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ORIGINAL ARTICLE

CANCER INNOVATION

Combination therapy using low-dose anlotinib and immune checkpoint inhibitors for extensive-stage small cell lung cancer

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Abstract

Background: This study evaluated the efficacy and safety of low-dose anlotinib combined with immune checkpoint inhibitors as second-line or later treatment for extensive-stage small cell lung cancer (ES-SCLC).

Methods: The study included 42 patients with ES-SCLC who were treated with low-dose anlotinib combined with programmed cell death protein 1/programmed cell death-ligand 1 inhibitors at Henan Cancer Hospital between March 2019 and August 2022. We retrospectively analyzed the efficacy and safety data for these patients. Indicators assessed included progression-free survival (PFS), overall survival (OS), the overall response rate (ORR), the disease control rate (DCR), and adverse events (AEs). Prognostic factors were identified in univariate and multivariate analyses.

Results: Median PFS was 11.0 months (95% CI: 7.868–14.132) and median OS was 17.3 months (95% CI: 11.517–23.083). The ORR was 28.5% and the DCR was 95.2%. Treatment-related AEs were noted in 27 patients (64.3%), the most common of which was thyroid dysfunction (26.2%). Grade 3/4 treatment-related AEs were observed in two patients (4.8%).

Abbreviations: AEs, adverse events; CI, confidence interval; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; ICIs, immune checkpoint inhibitors; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; SCLC, small cell lung cancer; VALG, Veterans Administration Lung Study Group.

Conclusions: A combination of low-dose anlotinib and immune checkpoint inhibitors as second-line or later treatment for ES-SCLC may achieve longer PFS and OS and have manageable AEs.

KEYWORDS
combination immunotherapy, extensive-stage small cell lung cancer, immune checkpoint inhibitors, low-dose antiangiogenic drugs

1 | INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers. According to the Veterans Administration Lung Study Group (VALG) staging system, SCLC is categorized as limited-stage or extensive-stage (ES). Owing to its rapid growth and lack of typical clinical symptoms, about two-thirds of SCLC patients are diagnosed with ES disease at the time of initial diagnosis [1, 2]. In recent decades, the standard first-line chemotherapy for ES-SCLC has been etoposide-platinum. However, agent resistance quickly emerges and disease relapse inevitably occurs in most patients. Topotecan is the only approved second-line agent used in the treatment of ES-SCLC in the European Union. However, topotecan not only has significant hematological toxicity but also has had much lower efficacy than expected. Furthermore, there is no standard follow-up treatment for ES-SCLC [3, 4].

In recent years, immune checkpoint inhibitors (ICIs), which include inhibitors of programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1), have attracted an increasing amount of research interest in the field of tumor therapy because of their unique mechanism of action. SCLC is characterized by genomic instability, a high tumor mutational burden, and high neoantigen diversity, so is theoretically sensitive to immunotherapy. However, an increasing number of studies have demonstrated that only a small percentage of patients with SCLC respond to single-agent ICI therapy [5]. Therefore, researchers are still trying to find the ideal combination of agents for immunotherapy.

Angiogenesis plays an essential role in tumor growth. Vascular endothelial growth factor is the most important protein with proangiogenic function. It is overexpressed in SCLC, and its overexpression is associated with a poor prognosis. Anlotinib is an orally administered small-molecule multitargeted tyrosine kinase receptor inhibitor that targets the vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, and c-Kit [6]. In the multicenter, randomized, double-blind, placebo-controlled Phase II ALTER1202 trial, median progression-free survival (PFS), and median overall survival (OS) were significantly longer in the anlotinib group than in the placebo group (4.1 months vs 0.7 months and 7.3 months vs 4.9 months, respectively) [7]. Based on these findings, anlotinib was approved by the China National Medical Products Administration as a third-line or later treatment for patients with ES-SCLC.

Antiangiogenesis therapy not only promotes the normalization of tumor vessels but can also change the tumor's immune environment from immunosuppressive to immunosupportive, thereby enhancing the efficacy of immunotherapy [8, 9]. Anlotinib has synergistic antitumor efficacy when combined with PD-1 inhibitors by promoting coactivation of innate immune cells [10]. Prospective clinical research has found that anlotinib plus anti-PD-1 antibody therapy has reliable antitumor efficacy and acceptable toxicity in patients with various types of advanced tumors [11]. Furthermore, the results of a retrospective real-world study suggested that a combination of anlotinib and PD-1 blockade may be effective for patients with relapsed SCLC [12]. In most studies, high-dose anlotinib (12 mg taken orally once daily on Days 1–14 of a 21-day cycle) has been used in combination with an ICI.

High doses of antiangiogenesis agents can reduce vascular perfusion and worsen hypoxia in tumor tissue by excessive pruning of tumor vessels. Therefore, the tumor cells ultimately evade surveillance by the immune system, which increases their potential for invasiveness and metastasis. In contrast, low-dose antiangiogenesis agents can trim some abnormal vessels and reshape the rest, producing a “normalized vasculature” [13–15]. In a breast tumor model, low-dose antiangiogenesis agents normalized tumor vessels more efficiently and promoted infiltration and activation of immune effector cells, such as $CD8^+$ T cells and macrophages, within the tumor microenvironment when combined with PD-1 blockade [16]. In another study, relatively low-dose anlotinib significantly reduced tumor vascular density and simultaneously improved vascular perfusion. Furthermore, compared with anlotinib administered alone, low-dose anlotinib plus PD-1 blockade was found to have more reliable antitumor effects and to be

associated with fewer adverse events (AEs) [17]. These findings suggested that a low-dose antiangiogenic agent combined with ICI therapy would be more effective than a high-dose antiangiogenic agent alone in the treatment of malignancy.

In a previous study, we found that low-dose anlotinib (8 or 10 mg orally once daily on Days 1–14 of a 21-day cycle) combined with ICI therapy improved survival in patients with advanced non-SCLC [18]. Therefore, we speculated that this may also be true for ES-SCLC. In this study, we investigated the efficacy and safety of low-dose anlotinib in combination with ICIs as second-line or later treatment for patients with ES-SCLC.

2 | METHODS

2.1 | Research subjects and study design

We retrospectively reviewed the clinical data for patients with ES-SCLC at the Affiliated Cancer Hospital of Zhengzhou University (Henan Cancer Hospital) between March 2019 and August 2022. The inclusion criteria were as follows: diagnosis confirmed by histology or cytology; diagnosis of ES-SCLC based on the VALG staging system, including postoperative recurrence; treatment with at least three cycles of anlotinib (8 or 10 mg orally once daily on a schedule of 2 weeks on/1 week off) in combination with an ICI every 3 weeks until disease progression or intolerance of treatment; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.1. Patients with other malignancies, those with limited-stage SCLC (based on the VALG staging system), and those without baseline imaging data were excluded. The study was performed according to the principles of the Declaration of Helsinki and the World Health Organization Guidelines for Good Clinical Practice.

2.2 | Clinical assessments and follow-up

The efficacy of treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) as a complete response, partial response, stable disease, or progressive disease. The overall response rate (ORR) was defined as the percentage of patients with a complete or partial response and the disease control rate (DCR) as the proportion of patients with a complete response, a partial response, or stable disease. PFS was defined as the interval between the start of treatment with anlotinib and an ICI and disease progression, death, or the last follow-up visit. OS was defined as the interval between the start of treatment with anlotinib and an ICI and death or the last follow-up visit. Safety assessments were performed before each therapy, including medical history, physical examination, and routine laboratory tests (including a complete blood count, liver and renal function tests, and myocardial zymography). AEs were recorded and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.

The main indicators evaluated were PFS, OS, ORR, DCR, and AEs. Follow-up data were obtained by review of medical records, telephone calls, and outpatient visits. The last follow-up was on March 1, 2023.

2.3 | Statistical analysis

Continuous data are presented as the median (range) and categorical data as the number (percentage). Survival data, including PFS and OS, along with their corresponding 95% confidence intervals (CIs), were estimated using the Kaplan–Meier method. Survival outcomes were compared between groups using the log-rank test. Univariate and multivariate analyses to identify factors associated with PFS and OS were performed using a Cox proportional hazards model. All statistical analyses were performed using IBM SPSS statistical software (version 26.0; IBM Corp). p values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Forty-two patients met the eligibility criteria and were enrolled in the study (Supporting Information S1: Figure 1). The median patient age was 61.5 years (range 39–86). Twenty-seven patients (64.3%) were male and 15 (35.7%) were female. The median number of treatments with a combination of low-dose anlotinib and an ICI was 5 (range 3–20). The ECOG score was 0–1 in 83.3% (35/42) of patients and 2 in the remaining 16.7% (7/42). Radiation therapy was administered in 66.7% of patients (28/42); 33.3% (14/42) had brain metastasis and 42.9% (18/42) had metastasis to three or more organs. Furthermore, 35.7% of patients (15/42) received second-line treatment and 50% (21/42) had a history of manageable chronic disease. The ICIs administered were sintilimab ($n = 24$), camrelizumab ($n = 7$), tislelizumab ($n = 4$), toripalimab ($n = 2$), pembrolizumab ($n = 2$), atezolizumab ($n = 1$), durvalumab ($n = 1$), and penpulimab ($n = 1$). The patients' clinical characteristics are shown in Table 1.

TABLE 1 Baseline demographic and clinical characteristics of 42 patients with extensive-stage small cell lung cancer.

Characteristics	No. of patients (%)
Doses of anlotinib	
8 mg	8 (19.0)
10 mg	34 (81.0)
Gender	
Male	27 (64.3)
Female	15 (35.7)
Age (year)	
<65	23 (54.8)
≥65	19 (45.2)
Eastern Cooperative Oncology Group status	
0–1	35 (83.3)
2	7 (16.7)
Smoking history	
Yes	21 (50.0)
No	21 (50.0)
Drinking history	
Yes	17 (40.5)
No	25 (59.5)
Metastatic organs	
≥3	18 (42.9)
<3	24 (57.1)
Brain metastasis	
Yes	14 (33.3)
No	28 (66.7)
Treatment baseline	
Second-line treatment	15 (35.7)
Above second-line treatment	27 (64.3)
Previous radioactive therapy	
Yes	28 (66.7)
No	14 (33.3)
History of chronic disease	
Yes	21 (50.0)
No	21 (50.0)
ICIs in the therapy	
Sintilimab	24 (57.1)
Camrelizumab	7 (16.7)
Tislelizumab	4 (9.5)
Toripalimab	2 (4.8)
Pembrolizumab	2 (4.8)
Atezolizumab	1 (2.4)
Durvalumab	1 (2.4)
Penpulimab	1 (2.4)

Abbreviation: ICIs, immune checkpoint inhibitors.

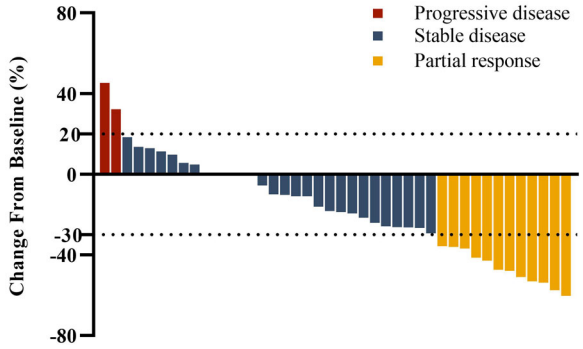

FIGURE 1 Waterfall plot showing the maximum change in the sum of target lesion diameters.

3.2 | Efficacy

We retrospectively evaluated the response to treatment in all patients. No patient achieved a complete response, 12 (28.5%) achieved a partial response, 28 (66.7%) had stable disease, and the remaining 2 (4.8%) had progressive disease, giving an ORR of 28.5% and a DCR of 95.2%. The waterfall plot in Figure 1 shows the change in the sum of target lesion diameters from baseline in response to optimal treatment with low-dose anlotinib combined with immunotherapy in all patients. The median follow-up duration was 22.5 months (95% CI: 19.0–26.0). At the last follow-up, 26 patients (61.9%) had died and 29 (69.0%) had progressive disease. Median PFS was 11.0 months (95% CI: 7.868–14.132; Figure 2a) and median OS was 17.3 months (95% CI: 11.517–23.083; Figure 2b).

3.3 | Relationship between clinical features and the prognosis

We conducted subgroup analyses to determine whether there were any clinical features that were associated with median PFS and median OS. The survival curves for PFS and OS in each subgroup are presented in Figures 3 and 4.

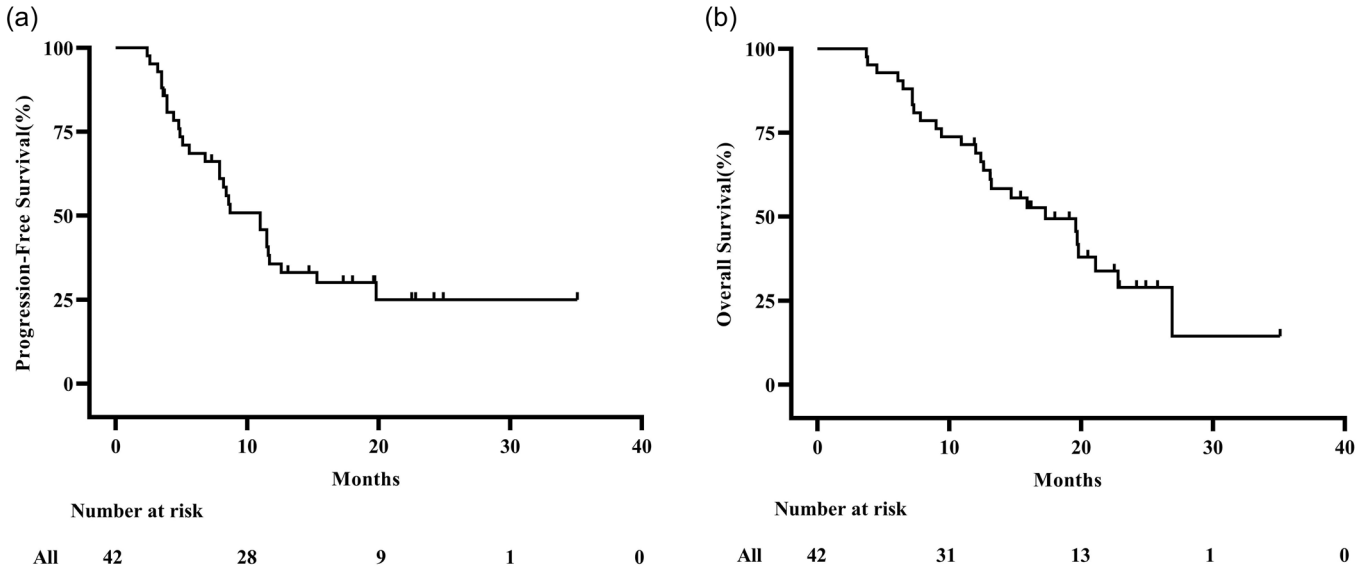

FIGURE 2 Progression-free survival and overall survival in patients who received low-dose anlotinib combined with an immune checkpoint inhibitor. (a) Kaplan–Meier curves showing progression-free survival. (b) Kaplan–Meier curves showing overall survival.

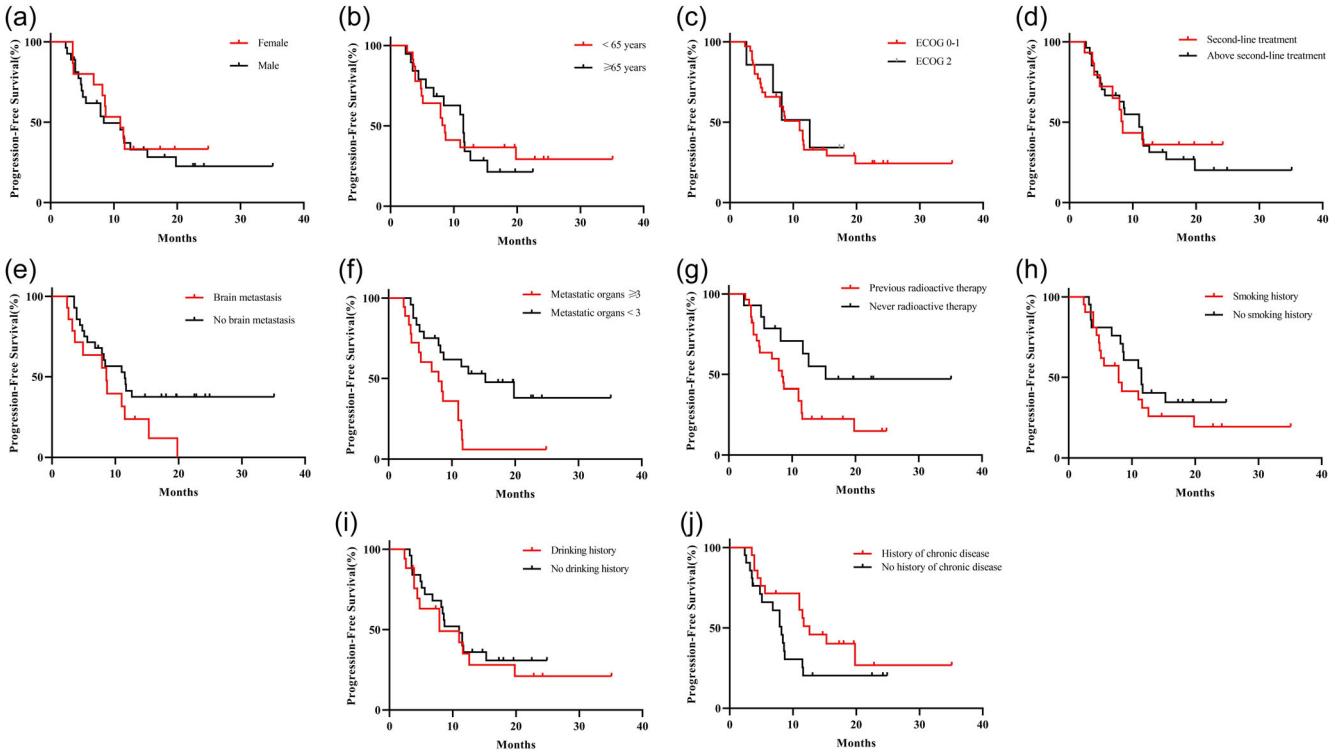

FIGURE 3 Results of subgroup analysis of progression-free survival. The following factors were identified to be important prognostic factors: (a) sex; (b) age; (c) ECOG score; (d) treatment at baseline; (e) brain metastasis; (f) number of organs with metastasis; (g) radiotherapy; (h) history of smoking; (i) history of alcohol consumption; and (j) history of chronic disease. ECOG, Eastern Cooperative Oncology Group.

The clinical features identified as potentially significant in terms of survival outcomes included sex (male or female, Figures 3a and 4a, respectively), age (<65 or ≥65 years, Figures 3b and 4b), ECOG score (0–1 or 2, Figures 3c and 4c), treatment at baseline (second-line or later, Figures 3d and 4d), brain metastasis (yes or no, Figures 3e and 4e), number of organs with metastasis (<3 or ≥3, Figures 3f and 4f), previous radiotherapy

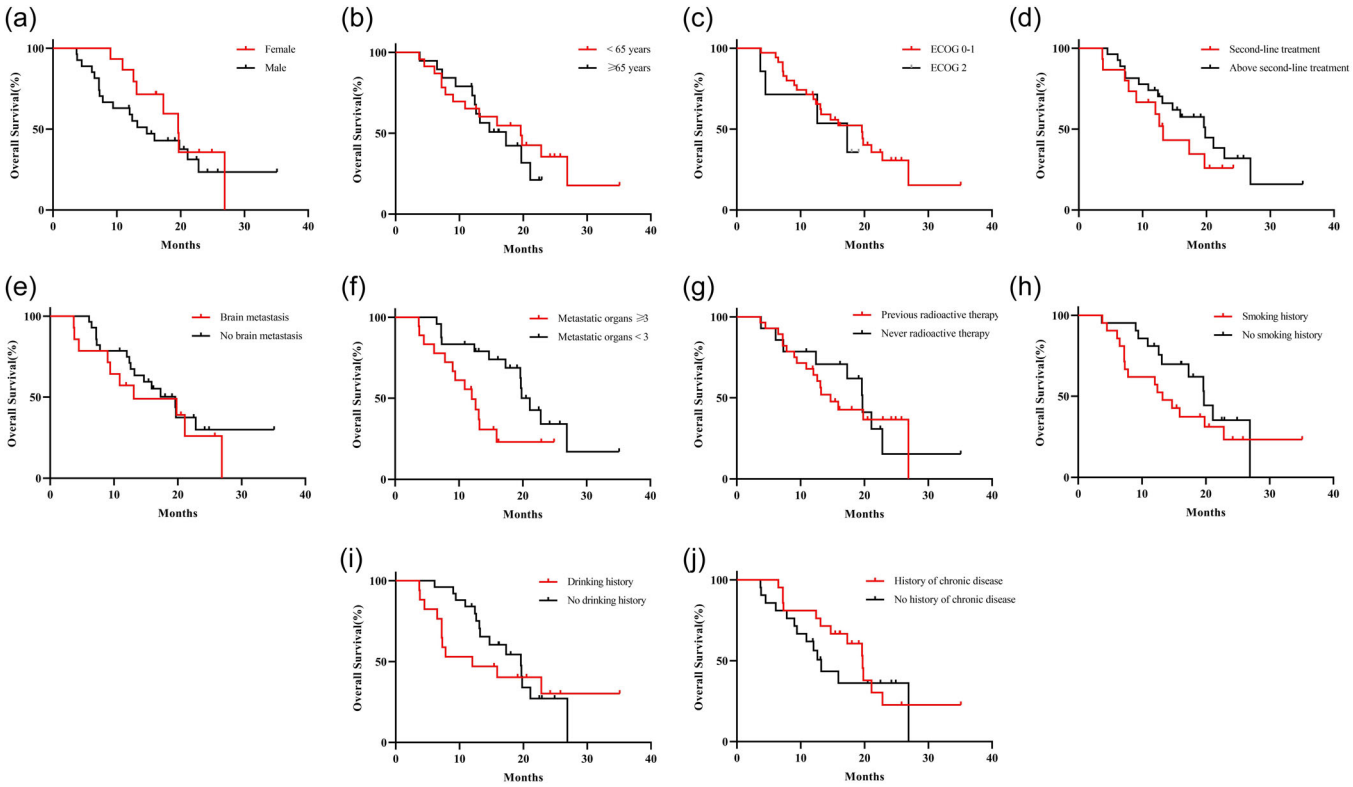

FIGURE 4 Results of subgroup analysis of overall survival. The following factors were identified to be important prognostic factors: (a) sex; (b) age; (c) ECOG score; (d) treatment at baseline; (e) brain metastasis; (f) number of organs with metastasis; (g) radiotherapy; (h) history of smoking; (i) history of alcohol consumption; and (j) history of chronic disease. ECOG, Eastern Cooperative Oncology Group.

(yes or no, Figures 3g and 4g), smoking history (yes or no, Figures 3h and 4h), history of alcohol consumption (yes or no, Figures 3i and 4i), and history of chronic disease (yes or no, Figures 3j and 4j). Univariate Cox regression analysis revealed that the number of organs with metastasis had a moderate influence on both PFS (hazard ratio [HR] 2.964, 95% CI: 1.388–6.329, $p = 0.005$; Figure 5a) and OS (HR: 2.509, 95% CI: 1.121–5.614, $p = 0.025$; Figure 5b). Specifically, fewer than three organs with metastasis were a protective factor for PFS and OS. The group of patients with metastasis to three or more organs had a 2.964-fold higher risk of disease progression and a 2.509-fold higher risk of mortality in comparison with the group with fewer organs with metastasis. Previous radiotherapy was also correlated with PFS (HR 2.408, 95% CI: 1.018–5.694, $p = 0.045$; Figure 5a). The risk of disease progression was 2.408 times higher in patients who had previously received radiotherapy than in those who had not. Notably, PFS tended to be longer in patients without brain metastases and those with no history of smoking (Figure 3e,h, respectively), suggesting that these factors may serve as protective factors for PFS. However, this finding was not statistically significant, possibly because of the limited sample size.

We also performed a multiple regression analysis using Cox proportional hazard models to identify whether there were any independent prognostic factors for PFS (Figure 6a) or OS (Figure 6b). The results indicated that the absence of brain metastases (HR: 0.242, 95% CI: 0.078–0.753, $p = 0.014$) and no history of smoking (HR: 0.106, 95% CI: 0.016–0.709, $p = 0.021$) were independent protective factors for PFS. Furthermore, the absence of brain metastases (HR: 0.290, 95% CI: 0.099–0.849, $p = 0.024$) and fewer than three organs with metastasis (HR: 0.106, 95% CI: 0.025–0.442, $p = 0.002$) were independent protective factors for OS. However, the CIs showed considerable width. Therefore, although the p values for certain findings reached statistical significance, there remains some uncertainty regarding their stability and reliability.

3.4 | Safety

Twenty-seven patients (64.3%) experienced treatment-related AEs, the most common of which was hypothyroidism (26.2%), followed by abnormal liver function (14.3%), abnormal myocardial enzyme levels (14.3%), hematological toxicity (11.9%), anorexia (9.5%), hypertension

(a)

Characteristic	Quantity (*n*)	mPFS (months)	*p* value	HR (95% CI)
Gender				
Male	27	8.433	0.662	1.187(0.550–2.564)
Female	15	11.033		
Age				
< 65 years	23	8.600	0.883	0.946(0.453–1.975)
⩾65 years	19	11.467		
ECOG score				
0–1	35	10.967	0.781	1.162(0.403–3.354)
2	7	12.600		
Treatment baseline				
Second-line treatment	15	8.433	0.751	0.880(0.400–1.935)
Above second-line treatment	27	11.033		
Brain metastasis				
yes	14	8.600	0.077	1.957(0.930–4.118)
no	28	11.467		
Metastatic organs				
⩾3	18	7.933	0.005	2.964(1.388–6.329)
< 3	24	15.300		
Previous radioactive therapy				
yes	28	8.433	0.045	2.408(1.018–5.694)
no	14	15.300		
Smoking history				
yes	21	7.933	0.276	1.507(0.720–3.154)
no	21	11.467		
Drinking history				
yes	17	7.933	0.583	1.232(0.585–2.596)
no	25	11.033		
History of chronic disease				
yes	21	12.600	0.112	0.549(0.262–1.151)
no	21	8.167		

0 1 2 4 6

(b)

Characteristic	Quantity (*n*)	mOS (months)	*p* value	HR (95% CI)
Gender				
Male	27	14.733	0.329	1.517(0.657–3.500)
Female	15	19.567		
Age				
< 65 years	23	19.567	0.597	0.806(0.363–1.790)
⩾65 years	19	17.300		
ECOG score				
0–1	35	19.567	0.508	0.691(0.231–2.068)
2	7	17.300		
Treatment baseline				
Second-line treatment	15	13.167	0.308	1.520(0.679–3.402)
Above second-line treatment	27	19.800		
Brain metastasis				
yes	14	13.100	0.439	1.370(0.617–3.042)
no	28	19.567		
Metastatic organs				
⩾3	18	11.967	0.025	2.509(1.121–5.614)
< 3	24	19.800		
Previous radioactive therapy				
yes	28	14.733	0.766	1.131(0.501–2.553)
no	14	19.667		
Smoking history				
yes	21	13.167	0.256	1.572(0.720–3.431)
no	21	19.667		
Drinking history				
yes	17	11.967	0.558	1.265(0.576–2.776)
no	25	19.567		
History of chronic disease				
yes	21	19.667	0.431	0.732(0.337–1.590)
no	21	13.167		

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FIGURE 5 Baseline patient characteristics identified to be prognostic factors in univariate analysis. (a) Progression-free survival. (b) Overall survival.

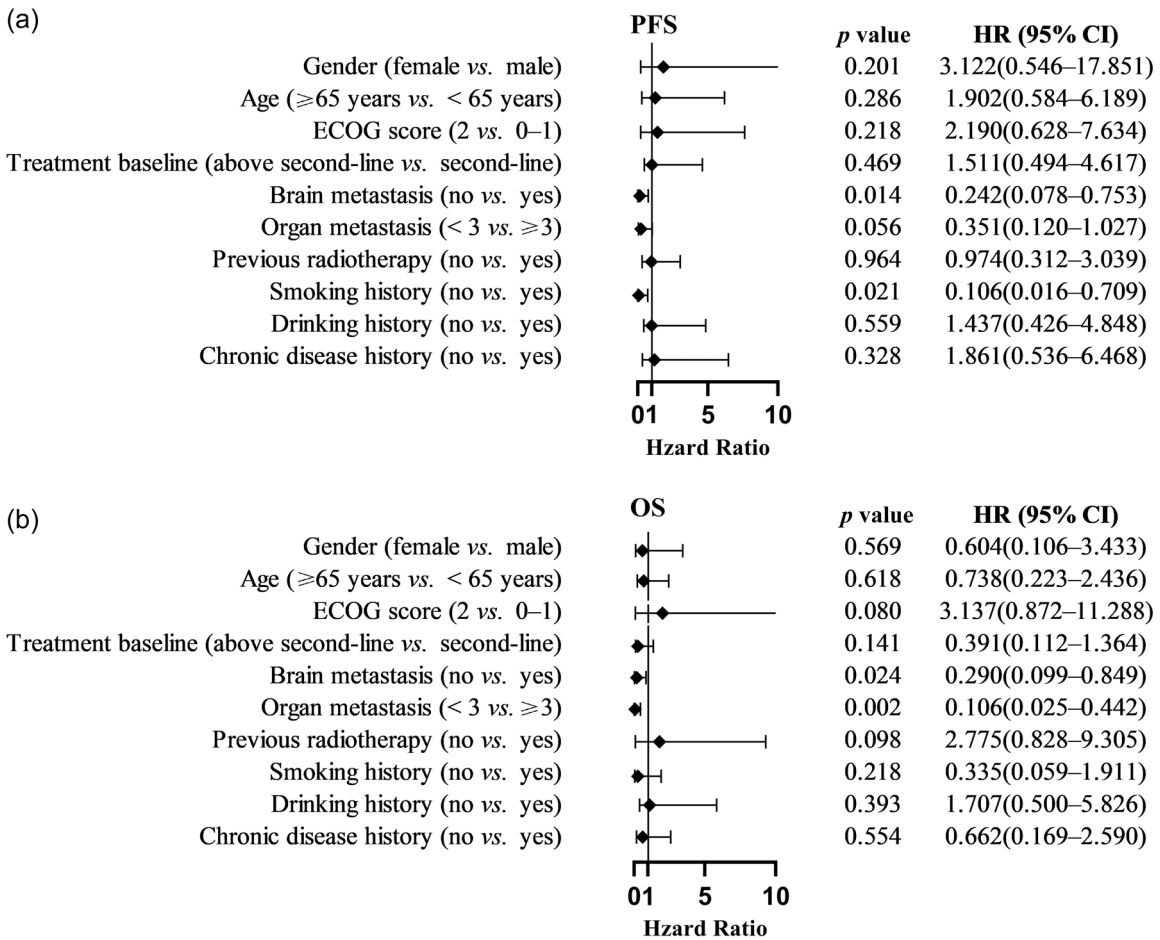

FIGURE 6 Prognostic factors identified using Cox proportional hazards models with corresponding hazard ratios. (a) Progression-free survival. (b) Overall survival.

(9.5%), fatigue (7.1%), gastrointestinal reactions (7.1%), hyperglycemia (7.1%), bleeding (7.1%), hand-foot syndrome (4.7%), rash/pruritus (2.3%), and ICI-associated myocarditis (2.3%). Grade 3 or 4 treatment-related AEs were observed in two patients (4.7%), namely abnormal myocardial enzyme levels ($n = 1$) and hand and foot syndrome ($n = 1$). There were no treatment-related deaths. Details of the treatment-related AEs are shown in Table 2.

4 | DISCUSSION

This study evaluated the efficacy and safety of combination therapy using low-dose anlotinib and ICIs as a second-line or later treatment for patients with ES-SCLC. We found that patients treated with this combined regimen had longer PFS, OS, and tolerable AEs. Median PFS was 11.0 months and median OS was 17.3 months. Furthermore, the ORR was 28.5% and the DCR was 95.2%.

Among the studies of nivolumab monotherapy for recurrent SCLC, the ORR, median PFS, and median OS were 11.9%, 1.4 months, and 5.6 months, respectively, in CheckMate 032 [19] and 13.7%, 1.4 months, and 7.5 months, respectively, in CheckMate 331 [20]. Moreover, in KEYNOTE-028 and KEYNOTE-158, pembrolizumab monotherapy as a second-line or later treatment for relapsed or metastatic SCLC had an ORR of 19.3%, a median PFS of 2.0 months, and a median OS of 7.5 months [21]. A multicenter, retrospective, non-interventional, real-world study of anlotinib for ES-SCLC found that the anlotinib monotherapy group had an ORR of 12.8%, a median PFS of 3.6 months, and a median OS of 4.8 months [22]. Unlike in those studies, a combination of anlotinib with immunotherapy had a longer survival benefit in our patients with ES-SCLC.

TABLE 2 Treatment-related adverse events classified by grade.

Adverse event	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 or 4 *n* (%)
Fatigue	2 (4.7)	1 (2.3)	0
Anorexia	1 (2.3)	3 (7.1)	0
Gastrointestinal reactions	2 (4.7)	1 (2.3)	0
Rash/pruritus	0	1 (2.3)	0
Abnormal liver function	3 (7.1)	3 (7.1)	0
Thyroid dysfunction	4 (9.5)	7 (16.6)	0
Abnormal myocardial enzyme	4 (9.5)	1 (2.3)	1 (2.3)
Hypertension	1 (2.3)	3 (7.1)	0
Hyperglycemia	2 (4.7)	1 (2.3)	0
Hematological toxicity	3 (7.1)	2 (4.7)	0
Bleeding	2 (4.7)	1 (2.3)	0
ICI-associated myocarditis	0	1 (2.3)	0
Hand-foot syndrome	1 (2.3)	0	1 (2.3)

Abbreviation: ICI, immune checkpoint inhibitor.

Our data indicate that a combination of anlotinib and ICIs is more efficacious than either treatment alone in SCLC. Similarly, Chen et al. [23] reported that 62 patients with ES-SCLC treated with anlotinib (low dose [8 or 10 mg], 40.3%; high dose [12 mg], 59.7%) plus ICIs had an ORR of 19.4% and a median PFS of 7.5 months. Although their report did not include OS, the efficacy of the combined therapy in terms of ORR and PFS was superior to that of monotherapy. Hao et al. [24] performed a study in which 36 patients received 10 mg ($n = 11$, 30.6%) or 12 mg ($n = 25$, 69.4%) of anlotinib in combination with anti-PD-1 therapy; the ORR was 27.8%, median PFS was 4.6 months, and median OS was 9.3 months. It appears that the higher the proportion of patients treated with a low dose, the longer the median PFS. The clinical efficacy of anlotinib combined with ICIs for SCLC was better in our study than in the above-mentioned two studies. Although the data are not directly comparable, the results suggest that low-dose anlotinib is more likely to improve patient survival when used in combination with ICI therapy.

In our study, treatment-related AEs occurred in 27 patients (64.3%), the most common being thyroid dysfunction (26.2%), which occurred in 11 patients (all were grade 1 or 2). Only two patients (4.8%) experienced grade 3 or 4 AEs. In a study by Hao et al. [24], the overall incidence of AEs was 88.9%, with 14 cases (38.9%) experiencing grade 3 or higher AEs. These findings suggest that, in terms of AEs, low doses of anlotinib have more promising results than higher doses.

This study had some limitations. First, it had a retrospective single-center design and did not include a comparison group. Therefore, there are several uncertainties when interpreting the results of this study as a basis for evaluation of treatment efficacy, and, our finding of longer PFS and OS in patients who received a combination of low-dose anlotinib and ICIs should be interpreted with caution. Second, owing to the small sample size, the CIs of the Cox model are relatively wide, which casts doubt on the stability of the results. Studies with larger sample sizes are needed to confirm the conclusions drawn from our relatively limited sample. Third, there is limited research on the treatment of SCLC by

anlotinib combined with ICIs; therefore, the positive antitumor efficacy and manageable AEs we observed need to be confirmed in larger clinical trials to rule out the possibility of chance. Fourth, owing to the limited sample size, the outcomes of treatment with 8 mg and 10 mg of anlotinib were not analyzed separately. To confirm the results of this retrospective study, we are currently conducting a prospective clinical investigation of the efficacy of anlotinib 10 mg in combination with anti-PD-1 antibodies in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT03975036).

5 | CONCLUSION

Unlike most of the studies of anlotinib in patients with ES-SCLC, which have used high doses, this study examined the efficacy and safety of low-dose anlotinib combined with ICI therapy in these patients. When used as a second-line or later treatment, this combined regimen prolongs PFS and OS in patients with ES-SCLC and has controllable AEs. Prospective clinical trials that include larger samples and more precise dosages are needed to validate the outcomes observed in our study.

AUTHOR CONTRIBUTIONS

Han Li: Conceptualization (equal); formal analysis (lead); investigation (equal); data curation (lead); writing—original draft (lead); visualization (equal). **Shumin Yuan**: Conceptualization (equal); methodology (lead); investigation (equal); data curation (equal). **Han Wu**: Conceptualization (equal); methodology (equal); writing—review and editing (equal). **Yajie Wang**: Writing—review and editing (equal). **Yichen Ma**: Writing—review and editing (equal). **Xiance Tang**: Resources (equal). **Xiaomin Fu**: Resources (equal). **Lingdi Zhao**: Resources (equal). **Benling Xu**: Formal analysis (equal). **Tiepeng Li**: Data curation (equal). **Peng Qin**: Resources (equal). **Hongqin You**: Data curation (equal). **Lu Han**: Formal analysis (equal). **Zibing Wang**: Conceptualization (equal); writing—review and editing (equal); visualization (equal); supervision (lead). All authors have read and agreed to the version of the manuscript submitted for publication. All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript and take responsibility for the integrity of the work as a whole.

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CONFLICT OF INTEREST STATEMENT

Professor Zibing Wang is the member of the *Cancer Innovation* Editorial Board. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. The remaining authors declare no conflict of interest. The funding bodies played no role in the design of the study, the collection, analysis, and interpretation of data, or in writing the manuscript.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

This is a retrospective study. The ethics committees of the Affiliated Cancer Hospital of Zhengzhou University (Henan Cancer Hospital, Zhengzhou, China) has confirmed that no ethical approval is required. The study was performed according to the principles of the Declaration of Helsinki and the World Health Organization Guidelines for Good Clinical Practice.

INFORMED CONSENT

The requirement for informed consent was waived in view of the retrospective nature of the research and the fact that no patient tissue specimens were used.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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