Each package contains 4.8 g of water-soluble herbal granules.
[b]Each package contains 12 g of water-soluble herbal granules.
[c]Each package contains 10 g of water-soluble herbal granules.
[d]Each package contains 4 g of water-soluble herbal granules.

For Chinese herbal medicine injection, patients will receive a huachansu injection (20 mL per day for days 1-10) every 28 days for 4 cycles. The huachansu injection is from a single lot (batch 170301-2) manufactured by Anhui Jinchan Biochemistry Sharers. Saline will be used as placebo and will be administered on the same schedule as the huachansu injection.

Diagnostic Criteria

The diagnostic criteria of NSCLC in this study are in accordance with published guidelines.[19] The tumor, node, metastasis classification system stage of NSCLC complies with the staging system of the 2009 International Union Against Cancer, version 7.[20]

Syndrome Differentiation Criteria

Syndrome differentiation criteria are based on published guidelines.[21] The 3 TCM syndromes are as follows:

1. Qi deficiency syndrome: The main symptoms are coughing, large amount of sputum, poor appetite, apathy and weakness, and pale and bulging tongue. Secondary symptoms include spontaneous sweating, loose stool, and thin superficial and smooth pulse.
2. Yin deficiency syndrome: The main symptoms are coughing, small amount of sputum, dry mouth, and red tongue. Secondary symptoms include night sweating, insomnia, low fever, and thready and rapid pulse.
3. Qi and yin deficiency syndrome: The main symptoms are coughing, small amount of sputum, shortness of breath, apathy and weakness, and thirst without the desire to drink. Secondary symptoms include spontaneous sweating, night sweating, reddish tongue or tongue with teeth marks, and thready and weak pulse.

The diagnosis can be made if at least two of the main symptoms and one of the secondary symptoms are present.

Eligibility Criteria

Patients eligible for the trial must comply with all of the following conditions at randomization: pathology-confirmed diagnosis of primary NSCLC; completely resected (R0) stage IB-IIIA disease; within 6 weeks of surgery; age 18 to 75 years; Eastern Cooperative Oncology Group (ECOG) PS score of ≤ 2; normal hematologic function with total neutrophil count of $> 1.5 \times 10^9$/L and platelet count of $> 80 \times 10^9$/L; normal liver and kidney function; TCM syndromes, including qi deficiency, yin deficiency, or qi and yin deficiency; and voluntarily involved in the clinical study and signed informed consent.

The exclusion criteria include the following: incomplete resection; presence of other primary malignant tumors; serious heart, liver, or kidney conditions with severe dysfunction; pregnant or breast-feeding; allergic to a study drug; participation in other drug trials; mental or cognitive disorders; and existence of any severe, unstable, or concurrent medical illnesses that would interfere with the study protocol.

Participant Randomization and Blinding

Random numbers will be automatically generated using the computer as per preconfigured stratified factors (ie, center, sex, age, pathologic stage, histologic subtype, and type of surgical resection). Central randomization will be performed by the Department of Health Statistics of Shanghai University of TCM via telephone. The block sizes and treatment-assignment table will not be disclosed to ensure concealment.

In this study, participants, investigators, outcome assessors, and statisticians will be unaware of the allocated treatment. Blinding will be ensured by the use of investigational products that are identical in appearance, packaging, and labeling.

Primary End Point

The primary end point is 2-year DFS, which is defined as patients without disease recurrence within 2 years after randomization as a percentage of all patients.

Secondary and Exploratory End Points

Secondary end points include DFS and quality of life. Other exploratory end points are TCM symptoms, PS, and regimen safety.

- Disease-free survival: DFS will be measured from the date of randomization to the date of the first recurrence, or until death from any cause. Patients without recurrence at cutoff will be censored on the date of the last contact.
- Quality of life: Quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC)

Table 2 Study Procedures

Characteristic	−28 Days Before Surgery	−14 Days Before Chemotherapy Start	Chemotherapy in Combination With TCM				TCM Alone				+7 Days After Last Cycle
			−3 Days Before Cycle 1 Start	−3 Days Before Cycle 2 Start	−3 Days Before Cycle 3 Start	−3 Days Before Cycle 4 Start	−3 Days Before Cycle 5 Start	−3 Days Before Cycle 6 Start	−3 Days Before Cycle 7 Start	−3 Days Before Cycle 8 Start	
Written informed consent/checking of inclusion and exclusion criteria		X									
Demographics		X									
Medical history		X									
Concomitant medication		X									
Physical examination		X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X
Height and weight		X	X	X	X	X	X	X	X	X	X
ECOG PS		X	X	X	X	X	X	X	X	X	X
TCM symptoms		X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 and EORTC QLQ-LC13		X	X	X	X	X	X	X	X	X	X
CT scans of chest	X				X		X		X		X
CT or MRI of upper abdomen	X[b]				X[b]		X[b]		X[b]		X[b]
CT or MRI of brain	X				X[b]		X[b]		X[b]		X
Bone scintigraphy	X				X[b]		X[b]		X[b]		X[b]
Abdominal ultrasound	X				X[b]		X[b]		X[b]		X
Tumor markers CEA, CA-125, CYFRA 21-1		X	X	X	X	X	X	X	X	X	X
Routine blood analysis		X	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Laboratory hepatic analysis		X	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Laboratory renal analysis		X	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Laboratory electrolyte analysis		X	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X

Table 2 Continued

Characteristic	−28 Days Before Surgery	−14 Days Before Chemotherapy Start	Chemotherapy in Combination With TCM				TCM Alone				+7 Days After Last Cycle
			−3 Days Before Cycle 1 Start	−3 Days Before Cycle 2 Start	−3 Days Before Cycle 3 Start	−3 Days Before Cycle 4 Start	−3 Days Before Cycle 5 Start	−3 Days Before Cycle 6 Start	−3 Days Before Cycle 7 Start	−3 Days Before Cycle 8 Start	
Urinalysis		X	X	X	X	X	X	X	X	X	X
Stool analysis		X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X	X	X	X	X	X	X	X	X	X
Adverse events		X	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Follow-up tumor assessment[c]											

Abbreviations: CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; FDG-PET = fluorodeoxyglucose-positron emission tomography; MRI = magnetic resonance imaging; PS = performance status; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer-Specific Module 13; TCM = traditional Chinese medicine.

[a]At least once weekly during chemotherapy phase.

[b]Optional: patients with suspicious clinical features should undergo evaluation.

[c]Relapse of disease should be confirmed by imaging techniques. If FDG-PET has been performed, bone scintigraphy, CT of chest, and CT or MRI of upper abdomen can be omitted.

Quality of Life Questionnaire Core 30 (QLQ-C30) and the associated EORTC Quality of Life Lung Cancer Specific Module (QLQ-LC13) before and after each cycle of treatment.

- Evaluation of performance status: PS of patients' physical conditions will be assessed according to ECOG PS standards before and after each cycle of treatment.
- Evaluation of traditional Chinese medicine symptoms: Scores of TCM symptoms will be based on the graded scale of lung cancer symptoms[21] before and after each cycle of treatment.
- Safety assessment: Patients will be monitored for adverse events using the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0[22] each week during the chemotherapy period, and before and after each cycle of TCM treatment.

Assessment and Follow-up

Before entry, patients will undergo a complete history, physical examination, and baseline evaluation (Table 2). Standard evaluations for each patient will be performed at the time of each cycle visit and will include routine blood work, renal and hepatic function tests, urine and stool analyses, electrocardiogram, and tumor marker testing for CEA, CA-125, and CYFRA 21-1. Weekly assessments of routine blood work and renal and hepatic function tests will be performed to assess the toxicity and adverse effects during chemotherapy. Computed tomography (CT) of the chest will be performed every 3 months. CT or magnetic resonance imaging of the upper abdomen and brain as well as bone emission CT will be performed if clinically indicated.

All patients will be assessed every 3 months during the first 2 years, then every 6 months until death or the cutoff date of the analysis. CT of the chest will be mandatory, and other examinations will be performed if clinically indicated. Investigators will assess local or distant relapse with conventional imaging consisting of ultrasound, bone scans, CT scans, and magnetic resonance imaging.

Sample Size Calculation

A meta-analysis of 4584 NSCLC patients who had complete resection and who received cisplatin-based AC reported a 2-year DFS of approximately 60%.[4] On the basis of the validity of assumptions and clinical experience in the past, we assume that the 2-year DFS in our study will reach 75% with AC combined with TCM treatment. With an inspection level of $\alpha = 0.05$, grasp 1-β of 0.80, and 20% dropout rate, we plan to enroll 312 patients.

Statistical Analyses

We will assess the efficacy in the intention-to-treat population, which will comprise all randomized participants. Safety outcomes will be analyzed in all participants who will receive at least one dose of study medication. The characteristics of the participants will be summarized as the mean $\pm$ standard deviation for continuous variables and as proportions for categorical variables. We will use the chi-square test to compare 2-year DFS between treatment and control groups. The survival curves for DFS will be estimated by the Kaplan-Meier method and will be compared between the two groups by the log-rank test. Changes in EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaire scores from

baseline scores will be assessed by the Wilcoxon rank sum test. All statistical tests will be carried out on the basis of a 2-sided $\alpha = 0.05$ and 95% confidence interval. Experts from the Department of Health Statistics, Shanghai University of TCM, will conduct the statistical analysis.

Ethics, Informed Consent, and Safety

The trial protocol and consent process are both approved by the ethics committee of Longhua Hospital affiliated with Shanghai University of TCM, Shanghai, PR China (ethical approval 2016LCSY039). The study is designed to comply with the Declaration of Helsinki, local laws and regulations, and good clinical practice guidelines. Before entering the study, each patient must sign a written informed consent statement, and will receive a dated copy of the informed consent form. They will be assured of their freedom to withdraw from the study at any time. Before starting, researchers will undertake a training course, which will include the study protocol, the recording method of the clinical record form, the researcher's responsibilities, and research monitoring.

Data Management and Monitoring

All study data will be kept in locked cabinets. Electronic case reports will be created, in which patients will be identified by initials and a unique code. After the completion of all follow-ups and double data entry, the data set will be reviewed for accuracy, then locked for analysis. The statistical analysis will be approved and completed before treatment group allocation unmasking.

Discussion

TCM treatment, in combination with AC, for completely resected stages IB-IIIA NSCLC is frequently used in China, but there is a lack of high-quality trials to prove its efficacy and safety. This study protocol is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidance for protocols of clinical trials.[23,24] This trial will apply high-quality clinical trial methodology to determine whether AC plus TCM treatment will prolong survival among patients with completely resected stage IB-IIIA NSCLC. We expect that this integrated approach could become a powerful treatment option for patients with NSCLC in the adjuvant setting.

Conclusion

Adjuvant platinum-based chemotherapy is the standard treatment for completely resected stage II-IIIA and stage IB NSCLC at a high risk of disease recurrence. The trial will show whether AC combined with TCM treatment is better than AC alone for postoperative NSCLC patients.

Acknowledgments

Supported in part by the National Natural Science Foundation of China (81703987), the Science and Technology Commission of Shanghai Municipality (16401970800), the Emerging Frontier Technology Joint Research Project of Shanghai Shenkang Hospital Development Center (SHDC12018124), the Shanghai Municipal Commission of Health and Family Planning (201840158), and the Longhua Scholar Plan of National Traditional Chinese Medicine Clinical Base of China (LYTD-43).

Disclosure

The authors have stated that they have no conflict of interest.

References

1. Chen WQ, Zheng RS, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66:115-32.
2. Williams CD, Gajra A, Ganti AK, et al. Use and impact of adjuvant chemotherapy in patients with resected non−small cell lung cancer. *Cancer* 2014; 120:1939-47.
3. Chemotherapy in non−small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non−Small Cell Lung Cancer Collaborative Group. *BMJ* 1995; 311:899-909.
4. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; 26:3552-9.
5. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non−small-cell lung cancer. *N Engl J Med* 2004; 350:351-60.
6. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non−small-cell lung cancer. *N Engl J Med* 2005; 352:2589-97.
7. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non−small-cell lung cancer (Adjuvant Navel-bine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006; 7:719-27.
8. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non−small-cell lung cancer. *J Natl Cancer Inst* 2003; 95:1453-61.
9. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non−small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004; 26:173-82.
10. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non−small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008; 26:5043-51.
11. Nie J, Zhao C, Deng LI, et al. Efficacy of traditional Chinese medicine in treating cancer. *Biomed Rep* 2016; 4:3-14.
12. Chen ZF, Li CZ, Liu SX. Meta-analysis on primary non−small cell lung cancer treated by TCM. *J TCM* 1999; 40:287-9.
13. Liu JX, Shi ZM, Xu ZY, et al. Studies on late primary adenocarcinoma of lung treated methods of nourishing yin to replenish fluid and warming yang to benefit qi. *J TCM* 1995; 36:155-8.
14. Guo H, Liu JX, Li H, et al. In metastatic non−small cell lung cancer platinum-based treated patients, herbal treatment improves the quality of life. A prospective randomized controlled clinical trial. *Front Pharmacol* 2017; 8:454.
15. Jiang Y, Liu LS, Shen LP, et al. Traditional Chinese medicine treatment as maintenance therapy in advanced non−small-cell lung cancer: a randomized controlled trial. *Complement Ther Med* 2016; 24:55-62.
16. Li X, Yang G, Li X, et al. Traditional Chinese medicine in cancer care: a review of controlled clinical studies published in Chinese. *PLoS One* 2013; 8:e60338.
17. Jiao LJ, Dong CS, Liu JX, et al. Effects of Chinese medicine as adjunct medication for adjuvant chemotherapy treatments of non−small cell lung cancer patients. *Sci Rep* 2017; 7:46524.
18. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non−small cell lung cancer, version 7 (China).2015 Available at: https://www.nccn.org/professionals/physician_gls/PDF/nscl-chinese.pdf 2015. Accessed: June 17, 2019.
19. Zhi XY, Shi YK, Yu JM. Guidelines and standards of diagnosis and therapy of lung neoplasms in China (2015). *Chin J Oncol* 2015; 37:67-78.
20. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009; 136:260-71.
21. Zheng XY. *The Guiding Principles of Clinical Research of New Chinese Medicine (Trial)*. Beijing: Chinese Medical Science and Technology Press; 2002:216-21.
22. National Cancer Institute. Common terminology criteria for adverse events v3.0 (CTCAE). Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf 2006. Accessed: May 30, 2019.
23. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; 158:200-7.
24. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346:e7586.