CLINICAL STUDY OF BUFEI HUAYU DECOCTION COMBINED WITH GEFITINIB IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

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ABSTRACT

Objective: *To explore the clinical efficacy and safety of Bufei Huayu Decoction combined with gefitinib in the treatment of advanced non-small cell lung cancer.*

Methods: *130 patients with advanced non-small cell lung cancer, who were diagnosed and treated in our hospital from January 2014 to June 2015, were enrolled in this study. These patients were randomly divided into observation group (n=65) and control group (n=65). The patients in the control group were administered gefitinib for 30 days. The patients in the observation group were administered Bufei Huayu Decoction besides gefitinib for 30 days. The clinical efficacy, coagulation indexes, prognostic difference and incidence of adverse drug reactions were compared before and after treatment in the two groups.*

Results: *The total response rate (92.31% vs 76.92%; χ^2=5.909, P=0.015) and clinical benefit rate (95.38% vs 83.02%; χ^2=5.123, P=0.024) were significantly higher in the observation group than those in the control group. There was no significant difference in coagulation indexes between the two groups before treatment (P>0.05). After treatment, PT, APTT, FIB, D-D, and PLT were significantly lower in the observation group than those in the control group (P<0.05). However, MPV and PDW were significantly higher in the observation group than those in the control group (P<0.05). Thrombosis risk (HR=0.3471, 95%CI[0.1376, 0.8756], P=0.028), mortality risk (HR=0.5664, 95%CI[0.3319, 0.9664], P=0.044), and disease progression risk (HR=0.5363, 95%CI[0.3365, 0.8549], P=0.027) were significantly lower in the observation group than in the control group. The incidence of skin rash and ALT level were significantly lower in the observation group than those in the control group after treatment (P<0.05).*

Conclusions: *Bufei Huayu Decoction combined with gefitinib in the treatment of advanced non-small cell lung cancer has a significant effect, can effectively regulate coagulation dysfunction, reduce the risk of thrombosis, improve the long-term prognosis of patients, and has good safety.*

Keywords: *Bufei Huayu Decoction, gefitinib, non-small cell lung cancer, coagulation dysfunction, prognosis.*

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Introduction

Epidemiological investigation shows that the incidence and mortality of lung cancer rank first among all malignant tumors in China, among which non-small cell lung cancer (NSCLC) accounts for 80-85% of the total number of lung cancer[(1)]. Because the early symptoms of NSCLC are not specific, and there is no effective and economical early screening program, the current clinical diagnosis is not timely enough. According to statistics, 2/3 of the patients with NSCLC are in the advanced stage at the time of diagnosis[(2)]. The patients with advanced NSCLC have lost the chance of operation and the traditional radiotherapy and chemotherapy have reached the plateau stage. Simultaneously, the adverse reactions are serious. With the development of molecular oncology and targeted therapy, molecular targeted therapy has become one of the main treatments for advanced NSCLC[(3)]. Gefitinib[(4)], as an epidermal growth factor receptor tyrosine kinase antagonist, has a certain effective rate and control rate

for advanced NSCLC, but there are some adverse reactions[5]. Traditional medicine believes that the adjuvant treatment of lung cancer with traditional Chinese medicine can improve the efficacy of targeted drugs and alleviate toxic and side effects[6, 7]. The effect of Bufei Huayu Decoction combined with gefitinib in the treatment of advanced NSCLC is not clear. This study mainly explores the clinical effect of Bufei Huayu Decoction combined with gefitinib in the treatment of NSCLC.

Materials and methods

General data

130 patients with advanced NSCLC, who were diagnosed and treated in Department of Respiratory Medicine and Department of Oncology, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, China from January 2014 to June 2015, were enrolled in this study. The trial was designed as a randomized parallel control study, and divided into a control group and an observation group. Attention was paid to the concealment of the random method. The random number table was generated by the SAS software. Distribution scheme was controlled by an independent person unrelated to this trial. The patients were randomly divided into the control group (65 cases) and the observation group (65 cases). There was no significant difference in the general data and it was comparable (Table 1). All patients signed the informed consent. This trial was approved by the Hospital Ethics Committee.

Item		Control group (n=65)	Observation group (n=65)	t/χ^2	P
Age (year)		61.21±9.41	63.35±8.61	1.353	0.179
Sex [n(%)]	Male	46(62.00)	50(56.00)		0.550
	Female	19(38.00)	15(34.00)		
BMI (kg/m^2)		21.46±4.87	21.57±4.21	0.235	0.814
History of smoking		47(72.31)	45(69.23)		0.847
TNM classification	Stage III	42(64.62)	38(58.46)		0.589
	Stage IV	23(35.38)	27(41.54)		
Pathological types	Squamous cell carcinoma	32(49.23)	28(43.08)		
	Adenocarcinoma	27(41.54)	30(46.15)	0.501	0.778
	Large cell carcinoma	6(9.23)	7(10.77)		
TCM syndrome scores		10.03±1.54	9.83±1.42	0.652	0.516
Karnofsky Performance Status Scale score		71.38±4.87	70.51±4.01	1.112	0.268

Table 1: General information of patients [n(%), ($\bar{x}$±s)].

Diagnostic criteria

Diagnostic criteria of western medicine:

There were the Diagnosis and Treatment Criteria of Common Malignant Tumors compiled by the Department of Medical Administration of China[8], TNM classification (7th edition in 2009) formulated by the Union for International Cancer Control, NSCLC stage IIIB or IV diagnosed by histopathological or cytological examination, and objective lesions as observable and evaluative indicators.

Basis of syndrome differentiation in traditional Chinese medicine

There were Guidelines for Clinical Research of New Chinese Medicines (Trial Implementation) issued by the Ministry of Health in 2002, Classification Criteria for Bronchogenic Carcinoma in Reference Criteria for Syndrome Differentiation of Deficiency in Traditional Chinese Medicine[9], and those with qi deficiency and blood stasis syndrome.

Inclusion criteria

Patients presenting with all of the following criteria were considered for study inclusion:

• Age of 18 to 70 years;

• Karnofsky Performance Status Scale score ≥60;

• No surgical indication, no radiotherapy or chemotherapy;

• Expected life span >3 months; (5) EGFR gene mutation;

• Willing to accept this protocol and with good compliance;

• Basically normal functions of heart, liver, kidney and hematopoietic system.

Exclusion criteria

Patients with one or more of the following conditions were excluded from this study:

• Combined with other tumors;

• Accompanied by severe heart, lung, liver, kidney and other organ disorders;

• Allergic to components of Bufei Huayu Decoction;

• Previous use of gefitinib or drugs containing components of Bufei Huayu Decoction.

Treatment programs

The patients in the control group were administered gefitinib (AstraZeneca; GYZZ J20070047, 0.25 g*10 pills), once a day, 1 pill every time, for 30 days as a course, orally, on an empty stomach or with food. The patients in the observation group were ad-

ministered Bufei Huayu Decoction besides gefitinib. The ingredients of this prescription contained codonopsis pilosula 20 g, astragalus membranaceus 15 g, rehmannia glutinosa 15 g, aster tataricus 10 g, szechwan lovage rhizome 10 g, red peony root 12 g, salvia miltiorrhiza 10 g, peucedanum praeruptorum dunn 10 g, semen armeniacae amarum 10 g, rhizoma curcumae zedoariae 10 g, sparganum stoloniferum 10 g, scutellaria barbata D.don 10 g, hedyotis diffusa willd 15 g, turtle carapace 10 g, and glycyrrhiza uralensis fisch 6 g. Above herbs were decocted into 200 ml water with 500 ml water and sub-packed in two bags with vacuum packaging, 100 ml/bag, one bag each time, twice a day, orally, for 30 consecutive days as a course. Both groups were treated for two consecutive months and followed up for two consecutive years.

Observation indicators and efficacy evaluation

The clinical efficacy, coagulation indexes, prognostic difference and safety were compared before and after treatment in the two groups.

Comparison of clinical efficacy

Therapeutic effect was assessed after two courses of treatment. The Response Evaluation Criteria in Solid Tumors[10], formulated by World Health Organization, is as follows: complete response, disappearance of lesions except for lymph node, all lymph nodes must be <10 mm short axis; partial response, >30% decrease in the sum of the longest diameters of lesions; progressive disease, >20% and >5 mm increase in the sum of the lesion measurements; stable disease, neither partial response or progressive disease. Total response rate = (complete response + partial response) / total number * 100%; clinical benefit rate = (complete response + partial response + stable disease)/total number * 100%.

Comparison of coagulation function

Fasting venous blood 8 ml was collected before and after treatment. Some of the blood sample was used to detect platelet (PLT) content, mean platelet volume (MPV), and platelet distribution width (PDW) using automatic blood routine analyzer. Others were used for centrifugation at 3000 r/min for 5 minutes. Serum was collected, and stored at -70°C. The coagulation method was utilized to measure prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB). Enzyme linked immunosorbent assay was applied to examine D-dimer (D-D) content.

Comparison of prognostic differences

The occurrence of thrombotic events, overall survival and progression free survival were compared between the two groups during the follow-up. Disease progression events include recurrence or metastasis of lung cancer.

Comparison of safety

Routine blood indexes, liver function, kidney function, and electrocardiogram were observed and recorded once before and after treatment. Simultaneously, NCI adverse reactions were recorded.

The patients with abnormal examination indicators were symptomatically treated and the protocol was adjusted if necessary in accordance with the Classification Criteria for Common Toxic and Side Effects in Clinical Trials, formulated by World Health Organization.

Follow-up

Follow-up was conducted monthly at the clinic after treatment. Thrombosis was measured with B-ultrasound and CT. During the follow-up, the primary endpoint event was all-cause mortality and the secondary endpoint event was disease progression. The follow-up was performed for 36 months and ended in June 2018.

Statistical analysis

Data were analyzed using SPSS 19.0 software and GraphPad Prism 7.0 software. Count data were expressed in n(%). Intergroup comparison was done using χ^2 test. Fisher's exact probability test was used when the expected value was below 1.

Measurement data were expressed as the mean ± standard deviation. Intergroup comparison was carried out using t-test. Intragroup comparison before and after treatment was conducted using paired t-test. Survival curve was drawn by the Kaplan-Meier method. P value was calculated by Log rank test. A value of $P<0.05$ was considered statistically significant.

Results

Comparison of clinical efficacy between the two groups

The total response rate (92.31% vs 76.92%; $\chi^2 = 5.909$, $P = 0.015$) and clinical benefit rate (95.38% vs 83.02%; $\chi^2 = 5.123$, $P = 0.024$) were significantly higher in the observation group than those in the control group (Table 2).

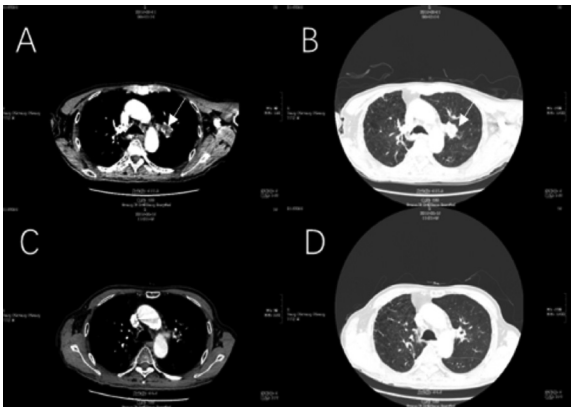

Figure 1: CT findings of typical NSCLC before and after treatment.

A, B: Before treatment, a mass (2 cm×1.5 cm, arrows) was seen near the hilum of the left lung on enhanced CT scanning of lung window and mediastinal window. C, D: After treatment, enhanced CT scan of lung window and mediastinal window showed that the mass contracted to 0.5 cm×0.5 cm after treatment in the same patient.

Group	*n*	Complete response	Partial response	Stable disease	Progressive disease	Total response rate	Clinical benefit rate
Observation	65	2(3.08)	58(89.23)	2(3.08)	3(4.62)	60(92.31)	62(95.38)
Control	65	1(1.54)	49(75.38)	4(15.38)	11(23.08)	50(76.92)	54(83.02)
χ^2						5.909	5.123
P						0.015	0.024

Table 2: Comparison of clinical efficacy between the two groups.

Comparison of coagulation function in both groups before and after treatment

There was no significant difference in each coagulation index in both groups before treatment (P>0.05). PT, APTT, TT, FIB, D-D, and PLT were significantly increased in both groups after treatment compared with that before treatment (P<0.05). MPV and PDW were significantly decreased in both groups after treatment compared with those before treatment (P<0.05).

After treatment, PT, APTT, FIB, D-D, and PLT were significantly lower in the observation group than those in the control group (P<0.05). However, MPV and PDW were significantly higher in the observation group than those in the control group (P<0.05; Table 3).

Group	*n*	Time	PT (s)	APTT (s)	TT (s)	FIB (g/L)	D-D (mg/L)
Observation	65	Before treatment	16.27±1.24	34.88±6.19	15.57±4.59	5.21±1.04	0.53±0.13
		After treatment	17.37±1.68[a]	38.59±6.08[a]	17.93±4.36[a]	6.01±1.47[a]	0.69±0.16[a]
Control	65	Before treatment	15.89±1.21[c]	35.79±5.89[c]	16.93±4.38[c]	5.17±1.02[c]	0.57±0.14[c]
		After treatment	18.94±1.75[ab]	41.37±6.33[ab]	18.93±4.17[a]	6.88±1.63[ab]	0.79±0.21[ab]

Group	*n*	Time	PLT (×10^9/L)	MPV (fl)	PDW (%)
Observation	65	Before treatment	116.23±28.64	37.82±8.14	25.87±5.19
		After treatment	125.37±21.68[a]	29.59±6.08[a]	21.93±4.36[a]
Control	65	Before treatment	115.69±31.01[c]	35.79±7.89[c]	26.03±4.88[c]
		After treatment	134.91±34.15[ab]	21.35±6.13[ab]	15.33±3.10[ab]

Table 3: Comparison of coagulation function in both groups before and after treatment.

Note: [a]P<0.05, vs. before treatment in the same group; [b]P<0.05, vs. after treatment in the observation group; [c]P<0.05, vs. before treatment in the observation group.

Comparisons of cumulative thrombotic events, overall survival and progression free survival between the two groups

Thrombosis risk (HR = 0.3471, 95%CI[0.1376, 0.8756], P = 0.028), mortality risk (HR = 0.5664, 95%CI[0.3319, 0.9664], P = 0.044), and disease progression risk (HR = 0.5363, 95%CI[0.3365, 0.8549], P = 0.027) were significantly lower in the observation group than those in the control group (Figures 2, 3, 4).

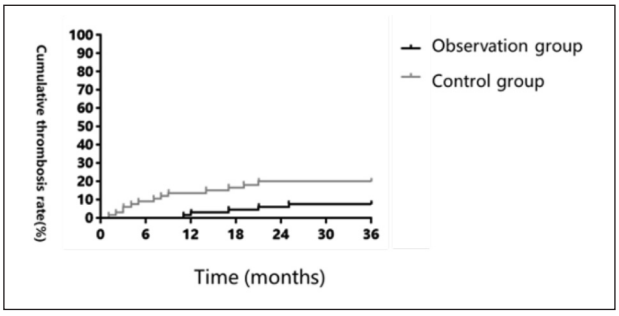

Figure 2: Cumulative thrombotic events in patients of the two groups.

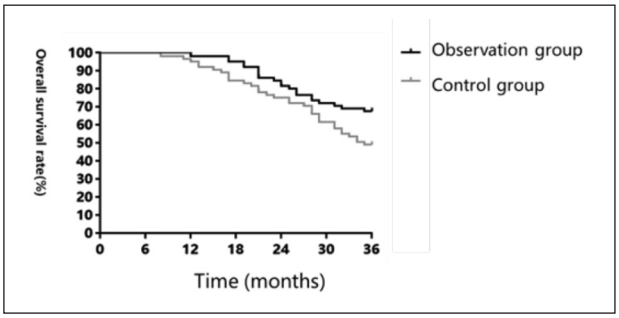

Figure 3: Overall survival in patients of the two groups.

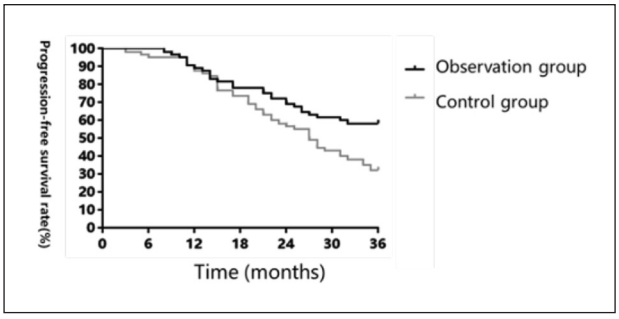

Figure 4: Progression free survival in patients of the two groups.

Comparison of therapeutic safety between the two groups

The incidence of skin rash was significantly lower in the observation group than in the control group (24.62% vs 49.23%; χ^2=8.455, P = 0.004). No significant difference in the incidence of diarrhea was determined between the two groups (P>0.05; Table 4). No serious adverse reactions, hematotoxicity or renal dysfunction were found in this study.

The main adverse reaction was the elevated ALT level. No significant difference in ALT level was found in both groups before treatment (P>0.05). ALT level was significantly lower in the observation group than in the control group after treatment (P<0.05; Table 5).

Group	*n*	Skin rash			Diarrhea	
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Observation	65	12(18.46)	4(6.15)	0	6(9.23)	2(3.08)
Control	65	22(33.85)	8(12.31)	2(3.08)	10(15.38)	4(6.15)
χ^2			8.455		2.000	
P			0.004		0.368	

Table 4: Skin rash and diarrhea in both groups.

Group	*n*	Before treatment	After treatment
Observation	65	29.21±4.87	29.49±13.28
Control	65	28.60±6.25	35.21±2.34
t		0.621	3.420
P		0.536	0.001

Table 5: ALT changes in both groups.

Discussion

Tumor-targeted therapy[11] refers to the combination of anti-tumor drugs and different specific sites of tumors to play a role in killing tumor cells. Epidermal growth factor receptor tyrosine kinase antagonists are the most mature and important targeted therapies at present. The representative drugs are gefitinib, erlotinib and icotinib[12]. Douillard[13] and other studies have shown that gefitinib has a good anti-tumor effect on NSCLC, especially in patients with point mutations in tyrosine kinase domain which often occurs in Asian, adenocarcinoma and women[14]. Simultaneously, with the deepening of cancer research, the relationship between coagulation and lung cancer is receiving more and more attention. Previous studies have suggested that tumor activated coagulation system increases the risk of invasion and metastasis[15]; high levels of hyperfibrinolysis markers are strongly associated with the decline of survival rate in patients with malignant tumors[16]. Although there is no case name of lung cancer in Chinese medicine, because of the diseases of "pulmonary retention, cough, mass formation in the lung, hemoptysis, abdominal mass, and consumptive disease", it is mostly classified into the categories of "pulmonary retention", "mass formation in the lung" and "abdominal mass" in traditional Chinese medicine. Modern Chinese medicine believes that lung cancer is caused by qi deficiency, exogenous evil invasion, impairment of dispersing and descending function of the lung, cohesion of phlegm and turbidity, qi stagnation and blood stasis, and phlegm stasis in the lung[17]. Although the syndrome differentiation of lung cancer is not uniform at present, some scholars have achieved remarkable results in the adjuvant treatment of lung cancer with traditional Chinese medicine[18,19]. This study mainly explored the clinical efficacy of Bufei Huayu Decoction combined with gefitinib in the treatment of NSCLC.

Results from this study demonstrated that the total response rate and clinical benefit rate were significantly higher in the observation group than those in the control group, indicating that the addition of Bufei Huayu Decoction could significantly improve the effect of targeted therapy with gefitinib. Bufei Huayu Decoction is from Bufei Decoction of Yong Lei Qian Fang and Sheng Mai San of Differentiation on Endogenous and Exogenous Diseases. Codonopsis pilosula and astragalus membranaceus benefit qi and strengthen spleen. Rehmannia glutinosa and turtle carapace focusing on nourishing yin and cultivating ben are as monarch drugs. Hedyotis diffusa willd, scutellaria barbata D.don and red peony root clear heat, detoxify and resist cancer. Salvia miltiorrhiza, rhizoma curcumae zedoariae, sparganum stoloniferum, and szechwan lovage rhizome focusing on promoting blood circulation, removing blood stasis and eliminating tumors are as ministerial drugs. Aster tataricus, peucedanum praeruptorum dunn,

and semen armeniacae amarum focusing on removing phlegm, relieving cough and asthma are as adjuvant drugs. Glycyrrhiza uralensis fisch focusing on reconciling various medicines is as the guiding drug. This prescription can effectively clear away heat without damaging yin, detoxify without damaging zheng, promote blood circulation without damaging qi, which can achieve the effects of normal circulation of qi and blood, blood stasis dispersal, swelling and pain relief. Aiming at lung cancer "deficiency of vital energy and unbalance of yin and yang", it has significant effect on replenishing qi and nourishing yin, removing blood stasis and resisting cancer, so it can effectively improve the treatment efficiency. Above-mentioned results are consistent with the results of Feng et al.'s study[20].

A previous study[21] has shown that patients with advanced NSCLC have significant hypercoagulability and disturbance of the fibrinolysis system, presenting the increased PT, APTT, TT, FIB, D-D, and PLT and the decreased MPV and PDW. This may be associated with tissue factors secreted by cancer itself. Tian et al.'s study[22] demonstrated that gefitinib aggravated coagulation disorders in NSCLC patients, which significantly increased the risk of thrombosis in NSCLC patients and seriously affected the prognosis. In this study, our results confirmed that after treatment, PT, APTT, FIB, D-D and PLT were significantly lower in the observation group than those in the control group; MPV and PDW were significantly higher in the observation group than those in the control group, indicating that the addition of Bufei Huayu Decoction significantly improved coagulation disorders caused by gefitinib in NSCLC patients.

Modern pharmacological studies have shown that scutellaria baicalensis has strong anti-inflammatory function; and hedyotis diffusa willd can promote the apoptosis of tumor cells and improve the level of inflammation in patients with tumors[23]. These combined effects can reduce the secretion of inflammatory factors in patients with NSCLC, diminish the platelets activated by cancer cells and produce fibrinolytic inhibitors, thereby reducing the effect on blood coagulation in patients. The cumulative thrombosis in this study indicates that the addition of Bufei Huayu Decoction can significantly diminish the risk of thrombosis, which is strongly associated with the improvement of coagulation dysfunction.

Nevertheless, this study also showed that there was no significant difference in TT between the observation and control groups after treatment, suggesting that the mechanism of coagulation disorder in NSCLC patients has not been fully understood, and needs further investigations.

The comparison of overall survival and progression free survival between the two groups during the 3-year follow-up showed that the mortality risk and disease progression risk of the observation group were significantly lower than those of the control group. It indicated that the addition of Bufei Huayu Decoction could effectively improve the prognosis of NSCLC patients and improve the overall survival rate and progression-free survival rate. The prognosis of patients with advanced NSCLC is poor. It is important to improve the survival rate of patients. The good therapeutic effect of Bufei Huayu Decoction and the improvement of coagulation disorder are helpful to improve the prognosis of patients. A previous study has verified that it has significant inhibitory effect on vascular endothelial growth factor in patients with NSCLC, and can improve immune function and reduce adverse reactions related to chemotherapy. The most common adverse reactions of gefitinib in the treatment of advanced NSCLC are skin rash and diarrhea[24], and its mechanism is still unclear.

Our results showed that the addition of Bufei Huayu Decoction significantly reduced the incidence of skin rash. The theory of traditional Chinese medicine believes that the occurrence of drug-induced rash is caused by the intrusion of the drug, and the exogenous pathogenic factor fights on the skin. Bufei Decoction in Bufei Huayu Decoction can dispel pathogenic factors and strengthen vital qi, in which hedyotis diffusa willd can clear away the heat evil and expel superficial evils, effectively detoxify, and diminish the incidence of skin rash.

Studies have shown that Chinese medicine reduces the incidence of rash, while does not reduce the efficacy of gefitinib. No major malignant adverse events occurred in this study. The main toxic side reaction was the elevated ALT, and all of them improved after symptomatic treatment. The ALT after the addition of Bufei Huayu Decoction was significantly lower than that treated with gefitinib alone, indicating that Bufei Huayu Decoction is safe and reliable, and can alleviate liver function injury to a certain extent.

In summary, Bufei Huayu Decoction combined with gefitinib in the treatment of NSCLC has significant effect, can effectively improve coagulation disorders, reduce the risk of thrombosis, and improve the prognosis of patients, and has good safety.

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