Original Article

Comparative efficacy and safety of anlotinib and topotecan as second-line treatment in small cell lung cancer: a retrospective cohort study

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Background: Small cell lung cancer (SCLC) presents considerable challenges regarding the availability of second-line treatment options, which remain limited. The paucity of effective therapeutic choices at this setting emphasizes the urgent requirement for rigorous research and investigation into novel treatment strategies. To address this clinical gap, the current study aimed to compare the efficacy and safety of anlotinib with the standard second-line treatment, topotecan, in patients with relapsed SCLC.

Methods: This retrospective collected data from SCLC patients who received either anlotinib or topotecan as second-line treatment. The primary endpoints were progression-free survival (PFS), while the secondary endpoints included the overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety assessment.

Results: The study included 46 SCLC patients, with 20 receiving anlotinib and 26 receiving topotecan as second-line treatment. The anlotinib group showed a significantly longer median PFS compared to the topotecan group [5.6 *vs.* 2.2 months; hazard ratio (HR) =0.50; 95% confidence interval (CI): 0.27–0.92; P=0.02]. However, there was no statistically significant difference in OS between the two groups (9.1 *vs.* 7.7 months; HR =0.88; 95% CI: 0.46–1.70; P=0.71). The ORRs were 20.0% and 7.7% (P=0.48), and the DCRs were 70.0% and 23.1% (P=0.007) for the anlotinib and topotecan groups, respectively. Treatment-related adverse events (TRAEs) occurred in 13 patients (65.0%) in the anlotinib group and 20 (76.9%) in the topotecan group (P=0.49).

Conclusions: Anlotinib shows the potential to extend PFS and manageable adverse events (AEs) compared to topotecan in the second-line setting for relapsed SCLC.

Keywords: Anlotinib; topotecan; small cell lung cancer (SCLC); efficacy; safety

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Introduction

Small cell lung cancer (SCLC) is characterized by aggressive tumor growth and is associated with poor prognosis. Although the majority of SCLC patients initially respond to first-line platinum-based chemotherapy, and immune checkpoint inhibitors such as atezolizumab and durvalumab have further enhanced these responses, relapse remains a prevalent and challenging outcome. Approximately 80% of patients with limited-stage disease and nearly all with extensive-stage disease experience disease recurrence within one year after completing initial treatment (1). This high relapse rate underscores the pressing need for more effective second-line treatment to address disease progression and improve patient outcomes in the relapsed setting. However, the options for second-line therapy in relapsed or refractory SCLC are notably constrained (2-4). As such, there is a critical need to explore and identify effective treatment alternatives to improve patient outcomes in this setting. Topotecan, approved by the US Food and Drug Administration (FDA), stands as the first single-agent drug for second-line treatment in relapsed SCLC (5,6). Nonetheless, the response to topotecan is modest and lacks durability, with an objective response rate (ORR) of 7% and a median overall survival (OS) of 6.4 months (7).

Anlotinib, an oral, small-molecule, multitargeted tyrosine kinase inhibitor (TKI), functions by inhibiting angiogenesis and anti-tumor proliferation (8-10). It targets various receptors, including vascular endothelial growth factor receptor (VEGFR)-1/2/3, platelet-derived growth factor receptor (PDGFR)-α/β, fibroblast growth factor receptor (FGFR)-1-4, and c-Kit in SCLC cell lines (11-13). Previous phase II trials showed that anlotinib improved progression-free survival (PFS) and OS as a third- or further-line treatment compared to placebo in Chinese patients with SCLC (14,15). And the China National Medical Products Administration (NMPA) has approved anlotinib as a third- and further-line treatment option for advanced SCLC patients. Additionally, recent studies have shown that the combination of anlotinib with ICIs or chemotherapy has significant efficacy in both first-line and subsequent-line treatments for SCLC (16,17). However, there are also significant increasing safety concerns. To address the pressing need for safe and effective options in the second-line setting, we conducted a retrospective comparative analysis to evaluate the efficacy and safety profiles of anlotinib as compared to topotecan. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-274/rc).

Highlight box

Key findings

- This study showed promising efficacy and safety of anlotinib in the second-line setting for relapsed small cell lung cancer (SCLC).

What is known and what is new?

- It is known that even with effective initial treatment, SCLC often relapses. However, second-line therapy opinions for relapsed or refractory SCLC are limited and there is a critical need to explore and identify effective treatment alternatives to improve patient outcomes.
- Anlotinib shows significantly better progression-free survival compared to topotecan in patients with relapsed SCLC, with a manageable safety profile.

What is the implication, and what should change now?

- Anlotinib shows the potential to be considered as second-line treatment for patients with relapsed SCLC.

Methods

Patient eligibility

This study included data from patients with SCLC who experienced documented disease progression or relapse during or after the first-line platinum-based therapy at Peking Union Medical College Hospital between January 2019 and June 2023. To be eligible for inclusion, patients had to meet specific criteria: (I) histological or cytological diagnosis of SCLC; (II) age ≥18 years; (III) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; and (IV) receiving second-line treatment with either anlotinib or topotecan. All these conditions were mandatory for participation in the study. Patients were excluded if there were significant deficiencies in the relevant medical records, such as lack of comprehensive treatment details or lack of essential follow-up data, including dates and results of imaging tests needed to assess disease progression or response to treatment. Additionally, patients were also excluded if they had no measurable tumor lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (18). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Review Committee of Peking Union Medical College Hospital (No. HS-2195). The need for obtaining informed consent was waived because of the retrospective nature of the study.

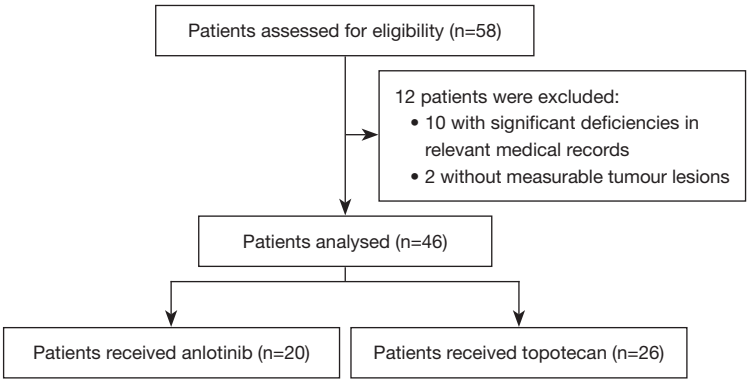

Figure 1 Flow diagram.

Data collection and endpoints

Data collected for analysis encompassed patient demographics and baseline characteristics (sex, age, smoking history, comorbidities, ECOG PS); disease characteristics (disease stage, metastatic sites, pattern of relapse from chemotherapy); interventions [previous surgery, previous radiotherapy, prophylactic cranial irradiation (PCI), brain radiotherapy]; and follow-up indicators [follow-up time, clinical efficacy, and adverse events (AEs)].

The primary endpoint of the study was PFS. PFS was defined as the duration from the initiation of second-line therapy to the time of disease progression according to RECIST 1.1 or death from any cause, whichever occurred first. Secondary endpoints included OS, ORR, disease control rate (DCR), and AEs. OS was defined as the period from the initiation of second-line therapy to the time of death.

Tumor assessments were conducted by investigators based on RECIST 1.1 criteria. Routine evaluation involved chest, abdominal, and pelvic computed tomography scans. Efficacy was initially assessed at the sixth week of treatment and subsequently every two cycles until disease progression was confirmed. AEs and clinical laboratory toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0).

Statistical analyses

Clinical characteristics, tumor response, and AEs were compared between the anlotinib and topotecan groups using appropriate statistical tests such as the Wilcoxon rank-sum test, Pearson's χ^2 test, or Fisher's exact test. PFS and OS were estimated using the Kaplan-Meier methodology and compared between the two groups using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for PFS and OS were estimated using the Cox proportional hazards model. Subgroup analyses were performed using stratified Cox regression, comparing anlotinib and topotecan for PFS and OS, stratified by gender, age, smoking history, pattern of relapse from chemotherapy, ECOG PS, disease stage, brain metastases, and previous radiotherapy. Furthermore, stepwise Cox regression analysis was employed to identify significant prognostic factors for PFS and OS among the listed variables, including second-line therapy, gender, age, smoking history, pattern of relapse from chemotherapy, ECOG PS, disease stage, brain metastases, and previous radiotherapy. A P value less than 0.05 was considered statistically significant. All statistical analyses were conducted using R version 4.2.1 (R Project for Statistical Computing) and Stata 17 (Stata, College Station, TX, USA).

Results

Patients and treatment

A total of 58 patients diagnosed with SCLC received second-line therapy with either anlotinib or topotecan at Peking Union Medical College Hospital between January 2019 and June 2023. Ten patients with significant deficiencies in the relevant medical records and 2 patients without measurable tumor lesions were excluded. Forty-six patients were included in the analysis (*Figure 1*). Among them, 20 (43.5%) patients were treated with anlotinib, and 26 (56.5%) patients were treated with topotecan as second-line therapy. All patients in both groups were aged between

18 and 75 years. The median age of patients was 67 years in the anlotinib group and 64 years in the topotecan group (P=0.29). In the anlotinib group, 15 (75.0%) patients were male, and 5 (25.0%) patients were female. In the topotecan group, 22 (84.6%) patients were male, and 4 (15.4%) patients were female. The two treatment groups were well-balanced in terms of demographics and disease characteristics (P>0.05). There were 11 (55.0%) patients and 7 (26.9%) patients with brain metastases in the anlotinib and topotecan groups, respectively, and the proportion of patients receiving previous PCI (10.0% *vs.* 3.8%; P=0.73) and brain radiotherapy (45.0% *vs.* 23.1%; P=0.21) did not show any statistically significant difference (*Table 1*). The last follow-up occurred in June 2023, with a median follow-up time of 7.7 months [interquartile range (IQR), 4.2–17.2 months] for all patients. The median follow-up time of surviving patients was 16.2 months (IQR, 11.8–46.3 months).

Efficacy

As at June 30, 2023, the cut-off date, all 20 patients in the anlotinib group and 26 patients in the topotecan group experienced a PFS event. Median PFS was significantly longer in the anlotinib group (5.6 months, 95% CI: 2.0–8.4) compared to the topotecan group (2.2 months, 95% CI: 1.6–3.2; HR =0.50; 95% CI: 0.27–0.92; P=0.02; *Figure 2A*). Throughout the study, 16 patients (80.0%) in the anlotinib group and 22 patients (84.6%) in the topotecan group had documented deaths.

No significant difference in OS was observed between the two groups. The median OS was 9.1 months (95% CI: 5.4–19.0) for anlotinib and 7.7 months (95% CI: 4.5–17.2) for topotecan (HR =0.88; 95% CI: 0.46–1.70; P=0.71; *Figure 2B*). The 6-month and 1-year survival rates were 90.0% and 40.0% in the anlotinib group, and 53.8% and 46.2% in the topotecan group, respectively.

Tumor response of 19 patients in the anlotinib group and 23 in the topotecan group could be evaluated. The anlotinib group showed an ORR of 20.0%, while the topotecan group showed an ORR of 7.7% (P=0.48). Ten (50.0%) patients in the anlotinib group and 4 (15.4%) patients in the topotecan group had stable disease (SD). The DCR was significantly higher in the anlotinib group (70.0%) compared to the topotecan group (*Table 2*). No complete response was observed in either group.

A higher proportion of patients in the topotecan group (73.1%) than in the anlotinib group (55.0%) received subsequent therapy after progression. Anlotinib was more frequently given as subsequent therapy after progression in the topotecan group (46.2%) than in the anlotinib group (5.0%). Patients might receive more than one type of subsequent therapy (Table S1).

Prognostic factors

Subgroup analysis showed that the PFS benefit of anlotinib was particularly strong in the following patient subgroups: male, age ≥65 years, smoking history, sensitive relapse, better performance status (ECOG PS of 0), extensive stage, and brain metastasis (*Figure 3A*). Neither anlotinib nor topotecan showed superior OS in any subgroup (*Figure 3B*). Stepwise Cox regression analyses for prognostic factors showed that anlotinib was the independent protective factor for PFS (HR =0.34; 95% CI: 0.17–0.66; P=0.001). Extensive stage was the independent risk factor for PFS (HR =4.21; 95% CI: 1.82–9.70; P=0.001). Previous radiotherapy was an independent protective factor for OS (HR =0.18; 95% CI: 0.08–0.41; P<0.001) (*Table 3*).

Safety

The incidence of AEs was 85.0% with anlotinib and 92.3% with topotecan (P=0.67) (*Table 4*), and the incidence of grade 3 or worse AEs was 35.0% with anlotinib and 84.6% with topotecan (P=0.009). The most common grade 3 or worse AEs (Table S2) were hypertension (5.0% *vs.* 0.0%), anorexia (0.0% *vs.* 7.7%), diarrhea (5.0% *vs.* 19.2%), fatigue (0.0% *vs.* 19.2%), hemoptysis (10.0% *vs.* 0.0%), limb pain (5.0% *vs.* 0%), anemia (0.0% *vs.* 7.7%), leukocytopenia (5.0% *vs.* 23.1%), neutropenia (0.0% *vs.* 26.9%), thrombocytopenia (5.0% *vs.* 11.5%), febrile neutropenia (0.0% *vs.* 7.7%), aspartate transaminase (AST) elevation (5.0% *vs.* 0%), and hyponatremia (0.0% *vs.* 7.7%). Treatment-related adverse events (TRAEs) occurred in 13 (65.0%) patients in the anlotinib group and 20 (76.9%) patients in the topotecan group (P=0.49). The grade 3 or worse TRAEs were observed in 5 (25.0%) patients receiving anlotinib and 13 (50.0%) patients receiving topotecan (P=0.19). Serious adverse events (SAEs) occurred in 5 (25.0%) patients in the anlotinib group and 11 (42.3%) patients in the topotecan group (P=0.32). Treatment-related SAEs were reported in 4 (20.0%) patients receiving anlotinib and 7 (26.9%) receiving topotecan (P=0.69). There were no treatment-related deaths in either group. Treatment discontinuation due to AEs occurred in 3 (15.0%) patients in the anlotinib group

Table 1 Baseline characteristics of patients

Characteristics	Anlotinib (n=20)	Topotecan (n=26)	P value
Age (years)			
Median (range)	67 (60, 73)	64 (57, 71)	0.29
Sex, n (%)			0.31
Male	15 (75.0)	22 (84.6)	
Female	5 (25.0)	4 (15.4)	
ECOG PS, n (%)			0.48
0	5 (25.0)	7 (26.9)	
1	9 (45.0)	15 (57.7)	
2	6 (30.0)	4 (15.4)	
Smoking history, n (%)			0.31
No	5 (25.0)	3 (11.5)	
Yes	15 (75.0)	23 (88.5)	
TNM stage, n (%)			0.16
I–II	2 (10.0)	0 (0.0)	
III	1 (5.0)	6 (23.1)	
IV	17 (85.0)	20 (76.9)	
Disease stage, n (%)			0.64
Limited	3 (15.0)	6 (23.1)	
Extensive	17 (85.0)	20 (76.9)	
Brain metastases, n (%)			0.11
No	9 (45.0)	19 (73.1)	
Yes	11 (55.0)	7 (26.9)	
Previous surgery, n (%)			0.95
No	19 (95.0)	25 (96.2)	
Yes	1 (5.0)	1 (3.8)	
Pattern of relapse from chemotherapy[†], n (%)			0.52
Sensitive	7 (35.0)	12 (46.2)	
Refractory/resistant	13 (65.0)	14 (53.8)	
Previous radiotherapy, n (%)			0.40
No	4 (20.0)	9 (34.6)	
Yes	16 (80.0)	17 (65.4)	
Previous PCI, n (%)			0.73
No	18 (90.0)	25 (96.2)	
Yes	2 (10.0)	1 (3.8)	
Brain radiotherapy, n (%)			0.21
No	11 (55.0)	20 (76.9)	
Yes	9 (45.0)	6 (23.1)	

[†], pattern of relapse from chemotherapy is dependent on the time from initial therapy to relapse. If the interval is 6 months or less, it is defined as a refractory/resistant relapse. If more than 6 months have relapsed, it is defined as a sensitive relapse. There were no significant differences between groups in a two-sided test with an α level of 0.05. ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis; PCI, prophylactic cranial irradiation.

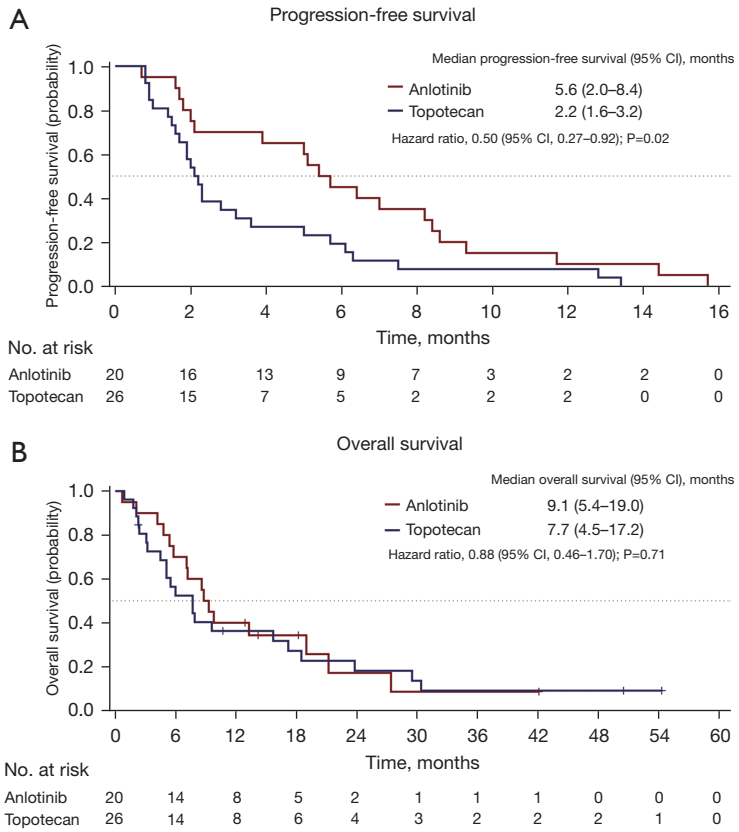

Figure 2 Kaplan-Meier curves for progression-free survival (A) and overall survival (B) were compared between the anlotinib group and topotecan group. CI, confidence interval.

Table 2 Tumor response

Response	Anlotinib (n=20)	Topotecan (n=26)	P value
Best overall response, n (%)			0.01
Complete response	0 (0.0)	0 (0.0)	
Partial response	4 (20.0)	2 (7.7)	
Stable disease	10 (50.0)	4 (15.4)	
Progressive disease	5 (25.0)	17 (65.4)	
Not estimated	1 (5.0)	3 (11.5)	
Objective response, n (%) (95% CI)	4 (20.0) (5.7, 43.7)	2 (7.7) (0.9, 25.1)	0.48
Disease control, n (%) (95% CI)	14 (70.0) (45.7, 88.1)	6 (23.1) (9.0, 43.6)	0.007

CI, confidence interval.

and 7 (26.9%) patients in the topotecan group (P=0.49), and dose adjustment due to AEs occurred in 2 (10.0%) patients receiving anlotinib and 4 (15.4%) patients receiving topotecan (P=0.76).

Discussion

To the best of our knowledge, this is the first clinical study comparing the efficacy and safety of anlotinib and topotecan in patients with relapsed SCLC in the second-

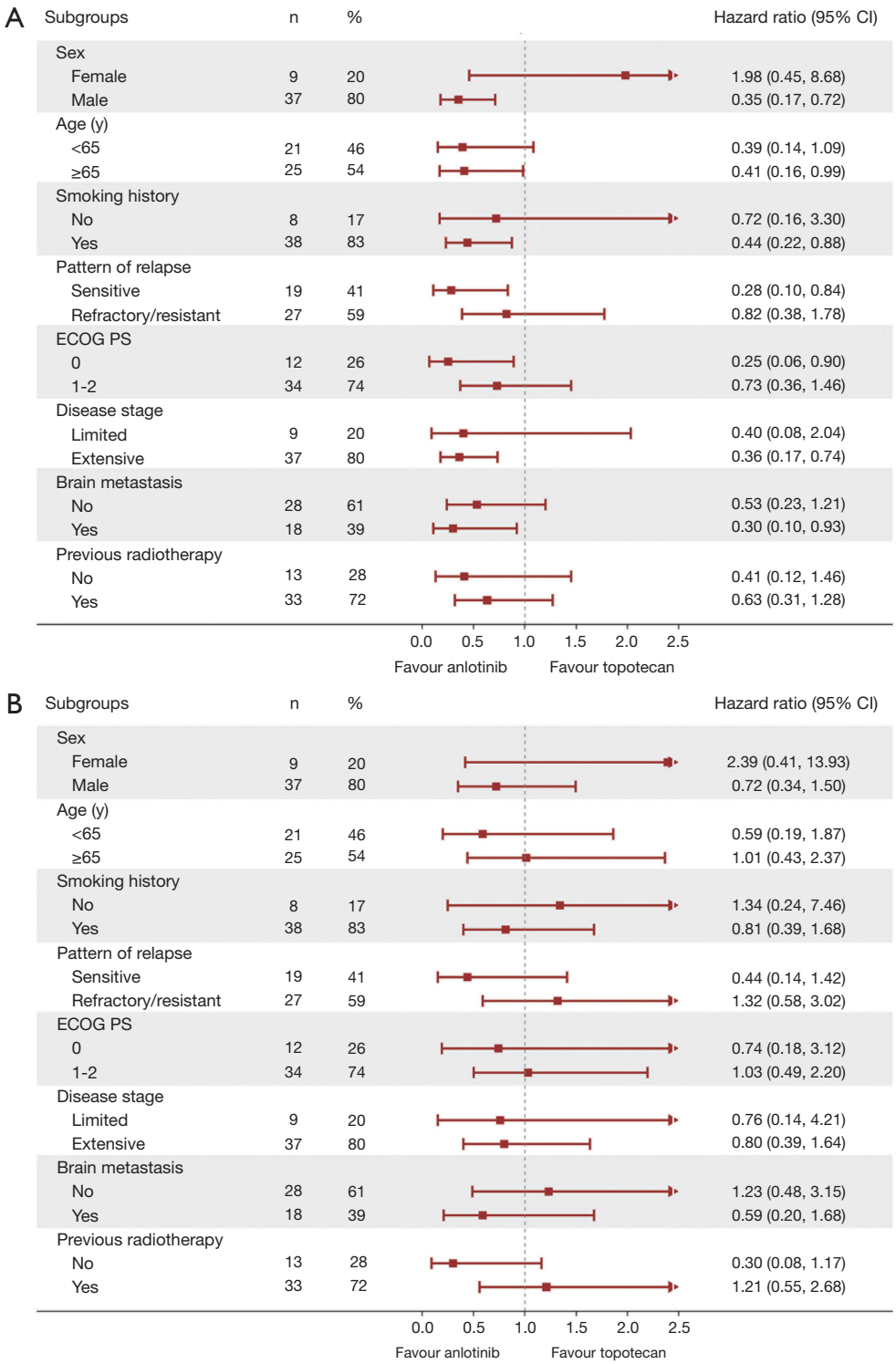

Figure 3 Forest plots showing hazard ratios of anlotinib relative to topotecan for progression-free survival (A) and overall survival (B) in different subgroups. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance statues.

Table 3 Stepwise Cox regression analyses for prognostic factors

Parameter	Reference	HR (95% CI)	P value
Progression-free survival			
Treatment: anlotinib	Topotecan	0.34 (0.17–0.66)	0.001
Disease stage: extensive	Disease stage: limited	4.21 (1.82–9.70)	0.001
Overall survival			
Previous radiotherapy: yes	Previous radiotherapy: no	0.18 (0.08–0.41)	<0.001

HR, hazard ratio; CI, confidence interval.

Table 4 Safety summary

Adverse events	Anlotinib (n=20), n (%)	Topotecan (n=26), n (%)	P value
Any AEs (all grades)	17 (85.0)	24 (92.3)	0.67
TRAEs (all grades)	13 (65.0)	20 (76.9)	0.49
Grade 3 or worse adverse events	7 (35.0)	22 (84.6)	0.009
Treatment-related grade 3 or worse events	5 (25.0)	13 (50.0)	0.19
Any SAEs	5 (25.0)	11 (42.3)	0.32
Treatment-related SAE[†]	4 (20.0)	7 (26.9)	0.69
AEs leading to death	0 (0.0)	0 (0.0)	NA
TRAEs leading to death	0 (0.0)	0 (0.0)	NA
AEs leading to discontinuation	3 (15.0)	7 (26.9)	0.49
TRAEs leading to discontinuation[‡]	2 (10.0)	6 (23.1)	0.45
AEs leading to dose adjustment[§]	2 (10.0)	4 (15.4)	0.76

[†], patients with treatment-related SAE in the anlotinib group: hypertension (n=1), hemoptysis (n=2) and diarrhea (n=1); in the topotecan group: diarrhea (n=4), thrombocytopenia (n=1) and neutropenia (n=2); [‡], patients with TRAE leading to drug interruption in the anlotinib group: hemoptysis (n=2); in the topotecan group: diarrhea (n=4), thrombocytopenia (n=1) and neutropenia (n=1); [§], dose reductions were reported in the anlotinib group: hypertension (n=1) and diarrhea (n=1); in the topotecan group: neutropenia (n=2), hyponatremia (n=1) and anemia (n=1). AEs, adverse events; TRAE, treatment-related adverse event; SAEs, serious adverse events; NA, not applicable.

line setting. Anlotinib showed significant clinical benefit, with a statistically improved PFS compared to topotecan, the current standard second-line treatment. The median PFS was prolonged by 5.6 months with anlotinib. Although the median OS in the anlotinib group (9.1 months) was longer than in the topotecan group (7.7 months), the difference did not reach statistical significance. Notably, the anlotinib group showed an increasing trend in ORR (20.0% *vs.* 7.7%, P=0.48) and a significant increase in DCR (70.0% *vs.* 23.1%, P=0.007).

SCLC is renowned for its aggressive tumor growth (19-22). In a prior clinical trial, patients with relapsed SCLC who received best supportive care experienced a mere median OS of 3.5 months (7). Presently, topotecan stands as the sole evidence-based standard of care approved for SCLC second-line therapy in the United States, Europe, and China (2,3,5,6,23). A phase III study investigating topotecan in relapsed SCLC reported an ORR of 7% and a median OS of 6.4 months (7). Despite exhaustive efforts to identify safe and effective alternatives to topotecan (24-28), no experimental drug has exhibited significantly superior efficacy and safety. For instance, lurbinectedin, a selective inhibitor of oncogenic transcription, demonstrated a median PFS of 3.5 months and a median OS of 9.3 months, yet it displayed evident marrow toxicity in a single-arm phase II trial (25). Similarly, amrubicin failed to show an OS benefit in a large randomized phase III trial when compared to topotecan (HR =0.88; 95% CI: 0.73–1.06; P=0.17) (26).

Although the breakthrough of cancer immunotherapies, such as programmed cell death-ligand 1 (PD-L1) and programmed death 1 (PD-1) inhibitors, have been approved by the FDA for use with platinum-based chemotherapy as first-line treatment for SCLC (6,29-31), their performance as second-line treatments have proven inadequate. For instance, nivolumab in the CheckMate 331 trial did not meet its primary endpoint of improving OS compared to topotecan or amrubicin as a second-line treatment (HR =0.86; 95% CI: 0.72–1.04; P=0.11) (27). Similarly, atezolizumab failed to improve survival outcomes compared to topotecan in the IFCT-1603 trial (HR =0.84; 95% CI: 0.45–1.58; P=0.60) (28).

Angiogenesis plays a crucial role in SCLC proliferation, enabling tumors to escape physiological control and immune surveillance (22). Vascular endothelial growth factor (VEGF) upregulation in SCLC is associated with poor prognosis (32). Consequently, inhibiting angiogenesis presents a promising treatment option for SCLC. Prior studies on sunitinib, cediranib, and nintedanib in relapsed SCLC yield unsatisfactory results (33-35). In contrast, anlotinib, distinguished by its unique structure, exhibits potent inhibition of VEGFR-1, -2, -3, and FGFR-1, contributing to its superior effects (12). The ALTER 1202 study conducted on 120 Chinese patients with advanced SCLC as third-line or beyond treatment demonstrated that anlotinib significantly prolonged PFS and OS and improved DCR (14). Consequently, the NMPA approved it as a third- and further-line treatment option for SCLC patients in China.

Our study findings suggest that anlotinib holds promise as a second-line treatment for patients with SCLC, as it improved PFS compared to topotecan. However, it did not yield a significant improvement in survival outcomes. It is worth considering that subsequent therapy might influence survival outcomes; the proportion of subsequent therapy in our study was 55.0% and 73.1% in the anlotinib and topotecan groups, respectively. Notably, 46.2% of patients in the topotecan group received further anlotinib treatment after their second line of therapy, which could have impacted survival outcomes in these patients. Additionally, the reported OS with topotecan as second-line therapy in previous studies ranged from 5.3 to 8.6 months, similar to the 7.7 months observed in the topotecan group in our study, indicating the comparability of our data with previous findings (23,24,36,37).

Subgroup analyses, while providing limited conclusive evidence, indicated that anlotinib was superior to topotecan for PFS in specific subgroups, including male patients, those aged ≥65 years, individuals with a smoking history, those with sensitive relapse, better performance status (ECOG PS of 0), extensive stage, and brain metastasis. Elderly patients tend to derive less benefit from chemotherapy than oral TKI for SCLC due to poor tolerance (38). Previous observational studies have identified the ECOG PS score as an independent prognostic factor (39), underscoring the need for tailored treatment for patients with poor ECOG PS scores. Recurrent SCLC with brain metastasis poses particular challenges (40); however, we observed a potential benefit from anlotinib treatment in this patient group, providing valuable insight into second-line treatment for SCLC with asymptomatic brain metastases. Our stepwise Cox regression analyses confirmed the PFS improvement resulting from anlotinib treatment, consistent with previous studies (41,42). Additionally, our analysis revealed that limited stage and previous radiotherapy were protective factors against poor prognosis.

The incidence of AEs in our study aligns with previous studies of anlotinib (10,14,38). Moreover, there were significantly fewer grade 3/4 toxicities in the anlotinib group than in the topotecan group. Notably, the typical AEs associated with VEGFR inhibition, such as hypertension, hemoptysis, hand and foot skin reactions, and proteinuria, were mostly mild and manageable (22). Consequently, anlotinib exhibited a more favorable safety profile compared to other multi-targeted TKIs. In contrast, 53.5% of patients treated with sunitinib experienced grade 3 or worse toxicities (33), and patients treated with cediranib experienced grade 3 or worse alanine aminotransferase (ALT)/AST elevation in 12% of cases (34). Similarly, patients treated with nintedanib had an incidence of grade 3 or worse ALT and AST elevation of 21% and 8%, respectively (35). In general, anlotinib was well-tolerated, with low rates of drug discontinuation and dose reduction.

However, our study had some limitations. Firstly, the sample size was small as it was conducted at a single center, which carries a risk of false positives due to selective bias, necessitating future multicenter and large-scale studies for further validation. Secondly, to enable robust statistical analysis, extending the follow-up period would be necessary to obtain sufficient OS data. Thirdly, being a retrospective study, the heterogeneity of baseline information might potentially lead to potential biases. Although we conducted a comparative analysis and found no statistical differences, the extent of similarities remained limited. Additionally, this study did not investigate predictive biomarkers of

anlotinib efficacy, an issue that should be addressed in future prospective studies. Furthermore, some mild adverse reactions might have resulted in missing data, which were not documented in the medical record system.

Conclusions

Our study indicates that anlotinib shows the potential to extend PFS compared to topotecan in second-line therapy for relapsed SCLC, though improvements in OS were not significant, with a manageable safety profile. However, further clinical validation is required to confirm these results.

Acknowledgments

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Footnote

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Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-274/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Review Committee of Peking Union Medical College Hospital (No. HS-2195). The need for obtaining informed consent was waived because of the retrospective nature of the study.

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Supplementary

Table S1 Subsequent therapy

Treatment	Anlotinib (n=20), n (%)	Topotecan (n=26), n (%)
Subsequent therapy	11 (55.0)	19 (73.1)
Chemotherapy	11 (55.0)	13 (50.0)
Radiotherapy	3 (15.0)	2 (7.7)
Immunotherapy	3 (15.0)	2 (7.7)
Targeted therapy	2 (10.0)	13 (50.0)
Anlotinib	1 (5.0)	12 (46.2)
Other	1 (5.0)	1 (3.8)

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Table S2 Adverse events

Adverse event	Anlotinib (n=20), n (%)		Topotecan (n=26), n (%)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Hypertension	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)
Weight loss	4 (20.0)	0 (0.0)	8 (30.8)	0 (0.0)
Anorexia	2 (10.0)	0 (0.0)	12 (46.2)	2 (7.7)
Vomiting	1 (5.0)	0 (0.0)	4 (15.4)	0 (0.0)
Diarrhea	0 (0.0)	1 (5.0)	6 (23.1)	5 (19.2)
Abdominal pain	1 (5.0)	0 (0.0)	2 (7.7)	1 (3.8)
Constipation	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)
Fatigue	5 (25.0)	0 (0.0)	13 (50.0)	5 (19.2)
Hemoptysis	1 (5.0)	2 (10.0)	3 (11.5)	0 (0.0)
Rash	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hand and foot skin reaction	1 (5.0)	1 (5.0)	4 (15.4)	1 (3.8)
Limb pain	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)
Anemia	4 (20.0)	0 (0.0)	9 (34.6)	2 (7.7)
Leukocytopenia	2 (10.0)	1 (5.0)	8 (30.8)	6 (23.1)
Neutropenia	2 (10.0)	0 (0.0)	7 (26.9)	7 (26.9)
Lymphopenia	2 (10.0)	0 (0.0)	8 (30.8)	1 (3.8)
Thrombocytopenia	1 (5.0)	1 (5.0)	2 (7.7)	3 (11.5)
Febrile neutropenia	0 (0.0)	0 (0.0)	1 (3.8)	2 (7.7)
Hypothyroidism	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine erythrocyte	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine leukocyte	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increase	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
ALT increase	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
GGT elevation	1 (5.0)	0 (0.0)	1 (3.8)	0 (0.0)
Conjugated bilirubin increase	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypercholesteremia	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	0 (0.0)	0 (0.0)	4 (15.4)	2 (7.7)
Hypochloridemia	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)
Hypocalcemia	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)
Hyperglycemia	1 (5.0)	0 (0.0)	2 (7.7)	0 (0.0)

AST, aspartate transaminase; ALT, alanine aminotransferase; GGT, glutamyl transpeptidase.

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