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ORIGINAL RESEARCH

The Efficacy and Safety of Apatinib and Anlotinib in Advanced Non-Small Cell Lung Cancer

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Background: Anlotinib and apatinib, both vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs), are clinically established in the treatment of advanced non-small cell lung cancer (NSCLC) in China, with anlotinib emerging as a standard treatment strategy. This study was conducted to evaluate the efficacy and safety of apatinib and anlotinib, and to compare their differences in treating patients with advanced NSCLC.

Patients and Methods: We retrospectively analyzed the data of patients with advanced NSCLC treated with apatinib or anlotinib at a hospital in Eastern China from January 2017 to December 2021. The primary endpoint was progression-free survival (PFS), while secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety profile.

Results: A total of 145 patients were included in this study. Median PFS (mPFS) was 3.53 months for the apatinib group and 5.3 months for the anlotinib group (HR = 0.59, 95% CI: 0.41–0.84; P = 0.004), and median OS (mOS) was 7.6 months versus 15.6 months (HR = 0.68, 95% CI: 0.46–1.00; P = 0.048), which all showed significant differences after adjusting for confounders (P < 0.05). Subgroup analysis revealed that the presence or absence of bone metastases significantly influenced PFS in both treatment groups. The ORR was 3.03% in the anlotinib group versus 10.13% in the apatinib group (P = 0.12), the DCR was 72.73% versus 51.90% (P = 0.21). No unanticipated adverse events (AEs) were observed. The incidence of grade 3–4 AEs was significantly higher in the apatinib group (31.65% vs 13.64%, P < 0.05).

Conclusion: Anlotinib demonstrated greater efficacy and safety compared to apatinib in the treatment of advanced NSCLC, particularly in patients with bone metastases and EGFR(-).

Keywords: non-small cell lung cancer, anti-angiogenic drug, VEGFR-TKIs, real-world research, bone metastases

Introduction

Lung cancer remains one of the most prevalent malignancies worldwide, accounting for 11.44% of all new cancer cases and possessing the highest fatality rate globally.[1] In China, lung cancer not only has the highest incidence and mortality rate, but also over 85% of lung cancer cases are categorised as non-small cell lung cancer (NSCLC).[2,3] The traditional standard treatment for advanced NSCLC has been platinum-based dual-agent chemotherapy, yet the five-year survival rate for this regimen is still dismally below 5%.[4] The selection of an appropriate therapy plan for patients who have not responded to second- or third-line treatments remains challenging. Moreover, many patients are unable to tolerate the adverse effects (AEs) associated with chemotherapy, thus underscoring the necessity to explore alternative therapeutic strategies for lung cancer.

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In recent decades, there has been a significant accumulation of evidence suggesting that anti-angiogenic drugs can yield substantial clinical benefits in the treatment of NSCLC.[5,6] Small-molecule anti-angiogenic tyrosine kinase inhibitors (TKIs), particularly multi-targeted vascular kinase inhibitors, selectively inhibit the VEGFR pathway-mediated activation, thus impeding tumor angiogenesis.[7–9] Various small-molecule anti-angiogenic TKIs, including apatinib, anlotinib, fruquintinib, and nintedanib, have been evaluated in numerous lung cancer clinical studies.[10–12] Research has increasingly demonstrated that VEGFR-TKI monotherapy, or in combination with other treatments, offers superior efficacy in treating NSCLC. For instance, nintedanib was approved in the European Union in 2014 as a second-line treatment for advanced or metastatic lung adenocarcinoma, in combination with docetaxel, following the phase 3 LUME-Lung 1 study.[13] Similarly, anlotinib was approved for the third-line treatment of advanced NSCLC in China in 2018, based on the results of the phase 3 ALTER0303 study.[14] Furthermore, a phase 3 trial presented at ESMO 2022 revealed that, in first-line treatment of advanced NSCLC, median progression-free survival (mPFS) was significantly longer in the anlotinib plus gefitinib group compared to the placebo plus gefitinib group (14.75 months vs 11.20 months, HR = 0.64; P = 0.003).[15]

Apatinib mesylate, the first domestically developed oral anti-angiogenic small-molecule TKI in China, exhibits high selectivity for VEGFR-2.[7] Initial results from a Phase II study indicated that apatinib monotherapy as a third-line treatment for advanced NSCLC extended the mPFS by 2.80 months compared to placebo (4.70 months vs 1.90 months, HR = 0.278; P < 0.0001).[16] Subsequently, the Phase 1 Ahead-L303 study showed that the combination of apatinib and gefitinib in the first-line treatment of epidermal growth factor receptor (EGFR)-mutant stage IIIB-IV non-squamous NSCLC resulted in an objective response rate (ORR) of 83.3%, a disease control rate (DCR) of 91.7%, and a mPFS of 19.2 months.[17] More recently, a randomized controlled phase 3 study demonstrated a significant prolongation of mPFS by 3.5 months in the apatinib plus gefitinib group compared to the placebo plus gefitinib group (P = 0.019).[18] Collectively, these studies underscore the superior efficacy of apatinib, both as a monotherapy and in combination treatments, in the management of NSCLC.

The present research focuses on a comprehensive analysis of clinical studies concerning anlotinib and apatinib in the treatment of advanced NSCLC. In China, VEGFR-TKIs, particularly anlotinib, have been established as a standard treatment strategy for NSCLC. Despite this, there remains a paucity of research examining the comparative efficacy and safety of these VEGFR-TKIs in advanced NSCLC. To address this gap, we conducted a retrospective observational study extensively examining apatinib and anlotinib in clinical settings. Our objective was to compare their efficacy and safety, as well as to delineate any differences in the treatment of advanced NSCLC in real-world scenarios. Additionally, we investigated the impact of various factors, including gender, age, sites of metastasis, pathological features, EGFR genotypes, and treatment modalities, on the efficacy and safety outcomes.

Materials and Methods

Study Design and Patients

This retrospective observational study was conducted at Yancheng First People's Hospital in Eastern China. We identified patients with advanced NSCLC who were treated with either apatinib/apatinib-containing or anlotinib/anlotinib-containing regimens between January 1, 2017, and December 31, 2021, via the Hospital Information System (HIS). Inclusion criteria encompassed patients with histologically or cytologically confirmed stage IIIb to IV NSCLC (according to the AJCC 8th edition); those aged 18 years or older; having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2 or less; undergoing anti-angiogenic therapy with either apatinib or anlotinib; not candidates for surgical intervention; possessing at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1); with adequate heart, liver, lung and kidney function; and having complete clinical data available. Exclusion criteria included patients with uncontrolled hypertension, diabetes mellitus, cardiac arrhythmias, coagulation abnormalities, concurrent untreatable malignant tumors, prior use of other anti-angiogenic targeted agents before apatinib or anlotinib, incomplete clinical data, or inability to follow up. The follow-up period for assessing PFS and overall survival (OS) extended until December 31, 2023.

Our research protocol and Patients' Informed Consent Form (Version number: V1.0; Date of Version: August 9, 2020) had been reviewed and approved by the Institutional Review Board of the First People's Hospital of Yancheng (approval number: [2020-(K-049)]). Informed consent of all subjects for using their medical records had been obtained in this study. It was conducted in compliance with the Declaration of Helsinki.

Treatment

Patients were categorised into apatinib and anlotinib groups based on their respective treatments. In the apatinib group, patients received an oral dose of 500 mg of apatinib daily. This dosage was reduced to 250 mg per day for those who experienced intolerable toxicity. Conversely, in the anlotinib group, patients commenced treatment with a daily dose of 12 mg of oral anlotinib on days 1–14 of a 21-day cycle. The dosage was adjusted to 10 mg daily in cases of toxicity intolerance. Treatment with both medications continued until the occurrence of disease progression (PD), intolerable toxicity, or death. AEs were assessed as per the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 6.0, with documentation of their causal relationship to the treatment. Instances where patients could not tolerate the medication due to progressive toxicity were recorded and followed up.

Clinical Assessments

Tumor responses were evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) in line with RECIST version 1.1, every six weeks. Immediate evaluations were conducted upon detection of significant PD signals. The primary endpoint was PFS, defined as the time from the initial dose of apatinib or anlotinib to the first evidence of PD or death from any cause. Secondary endpoints included the ORR (defined as the percentage of patients exhibiting a complete response [CR] or partial response [PR]), DCR (defined as the proportion of patients achieving CR, PR, or stable disease [SD]), OS (calculated from the date of the first dose to the date of death), and safety.

Statistical Analysis

Patient characteristics and treatment-related adverse events were summarized using descriptive statistics. Continuous variables were described through means and 95% confidence intervals, with *t*-tests conducted following tests for normal distribution. Categorical variables were presented as frequencies and percentages. Comparisons between the two groups were made using Chi-square and Student's *t*-tests for categorical and continuous variables, respectively. PFS and OS were estimated using the Kaplan-Meier method and compared with a two-sided Log rank test.

Univariate and multivariable analyses for safety were conducted using logistic regression. In contrast, analyses for PFS and OS employed the Cox regression model. Variables with $P < 0.2$ in the univariate analysis and factors that were unbalanced in the baseline characteristics (eg, smoking history, treatment line, and treatment method) were included in the multivariate analysis model. Analyses were executed using SPSS statistical software, version 23.0, with a P-value of ≤ 0.05 denoting statistical significance.

Results

Baseline Characteristics

Between January 1, 2017, and December 31, 2021, this study enrolled a cohort of 145 patients with advanced NSCLC. These patients were treated with either apatinib (n = 79) or anlotinib (n = 66).

During the PFS follow-up, the apatinib group experienced 15 truncated cases, all due to withdrawal caused by intolerance to AEs. In the anlotinib group, there were 5 truncated cases; 3 of these were due to AE intolerance and 2 were terminated due to follow-up issues. In the OS follow-up period, the apatinib group had 22 truncated cases, with 15 discontinuing due to AE intolerance, 4 terminated due to follow-up challenges, and 3 lost to follow-up. The anlotinib group saw 17 truncated cases, with 3 discontinuing due to AE intolerance and 14 terminated due to follow-up (Figure 1).

The baseline characteristics, including age, gender, ECOG PS, presence of bone and brain metastases, tumor histology, and EGFR mutation status, were well-balanced and comparable between the two groups, showing no statistical significance ($P > 0.05$). However, some baseline characteristics, such as smoking status, treatment line, and treatment

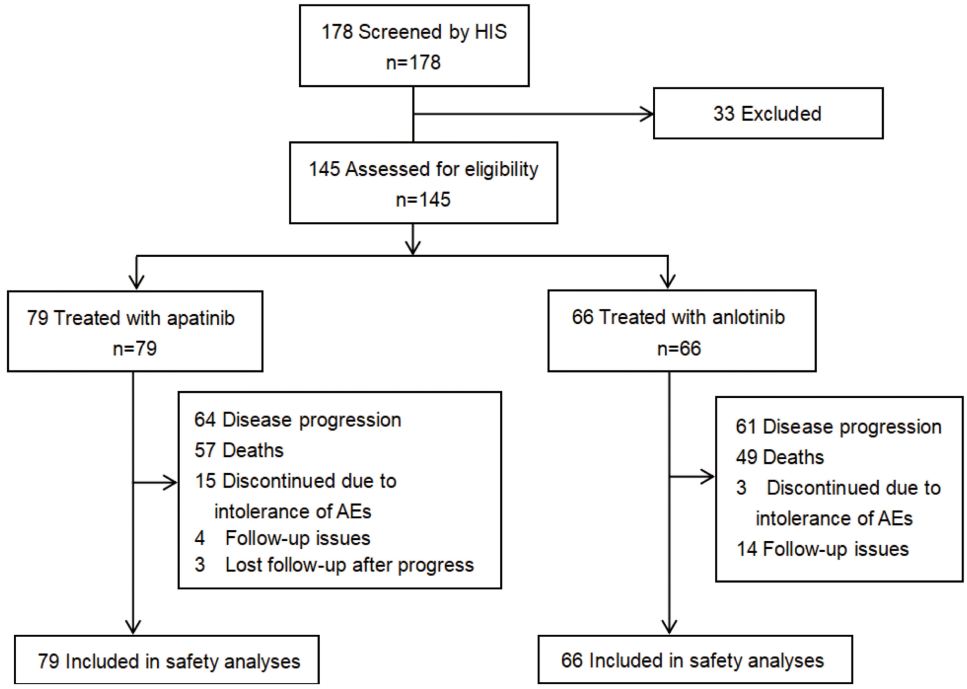

Figure 1 Flowchart of study selection and design.

method, were imbalanced ($P < 0.01$), so these factors must be considered in subsequent analyses to control for potential confounding effects (Table 1).

Clinical Efficacy

In the apatinib group, comprising 79 patients, 8 (10.13%) experienced a confirmed PR, 33 (41.77%) maintained SD, 23 (29.11%) exhibited PD, and 15 (18.99%) discontinued treatment due to severe adverse reactions. In contrast, among the

Table 1 Baseline Characteristics of Patients

Characteristics	Apatinib	Anlotinib	Statistical Quantity	P-value
N	79	66		
Mean age (95% CI), yr	64.58 (62.46–66.70)	64.47 (62.41–66.53)	t=0.075	0.83
Gender, n (%)				
Female	57 (72.2)	45 (68.2)	X^2=0.27	0.60
Male	22 (27.8)	21 (31.8)		
Smoking history, n (%)				
Yes	26 (32.9)	7 (10.6)	X^2=10.18	0.001
No	53 (67.1)	59 (89.4)		
ECOG/PS, n (%)				
0–1	64 (81.0)	54 (81.8)	X^2=0.02	0.90
2	15 (19.0)	12 (18.2)		

(*Continued*)

Table 1 (Continued).

Characteristics	Apatinib	Anlotinib	Statistical Quantity	P-value
Bone metastases, n (%)				
Yes	19 (24.1)	22 (33.3)	X^2=1.53	0.22
No	60 (75.9)	44 (66.7)		
Brain metastases, n (%)				
Yes	16 (20.3)	16 (24.2)	X^2=0.33	0.56
No	63 (79.7)	50 (75.8)		
Treatment line, n (%)				
First-line	22 (27.8)	7 (10.6)	X^2=13.48	0.001
Second-line	32 (40.5)	19 (28.8)		
≥Third-line	25 (31.6)	40 (60.6)		
Treatment method, n (%)				
VEGFR-TKIs monotherapy	38 (48.1)	22 (33.3)	X^2=20.20	0.000
VEGFR-TKIs + Chemotherapy	32 (40.5)	15 (22.7)		
VEGFR-TKIs + ICIs	7 (8.9)	25 (37.9)		
VEGFR-TKIs + Chemotherapy + ICIs	2 (2.5)	4 (6.1)		
Tumor histology, n (%)				
Adenocarcinoma	46 (58.2)	45 (68.2)	X^2=3.25	0.20
Squamous carcinoma	23 (29.1)	18 (27.3)		
Others	10 (12.7)	3 (4.5)		
EGFR mutation status, n (%)				
EGFR (+)	18 (22.8)	17 (25.8)	X^2=0.17	0.68
EGFR (-)	61 (77.2)	49 (74.2)		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; VEGFR-TKIs, vascular endothelial growth factor receptor-tyrosine kinase inhibitors; ICIs, Immune checkpoint inhibitors; EGFR, epidermal growth factor receptor.

66 patients in the anlotinib group, 2 (3.03%) achieved a confirmed PR, 46 (69.70%) had SD, 15 (22.73%) progressed, and 3 (4.55%) discontinued treatment owing to severe adverse reactions. It is noteworthy that no patients in either group achieved a complete response. The ORR in the apatinib group was 10.13% (8/79), with a DCR of 51.90% (41/79). In the anlotinib group, the ORR was 3.03% (2/66), and the DCR was 72.73% (48/79). There was no significant difference in ORR and DCR between the two groups (Table 2).

The mPFS for patients undergoing apatinib and anlotinib therapies were 3.53 months (95% CI: 2.63–4.47) and 5.3 months (95% CI: 4.1–7.93) respectively, indicating a statistically significant difference ($P < 0.01$, Figure 2a). The mOS for the apatinib and anlotinib groups were 7.6 months (95% CI: 5.73–11.40) and 15.6 months (95% CI: 11.27–19.97) respectively, also showing a statistically significant difference ($P < 0.05$, Figure 2b).

Table 2 Best Overall Tumor Response for the Apatinib and Anlotinib Groups

Observed indicators	Apatinib (n=79)	Anlotinib (n=66)	P-value
Best overall response, n (%)			
Complete response (CR)	0	0	
Partial response (PR)	8 (10.13)	2 (3.03)	
Stable disease (SD)	33 (41.77)	46 (69.70)	
Progressive disease (PD)	23 (29.11)	15 (22.73)	
Not evaluable	15 (18.99)	3 (4.55)	
Objective response rate (ORR), %	10.13	3.03	0.12
Disease control rate (DCR), %	51.90	72.73	0.21

Abbreviations: ORR, defined as the proportion of patients achieving CR or PR; DCR, defined as the proportion of patients achieving CR, PR, or SD.

Analysis of Influencing Factors in PFS and OS

Variables such as treatment group, gender, and age were incorporated as independent factors into the Cox proportional hazards model to assess their impact on PFS and OS. The univariate analysis indicated that both the treatment group and the presence of bone metastases significantly influenced patients' PFS and OS. Subsequently, we included factors with $P < 0.2$ and those that were unbalanced in the baseline characteristics into the multivariate Cox proportional hazards model. The final results demonstrated that, after adjusting for confounding factors, the treatment group and bone metastases were found to significantly affect both PFS and OS ($P < 0.05$). In addition, multi-drug combinations (VEGFR-TKIs + chemotherapy + ICIs) only significantly affected PFS ($P < 0.01$), and the treatment line only significantly impacted OS ($P < 0.05$), (Table 3 and Table 4). Given that only 6 patients received multi-drug combination therapy, the small sample size might have reduced statistical power; thus, this study did not delve deeply into the impact of multi-drug combination therapy on PFS. Similarly, we did not further analyze the effect of treatment lines on OS because of the baseline imbalance and the diversity of treatment regimens prior to the use of VEGFR-TKIs. However, the influence of bone metastases status on PFS and OS in different groups warrants further detailed analysis.

The Subgroup Analysis of PFS and OS with Bone Metastases

We further analysed the effects of bone metastasis status on PFS and OS among different groups (Figures 3 and 4). Initially, we analysed the impact of bone metastases on within-group PFS and OS in the apatinib and anlotinib cohorts.

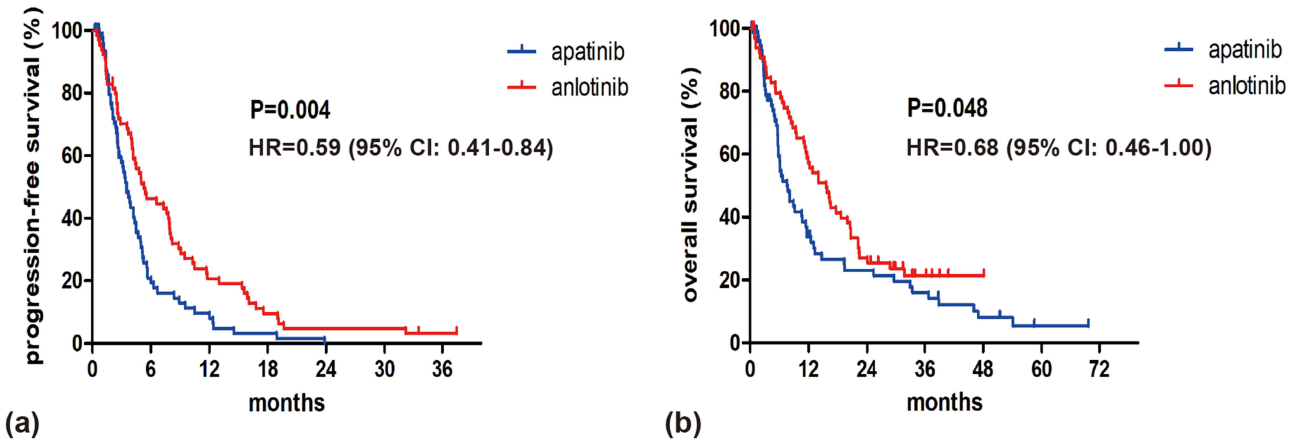

Figure 2 Kaplan-Meier estimates compared in the apatinib and anlotinib groups. (**a**), Kaplan-Meier estimates of PFS compared in the apatinib and anlotinib groups; (**b**), Kaplan-Meier estimates of OS compared in the apatinib and anlotinib groups.

Table 3 Multivariable Regression Model for PFS

Factors	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Group (Apatinib vs Anlotinib)	0.59 (0.41–0.84)	0.004	0.43 (0.27–0.70)	0.001
Gender (male vs female)	0.98 (0.67–1.44)	0.93		
Age (<65 yr vs ≥65 yr)	0.97 (0.68–1.38)	0.85		
Smoking history	0.75 (0.48–1.17)	0.21	0.90 (0.54–1.50)	0.68
ECOG/PS	0.87 (0.55–1.38)	0.54		
Bone metastases (yes vs no)	0.38 (0.25–0.57)	0.000	0.33 (0.21–0.52)	0.000
Brain metastases (yes vs no)	0.97 (0.64–1.48)	0.90		
Squamous carcinoma vs Adenocarcinoma	0.71 (0.47–1.07)	0.10	0.87 (0.56–1.36)	0.54
Others vs Adenocarcinoma	1.08 (0.59–1.99)	0.80	0.91 (0.48–1.72)	0.78
Genotype (EGFR+ vs EGFR-)	0.84 (0.55–1.28)	0.41		
Treatment line	0.98 (0.78–1.23)	0.83	1.14 (0.88–1.47)	0.32
VEGFR-TKIs + Chemotherapy vs VEGFR-TKIs monotherapy	0.95 (0.63–1.43)	0.80	0.97 (0.63–1.50)	0.89
VEGFR-TKIs + ICIs vs VEGFR-TKIs monotherapy	0.82 (0.51–1.30)	0.39	1.17 (0.69–1.97)	0.57
VEGFR-TKIs + Chemotherapy + ICIs vs VEGFR-TKIs monotherapy	5.38 (2.06–14.05)	0.001	4.77 (1.75–12.99)	0.002

Table 4 Multivariable Regression Model for OS

Factors	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Group (Apatinib vs Anlotinib)	0.68 (0.46–1.00)	0.05	0.59 (0.36–0.96)	0.03
Gender (male vs female)	1.25 (0.83–1.87)	0.29		
Age (<65 yr vs ≥65 yr)	1.35 (0.91–2.00)	0.14	1.45 (0.94–2.25)	0.09
Smoking history	0.88 (0.56–1.40)	0.60	1.11 (0.66–1.88)	0.68
ECOG/PS	1.10 (0.67–1.82)	0.71		
Bone metastases (yes vs no)	0.46 (0.30–0.70)	0.000	0.40 (0.26–0.63)	0.000
Brain metastases (yes vs no)	0.80 (0.51–1.24)	0.32		
Squamous carcinoma vs Adenocarcinoma	0.80 (0.51–1.26)	0.35	0.89 (0.54–1.48)	0.66
Others vs Adenocarcinoma	2.39 (1.25–4.59)	0.009	1.92 (0.97–3.83)	0.06
Genotype (EGFR+ vs EGFR-)	0.97 (0.61–1.54)	0.89		
Treatment line	1.10 (0.86–1.40)	0.46	1.39 (1.03–1.89)	0.03
VEGFR-TKIs + Chemotherapy vs VEGFR-TKIs monotherapy	1.04 (0.67–1.60)	0.88	1.11 (0.69–1.78)	0.67
VEGFR-TKIs + ICIs vs VEGFR-TKIs monotherapy	0.69 (0.40–1.17)	0.17	0.72 (0.40–1.29)	0.26
VEGFR-TKIs + Chemotherapy + ICIs vs VEGFR-TKIs monotherapy	0.86 (0.31–2.39)	0.77	0.66 (0.23–1.92)	0.45

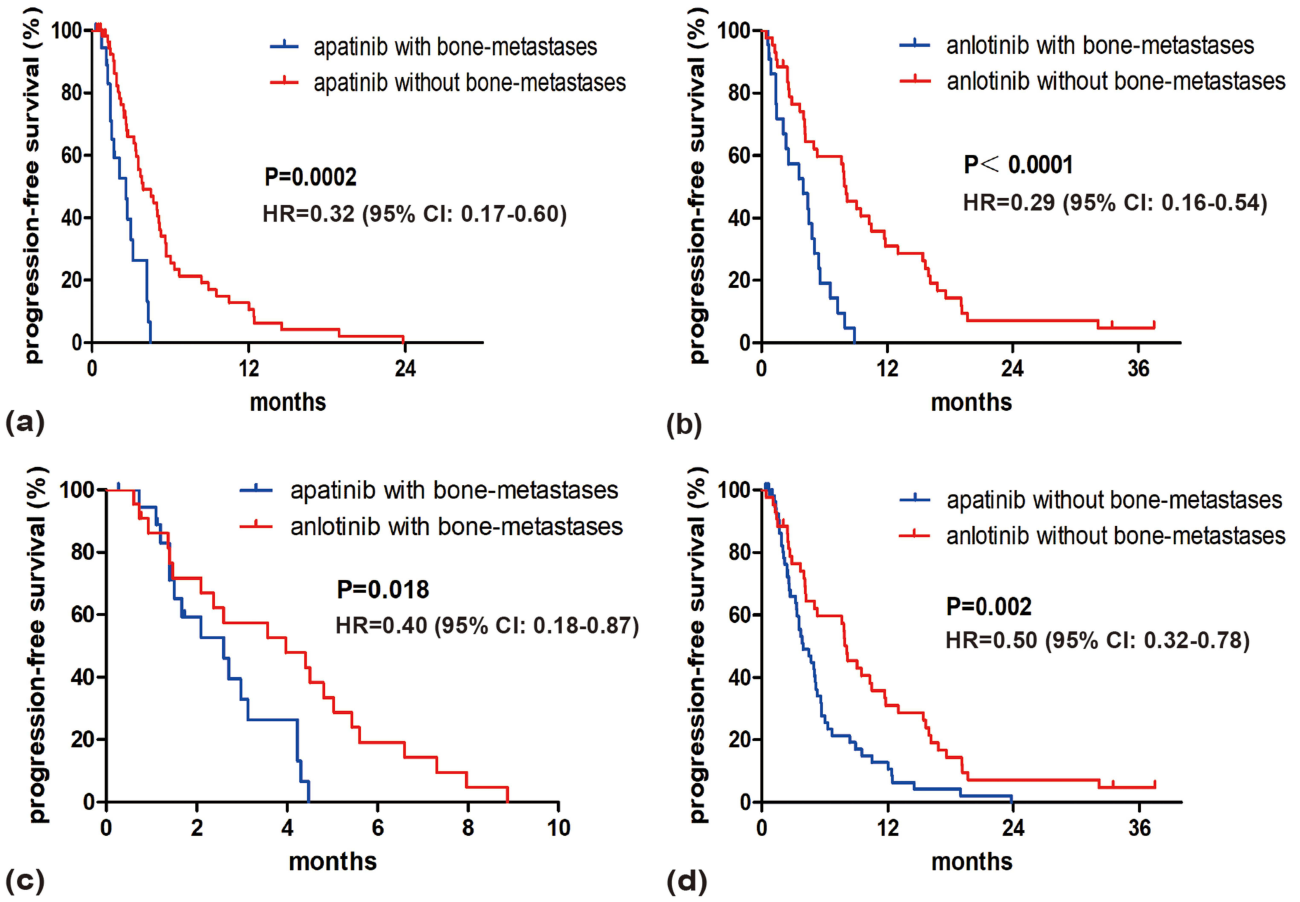

Figure 3 Kaplan-Meier estimates of PFS compared in different subgroups. (**a**), apatinib group with bone metastases vs apatinib group without bone metastases; (**b**), anlotinib group with bone metastases vs anlotinib group without bone metastases; (**c**), apatinib group with bone metastases vs anlotinib group with bone metastases; (**d**), apatinib group without bone metastases vs anlotinib group without bone metastases.

Results indicated that patients in the apatinib group without bone metastases exhibited a superior mPFS and mOS compared to those with bone metastases: 3.93 months (95% CI: 3.20–5.17) versus 2.6 months (95% CI: 1.40–3.13), P = 0.0002 (Figure 3a), and 9.2 months (95% CI: 6.10–12.53) versus 5.03 months (95% CI: 2.57–6.37), P = 0.002 (Figure 4a). A similar trend was observed in the anlotinib group, with patients without bone metastases achieving a mPFS of 8.07 months (95% CI: 4.2–11.73) compared to 3.97 months (95% CI: 1.47–5.03) for those with bone metastases, P < 0.0001 (Figure 3b), and a mOS of 20.53 months (95% CI: 13.97–22.47) compared to 8.73 months (95% CI: 5.17–12.83), P = 0.005 (Figure 4b). Subsequently, we compared the influence of bone metastases on PFS and OS between the apatinib and anlotinib groups. In this comparison, the mPFS for patients with bone metastases in the anlotinib group was more favourable than that in the apatinib group: 3.97 months (95% CI: 1.47–5.03) versus 2.6 months (95% CI: 1.40–3.13), P = 0.018 (Figure 3c). The comparative analysis of patients without bone metastases between the two groups yielded consistent results: 8.07 months (95% CI: 4.20–11.73) versus 3.93 months (95% CI: 3.20–5.17), P = 0.002 (Figure 3d). However, the analysis of OS between subgroups brought different results, with the presence of bone metastases not significantly affecting OS between the two groups (Figure 4c and 4d).

Safety

AEs potentially associated with the therapeutic drugs are detailed in Table 5. In the apatinib group, 65 (82.28%) patients experienced at least one AE, and 25 (31.65%) encountered grade 3 or higher AEs. In the anlotinib group, these figures were 49 (74.24%) and 9 (13.64%), respectively. The incidence rates of hypocalcemia, secondary hypertension, hypoproteinemia, hypokalemia, asthenia, hyponatremia, increased gamma-glutamyltransferase, and hypomagnesemia were

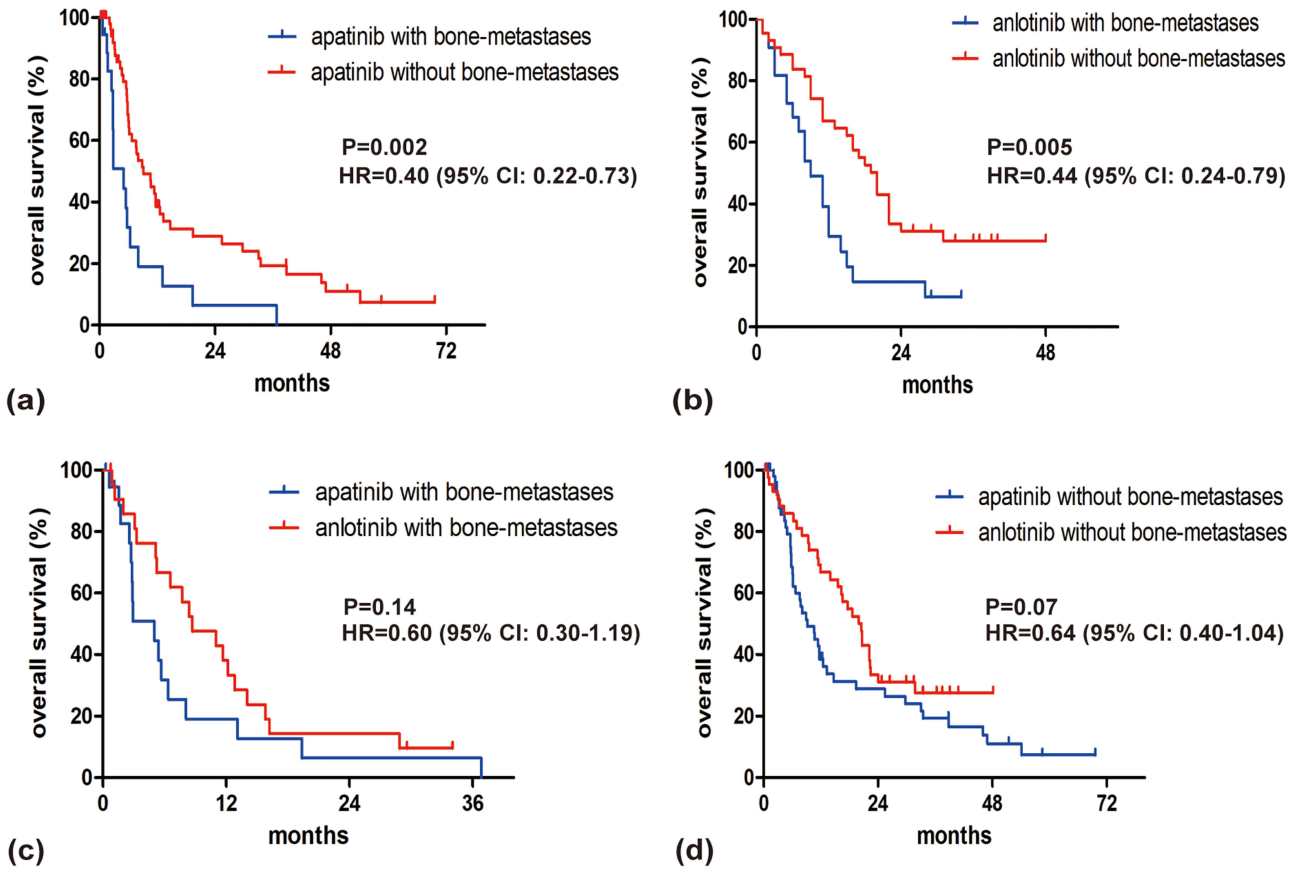

Figure 4 Kaplan-Meier estimates of OS compared in different subgroups. (**a**), apatinib group with bone metastases vs apatinib group without bone metastases; (**b**), anlotinib group with bone metastases vs anlotinib group without bone metastases; (**c**), apatinib group with bone metastases vs anlotinib group with bone metastases; (**d**), apatinib group without bone metastases vs anlotinib group without bone metastases.

significantly higher in the apatinib group ($P < 0.05$). Notably, the occurrence of hypothyroidism was significantly more prevalent in the anlotinib group ($P < 0.01$).

In terms of dosage adjustments, 13 (16.46%) patients in the apatinib group experienced dose reductions, and 15 (18.99%) discontinued treatment permanently due to AEs. In the anlotinib group, these figures were 6 (9.09%) and 3

Table 5 Adverse Events

Adverse Event	Apatinib (n = 79)		Anlotinib (n = 66)	
	Any Grade (n, %)	Grade 3–4 (n, %)	Any Grade (n, %)	Grade 3–4 (n, %)
Any adverse event	65 (82.28)	25 (31.65)*	49 (74.24)	9 (13.64)
Proteinuria	15 (18.99)	0	5 (7.58)	1 (1.52)
Hypocalcemia	15 (18.99)*	1 (1.27)	3 (4.55)	0
Hypertriglyceridemia	14 (17.72)	0	8 (12.12)	0
Secondary hypertension	14 (17.72)*	8 (10.13)*	2 (3.03)	0
Hypoproteinemia	14 (17.72)**	0	0	0
Hypokalemia	12 (15.19)*	1 (1.27)	2 (3.03)	0

(*Continued*)

Table 5 (Continued).

Adverse Event	Apatinib (n = 79)		Anlotinib (n = 66)	
	Any Grade (n, %)	Grade 3–4 (n, %)	Any Grade (n, %)	Grade 3–4 (n, %)
Myelosuppression	12 (15.19)	1 (1.27)	13 (19.70)	3 (4.55)
Anemia	11 (13.92)	2 (2.53)	3 (4.55)	1 (1.52)
Hepatic function abnormal	11 (13.92)	1 (1.27)	9 (13.64)	0
Blood creatinine increased	11 (13.92)	0	7 (10.61)	0
Asthenia	8 (10.13)*	1 (1.27)	1 (1.52)	0
Hyponatremia	8 (10.13)*	0	1 (1.52)	0
Blood bilirubin increased	8 (10.13)	0	2 (3.03)	0
Hyperuricemia	7 (8.86)	0	6 (9.09)	1 (1.52)
Hypophosphatemia	7 (8.86)	3 (3.80)	1 (1.52)	0
Hypercholesteremia	7 (8.86)	0	7 (10.61)	0
Gamma-glutamyltransferase increased	7 (8.86)*	0	0	0
Hand-foot syndrome	5 (6.33)	5 (6.33)	1 (1.52)	1 (1.52)
Hypomagnesemia	5 (6.33)*	0	0	0
Decreased appetite	3 (3.80)	1 (1.27)	1 (1.52)	0
Hematuria	3 (3.80)	0	0	0
Mouth ulceration	1 (1.27)	0	3 (4.55)	2 (3.03)
Diarrhea	1 (1.27)	0	0	0
Alimentary tract hemorrhage	1 (1.27)	1 (1.27)	1 (1.52)	0
Nausea	1 (1.27)	0	0	0
Hemorrhinia	1 (1.27)	0	0	0
Hypothyroidism	1 (1.27)**	0	17 (25.76)	0
Tachycardia	1 (1.27)	0	0	0
Lymphocytopenia	1 (1.27)	0	0	0
Hyperglycemia	0	0	2 (3.03)	0

Notes: *Compared with anlotinib group, P < 0.05; **Compared with anlotinib group, P < 0.01.

(4.55%), respectively. A significant difference was observed in the rate of treatment discontinuation due to AEs between the two groups ($X^2 = 5.46$, P = 0.019).

Analysis of Influencing Factors in AEs

Variables such as treatment group, gender, and age were included as independent factors in the univariate logistic regression model to evaluate their potential influence on the incidence of grade 3–4 adverse reactions. The analysis revealed that both the treatment group and genotype were significantly associated with the occurrence of serious adverse reactions in patients. Subsequently, factors with a P-value less than 0.2 in the univariate analysis and those that were unbalanced in the baseline characteristics were integrated into the multivariate logistic regression model. The results from the multivariable analysis confirmed that both the treatment group and genotype remained significant predictors. (Table 6)

Table 6 Multivariable Regression Model for Grade 3–4 AEs

Factors	Univariate		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Group	2.93 (1.26–6.85)	0.01	3.33 (1.19–9.36)	0.02
Gender	0.85 (0.37–1.94)	0.69		
Age (≤65 yr vs >65 yr)	1.53 (0.71–3.31)	0.28		
Smoking history	2.34 (1.00–5.46)	0.05	2.12 (0.82–5.50)	0.12
ECOG/PS	1.09 (0.40–2.96)	0.87		
Bone metastases (yes vs no)	1.84 (0.81–4.14)	0.14	2.19 (0.90–5.32)	0.08
Brain metastases (yes vs no)	0.54 (0.19–1.52)	0.24		
Squamous carcinoma vs Adenocarcinoma	0.93 (0.39–2.21)	0.87		
Others vs Adenocarcinoma	1.00 (0.25–3.97)	1.00		
Genotype (EGFR+ vs EGFR-)	2.50 (1.09–5.77)	0.03	3.03 (1.19–7.69)	0.02
Treatment line	1.10 (0.67–1.81)	0.71	1.00 (0.57–1.75)	0.99
VEGFR-TKIs + Chemotherapy vs VEGFR-TKIs monotherapy	0.97 (0.40–2.34)	0.95	1.10 (0.43–2.85)	0.84
VEGFR-TKIs + ICIs vs VEGFR-TKIs monotherapy	1.80 (0.59–5.51)	0.30	0.80 (0.22–2.91)	0.73
VEGFR-TKIs + Chemotherapy + ICIs vs VEGFR-TKIs monotherapy	0.67 (0.11–4.01)	0.66	0.91 (0.13–6.51)	0.92

In light of these findings, we further examined the differences in the incidence of grade 3–4 adverse reactions within or between the apatinib and anlotinib groups, considering different EGFR gene phenotypes. It was observed that the occurrence of serious adverse reactions did not significantly differ within the apatinib group or the anlotinib group when considering the EGFR gene status. However, a notable difference was identified in the incidence of grade 3–4 adverse reactions between the apatinib EGFR (-) group and the anlotinib EGFR (-) group. Specifically, the incidence of serious adverse events was significantly lower in the anlotinib EGFR (-) group compared to the apatinib EGFR (-) group ($X^2 = 4.52$, $P = 0.034$). (Table 7)

Table 7 Safety of the Apatinib Group and the Anlotinib Group Under Different EGFR Mutation Status

EGFR Mutation Status	Grade 3–4 AEs	Apatinib (n = 79)	Anlotinib (n = 66)	X^2	P-value
EGFR(+)	Yes	9	4	2.62	0.105
	No	9	13		
EGFR(-)	Yes	16	5	4.52	0.034
	No	45	44		
X^2		3.63	1.90		
P-value		0.057	0.168		

Discussion

According to data from the National Cancer Center of China, lung cancer predominantly affects the Eastern, Northern, and Northeastern regions of the country. Consequently, representative healthcare institutions in East China were selected for this study, which aimed to conduct a real-world assessment of apatinib versus anlotinib in the treatment of advanced NSCLC.

Our study revealed that, in terms of short-term efficacy, apatinib demonstrated notable performance in ORR, while anlotinib was more effective in DCR; however, these differences did not reach statistical significance ($P > 0.05$). In the context of long-term efficacy, the mPFS of the anlotinib group was significantly superior to that of the apatinib group, even after adjusting for confounding factors (5.3 months vs 3.53 months, HR = 0.59, P = 0.004). Notably, the mPFS for both the apatinib and anlotinib groups in our study appeared to be lower than those reported in clinical trials.[14–16,18] This discrepancy underscores the differences between real-world patient treatment and the more controlled environment of clinical trials, where factors such as patient age, physical condition, and treatment protocols are more rigorously standardized, potentially impacting outcomes. However, we also found a retrospective study on the use of apatinib in advanced NSCLC, in which the mPFS results were similar to our study (3.95 months vs 3.53 months).[19] The univariate analysis indicated a significantly higher mOS in the anlotinib group compared to the apatinib group (15.6 months vs 7.6 months, HR = 0.68, P = 0.048), which remained significant after controlling for confounding variables (P = 0.03). Conversely, the mOS for the anlotinib group in our study appeared to be longer than the results of the phase 3 ALTER0303 study (15.6 months vs 9.6 months).[14] This outcome may be attributed to the fact that all the patients included in ALTER0303 study were advanced NSCLC patients undergoing third- or further-line therapy.

Furthermore, our analysis demonstrated that the presence or absence of bone metastases significantly impacted both PFS and OS, in addition to the treatment group. Consequently, we conducted a detailed analysis of the subgroups. This investigation revealed that PFS and OS was significantly lower in patients with bone metastases in both treatment groups compared to those without bone metastases. We also focused on the differences in PFS and OS between the apatinib and anlotinib groups, considering the presence or absence of bone metastases. We found that the PFS of the anlotinib group was superior in the corresponding population, irrespective of bone metastasis status. This finding, not previously highlighted in other studies, suggests that patients with baseline bone metastases might derive greater benefits from anlotinib. However, the presence of bone metastases did not have an effect on OS between the two groups, and this outcome may be attributed to the deterioration of the physical condition and a broader range of subsequent treatment options available following progression on initial drug therapy.

The safety analysis revealed a significantly higher incidence of hypocalcemia, secondary hypertension, hypoproteinemia, hypokalemia, malaise, hyponatremia, elevated gamma-glutamyltransferase, and hypomagnesemia in the apatinib group compared to the anlotinib group ($P < 0.05$). Conversely, the incidence of hypothyroidism was significantly greater in the anlotinib group ($P < 0.01$). No unexpected AEs were observed in either group, which is consistent with other reports.[20,21] The frequency of grade 3–4 AEs was notably higher in the apatinib group ($P < 0.05$). The rate of treatment discontinuation due to AEs in the apatinib group was 18.99%, predominantly due to secondary hypertension (10.13%) and hand-foot syndrome (6.33%). In contrast, the anlotinib group had a treatment interruption rate of 4.55%, demonstrating a significant advantage in the occurrence of serious adverse reactions ($P < 0.05$). Multivariate logistic regression analysis, after adjusting for confounding factors, indicated that the treatment group significantly influenced the occurrence of serious AEs in patients (OR = 3.33, P = 0.02). Additionally, different EGFR genotypes also markedly impacted the incidence of AEs (OR = 3.03, P = 0.02). Further analysis showed that the incidence of serious AEs in the EGFR (-) anlotinib group was significantly lower than in the EGFR (-) apatinib group ($P < 0.05$). Therefore, the occurrence of serious AEs requires close monitoring during the administration of apatinib in EGFR (-) NSCLC patients.

However, this study has several limitations: it is retrospective in nature, carrying the inherent risk of patient selection bias; the limited sample size might affect the stability and reliability of the findings; and being a single-center study, it may not fully represent the experience of patients with advanced NSCLC at the national or global level.

In conclusion, for patients with advanced NSCLC, anlotinib, as an anti-angiogenic agent, presents a more favorable clinical option compared to apatinib. Future prospective, randomized controlled studies with larger samples and involving multiple centers are required to substantiate the findings of this study. The investigation of other potential

predictive factors related to efficacy and safety, as well as mechanisms of acquired resistance in NSCLC patients, is also essential to enhance precision in treatment selection and prognosis.

Conclusions

Anlotinib, a small-molecule oral anti-angiogenic agent, demonstrated greater efficacy and safety compared to apatinib in the treatment of advanced NSCLC. Anlotinib showed significant improvements in PFS and OS, particularly in patients with bone metastases. Additionally, anlotinib's safety profile was superior, especially in EGFR(-) patients. However, careful monitoring of thyroid function is advisable when prescribing anlotinib to the hypothyroid population.

Abbreviations

NSCLC, non-small cell lung cancer; AEs, adverse effects; TKIs, tyrosine kinase inhibitors; VEGFR-TKIs, vascular endothelial growth factor receptor-tyrosine kinase inhibitors; PFS, progression-free survival; mPFS, median progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; ORR, objective response rate; DCR, disease control rate; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; RECIST, Response Evaluation Criteria in Solid Tumors; ICIs, Immune checkpoint inhibitors.

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Disclosure

The authors report no conflicts of interest in this work.

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