Effectiveness and Safety of Anlotinib Monotherapy for Patients with Extensive-stage Small-Cell Lung Cancer Who Progressed to Chemotherapy: A Real-world Exploratory Study

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ABSTRACT

BACKGROUND: Anlotinib demonstrated promising efficacy for patients with extensive-stage small-cell lung cancer (ES-SCLC) in clinical trials. However, the real-world evidence of anlotinib monotherapy in ES-SCLC was still limited currently. Therefore, present study was to investigate the effectiveness and safety of anlotinib for patients with ES-SCLC who progressed to chemotherapy in real-world and the potential biomarker during anlotinib monotherapy.

METHODS: A total of 89 patients with ES-SCLC who failed the previous chemotherapy treatment were recruited. All the patients were administered with anlotinib monotherapy. Demographic data of the patients were collected; effectiveness and safety profile during anlotinib monotherapy were documented through electronic medical record system in the hospital. Progression-free survival (PFS) and overall survival (OS) were presented using Kaplan-Meier survival curves and multivariate analysis was adjusted by Cox regression analysis.

RESULTS: All the 89 patients with ES-SCLC who progressed to chemotherapy were available for the assessment of effectiveness and safety profile. Best overall response indicated that partial response was observed in 6 patients (6.7%), stable disease was noted in 61 patients (68.5%), and progressive disease was found in 22 patients (24.7%). Therefore, the objective response rate (ORR) and disease control rate (DCR) of the 89 patients with ES-SCLC was 6.7% (95% confidence interval [CI]: 2.5%-14.1%) and 75.3% (95% CI: 65.0%-83.8%), respectively. The prognostic data suggested that the median PFS of the 89 patients was 3.1 months (95% CI: 2.10-4.10), and the median OS was 8.6 months (95% CI: 7.42-9.78). In addition, the most common adverse reactions of the patients who received anlotinib monotherapy were hypertension (34.8%), hand-foot syndrome (30.3%), fatigue (29.2%), loss of appetite (27.0%), and hematological toxicity (21.3%). Association analysis between biomarker (hypertension status) and prognosis indicated that the median PFS of patients with hypertension and patients with non-hypertension was 5.5 and 3.0 months, respectively ($\chi^2 = 4.64$, $P = .031$). Furthermore, multivariate Cox analysis for PFS suggested that hypertension status was an independent factor for PFS (hazard ratio [HR] = 0.71, $P = .035$].

CONCLUSION: Anlotinib monotherapy showed encouraging effectiveness and acceptable safety profile for patients with ES-SCLC in real world. Hypertension induced by anlotinib administration might be used as a potential biomarker to predict superior PFS for patients with ES-SCLC.

KEYWORDS: Small-cell lung cancer, effectiveness, safety, anlotinib, biomarker

Introduction

It is estimated that there are approximately 815 000 new cases and 715 000 new deaths of lung cancer in China annually.[1] Small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancers.[2] Consequently, there are approximately 122 000 new cases and 107 000 death of SCLC in China each year.[3] Although recent years had witnessed significant progress for the diagnostic techniques in SCLC, almost two-thirds of the patients were diagnosed with extensive-stage SCLC (ES-SCLC) according to the veteran affairs lung group staging criteria.[4] Prognosis of patients with ES-SCLC was dismal with the 5-year survival rate <5% and median overall survival (OS) of 7-10 months.[5] Although platinum and etoposide exhibited promising overall response in the first-line setting, considerable patients with ES-SCLC would relapse ultimately.[6] Only a few drugs were available in second-line treatment for ES-SCLC. Topotecan was the standard second-line therapeutic regimen.[7] Unfortunately, the efficacy of topotecan was modest and hematologic toxicity was significant.[8] It should be noted that *PD-1/PD-L1* blockades exhibited dramatically clinical benefit for patients with different tumor types during the past years.[9] Pembrolizumab and nivolumab were all available for ES-SCLC as third-line

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effective regimens recently.[10] Although atezolizumab and durvalumab combined with chemotherapy demonstrated compelling efficacy for patients with ES-SCLC in the first-line setting according to Impower133 and CASPIAN clinical trials,[11,12] overall response of *PD-1/PD-L1* blockades monotherapy was disappointing clinically. Therefore, patients with ES-SCLC who progressed after the previous systemic chemotherapy were in urgent need of effective therapeutic regimens currently.

Angiogenesis played an important role in tumor proliferation and metastasis.[13] Previous in vitro study indicated that majority of SCLC tumor tissues exhibited positive VEGF expression, which was associated with worse prognosis.[14] Antiangiogenic targeted drugs were proved to show potential anticancer activity in the treatment for ES-SCLC.[15] Bevacizumab was reported to provide the patients with approximately 1 month of progression-free survival (PFS) benefits in a phase III clinical trial,[16] which was similar to the PFS benefits (approximately 1 month) that observed in the Impower133 clinical trial with the addition of atezolizumab.[11] It should be noted that anlotinib was found to improve PFS and OS in a phase II clinical trial (ALTER1202) even the OS of patients who received anlotinib was not amazing numerically.[17] As a result, anlotinib was licensed in 2019 by the National Medical Products Administration (NMPA) as the monotherapy for SCLC and was only available in China currently. To the best of our knowledge, overall response of antiangiogenic tyrosine kinase inhibitor (TKI) monotherapy was disappointing. Objective response rate (ORR) of antiangiogenic TKI monotherapy was less than 18% clinically.[18,19] Therefore, it was necessary to investigate the biomarkers that could predict the clinical activity of antiangiogenic-targeted drugs currently.[20]

Hypertension was the most common adverse reaction during anlotinib administration. Previous exploratory research indicated that elderly patients with adverse reaction of hypertension induced by anlotinib administration conferred superior PFS.[21] Consequently, this study was to investigate the effectiveness and safety of anlotinib monotherapy for patients with ES-SCLC who progressed after the chemotherapy in real world and the prognostic significance according to hypertension status.

Patients and Methods

Design of present study

Given that anlotinib was licensed in China for 2.5 years and considerable patients with SCLC were treated with anlotinib monotherapy, present study was designed as a real-world retrospective study. Patients with ES-SCLC who progressed after the previous systemic chemotherapy in the department of thoracic surgery of affiliated hospital of Hebei university from June 2018 to October 2020 were enrolled. Therefore, our study was retrospective analysis of real-world patients who were treated with anlotinib and the eligibility criteria were considered as investigator-based predefined selection criteria.

Inclusion criteria were as follows: (1) histological diagnosis of SCLC with imaging staging of extensive stage; (2) aged ≥18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 score; (4) anlotinib monotherapy was administered for patients who progressed after the previous systemic chemotherapy. Both patients with platinum-sensitive and platinum-resistant were included; (5) at least one measurable target lesion according to RECIST 1.1 criteria. Exclusion criteria included the following: (1) uncontrolled or newly diagnosed brain metastases; (2) exposure to anlotinib or other antiangiogenic TKIs previously; (3) concomitant with another cancer or serious diseases; (4) effectiveness assessment data were not available. As illustrated in Figure 1, a total of 89 patients were included in this study. This study was approved by the ethics committee of affiliated hospital of Hebei university (approved number: KY-2020616). Written informed consent was signed by each enrolled patient according to the recommendations of the Declaration of Helsinki.
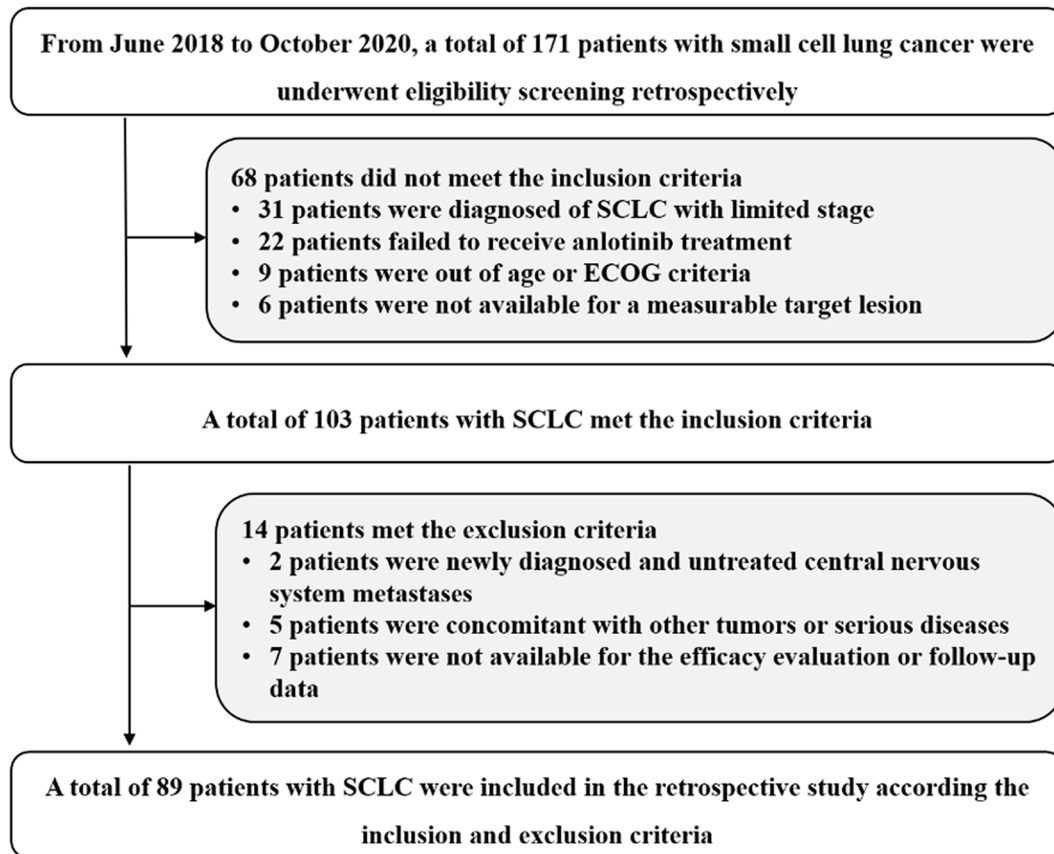
Anlotinib administration

Anlotinib was administered orally at an initial dosage of 12 or 10 mg per day before breakfast for 2 weeks and discontinued for 1 week, every 3 weeks as 1 cycle. The treatment was continued until progression or intolerable adverse reactions. In addition, dosage reduction was permitted according to the tolerance of the patients.

Assessment of effectiveness and adverse reactions

Treatment response was evaluated using RECIST version 1.1 criteria according to the judgment of investigator.[22] Target lesion in chest was used computed tomography (CT), target in other position was used CT or magnetic resonance imaging (MRI) for each patient before and after the administration of anlotinib. Target lesions were assessed every 2 cycles or when it was necessary in clinic (clinical symptoms of the patients were getting worse). In addition, safety profile was assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria.[23] Hypertension was defined as either new-onset hypertension or worsening grade (CTCAE v4.03) from baseline in patients with the history of hypertension using actual blood pressure measurements. For preexisting hypertension, any increase in drug dosage or initiation of a new antihypertensive agent was denoted as grade 3.[24]

Follow-up

Patients were followed up regularly. Initial follow-up was performed when the patient received anlotinib therapy, and then, the date of disease progression could be clearly obtained through the electronic medical record system. For OS, follow-up was mainly carried out by telephone. Patients were followed up once a month and the death status was mainly inquired. The progression or death event must be validated by at least 2

From June 2018 to October 2020, a total of 171 patients with small cell lung cancer were underwent eligibility screening retrospectively

68 patients did not meet the inclusion criteria
- **31 patients were diagnosed of SCLC with limited stage**
- **22 patients failed to receive anlotinib treatment**
- **9 patients were out of age or ECOG criteria**
- **6 patients were not available for a measurable target lesion**

A total of 103 patients with SCLC met the inclusion criteria

14 patients met the exclusion criteria
- **2 patients were newly diagnosed and untreated central nervous system metastases**
- **5 patients were concomitant with other tumors or serious diseases**
- **7 patients were not available for the efficacy evaluation or follow-up data**

A total of 89 patients with SCLC were included in the retrospective study according the inclusion and exclusion criteria

Figure 1. Flow chart of the retrospective study of anlotinib in the treatment for patients with previously treated extensive-stage small-cell lung cancer. ECOG indicates Eastern Cooperative Oncology Group; SCLC, small-cell lung cancer.

colleagues independently. The last follow-up date of this study was January 13, 2021.

Statistical analysis

All analyses were statistically analyzed using SPSS version 25.0. Difference of variables according to hypertension status was analyzed using chi-square test and the Mann-Whitney *U* nonparametric test, respectively. Objective response rate and DCR were assessed according to the best overall response of each patient; ORR was the proportion of complete response (CR) and partial response (PR) in total patients, and DCR was the proportion of CR and PR and stable disease (SD) in total patients. Survival curves were drawn using Stata software to present PFS and OS according to the hypertension status. The survival difference was analyzed using log-rank test; PFS and OS were defined according to the previous study.[21] Multivariate Cox regression analysis was constructed for PFS including the variables that were significant in univariate analysis; $P < .05$ was considered as statistical significance.

Results

Baseline characteristics

Baseline characteristics of 89 patients with previously treated ES-SCLC were shown in Table 1. The median age was 63 years

(range: 21-81 years); 61 patients were male (68.5%). ECOG performance status of 0-1 score was observed in 51 patients (57.3%). Nonsmoker and former smoker/smoker were found in 17 and 72 patients, respectively. All of the patients were extensive stage. Platinum-sensitive and platinum-resistant were reported in 43 and 40 patients, respectively. Previous second-line treatment was observed in 64 patients. A total of 72 patients had a history of previous radiotherapy. Besides, 12 patients (13.5%) had received targeted drug previously; 11 patients had received *PD-1/PD-L1* therapy previously. And the initial dosage of anlotinib with 12 and 10 mg was found in 78 and 11 patients, respectively. Patients with the history of hypertension were observed in 29 cases. The median systolic pressure level was 123 mm Hg (range: 95-139) and the median diastolic pressure level was 81 mmHg (range: 56-89). A total of 9 patients were of stable brain metastases.

Effectiveness of the patients who received anlotinib monotherapy

Objective response rate and DCR of the 89 patients who received anlotinib monotherapy were based on the best overall response during anlotinib treatment. No CR and PR were observed in 6 patients (6.7%), SD was noted in 61 patients (68.5%), and progressive disease was reported in 22 patients (24.7%). Consequently, ORR was 6.7% (95% confidence

Table 1. Baseline characteristics of the 89 patients with ES-SCLC according to hypertension status.

CHARACTERISTICS	TOTAL PATIENTS (N=89, %)	HYPERTENSION STATUS		P
		HYPERTENSION (N=31)	NON-HYPERTENSION (N=58)	
Age				
Median (range)	63 (21-81)	62 (25-79)	63 (21-81)	.435
Sex				
Male	61 (68.5)	21 (67.7)	40 (69.0)	.906
Female	28 (31.5)	10 (32.3)	18 (31.0)	
ECOG score				
0-1	51 (57.3)	18 (58.1)	33 (56.9)	.915
2	38 (42.7)	13 (41.9)	25 (43.1)	
Smoking status				
Nonsmoker	17 (19.1)	5 (16.1)	12 (20.7)	.602
Former smoker/smoker	72 (80.9)	26 (83.9)	46 (79.3)	
Clinical stages (VALG)				
Extensive	89 (100.0)	31 (100.0)	58 (100.0)	1.000
Relapse type of first-line regimen				
Platinum-sensitive	43 (48.4)	15 (48.4)	28 (48.3)	.997
Platinum-resistant	40 (44.9)	14 (45.2)	26 (44.8)	
NA	6 (6.7)	2 (6.5)	4 (6.9)	
Previous systemic treatment				
Second line	64 (71.9)	23 (74.2)	41 (70.7)	.726
Subsequent line	25 (28.1)	8 (25.8)	17 (29.3)	
History of previous radiotherapy				
Yes	72 (80.9)	26 (83.9)	46 (79.3)	.602
No	17 (19.1)	5 (16.1)	12 (20.7)	
History of targeted drug therapy				
Yes	12 (13.5)	5 (16.1)	7 (12.1)	.593
No	77 (86.5)	26 (83.9)	51 (87.9)	
History of *PD-1/PD-L1* therapy				
Yes	11 (12.4)	4 (12.9)	7 (12.1)	.909
No	78 (87.6)	27 (87.1)	51 (87.9)	
Initial dosage of anlotinib				
12 mg	78 (87.6)	26 (83.9)	52 (89.7)	.430
10 mg	11 (12.4)	5 (16.1)	6 (10.3)	
History of hypertension				
Yes	29 (32.6)	13 (41.9)	16 (27.6)	.169
No	60 (67.4)	18 (58.1)	42 (72.4)	

(Continued)

Table 1. (Continued)

CHARACTERISTICS	TOTAL PATIENTS (N=89, %)	HYPERTENSION STATUS		P
		HYPERTENSION (N=31)	NON-HYPERTENSION (N=58)	
Systolic pressure level (mm Hg)				
Median (range)	123 (95-139)	122 (95-138)	123 (95-139)	.536
Diastolic pressure level (mm Hg)				
Median (range)	81 (56-89)	81 (59-89)	81 (56-88)	.617
Brain metastases (stable status)				
Yes	9 (10.1)	4 (12.9)	5 (8.6)	.523
No	80 (89.9)	27 (87.1)	53 (91.4)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; NA, not available; VALG, veteran administration lung group.
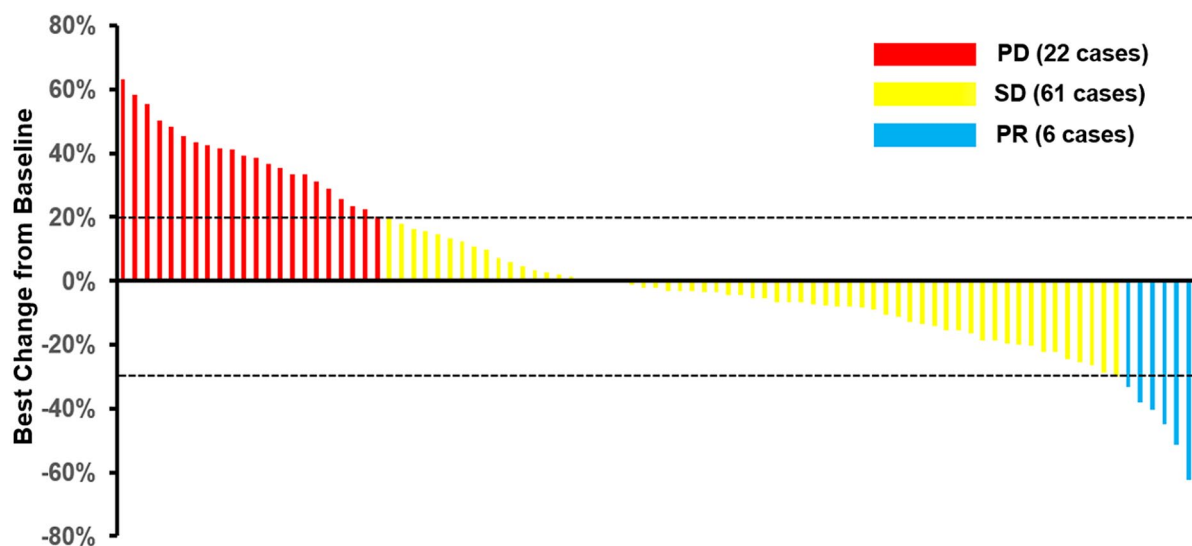

Figure 2. Waterfall plot for the change in target lesions of the 89 patients with extensive-stage small-cell lung cancer who received anlotinib monotherapy. PR indicates partial response; SD, stable disease; PD, progressive disease.

interval [CI]: 2.5%-14.1%) and DCR was 75.3% (95% CI: 65.0%-83.8%). And the waterfall plot for change in target lesion of 89 patients with previously treated ES-SCLC was illustrated in Figure 2. Furthermore, the CT scans for target lesion of lymph node in 1 patient with ES-SCLC who underwent 2 cycles of anlotinib monotherapy were illustrated in Figure 3. The target lesions were significantly reduced after anlotinib administration.

Prognosis of the patients who received anlotinib monotherapy

Median follow-up duration of all patients from the date of enrollment to the date of data cut-off was 8.5 months (follow-up range: 1-20 months). A total of 81 patients were observed the PFS events or death events when the data cutoff. Therefore, the PFS data maturity was 91.0%. As shown in Figure 4, the

median PFS of the 89 patients receiving anlotinib monotherapy was 3.1 months (95% CI: 2.10-4.10).

Univariate analysis for PFS according to baseline characteristic subgroups was performed in this study. As exhibited in Table 2, ECOG score was associated with PFS significantly in univariate analysis. The median PFS of patients with ECOG 0-1 score and patients with 2 score was 3.6 and 2.4 months, respectively (P=.023). Interestingly, patients with platinum resistance had a trend for worse PFS compared with those with platinum sensitivity (median PFS: 2.7 vs 3.6 months, P=.113). Besides, patients who were treated with 10 mg anlotinib also had a trend for worse PFS compared with those who were administered with 12 mg anlotinib. However, the difference was not statistically significant (P=.338).

A total of 66 patients were observed the death events when the data cutoff. Consequently, the OS data maturity was 74.2%. As exhibited in Figure 4, the median OS of the 89 patients who
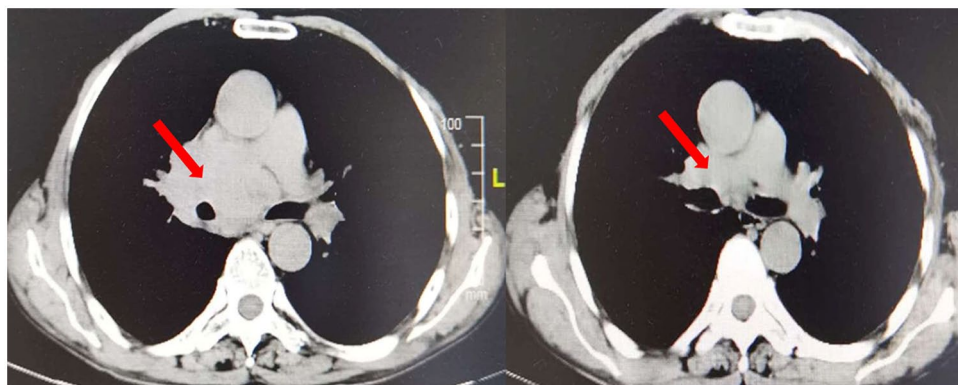
Figure 3. Computed tomographic scan results of the changes for target lesions in 1 patient with extensive-stage small-cell lung cancer after anlotinib monotherapy.
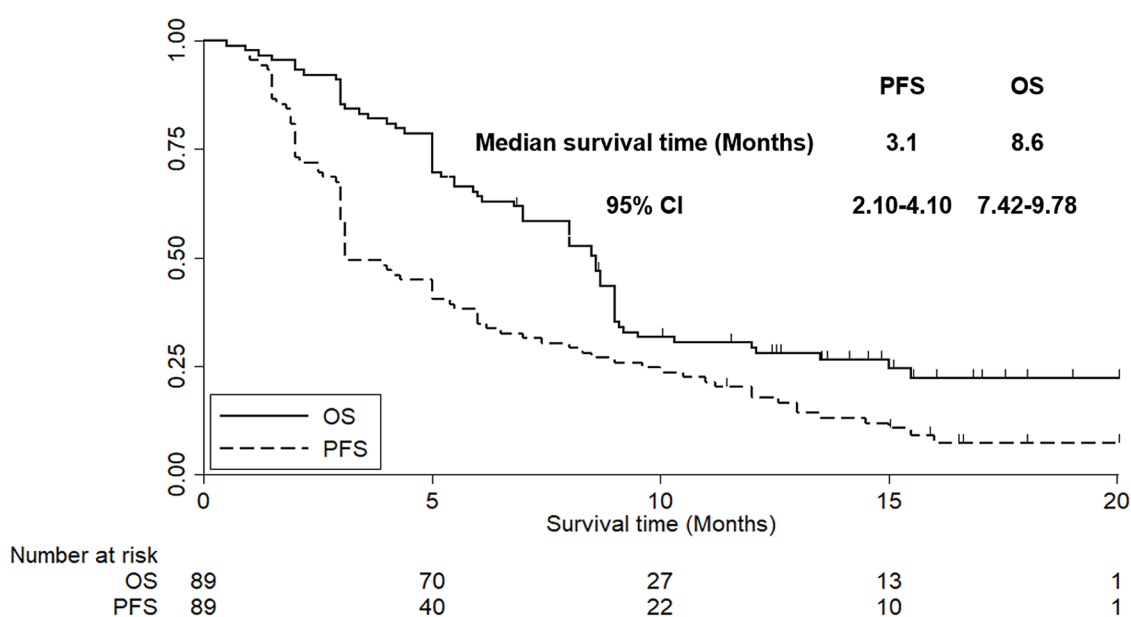
Figure 4. Progression-free survival and overall survival of the 89 patients with previously treated extensive-stage small-cell lung cancer who received anlotinib monotherapy. CI indicates confidence interval; OS, overall survival; PFS, Progression free survival.

received anlotinib monotherapy was 8.6 months (95% CI: 7.42-9.78).

Safety profile of the patients who received anlotinib monotherapy

The maximum toxicity during anlotinib administration was included in the analysis. Initial dosage of anlotinib with 12 or 10 mg was safety and tolerable. As exhibited in Table 3, the common adverse reactions of the patients with ES-SCLC during anlotinib monotherapy were hypertension (34.8%), hand-foot syndrome (30.3%), fatigue (29.2%), loss of appetite (27.0%), hematological toxicity (21.3%), hypertriglyceridemia (16.9%), diarrhea (15.7%), weight loss (14.6%), AST/ALT elevation (12.3%), proteinuria (11.2%), and hyponatremia (10.1%). Grade 3-4 adverse reactions were hypertension (9.0%), hand-foot syndrome (5.6%), fatigue (1.1%), loss of appetite (2.2%), hematological toxicity (2.2%) and hypertriglyceridemia (1.1%), AST/ALT elevation (1.1%) and hyponatremia (1.1%), respectively.

Patients with hypertension were found in 31 cases (34.8%) during anlotinib administration. As exhibited in Table 1, baseline characteristics of patients with hypertension and non-hypertension were comparable ($P > .05$). In addition, it should be noted that the median timing of the occurrence of hypertension was 6 days (range: 2-33 days) after the first dose of anlotinib administration.

Association between hypertension status and PFS

Given that hypertension was the most common adverse reaction and easy to monitor, the correlation analysis was performed between hypertension status and PFS. Therefore, PFS of 89 patients with ES-SCLC according to hypertension status was illustrated in Figure 5, and the median PFS of patients with hypertension and patients with non-hypertension was 5.5 months (95% CI: 0.16-10.84) and 3.0 months (95% CI: 2.66-3.34), respectively. And the difference was statistically significant ($\chi^2 = 4.64$, $P = .031$).

Table 2. Univariate analysis of PFS according to baseline characteristic subgroups.

CHARACTERISTICS	NO. OF PATIENTS	MEDIAN PFS (MONTHS)	95% CI	P
Age (Years)				
<63	42	3.3	2.13-4.47	.611
≥63	47	3.1	2.05-4.15	
Sex				
Male	61	2.8	1.96-3.64	.421
Female	28	3.3	1.92-4.68	
ECOG score				
0-1	51	3.6	3.09-4.11	.023
2	38	2.4	1.78-3.02	
Smoking status				
Nonsmoker	17	3.1	1.98-4.22	.782
Former smoker/smoker	72	3.1	2.03-4.17	
Relapse type of first-line regimen				
Platinum-sensitive	43	3.6	2.31-4.89	.113
Platinum-resistant	40	2.7	1.64-3.76	
Previous systemic treatment				
Second line	64	3.3	1.97-4.63	.515
Further line	25	3.1	2.03-4.17	
History of previous radiotherapy				
Yes	72	3.1	1.98-4.22	.433
No	17	2.8	1.55-4.05	
History of targeted drug therapy				
Yes	12	3.5	2.14-4.86	.347
No	77	3.1	2.08-4.12	
History of PD-1/PD-L1 therapy				
Yes	11	3.9	3.05-4.75	.527
No	78	3.0	2.11-3.89	
Initial dosage of anlotinib				
12 mg	78	3.3	2.19-4.41	.338
10 mg	11	2.5	1.67-3.33	
History of hypertension				
Yes	29	3.5	2.43-4.57	.313
No	60	2.9	1.92-3.88	
Brain metastases (stable status)				
Yes	9	3.3	2.18-4.42	.619
No	80	3.1	2.18-4.02	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival.

Table 3. Safety profile of the 89 patients with ES-SCLC who received anlotinib monotherapy.

ADVERSE REACTIONS	TOTAL (NO., %)	GRADES 1-2 (NO., %)	GRADE ≥3 (NO., %)
Hypertension	31 (34.8)	23 (25.8)	8 (9.0)
Hand-foot syndrome	27 (30.3)	22 (24.7)	5 (5.6)
Fatigue	26 (29.2)	25 (28.1)	1 (1.1)
Loss of appetite	24 (27.0)	22 (24.7)	2 (2.2)
Hematological toxicity	19 (21.3)	17 (19.1)	2 (2.2)
Hypertriglyceridemia	15 (16.9)	14 (15.7)	1 (1.1)
Diarrhea	14 (15.7)	14 (15.7)	0 (0.0)
Weight loss	13 (14.6)	13 (14.6)	0 (0.0)
AST/ALT elevation	11 (12.3)	10 (11.2)	1 (1.1)
Proteinuria	10 (11.2)	10 (11.2)	0 (0.0)
Hyponatremia	9 (10.1)	8 (9.0)	1 (1.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate amino transferase; ES-SCLC, extensive-stage small cell lung cancer.
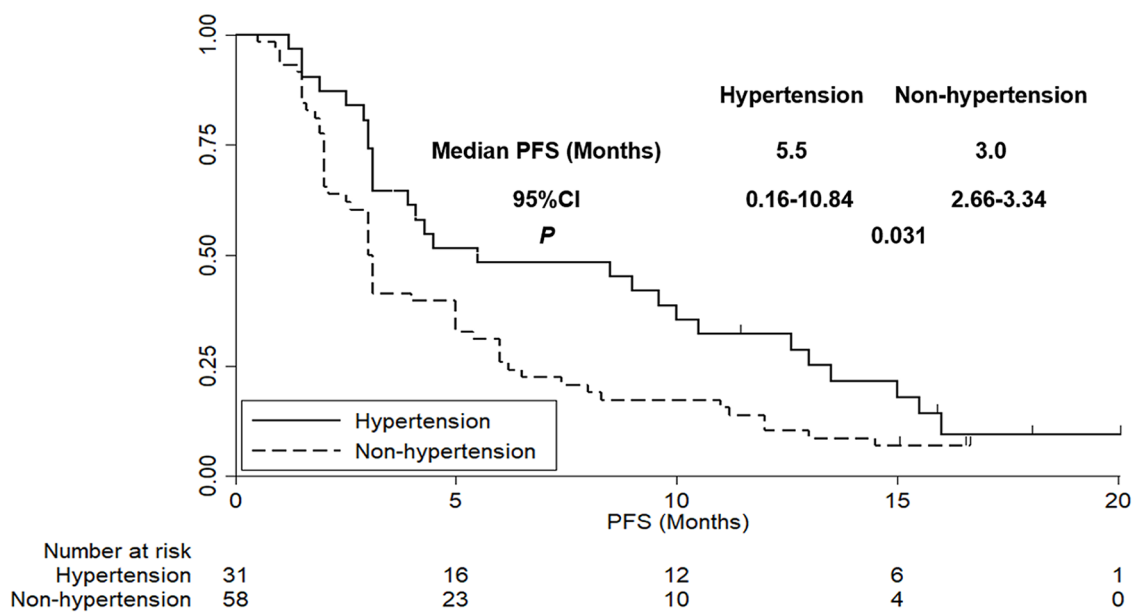
Figure 5. Progression-free survival of the 89 patients with previously treated extensive-stage small-cell lung cancer who received anlotinib monotherapy according to hypertension status. CI indicates confidence interval; PFS, progression-free survival.

Furthermore, Cox regression model was introduced to perform the multivariate analysis, which was shown in Table 4. After the multivariate adjustment, hypertension status was still an independent factor for PFS (hazard ratio [HR] = 0.71, $P = .035$). Interestingly, ECOG score was also an independent factor for PFS after multivariate adjustment (HR = 0.68, $P = .031$). Therefore, all the 31 patients with any grade hypertension were associated with superior PFS.

Discussion

For the past 30 years, etoposide plus platinum chemotherapy regimens were widely accepted as the standard first-line therapy for SCLC. Although a high rate of response of the regimen was achieved, majority SCLC always relapsed inevitably.[25] Fortunately, recent years witnessed that atezolizumab and durvalumab combined with platinum doublet chemotherapy exhibited promising efficacy and tolerable adverse reactions in the first-line setting for patients with ES-SCLC according to Impower133 and CASPIAN clinical trials, respectively.[11,12] However, treatment as subsequent line for patients with previously treated ES-SCLC remained dismal.[26] Although drugs with different mechanism of action were explored, the results were unsatisfactory.[27] As a novel oral multi-target TKI, anlotinib demonstrated promising anti-cancer activity for SCLC in clinical trials.[17]

Table 4. Multivariate Cox regression analysis for PFS according to baseline characteristic and hypertension status.

CHARACTERISTICS	HR (95% CI)	DF	P
ECOG score			
0-1 vs 2	0.68 (0.45-0.87)	1	.031
Hypertension status			
Hypertension vs nonhypertension	0.71 (0.42-0.91)	1	.035

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival.

Objective response rate of the 89 patients with ES-SCLC who received anlotinib monotherapy was 6.7%, DCR was 75.3% and the median PFS was 3.1 months, which was slightly lower than that in the ALTER1202 clinical trial (phase II clinical trial of anlotinib in ES-SCLC, patients received anlotinib therapy: ORR = 4.9%, DCR = 71.6% median PFS = 4.1 months).[17] We speculated that the retrospective design of our study might contribute to the discrepancy between the 2 studies. To our knowledge, the adherence of patients in retrospective study was inferior to that in clinical trial. And similar results were found in the another retrospective studies regarding the efficacy of antiangiogenic targeted drug in non–small-cell lung cancer (NSCLC) and SCLC.[28,29] In addition, the difference of ECOG performance status score should be taken into consideration; previous study indicated that patients with poor ECOG performance status was associated with worse prognosis.[30] Patients with ECOG 2 score accounted for 42.7% in our study, which was higher than that in ALTER1202 trial (4.9%). Furthermore, multivariate Cox results suggested that ECOG score was an independent factor for PFS. And the result was consistent with that of the previous study.[31] Interestingly, a recent study initiated by Song PF and colleagues included a total of 79 elderly patients with ES-SCLC who were treated with anlotinib monotherapy and the conclusion demonstrated that the efficacy of anlotinib monotherapy for elderly patients with SCLC was satisfactory,[21] which was consistent with the results in our study. In addition, a previous phase II clinical trial initiated by Wu and colleagues recruited 45 patients with relapsed SCLC who were treated with anlotinib monotherapy of 12 mg.[32] And the ORR and median PFS were 11% and 4.1 months, respectively. Effectiveness data were similar with those in our study. However, the median PFS was longer than that in our study. The reason could be the explanation that we discussed above. From the objective view, it should be noted that the OS in our study was slightly longer than that in the 2 clinical trials (median OS: 8.6 vs 6.1 and 7.3 months). A potential explanation for this discrepancy could be the fact that considerable patients with brain metastases (36%) were included in the study of Wu et al However, only 10.1% patients with stable brain metastases were included in our study. And 26% patients with brain metastases were included in ALTER1202 trial. Previous study suggested that patients with brain metastases were associated with worse prognosis.[33] Furthermore, we speculated that another possible interpretation could be the license of PD-1/PD-L1 blockades since the approval of anlotinib in 2018. To our knowledge, PD-1/PD-L1 blockades were still useful for patients with previously treated ES-SCLC as third-line therapy.[34] And it should be noted that a total of 11 patients were treated with PD-1/PD-L1 blockades previously in our study. Therefore, PD-1/PD-L1 blockades were also available for the patients when progressed after anlotinib administration, which provided the patients with survival benefits continuously.

Hypertension was one of the common adverse reactions in our study. And this finding was in line with the safety profile of ALTER1202 study. In addition, a recent retrospective study indicated that hypertension was also the most common adverse reaction for elderly patients (>60 years) with ES-SCLC who received anlotinib monotherapy.[21] Besides, other adverse reactions were hand-foot syndrome, fatigue, loss of appetite, hematological toxicity, hypertriglyceridemia, diarrhea, weight loss, AST/ALT elevation, proteinuria, and hyponatremia, which were the common adverse reactions that found in the ALTER1202 study and the other retrospective study. In addition, a total of 11 patients were treated with anlotinib of 10 mg and no new adverse reactions were observed during the study, which suggested that both 12 and 10 mg of anlotinib was safety for the patients. However, it should be noted that the overall incidence of the adverse reactions in our study was lower than that in ALTER1202 trial. We speculated that it might be attributed to the retrospective design of our study. Adverse reactions in retrospective study were documented poorly when compared with clinical trial. And this finding was in concert with the results in another retrospective study.[35]

Relevance analysis in our study indicated that hypertension could be used as a potential biomarker to predict PFS, which were consistent with the results of the previous retrospective studies.[21,36] In addition, previous retrospective study investigated the association between hypertension and efficacy of patients with advanced NSCLC who were treated with bevacizumab, and the results indicated that hypertension was associated with prognosis of the patients,[37] which was in accordance with that in our study as well. To our knowledge, hypertension

was a common adverse reaction that occurred during the treatment of angiogenesis inhibitors. Unfortunately, the mechanisms underlying were not investigated thoroughly. Hypertension induced by angiogenesis inhibitors might result from the inherent host biology which caused the difference in *VEGF/VEGFR* blockades and served as a biomarker for the efficacy of angiogenesis inhibitors.[38] Besides, it should be noted that patients who received anlotinib of 10 mg had a trend for worse PFS compared with those with 12 mg anlotinib therapy, even the difference was not statistically significant ($P = .338$). We speculated this might result from the fact that some patients with poor performance status stood a good chance to choose 10 mg anlotinib therapy according to the investigators' decision. In view of the positive association between hypertension with PFS, we thought anlotinib of 12 mg could be better for the patients if they could tolerate it and active measures should be used to control hypertension rather than interruption of anlotinib therapy clinically. However, the conclusion in our study should be validated in large-scale prospective trials subsequently.

Limitations were observed in present study inevitably. Obviously, this study was designed as a retrospective study and some inherent bias (a selection bias and the potentially low quality of collected data as not case report form (CRF)-based and monitored for consistency) could not be avoided. Still and all, we thought present study was of clinical significance for the prognostic evaluation of patients with previously treated ES-SCLC who received anlotinib monotherapy.

Conclusions

Collectively, present retrospective study highlighted the real-world evidence regarding the potential effectiveness and tolerable safety profile of anlotinib for patients with previously treated ES-SCLC. Hypertension induced by anlotinib therapy could be used as a potential biomarker to predict the superior PFS for patients with ES-SCLC.

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Author Contributions

YL and ZS designed the study, performed the data of this study, and wrote this manuscript. WS collected the data and participated in the patients' follow-up. HW and JZ guided the design of the study and supervised the results of the study. All authors participated in the reviewed of the manuscript and approved the final manuscript.

Ethical Approval

This study was approved by the ethics committee of affiliated hospital of Hebei University (approved number: KY-2020616).

Informed Consent

All patients in this study provided the written informed consent.

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