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ORIGINAL RESEARCH

Feasibility and Safety of Anlotinib Combined with Immune Checkpoint Inhibitors in Patients with Previously Immunotherapy-Treated Extensive-Stage Small Cell Lung Cancer: A Retrospective Exploratory Study

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Objective: This study aims to evaluate the efficacy and safety of anlotinib combined with immune checkpoint inhibitors (ICIs) in patients with previously immunotherapy-treated extensive-stage small cell lung cancer (ES-SCLC).

Methods: This retrospective study screened ES-SCLC patients who experienced failure after prior ICIs-based treatment and received anlotinib combined with ICIs therapy clinically. Anlotinib was administered at a standard dosage, ICIs regimens included PD-1 inhibitors (Tislelizumab, 200 mg; serplulimab, 4.5 mg/kg) and PD-L1 inhibitors. Efficacy and safety data during treatment were retrospectively collected, and patients were followed up regularly to obtain long-term survival data. Subgroup analysis was conducted to identify the differences in treatment outcomes in various baseline characteristics.

Results: Of the 68 ES-SCLC patients included, no complete response, 22 patients achieved partial response, 28 had stable disease, 14 experienced disease progression and 4 patients were not available for efficacy. Objective response rate (ORR) was 32.4% (95% CI: 21.5–44.8%), and disease control rate (DCR) was 73.5% (95% CI: 61.4–83.5%). The median progression-free survival (PFS) was 5.6 months (95% CI: 3.87–7.33), the median duration of response (DoR) was 6.8 months (95% CI: 0.80–12.83). At the data cutoff date, the median follow-up duration was 12.5 months (range: 1.1–31.5 months), yielding a median overall survival (OS) of 13.2 months (95% CI: 7.09–19.31). Subgroup analysis highlighted that patients who were previously intolerant to immunotherapy had a longer OS (median OS: 15.5 vs 10.9 months, $P = 0.031$). Safety analysis showed that 61 patients (89.7%) experienced treatment-related adverse events (TRAEs) of varying severity with 37 patients (54.4%) developing grade 3 or higher. The most common TRAEs included fatigue, nausea and vomiting, hypertension, hematologic toxicity, and liver function abnormalities.

Conclusion: Anlotinib combined with ICIs demonstrated that immunotherapy rechallenge in previously ICIs-treated ES-SCLC was feasible and of clinical significance preliminarily. However, larger-scale clinical studies were required to validate these findings subsequently.

Keywords: previously immunotherapy-treated, extensive-stage SCLC, anlotinib, immune checkpoint inhibitors, immune rechallenge, efficacy, safety

Introduction

Lung cancer is the most common malignancy globally, over 1.06 million new cases and approximately 730,000 deaths were reported annually in China.[1] Small cell lung cancer (SCLC) is a highly aggressive subtype, accounting for 10–15% in lung cancer.[2] Extensive-stage small cell lung cancer (ES-SCLC) accounts for approximately 70% of all SCLC patients. It is characterized by a high metastatic potential and rapid proliferation with a 5-year survival rate of less than 5%.[3]

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Although first-line treatment may control the disease in a short term, majority of patients experience rapid progression or relapse after treatment, and subsequent treatment options are extremely limited, leading to poor prognosis. Improving the treatment outcomes for these patients with SCLC has become a key challenge recently.[4]

In recent years, immune checkpoint inhibitors (ICIs) combined with chemotherapy have provided a breakthrough as the first-line treatment in ES-SCLC. IMpower133 study demonstrated that the combination of atezolizumab with carboplatin and etoposide significantly extended the median overall survival (OS) of patients to 12.3 months (10.3 months in chemotherapy) with a median progression-free survival (PFS) of 5.2 months (4.3 months in chemotherapy), and improved the 2-year survival rate from 16% to 22%.[5] Similarly, CASPIAN study showed that the combination of durvalumab with carboplatin or cisplatin and etoposide resulted in a median OS of 13.0 months (10.3 months in chemotherapy) and a 2-year survival rate of 22.9%.[6] Besides PD-L1 inhibitors, PD-1 inhibitors had also demonstrated encouraging efficacy in phase III studies for ES-SCLC. KEYNOTE-604 study assessed the efficacy of pembrolizumab combined with platinum-based chemotherapy and demonstrated a significant extension of median PFS to 4.5 months (4.3 months for chemotherapy; HR = 0.75), and improved the 2-year OS rate from 11.2% to 22.5%.[7] The latest RATIONALE-312 study further evaluated the efficacy of Tislelizumab combined with platinum-based chemotherapy (carboplatin or cisplatin plus etoposide) in ES-SCLC, which showed that the combination treatment extended the median OS from 13.5 months in the chemotherapy group to 15.5 months.[8] These studies further reinforced the central role of ICIs in SCLC treatment. Currently, a total of 7 ICIs had been approved as the first-line treatment for ES-SCLC in China. The combination of ICIs and chemotherapy has become the mainstream treatment option for ES-SCLC patients with coverage of ICIs under national insurance. Despite these findings showing significant improvements in first-line treatment outcomes for ES-SCLC, majority of the patients eventually experienced disease progression or relapse within one year, indicating that the current first-line therapies still offered limited benefits for long-term survival. Therefore, subsequent treatment options needed further optimization.[9]

For patients with ES-SCLC who had previously received immunotherapy, subsequent-line treatment options were quite limited.[10] Topotecan was the only chemotherapy drug approved for second-line treatment of SCLC, demonstrating moderate efficacy in platinum-resistant relapsed patients with an objective response rate (ORR) of approximately 20%–25%, a median PFS of 3–4 months and a median OS of 6–8 months.[11] Unfortunately, research data regarding the use of topotecan in patients with previously immunotherapy-treated SCLC was scanty. Furthermore, topotecan had numerous side effects, particularly bone marrow suppression, which limited its clinical application.[12] Therefore, exploration of more effective and less toxic treatment strategies to improve patients' prognosis remained a key focus of current research.

Immune rechallenge has gained attention as an emerging therapeutic strategy currently. The theoretical basis for immune rechallenge may be the following: despite disease progression after initial ICIs treatment, some patients' tumor microenvironments may regain conditions that are sensitive to immunotherapy. A retrospective study regarding non-small cell lung cancer (NSCLC) patients receiving immune rechallenge after ICI treatment failure showed an ORR of 22.5%, a disease control rate (DCR) of 85.0% and a median PFS of 6.8 months.[13] Additionally, immune rechallenge also demonstrated promising efficacy in esophageal squamous cell carcinoma (ESCC). A retrospective study of patients with ESCC who previously failed ICIs treatment found that the ORR of anlotinib combined with ICIs was 19.1% with a median PFS of 5.6 months and a median OS of 11.1 months, and no serious adverse events were observed.[14] These studies suggested that immune rechallenge might have potential clinical significance in ES-SCLC. However, research progress on immune rechallenge in SCLC remains scanty and warrants further exploration currently.

Anlotinib is a novel multi-targeted tyrosine kinase inhibitor (TKI) that exerts multiple anti-tumor activity by targeting angiogenesis-related signal pathways (eg, vascular endothelial growth factor receptor [VEGFR], fibroblast growth factor receptor [FGFR], platelet-derived growth factor receptor [PDGFR]) and tumor proliferation pathway.[15] ALTER1202 study showed significant efficacy of anlotinib as third-line and above treatment for SCLC with a median PFS of 4.1 months and a median OS of 7.3 months.[16] Additionally, ETERN701 study demonstrated that first-line treatment with anlotinib combined with Benmelstobart (a PD-L1 inhibitor) and chemotherapy significantly improved PFS and OS in patients with SCLC, highlighting the synergistic activity of anlotinib and ICIs.[17]

Moreover, anlotinib may modulate the tumor microenvironment by reducing tumor-associated macrophages and myeloid-derived suppressor cells, enhancing the function of effector T cells, thereby providing synergistic support for the

anti-tumor effects of ICIs.[18] The theoretical basis for combining anlotinib with ICIs lies in their potential for synergistic interaction. Additionally, anlotinib inhibits tumor angiogenesis and reduces immune suppression in the tumor microenvironment, thereby facilitating the infiltration of effector T cells. On the other hand, ICIs block the PD-1/PD-L1 pathway, restoring the anti-tumor activity of effector T cells.[19] And anlotinib may enhance the distribution of ICIs within tumors by alleviating the high-pressure conditions in tumor blood vessels.[20] These mechanisms suggest that combining anlotinib with ICIs may provide a new treatment strategy for SCLC in later-line settings, particularly offering significant survival benefits for patients who have failed immunotherapy previously.

Several retrospective studies had explored the efficacy of anlotinib with ICIs in ES-SCLC, particularly in second-line or later settings.[21,22] However, most of these investigations did not specifically analyze outcomes in patients previously exposed to ICIs, a clinically relevant population whose treatment remained underexplored. Rather than claiming novelty, this study served as an incremental addition to the current evidence, providing complementary insights into the feasibility of immunotherapy rechallenge and antiangiogenic synergy in a subset of patients with high unmet medical needs. Therefore, this study aims to identify the feasibility and safety of anlotinib combined with ICIs in ES-SCLC patients who have failed prior immunotherapy in clinical practice.

Materials and Methods

Study Design and Eligibility Criteria

This study was designed as a single-center, retrospective and exploratory study that included ES-SCLC patients who had previously failed immune-related therapy (disease progression or intolerance) between September 2018 and September 2024. These patients were treated with ICIs-related therapy in clinical practice, and the primary objective of this study was to evaluate the efficacy and safety of anlotinib combined with ICIs in this patient population. As a retrospective analysis, the study was based on the therapeutic records of patients in clinical practice to analyze the efficacy and safety of the combination treatment. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (ethics approval number: 2025-KY-0079). Due to the retrospective design, informed consent was waived for patients.

The inclusion criteria were: (1) histologically or pathologically confirmed SCLC, diagnosed as extensive-stage according to the VALG staging system by imaging;[23] (2) Eastern cooperative oncology group (ECOG) performance status of 0–2 score; (3) age of 18 years or older with no gender restriction; (4) patients were intolerant or progressed to prior ICIs-based therapy (including PD-1 or PD-L1 inhibitors) and subsequently received at least one cycle of anlotinib combined with ICIs (including PD-1 or PD-L1 inhibitors); (5) relatively complete demographic and clinical characteristics. Exclusion criteria included: (1) patients were concomitant with other types of malignancies (except for cured non-melanoma skin cancer or carcinoma in situ of the cervix); (2) patients with active infections, severe cardiopulmonary diseases, liver or kidney dysfunction or other life-threatening uncontrolled serious complications; (3) patients with active brain metastases requiring active treatment (patients with stable, asymptomatic brain metastases requiring no active treatment were permitted to include); (4) substantial missing of baseline clinical characteristics or treatment records. The detailed patient screening process, exclusion reasons and final cohort selection were illustrated in Figure 1. Ultimately, a total of 68 patients with previously immunotherapy-treated ES-SCLC who met the study's retrospective screening criteria and received anlotinib combined with ICIs were included.

Therapeutic Protocol

A total of 68 previously immunotherapy-treated ES-SCLC patients who met the inclusion criteria were enrolled in the study and received at least one cycle of the combination therapy of anlotinib plus ICIs. Anlotinib was administered at a dose of 8–12 mg, taken orally once daily, with a two-week on and one-week off schedule, and every three weeks was one treatment cycle. The ICIs used in this study included PD-1 inhibitors (Tislelizumab 200 mg, Serplulimab 4.5 mg/kg, intravenous infusion, every three weeks) and PD-L1 inhibitors (atezolizumab 1200 mg, adebrelimab 20 mg/kg, intravenous infusion, every three weeks). The treatment with anlotinib combined with ICIs continued until disease progression,

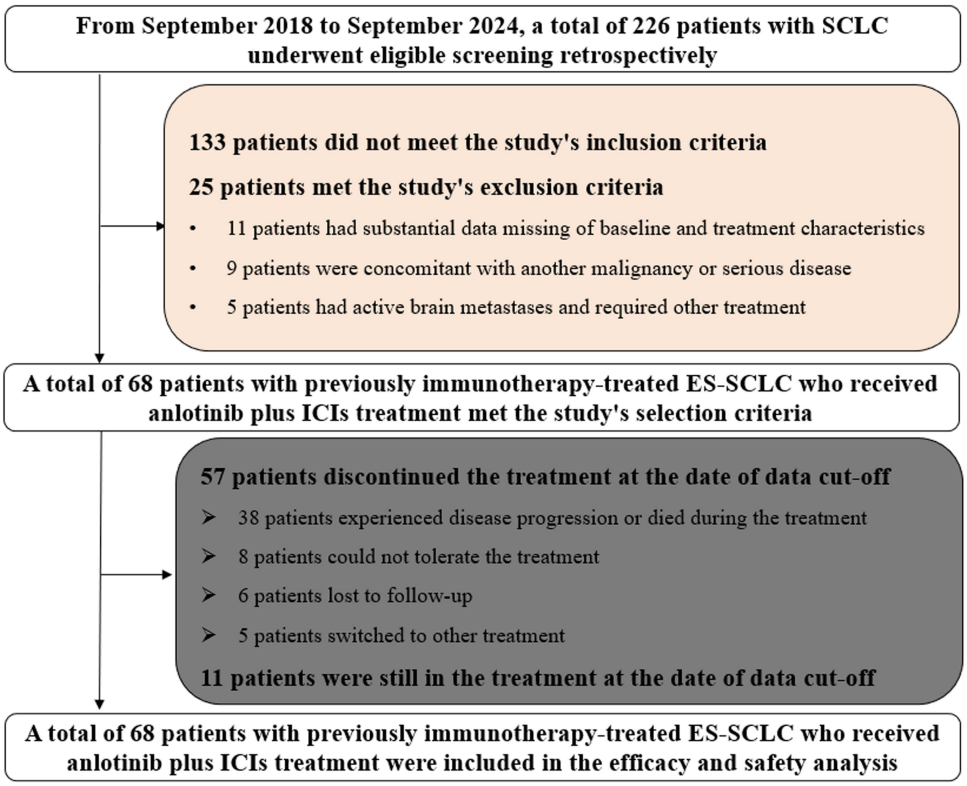

Figure 1 Flowchart of this retrospective study regarding 68 patients with previously immunotherapy-treated ES-SCLC who received anlotinib plus ICIs treatment.

intolerable side effects, or when the investigator determined that the patient might no longer benefit. If intolerable side effects occurred, the combination treatment could be discontinued, and the subsequent single-agent therapy was also permitted in this study.

Efficacy and Safety Assessment

To assess the efficacy of the anlotinib combined with ICI rechallenge regimen in ES-SCLC patients, clinical evaluations were performed every two therapeutic cycles or according to the patient's visit schedule using imaging techniques such as CT or MRI to assess the treatment response of target lesions. Efficacy was evaluated according to RECIST 1.1 criteria, and patient clinical manifestations, imaging, and other relevant examination results were also considered. The primary endpoint of the study was OS, and secondary endpoints included ORR, DCR, PFS and duration of response (DoR), which were defined according to the previous study.[24] All assessments were conducted by independent radiology experts and the research team to ensure the fairness and accuracy of the evaluations. ORR and DCR were based on the best treatment response observed during the therapeutic course of anlotinib combined with ICIs for each patient.

Safety evaluation aimed to assess the tolerance to anlotinib and ICI combination treatment. Adverse events (AEs) were assessed using the common terminology criteria for adverse events (CTCAE) version 5.0. Special attention was given to all AEs that occurred during the treatment process, and each AE was recorded and analyzed in detail based on its severity, frequency, and contributing factors.

Baseline demographic and clinical characteristics for each patient were collected from the hospital's HIS electronic medical record system. Imaging tests performed during treatment were used to assess disease progression. Post-treatment follow-up was mainly conducted by phone. After patients received anlotinib combined with ICIs and treatment failure occurred, follow-up was conducted once a month to gather information on subsequent treatments and death dates by communicating with patients or their relatives. Patients with previously ICIs-treated ES-SCLC who received anlotinib combined with ICIs between September 2018 and September 2024 were retrospectively identified. The data cutoff for survival follow-up was January 20, 2025, allowing adequate time to assess PFS and OS outcomes after treatment

initiation. All patients included had initiated treatment prior to September 2024 and were followed until disease progression, death or the data cutoff date, whichever occurred first.

Statistical Analysis

Data was analyzed using SPSS software (version 25.0). Continuous variables were presented as median and ranges and categorical variables were presented as frequency (percentage). ORR was defined as the percentage of patients achieving complete response (CR) or partial response (PR), DCR was defined as the percentage of patients achieving CR, PR or stable disease (SD). Patients with no evaluable response were considered non-responders and included in the denominator for proportion calculations. Survival data were processed using StataMP 14.0 software and presented using Kaplan–Meier survival curves. DoR was defined as the duration of response among patients who achieved CR or PR. PFS and OS were defined according to previous clinical study.[25] Additionally, subgroup analysis of baseline clinical characteristics and OS correlations were conducted using the Log rank test. Variables with statistically significant differences in univariate analysis were included in the multivariable Cox regression model for adjustment. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Demographic and baseline clinical characteristics of the 68 patients with previously immunotherapy-treated ES-SCLC were shown in Table 1. The enrolled patients displayed typical characteristics of ES-SCLC and were clinically representative of this patient population. The median age was 61 years (range: 21–77 years), and the majority of patients were male (75.0%). Of the enrolled patients, 24 (35.3%) received first-line therapy, while 44 (64.7%) had

Table 1 Baseline Characteristics of the 68 Patients with ES-SCLC

Baseline Characteristics	Total (N = 68)	Percentage
Age (year)		
Median (range)	61 (21–77)	
>61	31	45.6%
≤61	37	54.4%
Gender		
Male	51	75.0%
Female	17	25.0%
ECOG performance status		
0–1	53	77.9%
2	15	22.1%
Pathological stage		
Extensive stage	68	100.0%
Smoking status		
Non-smoker	11	16.2%
Former smoker	57	83.8%
Lines of previous treatment		
First-line	24	35.3%
Second-line or more	44	64.7%
Response to platinum-based treatment		
Platinum-sensitive	21	30.9%
Platinum-resistant	47	69.1%
Other systemic treatments between immunotherapy lines		
No	55	80.9%
Yes	13	19.1%

(*Continued*)

Table 1 (Continued).

Baseline Characteristics	Total (N = 68)	Percentage
Brain metastasis		
Present	18	26.5%
Absent	50	73.5%
Type of prior immunotherapy		
PD-1 Inhibitors	21	30.9%
PD-L1 inhibitors	47	69.1%
Reason for prior immunotherapy failure		
Progression	53	77.9%
Intolerance	15	22.1%
Radiotherapy status		
Yes	13	19.1%
No	55	80.9%
Anlotinib dosage (mg)		
8	17	25.0%
10	40	58.8%
12	11	16.2%
Immunotherapy types		
Tislelizumab	25	36.8%
Serplulimab	17	25.0%
Atezolizumab	15	22.1%
Adebrelimab	11	16.1%

received second-line or subsequent treatments previously. About 69.1% were platinum-resistant disease (defined as progression within 6 months). Thirteen patients (19.1%) received other systemic therapies between two immunotherapy lines, 18 patients had stable brain metastasis. Prior immunotherapy included PD-1 inhibitors in 30.9% and PD-L1 inhibitors in 69.1% of the patients. Regarding the failure of prior immunotherapy, 77.9% of patients experienced disease progression, and 22.1% were intolerant disease. The immunotherapy types used for the rechallenge were Tislelizumab (25 patients), Serplulimab (17 patients), Atezolizumab (15 patients) and Adebrelimab (11 patients). Additionally, a total of 13 patients (19.1%) received localized radiotherapy during their treatment course, primarily for local disease control or symptom palliation (eg, bone metastases or airway obstruction). These radiotherapy interventions were administered as needed clinically and were not part of a pre-specified combination protocol with anlotinib and ICIs.

Efficacy of Anlotinib Combined with ICIs in Patients with Previously Immunotherapy-Treated ES-SCLC

This study retrospectively collected the best treatment response during therapy and assessed it according to RECIST v1.1 criteria. After anlotinib combined with ICIs treatment, no patients achieved CR. Twenty-two patients (32.4%) achieved PR, 28 patients (41.2%) had SD, 14 patients (20.6%) experienced disease progression (PD), and 4 patients (5.9%) were not evaluable due to incomplete imaging assessments. Therefore, the ORR of anlotinib combined with ICIs in 68 patients with previously immunotherapy-treated ES-SCLC was 32.4% (95% confidence interval [CI]: 21.5–44.8%), and the DCR was 73.5% (95% CI: 61.4–83.5%). The waterfall plot showing the best percentage change in target lesions during treatment was presented in Figure 2. In the majority of ES-SCLC patients, target lesions showed varying degrees of shrinkage after receiving anlotinib combined with ICIs. The average percentage shrinkage in the 64 evaluable patients was −11.97%. A notable case was a 40-year-old female patient who had been intolerant to prior atezolizumab combined with chemotherapy previously. After treatment with anlotinib combined with Tislelizumab for almost six months, the patient's target lesions showed a significant reduction of over 80%. The CT

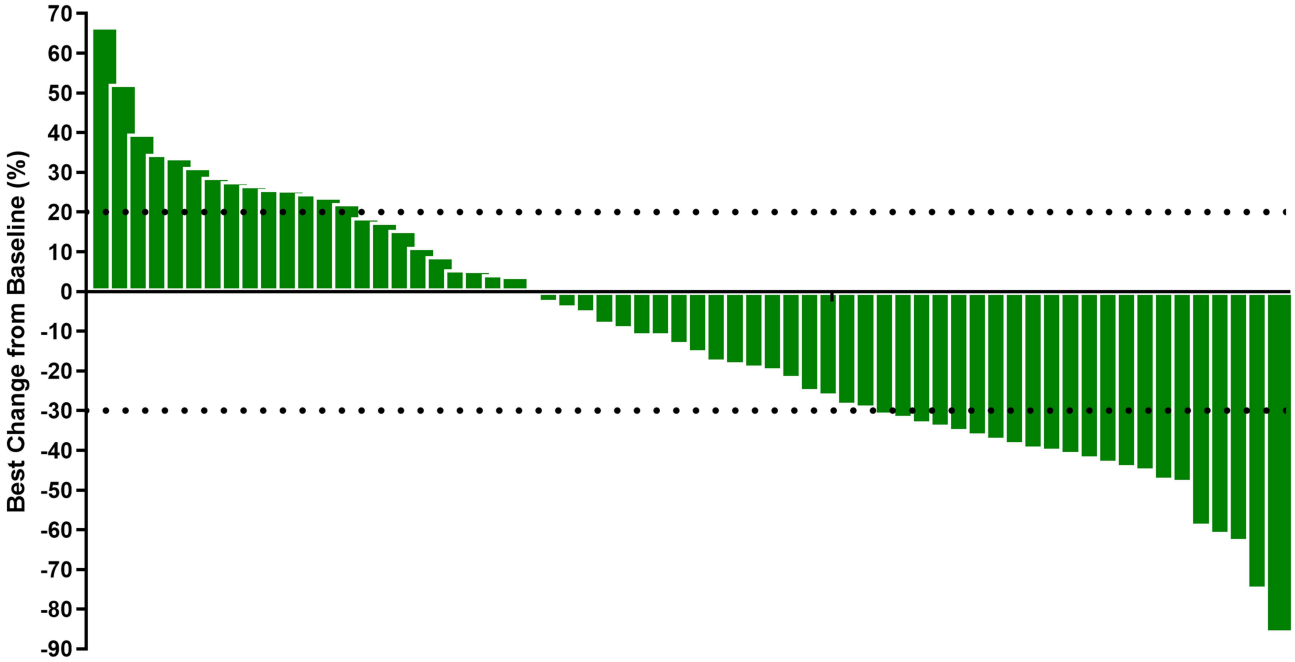

Figure 2 Waterfall plots of the best changes in target lesions of the 68 patients with previously immunotherapy-treated ES-SCLC who received anlotinib plus ICIs treatment.

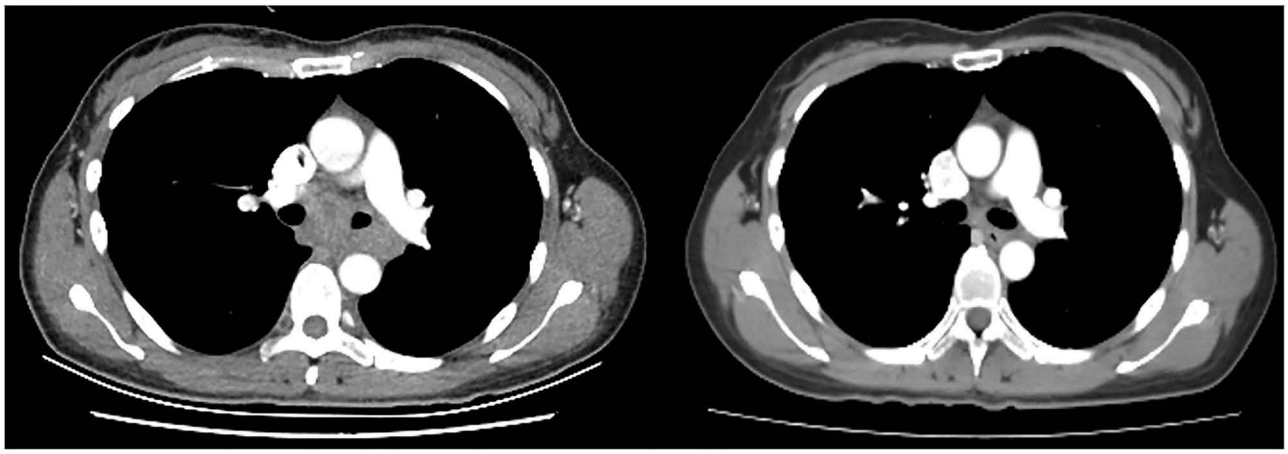

Figure 3 CT scan results of the changes for target lesions in the lung site of a female patient with ES-SCLC before and after the treatment of anlotinib plus tislelizumab.

scan comparison before and after treatment was shown in Figure 3, demonstrating significant benefit from anlotinib plus immunotherapy regimen treatment.

Prognosis of Anlotinib Combined with ICIs in Patients with Previously Immunotherapy-Treated ES-SCLC

As mentioned previously, by the date of data cutoff, 11 patients were still receiving anlotinib combined with ICIs treatment. This study analyzed the DoR of the 22 patients who achieved PR first. DoR was defined as the duration from first PR to subsequent PD or death. The results were presented in Figure 4. The median DoR of the 22 patients who achieved PR was 6.8 months (95% CI: 0.80–12.83) with a 12-month DoR rate of 40.4% (95% CI: 20.3–59.8%) and a 20-month DoR rate of 30.3% (95% CI: 10.4–53.3%).

In PFS analysis, 49 patients (72.1%) had experienced disease progression or death by the date of data cutoff. The PFS survival curve was shown in Figure 5. The median PFS of the 68 patients receiving anlotinib combined with ICIs was 5.6

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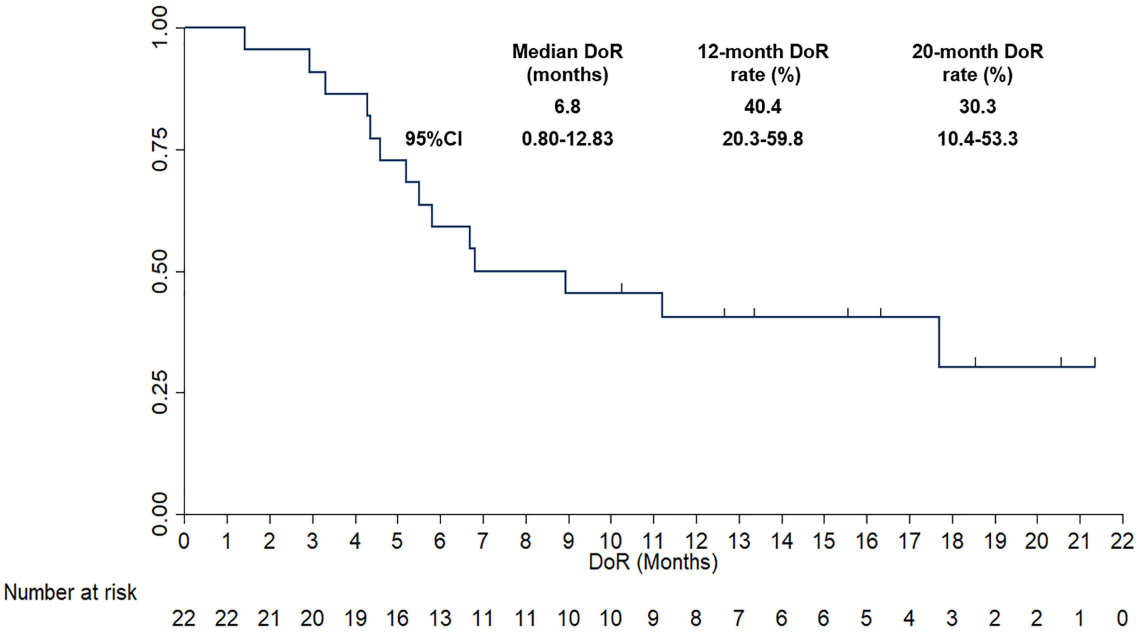

Figure 4 Duration of response among the 22 patients with ES-SCLC who achieved partial response.

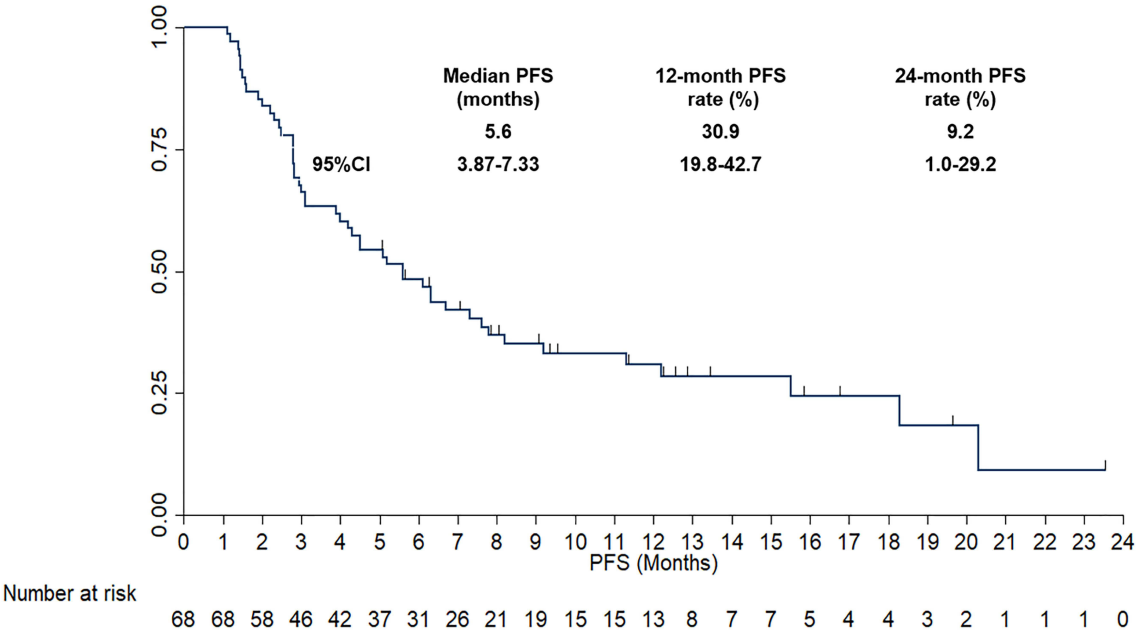

Figure 5 Progression-free survival of the 68 patients with previously immunotherapy-treated ES-SCLC who received anlotinib plus ICIs treatment.

months (95% CI: 3.87–7.33) with a 12-month PFS rate of 30.9% (95% CI: 19.8–42.7%) and a 24-month PFS rate of 9.2% (95% CI: 1.0–29.2%). Interestingly, the median PFS of patients receiving 8 mg, 10 mg and 12 mg anlotinib was 3.0 months (95% CI: 1.54–4.46), 6.1 months (95% CI: 3.71–8.49) and 7.8 months (95% CI: 0.00–17.91), respectively, which showed a trend toward statistical significance ($P = 0.136$).

By the date of data cutoff (January 20, 2025), the median follow-up duration for this study was 12.5 months (range: 1.1–31.5 months), and 44 patients (64.7%) were detected of death events. The OS survival curve was shown in Figure 6, the median OS of the 68 patients with previously immunotherapy-treated ES-SCLC receiving anlotinib combined with

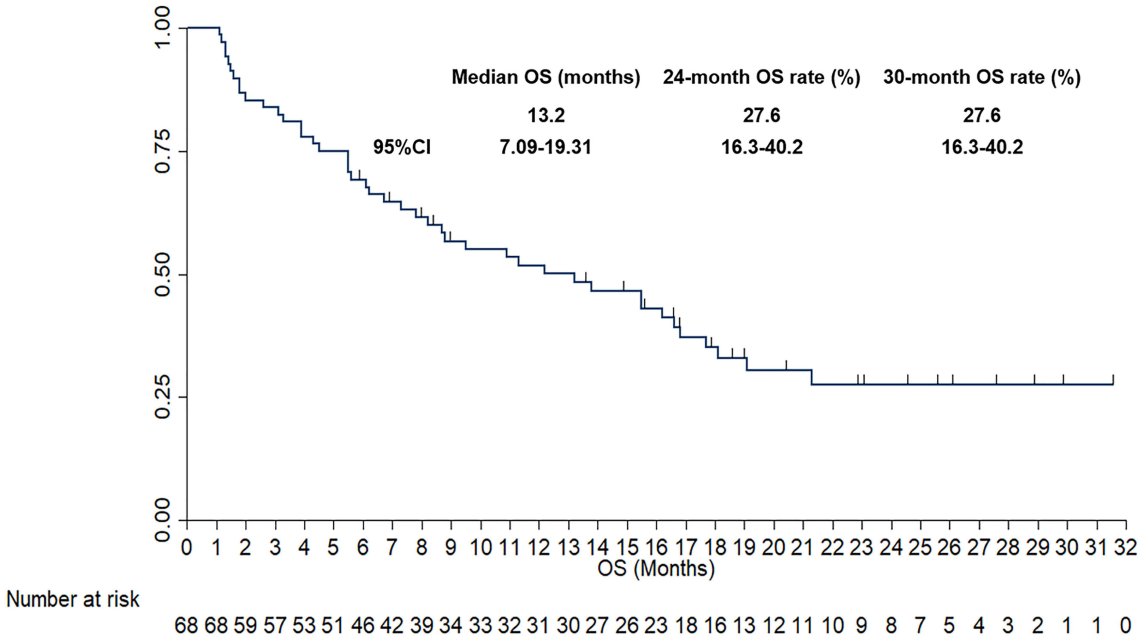

Figure 6 Overall survival of the 68 patients with previously immunotherapy-treated ES-SCLC who received anlotinib plus ICIs treatment.

ICIs was 13.2 months (95% CI: 7.09–19.31) with the 24-month and 30-month OS rates both of 27.6% (95% CI: 16.3–40.2%).

Additionally, this study further explored the association between baseline clinical characteristic subgroups and OS, which was shown in Table 2. Most baseline clinical subgroups showed balanced benefits from the combination treatment

Table 2 Association Analysis Between OS of 68 Patients with ES-SCLC and Baseline Characteristic Subgroups in Univariate Analysis and Multivariate Cox Analysis

Baseline Characteristics	Median OS (95% CI)	*P* (univariate)	Multivariate Analysis	
			HR (95% CI)	*P*
Age (year)		0.616		
>61	13.2 (8.26–18.14)			
≤61	13.8 (6.67–20.93)			
Gender		0.531		
Male	12.2 (6.83–17.57)			
Female	15.5 (8.89–22.11)			
ECOG performance status		0.021	0.60 (0.37–0.90)	0.031
0–1	16.2 (9.52–22.88)			
2	9.5 (6.13–12.87)			
Smoking status		0.315		
Non-smoker	15.5 (8.21–22.79)			
Former smoker	12.2 (6.89–17.51)			
Lines of previous treatment		0.637		
First-line	13.8 (6.89–20.71)			
Second-line or more	11.3 (7.11–15.49)			
Response to platinum-based treatment		0.183	0.91 (0.72–1.25)	0.216
Platinum-sensitive	15.5 (8.85–22.15)			
Platinum-resistant	10.9 (6.83–14.97)			

(*Continued*)

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Table 2 (Continued).

Baseline Characteristics	Median OS (95% CI)	*P* (univariate)	Multivariate Analysis	
			HR (95% CI)	*P*
Other systemic treatments between immunotherapy lines		0.432		
No	13.8 (7.33–20.27)			
Yes	12.2 (6.75–17.65)			
Brain metastasis		0.524		
Present	11.3 (8.13–14.47)			
Absent	13.8 (7.02–20.58)			
Type of prior immunotherapy		0.736	0.95 (0.89–1.18)	0.789
PD-1 Inhibitors	13.2 (7.35–19.05)			
PD-L1 inhibitors	12.2 (6.89–17.51)			
Reason for prior immunotherapy failure		0.031	1.41 (1.07–1.99)	0.043
Progression	10.9 (6.67–15.13)			
Intolerance	15.5 (8.35–22.65)			
Radiotherapy status		0.313		
Yes	12.2 (8.81–15.59)			
No	13.8 (8.21–19.39)			
Anlotinib dosage (mg)		0.497	1.13 (0.87–1.45)	0.515
8	8.8 (6.13–11.47)			
10	15.5 (8.34–22.66)			
12	12.2 (8.68–15.72)			
Immunotherapy types		0.568		
Tislelizumab	13.2 (8.31–18.09)			
Serplulimab	12.2 (6.55–17.85)			
Atezolizumab	13.8 (8.11–19.49)			
Adebrelimab	11.3 (7.22–15.38)			

($P > 0.05$). However, the ECOG performance status and reason for prior immunotherapy failure significantly influenced OS in univariate analysis: patients with ECOG scores of 0–1 had a median OS of 16.2 months, compared to 9.5 months for those with an ECOG score of 2 with a statistically significant difference ($P = 0.021$). Patients who were intolerant to prior immunotherapy had a better OS than those with disease progression (median OS: 15.5 months vs 10.9 months, $P = 0.031$). Therefore, these two variables were included in the multivariable Cox model for adjustment. Additionally, different ICI types (PD-1 vs PD-L1), varying doses of anlotinib and response to platinum-based treatment ($P < 0.20$ in univariate analysis) were also included for multivariate adjustment based on clinical relevance and prior literature, as well as their availability in our dataset. After multivariate correction, the ECOG performance status (HR = 0.60, $P = 0.031$) and reason for prior immunotherapy failure (HR = 1.41, $P = 0.043$) remained independent risk factors for OS.

Safety Profile of Anlotinib Combined with ICIs in Patients with Previously Immunotherapy-Treated ES-SCLC

AEs observed during treatment were retrospectively collected for all enrolled patients, and the results were shown in Table 3. A total of 61 patients (89.7%) experienced treatment-related adverse events (TRAEs) of varying severity with 37 patients (54.4%) experiencing grade ≥ 3. The most common TRAEs were fatigue (55.9%), nausea and vomiting (45.6%), hypertension (41.2%), hematologic toxicity (33.8%), liver function abnormality (26.5%), anorexia (22.1%), hand-foot syndrome (16.2%), pneumonia (11.8%) and rash (7.4%). The grade 3 or higher TRAEs included nausea and vomiting, hypertension, fatigue, liver function abnormality, hematologic toxicity, anorexia, and pneumonia. No unexpected or grade 5 TRAEs was detected during the study. The overall safety profile of anlotinib plus ICI among patients with previously-immunotherapy treated ES-SCLC was acceptable and manageable.

Table 3 Safety Profile of the 68 Patients with ES-SCLC Who Received Anlotinib Plus ICIs Treatment

Safety Profile	Total (N, %)	Grade 1–2 (N, %)	Grade ≥ 3 (N, %)
Treatment-related adverse events	61 (89.7)		37 (54.4)
Fatigue	38 (55.9)	29 (42.6)	9 (13.3)
Nausea and vomiting	31 (45.6)	21 (30.9)	10 (14.7)
Hypertension	28 (41.2)	18 (26.5)	10 (14.7)
Hematologic toxicity	23 (33.8)	18 (26.5)	5 (7.3)
Liver function abnormality	18 (26.5)	10 (14.7)	8 (11.8)
Anorexia	15 (22.1)	12 (17.7)	3 (4.4)
Hand-foot syndrome	11 (16.2)	9 (13.3)	2 (2.9)
Pneumonia	8 (11.8)	7 (10.3)	1 (1.5)
Rash	5 (7.4)	5 (7.4)	0 (0.0)

Discussion

This study aimed to evaluate the feasibility and safety of anlotinib combined with ICIs in patients with previously immunotherapy-treated ES-SCLC in clinical practice. A retrospective analysis of 68 patients with ES-SCLC suggested that the anlotinib combined with ICIs demonstrated potential efficacy and manageable safety profile in ES-SCLC. ECOG performance status and reason for prior immunotherapy failure might serve as predictive indicators for prognosis of this regimen.

Current ICIs combined with chemotherapy significantly improve first-line treatment outcomes in ES-SCLC and provide substantial survival benefits with the longest median OS exceeding 19 months.[17] Notably, the recent Phase III ASTRUM-005 trial of the anti-PD-1 antibody serplulimab plus chemotherapy demonstrates a significant improvement in OS in first-line ES-SCLC (median OS: 15.4 vs 13.3 months),[26] highlighting the advances of PD-1-targeted therapy in this disease. Unfortunately, the median PFS of patients remains generally below 7 months, and subsequent treatment options are extremely limited.[27] This study focused on this clinical dilemma and, for the first time, identified the efficacy and safety of anlotinib combined with ICIs in ES-SCLC patients who failed prior immunotherapy using real-world data. Although this study lacked a formal control group, the observed median OS of 13.2 months and median PFS of 5.6 months compared favorably with historical data from second-line ES-SCLC studies. For example, the median OS in patients receiving topotecan monotherapy or placebo following ICI failure was typically 7–9 months, suggesting potential clinical benefit with the anlotinib–ICI combination.[11,12] However, such cross-trial comparisons should be interpreted cautiously due to differences in baseline characteristics and study design. These findings not only provided important evidence for the application of immunotherapy rechallenge strategies in SCLC but also suggested that the synergistic effect of anti-angiogenesis and immunotherapy might be key to overcome the bottleneck in subsequent treatment.[28]

The 68 patients with ES-SCLC enrolled in this study had a median age of 61 years, and the patients were of typical characteristics of the clinically common SCLC population.[29] Among them, 69.1% of patients had platinum-resistant disease, and 77.9% failed prior immunotherapy (disease progression). These data reflected the treatment dilemmas currently faced by SCLC patients, as most patients did not achieve sustained response after initial immunotherapy, and treatment options were scanty in subsequent lines.[30] Notably, the proportion of patients who had previously received PD-L1 inhibitors (69.1%) was significantly higher than those who received PD-1 inhibitors (30.9%). This was likely due to the earlier approval of PD-L1 inhibitors (such as atezolizumab, durvalumab) as first-line therapy in China (before 2020), which was widely applied in clinical practice. Additionally, 65.7% of patients had received second-line or later treatments, indicating that the anlotinib combined with ICIs was predominantly used in later lines of treatment. Considering that anlotinib had a third-line indication and some PD-1 inhibitors exhibited medical evidence in second-line application, this regimen was clinically relevant and fitted current clinical practice. In this study, the ORR of the 68 patients with previously immunotherapy-treated ES-SCLC receiving anlotinib combined with ICIs was 32.4%, DCR was 73.5%, and median PFS was 5.6 months. Compared to historical data, this efficacy was superior to anlotinib

monotherapy or ICI monotherapy in treating SCLC (anlotinib: ORR = 5.0%, DCR = 71.6%, median PFS = 4.1 months; ICI: ORR = 10%–20%, DCR < 30%, median PFS < 2 months).[16] Additionally, the results also outperformed topotecan monotherapy (ORR < 25%, DCR < 40%, median PFS = 3–4 months).[31] From the perspective of combination therapy, the data from this study was consistent with previous research by Qing Chen et al who conducted a retrospective study comparing anlotinib plus ICIs versus anlotinib as later-line treatment for SCLC (ORR = 19.4%, DCR = 87.1%, median PFS = 7.5 months).[32] Furthermore, the average shrinkage degree of target lesions in the 64 available patients in this study was −11.97%, which suggested that anlotinib combined with ICIs still exerted synergistic therapeutic effects in previously immunotherapy-treated ES-SCLC. Possible mechanisms might be attributed to several factors: vessel normalization (anlotinib inhibited VEGFR pathways, reduced tumor interstitial pressure, and promoted CD8+ T cell infiltration), reversal of the immunosuppressive microenvironment (anlotinib reduced the proportion of myeloid-derived suppressor cells [MDSCs] and regulatory T cells [Tregs], while promoting the M2-to-M1 macrophage transition), and hypoxia regulation (anlotinib downregulated hypoxia-inducible factor HIF-1α, alleviating tumor hypoxia and enhancing ICI blockade effects).[33]

Moreover, the median DoR of 22 patients who achieved PR was 6.8 months with a 12-month DoR rate of 40.4%. This result highlighted that most patients who achieved PR might maintain response for a longer duration, which was of significant therapeutic implications in SCLC immunotherapy, as patients often had limited response duration following ICIs treatment (typically <6 months).[34] Therefore, anlotinib plus ICIs treatment might prolong response duration in some SCLC patients, thus translating into long-term survival benefits.

In this study, OS was chosen as the primary endpoint. As retrospective studies often faced challenges in obtaining efficacy data in clinical practice, OS was an objective gold standard for assessment, which was consistent with the design of other retrospective study.[35] After a median follow-up of 12.5 months, the median OS of ES-SCLC patients receiving anlotinib combined with ICIs was 13.2 months. This data demonstrated a significant advantage over traditional second-line chemotherapy, where topotecan's median OS was 6–8 months, and lurbinectedin's median OS was only 9.3 months.[36] The OS data also outperformed results from anlotinib monotherapy (7.3 months) or ICI monotherapy (7.7 months).[37] This improvement might be that patients previously eligible for ICIs therapy, especially PD-L1 inhibitors, tended to confer better economic status and higher adherence to treatment, facilitating better acceptance of new therapeutic options, contributing to longer OS ultimately. Additionally, OS data further suggested that immune rechallenge regimens usually involved combining ICIs with chemotherapy or targeted agents (eg, anti-angiogenesis drugs), and this multimodal treatment approach might enhance the immune system's ability to clear tumors, thus extending survival benefit.

The subgroup analysis of this study indicated that patients with ECOG performance status of 0–1 had significantly longer OS, suggesting that these patients might benefit from anlotinib plus ICIs treatment. Patients with poor performance status (ECOG ≥ 2) were often accompanied by chronic inflammation, which might lead to T cell exhaustion and an increase in immunosuppressive cells (such as MDSCs, Tregs), thus compromising the efficacy of ICIs.[38] Interestingly, subgroup analysis also found that patients who were intolerant to prior immunotherapy had a significantly longer median OS (15.5 months) than those with disease progression following prior ICIs treatment (10.9 months, $P = 0.031$). This phenomenon was consistent with the "treatment window" hypothesis in NSCLC: patients who discontinued treatment due to toxicity might not yet have fully developed immune escape, while those with disease progression might have developed resistance through upregulation of alternative immune checkpoints (eg, TIM-3, LAG-3) or recruitment of immunosuppressive cells (eg, Tregs).[39] However, in this study, only 15 patients were intolerant to prior immunotherapy, and further validation in larger-scale studies was needed. Moreover, this study included both platinum-resistant and platinum-sensitive patients. The results showed that the median OS for platinum-resistant patients was 10.9 months, slightly lower than platinum-sensitive patients (15.5 months), while the difference was not statistically significant ($P = 0.183$). This finding was consistent with the results of Lian Yu et al, who also found no significant difference in OS between platinum-sensitive and platinum-resistant patients (median OS 10.8 vs 6.2 months, $P = 0.256$).[24] The reason might be related to the fact that anlotinib inhibited platinum-resistance-associated pathways (eg, ABC transporters) and improved the immune microenvironment, partially reversing platinum resistance and immune resistance.[40] No significant

statistical differences were found in other subgroups, suggesting that anlotinib combined with ICIs offered balanced efficacy for previously immunotherapy-treated ES-SCLC in clinical practice.

Among the 68 patients with previously immunotherapy-treated ES-SCLC receiving anlotinib combined with ICIs, 89.7% experienced TRAEs of varying severity with 54.4% experiencing grade ≥ 3. This safety profile was consistent with previous study of anlotinib monotherapy.[16] The most common TRAEs included fatigue (55.9%), nausea and vomiting (45.6%) and hypertension (41.2%). The incidence of hypertension was similar to that observed in anlotinib monotherapy, while the incidence of pneumonia (11.8%) was significantly lower than that observed in PD-1 inhibitors monotherapy (20–30%).[41] This difference might be due to the inhibition of VEGF pathways by anlotinib, which reduced pulmonary edema.[42] Hypertension and hand-foot syndrome, common TRAEs, might be caused by anlotinib, while pneumonia might be resulted from ICIs.[43] In addition, anlotinib plus ICIs might increase the incidence of liver toxicity, especially in patients with pre-existing liver dysfunction.[44] Therefore, attention should be paid when using anlotinib combined with ICIs in patients with baseline liver dysfunction. Overall, no unexpected or grade 5 TRAEs were observed, and the combination regimen was considered as safety and manageable in patients with previously immunotherapy-treated ES-SCLC.

Despite the promising results, some limitations should be acknowledged in this study objectively: Firstly, the bias inherent existed in the single-center retrospective study with limited sample size, the higher proportion of patients with ECOG 0–1 performance status, and the exclusion of patients with active brain metastases might have overestimated the actual efficacy of the regimen. Given the small sample size in certain subgroups (eg, ECOG score of 2, previous ICI intolerance), the observed differences in survival outcomes might be prone to instability or overestimation. And due to the multiple subgroup comparisons conducted in this exploratory analysis, there was a risk of type I error. Although no formal multiple testing correction (eg, FDR) was applied, all results should be interpreted cautiously. And these exploratory findings required confirmation in larger, prospective cohorts subsequently. Secondly, the heterogeneity of ICIs used in our cohort might have influenced clinical outcomes and should be considered when interpreting the findings. Future prospective study with standardized immunotherapy regimens were warranted to validate these observations. And the varying initial dosage of anlotinib (8–12 mg) might have impacted the accuracy of efficacy assessment, reflecting the flexibility of clinical practice. Thirdly, this study failed to perform biomarker analysis, such as PD-L1 expression, tumor mutational burden (TMB), or circulating tumor DNA (ctDNA), which limited the potential for precision stratification. Lastly, another limitation of this study was the absence of a chemotherapy-only comparison group, which might compromise the interpretability of the findings. Nevertheless, the observed efficacy outcomes were numerically superior to historical data for topotecan monotherapy in similar settings, providing preliminary clinical rationale for further evaluation of this combination. Despite these limitations, this study provided valuable medical evidence for treatment strategy selection in ES-SCLC after the failure of prior immunotherapy. Future research should involve larger-scale, multicenter and prospective clinical trials to improve data quality and the reliability of results, ultimately guiding clinical practice more effectively. These studies might help optimize treatment regimens for previously immunotherapy-treated ES-SCLC, providing more efficacious treatment options for long-term benefits in ES-SCLC clinically.

Conclusion

Anlotinib plus ICIs demonstrated potential efficacy and manageable safety in patients with previously ICIs-treated ES-SCLC in clinical practice. Immunotherapy rechallenge in previously ICI-treated ES-SCLC was feasible and of clinical significance preliminarily. Despite the encouraging results, further validation in larger, multi-center trials was needed to confirm the long-term efficacy and safety subsequently.

Ethics Statement

Despite the informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

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Disclosure

The authors declare that there are no conflicts of interest.

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