Clinical study of lung-supplementing and stasis-dissolving decoction (*Bufei Huayu Tang*) combined with gefitnib for treatment of advanced non-small cell lung cancer

Feng Yuan[1*], Chen Si-ning[1], Zhou Ji-hong[1], Jiang Ying[2], Zhou Ying[3], Xie You-ke[4] and Li Jian-zhe[5]

[1]Department of Respiratory Medicine, Guangxi University of Chinese Medicine, Nanning City, Guangxi Province, China
[2]Department of Neurology, Guangxi University of Chinese Medicine, Nanning City, Guangxi Province, China
[3]Department of Radiotherapy, Guangxi University of Chinese Medicine, Nanning City, Guangxi Province, China
[4]Department of Oncology, Guangxi University of Chinese Medicine, Nanning City, Guangxi Province, China
[5]Department of Pharmacy, Guangxi University of Chinese Medicine, Nanning City, Guangxi Province, China

Abstract: To investigate the clinical efficacy and drug safety of Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) combined with gefitnib for treatment of advanced non-small cell lung cancer (NSCLC). Then, 80 patients with advanced NSCLC hospitalized in Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine were included, and were double-blindly randomized into 4 groups: control group (gefitinib alone 250mg, once daily), low-dose group (100mL/day), middle-dose group (150mL/day) and high-dose group (200mL/day) treated with different doses of *Bufei Huayu Tang* besides gefitinib. Clinical efficacy, life quality change before and after treatment, ECOG score, survival time and incidence of adverse drug reaction were compared. ECOG score in middle-dose group after treatment was significantly higher than other groups (P<0.05). Total efficiency of 4 groups was respectively 15%, 20%, 55% and 25%, and total efficiency in middle-dose group was significantly higher than that in other groups (P<0.05). According to TCM syndrome score, the improvement in middle-dose group was significantly better than that in other groups (P<0.05). Incidence of adverse drug reaction in high-dose group was significantly higher than that in other 3 groups (P<0.05). Self-designed *Bufei Huayu Tang* combined with gefitinib for NSCLC has a satisfactory clinical efficacy and high drug safety. Decoction dose needs more attention.

Keywords: Advanced non-small cell lung cancer (NSCLC); Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*); Gefitinib.

INTRODUCTION

Lung cancer, also known as primary bronchogenic carcinoma, mainly refers to malignant tumors in bronchial mucosal epithelium and alveolar, which can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (Jiang XD, *et al*., 2012) according to their clinical features and pathological features. Clinical statistics (Zhao L, *et al*., 2007) shows that lung cancer has the highest incidence and mortality rate of all malignant tumors all over the world which increases year by year. About 80-85% of lung cancer is NSCLC and 75-80% of patients are in stage II-III during outpatient visit. This phenomenon has seriously threatened the life safety of elderly patients (Lin LZ and Zheng XT, 2011). Combination therapy is usually used for clinical treatment wherein chemotherapy is the main method but has unsatisfactory efficacy. With the continuous progress of traditional Chinese medicine (TCM), integrated treatment of Chinese and Western medicine, which shows a satisfactory efficacy in the treatment of cancer and other diseases, is easily accepted by patients and their families and is being popularized and widely used in recent years for its simplicity and low toxic side effect (Wang YY, *et al*., 2013). There has been dozens of studies of Chinese medicine decoction combined with gefitinib in NSCLC treatment. Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) self-designed by TCM department of our hospital is combined with gefitinib in our study to compare with treatment of gefitinib alone and deeply evaluate the clinical efficacy and safety of different doses. The detailed report is presented below.

MATERIALS AND METHODS

Clinical data

This study was approved by medical ethics committee of our hospital. We proactively selected 80 elderly patients with pathologically proved NSCLC who were hospitalized from May 2012 to May 2014. Diagnosis of all patients were in line with “New Diagnosis and Treatment of Common Malignant Tumors" (Tang XH, 2010) compiled by Chinese Anti-cancer Association and were proved primary NSCLC by clinical syndrome and histological examination. There were 59 males and 21 females (age: 39-85 years old; mean age: 62.58 ± 6.46 years old) in the patients. Pathological types included squamous cell carcinoma (6 cases), adenocarcinoma (67

**Corresponding author:* e-mail: fengyuan14616@163.com

cases), large cell carcinoma (3 cases), adenosquamous carcinoma (3 cases) and other type (1 case). Clinical stages included stage IIIB (17 cases) and stage IV (63 cases). The patients were randomly and double-blindly divided into 4 groups: control group, low-dose group, middle-dose group and high-dose group with 20 patients in each. Difference in baseline data of gender constituent ratio, age, pathological type and TNM stage was not statistically significant (P<0.05) and was comparable.

Inclusion criteria

All patients included met the following criteria: (1) Age ≥18 years old, clinical stage in stage IIIB / IV; (2) Primary lesion and metastases can be clinically evaluated; (3) No severe dysfunction of vital organ; (4) Voluntary participation in this study after fully comprehension and a signed informed consent.

Exclusion criteria

Patients with the following conditions were excluded: (1) There were brain metastases revealed by relevant examination; (2) In combination with other severe acute or chronic disease (including mental disorder, etc.) and (or) severe dysfunction of vital organ; (3) Allergy to the drug used in the study.

Methods

TCM types

According to "Clinical guidelines of new Chinese medicine for the treatment of primary bronchogenic carcinoma" (Cui D, *et al*., 2014) while referring to actual conditions of patients, TCM types were divided into *qi* deficiency and phlegm-damp type, *yin* deficiency and toxic heat type, deficiency of both *qi* and *yin* type, *qi* stagnation and blood stasis type. Addition and subtraction formulae were determined according to syndrome type.

Selection and use of formula

Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) self-designed by TCM department of our hospital were selected and the herb composition includes Asiatic cornelian cherry fruit 12g, tree peony bark 12g, common yam rhizome 15g, dodder seed 15g, psoralea fruit 12g, ophiopogon tuber 15g, Poria 12g, prepared rehmannia root 12g, astragalus root 20g, Chinese angelica 12g, Chinese magnolivine fruit 12g, red peony root 12g, white atractylodes rhizome 10g, peach kernel 12g, licorice root 10g, codonopsis root 15g. Addition and subtraction formulae were determined by patient's conditions: addition of hemostatic herbs such as lotus rhizome node, pseudoginseng root, bletilla rhizome, imperata rhizome and so on for blood in sputum; addition of blood-cooling herbs such as gypsum, buffalo horn, woad root and so on for persistent high fever; addition of analgesic herbs such as corydalis rhizome, myrrh, common monkshood mother root and so on for chest pain; addition of *qi*-rectifying herbs such as pepperweed seed, plantain, Chinese date and so on for pleural rheum and fullness and depression in the chest and hypochondriac region.

Usage: All herbs, 1 dose per day, were decoted in clear water (1000mL) with mild flame for 30min; Decotion was used once every morning and evening for continuous use of 3 courses (a course of 30d). Decotions at different doses were used in different groups and the specific dosages were as follows: Low-dose group: 100mL / time; middle-dose group: 200mL / time; high-dose group: 300mL / time.

Usage of gefitinib

All patients received gefitinib tablets of the same dose and specification (250mg / time, once daily). Observation and evaluation criteria

Monitoring indicators

Multiple indicators were monitored to assist in assessing the conditions of patients before admission, during treatment and after treatment. Indicators included chest imaging, brain imaging, abdomen imaging, direct PET / CT if conditions permit and blood tests of routine blood test, liver function, kidney function and tumor markers.

Clinical observation item

Eastern Cooperative Oncology Group (ECOG) score was used in observing physical conditions of the patients

Response evaluation

According to "new guidelines to evaluate the response to treatment in solid tumors" (Chen CF and Feng ZQ, 2014), response evaluation contains 4 levels: complete remission (CR): all lesions disappeared; partial remission (PR): summation of long diameter of baseline lesions ≥30%; progressive disease (PD): summation of long diameter of baseline lesions increased ≥20% or new lesions occurred; stable disease (SD): lesions showed no increasing while shrinking degree did not reached PR; effective=CR+PR;

Response evaluation of TCM syndrome

Evaluation of TCM syndrome score: Referring to TCM syndrome score table (Uesato S, *et al*., 2014), all patients were scored before and after treatment. The improvement in score before and after treatment was compared. Complete response: syndrome score decreased by over 70%; effective response: syndrome score decreased by 30% -70%; no response: syndrome score decreased < 30%;

Drug Safety Evaluation

According to the WHO criteria for acute and subacute toxic reaction of anticancer drugs, adverse drug reaction during treatment was evaluated and divided into I-IV (Chow E, 2004).

Table 1: ECOG PS score in four groups before and after treatment

Group	n	Before treatment	After treatment	*P* value
Control group	20	1.44±0.85	1.59±0.56	0.5512
Low-dose group	20	1.41±0.79	1.60±0.62	0.4136
Middle-dose group	20	1.43±0.81	1.74±0.51[a]	0.2148
High-dose group	20	1.42±0.77	1.61±0.64	0.4055

Note: Comparison between middle-dose group and other groups after treatment [a] $P<0.05$.

Table 2: Evaluation of response in 4 groups [case, %]

Group	n	CR	PR	SD	PD	Total response
Control group	20	0	3(15%)	12(60%)	5(25%)	3(15%)
Low-dose group	20	0	4(20%)	10(50%)	6(30%)	4(20%)
Middle-dose group	20	0	11(55%)	6(30%)	3(15%)	11(55%)[a]
High-dose group	20	0	5(25%)	12(60%)	3(15%)	5(25%)

Note: Comparison of response rate between middle-dose group and other groups [a] $P<0.05$.

Table 3: Improvement in TCM syndrome score (case, %)

Group	n	Complete response	Effective response	No response
Control group	20	1(5%)	9(45%)	10(50%)
Low-dose group	20	3(15%)	11(55%)	6(30%)
Middle-dose group	20	8(40%)[a]	11(55%)	1(5%)
High-dose group	20	4(20%)	7(35%)	9(45%)

Note: Comparison between middle-dose group and other groups [a] $P<0.05$.

Table 4: Incidence of adverse drug reaction (case, %)

Group	n	I	II	III	IV	Total incidence rate
Control group	20	3(15%)	1(5%)	2(10%)	1(5%)	7(35%)
Low-dose group	20	2(10%)	3(15%)	2(10%)	1(5%)	8(40%)
Middle-dose group	20	3(15%)	1(5%)	2(10%)	2(10%)	8(40%)
High-dose group	20	8(40%)	5(25%)	3(15%)	2(10%)	18(90%)[a]

Note: Comparison between high-dose group and other groups after treatment [a] $P<0.05$.

STATISTICAL ANALYSES

All statistical analyses were performed with SPSS version 18.0. Measurement data were expressed as mean ± SD (x±s) and 't' test was used for intergroup comparison. Count data were analyzed using chi-square test. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Comparison of ECOG score of 4 groups before and after treatment

No patient dropped out of treatment or died after 3 courses (90d) of treatment. Difference of ECOG score in 4 groups before treatment was not statistically significant ($P<0.05$); ECOG score after treatment increased but had no statistical significance with that before treatment; ECOG score in middle-dose group after treatment was significantly higher than other groups and the difference was statistically significant ($P<0.05$, table 1).

Short-term efficacy after 3 courses of treatment in 4 groups was evaluated. Total response rate of control group, low-dose group, middle-dose group and high-dose group was respectively 15%, 20%, 55% and 25%. Response rate of middle-dose group was significantly higher than other groups and the difference was statistically significant ($P<0.05$, table 2).

According to TCM syndrome score table, the improvement in TCM syndrome score in middle-dose group was significantly better than other groups and the difference was statistically significant ($P<0.05$, table 3).

Incidence rate of adverse drug reaction in 4 groups was respectively 35%, 40%, 40% and 90%. Difference of incidence rate of adverse drug reaction in control group, low-dose group and middle-dose group was not significantly different ($P>0.05$); incidence rate of adverse drug reaction in high-dose group was significantly higher than other 3 groups and the difference was statistically significant ($P<0.05$, table 4).

DISCUSSION

Lung cancer presents a serious threat to human health. According to the published data of World Health Organization in 2008 (Ryu SH, *et al*., 2012), lung cancer

ranked first in the world for annual incidence and annual deaths. In China, lung cancer has become the leading cause of cancer death. A large number of studies (Gregory DL, *et al*., 2012) show that smoking is the leading cause of progressive increase in lung cancer mortality for that nicotine, benzopyrene, nitrosamines and a small amount of radioactive elements in smoke have carcinogenic effects, particularly vulnerable to lead to squamous cell carcinoma and undifferentiated small cell carcinoma. In addition, occupational carcinogen, air pollution, ionizing radiation, eating habits and genetic factors are common carcinogenic factors of lung cancer (Li J, 2015). Lung cancer is categorized into lung accumulation, *pǐ* and lump, lung abscess in TCM which is some kind of lung function disorder and lung *qi* constraint caused by healthy *qi* depletion, *yin-yang* disharmony, invasion and stagnation of pathogen in lung. The main pathogenesis is root deficiency and branch excess. According to the syndrome characteristics, lung cancer can be divided into *qi* deficiency and phlegm-damp type, *yin* deficiency and toxic heat type, deficiency of both *qi* and *yin* type, *qi* stagnation and blood stasis type (Feng ZQ, *et al*., 2014). Currently, western medicine treatment of lung cancer contains surgery, chemotherapy, radiotherapy, targeted therapy and other commonly used therapies chosen for their clinical progress (Sak A, *et al*., 2012). Clinical study shows that earlier performance of radical resection for lung cancer is the most effective treatment and can greatly improve the 5-year survival rate of patients (Shen FL, *et al*., 2014). TCM treatment mainly contains boost *qi* and nourish *yin*, boost *qi* and invigorate blood, dissolve phlegm and resolve constraint. With the progress of TCM, integration of Chinese and Western medicine achieves good efficacy in the treatment of various diseases. And treatment of advanced NSCLC with Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) combined with gefitinib is the therapy our hospital focuses on this year.

Gefitinib, also known as Iressa, is a selective tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), which is applicable to the treatment of locally advanced or metastatic NSCLC after receiving chemotherapy or unsuitable for chemotherapy, mainly used for the treatment of SCLC patients with little effect of chemotherapy or unbearable for chemotherapy. Gefitinib is one of molecular targeted drugs and has achieved certain effects in clinical treatment (Ramezanpour, *et al*., 2014; Xu L, *et al*., 2013). Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) self-designed by TCM department in our hospital mainly includes asiatic cornelian cherry fruit 12g, tree peony bark 12g, common yam rhizome 15g, dodder seed 15g, psoralea fruit 12g, ophiopogon tuber 15g, Poria 12g, prepared rehmannia root 12g, astragalus root 20g, Chinese angelica 12g, Chinese magnolivine fruit 12g, red peony root 12g, white atractylodes rhizome 10g, peach kernel 12g, licorice root 10g, codonopsis root 15g wherein codonopsis root, astragalus root, poria, white atractylodes rhizome and common yam rhizome can supplement and boost *qi*, warm liver and supplement spleen; ophiopogon tuber and Chinese magnolivine fruit can boost *qi* and diffuse lung; dodder seed, ophiopogon tuber, asiatic cornelian cherry fruit, prepared rehmannia root and psoralea fruit can fortify spleen and boost *qi*, supplement *qi* and nourish kidney; Chinese angelica, peach kernel, tree peony bark and red peony root can invigorate blood and dissolve stasis. All herbs act together and vary according to syndrome to harmonize five viscera and six bowels, improve *qi* and blood circulation, meanwhile avoid reinvasion of external pathogen (Badiyan SN, *et al*., 2013; Rong Z, *et al*., 2014; Li QQ and Li EZ, 2012).

A randomized control study was conducted in this study to compare the clinical efficacy of integrated treatment of Chinese and Western medicine and Western medicine treatment alone, as well as evaluate the dose selection and drug safety. Results show that integrated treatment of Chinese and Western medicine has a more significant effect in treating NSCLC and a higher ECOG score after treatment when comparing with gefitinib alone. So is the evaluation of TCM syndrome score. In terms of drug safety, gefitinib alone has toxic side effects but addition of small-dose and middle-dose of Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) does not increase its adverse drug reaction. In terms of dose selection, treatment effect of middle-dose Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) combined with equal amounts of gefitinib is more effective than low-dose and high-dose. Adverse reaction in high-dose group increases significantly which further confirms the importance of dose selection.

In conclusion, treatment of self-designed Lung-Supplementing and Stasis-Dissolving Decoction (*Bufei Huayu Tang*) combined with gefitinib for NSCLC has a satisfactory clinical efficacy and high drug safety. Decoction dose needs more attention since too small a dose shows hardly clinical efficacy and too large a dose will increase the incidence of adverse reaction.

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