Am J Cancer Res 2023;13(8):3679-3685
www.ajcr.us /ISSN:2156-6976/ajcr0151359

Brief Communication

Maintenance anlotinib improves the survival prognosis of extensive-stage small cell lung cancer: a single-arm, prospective, phase II study

Fanming Kong[1,2], Ziwei Wang[1,2], Na Wang[1,2], Dou Zhang[1,2], Dongying Liao[1,2], Jing Zhang[1,2], Yidan Sun[1,2], Haojian Zhang[1,2], Yingjie Jia[1,2]

[1]Department of Oncology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Anshanxi Road, Nankai District, Tianjin 300193, China; [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300193, China

Received May 21, 2023; Accepted July 27, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: The extent to which anlotinib provides survival benefits in the maintenance therapy of extensive-stage small cell lung cancer (ES-SCLC) remains unclear. Thus, this study aimed to assess the efficacy and safety of anlotinib monotherapy as maintenance therapy following induction chemotherapy in ES-SCLC patients. 27 ES-SCLC patients registered at the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine were screened from February 2022 to October 2022, of which 3 were not eligible. Eligible patients in stable status after first-line chemotherapy would subsequently accept oral anlotinib (12 mg, p.o., qd. on d1-d14, every 21 days). The maintenance method was continued until disease progression or unmanageable toxicity occurred. The primary endpoint is median progression-free survival (mPFS). The second endpoints include median duration of response (mDOR), median overall survival (mOS) and safety. The mPFS and mDOR have been determined (mPFS: 252 days, 95% CI: 217.782-286.218 days; mDOR: 126 days, 95% CI: 98.899-153.101 days). The mOS was not reached; only 7 patients were reached while 20 patients survived. The primary treatment-related adverse events included hypertension (n=7, 25.9%), fatigue (n=5, 18.5%), poor appetite (n=5, 18.5%), and others. Notably, no patients required a dose reduction due to the severity of adverse events. Patients were generally able to tolerate treatment with anlotinib and exhibited a favorable prognosis. Anlotinib achieved prospective efficacy and manageable safety in the maintenance treatment of ES-SCLC.

Keywords: Small-cell lung cancer, anlotinib, maintenance therapy, extensive-stage

Introduction

Small cell lung cancer (SCLC), an aggressive and neuroendocrine subtype of lung cancer, is associated with a near-uniformly fatal outcome [1]. Clinical prognosis is worse in patients with extensive-stage small cell lung cancer (ES-SCLC) compared to those with limited-stage. ES-SCLC accounts for around 70% of the classification and particularly has a terrible prognosis with a 2-year survival rate of only about 2% [2]. Despite the significant advancements made in targeted therapy and immunotherapy, SCLC remains an outlier in the precision medicine paradigm and chemotherapy remains the cornerstone of its management [3]. Therefore, it is crucial to investigate novel therapeutic approaches and medications to enhance the long-term outcome for ES-SCLC.

To achieve longer-term disease remission and survival, maintenance therapy entails receiving medication after a specific course of standard first-line treatment if the disease remains stable and the physical status score is satisfactory [4]. The medications used in maintenance therapy are typically one or more of the first-line chemotherapy regimens (described as same drug maintenance) or another regimen that no-cross-resistance with first-line chemotherapy drugs (described as dressing maintenance) [5]. In the absence of severe adverse effects, maintenance treatment will continue until the disease progresses or a predetermined time. Its

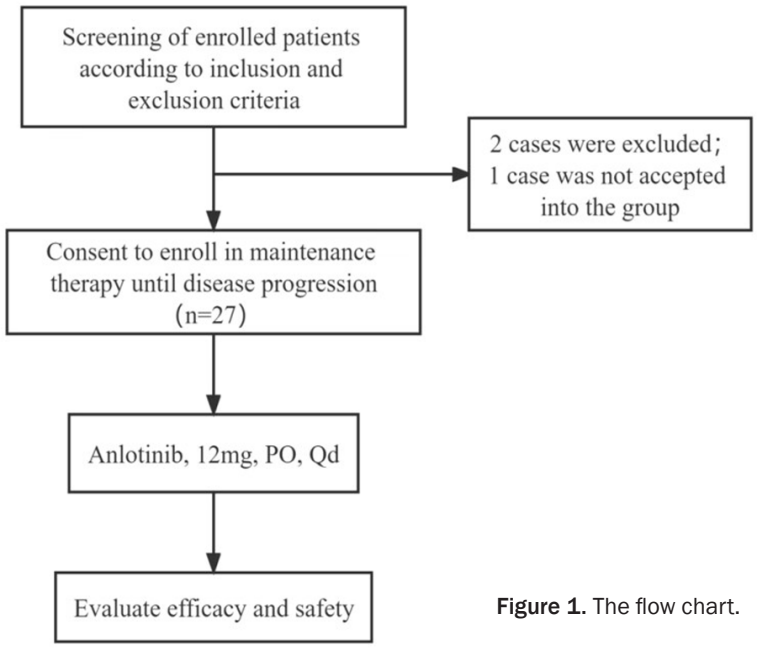

Figure 1. The flow chart.

theoretical basis comes from the hypothesis of Goldie and Coldman that early use of non-cross-inhibitory drugs can increase the efficacy of killing tumor cells before the emergence of drug resistance and optimize the therapeutic effect [6].

Anlotinib is an oral small molecule multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), c-kit proto-oncogene protein (c-Kit) and other targets, which can bind to a variety of cytokine receptors in the molecular pathway [7]. The advantage of anlotinib lies in the inhibition of tumor vascular growth by multiple pathways, fewer adverse drug reactions, and less occurrence of drug resistance [8]. Anlotinib has established the standard for third-line or beyond-treatment regimens of ES-SCLC, effectively addressing the unmet medical need in the domestic setting [9].

Based on the excellent performance of anlotinib and the exploration of maintenance treatment in ES-SCLC, this study aimed to assess the efficacy and safety of maintenance anlotinib following induction chemotherapy in ES-SCLC patients.

Methods

Study participants

27 eligible ES-SCLC patients who received maintenance anlotinib from February 2022 to October 2022 (**Figure 1**). The trial was performed by the principles of Good Clinical Practice and the Declaration of Helsinki, as well as all relevant regulations and laws in the applicable countries.

The inclusion criteria were composed of the following: (1) 18 to 75 years male or female with histologically or cytologically confirmed ES-SCLC; (2) there was at least one measurable objective lesion, which was evaluated according to the response evaluation criteria in solid tumors (RECIST 1.1); (3) following the completion of the required 4-6 phases of standard first-line chemotherapy, its efficacy is identified as complete response (CR), partial response (PR), or stable disease (SD). No further vascular targeted medications have been administered; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score: 0-2 and Karnofsky Performance Status (KPS) score scale: KPS≥60; (5) patients with well-preserved hematopoietic system, cardiac, pulmonary, hepatic, renal and other vital organ functions, especially without gastrointestinal disorders that affect the absorption of drugs; (6) survival time expectancy of 3 months or more; (7) patients actively collaborated with the doctors throughout clinical observation and follow-up, willingly signed the informed consent form, and all study participants adhered to the concept of voluntariness.

The exclusion criteria were comprised of the following: (1) patients with a previous history of hypertension that cannot be reduced to the normal range, and grade II or higher coronary artery disease, arrhythmia, or grade III/IV cardiac insufficiency; (2) patients with higher risk of gastrointestinal and respiratory tract bleeding or abnormal blood coagulation; (3) radiothe-

rapy/chemotherapy/immunotherapy and other targeted drugs and/or traditional Chinese medicine preparations are used to participate in this study; (4) the researchers believe that subjects may not be able to complete or comply with other requirements of the study (for management or other reasons).

Treatment procedures

The SCLC patients have conventional first-line treatment consisting of etoposide (100 mg/m^2, i.v., on d1-d3, every 21 days) and cisplatin (75 mg/m^2, i.v., on d1, every 21 days) or carboplatin (area under the curve 4-5, i.v., on d1, every 21 days) for 4-6 cycles. Following the completion of chemotherapy (>21 days and ≤42 days from the first day of the last chemotherapy) for patients with therapeutic efficacy, 12 mg of anlotinib is given orally once a day (12 mg, p.o., qd. on d1-d14, every 21 days). The maintenance therapy is continued unless the patients experience disease progression or intolerable adverse events (AEs). The medication should be administered promptly if the patient's condition is under control and the AEs can be tolerated. The administration should be stopped when AEs are grade 3 or above. The dose may be decreased to 10 mg or 8 mg once a day when AEs are grade 2 or less. The medicine is supposed to be stopped and the research would be discontinued if AEs have no improvements in two weeks. The trial will be stopped if the efficacy assessment reveals PD and suggest the patients are unsuitable for additional treatment.

Observation endpoints

The primary endpoint is progression-free survival (PFS), which is defined as the time from the start of induction chemotherapy until the time disease progressed or the patients passed away for any reason. In addition, patients lost to follow-up or patients without disease progression are treated according to censored data. The period of censoring is the final follow-up time to determine that there is no illness progression. The secondary endpoints consist of overall survival (OS), duration of response (DOR), and safety. OS is defined as the time from the beginning of induction chemotherapy until the time patients died for any reason or at the end of the last follow-up. Patients who survive and those who are lost to follow-up are handled using censored data, and the time of censoring is the final follow-up period to confirm death. DOR is defined as the period between the day patients first exhibited disease response and the day of disease progression. The severity of AEs is evaluated based on the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0).

Assessment methods

The evaluation criteria are examined every two cycles following maintenance therapy until the patient progressed, passed away, or after follow-up. Physical examinations are carried out, including electrocardiograms, routine blood tests, biochemical examinations, and imaging examinations such as Doppler ultrasounds, and computed tomography (CT). The curative impact is assessed by RECIST 1.1 through the reexamination of chest CT, abdomen CT, and brain CT and comparison with the prior imaging results. According to the medical records, outpatient revisits, and telephone follow-up, the therapy, disease progression, and time of death were documented during the entire follow-up period.

Statistical analysis

All the research data were statistically analyzed by IBM SPSS 25.0 statistical software for Windows. The measurement data will be expressed by mean ± standard deviation, a *t*-test will be used to accord with normal distribution, a nonparametric test will be used to disaccord with normal distribution, and χ^2 test will be used to count data. The survival curve was drawn by Kaplan-Meier, and *P*-values less than 0.05 were considered statistically significant. The safety evaluation is based on descriptive statistical analysis, and the AEs and adverse reactions that occurred in this trial are described in the table.

Results

Patients characteristic

The demographic and clinical characteristics of 27 patients were included in **Table 1**. The median age was 67.48 years, and 24 patients

Table 1. Population characteristics

Characteristic	N=27
Median age, years (SD)	67.48 (9.87)
<65	11 (40.7%)
≥65	16 (59.3%)
Gender (male)	24 (88.9%)
Smoking history, n (%)	
Never	2 (7.4%)
Pro-smoking	13 (48.1%)
Smoking	12 (44.4%)
Hypertensive, n (%)	8 (29.6%)
ECOG PS status, n (%)	
0	5 (18.5%)
1	14 (51.9%)
2	8 (29.6%)
Primary lesion	
Left lung	13 (48.1%)
Right lung	14 (51.9%)
Neoplasm staging, n (%)	
II	1 (3.7%)
III	6 (22.2%)
IV	20 (74.1%)
Metastatic sites, n (%)	
Lymph node	25 (92.6%)
Lung	4 (14.8%)
Pleural	1 (3.7%)
Bone	5 (18.5%)
Brain	4 (14.8%)
Liver	4 (14.8%)
Pancreas	5 (18.5%)
Adrenal glands	1 (3.7%)
Received radiotherapy, n (%)	
Yes	17 (63%)
No	10 (37%)

Data are n (%). ECOG PS = Eastern Cooperative Oncology Group performance status.

(88.9%) were male. 25 patients (92.5%) had a history of smoking, of which 13 patients (48.1%) had a history of quitting smoking. The ECOG PS of 19 patients (70.4%) was 0-1. 20 patients (74.1%) were in neoplasm stage IV. All patients had metastatic diseases at the time of study registration, and the most common site of metastasis was lymph nodes (25 cases, 92.6%).

Efficacy

The endpoint of PFS has been reached in SCLC patients treated with anlotinib. The mPFS from the time of maintenance therapy was 252 days (95% confidence interval (CI): 217.782-286.218 days; **Figure 2A**). The mDOR was 126 days (95% CI: 98.899-153.101 days; **Figure 2B**). However, the endpoint of OS has not yet been reached, of which only 7 patients reached the endpoint of OS and 20 survived (not reaching the mOS; **Figure 2C**). From first-line chemotherapy to the end of October 2022, the longest survival time of 27 patients was 387 days, and the shortest was 151 days. All patients were evaluated as PR or SD at the end of chemotherapy and then maintained with anlotinib. Most of the patients are currently in SD (**Figure 3**).

Safety

As shown in **Table 2**, the common treatment-related adverse events with anlotinib were grade 1-2, and the common symptoms were hypertension (25.9%), fatigue (18.5%), and loss of appetite (18.5%). The remaining symptoms were not intervened, except for 1 patient with elevated blood pressure and 1 patient with severe fatigue.

Discussion

ES-SCLC may theoretically be a suitable candidate for maintenance therapy due to its quick proliferation cycle and the rapid disease development following first-line chemotherapy, which can eventually improve prognosis [10]. However, the research on maintenance therapy of ES-SCLC has been involved in chemotherapeutic drugs, biological agents, molecularly targeted drugs, and even in the field of traditional Chinese medicine [11]. The results from a retrospective study indicated that maintenance apatinib showed a promising prognosis in ES-SCLC patients (mPFS: 8.3 months, 95% CI: 7.20-9.40 months; mOS: 17.0 months, 95% CI: 9.86-24.14 months) [12]. The ZL-2306-005 study demonstrated that maintenance niraparib had marginally increased PFS and manageable tolerability profile in patients with platinum-responsive ES-SCLC [13]. Maintenance atezolizumab was found to improve both OS and PFS in the phase 1/3 IMpower133 study [14]. Currently, the results are uneven and the clinical benefits are limited. There are still no clinically standard regimens and no recommended guidelines or consensus on the maintenance therapy of ES-SCLC.

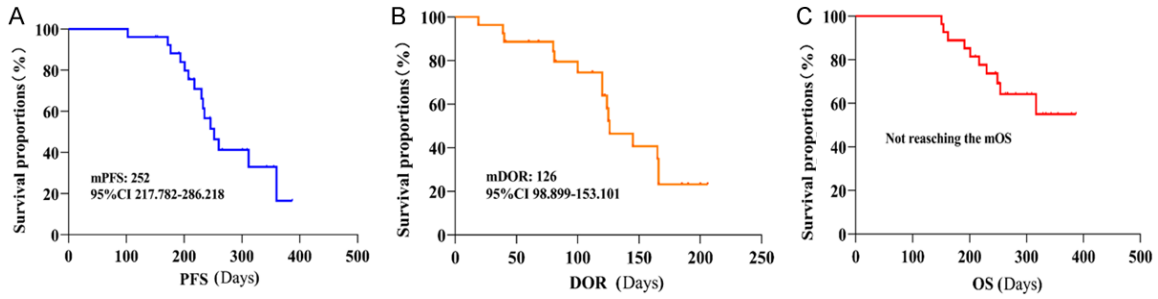

Figure 2. The efficacy of anlotinib in the maintenance treatment of small cell lung cancer.

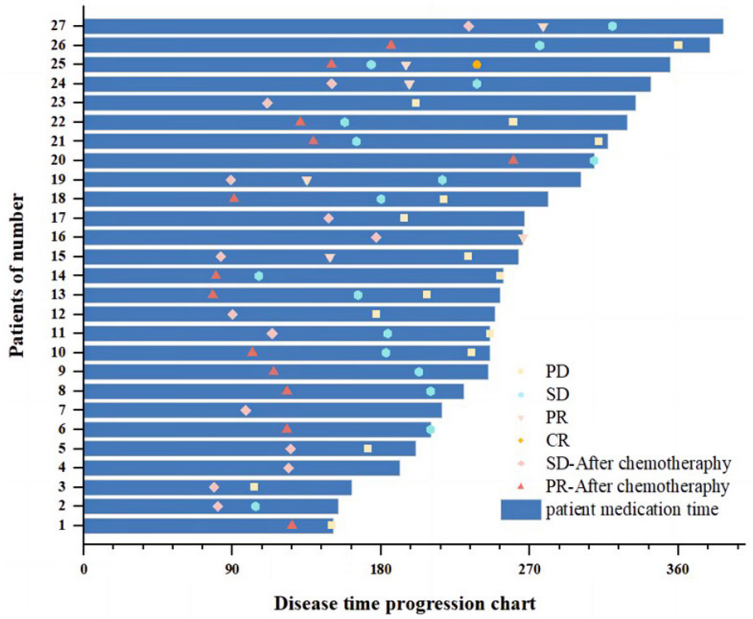

Figure 3. Patients were treated with chemotherapy for the anlotinib maintenance treatment until the disease progressed.

Table 2. Treatment-related adverse events with anlotinib in patients (n=27)

Adverse Events (AEs)	Frequency of Patients (%) by Toxicity Grade	
	Grades 1-2	Grades 3-4
Fatigue	5 (18.5%)	1 (3.7%)
Hypertension	7 (25.9%)	1 (3.7%)
Hand-foot syndrome	3 (11.1%)	0
Headache	2 (7.4%)	0
Poor appetite	5 (18.5%)	0
Lose weight	2 (7.4%)	0
ALT	3 (11.1%)	0
AST	3 (11.1%)	0
Anemia	2 (7.4%)	1 (3.7%)
Hemoptysis	1 (3.7%)	0

In this single-arm, prospective, phase II study, the outcomes of maintenance anlotinib were significantly advantageous for ES-SCLC patients who did not suffer from disease progression after first-line chemotherapy treatment (mPFS: 252 days, 95% CI: 217.782-286.218 days; mDOR: 126 days, 95% CI: 98.899-153.101 days). Of the 27 participants, the longest survival time was 387 days and the shortest was 151 days. After chemotherapy, all patients did not suffer from disease progression and were subsequently maintained with anlotinib. The majority of the patients are in stable status. Anlotinib also showed an acceptable safety profile. No patient stopped receiving therapy because of severe AEs, and no one died as a result of maintenance treatment.

Due to the small number of cases, the results of this study had a standard deviation. However, given the successful application of anlotinib as a third-line and further treatment option in ES-SCLC, more research is required to clarify the benefits and drawbacks of maintaining anlotinib. Furthermore, little research has been done in this area so far. This research, which has significant clinical significance, was conducted to preliminary explore the clinical effectiveness and safety of maintenance anlotinib in ES-SCLC. This study also offered clinical and theoretical support for more prospective, randomized investigations. Besides, controlling to-

xicity and pursuing effectiveness are essential in maintenance therapy. Further discussion is also necessary over the right dosage for maintenance treatment. The results revealed that the most common adverse events were hypertension (n=7, 25.9%), fatigue (n=5, 18.5%), and poor appetite (n=5, 18.5%). The adverse events of grades 3-4 only included hypertension, fatigue, and anemia with incidence rates of 3.7%, respectively. No individuals could tolerate the medication, and no dose decrease occurred. So, clinical tolerance was adequate with a maintenance dosage of 12 mg.

The results analysis revealed that patients receiving oral anlotinib as maintenance treatment typically kept a fulfilling personal life, serving as a foundation for future randomized controlled studies and thus making it a potent therapeutic option in clinical practice. Therefore, the further development of maintenance therapy requires more in-depth study of its molecular pathological mechanism to find potential therapeutic targets; the development of new drugs with high efficiency and low toxicity; the design of rigorous randomized controlled trials; and the search for people who can benefit from maintenance therapy.

Conclusion

These above outcomes demonstrated that anlotinib was a tolerable and potent maintenance treatment option following induction chemotherapy in ES-SCLC patients, providing multiple selective options and relevant evidence-based support for clinical treatment regimens.

Acknowledgements

This work was supported by grants from the National Administration of Traditional Chinese Medicine: The Seventh Batch of National Traditional Chinese Medicine Experts Academic Experience Inheritance Project, and the National Key Research and Development (R&D) Plan (No. 2018YFC1707400).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Fanming Kong, Department of Oncology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Anshanxi Road, Nankai District, Tianjin 300193, China. Tel: +86-22-27986525; E-mail: kongfanming08@163.com

References

[1] Wang WZ, Shulman A, Amann JM, Carbone DP and Tsichlis PN. Small cell lung cancer: subtypes and therapeutic implications. Semin Cancer Biol 2022; 86: 543-54.

[2] Zugazagoitia J and Paz-Ares L. Extensive-stage small-cell lung cancer: first-line and second-line treatment options. J Clin Oncol 2022; 40: 671-80.

[3] Belluomini L, Calvetti L, Inno A, Pasello G, Roca E, Vattemi E, Veccia A, Menis J and Pilotto S. SCLC treatment in the immuno-oncology era: current evidence and unmet needs. Front Oncol 2022; 12: 840783.

[4] Rossi A, Garassino MC, Cinquini M, Sburlati P, Di Maio M, Farina G, Gridelli C and Torri V. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 2010; 70: 119-28.

[5] Galetta D, Rossi A, Pisconti S, Millaku A and Colucci G. Maintenance or non-maintenance therapy in the treatment of advanced non-small cell lung cancer: that is the question. Cancer Treat Rev 2010; 36 Suppl 3: S30-33.

[6] Genestreti G, Di Battista M, Cavallo G, Bartolotti M and Brandes AA. Maintenance therapy in non-small cell lung cancer. Expert Rev Anticancer Ther 2015; 15: 839-46.

[7] Shen G, Zheng F, Ren D, Du F, Dong Q, Wang Z, Zhao F, Ahmad R and Zhao J. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol 2018; 11: 120.

[8] Lin B, Song X, Yang D, Bai D, Yao Y and Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRβ and FGFR1. Gene 2018; 654: 77-86.

[9] Syed YY. Anlotinib: first global approval. Drugs 2018; 78: 1057-62.

[10] Wang Y, Zou S, Zhao Z, Liu P, Ke C and Xu S. New insights into small-cell lung cancer development and therapy. Cell Biol Int 2020; 44: 1564-76.

[11] Saltos A, Shafique M and Chiappori A. Update on the biology, management, and treatment of small cell lung cancer (SCLC). Front Oncol 2020; 10: 1074.

[12] Teng F, Xing P, Yang K, Gao L, Tian Z and Li J. Apatinib as maintenance therapy following standard first-line chemotherapy in extensive disease small cell lung cancer: a phase II single-arm trial. Thorac Cancer 2022; 13: 557-62.

[13] Ai X, Pan Y, Shi J, Yang N, Liu C, Zhou J, Zhang X, Dong X, He J, Li X, Chen G, Li X, Zhang H, Liao W, Zhang Y, Ma Z, Jiang L, Cui J, Hu C, Wang W, Huang C, Zhao J, Ding C, Hu X, Wang K, Gao B, Song Y, Liu X, Xiong J, Liu A, Li J, Liu Z, Li Y, Wang M, Zhang B, Zhang D and Lu S. Efficacy and safety of niraparib as maintenance treatment in patients with extensive-stage SCLC after first-line chemotherapy: a randomized, double-blind, phase 3 study. J Thorac Oncol 2021; 16: 1403-14.

[14] Reck M, Mok TSK, Mansfield A, De Boer R, Losonczy G, Sugawara S, Dziadziuszko R, Krzakowski M, Smolin A, Hochmair M, Garassino MC, de Castro Junior G, Bischoff H, Lam S, Cardona A, Morris S and Liu SV. Brief report: exploratory analysis of maintenance therapy in patients with extensive-stage SCLC treated first line with atezolizumab plus carboplatin and etoposide. J Thorac Oncol 2022; 17: 1122-9.