Original Article

Cost-effectiveness analysis of anlotinib as a third-line or further treatment for advanced non-small cell lung cancer in China

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Background: The health expenditure on treatment of advanced non-small cell lung cancer (NSCLC) is enormous, especially in third-line or further therapy. Cost-effectiveness analysis for the treatment of advanced NSCLC is particularly important. Anlotinib has been approved by the China Food and Drug Administration (CFDA) for the third-line or further treatment of advanced NSCLC. The price of anlotinib in China fell in 2022. Thus, this study evaluated the cost-effectiveness of anlotinib in the third-line or further treatment of patients with advanced NSCLC based on the newest price from the Chinese health-care system perspective.

Methods: A Markov model was developed to compare the lifetime costs and effectiveness of anlotinib and a placebo in the third-line or further treatment of patients with advanced NSCLC based on outcome data from the ALTER 0303 phase-3 randomized clinical trial, which included 437 patients with advanced NSCLC and investigated the efficacy of anlotinib. The lifetime costs and quality-adjusted life years (QALYs) were estimated. One-way and probabilistic sensitivity analyses were performed to evaluate the model uncertainty.

Results: Anlotinib provided an additional 0.1161 QALYs compared to the placebo. The corresponding incremental cost was ¥22,729. The incremental cost-effectiveness ratio (ICER) of anlotinib compared to the placebo was ¥195,768 per QALY. From the perspective of the Chinese health-care system, anlotinib was found to be cost-effective compared to the placebo in the third-line or further treatment of patients with advanced NSCLC at a willingness-to-pay (WTP) threshold of ¥242,928 per QALY. Moreover, 1-way sensitivity analysis found that the results were sensitive to the utility of progressive disease (PD). The lower this parameter was, the higher the probability of ICER for anlotinib not being cost-effective. The cost-effectiveness acceptability curves showed that the base-case analysis results were relatively stable.

Conclusions: Considering the clinical efficacy, safety, and cost-effectiveness of anlotinib, it may be a valuable third-line or further treatment for advanced NSCLC in China.

Keywords: Anlotinib; cost-effectiveness; non-small cell lung cancer (NSCLC); targeted therapy

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Introduction

Lung cancer is one of the most common malignant tumours in the world. With an estimated 2.2 million new cases and 1.8 million deaths worldwide, lung cancer was the second most commonly diagnosed cancer and the leading cause of cancer-related death in 2020 (1). In recent years, there has been an upward trend in the incidence and associated mortality of lung cancer in China (2). In the clinic, lung cancer is usually broadly divided into the following two histological categories: (I) small cell lung cancer; and (II) non-small cell lung cancer (NSCLC). NSCLC accounts for 80–85% of lung cancers and is divided into adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma, among others (3,4). Approximately 70% of patients with NSCLC are locally advanced or metastatic at the time of their initial diagnosis (5).

Currently, in addition to chemotherapy, radiotherapy, surgery, and immunotherapy, targeted therapy has received much attention in tumour therapy, especially for NSCLC (2). For example, anlotinib, an oral multitarget receptor tyrosine kinase inhibitor (TKI), has been shown to inhibit tumour angiogenesis and tumour cell proliferation (6). A phase-3 clinical trial (ALTER 0303) demonstrated that anlotinib prolonged the median progression-free survival (mPFS) and median overall survival (mOS) of advanced NSCLC patients. Specifically, the mPFS of these patients was significantly increased in the anlotinib group compared to the placebo group {5.4 months [95% confidence interval (CI): 4.4–5.6 months] *vs.* 1.4 months (95% CI: 1.1–1.5 months)}. Additionally, the mOS was significantly longer in the anlotinib group than the placebo group [9.6 months (95% CI: 8.2–10.6 months) *vs.* 6.3 months (95% CI: 5.0–8.1 months)] (7). As a result, China Food and Drug Administration (CFDA) has approved the use of anlotinib for the third-line or further treatment of advanced NSCLC.

However, due to the high morbidity and relatively long therapy time, the treatment costs of NSCLC are expensive and consume many medical resources. In 2015, Zarogoulidou *et al.* conducted a study on the economic burden of lung cancer on health-care systems in Greece, and found that the total direct costs were €1,853,984, and chemotherapy drugs had the highest cost factor (€1,216,421) (8). Verleger *et al.* estimated the economic burden of advanced NSCLC (stage IIIB/IV) on European society, and reported that the weighted mean total per-patient costs were €21,273, ranging from €17,761 (England) to €30,854 (Sweden) and €15,446 (squamous NSCLC) to €26,477 (non-squamous NSCLC). The systemic drugs account for 77.4% of the total costs (9). Zeng *et al.* analyzed the health expenditure data of 253 patients with advanced NSCLC in China from 2006 to 2010, and reported that the mean costs of treatment for patients in progression-free survival (PFS) and progressive disease (PD) over 1 year were approximately US$11,566 and $14,519, respectively (10). Since 2017, pharmacoeconomics has been applied to decision-making in Chinese health care system (11). The costs of NSCLC treatment place a heavy financial burden on the health-care system and patients. Cost-effectiveness analysis for the treatment of advanced NSCLC is particularly important. Anlotinib is included in the reimbursement coverage of third-line treatment for NSCLC by China's National Health Care Security Administration. In 2022, the price of anlotinib in China decreased. The present analysis investigated the cost-effectiveness of anlotinib as a third-line or further treatment for advanced NSCLC based on the latest price from the Chinese health-care system perspective. We present this article in accordance with the CHEERS reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-456/rc).

Highlight box

Key findings

- From the perspective of the Chinese health-care system, anlotinib was found to be cost effective compared to the placebo in the third-line or further treatment of patients with advanced non-small cell lung cancer (NSCLC) at a willingness-to-pay (WTP) threshold of ¥242,928 per QALY.

What is known and what is new?

- The treatment costs of NSCLC are enormous, consuming many medical resources, especially in third-line or further therapy. Anlotinib has been approved by the CFDA for third-line or further treatment of advanced NSCLC.
- This study evaluated the cost-effectiveness of anlotinib in the third-line or further treatment of patients with advanced NSCLC based on the newest price of anlotinib.

What is the implication, and what should change now?

- Anlotinib may be a valuable therapy for advanced NSCLC. We hope this study can provide a reliable reference for decision-making in the Chinese health care system and clinical treatment.

Methods

A Markov model was developed to estimate the costs and quality-adjusted life years (QALYs) of the third-line or

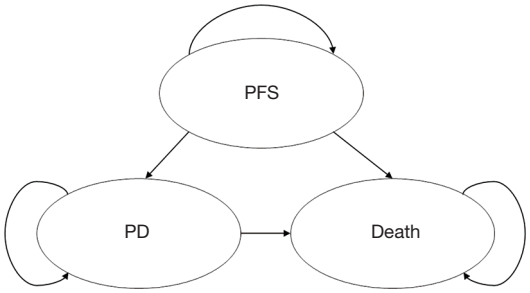

Figure 1 Markov model with 3 exclusive health states for advanced NSCLC. PFS, progression-free survival; PD, progressive disease; NSCLC, non-small cell lung cancer.

further treatment of patients with advanced NSCLC. The clinical data were derived from a multicentre, double-blind, randomized phase-3 clinical trial (7) (ALTER 0303, NCT02388919) that compared anlotinib to a placebo in patients with advanced NSCLC. ALTER 0303 trial was currently the highest quality clinical study published for the use of anlotinib in Chinese patients with advanced NSCLC. The enrolled patients of ALTER 0303 were basically consistent with the target patient population of this study, so our study conducted pharmacoeconomic evaluation based on the ALTER 0303 trial. All the patients with driver alterations (epidermal growth factor receptor mutation or anaplastic lymphoma kinase rearrangement) had experienced the failure of at least 1 line of chemotherapy and TKI therapy, and all the patients without driver alterations had experienced the failure of at least 2 lines of chemotherapy. Patients were randomly assigned at a 2-to-1 ratio to receive either 12 mg/d anlotinib (n=294) or a placebo (n=143). Each cycle was defined as 2 weeks of treatment followed by 1 week without treatment. The treatment continued until disease progression or treatment intolerance. The baseline characteristics were well-balanced between the two groups.

Three kinds of disease states were chosen in the Markov model, including PFS, PD and death (*Figure 1*). The time horizon of the Markov cycle was from the initiation of therapy to death throughout the patients' lifetime. Each model cycle represented 3 weeks. The construction and analysis of the model were carried out using Microsoft Office 365 Excel software. A 5% discount rate per year was adopted for both the costs and outcomes, which was recommended by China guidelines for pharmacoeconomic evaluations in 2020 (12). Since the research perspective of this study was the Chinese health-care system, only direct medical costs were considered. According to China guidelines for pharmacoeconomic evaluations (12), the willingness-to-pay (WTP) threshold was set at 3 times the gross domestic product (GDP) per capita of China. China's GDP per capita in 2021 was ¥80,976. When the incremental cost-effectiveness ratios (ICERs) were ≤¥242,928, anlotinib was considered a cost-effective therapy compared to the placebo. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the Affiliated Hospital of Nantong University approved this study (No. 2022-K007-01). Individual consent for this retrospective analysis was waived.

Model survival and progression risk estimates

The probability of the Markov model mainly includes the probability of patients maintaining the PFS or PD state (*Figure 1*), the probability of patients transferring from the PFS state to the PD state, and the probability of patients transferring from the PFS or PD state to death. The transition probabilities in this study were taken from the Kaplan-Meier survival curves in the ALTER 0303 study. This research recreated the individual patients' data from the Kaplan-Meier survival curves using standard statistical analyses described by Guyot (13) using Engauge Digitizer software and R software. Parametric distributions, including log-normal, log-logistic, generalized gamma, Gompertz, Weibull, and exponential distributions, were used to fit the pseudoindividual patient. The optimal parameter distribution model was selected according to the Akaike Information Criterion and Bayesian information criterion. Finally, the Weibull parameter model was selected as the parameter survival model to calculate the transition probability in the Markov model (see *Table 1* and *Figure 2*). Considering the internal correlation of the parameters in the survival function, a probabilistic sensitivity analysis of the parameters in the survival function was carried out after Cholesky decomposition.

Utility estimates

In this study, the QALYs were calculated by assigning utilities to different states. The health utilities of all the health states were derived from a published study (14) that measured the health utilities for advanced NSCLC using anlotinib and a placebo (*Table 2*). In the model, we assumed that the utilities were only related to the health states and had no connection to the therapies.

Table 1 Risk function based on the Weibull distribution

Model	Regression coefficient	Standard error
OS-anlotinib		
Constant term	–3.5607	0.2199
lnGamma	0.3190	0.0611
PFS-anlotinib		
Constant term	–2.7380	0.1654
lnGamma	0.3484	0.0529
OS-placebo		
Constant term	–2.6373	0.2336
lnGamma	0.1376	0.0813
PFS-placebo		
Constant term	–1.0576	0.1275
lnGamma	0.2692	0.0646

OS, overall survival; PFS, progression-free survival.

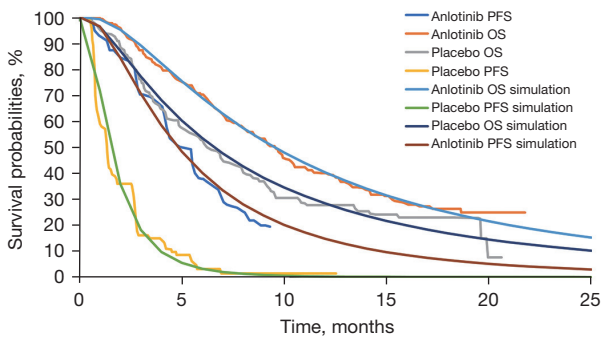

Figure 2 Results of the survival analyses. PFS, progression-free survival; OS, overall survival.

Measurement of costs

The analysis included the costs of registration, operation, drugs, nursing, medical materials, tests, management of adverse events (AEs), and hospitalization. The price of anlotinib was the latest medical insurance price from the open government data. The costs of subsequent therapy were calculated using real-world data from the Affiliated Hospital of Nantong University from 2019 to 2021 (*Table 3*). According to the real-world data, immunotherapy, chemotherapy, palliative care, and no treatment were often used after disease progression and the costs of subsequent therapy were calculated by weighting the proportion and cost of each treatment. The proportion of patients receiving follow-up treatment was approximately 59.3%.

Table 2 Health utility values

State/AEs	Utility value	Range
Progression-free survival (14)	0.60	(0.48, 0.72)
Stage of disease progression (14)	0.56	(0.45, 0.67)
Hypertension (15)	–0.12	–
Hand-foot syndrome (15)	–0.10	–

AEs, adverse events.

Table 3 Costs

Cost type	Costs (¥)	Frequency (of each cycle)
Anlotinib (12 mg ×7)	4,104.8	Every 3 weeks
Follow-up	1,036.23	Every 6 weeks
Treatment after progression	8,703.23	Every 3 weeks
Hypertension	120	–
Hand-foot syndrome	0	–

Table 4 The incidence of AEs (7)

AEs	Anlotinib (%)	Placebo (%)
Hypertension	13.6	0
Hand-foot syndrome	3.7	0

AEs, adverse events.

Safety parameters

The following two types of AEs were considered in the model: (I) AEs that resulted in obvious pain, discomfort, and other symptoms to patients, resulting in loss of quality of life; (II) AEs that were serious or had a certain risk, which required treatment and resulted in additional costs. According to the ALTER 0303 study, grade 3 or 4 AEs included hypertension and hand-foot syndrome. The incidence of the AEs was obtained from the ALTER 0303 study (see *Table 4*), and the loss of quality of life and treatment costs caused by the AEs were obtained from other published study (15) and real-world data (see *Tables 2,3*).

Sensitivity analysis

A series of sensitivity analyses were performed to test the

Table 5 Base-case results

Variables	Anlotinib	Placebo	Anlotinib *vs.* placebo
Cost (¥)	92,334	69,606	22,729
QALY	0.6031	0.4870	0.1161
ICER (¥/QALY)	195,768	–	–

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

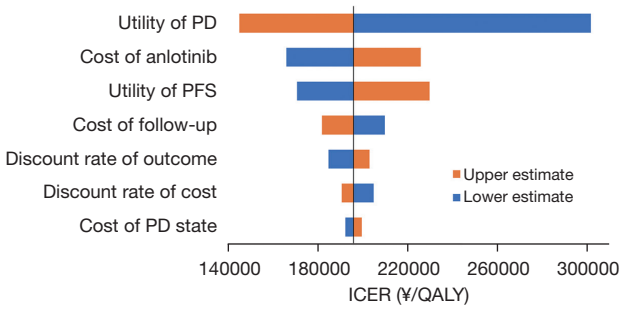

Figure 3 Tornado diagram. PD, progressive disease; PFS, progression-free survival; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

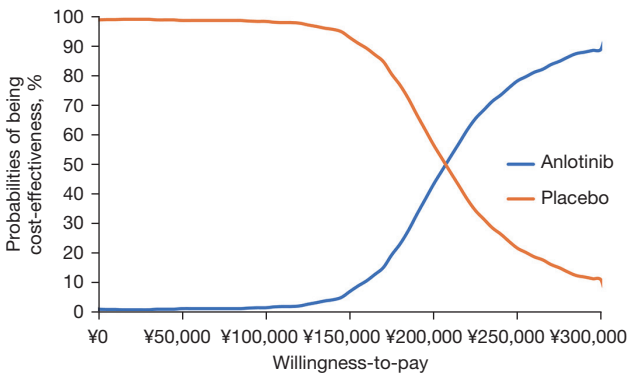

Figure 4 Cost-effectiveness acceptability curves.

uncertainty of the model. In a 1-way sensitivity analysis, all of the variables varied over a plausible range. A tornado diagram was drawn to determine the factors that significantly affected the results. In this study, the cost data were allowed to fluctuate by 10%, the utility data varied within 95% CIs, and the discount rate varied between 0% and 8%. In the probabilistic sensitivity analysis, a Monte Carlo simulation of 1,000 iterations was performed with all the parameters simultaneously varied with a specific distribution pattern. According to the simulation results, a cost-effectiveness acceptability curve (CEAC) was drawn to evaluate the economics of the two treatments with different WTP thresholds. The costs were assumed to follow the gamma distribution, the utility value was assumed to follow the beta distribution, and the relevant parameters in the survival analysis were assumed to follow the log-normal distribution.

Results

Base-case results

The incremental cost-effectiveness analysis results of anlotinib versus the placebo for the third-line treatment of advanced NSCLC are shown in *Table 5*. The costs in the anlotinib group and placebo group were ¥92,334 and ¥69,606, respectively. Compared to the placebo group, the anlotinib group had an incremental increase of 0.1161 QALYs. The ICER was ¥195,768 per QALY, which was lower than 3 times per capita GDP (¥242,928). Thus, anlotinib may be a cost-effective choice for the third-line treatment of advanced NSCLC.

Sensitivity analysis

One-way sensitivity analysis

The results of the 1-way sensitivity analysis, including the utility of PFS and PD and the costs of anlotinib, are shown in *Figure 3*. The tornado diagram showed that the base-case results were sensitive to the utility of PD. The ICER would be higher than the threshold when this parameter was set as lower estimate, which meant that anlotinib was not cost-effective. The other variables had little influence on the base-case results.

Probability sensitivity analysis

It was assumed that the WTP varied from 0 to ¥300,000. The CEAC is shown in *Figure 4*. When the WTP was <¥200,000, the placebo was cost effective compared to anlotinib. When the WTP was >¥200,000, the third-line treatment of anlotinib was cost effective. The probability of being cost effective between anlotinib and placebo was equivalent when the WTP was ¥200,000. The results were basically consistent with the basic analysis results, indicating that the base-case analysis results were relatively stable.

Discussion

At present, the main treatments for advanced NSCLC include chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy (16,17). Most patients will develop progressive disease after response to first- and second-line therapy. The mechanism of acquired resistance after targeted drug treatment has attracted increasing attention (18). However, the subsequent treatment is less hopeful and a clear standard has not been established (19). Currently, molecular-targeted therapy has received much attention, especially anlotinib. Third-line treatment with anlotinib has a significant effect on NSCLC and the AEs are controllable (7,20). The health expenditure on cancer care has been a global concern. It is particularly important to achieve a balance between treatment costs and clinical outcomes (21). Thus, the cost-effectiveness of anlotinib for NSCLC treatment was investigated in this study. Specifically, the health and economic outcomes of anlotinib for NSCLC therapy were analysed based on the newest price of anlotinib and clinical trial results (ALTER 0303).

Through the Markov model simulation, we found that patients with anlotinib treatment costs of ¥92,334 survived 1.04 years, and patients with placebo costs of ¥69,606 survived 0.85 years. The incremental cost-effectiveness analysis showed that compared to the NSCLC patients who received the placebo, those who failed second-line therapy needed to pay ¥195,768 per QALY. According to the WTP threshold recommended by the China guidelines for pharmacoeconomic evaluations [2020] (12), it is more cost effective to use anlotinib for patients with advanced NSCLC. Moreover, 1-way sensitivity analysis found that the results were sensitive to the utility of PD. The lower this parameter was, the higher the probability was of ICER for anlotinib not being cost-effective.

The results of our study are inconsistent with those of a previous study by Huang (22), who conducted a pharmacoeconomic evaluation of anlotinib as a third-line and later therapy for NSCLC patients and found that anlotinib was not a cost-effective regimen. In addition, Ding *et al.* also reported that anlotinib was not cost effective as a third-line therapy for NSCLC (23). The following reasons may account for the inconsistencies in these results: (I) our study added the costs after the failure of the third-line therapy; (II) the price of anlotinib was significantly reduced in 2022, and the newest price was applied in our study. The study by Huang and Ding (22,23) applied the previous price of anlotinib; and (III) the analytical method of our study differed to the methods of the two other studies. In a previous study, DEALE's method was used to calculate the transition probabilities between different states, ignoring changes in patient event risk over time (23). In the present study, the survival analysis was conducted according to the reported clinical data, and transition probabilities were evaluated through optimal models, ensuring that the transition of patients between different states matched the clinical trial data.

The present study had limitations. The efficacy data of this study was obtained from the ALTER 0303 trial. However, there were still differences between the clinical trial and the real world, leading to potential uncertainty in the extrapolation of research results in the real world. For example, the control group patients in ALTER 0303 trial were treated with placebo. However, in the real world, the third-line treatment options for advanced NSCLC include immunotherapy, chemotherapy, other anti angiogenic therapies, or participation in clinical trials. Among them, the cost-effectiveness of immunotherapy in advanced NSCLC has received considerable attention (24). Besides that, individual patient data from the ALTER 0303 study were unavailable, and we used the KM survival curve reported in the ALTER 0303 trial to reconstruct individual data. Although this is currently the most common method in the field of pharmacoeconomics, there may still be differences with real individual patient data, leading to some bias in the research results. Our next research plan is to collect real-world data and further investigate the cost-effectiveness of different treatments for advanced NSCLC.

Conclusions

From the perspective of the Chinese health-care system, anlotinib was cost-effective compared to the placebo in the third-line or further treatment of patients with advanced NSCLC at a WTP threshold of 3 times the GDP per capita of China per QALY. Anlotinib may be a valuable therapy for advanced NSCLC.

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Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-456/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-456/coif). All authors report funding support from the Research Project of the Tianqing Clinical Pharmacy Foundation of Jiangsu Pharmaceutical Association (No. Q2019161). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the Affiliated Hospital of Nantong University approved this study (No. 2022-K007-01). Individual consent for this retrospective analysis was waived.

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