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A phase II study of anlotinib combined with etoposide and platinum-based regimens in the first-line treatment of extensive-stage small cell lung cancer

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Abstract

Background: The aim of this prospective, pilot, single-arm phase II trial was to evaluate the safety and efficacy of anlotinib combined with etoposide and platinum-based regimens in the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC).

Methods: This phase II study was conducted at Fudan University Shanghai Cancer Center between December 2018 and December 2020. All patients received standard chemotherapy (etoposide plus cisplatin/carboplatin) consisting of four courses and anlotinib at 12 mg once per day for 2 weeks followed by a one-week rest. Anlotinib administration was continued until disease progression, intolerable adverse events (AEs) or patient withdrawal from the study. The primary outcome measure was progression-free survival (PFS). The secondary outcome measures were overall survival (OS), objective control rate (ORR), disease control rate (DCR) and AEs.

Results: Thirty-seven patients were included in this study, and 30 patients were eligible for efficacy analysis. ORR and DCR were 90.0% and 96.7%, respectively. The estimated PFS and OS were 6.0 months (95% CI: 1.1–11.9 months) and 14.0 months (95% CI: 8.6–19.4 months), respectively. No unexpected adverse effects were reported. Hypertension (20/37, 54.1%), anemia (16/37, 43.2%), alopecia (15/37, 40.5%), elevated transaminases (9/37, 24.3%) and alkaline phosphatase (9/37, 24.3%) were the most commonly reported AEs. Thirteen patients (35.1%) reported grade 3–5 AEs. No treatment-related deaths occurred during this study.

Conclusion: The addition of anlotinib to standard etoposide/platinum chemotherapy achieved encouraging PFS and OS in previously untreated ES-SCLC patients, with an acceptable tolerability profile and no new safety signals observed.

KEYWORDS
anlotinib, antiangiogenic therapy, first-line therapy, small cell lung cancer

INTRODUCTION

Lung cancer ranks first in cancer mortality rates worldwide and accounts for 18.0% of total cancer deaths.[1] Small cell lung cancer (SCLC) represents approximately 15% of lung cancers and is defined as the most malignant type.[2,3] Due to its strong invasiveness and early metastases, nearly 70% of SCLC patients present with extensive-stage SCLC (ES-SCLC) at initial diagnosis, with a median overall survival (OS) of only 10 months.[4]

For decades, etoposide/platinum-doublet chemotherapy has been the standard first-line treatment for SCLC

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patients.[3] Despite initially high response rates, most patients experience quick disease progression.[5] Recently, the addition of an immune checkpoint inhibitor (atezolizumab or durvalumab) in platinum-etoposide chemotherapy for ES-SCLC patients has shown improvements in OS, which has thus revolutionized the first-line treatment paradigm for SCLC.[6,7] The immunotherapy outcomes in SCLC are, however, less effective than that of non–small cell lung cancer (NSCLC) due to the immunosuppressive phenotype of SCLC.[8]

Angiogenesis plays an essential role in cancer progression.[9] Targeting vascular endothelial cells has been a promising therapeutic strategy in SCLC. Studies indicate that bevacizumab, a vascular endothelial growth factor (VEGF) antibody, only exhibits prolonged progression-free survival (PFS) but not OS when combined with platinum-etoposide chemotherapy as a first-line treatment of ES-SCLC.[10–12] Other angiogenesis inhibitors such as sunitinib,[13] ziv-aflibercept,[14] pazopanib[15] and patina[16] have demonstrated therapeutic potential in maintenance therapy or the second-line treatment of SCLC. There are no reports, however, of them showing survival benefits in previously untreated ES-SCLC.

Anlotinib (AL3818), an oral, small-molecular tyrosine kinase inhibitor (TKI), has displayed significant anti-angiogenesis and anti-tumor growth effects through the inactivation of the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and stem cell factor receptor (c-Kit).[17–19] Anlotinib monotherapy was approved as a first third- and further-line treatment regime of relapsed SCLC in China because it significantly improved PFS (4.1 vs. 0.7 months) and OS (7.3 vs. 4.9 months) in the ALTER1202 study.[20,21] Another single-arm phase II study also demonstrated similar clinical benefits of anlotinib in relapsed SCLC,22 indicating its good efficacy and safety in the treatment of SCLC.

As of now, there are no reports in the literature on the clinical outcomes of VEGF-VEGFR pathway–targeted drugs plus etoposide and platinum in untreated patients with SCLC. Thus, the aim of this prospective, pilot, single-arm phase II trial is to evaluate the safety and efficacy of anlotinib combined with etoposide and platinum-based regimens in the first-line treatment of ES-SCLC.

METHODS

Study design

This was a single-arm, single-center, prospective, phase II study (ClinicalTrials.gov number NCT03841136) conducted at Fudan University Shanghai Cancer Center between December 2018 and December 2020. The primary outcome measure was PFS. The secondary outcome measures were OS, objective control rate (ORR), disease control rate (DCR) and adverse events (AEs).

Patients

The inclusion criteria were (a) ages from 18 to 75 years; (b) a histological or cytological diagnosis of ES-SCLC; (c) no prior systematic treatment for metastatic disease, though adjuvant chemotherapy was allowed if completed at least 6 months before enrollment; (d) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (e) at least one measurable lesion defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; (f) an expected survival time of more than 3 months; (g) hemoglobin ≥90 g/L, an absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 80 \times 10^9$/L, total bilirubin ≤1.5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 ULN (≤5 ULN given liver metastasis), serum creatinine ≤1.5 ULN or a creatinine clearance rate ≥ 60 ml/min, and a left ventricular ejection fraction ≥ the lower limit of normal (50%) evaluated by Doppler ultrasound; (h) patients with previously treated asymptomatic central nervous system (CNS) metastases if no ongoing corticosteroids therapy for CNS metastases was required; (i) no radiotherapy received within 7 days before enrollment; (j) no radiological CNS progression from the end of radiotherapy to enrollment and (k) voluntary participation in this study after signed, informed consent.

The exclusion criteria were: (a) previous treatment with anlotinib; (b) previous antitumor treatment including systemic chemotherapy, signal transduction inhibitors, targeted therapies, hormone and endocrine therapy; (c) a previous diagnosis with another malignancy within 5 years before enrollment (except for cured carcinoma in situ of the cervix, superficial bladder tumors, basal cell or squamous cell skin carcinoma, localized prostate cancer and ductal carcinoma in situ of the breast); (d) any treatment-related unresolved toxicities (except for alopecia) of Grade 2 or worse according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0; (e) difficulty with oral drug administration or absorption (including dysphagia, gastrointestinal resection, chronic diarrhea and intestinal obstruction); (e) symptomatic CNS metastases; (f) radiographic evidence of tumors that have invaded tissues surrounding vital blood vessels or a high probability of fatal bleeding due to the invasion of tumors to vital blood vessels according to the judgment of the researchers during the follow-up study and (g) uncontrolled pleural, pericardial or peritoneal effusion requiring repeated drainage.

Treatments

All patients received oral administration of anlotinib at 12 mg once per day for 2 weeks followed by a one-week rest (one course consists of 2 weeks on and 1 week off). Etoposide (100 mg/m^2) was intravenously administered from day one to day three of each course. Carboplatin (area under the concentration time curve, 5 mg/ml/min) or

cisplatin (75 mg/m^2) was intravenously administered on day one of each course. Antiemetic therapy and hydration were routinely performed during each course of chemotherapy.

Treatment was continued with tumor response assessments of complete response (CR), partial response (PR) or stable disease (SD). Anlotinib administration was continued until disease progression, intolerable AEs or patient withdrawal from the study. Chemotherapy (etoposide plus cisplatin/carboplatin) consisted of four courses.

Assessments

Efficacy was assessed by PFS, OS, ORR and DCR. PFS was defined as the time from the enrollment date until progressive disease (PD) occurrence or death from any cause. Patients alive without progression at the time of analysis were censored at their last follow-up. OS was defined as the time from enrollment date to death due to any cause. Patients alive at the cutoff date were censored. DCR was defined as the percentage of patients with a complete response (CR), partial response (PR) or stable disease (SD). ORR was defined as the percentage of patients with CRs and PRs. The tumor response was assessed every two courses using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Patients without brain metastasis and without brain symptoms underwent chest computed tomography (CT) examination and abdominal ultrasound examination of metastasized lesions, as well as CT/magnetic resonance (MR) examination, every two courses, and they underwent brain MR/CT every 6 months. Patients with brain metastases underwent chest CT examination, abdominal ultrasound examination and brain MR/CT of metastasized lesions, as well as CT/MR examination, every two courses. Patients routinely underwent brain MR/CT examination and positron emission tomography (PET)-CT at the baseline.

Adverse events (AEs) were assessed every month according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

This study was designed as a single-arm, prospective exploratory phase II clinical study, with PFS as the primary research endpoint. The median PFS was expected to increase from 4.5 to 6.0 months. The duration of enrollment was 24 months, and the follow-up time was 6 months, with $\alpha = 0.10$ and $\beta = 0.20$. The sample size was calculated to be 64 cases. Considering the influence of the dropout rate, the sample size was set to 70 cases. However, due to the COVID-19 pandemic, enrollment was slow. And since the IMPOWER133 and CASPAIN studies confirmed that chemotherapy plus immunotherapy can prolong survival, which is the current standard treatment, we ended enrollment.

TABLE 1 Baseline characteristics

Characteristics	ITT set ($n = 37$) number of patients (%)	PP set ($n = 30$) number of patients (%)
Age, years		
Mean	61	61
Median	63	62
Range	44–75	44–74
Age group		
<65 years	21 (56.8)	17 (56.7)
≥65 years	16 (43.2)	13 (43.3)
Sex		
Male	32 (86.5)	25 (83.3)
Female	5 (13.5)	5 (16.7)
Smoking history		
Never-smoker	9 (24.3)	8 (26.7)
Former or current smoker	28 (75.7)	22 (73.3)
ECOG PS at baseline		
1	37 (100.0)	30 (100.0)
Metastatic sites at baseline		
Bilateral lung	9 (24.3)	8 (26.7)
Brain	10 (27.0)	9 (30.0)
Bone	11 (29.7)	10 (33.3)
Liver	11 (29.7)	10 (33.3)
Adrenal gland	5 (13.5)	5 (16.7)
Supraclavicular lymph node	7 (18.9)	6 (20.0)
Pleural	9 (24.3)	6 (20.0)
Others	11 (29.7)	6 (20.0)
Chemotherapy		
EP	17 (45.9)	12 (40.0)
EC	20 (54.1)	18 (60.0)

Data were summarized by frequency and percentage for categorical variables and by medians and ranges for continuous variables. PFS and OS were estimated by the Kaplan–Meier method, along with hazard ratios(HRs). All outcome measures were calculated with 95% confidence intervals (CIs), which were estimated using the Cox proportional hazard model. Differences between baseline clinicopathological characteristics of the groups were assessed using Pearson's χ^2 or Fisher's exact test.

Exploratory univariate analyses were performed with a log-rank test. The significance level of the statistical tests was set at $p < 0.05$. All expressed p-values and CIs were two-tailed. AEs were summarized using percentages and frequency counts. All statistical analyses were conducted using IBM SPSS Statistics version 24.

TABLE 2 Tumor responses

Responses	PP set ($n = 30$) [*n* or %]	ITT set ($n = 37$) [*n* or %]
CR	0 (0.0)	0 (0.0)
PR	27 (90.0)	27 (73.0)
SD	2 (6.7)	2 (5.4)
PD	1 (3.3)	1 (2.7)
Ineligible	0 (0.0)	7 (18.9)
ORR	90.0% [95% CI: 79.1%–100.9%]	73.0% [95% CI: 58.5%–87.5%]
DCR	96.7% [95% CI: 90.2%–103.2%]	78.4% [95% CI: 65.0%–91.8%]

Abbreviations: CR, complete response; DCR, disease control rate; ITT intention-to-treat; ORR, objective response rate; PD, progressive disease; PP, per protocol; PR, partial response; SD stable disease.

RESULTS

Patient baseline characteristics

A total of 37 treatment-naïve ES-SCLC patients were enrolled in this study at Fudan University Shanghai Cancer Center between December 2018 and December 2020. Their baseline characteristics at the initiation of treatment are summarized in Table 1 ($n = 37$; intention-to-treat set, ITT set). The patients' median age was 63 years old (ranging from 44 to 75 years old), and 56.8% (21/37) were younger than 65. A total of 86.5% (32/37) of the patients were male, and 75.7% (28/37) were former or current smokers. All 37 patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 at baseline. The most

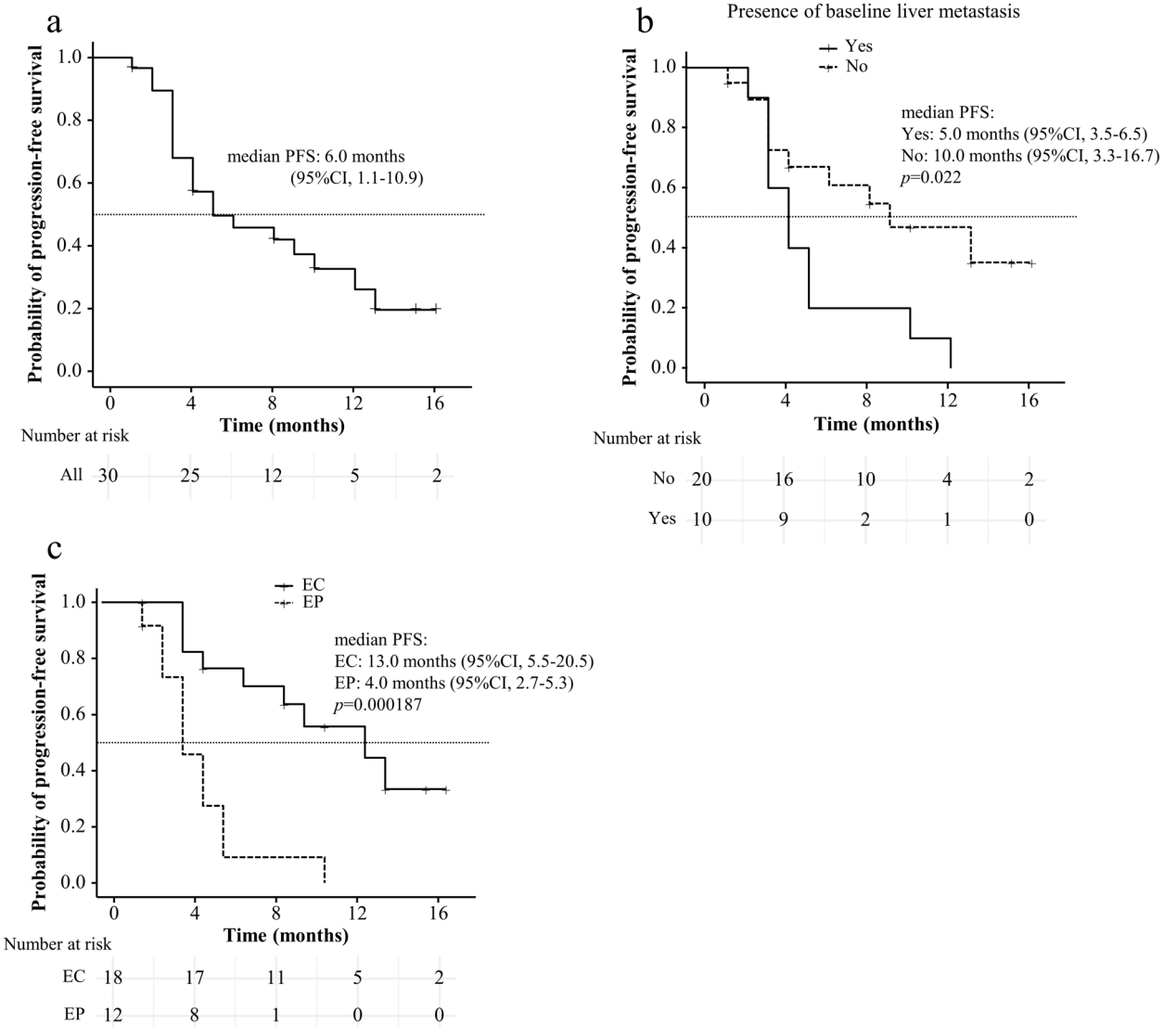

FIGURE 1 Kaplan–Meier curve of PFS (a) of all patients in PP set ($n = 30$) and (b) of patients with/without baseline liver metastases; (c) of patients receiving EP/EC plus anlotinib therapy

TABLE 3 Cox multivariate analysis of progression-free survival in PP set ($n = 30$)

Variables	Log-rank tesk	Multivariate analysis		
		HR	95% CI	*p*-value
Sex (male vs. female)	0.984			
Age (<65 vs. ≥ 65 years)	0.056			
Smoking history (yes vs. no)	0.265			
Brain metastasis (yes vs. no)	0.494			
Bone metastasis (yes vs. no)	0.158			
Lung metastasis (yes vs. no)	0.273			
Liver metastasis (yes vs. no)	0.022	0.694	0.244–1.973	0.493
Adrenal gland metastasis (yes vs. no)	0.726			
Supraclavicular lymph node metastasis (yes vs. no)	0.313			
Pleural metastasis (yes vs. no)	0.232			
Chemotherapy (EP vs. EC)	0.000187	4.218	1.375–12.942	0.012

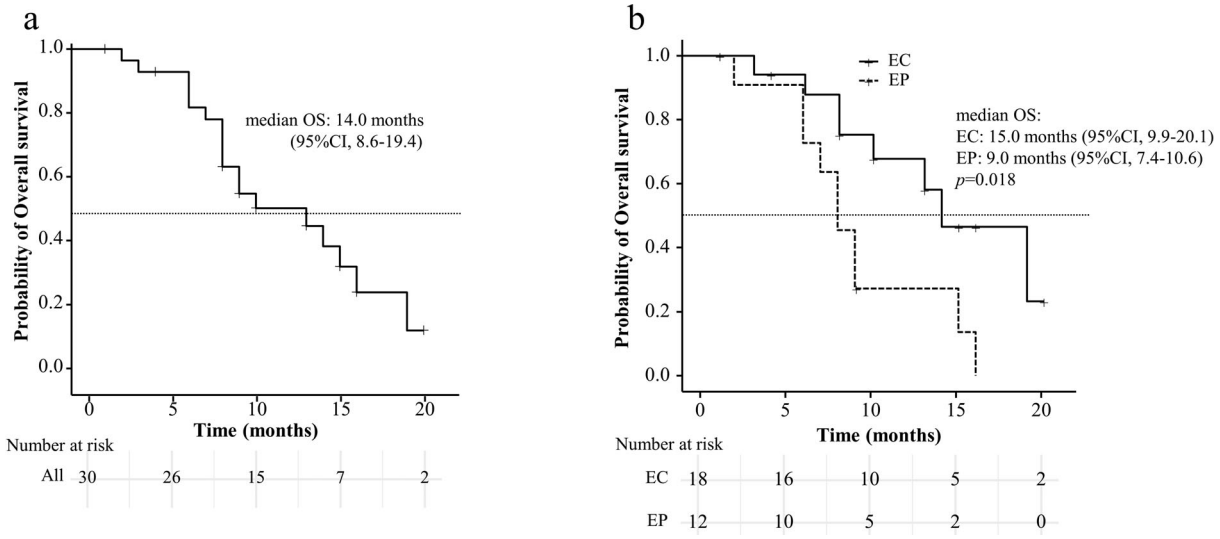

FIGURE 2 Kaplan–Meier curve of OS (a) of all patients in PP set ($n = 30$) and (b) of patients receiving EP/EC plus anlotinib therapy

common metastatic sites at baseline were bone (29.7%), liver (29.7%), brain (27.0%), pleural (24.3%) and bilateral lung (24.3%). Seventeen (45.9%, 17/37) patients received cisplatin, and 20 (54.1%, 20/37) patients received carboplatin.

Due to the failure to complete two cycles of treatment, seven patients were excluded from the efficacy analysis. Among these seven patients who did not receive efficacy evaluations, one patient withdrew from the study due to phlebitis after one cycle of treatment. Three patients withdrew from the study, and another three patients were lost to follow-up due to anti-COVID-19 measures or other reasons, though they returned to local hospitals for treatment. A total of 30 patients were eligible for efficacy analysis (per-protocol set, PP set). Their baseline characteristics at the initiation of treatment are summarized in Table 1 ($n = 30$). The median age of patients was 62 years old (ranging from 44 to 74 years old), and 56.7% (17/30) of them were younger than 65. A total of 83.3% (25/30) patients were male, and 73.3% (22/30) were former or current smokers. All 30 patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 at baseline. The most common metastatic sites at baseline were bone (33.3%), liver (33.3%), brain (30.0%) and bilateral lung (26.7%). Forty percent (12/30) of the patients received cisplatin, and 60% (18/30) of the patients received carboplatin. In the PP set ($n = 30$), eight patients (26.7%) received prophylactic cranial irradiation (PCI).

In the PP set, the baseline characteristics of etoposide/cisplatin (EP) group ($n = 12$) and etoposide/carboplatin (EC) groups ($n = 18$) are shown in Table S1. There were no significant differences in baseline characteristics between the EP and EC groups, except for smoking history. There were more former or current smokers in the EC group (16/18, 88.9%) than the EP group (6/12, 50.0%) ($p = 0.034$).

Tumor responses

Tumor responses are shown in Table 2. In the PP set, 27 patients (90.0%) achieved PR. Two patients (6.7%) had SD, and one patient (3.3%) reported PD as the best response, resulting in an ORR of 90.0% (95% CI: 79.1%–100.0%) and a DCR of 96.7% (95% CI: 90.2%–103.2%). In the ITT set, 27 patients (73.0%) achieved PR. Two patients (5.4%) had SD, and one patient (2.7%) reported PD as the best response. Seven patients (18.9%) were ineligible for efficacy analysis, resulting in an ORR of 73.0% (95% CI: 58.5%–87.5%) and a DCR of 78.4% (95% CI: 65.0%–91.8%).

Analysis of progression-free survival time in the PP set ($n = 30$)

By the cutoff day (May 21, 2021), 20 (66.7%) patients had developed disease progression. The estimated median PFS was 6.0 months (95% CI: 1.1 to 10.9 months) (Figure 1a). Several factors were analyzed to predict the PFS (Table 3). A log-rank test demonstrated that baseline liver metastases ($p = 0.022$) and chemotherapy regimens ($p = 0.000187$) were significantly associated with PFS. Patients with baseline liver metastases had a significantly shorter PFS than those without baseline liver metastases (5.0 months, 95% CI: 3.5 to 6.5 vs. 10.0 months, 95% CI: 3.3 to 16.7 month; $p = 0.022$) (Figure 1b). On multivariable analysis, only chemotherapy regimen (EP vs. EC; 4.0 months, 95% CI: 2.7 to 5.3 vs. 13.0 months, 95% CI: 5.5 to 20.5 months; $p = 0.012$) (Figure 1c) was independent risk factor for PFS. Of 20 patients developing disease progression, 10 patients (50%) received second-line therapy; eight patients (40%) received best supporting care, and two patients (10%) were lost to follow-up.

Analysis of overall survival time of all patients in the PP set ($n = 30$)

The estimated median OS was 14.0 months (95% CI: 8.6 to 19.4 months) (Figure 2a). A log-rank test demonstrated that only chemotherapy regimens ($p = 0.018$) were significantly associated with OS (Table 4). Patients receiving EC chemotherapy had a significantly longer OS than those receiving EP chemotherapy (EP vs. EC; 9.0 months, 95% CI: 7.4 to 10.6 vs. 15.0 months, 95% CI: 9.9 to 20.1 months; $p = 0.018$) (Figure 2b).

TABLE 4 Cox multivariate analysis of overall survival in PP set ($n = 37$)

Variables	Log-rank test
Sex (male vs female)	0.541
Age (<65 vs. ≥65 years)	0.112
Smoking history (yes vs. no)	0.921
Brain metastasis (yes vs. no)	0.668
Bone metastasis (yes vs. no)	0.373
Lung metastasis (yes vs. no)	0.620
Liver metastasis (yes vs. no)	0.244
Adrenal gland metastasis (yes vs. no)	0.258
Supraclavicular lymph node metastasis (yes vs. no)	0.287
Pleural metastasis (yes vs. no)	0.384
Chemotherapy (EP vs. EC)	0.018

Safety in the ITT set ($n = 37$)

All 37 enrolled patients were included in the safety analysis set. Hypertension (20/37, 54.1%), anemia (16/37, 43.2%), alopecia (15/37, 40.5%), elevated transaminases (9/37, 24.3%) and elevated alkaline phosphatase (9/37, 24.3%) were the most commonly reported adverse effects (AEs) (Table 5). Thirteen patients reported grade 3–5 AEs (35.1%), including two patients with grade 3 hypertension, two patients with grade 4 hyponatremia, two patients with grade 3 hyponatremia, three patients with grade 3 neutropenia, one patient with grade 3 elevated white blood cells, one patient with grade 3 hypophosphatemia, one patient with both grade 3 thrombosis and hypertension, and one patient with both grade 3 hyponatremia and grade 3 neutropenia. No unexpected AEs were observed. No treatment-related deaths occurred during this study.

TABLE 5 Adverse events reported in the ITT set ($n = 37$)

Adverse events	All grades [no. (%)]	≥Grade 3 [no. (%)]
Any	35 (94.6%)	13 (35.1%)
Hypertension	20 (54.1%)	2 (5.4%)
Anemia	16 (43.2%)	
Alopecia	15 (40.5%)	
Elevated transaminases	9 (24.3%)	
Elevated alkaline phosphatase	9 (24.3%)	
Thrombocytopenia	8 (21.6%)	
Leukopenia/hyponatremia	7 (18.9%)	
Neutropenia	6 (16.2%)	5 (13.5%)
Fatigue	5 (13.5%)	4 (10.8%)
Oral pain	4 (10.8%)	
Elevated white blood cells	4 (10.8%)	
Rash	3 (8.1%)	1 (2.7%)
Constipation	3 (8.1%)	
Nausea	3 (8.1%)	
Diarrhea	3 (8.1%)	
Hemorrhage	2 (5.4%)	
Hyperuricemia	2 (5.4%)	
Thrombosis	2 (5.4%)	
Hypophosphatemia	1 (2.7%)	1 (2.7%)
Hypocalcemia	1 (2.7%)	1 (2.7%)
Hyperkalemia	1 (2.7%)	
Decreased appetite	1 (2.7%)	
Vomiting	1 (2.7%)	

DISCUSSION

With conventional etoposide/platinum chemotherapy, most patients with ES-SCLC relapsed quickly, with a median progression-free survival (PFS) of less than 6 months and an overall survival (OS) limited to approximately 10 months.[7,23] It is reported that VEGF and vascular endothelial growth factor receptor (VEGFR) are both highly expressed in SCLC,[24] which provides a basis for the angiogenesis inhibition treatment strategy for patients with SCLC. As a multitarget antiangiogenesis agent that inhibits tumor angiogenesis and proliferative signaling,[18] anlotinib demonstrated its significant survival benefits in the third-line treatment of SCLC patients (OS: 7.3 vs. 4.9 months, HR 0.50; 95% CI: 0.31–0.82), as well as in patients with brain metastases (OS: 6.3 vs. 2.6 months, HR 0.23; 95% CI: 0.09–0.59), with manageable toxicities compared to the placebo in the ALTER1202 study.[21] With its advantages of convenient administration by oral dosing and its favorable safety profile, anlotinib is promising for the early treatment of SCLC patients. The current single-arm study aimed to evaluate whether anlotinib combined with front-line etoposide/platinum chemotherapy can safely benefit patients with ES-SCLC by delaying disease progression and prolonging overall survival. The results show an estimated median PFS of 6.0 months and an estimated median OS of 14 months, with an ORR of 90.0% and a DCR of 96.7%. The most common AE was hypertension, and no new AEs occurred, which was consistent with other studies that applied anlotinib in SCLC.[22,25] The primary endpoint of PFS was met in our study. And the treatment of anlotinib plus etoposide/platinum chemotherapy was promising due to the encouraging PFS and OS achieved in previously untreated ES-SCLC patients, with an acceptable tolerability profile and no new safety signals observed.

Several other angiogenesis inhibitors have also been evaluated in the first-line treatment of ES-SCLC patients, but these have demonstrated less satisfying clinical outcomes. In the SALUTE II study assessing the efficacy of adding bevacizumab to standard chemotherapy for ES-SCLC, the median PFS of patients in the etoposide-platinum-bevacizumab combination group was 5.5 months, which was 1.1 months longer than that of the only etoposide-platinum group. No statistically significant differences in OS, however, were observed (9.4 vs. 10.9 months for bevacizumab and the placebo groups, respectively).[12] Similar results were also observed in another multicenter, phase III clinical trial that included 204 treatment-naive ES-SCLC patients, with a statistically significant improvement in PFS (5.7 vs. 6.7 months, $p = 0.030$) but not in OS (9.8 vs. 8.9 months, $p = 0.113$).[10] The addition of rh-endostatin (a recombinant human endostatin) to first-line chemotherapy did not significantly improve PFS (6.4 vs. 5.9 months, $p = 0.2126$), OS (12.1 vs. 12.4 months, $p = 0.8119$), nor did it improve ORR (75.4% vs. 66.7%, $p = 0.3483$) compared with chemotherapy alone in a multicenter, randomized phase II controlled study.[26] For patients with ES-SCLC who benefited from etoposide/platinum therapy, the median PFS of patients treated with pazopanib (a TKI inhibiting VEGFR2, with PDGFR and c-Kit) had a maintenance of 3.7 and 1.8 months for the placebo (HR 0.44, 95% CI: 0.29–0.69, $p < 0.0001$).[27] A phase II study that enrolled 24 ES-SCLC patients showed that apatinib (a VEGFR-2 inhibitor) combined with first-line chemotherapy can prolong the PFS (7.8 vs. 4.9 months, HR 0.18; 95% CI: 0.06–0.60) and OS (12.1 vs. 8.2 months, HR 0.38; 95% CI: 0.16–0.90) compared with chemotherapy alone,[28] although these results must be confirmed in larger trials. Few studies provide mature results on anlotinib plus chemotherapy as a first-line treatment of ES-SCLC. We first found that the addition of anlotinib to standard etoposide/platinum chemotherapy achieved encouraging PFS and OS in previously untreated ES-SCLC patients, with an acceptable tolerability profile and no new safety signals observed. This has innovated new prospects in the field of antiangiogenesis therapy for ES-SCLC.

In recent years, immunotherapy has made significant progress in SCLC treatment. The phase III IMPOWER133 and CASPIAN studies demonstrate that compared with etoposide/platinum chemotherapy alone, the addition of programmed cell death-ligand 1 (PD-L1) inhibitors (atezolizumab or durvalumab) can significantly improve the survival of patients with ES-SCLC.[6,7] Chemotherapy plus immunotherapy has provided the basis for a new standard first-line treatment of ES-SCLC. It has also been reported that antiangiogenic therapy not only inhibits new vascular formation but also modulates the immune microenvironment.[29] In light of the success of immunotherapy for the treatment of SCLC, the clinical efficacy of combinations of antiangiogenic agents such as anlotinib and immune checkpoint inhibitors may be worth investigation.

Although this was a prospective study, there were several limitations to it, including its single-arm design, limited number of enrolled patients due to the COVID-19 pandemic and early termination due to ES-SCLC first-line treatment landscape changes upon the addition of atezolizumab or durvalumab to etoposide/platinum chemotherapy.

In conclusion, the results of our study confirm the efficacy and safety of anlotinib in combination with chemotherapy in treatment-naive ES-SCLC. In the future, larger, randomized controlled phase III clinical studies are needed to further confirm the efficacy of anlotinib in the first-line treatment of ES-SCLC.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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