Anlotinib Is Active for the Patients Failed From the Prior Antiangiogenic Therapy: Anti-angiogenic Therapy Might Be Cross-line Used

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Abstract

Objective The purpose of this study was to initially investigate whether previous antiangiogenic therapy (bevacizumab and endostar) affect the efficacy of anlotinib in patients with lung cancer (LC).

Methods We retrospectively collected the clinical data of LC patients treated with anlotinib. They were divided into two groups, namely group A (anlotinib after failure of previous antiangiogenic drugs and group B (no prior use of antiangiogenic drugs). Use propensity score matching (PSM) to control the confounding factors between the groups.

Results A total of 160 patients were included in the analysis. The median OS in group A and group B was 11.8 months vs. 16.1 months ($P=0.120$), and the median PFS was 3.1 months, 4.7 months, respectively ($P=0.009$). The ORR of the two groups was 9.6% vs. 10.4% ($P=0.874$), and the DCR was 71.1 % vs. 80.5% ($P=0.165$).

After PSM ($n=46$), baseline characteristics were equitably comparable between the two groups. It was found that the median OS of the two groups was 14.6 months vs. 16.2 months ($P=0.320$), and the median PFS was 3.5 months vs. 4.5 months ($P=0.040$). The ORR of the two groups were 13.0%, 10.9% ($P=0.748$), and the DCR were 78.3%, 82.6% ($P=0.599$), respectively. These results provided further evidence that although PFS of group A was relatively shorter than that of group B, it may not affect patients' OS.

Conclusions Previous antiangiogenesis treatments may affect the PFS of patients who receive anlotinib later, but it might not affect the patient's ORR and OS.

Background

In recent years, malignant tumors have become one of the major global public health problems, among which lung cancer (LC) is one of the most common malignant tumors[1]. In 2020, the newly diagnosed patients with lung cancer accounted for 11.4% of all malignant tumors, and 1.8 million people died of lung cancer, which posed a great burden to individuals, families and society[2].

According to the NCCN guidelines[3], for advanced non-small cell lung cancer (NSCLC) without driver gene mutations, platinum-containing chemotherapy with or without antiangiogenesis therapy (bevacizumab or endostar) or immune checkpoint inhibitors significantly prolonged the patients' overall survival (OS) and progression-free survival (PFS) and was the standard first-line treatment [4-6]. Docetaxel, pemetrexed and immune checkpoint blockers were considered second-line therapies [7-9]. For small cell lung cancer (SCLC), etoposide + platinum combined with atezolizumab was recommended as the first-line treatment [10], while irinotecan, docetaxel, paclitaxel, pembrolizumab and other drugs can be selected as the second-line treatment [11]. First- and second-line treatment have significantly improved the survival of LC patients. More LC patients are still in good physical condition after receiving the recommended standard treatment, they need safe and more effective third- and further-

line treatment. Anlotinib is an oral antiangiogenic tyrosine kinase inhibitor (TKI), studies have shown that anlotinib could significantly improve PFS and OS of patients with advanced LC in third- and further-line treatment, and had acceptable tolerance [12-15]. Anlotinib was approved for the treatment of patients with advanced LC who progressed after two-line therapy.

In addition to chemotherapy, radiotherapy, targeted therapy and immunotherapy, anti-angiogenesis therapy is one of the important anti-tumor methods for advanced lung cancer [16]. Bevacizumab was one of the first approved and most widely used macromolecular angiogenesis inhibitor. Bevacizumab targeted the tumor microenvironment and provided a significant survival benefit in combination with standard chemotherapy for patients with advanced LC (excluding squamous cell carcinoma) [17]. Subsequently, recombinant human endostatin endostar combined with chemotherapy also prolonged PFS and OS in NSCLC patients and was approved as first-line therapy [18]. Anlotinib simultaneously inhibits vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR)- α , fibroblast growth factor receptor (FGFR) 1-3, c-kit and c-met. It can competitively bind intracellular tyrosine kinase domain, inhibit the phosphorylation process of intracellular tyrosine kinase domain, block downstream ERK signaling pathway, and effectively inhibit tumor angiogenesis and tumor growth [19].

In advanced colorectal cancer, several studies have demonstrated that bevacizumab cross-line therapy provides a definite benefit in OS and PFS [20, 21]. Moreover, continued antiangiogenic therapy with regorafenib still benefited colorectal cancer patients after progression with bevacizumab [22, 23]. The possible mechanism was that regorafenib not only inhibited the VEGF pathway, but also inhibited other angiogenic bypasses. In lung cancer, it is not clear whether antiangiogenic drugs can be cross-line used to induce sustained vascular inhibition. A retrospective study of 118 patients with advanced NSCLC showed no benefit from continued second-line bevacizumab after progression of first-line treatment with bevacizumab or endostar [24]. After failure of single-target bevacizumab therapy, the effectiveness of switching to another small-molecule multi-target antiangiogenic agent deserves further investigation. Retrospective studies have shown that previous antiangiogenesis therapies (bevacizumab or endostar) may not affect the efficacy of retro-line anlotinib therapy, suggesting that there may be no cross-resistance between anlotinib and other antiangiogenesis agents [25-27]. Existing research sample size was small, so this study retrospectively analyzed the efficacy of anlotinib in patients with advanced LC, and preliminarily observed whether previous antiangiogenic drugs affected the efficacy of anlotinib.

Methods

Patients

We scanned the medical data of LC patients treated with anlotinib admitted to West China hospital from June 2018 to January 2021. One hundred and seventy-two patients were treated with anlotinib. Three cases were lost to follow-up, 2 cases were discontinued anlotinib several days, of which one was due to dizziness, the other was due to fatigue, hypertension, and proteinuria. And 7 cases could not be

performed efficacy evaluation (due to imaging inaccessibility), therefore excluded. A total of 160 patients were included in the analysis.

Groups

Group A: patients treated with anlotinib after failure of antiangiogenesis therapy (bevacizumab or endostar), were assigned to group A (83 cases).

Group B: patients treated with anlotinib without any previous antiangiogenic therapy, were assigned to group B (77 cases).

Therapeutic regimen

The initial dose of anlotinib was 12mg or 10mg orally once daily on day 1-14, every 3 weeks. Some patients were reduced to 10mg/ day or 8mg/ day due to intolerant adverse reactions. Anlotinib was continued until disease progression or the adverse reaction was not tolerated. The regimens for anlotinib include:(1) anlotinib monotherapy;(2) anlotinib combined with chemotherapy (no restriction on chemotherapy regimen); (3) anlotinib combined with immune checkpoint inhibitors (anti-PD-1 /L1 antibodies); (4) anlotinib combined with targeted agents (including epidermal growth factor receptor TKI and ALK/ROS inhibitors); (5) anlotinib combined with local radiotherapy (no limitation on radiotherapy site and dose).

Efficacy evaluation

Radiographic examinations were performed to evaluate the efficacy 2 cycles after initiation, and then every 2 cycles or periodically according to clinical conditions. Efficacy evaluation was performed by the researchers directly through Picture Archiving and Communication Systems (PACS) in the hospital according to Response Evaluation Criteria In Solid Tumour 1.1(RECIST 1.1), with reference to imaging reports and clinical practice. The best response evaluation was the best response record from the beginning to the end of treatment with anlotinib.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test. Create a survival curve using the Kaplan–Meier method. Propensity score matching (PSM) was performed with 1:1 nearest neighbor matching (caliper 0.2) using R 4.0.3 software. $P < 0.05$ (both sides) was considered statistically significant.

Results

Baseline characteristics of patients

A total of 160 patients were eligible for efficacy analysis. The research flow chart was shown in Figure 1. The median age of patients was 55 years (range 34-80 years) in group A and 63 years (range 29-85

years) in group B. The pathological types of group A were adenocarcinoma (71 cases, 85.5%), squamous cell carcinoma (6 cases, 7.2%) and other types (6 cases, 7.2%). The pathological types of patients in group B were adenocarcinoma (42 cases, 54.5%), squamous cell carcinoma (19 cases, 24.7%) and other types (16 cases, 20.8%). Patients in group A were all stage IV, while group B were mainly stage IV (70 patients, 90.9%), including 7 patients (9.1%) who were inoperable stage $\geq$ B/ C. Median prior treatment lines were 3 in group A and 2 in group B. Other baseline characteristics included PD-L1 expression level, brain metastasis, liver metastasis, Eastern Cooperative Oncology Group (ECOG) score, smoking history, history of targeted therapy, and specific treatment regimens, etc. were shown in Table 1.

Baseline characteristics of patients after matching

Comparing the baseline characteristics of patients, the two groups were not balanced in the following factors: gender ($P=0.020$), age ($P=0.000$), pathological type ($P=0.000$), clinical stage ($P=0.015$), PD-L1 expression level ($P=0.019$), smoking history ($P=0.02$), number of previous treatment lines ($P=0.000$), history of targeted therapy ($P=0.024$), therapeutic schemes ($P=0.014$), the difference was statistically significant (Table 1). In order to control the influence of confounding factors between the two groups, PSM was used to match the two groups in a 1:1 ratio (caliper 0.2). The matching factors were gender, age (< 60 years old, ≥ 60 years old), histological subtypes (adenocarcinoma, squamous cell carcinoma, others), clinical stage (stage IV), and the number of previous treatment lines (<3 lines, ≥ 3 lines). After matching, the baseline characteristics of the two groups were equalized and comparable (Table 2).

Comparison of efficacy between two groups

The optimal response of group A was partial response (PR) ($n=8$), stable disease (SD) ($n=51$) and progression disease (PD) ($n=24$). The optimal response of group B was PR ($n=8$ cases), SD ($n=55$ cases) and PD ($n=14$ cases). The objective response rate (ORR) and disease control rate (DCR) of the two groups were 9.6% in group A vs. 10.4% in group B ($P=0.874$), and 71.1% in group A vs. 80.5% in group B ($P=0.165$), respectively (Table 3).

The median OS was 14.6 months (95%CI 11.1-18.1) and the median PFS for the overall population was 3.8 months (95%CI 3.1-4.5). The median OS was 11.8 months (95%CI 6.7-16.9) in group A vs. 16.1 months (95%CI 12.6-19.6) in group B ($P=0.121$) (Figure 2). Median PFS was 3.1 months in group A (95%CI 2.3-3.9) vs. 4.7 months in group B (95%CI 3.9-5.5), $P=0.009$ (Figure 3).

After matching, the median OS of the two groups was 14.6 months (95%CI 10.1-19.1) in group A vs. 16.2 months (95%CI 9.2-23.2) in group B, $P=0.320$ (Figure 4). Median PFS was 3.5 months (95%CI 2.7-4.3) in group A vs. 4.5 months (95%CI 3.7-5.3) in group B, $P=0.040$ (Figure 5). The ORR and DCR of two groups were 13.0% in group A vs. 10.9% in group B ($P=0.748$) and 78.3% in group A vs. 82.6% in group B ($P=0.599$), respectively (Table 3).

Effect of previous antiangiogenic therapy on anlotinib

The effect of previous antiangiogenic treatment on anlotinib in group A was further analyzed, and Kaplan-Meier analysis showed that the different drug used previously (bevacizumab or endostar), the best response (PR, SD or PD) of the prior antiangiogenesis therapy, and PFS (≤ 6 months or > 6 months) of the prior antiangiogenesis therapy had no significant effect on the efficacy (PFS and OS) of patients received anlotinib ($P > 0.05$) (Table 4).

Safety analysis

No life-threatening adverse events associated with anlotinib were found in the study. In group A, 6 patients were discontinued spontaneously due to intolerant adverse reactions, including 1 patient due to vaginal bleeding and fatigue, 1 patient due to hematuria, 3 patients due to skin symptoms, and 1 patient due to nausea and vomiting. In group B, 4 patients were discontinued due to intolerant adverse reactions, including 1 patient due to nausea and vomiting, 1 patient due to hand-foot syndrome, 1 patient due to acute stroke, and 1 patient due to upper gastrointestinal bleeding after diagnosis of esophageal cancer.

There was no statistical difference in the incidence of adverse events between the two groups. The most common adverse events in group A were skin symptoms (24.1%), including rash, pruritus, hand and foot syndrome, followed by hypertension (8.4%) and fatigue (6.0%). Other relatively rare adverse events of concern included vaginal bleeding (3.6%), nosebleeds (2.4%), and hematuria (1.2%). The most common adverse events in group B were skin symptoms (14.3%), hypertension (10.4%), and anorexia (10.4%), followed by diarrhea (7.8%) and fatigue (7.8%). Other relatively uncommon adverse events of concern included hemoptysis (2.6%), upper gastrointestinal bleeding (1.3%), and stroke (1.3%) (Table 5).

Analysis of the subsequent treatment after the progression of anlotinib

After progression of anlotinib, 57 patients (68.7%) in group A and 61 patients (79.2%) in group B received subsequent therapy. There was no statistically significant difference of subsequent line therapy between the two groups before and after matching. The most common posterior line treatments in both groups were targeted therapy, immunotherapy, and radiotherapy, while the other relatively uncommon treatments were chemotherapy and liver interventional therapy. The posterior line treatment of a few patients were unknown (Table 6).

Discussion

Angiogenesis plays an important role in the growth, proliferation and metastasis of tumors[28]. There are two main approaches to target tumor angiogenesis, one is the monoclonal antibody that prevents VEGF from interacting with endothelial cell surface VEGFR, and the other is the small molecule TKI that simultaneously inhibits VEGFR, PDGFR and FGFR. Bevacizumab is a recombinant human-derived IgG1 monoclonal antibody that binds to VEGF to inhibit binding to VEGFR 1-2 [29]. Bevacizumab in combination with chemotherapy was a first-line treatment for advanced NSCLC, the median PFS was about 5.9-9.2 months[4, 6, 30], and the ORR was about 35%[31]. Among the small-molecule TKIs, except nintedanib[32] and anlotinib[13, 15], most TKIs, such as sorafenib, sunitinib and apatinib, can

significantly prolong the PFS of patients, but do not significantly increase the OS benefit [28, 29, 33-36]. Anlotinib became one of the few multitarget angiogenesis inhibitors with survival benefit. In the ALTER0303 study, anlotinib as third- and further-line treatment in patients with advanced NSCLC was found to have a significant PFS extension of 4.0 months compared with placebo, a median OS extension of 3.3 months and a 32% reduction in risk of death[13]. In the ALTER1202 study, patients with limited or extended-stage SCLC received anlotinib in the third- and further-line setting, achieved PFS of 4.1 months (0.7 months in the placebo group)[37].

In this study, the median PFS of the whole population was 3.8 months and the median OS was 14.6 months, which also confirmed that in the real world, anlotinib could bring PFS and OS benefit in patients with advanced lung cancer, and the benefit seemed to be not inferior to the previously reported second-line docetaxel and immune checkpoint inhibitors [38, 39].

We found that patients who had previously received bevacizumab and endostar had a shorter PFS (3.1 months vs. 4.7 months), but the ORR, DCR, and OS were similar to those who had received the first antiangiogenesis therapy (anlotinib). The PFS of our study was similar to the PFS reported in the ALTER0303 trial, with a slightly longer OS than that of ALTER0303, which might be due to the higher subsequent-line treatment rate in our study. After reducing potential confounders between groups by PSM, it was also found that previous antiangiogenic therapy only affected PFS in patients treated with anlotinib, but may not affect OS, and the survival benefit may be due to the multi-target inhibition of anlotinib.

The incidence of adverse events recorded in both groups was low and similar to those reported in the literature[25, 40-46]. In this study, the proportion of patients rechecking ECG, thyroid function and urine routine was small. Therefore, the incidence of abnormal ECG, increased thyroid stimulating hormone (TSH) and proteinuria were lower than the actual situation and the incidence reported in previous studies. It is necessary to further strengthen the monitoring of adverse reactions during treatment.

Most patients received subsequent therapy after failure of anlotinib, and there was no difference in subsequent therapy between two groups. The most common treatment were targeted therapy and immunotherapy. With the popularity of more targeted agents and immunotherapy drugs, as well as lower toxicity compared with chemoradiotherapy, targeted therapy and immunotherapy have become the alternatives for patients with poor ECOG scores after multiline therapy, which may be one reason why the median OS in this study was slightly longer than that in ALTER0303.

Limitations

Results of this study was according to the experience of single-center, small sample size. The baseline characteristics of patients between the two groups were influenced by confounding factors before matching. The variety of drugs used in combination with anlotinib may affect the outcome.

Conclusions

Based on limited data available in this study, anlotinib may bring PFS and OS benefits to patients with advanced lung cancer. Previous antiangiogenesis treatments may affect the PFS of patients who receive anlotinib later, but it might not affect the patient's ORR and OS. The use of anlotinib in patients with advanced lung cancer after the progression of antiangiogenic therapy is worthy of subsequent prospective, large-sample clinical studies.

Declarations

Consent for publication We agree to publish the magazine.

Availability of data and material We have full control of all primary data and agree to allow the journal to review their data if requested.

Authors' contributions All authors contributed to the study conception and design. Data collection and analysis were performed by Jiaojiao Suo, Weigang Xiu and Hao Wei. The first draft of the manuscript was written by Jiaojiao Suo, Yu Sun and Yan Fu. Yan Wang: Determination of topics, essay structure and revision of manuscripts. Jiang Zhu: In charge of the whole study, perform the final revision of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by Biomedical Research Ethics Committee (approval number: 2020162), West China Hospital, Sichuan University and performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and all subsequent

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Tables

Table1 Baseline characteristics of Patients

Characteristics	Group A n=83,%	Group B n=77,%	P value
Gender			0.020
Male	41 49.4	52 67.5	
Female	42 50.6	25 32.5	
Age (years)			0.000
median (range)	55 34-80	63 29-85	
<60	59 71.1	33 42.9	
≥60	24 28.9	44 57.1	
Pathology			0.000
Adenocarcinoma	71 85.5	42 54.5	
Squamous cell carcinoma	6 7.2	19 24.7	
Others	6 7.2	16 20.8	
Stage			0.015
IIIB/IIIC	0 0	7 9.1	
IV	83 100.0	70 90.9	
PD-L1			0.019
0	42 50.6	21 27.3	
1-49	12 14.5	13 16.9	
≥50	11 13.3	13 16.9	
NA	18 21.7	30 39.0	
Brain metastases			0.150
Yes	35 42.2	24 31.2	
No	48 57.8	53 68.8	
Liver metastasis			0.654
Yes	18 21.7	19 24.7	
No	65 78.3	58 75.3	
ECOG			0.895
0	10 12.0	9 11.7	
1	37 44.6	33 42.9	

Characteristics	Group A n=83,%	Group B n=77,%	P value
2	32 38.6	29 37.7	
3	4 4.8	6 7.8	
Smoking history			0.02
Yes	23 27.7	35 45.5	
No	60 72.3	42 54.5	
No. of Previous therapy lines			0.000
median (range)	3	2	
<3	36 43.4	57 74.0	
≥ 3	47 56.6	20 26.0	
History of targeted therapy			0.024
Yes	32 38.6	17 22.1	
No	51 61.4	60 77.9	
Previous antiangiogenic drugs			-
Bevacizumab	73 88.0	0 0	
Endostar	10 12.0	0 0	
Therapeutic schemes			0.014
Anlotinib monotherapy	47 56.6	40 51.9	
Chemotherapy+anlotinib	23 27.7	11 14.3	
Immunotherapy+anlotinib	6 7.2	17 22.1	
Radiotherapy+anlotinib	4 4.8	8 10.4	
Targeted therapy+anlotinib	3 3.6	1 1.3	

Note: NA, not available; ECOG, Eastern Cooperative Oncology Group

Table 2 Comparison of baseline characteristics of patients after 1:1 matching of propensity score matching

Characteristics	Group A n=46,%	Group B n=46,%	P value
Gender			0.529
Male	24 52.2	27 58.7	
Female	22 47.8%	19 41.3	
Age (years)			0.833
median (range)	57 34-80	57 29-82	
<60	26 56.5	27 58.7	
≥60	20 43.5	19 41.3	
Pathology			0.778
Adenocarcinoma	34 73.9	31 67.4	
Squamous cell carcinoma	6 13.0	7 15.2	
Others	6 13.0	8 17.4	
Stage			1.000
IIIB/IIIC	0 0	0 0	
IV	46 100.0	46 100.0	
PD-L1			0.239
0	21 45.7	16 34.8	
1-49	8 17.4	4 8.7	
≥50	6 13.0	7 15.2	
NA	11 23.9	19 41.3	
Brain metastases			0.832
Yes	19 41.3	18 39.1	
No	27 58.7	28 60.9	
Liver metastasis			0.470
Yes	10 21.7	13 28.3	
No	36 78.3	33 71.7	
ECOG			0.393
0	6 13.0	7 15.2	
1	24 52.2	18 39.1	

Characteristics	Group A n=46,%	Group B n=46,%	P value
2	14 (30.4)	17 (37.0)	
3	2 (4.3)	4 (8.7)	
Smoking history			0.825
Yes	31 (67.4)	30 (65.2)	
No	15 (32.6)	16 (34.8)	
No. of previous therapy lines			0.400
≤3	24 (52.2)	28 (60.9)	
≥3	22 (47.8)	18 (39.1)	
History of targeted therapy			1.000
Yes	15 (32.6)	15 (32.6)	
No	31 (67.4)	31 (67.4)	
Therapeutic schemes			0.053
Anlotinib monotherapy	19 (41.3)	24 (52.2)	
Chemotherapy+anlotinib	15 (32.6)	8 (17.4)	
Immunotherapy+anlotinib	5 (10.9)	11 (23.9)	
Radiotherapy+anlotinib	4 (8.7)	3 (6.5)	
Targeted therapy+anlotinib	3 (6.5)	0 (0)	

Note: NA, not available; ECOG, Eastern Cooperative Oncology Group

Table 3 Comparison of the best response between the two Groups

Best response	Before matching		P value	After matching		P value
	Group A	Group B		Group A	Group B	
	n=83	n=77		n=46	n=46	
PR	8	8	-	6	5	-
SD	51	55	-	30	33	-
PD	24	14	-	10	8	-
ORR	9.6%	10.4%	0.874	13.0%	10.9%	0.748
DCR	71.1%	80.5%	0.165	78.3%	82.6%	0.599

Note: PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate

Table 4 Analysis of the efficacy of anlotinib in Group A

	PFS months	P value	OS months	P value
Previous antiangiogenic drugs		0.973		0.249
Bevacizumab (n=73)	3.22.3-4.1		11.88.3-15.3	
Endostar (n=10)	2.10.0-4.9		15.26.1-24.3	
Optimal response of Previous antiangiogenic therapy		0.918		0.859
PR	2.7(0.9-4.5)		17.05.6-28.4	
SD	3.1(2.0-4.2)		10.04.4-15.6	
PD	3.8(1.7-5.9)		15.25.2-25.2	
PFS of previous antiangiogenic therapy		0.592		0.131
≤6months	2.91.7-4.1		11.16.6-15.6	
>6months	3.31.8-4.8		12.73.1-22.3	

Table 5 Adverse events with anlotinib

Adverse events	Group A n=83,%	Group B n=77,%	P value
General reaction			
Fatigue	5 (6.0%)	6 (7.8%)	0.659
Decreased appetite	4 (4.8%)	8 (10.4%)	0.181
Weight loss	1 (1.2%)	0 (0%)	1.000
Gastrointestinal reactions			
Diarrhea	2 (2.4%)	6 (7.8%)	0.231
Oral mucositis	3 (3.6%)	3 (3.9%)	1.000
Nausea/vomiting	3 (3.6%)	3 (5.2%)	1.000
Constipation	0 (0%)	1 (1.3%)	0.481
Hiccup	1 (1.2%)	1 (1.3%)	1.000
Cardiovascular symptoms			
Hypertension	7 (8.4%)	8 (10.4%)	0.672
Premature atrial contractions	1 (1.2%)	0 (0%)	1.000
Skin symptom	20 (24.1%)	11 (14.3%)	0.117
Proteinuria	1 (1.2%)	0 (0%)	1.000
Hemorrhage			
Vaginal haemorrhage	3 (3.6%)	0 (0%)	0.271
Nasal hemorrhage	2 (2.4%)	0 (0%)	0.498
Hematuria	1 (1.2%)	0 (0%)	1.000
Upper gastrointestinal hemorrhage	0 (0%)	1 (1.3%)	0.481
Hemoptysis	0 (0%)	2 (2.6%)	0.230
Myelosuppression	3 (3.6%)	3 (3.9%)	1.000
Neurologic symptom			
Dizziness	1 (1.2%)	1 (1.3%)	1.000
Insomnia	1 (1.2%)	0 (0%)	1.000
Stroke	0 (0%)	1 (1.3%)	0.481
Hypothyroidism	0 (0%)	1 (1.3%)	0.481

Table 6 Subsequent treatment after the Progression of amlotinib therapy

Subsequent treatment	Before matching		<i>P</i> value	After matching		<i>P</i> value
	Group A	Group B		Group A	Group B	
	n=83	n=77		n=46	n=46	
None	26(31.3)	16(20.8)	0.130	10(21.7)	8(17.4)	0.599
Targeted therapy	20(24.1)	13(16.9)	0.260	12(26.1)	12(26.1)	1.000
Immunotherapy	17(20.5)	16(20.8)	0.963	9(19.6)	12(26.1)	0.456
Radiotherapy	13(15.7)	9(11.7)	0.466	11(23.9)	6(13.0)	0.179
Chemotherapy	8(9.6)	14(18.2)	0.117	4(8.7)	8(17.4)	0.216
Interventional therapy	0(0)	1(1.3)	0.481	0(0)	0(0)	1.000
Unknown	6(7.2)	6(7.8)	0.892	5(10.9)	3(6.5)	0.711

Figures

Figure 1

The research flow chart

Figure 2

Comparison of OS between the two groups.

Figure 3

Comparison of PFS between the two groups.

Figure 4

Comparison of OS between the two groups after matching.

Figure 5

Comparison of PFS between the two groups after matching.