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Research Article
Factors Influencing the Efficacy of Anlotinib in the Treatment of Advanced Non-Small Cell Lung Cancer

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Abstract

Background and Objective: Anlotinib as a third-line or beyond therapy can prolong the survival of patients with intermediate-stage Non-Small Cell Lung Cancer (NSCLC). However, there are few reports on the factors related to anlotinib. This study aimed to analyze the efficacy of anlotinib on advanced NSCLC and the factors affecting the efficacy. **Materials and Methods:** Two hundred patients with advanced NSCLC were randomly grouped into the control group (CNG) (N = 100) treated with cisplatin combined with Gemcitabine and the experimental group (EG) (N = 100) treated with anlotinib. The efficacy, erythrocytes index, Vascular Endothelial Growth Factor (VEGF), tumour markers and adverse effects of the two groups were compared. **Results:** The EG had higher DCR than the CNG ($p<0.05$) and lower incidence of loss of appetite and gastrointestinal reactions than the CNG ($p<0.05$), The EG had lower FEIR, FEER, ATER, DTER, lower serum VEGFA, VEGFB, VEGFC, BFGF, HDGF levels and lower serum CYFRA21-1, CEA, CA125, CA199 levels than the CNG ($p< 0.05$), Multivariate results showed that age (≥60 years), tumour stage (stage IV), tumour diameter (≥3 cm), pre-treatment ECOG score (≥2), EGFR mutation (mutant type) and treatment timing (fourth line and above) were all possible risk factors affecting the efficacy of NSCLC ($OR>1$, $p<0.05$). **Conclusion:** Anlotinib can improve the efficacy of treatment on advanced NSCLC and the efficacy is affected by patient age, tumour stage, tumour diameter and EGFR mutation.

Key words: Advanced non-small cell lung cancer, anlotinib, efficacy, erythrocyte immune function, tumour vascular neoplasia, influencing factors

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Patients with Non-Small Cell Lung Cancer (NSCLC) showed no specific symptoms in the early stage and when manifestations such as hemoptysis and dry coughs appear, the tumour load is already too high. Most patients are already in the middle and late stages when diagnosed, missing the best time window for complete surgical excision, so chemotherapy, radiotherapy and targeted therapy are preferred[1,2]. Two-drug combination chemotherapy containing platinum-based drugs is a common treatment regimen for advanced NSCLC. Traditional chemotherapeutic drugs are primarily cytotoxic drugs, which promote apoptosis and inhibit tumour cells by affecting nucleic acid synthesis and destroying DNA structure but they also inhibit cells that divide and proliferate faster, such as mucosal epithelial cells of the digestive tract, human bone marrow hematopoietic cells, germ cells and hair follicle cells and destroy healthy cells and immune cells[3,4]. The essential role of angiogenesis in tumour growth was first proposed in 1971 by Judah Folkman, which provided the theoretical basis and research direction for the subsequent discovery of new multi-targeted drugs[5].

Studies have found that the expression of protein tyrosine kinase (PTK) is closely related to the biological behaviours of tumour cell proliferation, differentiation and apoptosis, so effective blockade of the complex kinase (TK) signalling expression is particularly crucial for prolonging the survival of tumour patients and inhibiting proliferation and growth of tumour cells[6]. Anlotinib is a new tyrosine kinase inhibitor, which can efficiently inhibit the activity of Fibroblast Growth Factor Receptor (FGFR), Platelet-Derived Growth Factor Receptor (PDGFR) and Vascular Endothelial Growth Factor (VEGFR) to comprehensively block tumour growth and angiogenesis[7]. On May 10, 2018, China food and drug administration (CFDA) approved the use of anlotinib in the treatment of advanced NSCLC[8]. Clinical trials have demonstrated dual benefits of progression-free survival (PFS), overall survival (OS) and a high safety profile for anlotinib as a third-line or beyond therapy in the treatment of intermediate-stage NSCLC[9,10]. However, most studies have focused on exploring the efficacy and safety of anlotinib and fewer studies have been published centring on factors associated with anlotinib efficacy. This study used the principle of randomized control to comparatively assess the efficacy and mechanism of action of anlotinib in the treatment of advanced NSCLC and to analyze the relevant factors affecting the efficacy, aiming to aid the exploration of predictive markers and screening susceptible populations.

MATERIALS AND METHODS

Clinical data: Two hundred patients with advanced NSCLC who visited the hospital from September, 2018 to May, 2020 were grouped according to the random number table. In the control group (CNG), there were 100 cases, 60 males and 40 females, aged 43-81 years, mean age of 64.03±5.27 years, tumour diameter 4.36±1.15 cm, pathological type: 72 squamous carcinomas, 15 adenocarcinomas, 13 others, tumour stage: 33 stages IIIB, 32 stage IIIC, 35 stages IV, 46 cases with smoking history, 21 cases with a family history of tumour, 35 cases with surgical history. In the experimental group, there were 100 cases, 63 males and 37 females, aged 46-78 years, mean age of 63.86±4.19 years, tumour diameter 4.21±1.06 cm, pathological type: 75 squamous carcinomas, 14 adenocarcinomas, 11 others, tumour stage: 31 stages IIIB, 32 stage IIIC, 37 stages IV, 51 cases with smoking history, 18 cases with a family history of tumour, 38 cases with surgical history. The baseline data of the EG and the CNG was comparable ($p>0.05$). This study was approved by the medical ethics committee of Yichun People's Hospital. All patients provided written informed consent.

Inclusion criteria: Patients who meet the relevant diagnostic criteria in the Chinese Medical Association Clinical Guidelines for the treatment of Lung Cancer[11], Patients who were diagnosed with NSCLC by puncture with at least one measurable lesion, Patients whose expected survival >3 months, clinical stage IIIB, IIIC, IV, karnofsky functional status (KPS) score >60, unable to receive surgical treatment, voluntarily signed informed consent.

Exclusion criteria: The presence of cachexia, brain metastasis, concomitant other types of lung disease, pathological type of small cell lung cancer, tumour invasion of blood vessels, concomitant hematopoietic dysfunction of heart, brain, liver, kidney and bone marrow, intolerance to study drugs due to chronic diarrhoea, dysphagia, intestinal obstruction, coagulation dysfunction, history of receiving other antitumor drugs 4 weeks before enrollment, the presence of any bleeding, hemoptysis (>50 mL/day), concomitant urinary protein abnormalities or uncontrolled hypertension, mental abnormalities, mental retardation, women during pregnancy or lactation.

Methods:

- **CNG:** Cisplatin combined with gemcitabine was administrated, i.e., at day 2-6, 75 mg m^{-2} cisplatin (10 mg, Yunnan Plant Pharmaceutical Co., Ltd., H53021679) was administered intravenously, at day 1 and 8, 1000 mg m^{-2}

Gemcitabine (0.2 g, Harbin Yu Heng Pharmaceutical Co., Ltd., H20040958) was administered intravenously. The 21 days was 1 course of treatment and a total of 2 courses of treatment were administrated

- **EG:** Third-line therapy with anlotinib hydrochloride, i.e., anlotinib hydrochloride (12 mg C23H22FN3O3, Zhengda Tianqing Pharmaceutical Group Co., Ltd., H20180004) was orally taken before breakfast, 12 mg/day, 1 time/day. The treatment was continued for 2 weeks and interrupted for 1 week, i.e., 21 days as 1 course of treatment, was a total of 2 courses was offered

Outcome measurement:

- **Therapeutic effect:** On basis of efficacy criteria for solid tumours (RECIST) 1.1[12], complete remission (CR) was indicated by the complete disappearance of tumour after 2 courses of treatment, partial remission (PR): >30% reduction in lesion diameter without new lesions, Stable Disease (SD): <30% reduction in lesion diameter or an increase of <20% without new lesions, disease progression (PD): An increase of >20% in lesion diameter or the appearance of new lesions:

$$\text{Disease control rate (DCR)} = \frac{\text{CR+PR+SD}}{\text{Total number of cases}} \times 100\%$$

$$\text{Objective effective rate (RR)} = \frac{\text{CR+PR}}{\text{Total number of cases}} \times 100\%$$

- **Red blood cell immune indices:** Three milliliter of peripheral venous blood was collected before and after 2 courses of treatment and anticoagulated with heparin. Red blood cells were isolated after dilution using 0.9% sodium chloride solution, washed and centrifuged, prepared as 0.5 mL of red blood cell suspension, followed by treatment with 0.25% complement-sensitizing yeast polysaccharide suspension, fixing with glutaraldehyde and staining. The immune adhesion inhibitor (FEIR), immune adhesion-promoting factor (FEER), erythrocyte synergism with tumour erythrocyte wreath rate (ATER) and erythrocyte direct to tumour erythrocyte wreath (DTER) of erythrocytes were PUZS-300 automatic biochemical analyzers (Shanghai YuYan Scientific Instruments Co.)
- **VEGF and tumour markers:** Three milliliter of fasting venous blood was collected from both groups before and after 2 courses of treatment, centrifuged for 5 min on a Hettich MIKRO220/220R centrifuge (Germany). The supernatant was extracted for the determination of VEGF isoforms VEGFA, VEGFB, VEGFC and fine basic fibroblast growth factor (BFGF) and hepatoma-derived growth factor (HDGF) levels using an enzyme-linked immunosorbent assay (Wuxi Yuncui Biotechnology Co.). VEGFC, BFGF and HDGF levels were measured by ELISA (Shanghai Harco Biotechnology Co. 199 (CA199) levels
- **Adverse effects:** Adverse reactions were evaluated concerning the National Cancer Institute's Common Toxic Reactions Grading Scale 4.0[13], including hypertension, bone marrow suppression, loss of appetite, hepatic and renal impairment, gastrointestinal reactions and malaise

Statistical analysis: SPSS 23.0 was used to process the data. The measurement data conforming to normal distribution were expressed as $\bar{x} \pm s$ and paired t and independent t-tests were used for between-group and within-group comparisons, respectively, count data (%) was compared using χ^2 test, unconditional logistic regression analysis was used to analyze the relevant factors affecting the efficacy of anlotinib for NSCLC, with a = 0.05 and $p<0.05$ as significant differences.

RESULTS

Therapeutic efficacy: RR was 43.00% in the EG and 40.00% in the CNG (40.00%) ($p>0.05$), indicating no statistically significant difference, DCR was 74.00% in the EG, which was higher than 59.00% in the CNG, exhibiting significant difference ($p<0.05$) in Table 1, suggesting that anlotinib could effectively improve the efficacy in the treatment of advanced NSCLC.

Erythrocyte immune indexes: The levels of erythrocyte immune indexes showed no significant difference between the two groups before treatment ($p>0.05$). After treatment, FEIR, FEER, ATER and DTER were 49.62±4.03, 44.03±3.76, 46.25±5.52 and 23.34±3.46% in the CNG and 42.02±3.92, 54.03±4.86, 54.61±4.36 and 31.25±4.25% in the EG, respectively. The EG had lower FEIR and higher FEER, ATER and DTER after treatment than the CNG ($p<0.05$) shown in Fig. 1, indicating that anlotinib could improve erythrocyte immune function in patients with advanced NSCLC.

Vascular endothelial growth factor: There was no significant difference in the levels of vascular endothelial growth factor before treatment between the two groups ($p>0.05$). After treatment, VEGFA, VEGFB, VEGFC, BFGF and HDGF were 126.72±21.03, 125.67±17.03, 103.38±24.09 pg mL^{-1}, 22.03±3.38 and 15.72±2.97 ng L^{-1} in the CNG and 73.36±15.57, 81.06±10.16, 67.72±15.62 pg mL^{-1}, 16.27±3.02 and 11.02±3.02 ng L^{-1} in the EG, respectively. The

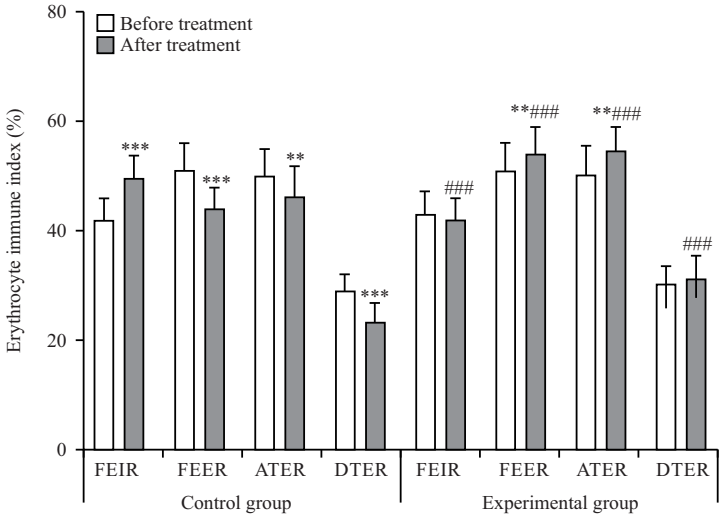

Fig. 1: Comparison of erythrocyte immune parameters (%)

Anlotinib enhances the erythrocyte immune function of patients with advanced NSCLC, improve the ability of erythrocytes to adhere to tumour cells and reduce the immune damage, compared to experimental group before treatment, **p<0.01, ***p<0.001, compared to the control group and ###p<0.001

Table 1: Comparison of efficacy (n (%))

Groups	CR	PR	PD	SD	RR	DCR
Control group (n = 100)	2 (2.00)	38 (38.00)	19 (19.00)	41 (41.00)	40 (40.00)	59 (59.00)
Experimental group (n = 100)	6 (6.00)	37 (37.00)	31 (31.00)	26 (26.00)	43 (43.00)	74 (74.00)#

Compared to the control group and #p<0.05

Table 2: Comparison of adverse effects (n (%))

Groups	Hypertension	Grade III and loss bone marrow suppression	Loss of appetite	Impairment of liver and kidney function	Gastrointestinal reactions	Fatigue
Control group (n = 100)	8 (8.00)	5 (5.00)	16 (16.00)	11 (11.00)	27 (27.00)	7 (7.00)
Experimental group (n = 100)	10 (10.00)	1 (1.00)	7 (7.00) #	8 (8.00)	14 (14.00) #	5 (5.00)

Compared to the control group and #p<0.05

levels of serum VEGFA, VEGFB, VEGFC, BFGF and HDGF were lower in the EG after treatment than in the CNG (p<0.05) in Fig. 2, indicating that anlotinib could inhibit tumour vascularization and tumour cell growth.

Tumour markers: There was no significant difference in tumour marker levels before treatment between the two groups (p>0.05). After treatment, CYFRA21-1, CEA, CA125 and CA199 were 12.26±3.16 and 15.13±3.26 μg L^{-1}, 39.73±4.25 and 15.72±3.28 U mL^{-1} in the CGN and 7.25±2.01 and 11.25±2.85 μg L^{-1}, 31.02±3.49 and 11.02±2.75 U mL^{-1} in the EG. The levels of serum CYFRA21-1, CEA, CA125, CA199 were lower in the EG after treatment than in the CNG (p<0.05) in Fig. 3, indicating that anlotinib could down-regulate expression of tumour marker.

Adverse effects: The CG had 8 cases of hypertension, 5 cases of grade III and bone marrow suppression, 16 cases of loss of appetite, 11 cases of impairment of liver and kidney function, 27 cases of gastrointestinal reactions and 7 cases of fatigue, while the cases of the above-mentioned adverse effects in the EG were 10, 1, 7, 8, 14 and 5, respectively. The incidence of loss of appetite and gastrointestinal reactions was 7.00 and 8.00% in the EG, which was lower than 16.00 and 11.00% in the CNG, showing a significant difference (p<0.05) in Table 2.

Univariate analysis affecting the efficacy of anlotinib for NSCLC: There was no significant difference in gender, smoking history, family history of tumours, surgical history and pathological type between the DCR group and the non-DCR group (p>0.05), indicating that these factors had little influence on the efficacy of anlotinib in the treatment of NSCLC. The proportion of age <60 years (31 cases vs. 4 cases), tumour stage of stage IIIB+IIIC (55 cases vs. 8 cases), tumour diameter of <3 cm (24 cases vs. 2 cases), pre-treatment ECOG score of 0-1 point (63 cases vs. 9 cases), EGFR mutation (wild type) (65 cases vs. 13 cases) and three-line treatment (39 cases vs. 4 cases) in DCR group was significantly higher than that in

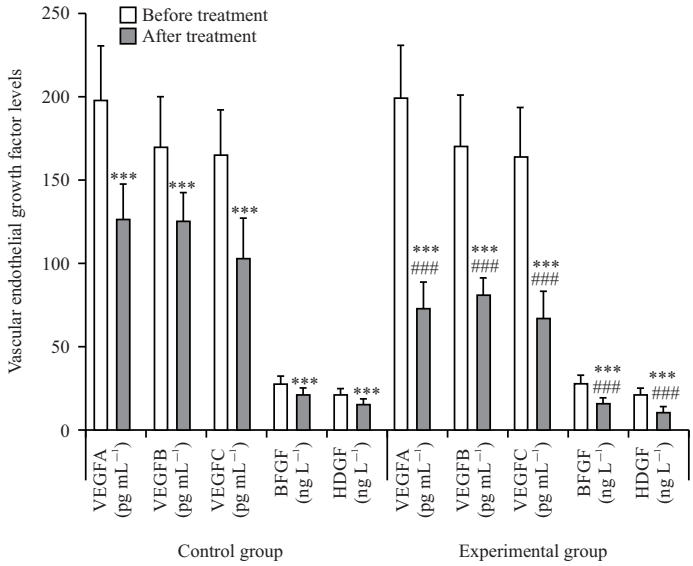

Fig. 2: Comparison of vascular endothelial growth factor

Anlotinib inhibits tumour angiogenesis and tumour cell growth, compared to experimental group before treatment, ***p<0.001, compared to the control group and ###p<0.001

Table 3: Univariate analysis of factors affecting the efficacy of anlotinib for NSCLC

Factors	Number of cases	DCR (n = 74)	Non-DCR (n = 26)	χ^2	p-value
Gender					
Male	63	47	16	0.032	0.858
Female	37	27	10		
Age					
<60 years	35	31	4	6.533	0.011
≧60 years	65	43	22		
Smoking history					
Yes	51	38	13	0.014	0.906
No	49	36	13		
Family history of tumours					
Yes	18	11	7	1.895	0.169
No	82	63	19		
Surgical history					
Yes	38	24	14	3.745	0.053
No	62	50	12		
Pathological type					
Squamous carcinoma	75	56	19	0.011	0.994
Adenocarcinoma	14	10	4		
Other	11	8	3		
Tumor stage					
Stage IIIB+IIIC	63	55	8	24.429	0.000
Stage IV	37	10	18		
Tumor diameter					
<3cm	26	24	2	7.257	0.007
≧3 cm	74	50	24		
Pre-treatment ECOG score					
0-1 point	72	63	9	22.836	0.000
≧2 points	28	11	17		
EGFR mutation					
Mutant	22	9	13	14.557	0.000
Wild type	78	65	13		
Timing of treatment					
Three line	43	39	4	4.224	0.040
Fourth line and above	57	35	12		

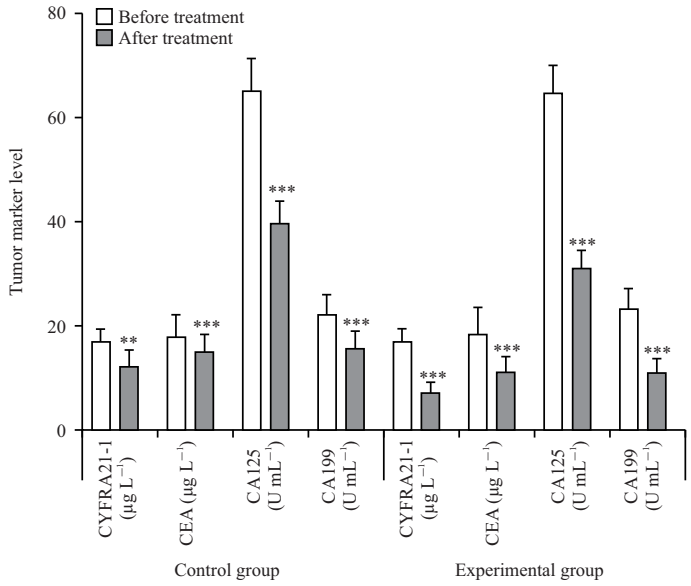

Fig. 3: Comparison of tumour marker levels

Anlotinib can effectively treat advanced NSCLC and down-regulate tumor marker expression, compared to experimental group before treatment, ***p<0.001, compared to the control group and ###p<0.001

Table 4: Multifactorial analysis of factors affecting the efficacy of anlotinib for NSCLC

Factors	B	Standard error	Wald	p-value	OR	95% CI
Age (≧60 years)	1.378	0.592	5.407	0.020	3.965	1.242-12.663
Tumor stage (stage IV)	2.516	0.547	21.185	0.000	12.375	4.239-36.123
Tumor diameter (≧3 cm)	1.751	0.777	5.081	0.024	5.760	1.257-26.399
Pre-treatment ECOG score (≧2)	2.381	0.526	20.491	0.000	10.818	3.858-30.333
EGFR mutation (mutant type)	1.977	0.529	13.944	0.000	7.222	2.558-20.387
Timing of treatment (4th line and above)	1.070	0.335	10.239	0.001	3.343	0.987-11.324

the non-DCR group, with significant difference ($p<0.05$), indicating that age (≧60 years), tumour stage (stage IV), tumour diameter (≧3 cm), pre-treatment ECOG score (≧2), EGFR mutation (mutant type) and timing of treatment (fourth line and above) may be the influencing factors for the efficacy of anlotinib in the treatment of NSCLC in Table 3.

Multifactor analysis affecting the efficacy of anlotinib for NSCLC: The multifactorial results showed that age (60 years) (OR = 3.965, $p = 0.020$), tumor stage (stage IV) (OR = 12.375, $p = 0.000$), tumor diameter (≧3 cm) (OR = 5.760, $p = 0.024$), pre-treatment ECOG score (≧2) (OR =10.818, $p = 0.000$), EGFR mutation (mutant type) (OR = 7.222, $p = 0.000$) and timing of treatment (fourth line and above) (OR = 3.343, $p = 0.000$) were all possible risk factors for NSCLC outcomes (OR>1, $p<0.05$) in Table 4.

DISCUSSION

Anlotinib is a new, orally administered tyrosine kinase inhibitor with dual efficacy of tumour growth inhibition and anti-angiogenesis. Gao *et al.*[14] found in an ALTER0303 multicenter, double-blind, randomized, controlled, phase III, clinical trial that mPFS and mOS were longer in the anlotinib group than placebo (5.37 vs. 1.40 months and 9.46 vs. 6.37 months), so anlotinib is clinically approved for the treatment of advanced NSCLC in the third line and beyond. Han *et al.*[15] found in another multicenter randomized double-blind trial that anlotinib prolonged PFS and OS in IIIB/IV stage patients who were intolerant or developed drug resistance after treatment with targeted drugs. An *ex vivo* experiment by Lu[16] found that anlotinib downregulated serum CCL2 levels and inhibited tumour cell proliferation and tumour angiogenesis through the CCL2/MMP9 signalling pathway and that CCL2 may be a biomarker for predicting efficacy. In this study, the DCR of the EG was higher than that of the CNG while the incidence of loss of appetite and gastrointestinal reactions was lower than that of the CNG. The serum CYFRA21-1, CEA, CA125 and CA199 levels were lower after treatment than that of the CNG, indicating that anlotinib can effectively improve advanced NSCLC, down-regulate expression of tumour marker, exhibiting a high safety profile.

Studies on immune status have mostly focused on humoral and cellular immunity and there are fewer studies on the relationship between erythrocyte immune function and tumour, while erythrocyte adhesion is closely related to antitumor immunity and disease regression. A previous study[17] reported that most patients with advanced NSCLC exhibited abnormally decreased serum FEER, ATER and DTER levels and most of them experience a secondary decrease in erythrocyte immune function. In this study, FEIR was lower and FEER, ATER and DTER were higher in the EG than in the CNG after treatment, indicating that anlotinib enhances erythrocyte immune function in patients with advanced NSCLC, improve the ability of erythrocytes to adhere to tumour cells and reduce the immune damage. However, the specific mechanism of action still needs to be further explored.

Tumour cells can secrete angiogenic cytokines that promote endothelial cell migration and angiogenesis. VEGF is expressed in several malignant tumours and VEGF combined with VEGFR activates the complexine kinase receptor, causing conduction of downstream signalling and promoting endothelial cell survival, proliferation and migration[18,19]. Shen[20] found that anlotinib blocked VEGF/PDGF-BB/FGF-2-induced angiogenesis and reduced VEGF/PDGF-BB/FGF-2-induced cell migration and capillary formation in endothelial cells. Lin[21] also found that anlotinib can inhibit microvessel formation and affect endothelial cell migration, proliferation and lumen formation by antagonizing downstream signalling pathways mediated by PDGFR, VEGFR, FGFR and other angiogenesis-related factors and can also be involved in many biological processes in tumour cells by affecting c-Kit kinase activity. In this study, the levels of VEGFA, VEGFB, VEGFC, BFGF and HDGF were lower in the EG after treatment than in the CNG, indicating that anlotinib could inhibit tumour vascularization and tumour cell growth. The reason may be that the PTK signalling pathway is closely associated with biological behaviours of tumour cells such as proliferation, differentiation, migration and kinase activation can activate tumour signalling pathways such as RAS/RAF/MEK/MAPK () and PI3K/AKT/mTOR and vascular endothelial cell survival to regulate tumour angiogenesis, which affects tumour cell growth[22]. Anlotinib can block the PTK signaling pathway and produce potent antagonistic effects on c-Kit, Ret and other kinases related to tumour cell proliferation, thus preventing angiogenesis VEGFR1/2/3, FGFR1/2/3 and other related kinases and inhibiting tumour angiogenesis and proliferation, Moreover, VEGFR2 is the main target of Anrotinib regarding anti-angiogenesis, which affects the downstream signalling pathway by inhibiting VEGFR2 phosphorylation, thus inhibiting angiogenesis[23,24].

This study analyzed the factors associated with the efficacy of anlotinib and found that age, tumour stage, tumour diameter, pre-treatment ECOG score, EGFR mutation and timing of treatment may be risk factors affecting the efficacy of NSCLC and it was concluded that age <60 years, IIIB+IIIC stage, tumour diameter <3 cm, pre-treatment ECOG score of 0-1, EGFR wild type and third-line treatment were more likely to benefit from anlotinib treatment. Han *et al.*[15] found that anlotinib as a third-line treatment provided significant PFS benefits in patients with RA-NSCLC compared with placebo and toxicity profiles showed good tolerance, similar to the findings of this study. However, due to the small sample size of this study, the research results need to be further confirmed. It is still necessary to extend the follow-up period, expand the sample size and conduct multi-centre and prospective studies to confirm the findings of this study.

CONCLUSION

To summary, anlotinib may enhance the efficacy of treatment on advanced NSCLC through various mechanisms such as enhancing erythrocyte immune function, inhibiting tumour angiogenesis and downregulating the expression of tumour markers and the efficacy is affected by patient age, tumour stage, tumour diameter and EGFR mutation.

SIGNIFICANCE STATEMENT

This study discovered that patients' age, tumour stage, tumour diameter, EGFR mutation and other factors may be important factors affecting the efficacy of anlotinib, which can be beneficial for clinicians to select appropriate treatment options for lung cancer based on these factors. This study will help the researchers to uncover the critical area of suitability for anlotinib treatment in populations that many researchers were not able to explore. Thus a new theory on the suitability of anlotinib for the population may be arrived at.

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