Proceedings of Anticancer Research, 2024, Volume 8, Issue 1
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

# Analysis of the Efficacy, Progression-Free Survival, and Safety of Anlotinib in Advanced Lung Cancer Treatment

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**Abstract:** *Objective:* To analyze the clinical efficacy, progression-free survival, and safety of anlotinib in the treatment of advanced lung cancer. *Methods:* A retrospective analysis was conducted using data from 60 patients with advanced lung cancer treated with anlotinib from May 2019 to May 2021. This analysis aimed to comprehensively evaluate the clinical efficacy, progression-free survival, and adverse reactions of anlotinib. *Results:* The median progression-free survival (PFS) for the 60 patients was 5.79 months, with an overall response rate (ORR) of 21% and a disease control rate (DCR) of 90%. In the first-line group, the median PFS was 6.20 months, ORR was 76.92%, and DCR was 84.61%. The second-line group showed a median PFS of 6.30 months, ORR of 28.57%, and DCR of 90.48%. In the third-line group, the median PFS was 5.34 months, ORR was 19.23%, and DCR was 92.30%. The single-agent group exhibited a median PFS of 5.09 months, ORR of 23.33%, and DCR of 76.67%. In the combination group, the median PFS was 6.53 months, ORR was 46.67%, and DCR was 100%. The combination group demonstrated a significantly higher medication effect than the single-drug group, and adverse drug reactions were mostly grade 1–2. *Conclusion:* Anlotinib exhibits a better disease control rate and survival benefit in the treatment of advanced lung cancer. The combination effect is superior to monotherapy, with relatively controllable adverse effects.

**Keywords:** Anlotinib; Advanced lung cancer; Vascular targeted therapy; Recent efficacy; Drug safety

**Online publication:** January 26, 2024

## 1. Introduction

Lung cancer ranks among the cancers with the highest mortality rate globally. According to data from the Annual Cancer Report 2023 published online in the Journal of Cancer for Clinicians, China recorded three million cancer-related deaths in 2020. Among these, lung cancer accounted for a staggering 710,000 deaths, making up 23.8% of the total cancer fatalities. Furthermore, the incidence rate of lung cancer is steadily increasing year by year [1-3].

For patients grappling with advanced lung cancer, targeted therapy, immunotherapy, and chemotherapy are recommended as standard treatments for prolonged survival. While the advent of targeted drugs has instilled

hope among patients with gene target mutations, it is noteworthy that such mutations primarily occur in lung adenocarcinoma, with a mutation rate of approximately 40% [4,5]. Consequently, the focus in recent years within the field of lung cancer treatment has shifted towards target detection and targeted therapy.

Anlotinib, an oral small-molecule multi-target tyrosine kinase inhibitor (TKI), effectively inhibits multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors 1-3 (VEGFR1-3), c-Kit, platelet-derived growth factor receptor-α (PDGFR-α), and fibroblast growth factor receptors 1-3 (FGFR1-3) [6,7]. It plays a role in anti-tumor angiogenesis and tumor growth inhibition. Recognized by the National Medical Products Administration (NMPA), anlotinib is approved for the third-line treatment of patients with advanced non-small cell lung cancer (NSCLC) [8,9]. Therefore, this study primarily focuses on evaluating the clinical efficacy of anlotinib in advanced lung cancer.

## 2. Materials and methods

### 2.1. General information

A retrospective analysis of data from 60 cases of advanced lung cancer patients treated with anlotinib at Yan'an People's Hospital from May 2019 to May 2021 was conducted. Among them, there were 39 male and 21 female patients, with ages ranging from 43 to 87 years, and an average age of 63.52 ± 9.74 years. Smoking history was present in 36 cases, while 24 cases were non-smokers. Pathologically, there were 24 cases of squamous carcinoma, 20 cases of adenocarcinoma, and 16 cases of small cell carcinoma. The patients were categorized into treatment groups based on clinical modalities: 13 cases in the first-line treatment group, 21 in the second-line treatment group, and 26 in the third-line treatment group. Additionally, they were divided into 30 cases in the single-drug group and 30 cases in the combined-drug group based on medication modalities. The study aimed to evaluate the clinical efficacy, progression-free survival, and drug safety in different treatment groups.

Inclusion criteria: (1) Cancer patients diagnosed with lung cancer through clinicopathology or cytology with a pathological stage of IIIb or IV; (2) Eastern Cooperative Oncology Group (ECOG) score of 0-2, with an expected survival of more than 8 weeks; (3) Presence of evaluable lesions.

Exclusion criteria: (1) Lung mass invading large vessels such as aorta, pulmonary artery, vena cava, etc., with a recent bleeding risk assessment; (2) Patients with lower extremity venous thrombosis or pulmonary embolism within the last 3 months; (3) Presence of urinary protein in urine; (4) Absence of evaluable foci; (5) History of hypertension, with blood pressure not controlled at 140/90 mmHg or less; (6) Patients with other malignant tumors; (7) Inability to swallow medications; (8) Severe cardiac, hepatic, renal, and pulmonary failure; (9) Hemoptysis (> 50 mL/day); (10) Expected survival less than 8 weeks.

### 2.2. Treatment method

In the single-agent group, oral anlotinib hydrochloride (Zhengda Tianqing Pharmaceutical Group) was administered in a 21-day treatment cycle. The dosage was 12 mg per day for the first 14 days, with drug discontinuation on days 15 to 21. A single-dose reduction or cessation of the drug due to toxicity was permitted.

In the combination group, additional therapeutic measures were implemented based on the treatment protocol of the single-drug group for different types of lung cancer:

(1) Adenocarcinoma with EGFR mutation: Osimertinib mesylate tablets (AstraZeneca) at 80 mg orally once daily.

(2) Adenocarcinoma without mutation: Pemetrexed disodium (Qilu Pharmaceutical Co., Ltd.) at 500 mg/m$^2$ via static drip on Day 1, once every 3 weeks. Carboplatin (Qilu Pharmaceutical Co., Ltd.) at AUC 5 mg/mL/min intravenously on Day 1, every 3 weeks, for 4–6 cycles.

(3) Squamous carcinoma: Paclitaxel liposome (Nanjing Greenleaf Pharmaceutical Co., Ltd.) at 135–175 mg/m$^2$ intravenously on Day 1, every 3 weeks. Carboplatin (Qilu Pharmaceutical Co., Ltd.) at AUC 5 mg/mL/min intravenously on Day 1, every 3 weeks, for 4–6 cycles.
(4) Small cell lung cancer: Etoposide (Jiangsu Hengrui Pharmaceutical Co., Ltd.) at 60–100 mg/m$^2$ intravenously on Days 1–3, every 3 weeks. Carboplatin (Qilu Pharmaceutical Co., Ltd.) at AUC 5 mg/mL/min intravenously on Day 1, every 3 weeks, for 4–6 cycles.

### 2.3. Effect evaluation

Tumor response was assessed every two cycles or earlier when clear signs of progression emerged. The evaluation followed the response evaluation criteria for solid tumors: complete remission (CR), partial remission (PR), stable disease (SD), and disease progression (PD). The objective remission rate (ORR) was defined as the sum of CR and PR, while the disease control rate (DCR) encompassed CR, PR, and SD. Progression-free survival (PFS) represented the time from the initiation of treatment with the drug to the occurrence of disease progression or death from any cause.

Adverse reactions were assessed in accordance with the International System for Evaluation of Adverse Reactions to Chemotherapeutic Drugs in Oncology (CTCAE) version 5.0. Adverse reactions were graded from 1 to 5 based on their severity.

### 2.4. Statistical analysis

The study data were input into SPSS 26.0 software for statistical analysis. Quantitative data conforming to normal distribution were presented as mean ± standard deviation (SD). Intergroup comparisons were conducted using the *t*-test or ANOVA. For data not conforming to a normal distribution, the median and interquartile range (M [P25, P75]) were employed, and comparisons were made using the rank-sum test. Qualitative data were expressed as rates or constitutive ratios. Comparisons for these data were categorized into grades 1–5 based on the severity of adverse reactions using a four-cell table or the R×C list chi-squared test. The statistical significance level was set at $P < 0.05$.

## 3. Results

### 3.1. Results of clinical efficacy evaluation

Based on the solid tumor response evaluation criteria (**Table 1**), the 60 patients in the study were categorized as follows: 0 patients with CR (0%), 21 patients with PR (35%), 33 patients with SD (55%), and 6 patients with PD (10%). The ORR was 21%, and the DCR was 90%.

**Table 1.** Efficacy evaluation [*n* (%)]

| Cases | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|
| 60 | 0 (0.00) | 21 (35.00) | 33 (55.00) | 6 (10.00) | 21 (35.00) | 54 (90.00) |

### 3.2. Comparison of recent efficacy of different treatment program groups

**Table 2** shows the comparison of the recent efficacy of different treatment program groups:

(1) First-line treatment: 0 patients with CR (0%), 10 patients with PR (76.92%), 1 patient with SD (7.69%), 2 patients with PD (15.38%), ORR 76.92%, DCR 84.61%.
(2) Second-line treatment: 0 patients with CR (0%), 6 patients with PR (28.57%), 13 patients with SD (61.90%), 2 patients with PD (9.52%), ORR 28.57%, DCR 90.48%.

(3) Third-line treatment: 0 patients with CR (0%), 5 patients with PR (19.23%), 19 patients with SD (73.07%), 2 patients with PD (7.69%), ORR 19.23%, DCR 92.30%.

**Table 2.** Comparison of recent efficacy of first-, second-, and third-line treatments [*n* (%)]

| Group | *n* | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|---|
| First-line treatment | 13 | 0 (0.00) | 10 (76.92) | 1 (7.69) | 2 (15.38) | 10 (76.92) | 10 (84.61) |
| Second-line treatment | 21 | 0 (0.00) | 6 (28.57) | 13 (61.90) | 2 (9.52) | 6 (28.57) | 19 (90.48) |
| Third-line treatment | 26 | 0 (0.00) | 5 (19.23) | 19 (73.07) | 2 (7.69) | 7 (19.23) | 24 (92.30) |

## 3.3. Comparison of recent efficacy of different medication modalities

**Table 3** shows the comparison of the recent efficacy of different medication modalities:

(1) Monotherapy group: 0 patients with CR (0%), 7 patients with PR (23.33%), 17 patients with SD (56.67), 6 patients with PD (20.00%), ORR 23.33%, DCR 76.67%.

(2) Combination therapy group: 0 patients with CR (0%), 14 patients with PR (46.67%), 16 patients with SD (53.33%), 0 patients with PD (0%), ORR 46.47%, DCR 100%.

**Table 3.** Comparison of recent efficacy of monotherapy and combination therapy [*n* (%)]

| Group | *n* | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|---|
| Monotherapy | 30 | 0 (0.00) | 7 (23.33) | 17 (56.67) | 6 (20.00) | 8 (23.33) | 25 (76.67) |
| Combination therapy | 30 | 0 (0.00) | 14 (46.67) | 16 (53.33) | 0 (0.00) | 14 (46.67) | 30 (100.00) |

## 3.4. Comparison of progression-free survival of different treatment regimens

The results indicated a median PFS of 5.79 months. Specifically, the median PFS for first-line treatment was 6.20 months, for second-line treatment was 6.30 months, and for third-line treatment was 5.34 months. The monotherapy group had a median PFS of 5.09 months, while the combination therapy group showed a median PFS of 6.53 months, with the latter being significantly higher than the monotherapy group ($P < 0.05$). Refer to **Table 4**.

**Table 4.** Comparison of PFS in different treatment regimen groups (months)

| Treatment regimens | | Number of cases | Median PFS | Standard deviation |
|---|---|---|---|---|
| First-line treatment | Monotherapy | 10 | 6.25 | 3.862 |
| | Combination | 3 | 6.00 | - |
| | Total | 13 | 6.20 | 3.347 |
| Second-line treatment | Monotherapy | 8 | 4.75 | 3.34 |
| | Combination | 13 | 7.33 | 1.966 |
| | Total | 21 | 6.30 | 2.751 |
| Third-line treatment | Monotherapy | 13 | 4.69 | 2.434 |
| | Combination | 13 | 6.00 | 1.852 |
| | Total | 26 | 5.34 | 2.196 |
| Total | Monotherapy | 30 | 5.09 | 2.900 |
| | Combination | 30 | 6.53 | 1.885 |
| | Total | 60 | 5.79 | 2.529 |

### 3.5. Comparison of adverse drug reactions

Based on grades 3 to 4 adverse reactions assessed by CTCAE, no drug-related deaths occurred in this study. Most adverse reactions were in grades 1 to 2, with only 2 cases of grades 3 to 4 adverse reactions in the combination treatment group. This occurrence might be attributed to prolonged chemotherapy, coupled with patients having longer periods of transitional rest, leading to decreased physical ability and diminished activity levels. As a result, after using the drug, these patients experienced physical weakness and loss of appetite, which could be alleviated through slight adjustments in later-stage treatment. Refer to **Table 5**.

**Table 5.** Comparison of adverse reactions to medication (*n*)

| Cases | All Grades | | Grades 3 to 4 | |
|---|---|---|---|---|
| | Monotherapy | Combination | Monotherapy | Combination |
| Fatigue | 8 | 12 | 0 | 1 |
| High blood pressure | 4 | 6 | 0 | 0 |
| Loss of appetite | 7 | 12 | 0 | 1 |
| Capillary reaction syndrome | 2 | 2 | 0 | 0 |
| Liver damage | 0 | 4 | 0 | 0 |
| Nausea/vomiting | 3 | 5 | 0 | 0 |
| Proteinuria | 1 | 3 | 0 | 0 |
| Oral ulcers | 0 | 0 | 0 | 0 |
| Breathlessness | 0 | 0 | 0 | 0 |
| Bone marrow system | 0 | 2 | 0 | 0 |
| Hemoptysis | 1 | 1 | 0 | 0 |

## 4. Discussion

Due to the insidious onset and complex biological characteristics of lung cancer, about two-thirds of patients reach advanced stages at the time of clinical diagnosis, missing the opportunity for surgical cure [10]. Several molecular pathways, including the cell cycle control pathway, proliferation pathway, and angiogenesis, play crucial roles in the occurrence and development of cancer. Multi-targeted TKIs have demonstrated significant anti-tumor effects in various types of tumors by inhibiting angiogenesis and proliferation signaling [5].

Anlotinib is a novel oral multi-targeted TKI. Isoforms of VEGF and its receptors have been identified as effective anticancer targets. Dysregulation of the FGFR axis can promote cancer progression and enhance the angiogenic potential of the tumor microenvironment, leading to an aggressive cancer phenotype [11].

In this study, anlotinib was used in patients with advanced lung cancer, resulting in a PFS of 5.79 months, an ORR of 21%, and a DCR of 90%. These results suggest that the efficacy of anlotinib for advanced lung cancer is promising and effective in both first- and second-line treatments. In the first-line treatment group, patients had a PFS of 6.20 months, an ORR of 76.92%, and a DCR of 76.92%.

Compared with the study on first-line treatment of elderly non-small cell lung cancer with anlotinib conducted by Zhang *et al.* [12], where the PFS was 4.9 months, the ORR was 39.9%, and the DCR was 71.4%, the PFS was significantly prolonged in this group. This suggests that the first-line combination therapy was significantly better than the first-line single-agent therapy, possibly related to the small sample size considered.

In the second-line treatment group, patients had a PFS of 6.30 months, an ORR of 28.57%, and a DCR

of 90.48%. Compared with the study conducted by Zhou *et al.* on the second-line treatment of advanced lung cancer with anlotinib hydrochloride (PFS 3.61 months, ORR 20%, DCR 86.67%) [13], the ORR and DCR were roughly in line with each other, but the PFS was significantly prolonged. This could be attributed to the presence of two patients with EGFR positivity in the second-line treatment, significantly extending the patients' PFS.

In the third-line treatment group, patients had a PFS of 5.34 months, an ORR of 26.92%, and a DCR of 92.30%. Compared with the studies conducted by Han *et al.* (ALTER0302 and ALTER0303) [14,15], the PFS was roughly similar, while the ORR and DCR were slightly higher. In monotherapy and combination therapy, monotherapy resulted in a PFS of 5.09 months, an ORR of 26.67%, and a DCR of 83.33%. Combination therapy resulted in a PFS of 6.53 months, an ORR of 46.47%, and a DCR of 100%. These findings suggest that combination therapy is more effective than monotherapy in terms of PFS, but the adverse effects are significantly more pronounced than in the monotherapy group.

In addition, this study observed the safety of anlotinib, finding that malaise, hypertension, and loss of appetite were the most common adverse reactions. Most of these reactions were grades 1–2, with only two cases reaching grade 3 or above, mainly considered related to combination therapy. Hemoptysis was observed in two patients, and the adverse reaction symptoms were relieved after dose reduction or suspension of the drug and active symptomatic treatment. The adverse reactions could be controlled.

In conclusion, the efficacy of anlotinib in treating advanced lung cancer is promising, with controllable adverse reactions. Combination therapy is superior to monotherapy in terms of PFS, but adverse reactions in the combination therapy group are more pronounced. Third-line treatment exhibits certain objective efficacy and survival benefits. Second-line and first-line treatments show better effectiveness than third-line treatment, although due to the small sample size and retrospective analysis, the results may have some bias. Further research and studies with larger sample sizes and controlled trials are needed for the next phase of investigation.

## Funding

Key R&D Program of Yan'an Municipal Bureau of Science and Technology (Project No. 2021YF-21)

## Disclosure statement

The authors declare no conflict of interest.

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