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ORIGINAL RESEARCH

Clinical Activity and Safety of Anlotinib Combined with PD-1 Blockades for Patients with Previously Treated Small Cell Lung Cancer

Yan-Yan Hao[1,2,]*
Yi-Peng Qiao[3,]*
Jian-De Cheng[1,2]

[1]Department of Respiratory and Critical Care Medicine, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, 030032, Shanxi, People's Republic of China; [2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Hubei, People's Republic of China; [3]Department of Internal Medicine, Qing-Xu County People's Hospital, Taiyuan, 030499, Shanxi, People's Republic of China

*These authors contributed equally to this work

Objective: Anlotinib was the standard monotherapy for patients with previously treated small cell lung cancer (SCLC) in recent years. Programmed cell death protein 1 (PD-1) blockade combined with antiangiogenic targeted drugs have proved to play a synergistic action for cancer treatment clinically. Consequently, the present study was to investigate the efficacy and safety of anlotinib combined with PD-1 blockades for patients with previously treated SCLC.

Methods: A total of 36 patients with SCLC who were treated with at least one previous systemic chemotherapy regimen participated in this study retrospectively. All the patients were administered with anlotinib plus PD-1 blockades therapy. Clinical activity was assessed according to the change of target lesion by imaging evidence and all the subjects were followed up regularly. Safety profiles were collected and documented during the treatment. Univariate analysis was carried out using Log rank test and multivariate analysis was adjusted by Cox regression analysis.

Results: All the 36 patients with previously treated SCLC were able to have their efficacy and safety profile evaluated. The best overall response of the combination regimen showed that complete response was observed in one patient, partial response was noted in 9 patients, stable disease was reported in 19 patients, progressive disease was seen in 7 patients. Therefore, the objective response rate (ORR) of the 36 patients was 27.8% (95% CI: 14.2–45.2%), disease control rate (DCR) was 80.6% (95% CI: 64.0–91.8%). Regarding the prognostic data, the median PFS and OS of the 36 patients was 4.6 months (95% CI: 3.13–6.07) and 9.3 months (95% CI: 3.30–15.30), respectively. The most common treatment-related adverse reactions were hypertension (52.8%), fatigue (47.2%), diarrhea (38.9%), hand and foot reaction (38.9%) and dermal toxicity (33.3%). Furthermore, multivariate Cox regression analysis for PFS indicated that ECOG performance status was an independent factor to predict PFS.

Conclusion: Anlotinib combined with PD-1 blockades regimen preliminarily demonstrated encouraging efficacy and tolerable safety for patients with previously treated SCLC. The conclusion should be validated in prospective clinical trials subsequently.

Keywords: small cell lung cancer, anlotinib, PD-1 blockade, efficacy, safety

Correspondence: Jian-De Cheng
Department of Respiratory and Critical Medicine of Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, 030032, Shanxi, People's Republic of China
Tel +86 13834668789
Email chenjiande_2001@163.com

Introduction

As an aggressive and devastating malignancy, small cell lung cancer (SCLC) is characterized by rapid growth and early metastasis, and accounts for approximately 15% of all diagnosed lung cancers.[1] The estimated prevalence of SCLC was approximately 122,000 new cases and 107,000 new deaths of SCLC in China annually.[2] Almost 70%

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of the patients with SCLC presented with extensive-stage SCLC (ES-SCLC), which was of dismal prognosis with the 5-year survival rate <3% and median overall survival (OS) of <12 months.[3] To our knowledge, after the failure for first-line regimen of etoposide plus platinum doublet chemotherapy, topotecan remained the recommended second-line treatment in China with the median duration of response only 3 months.[4] Therefore, effective regimens with tolerable safety profile as second-line and above therapy for patients with ES-SCLC are needed currently.

It was reported that approximately 80% of SCLC was associated with positive vascular endothelial growth factor (VEGF) expression.[5] Therefore, antiangiogenic targeted drugs demonstrated encouraging efficacy for patients with ES-SCLC recently.[6] Additionally, anlotinib was reported to improve PFS and OS dramatically in a phase II clinical trial (ALTER1202) for patients with SCLC.[7] Consequently, anlotinib had become the standard regimen as third-line monotherapy for patients with SCLC by NMPA since 2019.

Furthermore, SCLC was correlated with tobacco exposure and progressed rapidly, which frequently involved in central nervous system (CNS) metastasis.[8] Additionally, SCLC was also associated with high tumor mutation burden and patients with SCLC might benefit from PD-1/PD-L1 blockades treatment.[9] To our knowledge, although the combination of PD-L1 blockade with first-line platinum–etoposide doublet chemotherapy regimen exhibited superior improvement for clinical outcomes of patients with SCLC according to the two randomized phase III clinical trials (atezolizumab in Impower 133 and durvalumab in CASPIAN),[10,11] the current clinical evidence data suggested that immunotherapy for SCLC still faced considerable challenges, including limited efficacy of immunotherapy, unknown predictive biomarkers, unknown efficacy in elderly and poor performance status patients and controversial application effect of brain/liver metastases.[12] Consequently, more effective combination treatment regarding immunotherapy was needed to prolong the survival for patients with SCLC urgently.[13]

Interestingly, the combination of immunotherapy with antiangiogenic targeted drugs exhibited a promising synergistic action in cancer treatment, which indicated that the antiangiogenic drugs reprogrammed the tumor milieu from an immunosuppressive to an immune permissive microenvironment. And the activated immunity by PD-1/PD-L1 blockades also facilitated anti-angiogenesis by downregulating the expression of vascular endothelial growth factor and alleviating hypoxia condition.[14] Furthermore, recent years had witnessed that atezolizumab plus bevacizumab exhibited promising clinical efficacy in unresectable hepatocellular carcinoma, thus becoming the standard treatment as first-line therapy for unresectable hepatocellular carcinoma.[15] Nevertheless, the clinical activity and safety of anlotinib combined with PD-1 blockades for patients with previously treated SCLC was still scanty. Therefore, the present study was to investigate the efficacy and safety of anlotinib combined with PD-1 blockades for patients with previously treated SCLC retrospectively.

Patients and Methods
Design of This Study and Eligibility Criteria
Given that anlotinib and PD-1 blockades were licensed in China almost 3 years ago, some patients with SCLC had received anlotinib combined with PD-1 blockades therapy clinically, thus our study was designed as a retrospective study. Patients with ES-SCLC who were treated with at least one systemic chemotherapy regimen in the Department of Respiratory and Critical Care Medicine of the Shanxi Bethune Hospital from August 2018 to May 2021 were recruited in this study consecutively. Inclusion criteria were: (a) histological or cytological diagnosis of SCLC with imaging staging of extensive stage; (b) age ≥18 years old; (c) eastern cooperative oncology group (ECOG) performance status (PS) of 0–2 score; (d) patients progressed after at least one systemic chemotherapy regimen, including those who relapsed >3 months after the completion of first-line chemotherapy (platinum-sensitive) and those who relapsed <3 months after the completion of first-line chemotherapy or during chemotherapy (platinum-resistant); (e) patients were administered with anlotinib plus PD-1 blockades combination therapy; (f) at least one measurable target lesion to present the drug response according to response evaluation criteria in solid tumors (RECIST 1.1). The exclusion criteria were: (a) previous exposure to PD-1/PD-L1 blockades, or anlotinib was administered previously. However, other antiangiogenic targeted drugs exposure was permitted; (b) clinically active brain metastases, patients with stable brain metastases were permitted; (c) active or uncontrolled autoimmune disease; (d) concomitant with another cancer or serious disease that might compromise the survival of the patients; (e) efficacy assessment data were not available. The study profile of the present study is illustrated in Figure 1. Finally, a total of 36 patients with ES-SCLC was enrolled. This study was approved by the ethics committee of the Shanxi Bethune Hospital. Written informed consent was
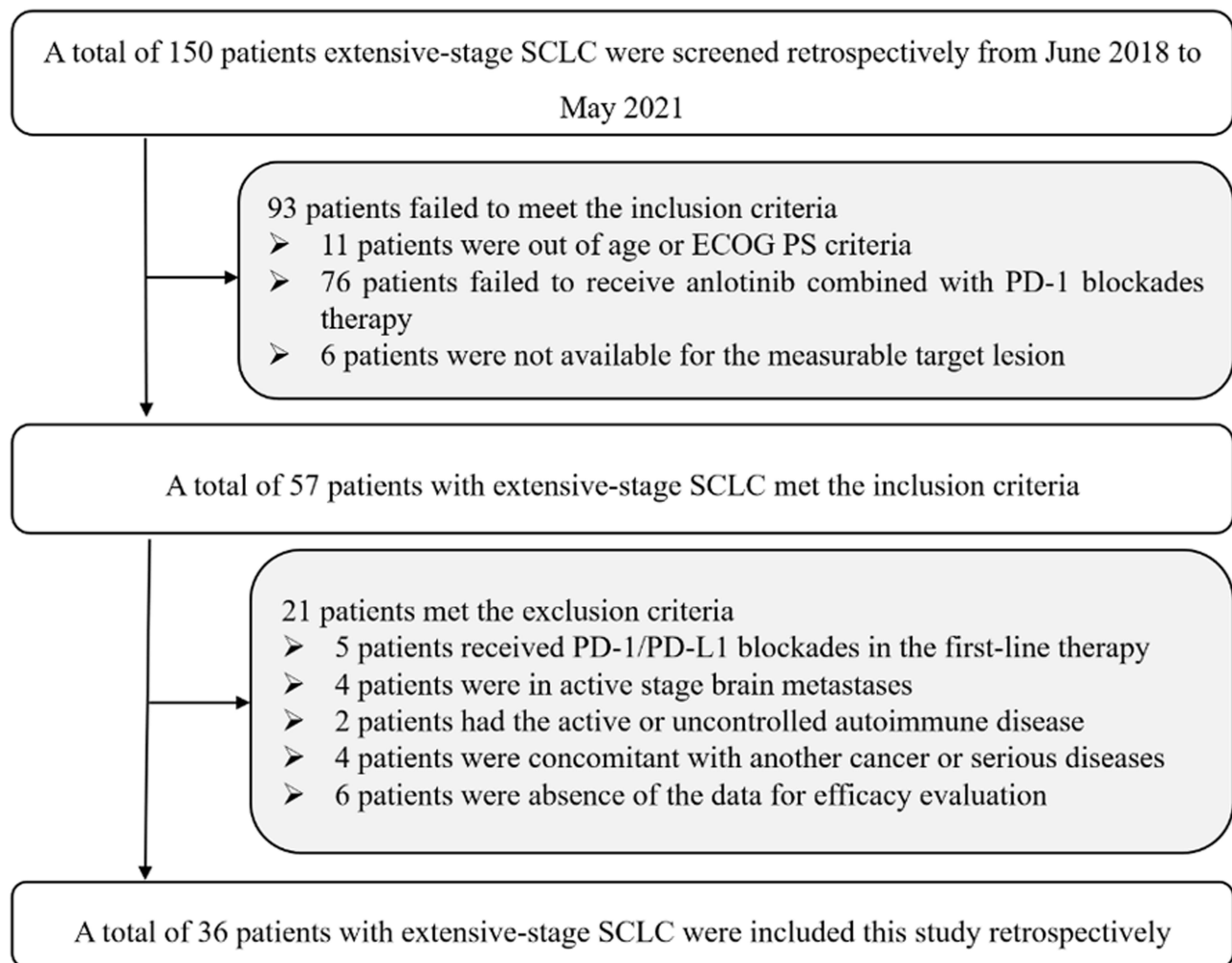
Figure 1 Flow chart of the retrospective study of anlotinib combined with PD-1 blockades in the treatment for patients with previously treated small cell lung cancer.

obtained by each enrolled patient according to the recommendations of the Declaration of Helsinki.

Therapeutic Regimens

Patients included were treated with anlotinib combined with PD-1 blockades. Anlotinib was administered orally at an initial dosage of 12 mg or 10 mg per day with warm water for two weeks and discontinued for one week, every three weeks as one cycle. PD-1 blockades consisted of camrelizumab (200 mg), sintilimab (200 mg) and pembrolizumab (200 mg), which were intravenously administered on day 1, every three weeks as one cycle. The treatment continued until disease progression or intolerable adverse reactions. Dosage adjustment of anlotinib to either 10 mg or 8 mg once daily was permitted according to the toxicity during the treatment. Overall response was evaluated according to RECIST version 1.1 criteria based on the judgement of the investigators.[16]

Imaging examination of the target lesions using computed tomography (CT) or magnetic resonance imaging (MRI) was implemented for each patient before and during the combination therapy. The change of target lesions was evaluated using CT or MRI scans every two cycles or depending on the actual situation when it was necessary for the patients. Primary endpoint of this study was progression-free survival (PFS), secondary endpoint was overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety profile of the combination regimen.

Follow-Up and Assessment of the Safety Profile

When the patients underwent treatment in the hospital, clinical characteristics, adverse reactions and status of disease progression of each patient were collected through the electronic medical record system. Besides, the subsequent

follow-up was performed mainly using telephone. Patients were followed up every one month for the treatment after anlotinib combined with PD-1 blockades therapy and death status was mainly inquired. Furthermore, adverse reactions during treatment were documented by Common Terminology Criteria for Adverse Events (CTCAE) 4.03 version to present the toxicity profile that might be drug-related.[17]

Statistical Analysis

Data in this study were analyzed using the statistical software SPSS version 25.0 (IBM, USA). ORR was the percentage of complete response (CR) and partial response (PR) in total patients. DCR was the percentage of CR and PR and stable disease (SD) in total patients. PFS was defined as the interval from the onset of anlotinib combined with PD-1 blockades treatment to disease progression or death, whichever occurred first. OS was defined as the interval from the onset of anlotinib combined with PD-1 blockades treatment to death of the patients from any cause.[18] When no prognostic events were observed, survival end points were censored at the date of last follow-up. Kaplan-Meier curves were drawn using Stata version 14.0 to present the PFS and OS data. Survival difference according to baseline characteristic subgroup was calculated using Log rank test. Cox regression analysis was introduced for PFS in multivariable analysis. $P<0.05$ was considered as statistically significant.

Results

Baseline Characteristics of the 36 Patients with ES-SCLC

Baseline characteristics of the 36 patients with ES-SCLC was exhibited in Table 1. Median age of the 36 patients was 68 years (range: 21–83 years), patients with ≥68 and <68 years were observed in 20 and 16 cases, respectively. ECOG performance status of 0–1 and 2 score was observed in 17 and 19 patients, respectively. Male and female was noted in 72.2% and 27.8% patients, respectively. Non-smoker and former smoker/smoker was reported in 9 and 27 patients, respectively. Patients with platinum-sensitive and platinum-resistant were observed in 17 and 19 cases, respectively. Interestingly, lines of previous treatment with first-line, second-line and subsequent-line were seen in 5, 16 and 15 patients, respectively. Patients with stable brain metastases were observed in 7 cases. A total of 30 patients (83.3%) had experienced radiotherapy previously. Besides, a total of 6 patients (16.7%) were treated with targeted-drugs previously. Interestingly, it should be noted that initial dosage of anlotinib with 12 mg and 10 mg was reported in 25 and 11 patients, respectively. And PD-1 blockades of camrelizumab, sintilimab and pembrolizumab were found in 17, 13 and 6 patients, respectively.

Efficacy of the 36 Patients with ES-SCLC Receiving Anlotinib Combined with PD-1 Blockades

All the 36 patients with previously treated SCLC were able to assess the efficacy data. And the best overall response suggested that CR was observed in one patient, PR was noted in 9 patients, SD was reported in 19 patients, progressive disease was seen in 7 patients. Consequently, ORR of the 36 patients was 27.8% [95% confidence interval (CI): 14.2–45.2%], DCR was 80.6% (95% CI: 64.0–91.8%). The waterfall plot for the best percentage change in target lesion of the 36 patients with ES-SCLC is presented in Figure 2. Most of the target lesions among the 36 patients with ES-SCLC shrank dramatically. Interestingly, we observed one patient with SCLC achieved CR after the administration of anlotinib combined with sintilimab regimen. This was a female patient with extensive stage SCLC and ECOG performance status of 0 score. She had received etoposide plus carboplatin as first-line therapy and achieved PR after the first-line therapy and progressed after 8 months response. Then she was included in the present study. The CT scan of the target lesion in lung site before and after the combination therapy is illustrated in Figure 3. The target lesion disappeared completely after the therapy of anlotinib combined with sintilimab. Additionally, all non-target lesions disappeared as well. This patient benefited from the combination administration significantly.

Prognosis of the 36 Patients with ES-SCLC Receiving Anlotinib Combined with PD-1 Blockades

Follow-up was implemented in this study appropriately. The last follow-up date of the present study was June 30, 2021. The median follow-up duration for the 36 patients with ES-SCLC from the date of treatment to the date of data cut-off was 8.5 months (follow-up range: 0.6–23.5 months). As illustrated in Figure 4, the median PFS of the 36 patients with ES-SCLC receiving anlotinib combined with PD-1 blockades was 4.6 months (95% CI: 3.13–6.07). And the 6-month and 12-month

Table 1 Baseline Characteristics of the 36 Patients with ES-SCLC

Characteristics	Total Patients (N=36)	Percentage
Age (years)		
Median (range)	68 (21–83)	NA
≥68	20	55.%
<68	16	44.4%
ECOG PS score		
0–1	17	47.2%
2	19	52.8%
Gender		
Male	26	72.2%
Female	10	27.8%
Smoking status		
Non-smoker	9	25.0%
Former smoker/smoker	27	75.0%
Relapse type of first-line regimen		
Platinum-sensitive	17	47.2%
Platinum-resistant	19	52.8%
Lines of previous treatment		
First-line	5	13.9%
Second-line	16	44.4%
Subsequent-line	15	41.7%
Presence of brain metastases		
Yas	7	19.4%
No	29	80.6%
Previous radiotherapy		
Yes	30	83.3%
No	6	16.7%
Previous targeted-drugs therapy		
Yes	6	16.7%
No	30	83.3%
Initial dosage of anlotinib		
12mg	25	69.4%
10mg	11	30.6%
PD-1 blockades		
Camrelizumab	17	47.2%
Sintilimab	13	36.1%
Pembrolizumab	6	16.7%

Abbreviations: ES-SCLC, extensive-stage small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NA, not available.

PFS rate was 38.9% (95% CI: 23.3–54.2%) and 24.3% (95% CI: 11.7–39.3%), respectively. Furthermore, given that follow-up duration of the present study was accurate and enough, OS was analyzed meanwhile. As shown in Figure 5, the median OS of the 36 patients with ES-SCLC receiving anlotinib combined with PD-1 blockades was 9.3 months (95% CI: 3.30–15.30). And the 6-month and 12-month OS rate was 69.4% (95% CI: 51.7–81.8%) and 47.1% (95% CI: 30.3–62.2%), respectively.

Furthermore, the median PFS and 95% CI according to baseline characteristic subgroups in univariate analysis were performed. As shown in Table 2, ECOG performance status score and relapse type of first-line regimen were significantly correlated with PFS in univariate analysis, which indicated that the median PFS of patients with ECOG performance status of 0–1 score was dramatically longer than that of patients with a 2 score (median PFS: 5.6 vs 3.8 months, $P = 0.021$), and the median PFS of patients with platinum-resistant was shorter than that of patients with platinum-sensitive (median PFS: 3.8 vs 5.2 months, $P = 0.041$). Additionally, it should be noticed that patients with 12 mg initial dosage of anlotinib had a trend
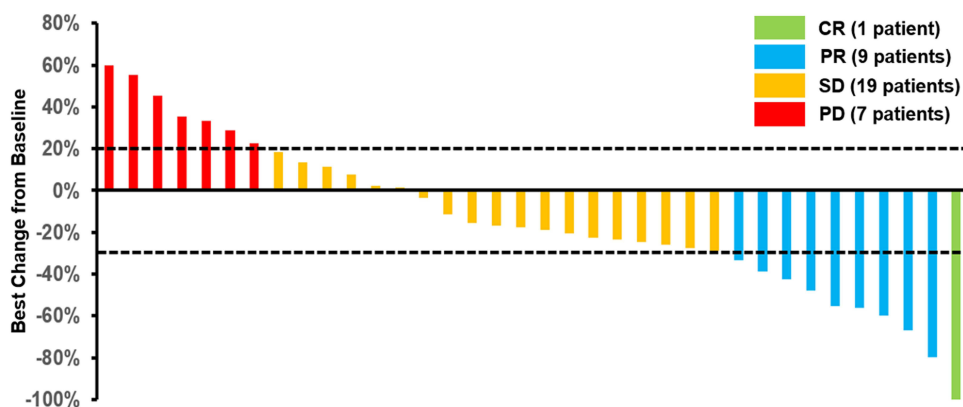
Figure 2 Waterfall plot for the best percentage change in target lesion of the 36 patients with previously treated small cell lung cancer receiving anlotinib combined with PD-1 blockades therapy.
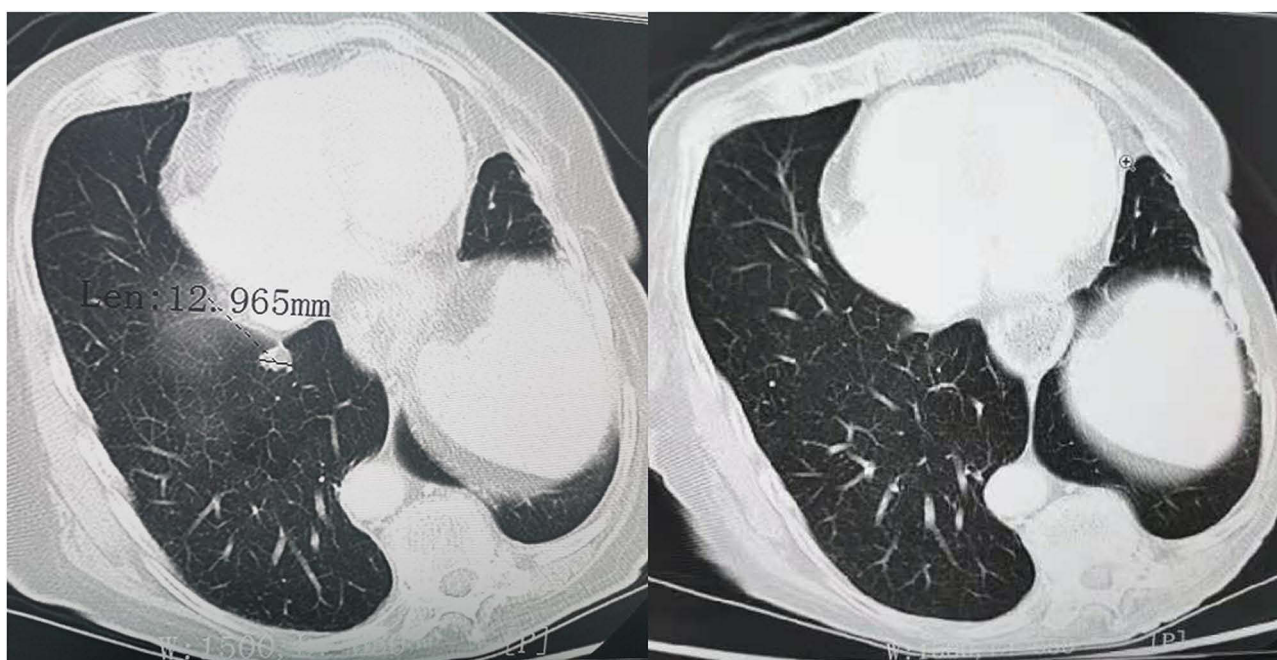

Figure 3 CT scan results of the changes for target lesions in one patient with small cell lung cancer before and after anlotinib combined with PD-1 blockade therapy.

for superior PFS compared with those with 10 mg dosage of anlotinib even the difference was not statistically significant (median PFS: 5.2 vs 4.3 months, $P = 0.231$).

Furthermore, multivariate Cox regression analysis was introduced for PFS adjustment including the baseline characteristics that were significant in univariate analysis. And the multivariate analysis results were illustrated in Table 3. The results demonstrated that ECOG PS score was an independent factor for PFS [hazard ratio (HR) = 0.68, $P = 0.029$]. Nevertheless, as shown in Table 3, after adjustment in the Cox regression analysis, relapse type of first-line regimen failed to influence the PFS independently (HR = 0.75, $P = 0.063$).

Safety Profile of the 36 Patients with ES-SCLC Receiving Anlotinib Combined with PD-1 Blockades

Maximum toxicity of the 36 patients with ES-SCLC experienced during the combination therapy was collected and analyzed in this study. Adverse events regardless of attribution were observed in all the 36 patients (100%). Nevertheless, the treatment related adverse reactions (TRARs) were noted in 32 patients (88.9%). And the grade ≥3 TRARs were seen in 14 patients (38.9%).

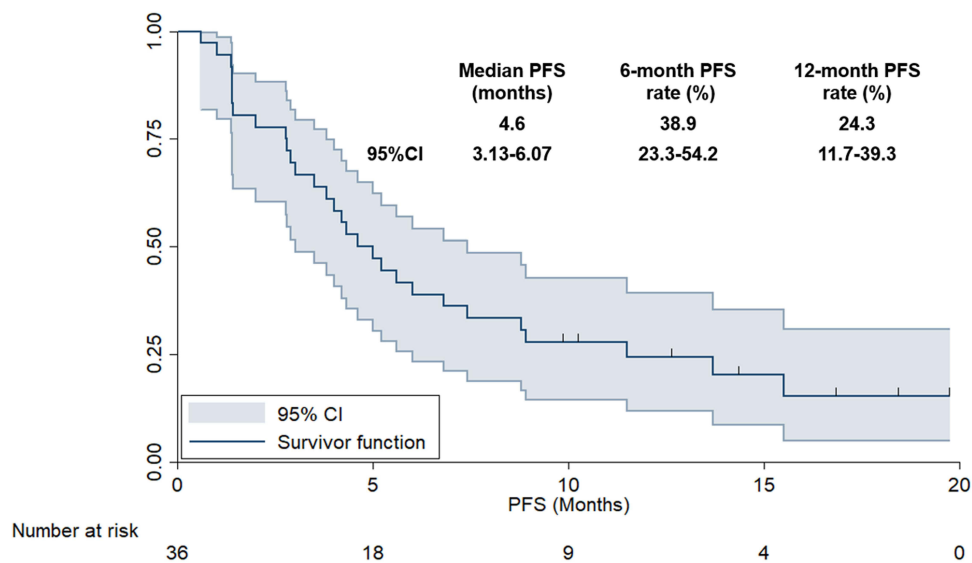Specifically, as shown in Table 4, the common TRARs were hypertension (52.8%), fatigue (47.2%), diarrhea

Figure 4 Progression-free survival of the 36 patients with previously treated small cell lung cancer receiving anlotinib combined with PD-1 blockades therapy.
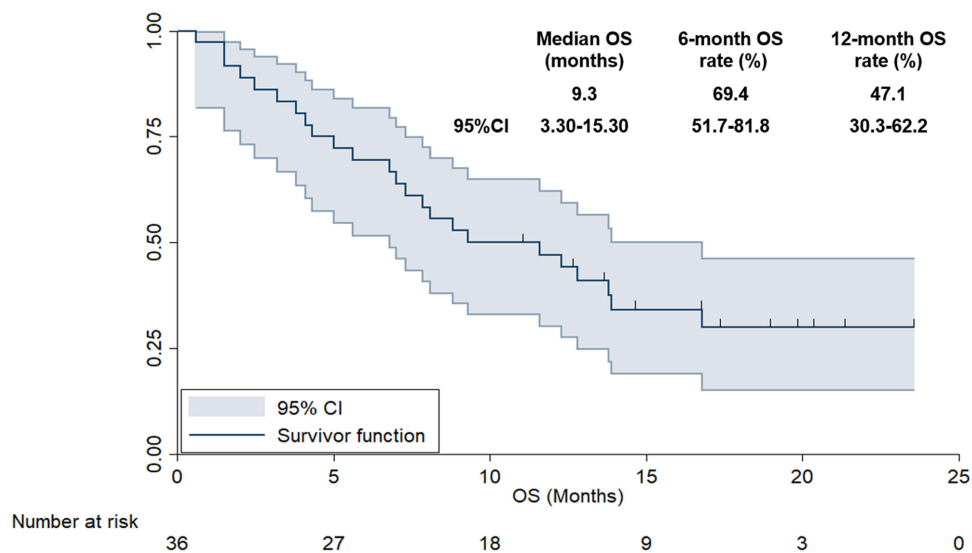

Figure 5 Overall survival of the 36 patients with previously treated small cell lung cancer receiving anlotinib combined with PD-1 blockades therapy.

(38.9%), hand and foot reaction (38.9%), dermal toxicity (33.3%), anemia (25.0%), ASL/ALT elevation (19.4%), proteinuria (16.7%), RCCEP (11.1%), hemoptysis (8.3%) and pneumonia (8.3%). Furthermore, the grade ≥3 adverse reactions were observed in hypertension (13.9%), HFS (11.1%), diarrhea (8.3%), fatigue (5.6%), dermal toxicity (5.6%), AST/ALT elevation (2.8%) and proteinuria (2.8%). Overall TRARs were tolerable and controllable.

Discussion

To our knowledge, present study highlighted the real-world evidence regarding the clinical activity and safety of anlotinib plus PD-1 blockades for patients with previously treated SCLC. Anlotinib combined with PD-1 blockades could be an effective and safe regimen for patients with previously treated ES-SCLC potentially.

For the past 30 years, etoposide and platinum chemotherapy regimens were widely established as the standard regimen as first-line therapy for patients with SCLC. Although a relatively high response rate of this regimen was observed, SCLC would always relapse inevitably.[19] The past three years had witnessed that atezolizumab and durvalumab combined with platinum doublet chemotherapy in the first-line setting for patients with ES-SCLC exhibited promising

Table 2 Univariate Analysis for PFS of the 36 Patients with ES-SCLC According to Baseline Characteristics

Characteristics	No. of Patients	Median PFS (Months)	95% CI	P
Age (Years)				
<68	16	4.6	3.22–5.98	0.632
≥68	20	4.3	3.01–5.59	
ECOG PS score				
0–1	17	5.6	4.31–6.89	0.021
2	19	3.8	2.68–4.92	
Gender				
Male	26	4.2	3.05–5.35	0.438
Female	10	5.0	3.93–6.07	
Smoking status				
Non-smoker	9	5.0	3.78–6.22	0.515
Former smoker/smoker	27	4.0	3.02–4.98	
Relapse type of first-line regimen				
Platinum-sensitive	17	5.2	3.91–6.49	0.041
Platinum-resistant	19	3.8	2.73–4.87	
Lines of previous treatment				
First-line	5	5.0	3.51–6.49	0.417
Second-line	16	4.31	3.27–5.35	
Subsequent-line	15	4.6	3.55–5.65	
Presence of brain metastases				
Yas	7	4.2	3.02–5.38	0.336
No	29	5.0	3.88–6.12	
Previous radiotherapy				
Yes	30	4.6	3.42–5.78	0.533
No	6	5.0	4.06–5.94	
Previous targeted-drugs therapy				
Yes	6	5.0	3.89–6.11	0.423
No	30	4.3	3.09–5.51	
Initial dosage of anlotinib				
12mg	25	5.2	3.97–6.43	0.231
10mg	11	4.3	3.08–4.72	
PD-1 blockades				
Camrelizumab	17	4.2	3.07–5.33	0.418
Sintilimab	13	5.2	3.98–6.42	
Pembrolizumab	6	5.0	3.79–6.21	

Abbreviations: PFS, progression-free survival; ES-SCLC, extensive-stage small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval.

clinical activity and tolerable adverse reactions according to Impower133 and CASPIAN clinical trials, respectively.[10,11] However, treatment in subsequent lines for patients with ES-SCLC who failed the standard first-line regimen remained limited.[20] Although numerous drugs with different mechanisms of action were explored in subsequent line therapy for patients with ES-SCLC, the results were unsatisfactory.[21] As a novel oral multi-target tyrosine kinase inhibitor, anlotinib inhibited tumor angiogenesis through the target of antiangiogenic signal pathway.[22] Proliferation of cancer cell was blocked by anlotinib through the newly identified signal pathway involved in the tumor

progression.[23] As a result, anlotinib exhibited promising anticancer activity for patients with previously treated SCLC.[24] Besides, in spite of the fact that pembrolizumab and nivolumab monotherapy demonstrated potential efficacy and tolerable safety for patients with ES-SCLC over the past three years in phase II trials,[25,26] the indication for SCLC of pembrolizumab and nivolumab had been withdrawn recently owing to the negative results for OS in the phase III clinical trials. Therefore, these results highlighted the necessity of combination therapy for patients with previously treated SCLC, especially the exploration of PD-1 blockades combined with antiangiogenic targeted drugs.[18]

Table 3 Multivariate Cox Regression Analysis for PFS According to Baseline Characteristics

Characteristics	HR (95% CI)	df	P
ECOG PS score			
0–1 vs 2	0.68 (0.37–0.91)	1	0.029
Relapse type of first-line regimen			
Platinum-sensitive vs platinum-resistant	0.75 (0.49–1.05)	1	0.063

Abbreviations: PFS, Progression-free survival; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HR, hazard ratio; CI, confidence interval; df, degree of freedom.

Table 4 Safety Profile of the 36 Patients with ES-SCLC Receiving Anlotinib Combined with PD-1 Blockades

Adverse Reactions	Total (N, %)	Grade ≥3 (N, %)
Hypertension	19 (52.8)	5 (13.9)
Fatigue	17 (47.2)	2 (5.6)
Diarrhea	14 (38.9)	3 (8.3)
Hand and foot reaction	14 (38.9)	4 (11.1)
Dermal toxicity	12 (33.3)	2 (5.6)
Anemia	9 (25.0)	0 (0.0)
AST/ALT elevation	7 (19.4)	1 (2.8)
Proteinuria	6 (16.7)	1 (2.8)
RCCEP	4 (11.1)	0 (0.0)
Hemoptysis	3 (8.3)	0 (0.0)
Pneumonia	3 (8.3)	0 (0.0)

Abbreviations: ES-SCLC, extensive-stage small cell lung cancer; AST, aspartate amino transferase; ALT, alanine aminotransferase; RCCEP, reactive cutaneous capillary endothelial proliferation.

Patients included in the present study was the ES-SCLC who were treated with at least one systemic chemotherapy treatment, which were similar with the baseline characteristics of Keynote 028 clinical trial.[27] Collectively, ORR of the 36 patients receiving anlotinib combined with PD-1 blockades was 27.8%, DCR was 80.6% and the median PFS was 4.6 months. And the results were better than that in the trial of topotecan as second-line therapy for patients with SCLC, which yielded an ORR of 21.7%, DCR of 64.5% and median PFS of 2.8 months.[28] Another second-line regimen of lurbinectedin achieved an ORR of 35%, DCR of 68%, a median PFS of 3.5 months and a median OS of 9.3 months in patients with previously treated SCLC,[29] which demonstrated comparable and similar clinical activity compared with the results of our study. Furthermore, to our knowledge, ORR of anlotinib monotherapy for patients with SCLC was 4.9%.[7] ORR of PD-1 blockades monotherapy was approximately <20% regardless of PD-L1 expression.[13] The overall response of anlotinib plus PD-1 blockades in our study suggested the potentially synergistic action for cancer therapy, which was in accordance with the conclusion observed in patients with hepatocellular carcinoma who were treated with atezolizumab plus bevacizumab combination therapy.[15] Interestingly, a recent study initiated by Fan et al. performed a multicenter phase II clinical trial to identify the efficacy and safety of camrelizumab (PD-1 blockade) plus apatinib (another antiangiogenic targeted drug) in ES-SCLC.[30] A total of 59 patients with ES-SCLC who received camrelizumab plus apatinib treatment were included. The ORR of the 59 patients was 34%, which was higher than that in our study. We speculated the retrospective design of our study might contribute to the discrepancy between the two studies. To our knowledge, the adherence of the patients in the retrospective study was inferior to that in clinical trial. Besides, ECOG performance status proportion should be taken into consideration, previous study indicated that poor PS status was associated with worse prognosis.[31] Patients with ECOG 2 score in our study accounted for 52.8%, which was higher than that in Yun Fan's trial (0.0%). Also, the multivariate Cox result suggested that ECOG PS status was an independent factor for PFS. The result was consistent with the previous study.[32] Nevertheless, it should be noted that the OS in present study was slightly longer than that in the phase II clinical trial (median OS: 9.3 vs 8.4 months). One possible reason might be the fact that more patients with platinum-resistant (66.0% vs 52.8%) were included in the study of Yun Fan et al. The results of PFS according to baseline characteristics in our study suggested that patients with platinum-resistant had a trend for worse PFS compared with patients with platinum-sensitive. Furthermore, we speculated that another explanation could be attributed to the license of PD-1/PD-L1 blockades since 2018. To our knowledge, PD-1/PD-L1 blockades demonstrated potential benefit for patients with chemotherapy-refractory ES-SCLC in the subsequent line therapy.[13] As a result, more PD-1/PD-L1 blockades were still available for the patients when they progressed after anlotinib plus PD-1 blockades treatment, thus providing the patients with survival benefits successively. Additionally, a total of 7 patients with stable brain metastases were also included in our study and the relevance

analysis exhibited that those patients could benefit from anlotinib combined with PD-1 blockades regimen as well, which was consistent with the previous study of anlotinib plus PD-1 blockades in patients with NSCLC.[33] Furthermore, to our knowledge, the blood-brain barrier limited the delivery of chemotherapy and considerable targeted drugs to the brain. However, T cells could cross the blood-brain barrier easily, thus highlighting a positive role for immunotherapy in tumor with brain metastases.[34] Besides, it should be noted that patients with 10 mg anlotinib had a trend for worse PFS compared with those with 12 mg dosage, although the difference was not statistically significant ($P = 0.231$). We speculated this could reflect a possibility that some patients with poor performance status stood a good chance to choose 10 mg anlotinib therapy, thus contributing to the worse PFS to some extent. However, the conclusion should be validated in large-scale prospective trials in the future.

Overall adverse reactions of the combination regimen were acceptable and tolerable, which was consistent with the previous report regarding the combination therapy of anlotinib plus PD-1 blockades in lung cancer.[18] Interestingly, the incidence of grade ≥3 TRARs was 38.9%, which was lower than that observed in the treatment of camrelizumab plus apatinib (grade ≥3 TRARs was 72.9%). It seemed that anlotinib plus PD-1 blockades was more tolerable for the patients with ES-SCLC. Additionally, the most common TRARs of the combination regimen were hypertension, fatigue, diarrhea and hand and foot reaction, which might be attributed to the administration of anlotinib and were consistent with the safety profile of the previous study regarding anlotinib in patients with ES-SCLC.[35] Other immunotherapy-related adverse reactions such as dermal toxicity, reactive cutaneous capillary endothelial proliferation (RCCEP) and pneumonia were observed with low incidence, which might have resulted from the therapy of PD-1 blockades. RCCEP seemed to be the specific adverse reaction of camrelizumab that was administered in 17 patients in our study. Therefore, the actual incidence of RCCEP for camrelizumab administration could be 23.5%, which was lower than that of the camrelizumab monotherapy in the other cancers (above 60%).[36] This discrepancy of the RCCEP incidence could be attributed to the fact that anti-angiogenic targeted drugs might play a key role to attenuate the incidence of RCCEP during camrelizumab administration.[37] Collectively, the safety profile of anlotinib combined with PD-1 blockades was manageable and controllable.

Limitations were observed in the present study, inevitably. Firstly, the sample size was small, only 36 subjects were enrolled. Clinical activity of anlotinib combined with PD-1 blockades still needs to be confirmed in more patients. Secondly, this study was designed as a retrospective study and some bias could not be avoided. Thirdly, we failed to perform the PD-L1 expression examination and the relevance of PD-L1 expression to clinical activity of the combination regimen needs to be explored subsequently. However, overall, we thought the present study was of potential clinical significance to provide real-world evidence regarding anlotinib combined with PD-1 blockades for patients with previously treated ES-SCLC.

Disclosure

The authors declare that there are no conflicts of interest.

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