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ORIGINAL ARTICLE

Clinical analysis of anlotinib in the third-line treatment of advanced non-small cell lung cancer

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Summary

Purpose: *To evaluate the efficacy and safety of anlotinib in the third-line treatment of advanced non-small cell lung cancer (NSCLC) and assess its effect on the patient quality of life.*

Methods: *The patients, who were pathologically diagnosed with advanced (stage IIIB/IV) NSCLC and had been treated with at least first-line and second-line systemic chemotherapy, admitted to and treated in the hospital were selected and randomly assigned into the anlotinib group and thecontrol group (1:1). The patients in the two groups took orally 12 mg anlotinib and placebo, respectively, once a day for 14 consecutive days, with 21 d as 1 cycle, until disease progressed or intolerable adverse events occurred. The clinical efficacy, incidence rate of adverse events and quality-of-life score were recorded. In addition, patients were followed up, and their survival was recorded.*

Results: *The objective response rate (ORR) and disease control rate (DCR) were 12.5% (6/48) and 68.8% (33/48) in the anlotinib group and 0% and 31.3% (15/48) in the control group, respectively, significantly better in the anlotinib group than those in the control group (p=0.011, p<0.001). Through the Common Terminology Criteria Adverse Events (CTCAE) evaluation, the common adverse reactions observed in patients in the anlotinib group were mostly of grade I-II, and grade III-IV adverse reactions included hypertension, hand-foot syndrome, thyroid dysfunction, oral mucositis, hemoptysis, and fatigue. Compared with those before treatment, the scores of physical function, emotional function, general health status and fatigue in the Quality of Life Questionnaire Core 30 (QLQ-C30) scale were significantly increased (p<0.001, p=0.044, p=0.002, p=0.034), whereas the scores of pain and dyspnea significantly declined (p=0.039, p=0.011). In the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) scale, the scores of cough, shortness of breath, and chest pain were significantly lower than those before treatment, implying relieved symptoms after treatment, while the scores of oral pain and pricking in hands and feet were higher than those before treatment (p<0.05). Based on the results of follow-up, the 1-year overall survival (OS) and progression-free survival (PFS) were 54.2% (26/48) and 4.2%(2/48) in the anlotinib group and 39.6% (19/48) and 0% in the control group, respectively, showing no statistically significant differences between the two groups (p=0.469, p=0.068).*

Conclusions: *Anlotinib is safe and effective in the third-line treatment of advanced NSCLC, which is able to significantly improve the quality of life of patients.*

Key words: *Anlotinib, non-small cell lung cancer, third-line treatment, efficacy*

Introduction

Lung cancer is one of the malignancies with the highest incidence and mortality rates at present [1]. Patients with advanced lung cancer are mainly treated with chemotherapy, but many of them cannot tolerate chemotherapy due to poor fitness score, older age, and adverse reactions.Patients with failed second-line chemotherapy can only undergo supportive treatment and palliative radiotherapy [2,3].

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Anlotinib, a new multi-target tyrosine kinase inhibitor (TKI), mainly represses vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs), platelet-derived growth factor receptors (PDGFRs) and stem cell factor receptors [4]. Previous clinical studies have manifested that anlotinib is effective against non-small cell lung cancer (NSCLC), medullary thyroid carcinoma and soft tissue sarcoma, with controllable toxicity [5-8]. Anlotinib has been approved for marketing to treat NSCLC that has failed first-line and second-line treatment in China. Currently, there is no standard third-line therapeutic regimen for advanced lung cancer patients having progression after second-line chemotherapy.

In the present study,the efficacy and safety of anlotinib in the third-line treatment of advanced NSCLC and its effect on the quality of life of patients were investigated.

Methods

General data

The clinical data of 66 advanced NSCLC patients admitted to the hospital were collected. *The inclusion criteria* were set as follows: 1) patients aged ≥18 years old, 2) those pathologically diagnosed with advanced (IIIB/IV) NSCLC with measurable lesions, 3) those with disease progression after receiving at least two systemic chemotherapy regimens or intolerant of chemotherapy, 4) those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 point(s), 5) those with a life expectancy of over 3 months, and 6) those with sufficient bone marrow function (neutrophil count >1.5×10^9 cells/L, platelet count >100×10^9 cells/L, and hemoglobin >10 g/L), liver function (total bilirubin <1.0 times the upper limit of normal, alanine transaminase<1.5 times the upper limit of normal, and aspartate aminotransferase <1.5 times the upper limit of normal), renal function (serum creatinine level <133 μmol/L and urea nitrogen <8.3 mmol/L) and arterial blood oxygen partial pressure >60 mmHg without oxygen inhalation. *The exclusion criteria* involved: 1) patients with central or cavity lung squamous cell carcinoma, or accompanied by hemoptysis (hemoptysis volume >50 mL/d), 2) those with uncontrolled central nervous system metastasis, 3) those with severe cardiopulmonary diseases, such as interstitial lung disease, 4) those with gastrointestinal diseases affecting drug absorption, such as habitual diarrhea or constipation, 4) those with arterial/venous thrombosis in the past 6 months, such as cerebrovascular accidents, deep vein thrombosis, or pulmonary embolism. The baseline data of the two groups of patients, including age, gender, tumor pathologic type, clinical stage, and ECOG score, are shown in Table 1. All patients enrolled were informed and signed the informed consent in accordance with *Declaration of Helsinki*.This study was approved by the ethics committee of Xijing Hospital.

Table 1. Baseline characteristics of the studied patients

Characteristics	*Anlotinib group (n=48)* *n(%)*	*Control group (n=48)* *(%)*	*p value*
Age (years)	58.6±7.9	59.8±8.3	0.470
Gender			
Male	25 (52.1)	29 (60.4)	0.538
Female	23 (47.9)	19 (39.6)	
Pathologic type			0.399
Squamous cellcarcinoma	15 (31.3)	13 (27.1)	
Adenocarcinoma	28 (58.3)	33 (68.7)	
Others	5 (10.4)	2 (4.2)	
Smoking history			0.401
Yes	31 (64.6)	27 (56.3)	
No	17 (35.4)	21 (43.7)	
Clinical stage			0.516
IIIB	18 (37.5)	14 (29.2)	
IV	30 (62.5)	34 (70.8)	
ECOG PS score (points)			0.580
0	22 (45.8)	19 (39.6)	
1	26 (54.2)	29 (60.4)	
Previous chemotherapy			0.414
Second-line chemotherapy	28 (58.3)	25 (52.1)	
Third-line chemotherapy	20 (41.7)	23 (47.9)	

ECOG: Eastern Cooperative Oncology Group.

Therapeutic methods

In the anlotinib group, patients took orally anlotinib hydrochloride (trade name: Fucovi, Chia Tai Tianqing Pharmaceutical Group Co., Ltd.,Lianyungang, China, NMPN: H20180004) at a dose of 12 mg (half an hour after a meal, once a day for 14 d, rest 7d), with 21 d as 1 cycle. The medication was stopped if the disease progressed, intolerable adverse events occurred, or patients died or refused to continue treatment. The dose was adjusted to 10 mg once a day when adverse events of grade 3 and above were observed during treatment, and it was reduced to 8 mg once a day in the case of intolerable adverse reactions. The drug should be discontinued if adverse reactions were remained intolerable.

In the control group, patients took 1 tablet of placebo once a day for 14 consecutive days, with 21 d as 1 cycle.

Observation indexes

The efficacy was assessed based on RECIST 1.1, categorized as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR, the percentage of patients with CR+PR in all patients) and disease control rate (DCR, the percentage of patients with CR+PR+SD in all patients) were calculated. Adverse reactions after taking the drug were evaluated as per National Cancer Institute-Common Terminology Criteria Adverse Events (NCI-CTCAE) Version 4.0.

The quality of life of patients was assessed through two scales of the European Organization for Research and Treatment of cancer (EORTC) [Quality of Life Questionnaire Core 30 (QLQ-C30, 3.0 version) and Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)] [9]. Patients were followed up, and their overall survival (OS, time from random enrollment to death from any cause) and progression-free survival (PFS, time from random enrollment to disease progression or death) were recorded.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s), and compared between groups through t-test. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison between groups. Survival curves were plotted according to the Kaplain-Meier method, and Log-rank test was adopted to verify whether the difference in survival were statistically significant between the two groups. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of short-term efficacy between the two groups of patients

After treatment, there were 6 cases of PR, 27 cases of SD and 15 cases of PD in the anlotinib group (n=48), with an ORR of 12.5% (6/48) and a DCR of 68.8% (33/48), and 0 cases of PR, 15 cases of SD and 33 cases of PD in the control group (n=48), with an ORR of 0% and a DCR of 31.3% (15/48). The ORR and DCR showed statistically significant differences between the two groups, significantly better in anlotinib group than those in control group (p=0.011, p<0.001).

Incidence rate of adverse reactions in patients

In the anlotinib group, adverse reactions such as hypertension, hand-foot syndrome and thyroid dysfunction were most commonly observed, which were grade I-II in most patients according to CTCAE evaluation. Besides, there were grade

Table 2. Comparison of adverse reactions of patients in the two studied groups

	Anlotinib group (n=48)		*Control group (n=48)*		*p value*
	Grade I-IV n(%)	*Grade III-IV n(%)*	*Grade I-IV n(%)*	*Grade III-IV n(%)*	
Fatigue	14 (29.2)	1 (2.1)	11 (22.9)	0 (0)	0.485
Nausea and vomiting	4 (8.3)	0 (0)	3 (6.3)	0 (0)	0.695
Diarrhea	9 (18.8)	0 (0)	4 (8.3)	0 (0)	0.136
Hemoptysis	12 (25.0)	2 (4.2)	6 (12.5)	0 (0)	0.117
Hypertension	33 (68.8)	11 (22.9)	15 (31.3)	0 (0)	0.001
Proteinuria	10 (20.8)	0 (0)	5 (10.4)	0 (0)	0.160
Hypertriglyceridemia	7 (14.6)	0 (0)	5 (10.4)	0 (0)	0.537
Hypercholesterolemia	8 (16.7)	0 (0)	3 (6.3)	0 (0)	0.109
Hyperglycemia	6 (12.5)	0 (0)	4 (8.3)	0 (0)	0.230
ALT/AST elevation	7 (14.6)	0 (0)	5 (10.4)	0 (0)	0.537
Thyroid dysfunction	20 (41.7)	2 (4.2)	0 (0)	0 (0)	0.001
Oral mucositis	14 (29.2)	3 (6.3)	0 (0)	0 (0)	0.001
Hand-foot syndrome	18 (37.5)	2 (4.2)	1 (2.1)	0 (0)	0.001

III-IV adverse reactions including hypertension, hand-foot syndrome, thyroid dysfunction, oral mucositis, hemoptysis and fatigue. No drug-related death ooccured. Hemoptysis was observed in 12 patients, with grade I-II hemoptysis (relieved after symptomatic cough suppressant and expectorant or carbazochrome sodium sulfonate injection) in 10 of them and grade III hemoptysis (relieved after intravenous injection of Agkistrodon acutus blood thrombin and discontinuance of anlotinib) in the remaining two. The blood pressure of patients with hypertension was controlled after administration of antihypertensive drugs, and no hypertensive crisis or hypertensive emergency were found. In addition, no hypertension-induced dose reduction or anlotinib discontinuation was observed. Grade III hand-foot syndrome was found in 2 patients, which was attenuated to grade I after the dose of anlotinib was reduced to 10 mg once a day. There were 15 cases of hypothyroidism, including 13 cases of grade I-II (no special treatment was performed) and 2 cases of grade III (alleviated to grade I after thyroxine replacement therapy). Grade I hyperthyroidism was observed in 5 patients, and no special treatment was given. There was no thyroid dysfunction-induced dose reduction or drug discontinuation. Fourteen patients had oral mucositis and were recommended to have good oral hygiene, use mouthwashand eat no spicy foods. Among them, 3 suffered grade III oral mucositis that was relieved to grade I after the dose of anlotinib was reduced to 10 mg once a day.

Table 3. Comparison of posttreatment EORTC-QLQ-C30 and EORTC-QLQ- LC13 scale scores of patients treated with Anlotinib

Characteristics	*Pretreatment*	*1 month posttreatment*	*p value*
QLQ-C30			
Functioning scales			
Physical	65.33±14.41	77.20±13.19	0.001
Role	53.21±19.52	60.60±20.68	0.094
Emotional	74.73±15.74	80.96±14.49	0.044
Social	49.11±12.65	56.84±13.90	0.101
Cognitive	83.36±18.05	81.67±17.55	0.643
General health status	42.46±12.55	49.97±10.08	0.002
Symptom scales			
Appetite loss	30.73±21.15	35.52±20.04	0.258
Constipation	9.64±12.89	9.07±13.35	0.513
Dyspnea	34.34±12.98	26.90±15.09	0.011
Fatigue	40.35±18.26	48.24±29.02	0.034
Financial impact	34.58±17.45	30.63±18.33	0.511
Nausea and vomiting	15.88±19.48	22.03±16.93	0.102
Diarrhea	10.33±7.53	16.56±9.29	0.179
Pain	34.39±18.75	27.83±19.73	0.039
Sleep disturbance	36.98±20.95	31.68±19.53	0.203
QLQ-LC13			
Cough	42.74±10.47	27.80±10.85	0.001
Hemoptysis	10.46±10.45	12.52±11.04	0.350
Shortness of breath	31.83±13.31	16.51±15.65	0.001
Dysphagia	5.89±9.79	9.41±8.80	0.691
Oral pain	12.68±10.15	18.54±12.30	0.013
Pricking in hands and feet	13.58±10.62	20.41±11.56	0.003
Alopecia	23.76±13.33	26.73±10.59	0.230
Chest pain	36.64±10.97	30.93±11.48	0.015
Shoulder Pain	26.16±10.84	22.03±12.77	0.091
Other sites pain	30.39±14.47	26.27±11.44	0.125

EORTC: European Organization for Research and Treatment of Cancer.

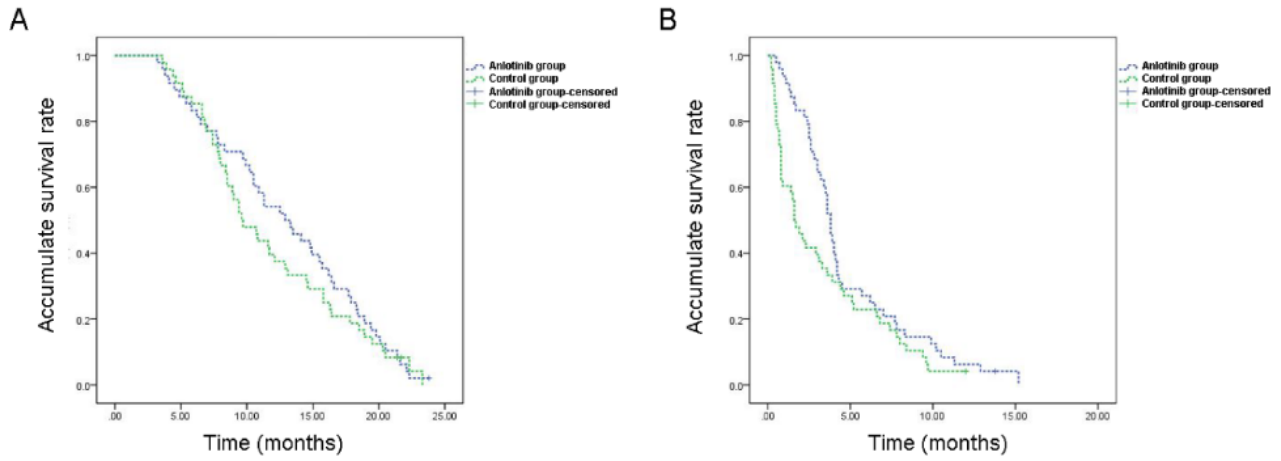

Figure 1. Kaplan-Meier survival curves of patients in the anlotinib group and Control group. The differences between overall survival rate **A:** and progression free survival rate **B:** of patients in the anlotinib group and Control group had no statistical difference (p=0.469, p=0.068).

The incidence rates of hypertension, oral mucositis, hand-foot syndrome, and thyroid dysfunction were significantly higher in the anlotinib group than those in the control group (p<0.001), while the incidence rate of other adverse reactions exhibited no statistically significant difference between the two groups (p>0.05)(Table 2).

Score of patient quality of life

Compared with those before treatment, the scores of physical function, emotional function and general health status in the Quality of Life Questionnaire Core 30 (QLQ-C30) scale were significantly increased (p<0.001, p=0.044, p=0.002), implying that the quality of life of patients is improved after treatment with anlotinib. The score of fatigue was significantly higher (p=0.034), whereas the scores of pain and dyspnea were significantly lower than those before treatment (p=0.039, p=0.011). In the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) scale, the scores of cough, shortness of breath, chest pain, oral pain and pricking in hands and feet displayed statistically significant differences before and after treatment (p<0.05). The scores of cough, shortness of breath and chest pain were significantly lowered, suggesting relieved symptoms after treatment, while the scores of oral pain and pricking in hands and feet were increased compared with those before treatment (Table 3).

Patient survival and follow-up results

Patients were followed up for 3-24 months, with 1 and 2 case(s) of loss to follow-up in the anlotinib group and control group, respectively. Based on the results of follow-up, the median OS and PFS were 12.9 and 4.1 months in the anlotinib group and 11.3 and 1.7 months in the control group, respectively. The 1-year OS and PFS were 54.2% (26/48) and 4.2%(2/48) in the anlotinib group and 39.6% (19/48) and 0% in the control group, respectively. Survival curves of patients (Figure 1) were plotted by the Kaplain-Meier method. Log-rank test was conducted, and it was found that the OS and PFS displayed no statistically significantly differences between the two groups (p=0.469, p=0.068).

Discussion

As a small-molecule multi-target tyrosine kinase inhibitor newly developed, anlotinib is one of the most important advances in NSCLC treatment in recent years, which affects tumor angiogenesis and exerts anti-tumor effects by targeting kinases including VEGFR, PDGFR, FGFR and c-Kit and inhibiting their activity [10]. Various existing phase II and III clinical studies have demonstrated that anlotinib is effective against many solid tumors like NSCLC, soft tissue sarcoma, gastric cancer, colorectal cancer, medullary thyroid cancer, differentiated thyroid cancer, and esophageal squamous cell carcinoma [11-13]. According to the results of a randomized, double-blind, placebo-controlled phase II clinical study of anlotinib in the treatment of advanced NSCLC (ALTER0302), the DCR and ORR were 83.3% and 10% in the anlotinib group, respectively [14]. The results of a subsequent phase III clinical study (ALTER0303) revealed that, in contrast with theplacebo group, the anlotinib group had significantly prolonged OS (9.63 months *vs.* 6.30 months), and increased PFS (by 3.97 months, 5.37 months *vs.* 1.40 months),

DCR (80.95% *vs.* 37.06%) and ORR (9.18% *vs.* 0.7%) [15]. In this study, the ORRand DCR were 12.5% and 68.8%, respectively, slightly lower than those in the ALTER0303 study. This may be caused by the small sample size, advanced overall stage and low ECOG score. The median OS and PFS, ORR, and DCR were significantly better in the anlotinib group than those in the control group.

The major adverse events caused by anlotinib were hypertension, hand-foot syndrome, thyroid dysfunction, fatigue and oral mucositis based on their incidence rate. Hypertension, the most common adverse reaction of anti-angiogenic anti-tumor drugs, is found in almost all patients using VEGF-TKIs [16]. In the present study, the incidence rate of hypertension was 68.8%, including grade III (22.9%) and no grade IV. Patients with grade I and II hypertension continuously took the drug and were observed closely, while for those with grade III hypertension, ACEI/ARB or calcium antagonists were given to effectively control blood pressure at 120-140/80-100 mmHg. Hand-foot syndrome refers to dullness or redness of the extremities, obvious discomfort, swelling, and tingling of the palms and soles. In this study, hand-foot syndrome was observed in 37.5% of patients, mostly grade I-II and mainly manifested as painless minor skin changes or dermatitis occasionally with mild exfoliative changes or blisters. Only 1 patient had skin changes with pain. Patients with such a symptom were instructed to wear soft cotton clothes and socks to avoid injury and rubbing of the affected area. The symptom gradually subsided after observation or application of urea ointment or vaseline ointment. In this study, anlotinib-related diarrhea was grade I-II, and patients were advised to drink plenty of water, eat light and digestible foods, avoid eating greasy and spicy foods, and take intestinal probiotics and montmorillonite powder. During treatment with anlotinib, the thyroid function was monitored, attention was paid to symptoms of hypothyroidism or hyperthyroidism, and symptomatic treatment was given if necessary.

EORTC QLQ-C30, the core scale in the scale system for measurement of quality of life of cancer patients, is researched and developed by EORTC to evaluate the quality of life of all cancer patients. On this basis, specific modules for different characteristics and clinical symptoms of different tumors have been formulated [17]. QLQ-LC13, one of the standard tools for measurement of quality of life of lung cancer patients, has been translated into over 60 languages, widely used in the world's countries [18]. In this study it was found that the scores of physical function, emotional function, and general health of patients significantly rose after anlotinib treatment compared with those before treatment ($p<0.05$), suggesting that anlotinib improves the overall health of patients. The improvement of physical function may be because the reduction of tumor foci or tumor burden alleviates the pressure on organs and weakens the discomfort, thus improving the general health status. The improved emotional function of patients after the medication may be related to the relieved physical discomfort of patients due to the relief of lung cancer-related symptoms such as cough, sputum, chest pain and pain, resulting in ameliorated depression and anxiety. Symptoms such as pain, dyspnea, chest pain, cough and shortness of breath were significantly improved compared with those before treatment, suggesting that anlotinib relieves the clinical symptoms of lung cancer. The constipation score was decreased with treatment, while the diarrhea score was increased, which may be because anlotinib treats diarrhea. Fatigue, oral pain, and pricking in hands and feet were worse than those before treatment, which may be also caused by drug-induced adverse reactions. The above results indicate that anlotinib can relieve symptoms to some extent and improve the overall quality of life, but during treatment, close monitoring and prompt management of adverse reactions are essential.

There were still some shortcomings in this study. Specifically, the sample size was small, the time and content of follow-up were separately short and not comprehensive, and the effects of differences in education, social background, and personal feelings on the quality of life score were not taken into account. Therefore, further multicenter randomized controlled trials with a large sample size should be carried out in the future to confirm the conclusion of this study.

Conclusions

Anlotinib is safe and effective in the third-line treatment of advanced NSCLC, which can evidently improve the quality of life of patients.

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Conflict of interests

The authors declare no conflict of interests.

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