

CLINICAL RESEARCH

## **Efficacy of Bufe Sanjie Decoction in Adjuvant Treatment of Advanced Lung Cancer with the Pattern of Qi Deficiency and Phlegm Obstruction and its Effect on Serum Index**

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### **Keywords**

Bufe Sanjie decoction, Pattern of qi deficiency and phlegm obstruction, Advanced lung cancer, Efficacy, Serum index

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### **Abstract**

**Objective:** The work explored the clinical efficacy of treatment of Bushen Sanjie decoction combined with apatinib mesylate in patients with advanced lung cancer of the pattern of qi deficiency and phlegm obstruction and its effect on serum index. **Methods:** A total of 128 patients with advanced lung cancer of the pattern of qi deficiency and phlegm obstruction in our hospital from Jun. 2018 to Jun. 2020 were divided into control group (n=64) and study group (n=64) by using the random number table method. Control group was treated with apatinib mesylate and study group was treated with Bufe Sanjie decoction combined with apatinib mesylate. The clinical efficacy, serum index, tumor marker, quality of life before and after treatment, and adverse reaction were compared between the two groups. **Results:** The total effective rate was obviously higher in the study group than in the control group ( $P<0.05$ ). The levels of vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), cytokeratin fragment 19 (CYFRA21-1), carcino-embryonic antigen (CEA) and neuron-specific enolase (NSE) of both groups after treatment were obviously decreased in comparison with those before treatment ( $P<0.05$ ), and those in study group were obviously decreased in comparison with those in control group ( $P<0.05$ ). The life quality score of both groups after treatment obviously increased in comparison with that before treatment ( $P<0.05$ ), and that in study group obviously increased in comparison with that in control group ( $P<0.05$ ). The adverse reaction rate was obviously lower in study group than that in control group ( $P<0.05$ ). **Conclusion:** The clinical efficacy of Bufe Sanjie decoction combined with apatinib mesylate in the treatment

of advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction was

significant and it could inhibit the tumor angiogenesis, decrease tumor marker level and improve the life quality of patients.

### Introduction

Lung cancer is one of common malignancies consisting of small cell carcinoma and non-small cell carcinoma. Among lung cancer, non-small cell lung cancer is the most common type, mainly including adenocarcinoma, squamous cell carcinoma and large cell lung cancer. At present, patients with advanced lung cancer are primarily treated with radiotherapy and chemotherapy clinically, but there still exists possibility of tumor cell invasion and metastasis after treatment. Apatinib is an inhibitor of both vascular endothelial growth factor receptor 2 (VEGFR-2) and tyrosine kinase, which can suppress proliferation and induce apoptosis of tumor cells. And the application of apatinib in clinical treatment for lung cancer ameliorates clinical symptoms and effectively prolongs the survival of patients. In recent years, the integration of traditional Chinese and western medicine have been gradually adopted for treatment of patients with advanced lung cancer in clinic. In traditional Chinese medicine science, qi deficiency and phlegm obstruction is a syndrome type of lung cancer and the clinical manifestations of advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction are chest distress, shortness of breath, cough, bloody phlegm and dyspnea, bringing great negative impact upon physical and mental health of patients. Xu et al. used Yiqi Yangyin Jiedu Formula combined with chemotherapy for treatment of advanced non-small cell lung cancer, which resulted

in good therapeutic effect and promoted recovery of patients. This research investigated the clinical efficacy of Bufe Sanjie decoction in combination with apatinib mesylate on advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction and its influence on serum index, aiming to probe into the effective treatment method for patients.

### Materials and methods

#### Clinical data

##### General information

A total of 128 cases with advanced lung cancer of pattern of qi deficiency and phlegm obstruction in our hospital from Jun. 2018 to Jun. 2020 were divided into control group (n=64) and study group (n=64) using the random number table method. The clinicopathological variables of each case including gender, age, tumor stage (TNM stage) and pathological type were collected from patient records. As shown in Table 1, the two groups had comparability because there was no significant difference of general information (gender, age, TNM stage and pathological type) between two groups ( $P>0.05$ ). The research was approved by the Ethics Committee of x(第一作者医院) Hospital (第一作者医院首字母缩写 2 位字母), as all patients volunteered to participate and signed the informed consent.

Table 1 General information between two groups

Group	n	Gender (n)		Age (year)	TNM stage (n)		pathological type (n)	
		Male	Female		IIIb	IV	Squamous cell carcinoma	adenocarcinoma
Study	64	37	27	60.54±8.83	42	22	26	38
Control	64	40	24	59.24±7.92	38	26	23	41
$\chi^2/t/Z$		0.293		0.877	-0.727		0.298	
<i>P</i>		0.588		0.382	0.467		0.585	

### Inclusion and exclusion criteria

Inclusion criteria were: 1. meeting the diagnostic criteria of lung cancer in *Diagnosis and Treatment of Lung Cancer (2nd Edition)* and diagnosed as advanced lung cancer; 2. meeting the diagnostic criteria of lung cancer with the pattern of qi deficiency and phlegm obstruction in *Traditional Chinese Medicine Diagnosis*; 3. no drug treatment received recently.

Exclusion criteria were: 1. allergic to apatinib mesylate; 2. allergic to traditional Chinese medicine; 3. other syndrome types of traditional Chinese Medicine of lung cancer; 4. heart, liver or renal dysfunction combined; 5. other malignant tumor; 6. immune system diseases combined; 7. cognitive dysfunction or mental disorder; 8. chemoradiotherapy received before treatment; 9. women in pregnancy and lactation.

### Method

#### Control group

Control group was treated with apatinib mesylate (Jangsu Hengrui Pharmaceutical Co., Ltd., H20140103, 0.25 g\*10 tablets): oral administration, 0.5 g for once, once a day for 4 weeks continuously.

#### Study group

Based on the treatment of control group, study group was additionally treated with Bufe Sanjie decoction. The major ingredients of that recipe consisted of 15 g *Radix Astragali seu Hedysari*, 15 g *Radix Codonopsis*, 15 g *Semen Coicis*, 15 g *Solanum lyratum Thunb.*, 15 g *Poria*, 15 g *Herba Hedyotis*, 9 g fried *Rhizoma Atractylodis Macrocephalae*, 9 g *Radix Platycodonis*, 9 g *Radix Paeoniae Alba*, 9 g *Pericarpium Citri Reticulatae*, 9 g *Rhizome Pinelliae Preparata*, 6 g *Semen Armeniacae Amarum*, 6 g *Rhizoma Atractylodis*, 6 g *Fructus Amomi Villosi*, 6 g *Glycyrrhizae*, 6 g *Rhizoma Coptidis*, 3 pieces of *Fructus Jujubae*. The modification was made according to symptoms: *Flos Farfarae* for prolonged cough; *Os Draconis* for dizziness or palpitation; powder of *Radix Notoginseng* for bloody sputum; *Semen Ziziphi Spinosae* for difficulty falling asleep; *Endothelium Corneum Gigeriae Galli* for anorexia.

The decoction was taken one dose a day with each dose divided into 2 portions for the morning and the evening. The treatment was lasted for 4 weeks.

### Outcome measures

Clinical efficacy: the clinical efficacy of two groups was evaluated in accordance with the standard of *Guidelines for Clinical Research of Traditional Chinese Medicine New Drugs*. Cured: the clinical symptoms of patients disappeared and the reduction of traditional Chinese medicine syndrome score  $\geq 80\%$ ; markedly effective: the clinical symptoms of patients were obviously improved and  $30\% \leq$  the reduction of traditional Chinese medicine syndrome score  $< 80\%$ ; effective: the clinical symptoms of patients were improved in a certain extent and the reduction of traditional Chinese medicine syndrome score  $< 30\%$ ; ineffective: the clinical symptoms of patients did not change prominently or even exacerbated and the traditional Chinese medicine syndrome score rose. Total effective rate = (the number of cured, markedly effective and effective cases/the number of total cases)  $\times 100\%$ .

Serum index: fasting venous blood was taken from patients before and after treatment, subsequent to which the levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9) were detected by enzyme linked immunosorbent assay (ELISA).

Tumor marker: fasting venous blood was taken from patients before and after treatment, following which the levels of cytokeratin-19-fragment (CYFRA21-1) and carcino-embryonic antigen (CEA) were determined through chemiluminescence immunoassay (CLIA) with ELISA adopted for measurement of neuron-specific enolase (NSE) expression.

Quality of life: the life quality was assessed using European organization for research and treatment (EORTC-C30) scale composed of 30 items, among which 4 grads (1-4) for 1<sup>st</sup>-28<sup>th</sup> items while 7 grades (1-7) for 29<sup>th</sup>-30<sup>th</sup> items. The scale involved 15 domains: 5 functional domains (physical, role, cognitive, emotional and social); 3 symptom domains (fatigue, pain and nausea/vomiting); 1 global

evaluation for quality of life; 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial stability). The score of each domain = sum of scores of items in the domain/the number of item in the domain. The score of life quality was the sum of scores of all domains and the higher score indicated a better quality of life.

Adverse reaction: The occurrence of hypertension, decreased platelet count and anemia in the two groups was observed.

### Statistical analysis

Statistical analysis was operated by SPSS 20.0 (IBM, Armonk, NY, USA).  $\chi^2$  test was employed to compare the enumeration data, whereas the measurement data were performed as the means  $\pm$  standard deviation and contrasted through Student's *t* test. A statistically

significant difference was accepted when  $P < 0.05$ .

## Results

### Clinical efficacy

The total effective rate has a notable difference between two groups, as that of study group was prominently higher than that of control group (Table 2,  $P < 0.05$ ).

### Serum index level

No marked difference of VEGF and MMP-9 levels was observed between two groups before treatment (Table 3,  $P > 0.05$ ) while VEGF and MMP-9 levels of both groups after treatment appreciably declined in comparison with before treatment (Table 3,  $P < 0.05$ ), with those in study group dramatically lower than those in control group (Table 3,  $P < 0.05$ ).

Table 2 Clinical efficacy between two groups [n (%)]

Group	n	Cured	Marked effective	effective	ineffective	Total effective rate
Study	64	18 (28.13)	21 (32.81)	18 (28.13)	7 (10.94)	57 (89.06)
Control	64	12 (18.75)	19 (29.69)	16 (25.00)	17 (26.56)	47 (73.44)
$\chi^2$						5.128
<i>P</i>						0.024

Table 3 Serum index level between two groups

Group	n	VEGF (pg/mL)		MMP-9 (ng/mL)	
		Before	After	Before	After
Study	64	326.74 $\pm$ 42.85	176.74 $\pm$ 25.38*	534.74 $\pm$ 62.85	312.74 $\pm$ 43.70*
Control	64	330.68 $\pm$ 38.45	215.78 $\pm$ 30.55*	541.77 $\pm$ 72.11	384.56 $\pm$ 50.85*
<i>t</i>		-0.547	-7.864	-0.588	-8.569
<i>P</i>		0.585	0.000	0.558	0.000

Note: Compared with before treatment, \* $P < 0.05$

### Tumor marker level

Before treatment, the levels of CYFRA21-1, CEA and NSE did not differ significantly between two groups (Table 4,  $P > 0.05$ ). CYFRA21-1, CEA and NSE levels in two groups after treatment were obviously lower than those before treatment (Table 4,  $P < 0.05$ ) and those of study group markedly decreased in contrast with those of control group (Table 4,  $P < 0.05$ ).

### Life quality score

There was no prominent difference of life quality score between two groups before treatment (Table 5,  $P > 0.05$ ). When compared with before treatment, the life quality scores of two groups notably increased after treatment (Table 5,  $P < 0.05$ ), as life quality of study group was higher than that of control group (Table 5,  $P < 0.05$ ).

**Adverse reaction**

As shown in Table 6, a significant difference of adverse reaction rate between two groups was viewed

and the rate in study group was appreciably lower than that in control group ( $P<0.05$ ).

Table 4 Tumor marker level between two groups (ng/mL)

Group	n	CYFRA21-1		CEA		NSE	
		Before	After	Before	After	Before	After
Study	64	20.73±5.26	8.46±2.13*	112.74±22.76	58.74±12.83*	28.76±5.94	12.34±3.72*
Control	64	21.48±4.85	11.74±2.76*	109.56±20.78	72.64±15.88*	27.64±6.28	15.84±4.11*
<i>t</i>		-0.839	-7.527	0.825	-5.447	1.037	-5.051
<i>P</i>		0.403	0.000	0.411	0.000	0.302	0.000

Note: Compared with before treatment, \* $P<0.05$

Table 5 Life quality score between two groups (point)

Group	n	Before	After
Study	64	54.76±12.38	82.76±8.55*
Control	64	56.24±10.81	75.34±9.95*
<i>t</i>		-0.720	4.525
<i>P</i>		0.473	0.000

Note: Compared with before treatment, \* $P<0.05$

Table 6 Adverse reaction between two groups [n (%)]

Group	n	Hypertension		Decreased platelet count		Anemia		Total
		1~2 grade	3 grade	1~2 grade	3 grade	1~2 grade	3 grade	
Study	64	3 (4.69)	1 (1.56)	3 (4.69)	1 (1.56)	4 (6.25)	1 (1.56)	13 (20.31)
Control	64	6 (9.38)	3 (4.69)	6 (9.38)	2 (3.13)	5 (7.81)	2 (3.13)	24 (37.50)
$\chi^2$								4.600
<i>P</i>								0.032

**Discussion**

In recent years, with economy development, environmental deterioration and the formation of bad living habits, the number of patients with lung cancer gradually increases. Patients easily ignore the hidden and atypical clinical symptoms of early lung cancer to delay treatment, leading to an unsatisfactory prognosis in advanced stage. The pathogenesis of lung cancer remains unclear, with smoking, genetics, metabolism and environmental factors may bring about the disease. In traditional Chinese medicine science, lung cancer belongs to the categories of "pulmonary retention", "lung amassment", "chest pain", "cough" and "hemoptysis" and the long-term obstruction of qi

stagnation, phlegm turbidity, static blood and heat-toxicity in the lung owing to exogenous disease and internal damage results in lung cancer. Caused by multiple factors, lung cancer in different stages has different symptoms of traditional Chinese medicine, especially lung cancer in advanced stage. Specifically, the major pathogenesis of advanced lung cancer is qi deficiency which is common in lung, spleen and kidney, whereas phlegmatic hygrois and obstruction is the symptoms of the disease, which stagnates in sanjiao to exacerbate deficiency of lung, spleen and kidney. Thus, the main treatment approaches of advanced lung cancer with the pattern of qi deficiency and phlegm obstruction should be invigorating the

spleen-lung, nourishing yin and moistening lung as well as promoting blood circulation for removing blood stasis. In the present work, control group was given treatment of apatinib mesylate while study group was treated with Bufeì Sanjie decoction combined with apatinib mesylate and the consequences showed that total effective rate of study group was significantly higher than that of control group, implicating that the combined therapy possessed a better efficacy on advanced lung cancer with the pattern of qi deficiency and phlegm obstruction.

Angiogenesis is closely associated with growth, proliferation, progression and metastasis of malignant tumors. VEGF is a powerful angiogenic factor, which is able to bind to VEGFR-2 so as to advance angiogenesis and facilitate tumor cell proliferation. MMP-9 promotes angiogenesis and induces metastasis of tumor cells. Apatinib mesylate binds to Adenosine triphosphate (ATP) of VEGFR-2 to repress activation of VEGFR-2, block the combination of VEGF and VEGFR-2 and reduce tumor angiogenesis, thereby inhibiting tumor invasion and metastasis. The primary constituents of Bufeì Sanjie decoction are *Radix Astragali seu Hedysari*, *Radix Codonopsis*, *Semen Coicis*, *Solanum lyratum Thunb.*, *Poria*, *Herba Hedyotis*, fried *Rhizoma Atractylodis Macrocephalae*, *Radix Platycodonis*, *Radix Paeoniae Alba*, *Pericarpium Citri Reticulatae*, *Rhizome Pinelliae Preparata*, *Semen Armeniacae Amarum*, *Rhizoma Atractylodis*, *Fructus Amomi Villosi*, *Glycyrrhizae*, *Rhizoma Coptidis* and *Fructus Jujubae*, with *Radix Astragali seu Hedysari* for replenishing qi, invigorating spleen-stomach, liver protection and diuresis; *Radix Codonopsis* for invigorating spleen and stomach, replenishing qi and benefiting lung; *Semen Coicis*, *Solanum lyratum Thunb.* for strengthening the spleen, tonifying the lung, clearing heat and promoting diuresis; *Poria* for invigorating the spleen, regulating stomach qi, calming the heart and soothing the nerves; *Herba Hedyotis* for clearing heat-toxicity and promoting diuresis for stranguria; fried *Rhizoma Atractylodis Macrocephalae* for strengthening the spleen, replenishing qi, eliminating

dampness and relieving diuresis; *Radix Platycodonis* for antipyretic and analgesia, dispelling phlegm and relieving cough; *Radix Paeoniae Alba* for calming the liver, relieving pain, nourishing blood and astringing yin fluid; *Pericarpium Citri Reticulatae* for invigorating the spleen, regulating circulation of qi, eliminating dampness and phlegm, *Rhizome Pinelliae Preparata* for relieving cough, eliminating phlegm, lowering adverse qi and stopping vomiting, *Semen Armeniacae Amarum* for arresting cough, moistening lung, smoothing the intestine and relaxing bowels; *Rhizoma Atractylodis* for eliminating dampness, invigorating the spleen, expelling wind and removing cold; *Fructus Amomi Villosi*, *Glycyrrhizae* for warming the spleen, stimulating the appetite, dissipating dampness and regulating circulation of qi; *Rhizoma Coptidis* for invigorating spleen, replenishing qi, stopping cough and relieving pain; *Fructus Jujubae* for invigorating spleen-stomach, replenishing qi and nourishing blood for tranquillization. The combination of all drugs above realizes effects on replenishing qi and nourishing yin, invigorating the spleen and tonifying stomach as well as dissipating phlegm and resolving masses. Besides, *Radix Astragali seu Hedysari* of Bufeì Sanjie decoction can repress PI3K/Akt signaling pathway, mitosis and proliferation of tumor cells to decline tumor angiogenesis. *Semen Armeniacae Amarum* and *Radix Codonopsis* decrease VEGF level, restrain growth and proliferation of vascular endothelial cells and inhibit angiogenesis so as to suppress tumor growth and metastasis. The results of our research presented that both groups reduced VEGF and MMP-9 levels after treatment when contrasted with before treatment, as VEGF and MMP-9 levels in study group were lower than those in control group, which suggested that Bufeì Sanjie decoction combined with apatinib mesylate could effectively repress tumor angiogenesis of advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction.

Serum tumor markers are key indicators for evaluation of disease progression. CYFRA21-1 is an acidic protein while CEA is an acid glycoprotein and

the levels of the two factors reflect development of tumors. NSE is a specific acid protease secreted by neurons and neuroendocrine cells, which is upregulated when the carcinogenesis happens. It was observed that CYFRA21-1, CEA and NSE levels declined and life quality score rose after treatment relative to before treatment and the amelioration of study group was better than that of control group. Those findings implied that Bufe Sanjie decoction combined with apatinib mesylate down-regulated levels of tumor markers and raised life quality of advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction. Apatinib mesylate is capable of inhibiting VEGFR receptor protein tyrosine kinase ERK1/2-MAPK pathway and restraining tumor cell growth and proliferation to induce tumor cell apoptosis and decline levels of tumor markers. It is reported that p53 is a cancer suppressor gene which can achieve antitumor activity through modulating its downstream target genes such as Bcl-xl and Bax. *Semen Coicis*, *Herba Hedyotis* and *Radix Platycodonis* of Bufe Sanjie decoction are able to elevate p53 and Bax levels as well as repress Bcl-xl expression, thereby inducing tumor cell apoptosis and reducing generation of tumor markers. *Poria* activates macrophages and T cells, facilitates release of cytokines like TNF- $\alpha$  and IL-2, mediates the immune function and enhances the anti-tumor ability so as to eliminate tumor focus, restore physical function and improve quality of life of patients.

In a word, Bufe Sanjie decoction combined with apatinib mesylate had a significant therapeutic efficacy in the treatment of advanced lung cancer patients with the pattern of qi deficiency and phlegm obstruction, which could inhibit the tumor angiogenesis, **decrease tumor marker level** and improve the life quality of patients.

#### Declaration of conflict-of-interest

The authors declare no conflict-of-interest.

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