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Original Article

Clinical observations of sunitinib combined with docetaxel for advanced non-small cell lung cancer and its effects on serum IL-6 and TNF-α

Wang Ming[1], Bao Hui[2]

[1]Department of Oncology, Weihai Central Hospital, Weihai 264400, Shandong, China; [2]Department of Oncology, Yan'an University Affiliated Hospital, Yan'an 716000, Shaanxi Province, China

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Abstract: Objective: The aim of the current study was to investigate the clinical efficacy and safety of sunitinib combined with docetaxel for advanced non-small cell lung cancer (NSCLC). Methods: A total of 78 patients with advanced NSCLC, admitted to Yan'an University Affiliated Hospital, were enrolled in the study. They were randomly divided into Group A and Group B, with 39 cases in each group. Patients in Group A were treated with sunitinib + docetaxel, while patients in Group B were treated with docetaxel + cisplatin. Treatment effective rates, toxic and side effects rates, quality of life, and overall survival (OS) were observed. Serum concentrations of IL-6 and TNF-α were measured by ELISA, before and after treatment. Results: There were no significant differences in disease control rates (DCR) and incidence rates of nausea, vomiting, alopecia, liver dysfunction, renal insufficiency, leukopenia, and hand-foot syndrome, after treatment, between Group A and Group B ($P>0.05$). However, incidence rates of diarrhea, edemas, and oral ulcers in Group A were significantly higher than those in Group B ($P<0.05$). Serum concentrations of IL-6 and TNF-α in Group A and Group B, after treatment, were significantly lower than those before treatment. There were no significant differences in serum concentrations of IL-6 and TNF-α between Group A and Group B after treatment ($P>0.05$). There were no significant differences in improvement rates of quality of life between Group A and Group B ($P>0.05$). There were no significant differences in 3-year OS between Group A and Group B ($P>0.05$). Conclusion: Sunitinib combined with docetaxel is a feasible treatment approach for advanced NSCLC, although some toxic and side effects occur during treatment. Inhibition of IL-6 and TNF-α may be one of the mechanisms of sunitinib combined with docetaxel for treatment of patients with advanced NSCLC.

Keywords: Non-small cell lung cancer, sunitinib, docetaxel, inflammatory factor

Introduction

Lung cancer is one of the common malignant tumors in humans and the main cause of cancer-related deaths [1]. The most common type of lung cancer is non-small cell lung cancer (NSCLC). Its incidence accounts for 85-90% of lung cancers, including large cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Squamous cell carcinoma and adenocarcinoma are the most common types in clinic [2]. NSCLC is characterized by slow cell proliferation, late metastasis, high metastasis rates, and high mortality [3]. At present, treatments for NSCLC include surgical treatment, chemotherapy, and immunotherapy. However, onset of most cases of NSCLC is hidden. It often develops to advanced stages before diagnosis, accompanied by hematogenous metastasis or lymph node metastasis [4, 5]. Therefore, for advanced NSCLC patients, drug therapy is the main treatment [6]. Previous studies have demonstrated that combination chemotherapy based on platinum is the primary treatment for patients with advanced NSCLC. It can alleviate clinical symptoms, improve quality of life, and enhance overall survival (OS) [7]. However, chemotherapy resistance or intolerance is prone to appear in some patients due to personal factors. Chemotherapy often has ineffective therapeutic effects in clinical practice [8]. Therefore, new treatments are particularly important for treatment of patients with advanced NSCLC.

With the development of tumor targeting therapy, targeting therapy drugs for NSCLC have gradually attracted increased attention [9]. Epidermal growth factor receptor (EGFR) is a com-

mon driver gene for lung cancer. It is mainly distributed on the surface of fibroblasts, keratinocytes, and glial cells. It also plays an important role in various physiological processes, such as cell proliferation and growth [10]. Common targeting therapies for EGFR include cetuximab, panitumumab, and sunitinib [11]. Of these, sunitinib is a multi-target EGFR-tyrosine kinase inhibitor with good anti-tumor and anti-angiogenic effects [12]. Docetaxel is a taxane anticancer drug that can induce cell cycle arrest by binding to β-tubulin. Cell cycle can be organized and apoptosis can be promoted, in turn. In clinical settings, docetaxel can be used alone or in combination with other drugs, treating a variety of malignant solid tumors, such as breast cancer and lung cancer [13, 14].

In the past, there have been many clinical applications of sunitinib and docetaxel [15-17]. However, therapeutic effects and safety levels of combination usage in patients with advanced NSCLC requires further investigation. In this study, patients with advanced NSCLC were treated with sunitinib combined with docetaxel. Clinical efficacy, safety, and effects on terleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in patients with advanced NSCLC were observed. The current study aims to provide reference for new chemotherapy regimens in patients with advanced NSCLC.

Data and methods

Baseline data

From January to October 2018, a total of 78 patients with advanced NSCLC, admitted to Yan'an University Affiliated Hospital, were selected. They were randomly divided into Group A and Group B, with 39 cases in each group. There were 23 males and 16 females in Group A, with ages from 23-74 years. The mean age was (46.83±8.51) years old. There were 9 cases of large cell carcinoma, 14 cases of squamous cell carcinoma, and 16 cases of adenocarcinoma. According to TNM staging criteria for lung cancer from Union for International Cancer Control (UICC) [18], there were 10 cases at stage IIIb and 29 cases at stage IV. There were 20 males and 19 females in Group B, with ages from 22-76 years. The mean age was (47.05±9.28) years old. There were 8 cases of large cell carcinoma, 13 cases of squamous cell carcinoma, and 18 cases of adenocarcinoma. Regarding clinical stage, there were 14 cases in stage IIIb and 25 cases in stage IV. This study was approved by the Ethics Committee and all included subjects and family members provided informed consent.

Inclusion and exclusion criteria

Inclusion criteria: Advanced NSCLC confirmed by cytology, histology, and imaging [19]; Age range of 20-77 years old; Normal vital organs, such as normal liver or kidneys, blood routine, and electrocardiogram; Expected lifetime >3 months. Exclusion criteria: Patients having contraindications for chemotherapy drugs, such as sunitinib, docetaxel, and cisplatin; No scheduled chemotherapy regimen or midway change of treatment regimen; Treatment with other anticancer drugs for nearly 1 month; Usage of anti-inflammatory and immunosuppressive drugs for nearly 1 month; Combined with tuberculosis, lung abscess, pneumonia, pulmonary interstitial fibrosis, pulmonary heart disease, other malignant tumors, and serious infections; Mental illness or family mental illness.

Treatment methods

Before chemotherapy, Group B was orally administered dexamethasone (Tianjin Pharmaceutical Xinzheng Co., Ltd., China, batch number: H41021255) at 8 mg/time. It was taken once a day for 3 days. On the first day of chemotherapy, docetaxel (Zhejiang Haizheng Pharmaceutical Co., Ltd., China, batch number: HZ0041129) was intravenously given at a dose of 75 mg/m^2. At the same time, cisplatin (Shandong Qilu Pharmaceutical Co., Ltd., China, batch number: H37021358) was intravenously given at a dose of 25 mg/m^2 for 60 minutes. One course of treatment was 21 days, with 2 courses of treatment given in total.

In Group A, based on docetaxel, sunitinib (Pfizer Italia S. RL, batch number: H20090030) was orally given at a dose of 37.5 mg/time on the first 3 days of chemotherapy. It was taken once a day and discontinued after 4 weeks. Two weeks equals 1 cycle. During treatment, if any discomfort or adverse drug reactions occurred, the dosage was reduced. According to the type and severity of adverse reactions, a gradient of 12.5 mg was used for reduction. The lowest dose was 12.5 mg. The medication should not be discontinued.

Efficacy evaluation

All subjects were evaluated for clinical efficacy 2 months after treatment. According to Response Evaluation Criteria in Solid Tumor (RECIST) from World Health Organization (WHO), they were divided into 4 categories [20]: 1) After treatment, target lesions were completely resolved and 1 month later, complete remission (CR) was reached; 2) After treatment, target lesion diameter was gradually reduced and the reduction ratio of the diameter was more than 50%, compared with that before treatment. One month later, if no new lesions developed, it was considered partial remission (PR); 3) After treatment, target lesion diameter was gradually reduced and the reduction ratio of the diameter was less than 25%, compared with that before treatment. If no new lesions developed, it was defined as stable disease (SD); 4) After treatment, target lesion diameter was increased by more than 25%, compared with that before treatment. If new lesions developed, it was defined as progression disease (PD). CR and RP are clinical efficacy rates. Disease control rate (DCR) = (CR + PR + SD)/total number of cases × 100%. According to Tumor Terminology Criteria for Adverse Reaction (CTCAE), toxic side effects of patients during treatment should be evaluated. Main toxic side effects include nausea, vomiting, alopecia, diarrhea, edema, oral ulcers, liver and kidney dysfunction, leukopenia, and hand foot syndrome.

Quality of life of patients, after treatment, was evaluated according to Karnofsky (KPS) scores [21]. 1) After treatment, if KPS score increases by more than 10 points, it was defined as improved; 2) After treatment, if KPS scores decrease or increase by more than 10 points, it was defined as stable; 3) After treatment, if KPS scores decrease by more than 10 points, it was defined as deteriorative. Improvement rate of quality of life = (improvement + stability)/total number of cases × 100%.

Follow-ups were conducted by telephone or direct communication. Follow-ups were carried out based on NSCLC guidelines published by National Comprehensive Cancer Network (NCCN) [22]. Follow-ups were performed every 3 months for 3 years. The deadline was up to January 2018. OS is the time from initial chemotherapy to the date of last follow-up or death.

Detection methods

On the 1st day before treatment, 5 mL of fasting venous blood was taken from the subjects, as well as 2 months after treatment. It was placed in a vacuum tube containing no anticoagulants. The serum was separated by centrifugation and placed in a refrigerator at -20°C for later use. Serum concentrations of IL-6 and TNF-α were measured by ELISA [23]. Levels were detected according to ELISA test kit instructions for human IL-6 and TNF-α (Thermo Fisher Scientific (China) Co., Ltd.). Samples to be tested and the kits were taken from the refrigerator 30 minutes in advance, balancing the room temperature. A blank hole, a standard hole, and a sample hole for testing were, respectively, established. Moreover, 100 μL of the sample dilution was added to the blank hole and 100 μL of the standards or samples to be tested were added to the rest of the holes, respectively. They were mixed gently, covered with the membrane, and incubated at 37°C for 120 minutes. The liquid in each hole was discarded and each hole was dried. Next, 100 μL of biotin labeling antibody working solution was added to each hole. It was mixed gently and incubated at 37°C for 60 minutes. The liquid in each hole was discarded and each hole was dried. It was washed 3 times. Afterward, 100 μL of horseradish peroxidase labeled avidin working solution was added to each hole. Each hole was then incubated at 37°C for 60 minutes. The liquid in each hole was discarded and each hole was dried. It was washed 3 times, then 90 μL of the substrate solution was added to each hole in order. It was kept from light, developing for 15 minutes at 37°C. Moreover, 50 μL of the stop solution was added to each hole to terminate the reaction. OD values of each hole were measured at a wavelength of 450 nm using a BIOBASE2000 full-automatic TRITURUS (Jinan Xinbeixi Biotechnology Co., Ltd., China). Concentrations of IL-6 and TNF-α were also calculated.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (IBM Corp, Armonk, NY, USA). Data was plotted using GraphPad Prism 7. Enumeration data are expressed by [n (%)] and comparisons between groups were performed by Chi-squared tests. Measurement data are expressed by mean ± standard deviation ($\bar{x}$ ± sd). Student's

Table 1. Baseline data for Group A and Group B [n (%)] ($\bar{x}$ ± sd)

Category	Group B (n=39)	t/χ^2 value	*P* value
Gender		0.466	0.495
Male	20 (51.28)		
Female	19 (48.72)		
Age	47.05±9.28	0.109	0.913
BMI (kg/m^2)	24.73±2.53	0.612	0.543
Pathological type		0.214	0.899
Large cell carcinoma	8 (20.51)		
Squamous cell carcinoma	13 (33.33)		
Adenocarcinoma	18 (46.15)		
TNM staging		0.326	0.963
IIIb	14 (35.90)		
IV	25 (64.10)		
KPS score	62.35±5.08	0.396	0.693
EGFR		0.467	0.792
Mutant	31 (79.49)		
Wild type	1 (2.56)		
Unknown	7 (17.95)		
CA125 (U/mL)	270.16±7.68	1.811	0.074
CEA (ng/mL)	126.59±10.24	0.759	0.450
Smoking history		0.831	0.362
Yes	31 (79.49)		
No	8 (20.51)		
Drinking history		0.206	0.650
Yes	22 (56.41)		
No	17 (43.59)		
Marital status		0.717	0.699
Unmarried	5 (12.82)		
Married	27 (69.23)		
Other	7 (17.95)		

Table 2. Comparison of clinical efficacy results between Group A and Group B [n (%)]

Category	Group A (n=39)	Group B (n=39)	χ^2 value	*P* value
CR	5 (12.82)	2 (5.13)	-	-
PR	21 (53.85)	12 (30.77)	-	-
SD	11 (28.21)	21 (53.85)	-	-
PD	2 (5.13)	4 (10.26)	-	-
DCR	94.87	89.74	0.722	0.395

t-test of independent samples was used to compare measurement data between groups. Paired t-test was used for comparisons within groups, before and after treatment. The OS of patients with advanced NSCLC was drawn by the Kaplan-Meier method. Log-rank test was used for comparisons. P<0.05 indicates statistically significant differences.

Results

No significant differences in baseline data between the two groups

There were no significant differences in baseline data, including gender, age, body mass index (BMI), pathological type, TNM stage, KPS score, EGFR, carbohydrate antigen (CA) 125, carcinoembryonic antigen (CEA), smoking history, drinking history, and marital status, between Group A and Group B (P>0.05; **Table 1**).

No significant differences in clinical efficacy between the two groups

After treatment, there were 5 cases of CR (12.82%), 21 cases of PR (53.85%), 11 cases of SD (28.21%) and 2 cases of PD (5.13%) in Group A. The DCR was 94.87%. After treatment, there were 2 cases of CR (5.13%), 12 cases of PR (30.77%), 21 cases of SD (53.85%), and 4 cases of PD (10.26%) in Group B. The DCR was 89.74%. There were no significant differences in DCR between Group A and Group B after treatment (P>0.05; **Table 2**).

Incidence rates of diarrhea, edemas, and oral ulcers in Group A significantly higher than those in Group B

In Group A, there were 23 cases (58.97%) of nausea and vomiting, 1 case (2.56%) of alopecia, 24 cases (61.54%) of diarrhea, 21 cases (53.85%) of edema, 17 cases (43.59%) of oral ulcers, 15 cases (38.46%) of liver dysfunction, 17 cases (43.56%) of renal insufficiency, 14 cases (35.90%) of leukopenia, and 12 cases (30.77%) of hand foot syndrome. In Group B, there were 16 cases (41.03%) of nausea and vomiting, 5 cases (12.82%) of alopecia, 11 cases (28.21%) of diarrhea, 2 cases (5.13%) of edema, 2 cases (5.13%) of oral ulcers, 13 cases (33.33%) of liver dysfunction, 16 cases of renal insufficiency (41.03%), 13 cases of leukopenia (33.33%), and 5 cases of hand foot syndrome (12.82%).

Table 3. Comparison of incidence of toxic side effects in Group A and Group B [n (%)]

Category	Group A (n=39)	Group B (n=39)	χ^2 value	*P* value
Nausea and vomiting	23 (58.97)	16 (41.03)	2.513	0.113
Alopecia	1 (2.56)	5 (12.82)	2.889	0.089
Diarrhea	24 (61.54)	11 (28.21)	8.759	0.003
Edema	21 (53.85)	2 (5.13)	22.260	<0.001
Oral ulcer	17 (43.59)	2 (5.13)	15.660	<0.001
Liver dysfunction	15 (38.46)	13 (33.33)	0.223	0.637
Renal insufficiency	17 (43.59)	16 (41.03)	0.052	0.819
Leukopenia	14 (35.90)	13 (33.33)	0.057	0.812
Hand foot syndrome	12 (30.77)	5 (12.82)	3.686	0.055

There were no significant differences in incidence rates of nausea, vomiting, alopecia, liver dysfunction, renal insufficiency, leukopenia, and hand-foot syndrome between Group A and Group B (P>0.05). However, incidence rates of diarrhea, edema, and oral ulcers in Group A were significantly higher than those in Group B (P<0.05; **Table 3**).

No significant differences in changes of serum IL-6 and TNF-α before and after treatment of the two groups

There were no significant differences in serum concentrations of IL-6 and TNF-α between Group A and Group B before treatment (P> 0.05). Serum concentrations of IL-6 and TNF-α in Group A and Group B, after treatment, were significantly lower than those before treatment (P<0.001). There were no significant differences in serum concentrations of IL-6 and TNF-α, after treatment, between Group A and Group B (P>0.05; **Table 4** and **Figure 1A**, **1B**).

No significant differences in improvements of quality of life between the two groups

After treatment, regarding quality of life in Group A, 14 cases (35.90%) were improved, 20 cases (51.28%) were stable, and 5 cases (12.82%) were worsened. The improvement rate of quality of life was 35.90%. Regarding quality of life in Group B, 12 cases (30.77%) were improved, 21 cases (53.85%) were stable, and 6 cases (15.38%) were worsened. The improvement rate of quality of life was 30.77%. There were no significant differences in improvement rates of quality of life between Group A and Group B (P>0.05; **Table 5**).

No significant differences in 3-year OS between the two groups

Follow-up results showed that the 3-year OS of Group A was 28.21% (11/39), while the 3-year OS of Group B was 25.64% (10/39). There were no significant differences in 3-year OS between Group A and Group B (P> 0.05; **Figure 2**).

Discussion

NSCLC is a malignant tumor that poses a great threat to human life. Its morbidity and mortality rank among the top malignant tumors [24]. Chemotherapy is the main treatment for advanced NSCLC. Combination chemotherapy based on platinum is the main way to improve the OS of patients with advanced NSCLC [25]. Clinically, docetaxel combined with cisplatin is one of the first-line medications for patients with advanced NSCLC. Although combined chemotherapy greatly improves patient OS, the bodies of patients with advanced NSCLC will rapidly worsen. Some patients are not sensitive to chemotherapy regimens, resulting in poor clinical prognosis and quality of life [26, 27]. Therefore, it is particularly important to explore new treatment approaches for patients with advanced NSCLC.

With the continuous development of molecular genetics and molecular targeted drugs, key mutant genes that cause NSCLC have been identified [28]. EGFR gene mutations play an important role in the pathogenesis of NSCLC patients. Therefore, EGFR is an important target for treatment of NSCLC. EGFR ligand competitive inhibitor is an EGFR molecular targeted drug. It is a research hotspot for treatment of malignant solid tumors. Objective effects have been achieved in clinical practice [29, 30]. Sunitinib is in a class of oral EGFR-tyrosine kinase inhibitors that can competitively bind to EGFR with EGFR endogenous ligands. By inhibiting the activation of tyrosine kinase, EGFR signaling pathways can be inhibited. It plays a role in inhibiting tumor growth and angiogenesis. Growth, proliferation, and metastasis levels of tumor cells are affected [31]. Docetaxel is a taxane antitumor drug, confirmed to inhibit

Table 4. Comparison of serum concentrations of IL-6 and TNF-α before and after treatment between Group A and Group B ($\bar{x} \pm sd$)

Group	n	IL-6 (ng/L)		t value	*P* value	TNF-α (μg/L)		t value	*P* value
		Before treatment	After treatment			Before treatment	After treatment		
Group A	39	226.41±17.43	171.65±12.58	15.910	<0.001	2.62±0.16	1.69±0.24	20.140	<0.001
Group B	39	228.54±15.25	168.41±11.73	19.520	<0.001	2.57±0.13	1.61±0.19	26.040	<0.001
t value	-	0.574	1.176	-	-	1.515	1.632	-	-
P value	-	0.567	0.243	-	-	0.134	0.107	-	-

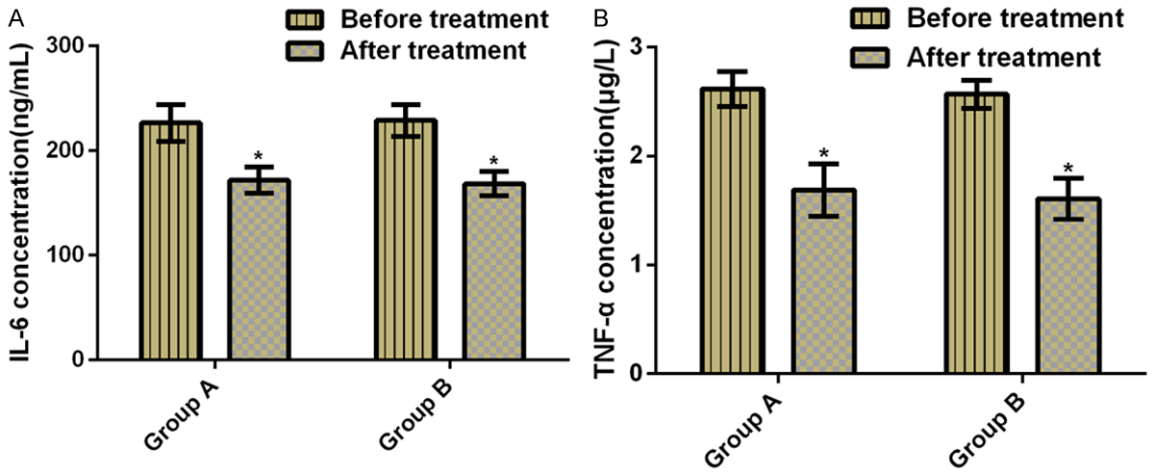

Figure 1. Comparison of serum concentrations of IL-6 and TNF-α before and after treatment between Group A and Group B. Comparison of serum concentration of IL-6 before and after treatment between Group A and Group B (A); Comparison of serum concentration of TNF-α before and after treatment between Group A and Group B (B). Note: *P<0.001 means comparison with that before treatment.

Table 5. Comparison of improvement rate results of quality of life between Group A and Group B [n (%)]

Group	n	Improve	Stable	Deterioration	Improvement rate (%)
Group A	39	14 (35.90)	20 (51.28)	5 (12.82)	35.90
Group B	39	12 (30.77)	21 (53.85)	6 (15.38)	30.77
χ^2 value	-	-	-	-	0.231
P value	-	-	-	-	0.631

tumor capillary formation and vascular endothelial cell growth in a dose-dependent manner [32]. The anti-tumor effects of sunitinib combined with docetaxel have been previously demonstrated. For example, in the study of Pan, as a single agent, sunitinib can play an anti-cell proliferation role in NSCLC cell lines with EGFR-T790M and K-ras mutations [33]. Moreover, anti-cell proliferation effects of docetaxel and sunitinib were significantly better, compared with sunitinib alone. Robert confirmed that sunitinib combined with docetaxel for patients with advanced solid tumors has controllable safety [34]. No pharmacokinetic drug interactions will occur. Antitumor activity in patients with advanced solid tumors has been demonstrated. Therefore, sunitinib may become a new targeted therapy for treatment of NSCLC. However, its efficacy and safety should be discussed. Results of this study showed no significant differences in DCR, improvement rates of quality of life, and 3-year OS between Group A and Group B after treatment. This suggests that sunitinib combined with docetaxel is a feasible treatment approach for advanced NSCLC. In the study of Yi, combined docetaxel with sunitinib or docetaxel alone in patients with metastatic gastric cancer did not significantly prolong disease progression [35]. However, it increased objective remission rates. These results are in ac-

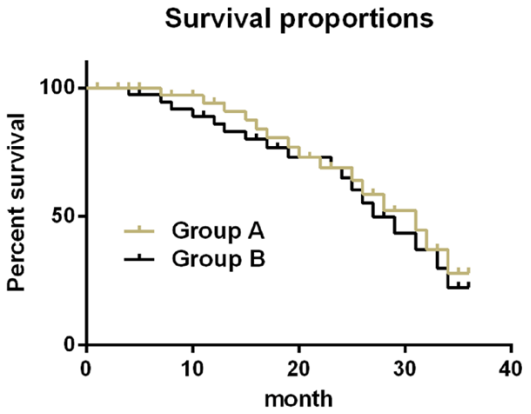

Figure 2. Comparison of 3-year OS between Group A and Group B.

cord with present results. Patients in the abovementioned study developed toxic side effects, such as stomatitis, diarrhea, and hand foot syndrome. In the current study, patients with advanced NSCLC developed toxic effects, such as diarrhea, edema, and oral ulcers during the combined treatment of sunitinib and docetaxel.This may be the reason that sunitinib has a long half-life and wide effect range. It can act on a variety of receptor tyrosine kinases. Its action is non-specific and extensive. Thus, it is easy to cause a wide range of toxic side effects [36].

Many oxygen free radicals can be induced from inflammatory reactions during the occurrence and development of NSCLC. Oxidative stress damage and lipid peroxidation can be caused [37]. IL-6 and TNF-α are inflammatory cytokines. IL-6 can induce many inflammatory cells by activating macrophages and T-cells. Therefore, an inflammatory response occurs [38]. TNF-α can promote the adhesion and aggregation of inflammatory cells, causing an inflammatory reaction. It can promote neovascularization, apoptosis, and necrosis [39]. IL-6 and TNF-α play an important role in treatment and prognosis of malignant tumors. In the study of Schneider, serum inflammatory factors, such as TNF-α, were shown to be clinical efficacy predictors of radiofrequency ablation for treatment of NSCLC [40]. In addition, a study by Chang confirmed that IL-6 is a prognostic marker of chemotherapy survival in patients with advanced NSCLC [41]. To further analyze the possible mechanisms of sunitinib combined with docetaxel for treatment of advanced NSCLC, the current study used ELISA to detect serum concentrations of IL-6 and TNF-α, before and after treatment. Results showed that serum concentrations of IL-6 in Group A and Group B, after treatment, were significantly lower than those before treatment. In a study by Zhu, rapid changes in tumor vascular permeability and circulating inflammatory biomarkers were shown to be potential determinants of response and resistance to sunitinib in hepatocellular carcinoma [42]. Inflammation control may be crucial to improving therapeutic effects for advanced hepatocellular carcinoma. Therefore, inhibition of inflammatory response may be one of the mechanisms of action for sunitinib combined with docetaxel in patients with advanced NSCLC. However, specific regulatory mechanisms remain to be determined.

Although this study confirmed that sunitinib combined with docetaxel is a feasible approach for treatment of advanced NSCLC, there were still some shortcomings. First, this study did not use sunitinib alone for treatment of advanced NSCLC. Thus, the clinical efficacy of single sunitinib in advanced NSCLC has not been determined. Second, this study did not conduct *in vitro* experiments to observe the specific regulation mechanisms of sunitinib combined with docetaxel for NSCLC. Therefore, there were certain defects. These shortcomings need to be addressed in the future for the sake of supporting present conclusions.

In summary, sunitinib combined with docetaxel is a feasible approach for treatment of advanced NSCLC. Although some toxic and side effects occur during treatment, they are controllable. Inhibition of IL-6 and TNF-α may be one of the mechanisms of action for sunitinib combined with docetaxel for treatment of patients with advanced NSCLC.

Disclosure of conflict of interest

None.

Address correspondence to: Bao Hui, Department of Oncology, Yan'an University Affiliated Hospital, Yan'an 716000, Shaanxi Province, China. Tel: 0911-2881796; E-mail: baohuiyx@163.com

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