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RESEARCH ARTICLE

Anlotinib as third- or further-line therapy for short-term relapsed small-cell lung cancer: subgroup analysis of a randomized phase 2 study (ALTER1202)

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Abstract **Patients with small-cell lung cancer (SCLC) relapse within months after completing previous therapies. This study aimed to investigate the efficacy and safety of anlotinib as third- or further-line therapy in patients with short-term relapsed SCLC from ALTER1202. Patients with short-term relapsed SCLC (disease progression within 3 months after completing ⩾ two lines of chemotherapy) in the anlotinib (*n* = 67) and placebo (*n* = 34) groups were analyzed. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival, objective response rate (ORR), disease control rate, and safety. Anlotinib significantly improved median PFS/OS (4.0 vs. 0.7 months, *P* < 0.0001)/(7.3 vs. 4.4 months, *P* = 0.006) compared with placebo. The ORR was 4.5%/2.9% in the anlotinib/placebo group (*P* = 1.000). The DCR in the anlotinib group was higher than that in the placebo group (73.1% vs. 11.8%, *P* < 0.001). The most common adverse events (AEs) were hypertension (38.8%), loss of appetite (28.4%), and fatigue (22.4%) in the anlotinib group and gamma-glutamyl transpeptidase elevation (20.6%) in the placebo group. No grade 5 AEs occurred. For patients with short-term relapsed SCLC, third- or further-line anlotinib treatment was associated with improved survival benefit. Further studies are warranted in this regard.**

Keywords anlotinib; chemotherapy; short-term relapsed; small-cell lung cancer

Introduction

Lung cancer is the leading cause of cancer death worldwide. Approximately 15% of patients were diagnosed with small-cell lung cancer (SCLC) [1,2]. SCLC can be classified as limited- and extensive-stage diseases; both of these are aggressive. The median overall survival (OS) is 15–20 months for limited-stage SCLC and 8–13 months for extensive-stage SCLC [3,4]. The 5-year survival rate is only 20%–25% for limited-stage SCLC and even worse (2%) for extensive-stage SCLC [5].

SCLC is well known for its high sensitivity to initial chemotherapy, high metastasis and recurrence rates, and easy acquirement of chemotherapy resistance [6]. The first-line therapy for SCLC includes combination chemotherapy. The prognosis of patients who are refractory to first-line chemotherapy and continue to receive the second-line treatment is dismal [7]. Second-line topotecan treatment was found to be as effective and safe as second-line therapy in many phases 2 and 3 trials [8,9]. However, Ardizzon *et al*. [10] showed that the median OS of patients with relapsed SCLC after receiving topotecan-based second-line chemotherapy was still 4.1 months.

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Patients who have received two or more previous lines of therapy for SCLC are often symptomatic due to the progression of cancer, side effects of previous therapies, and comorbidities [7]. Considering that standard third-line treatment has not yet been established, physicians are commonly impeded in selecting treatment options for SCLC after the failure of second-line chemotherapy [11]. Therefore, the choices for such patients in the past included only the best supportive care with hospice, additional cytotoxic chemotherapy, and clinical trials. Immunotherapies have been approved for third-line use, but the response rate is low, and a large number of patients do not benefit from them [12,13]. Unfortunately, due to the failure of phase 3 clinical trials, the third-line indications of nivolumab and pembrolizumab for SCLC were withdrawn, which indicates that patients who are resistant to second-line chemotherapy need more treatment options.

Anlotinib is an oral multitarget tyrosine kinase inhibitor that targets the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and c-Kit [14–16], thus inhibiting tumor angiogenesis and cell proliferation. The National Medical Products Administration has approved it as the third-line treatment for advanced non-SCLC on the basis of ALTER0303 trial [17]. A multicenter, randomized phase 2 trial (ALTER1202) was recently conducted to evaluate the efficacy and safety of anlotinib as third- or further-line treatment in patients with sensitive and refractory relapsed SCLC, including limited- and extensive-stage diseases [18]. The results demonstrated a significant improvement in median progression-free survival (4.1 vs. 0.7 months) with anlotinib compared with placebo [19].

In this study, patients with short-term relapsed (disease progression within 3 months after completing ⩾ two lines of chemotherapy) SCLC were selected from the ALTER1202 study, and a subgroup analysis was conducted to evaluate the efficacy and safety of third- or further-line anlotinib treatment for patients with short-term relapsed SCLC.

Materials and methods

Study design

This study was a subgroup analysis of a multicenter, double-blind, randomized phase 2 trial (ALTER1202, NCT03059797). The original study was conducted to evaluate the efficacy and safety of anlotinib as third-line or further-line therapy in patients with relapsed SCLC compared with placebo. Patients were recruited from 11 centers in China between March 2017 and May 2018. The ethics committee of each participating center approved the trial, and signed informed consent was obtained from each patient.

Patients were randomly assigned to receive anlotinib or placebo treatment in a 2:1 ratio. Stratified randomization was conducted centrally via the interactive web response system. The stratification was performed on the basis of the Veterans Administration Lung Group stage (limited stage vs. extensive stage) and the pattern of relapse (sensitive relapse vs. refractory relapse). Oral anlotinib or placebo 12 mg once daily was administered for 14 days every 21-day cycle. The investigators and patients were blinded to treatment allocation throughout the trial. Dose reductions to 10 or 8 mg once daily were allowed in the case of toxicity. Treatment was continued until disease progression, intolerable toxicity, physician's decision, or patient's request. Treatment crossover was not permitted.

The present subgroup study selected patients with short-term relapse for analysis. Short-term relapse was defined as disease progression within 3 months after completing the last-line chemotherapy [20].

Eligibility criteria

Eligible patients were aged 18–75 years, with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and pathologically confirmed SCLC. Other inclusion criteria were disease progression within 3 months after completing the last-line chemotherapy, life expectancy > 3 months, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and adequate major organ function within 7 days before enrollment. The key exclusion criteria were previous targeted therapy or immunotherapy, other cancers within 5 years (except for cured cervical cancer *in situ*, nonmelanoma skin cancer, and superficial bladder cancer), central nervous system metastases, and/or spinal cord compression (patients were eligible if the brain metastases were asymptomatic or adequately treated and stable), uncontrolled hypertension or diabetes mellitus, history of immune deficiency or organ transplantation, or participation in other trials within 4 weeks.

Endpoints and assessments

The primary endpoint was PFS (defined as the time from randomization to disease progression or any-cause death, whichever occurred first). The secondary endpoints included OS (defined as the time from randomization to death), objective response rate (ORR), disease control rate (DCR), and safety.

Investigators evaluated tumor response by using chest, abdominal, and pelvic computed tomography/magnetic resonance imaging in accordance with RECIST 1.1. Efficacy was assessed preliminarily in the third week of treatment, confirmed in the sixth week, and continuously assessed every two cycles until disease progression was

confirmed. Patients were routinely monitored throughout the study. Any occurrences of adverse events (AEs) were recorded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

All statistical analyses were conducted using SAS 9.4. Kaplan–Meier method was performed to estimate PFS and OS, and log rank was used for estimating the difference. Cox proportional hazard model was used for evaluating PFS and OS with hazard ratios (HRs) and 95% confidence intervals (CIs). ORR and DCR were compared between groups by using Pearson's chi-square test or Fisher's exact test when appropriate. All statistical tests were two-sided, and *P*-values < 0.05 indicated a statistically significant difference. All variables of *P*-values < 0.2 from the univariate analysis were entered into multivariate model to identify independent risk factors for PFS and OS.

Full analysis set was used for analyzing the efficacy, which included all patients randomly assigned to have at least one efficacy assessment after randomization. Safety was analyzed in the safety set, which included all randomized patients who received at least one dose of the study drug and had safety evaluation.

Results

Patient characteristics

A total of 101 patients with SCLC having a short-term relapse after second-line chemotherapy received anlotinib (n = 67) or a placebo (n = 34) in this study. The baseline characteristics are summarized in Table 1. The median age was 57 and 58.5 years in the anlotinib and placebo groups, respectively. Majority of patients in the anlotinib and placebo groups were male (45 (67.2%) and 27 (79.4%)), had an ECOG performance status of 1 (60 (89.6%) and 28 (82.4%)), at extensive stage (61 (91.0%) and 27 (79.4%)), received previous radiotherapy (35 (52.2%) and 20 (58.8%)), and received only two lines of chemotherapy (51 (76.1%) and 26 (76.5%)).

Efficacy

The follow-up ended on June 30, 2018. For PFS, 48 and

Table 1 Baseline characteristics

Variable	Anlotinib (total = 67)		Placebo (total = 34)		*P*
	n	%	*n*	%	
Median age, year (range)	57 (31–71)		58.5 (43–75)		0.1621
Sex					0.1986
Male	45	67.2	27	79.4	
Female	22	32.8	7	20.6	
ECOG performance status					0.0916
0	3	4.5	0	0	
1	60	89.6	28	82.4	
2	4	6.0	6	17.6	
Smoking history					0.0958
Never	28	41.8	8	23.5	
Former	37	55.2	26	76.5	
Current	2	3.0	0	0	
Disease stage					0.1211
Limited stage	6	9.0	7	20.6	
Extensive stage	61	91.0	27	79.4	
Previous lines of chemotherapy					0.9687
two	51	76.1	26	76.5	
⩾ three	16	23.9	8	23.5	
Previous radiotherapy					0.6186
No	32	47.8	14	41.2	
Yes	35	52.2	20	58.8	

The *t* test was used for age; Wilcoxon rank-sum test was used for time from diagnosis; others were tested using chi-square test or Fisher's exact test. ECOG, Eastern Cooperative Oncology Group.

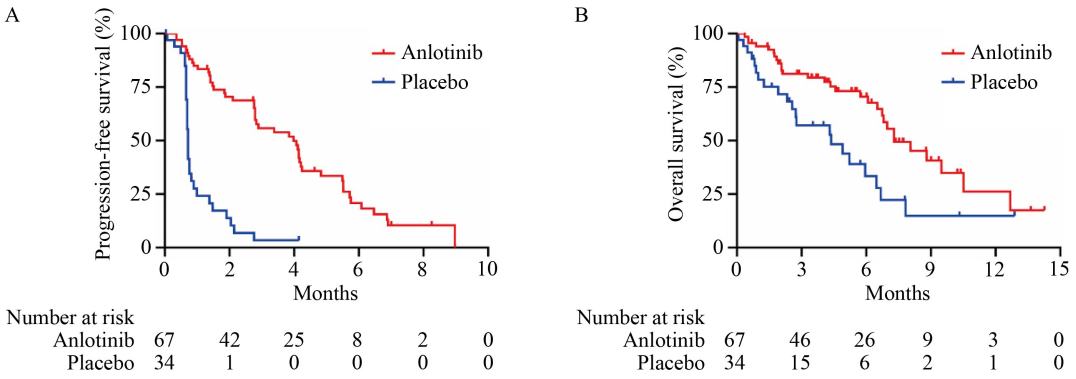

Fig. 1 Kaplan–Meier curves. (A) Progression-free survival (PFS). Median PFS was 4.0 months in the anlotinib group and 0.7 months in the placebo group. (B) Overall survival (OS). Median OS was 7.3 months in the anlotinib group and 4.4 months in the placebo group.

Table 2 Response rate

Variable	Anlotinib (total = 67)	Placebo (total = 34)	*P*
Best response, *n* (%)			
CR	0	0	
PR	3 (4.5)	1 (2.9)	
SD	46 (68.7)	3 (8.8)	
PD	15 (22.4)	22 (64.7)	
NE	3 (4.5)	8 (23.5)	
ORR, *n* (%)	3 (4.5)	1 (2.9)	1.000
DCR, *n* (%)	49 (73.1)	4 (11.8)	<0.001

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

29 events were observed in the anlotinib and placebo groups, respectively (Fig. 1A). The median PFS was significantly longer in the anlotinib group than in the placebo group (4.0 vs. 0.7 months; HR = 0.185; 95% CI 0.108–0.319; $P < 0.0001$).

For OS, 29 and 21 events were detected in the anlotinib and placebo groups, respectively (Fig. 1B). The median OS was significantly better with anlotinib than with placebo (7.3 vs. 4.4 months; HR = 0.460; 95% CI 0.261–0.811; $P = 0.006$). No patient achieved complete response (CR). Three (4.5%) patients achieved partial response (PR) in the anlotinib group, while one (2.9%) patient achieved PR in the placebo group, with an ORR of 4.5% versus 2.9% ($P = 1.000$, Table 2). The DCR was significantly higher in the anlotinib group than in the placebo group (73.1% vs. 11.8%, $P < 0.001$, Table 2). After adjusting the factors, such as sex, age, previous radiotherapy, ECOG performance status, smoking history, and previous lines of chemotherapy, grouping (placebo vs. anlotinib) was found to be an independent factor associated with PFS (HR = 5.005, 95% CI 2.902–8.633, $P < 0.0001$) and the ECOG performance status (2 vs. 0) was independently associated with OS (HR = 10.411, 95% CI 1.181–91.733, $P = 0.0348$). The grouping (placebo vs. anlotinib) did not show a statistically significant influence on OS.

Safety

The overall toxicity profile was manageable but not insignificant. The most common AEs were hypertension (26 (38.8%)), loss of appetite (19 (28.4%)), and fatigue (15 (22.4%)) in the anlotinib group and gamma-glutamyl transpeptidase (GGT) elevation (7 (20.6%)), alanine aminotransferase (ALT) elevation (5 (14.7%)), and aspartate aminotransferase (AST) elevation (5 (14.7%)) in the placebo group (Table 3). The most common grades 3–4 AEs were hypertension (9 (13.4%)) and GGT elevation (4 (6.0%)) in the anlotinib group and GGT elevation (3 (8.8%)) and ALT elevation (2 (5.9%)) in the placebo group (Table 3). No death occurred in the two groups.

Discussion

Third-line treatment for short-term relapsed SCLC is urgently needed, especially for those with chemotherapy resistance. In this study, a subgroup analysis of the ALTER1202 study [18] was conducted to evaluate the efficacy and safety of third- or further-line anlotinib

Table 3 Treatment-emergent adverse events with incidence ⩾ 15% in either group

Variable	Anlotinib (total = 67)		Placebo (total = 34)	
	Any grade, *n* (%)	Grades 3–4, *n* (%)	Any grade, *n* (%)	Grades 3–4, *n* (%)
Hypertension	26 (38.8)	9 (13.4)	2 (5.9)	1 (2.9)
Loss of appetite	19 (28.4)	1 (1.5)	4 (11.8)	0
Fatigue	15 (22.4)	1 (1.5)	4 (11.8)	0
ALT elevation	12 (17.9)	1 (1.5)	5 (14.7)	2 (5.9)
Hypertriglyceridemia	12 (17.9)	3 (4.5)	1 (2.9)	0
Decreased lymphocyte count	12 (17.9)	2 (3.0)	0	0
AST elevation	12 (17.9)	2 (3.0)	5 (14.7)	0
TSH elevation	12 (17.9)	0	0	0
QT prolongation	11 (16.4)	0	3 (8.8)	1 (2.9)
Hand-foot syndrome	11 (16.4)	1 (1.5)	0	0
GGT elevation	8 (11.9)	4 (6.0)	7 (20.6)	3 (8.8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; TSH, thyroid stimulating hormone.

treatment for patients with short-term relapsed SCLC. The results indicated that median PFS, median OS, and DCR were significantly better with anlotinib than with placebo, although the anlotinib group had more patients at the extensive stage than the placebo group (91.0% vs. 79.4%).

Anlotinib is one of the antiangiogenic tyrosine kinase inhibitors. It can inhibit receptors, such as VEGFR, PDGFR, and FGFR, on vascular endothelial cells, inhibiting the activation of tyrosine kinase and consequently inhibiting tumor angiogenesis and tumor growth [14–16]. The mechanism is independent of primary chemotherapy resistance, which may be the reason why the median PFS was significantly longer in the anlotinib group than in the placebo group in the present study. The delay in disease progression may lead to prolonged OS.

Notably, the median PFS/OS with anlotinib as at least third-line therapy in this study was higher (4.0/7.3 months) than that with third-line chemotherapy in an international retrospective study (2.0/4.7 months) [21]. The median OS with anlotinib in the present study was 7.3 months, which was higher than 5.8 months in the phase 2 trial of temozolomide, a non-classic oral alkylating agent, which produced O6-alkylguanine lesions on DNA in patients with SCLC [22]. It was also higher than 5.6 months for rovalpituzumab tesirine, an antibody-drug conjugate targeting delta-like ligand 3, as third-line treatment in the phase 2 TRINITY study [23]. In addition, patients with recurrent limited-stage or extensive-stage SCLC treated with nivolumab (a fully human immunoglobulin G4 programmed death 1 immune checkpoint inhibitor antibody) had a median PFS of 1.4 months and an OS of 5.6 months; they were also previously treated with one or more platinum-based chemotherapy regimens [12]. The median OS of patients in the subgroup (platinum resistance) was only 3.1 months [24]. In addition, the use of oral anlotinib obviously brought relief compared with pembrolizumab (10 mg/kg every 2 weeks in KEYNOTE-028 or 200 mg every 3 weeks in KEYNOTE-158) after two or more lines of previous therapy in patients with recurrent or metastatic SCLC [13]. The median OS was similar to that in the present study (7.7 vs. 7.3 months). These results indicated that anlotinib monotherapy could be a suitable option as at least third-line treatment for short-term relapsed SCLC.

The AEs in the anlotinib group were manageable, with profiles similar to those in previous studies on anlotinib [17,25,26]. No death occurred. The safety was acceptable.

This study had some limitations. The sample size was relatively small. The results may also be underpowered because this was a subgroup analysis of a phase 2 trial. In addition, subsequent treatments after progression on anlotinib or placebo treatment may influence the OS comparison between the two groups. Large-scale randomized controlled trials are needed to confirm the results.

Despite the rapid progression on previous second- or further-line chemotherapy, PFS and OS improved with subsequent anlotinib treatment compared with placebo. The safety profile was consistent with previous reports, and no new safety signals were identified. Thus, for patients with short-term relapsed SCLC, anlotinib may be considered as a third- or further-line treatment option. These data warrant the investigation of targeted therapy approaches in SCLC.

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Compliance with ethics guidelines

Jianhua Shi, Ying Cheng, Qiming Wang, Kai Li, Lin Wu, Baohui Han, Gongyan Chen, Jianxing He, Jie Wang, Haifeng Qin, and Xiaoling Li declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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