Original Article

Apatinib with etoposide capsules as a third- or further-line therapy for extensive-stage small cell lung cancer: an open-label, multicenter, single-arm phase II trial

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Background: Patients with extensive-stage small-cell lung cancer (ES-SCLC) have a particularly poor prognosis. And the treatment options for patients with relapsed or refractory ES-SCLC are limited. Thus, we conducted an open-label, multicenter, single-arm phase II clinical trial to assess the efficacy and safety of apatinib plus etoposide capsules as the third- or further-line treatment in ES-SCLC patients.

Methods: Patients with ES-SCLC who experienced disease progression following 2 to 3 previous therapies from 11 medical centers in China were enrolled to receive apatinib (250 mg/d, continuously) and etoposide capsules (50 mg/d, on day 1–21, per 28 days). The treatment continued until disease progression, treatment intolerance, or death. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were objective response rate (ORR), overall survival (OS), and safety.

Results: Fifty-six patients with relapsed or refractory ES-SCLC were enrolled from January 2018 to February 2020 and 53 of them were eventually included in the evaluation population. The median follow-up was 9.8 months. At the data cut-off time (March 5, 2020), 39 patients (74%) had died and 44 (83%) had progressed. The median PFS was 3.0 months (95% CI, 2.1–3.9) and the median OS was 5.0 months (95% CI, 3.6–6.4). No complete responses were seen. Eleven patients (21%) showed a best response of partial response and 37 (70%) patients achieved stable disease. The ORR was 20.8% (11/53), and the disease control rate (DCR) was 90.6% (48/53). The 6-month OS rate was 40.1% (95% CI, 26.2–54). After 12 months, the OS rate was 18.4% (95% CI, 4.7–32.1). Possible treatment-related grade III/IV adverse events included leukopenia [8 (15.1%)], neutropenia [7 (13.2%)], anemia [4 (7.4%)], and hand-foot syndrome [2 (3.8%)]. During the study, no mortality occurred as a consequence of treatment.

Conclusions: Apatinib combined with etoposide capsules exhibits efficacy and has an acceptable safety profile. It could be used as a later-line treatment for ES-SCLC patients who have been heavily pretreated

with standard therapies. Further exploration of apatinib combined with etoposide capsules in phase III trials is warranted.

Keywords: Small cell lung cancer (SCLC); apatinib; etoposide capsules; efficacy; safety

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Introduction

Small cell lung cancer (SCLC) comprises approximately 15% of lung cancers. Patients with SCLC typically exhibit rapid tumor growth and early metastatic dissemination. Diagnoses of SCLC are often made at an extensive stage and the prognosis is extremely poor (1). The survival rate of patients with extensive-stage SCLC (ES-SCLC) at 5 years after diagnosis does not exceed 7%, and the median overall survival (OS) is a mere 9–11 months (2).

Although most patients are sensitive to the standard first-line chemotherapy of etoposide plus platinum (EP), with response rates of 60% to 70%, almost every patient goes on to develop progressive disease or relapse with resistance to further therapy (3,4). Generally, the clinical response to follow-up treatment is limited and is mainly dependent on the response time after the initial treatment. Patients whose disease relapses more than 3 months after the end of first-line treatment have a higher response rate than those whose disease relapses within 3 months (25% *vs.* 10%) (3,5). The OS of the standard second-line chemotherapy topotecan is only approximately 30 weeks and alternative regimens for third- or further-line therapy are limited (6). Therefore, a novel treatment strategy for patients with refractory or relapsed ES-SCLC is urgently needed.

Sustained angiogenesis is a hallmark and essential alteration in the growth process of malignant tumors and represents a uniquely promising therapeutic target (7). Angiogenesis inhibitors, which include anti-vascular endothelial growth factor (VEGF) antibodies and multi-receptor tyrosine kinase inhibitors (TKIs), have shown anti-tumor activity in various cancers (2,8,9). However, a meta-analysis showed that the combination of bevacizumab and chemotherapy as a first-line treatment for ES-SCLC demonstrated no significant survival benefit, which is consistent with the results of two clinical trials (10-12). However, a recent phase III study showed that bevacizumab combined with EP exhibited manageable toxicities and a significant improvement in progression-free survival (PFS) (13).

Apatinib, as a small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR)-2 tyrosine kinase, can block the transmission of the VEGF/VEGFR-2 signaling pathway, and has shown efficacy against several cancers, including SCLC (14,15). A retrospective study revealed that apatinib at a dose of 250 mg displayed promise as an option for maintenance treatment in a Chinese ES-SCLC cohort following the failure of etoposide plus platinum-containing chemotherapy (16). Despite etoposide plus platinum-based chemotherapy being used as the first-line treatment for patients with ES-SCLC for more than three decades (17), daily oral etoposide (50 mg once daily) was reported to be capable of producing a palliative effect and objective responses in heavily pretreated patients (18). Thus, apatinib (250 mg once daily) plus oral etoposide (50 mg once daily) could be a potential treatment strategy for heavily pretreated cancer patients. In the AEROC study, apatinib combined with etoposide capsules showed promising efficacy and safety in ovarian cancer patients with platinum-resistant or platinum-refractory disease (19). However, the efficacy and safety of apatinib plus etoposide capsules in patients with ES-SCLC as the third- or further-line therapy is unclear. Therefore, we conducted this prospective, single-arm, phase II clinical trial to evaluate the efficacy and safety of apatinib combined with etoposide capsules as a third or further line of treatment for ES-SCLC. We present the following article in accordance with the TREND reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1235).

Methods

Patients and study design

We conducted the present phase II, open-label, multicenter, single-arm clinical trial at 11 Chinese medical centers and registered in a clinical trial registry (ClinicalTrials.gov identifier: NCT03389087). Patients between the

ages of 18–75 years who had a diagnosis of ES-SCLC and had relapsed or progressed following second- or further-line treatment, including the EP regimen, were eligible to participate in the study. Other inclusion criteria were: at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1); an Eastern Cooperative Group performance status (ECOG PS) score of 0–2; a minimum predicted life expectancy of 3 months; and adequate bone marrow function (a white blood cell count of $\geq 3.5\times10^3$ cells/μL, an absolute neutrophil count of $\geq 1.5\times10^3$ cells/μL, a platelet count of $\geq 100\times10^3$ cells/μL, and a hemoglobin concentration of ≥90 g/L), adequate liver function [a total bilirubin level ≤1.5 times the upper limit of normal (ULN), an aspartate transaminase (AST) level ≤2.5 times the ULN, an alanine transaminase (ALT) level ≤2.5 times ULN. An AST and ALT level ≤5 times the ULN if the patient had hepatic metastasis], and adequate renal function (serum creatinine ≤1.25 times the ULN or endogenous creatinine clearance ≥45 mL/min).

The main exclusion criteria included: prior treatment with apatinib or any angiogenesis inhibitors; active or newly diagnosed untreated metastatic lesions of the central nervous system (CNS) (not including brain metastases that were stable or treated at least 21 days before the start of the study); uncontrolled hypertension; clinically significant hemoptysis within the 2 months prior to the study; abnormal coagulant function; and significant bleeding tendency or signs of hemorrhage. Patients with any one or more of the following conditions were also excluded: myocardial infarction; uncontrolled arrhythmia; class III or IV congestive heart failure as defined by the New York Heart Association; arterial or venous thrombosis within the 12 months prior to day 1 of this study; undergoing current anticoagulant therapy; and proteinuria (defined as urine protein ≥ ++ or 24-hour urinary protein ≥1.0 g).

The independent ethics committee of Henan Cancer Hospital of Zhengzhou University granted approval for this study, which was carried out in adherence to the Declaration of Helsinki (as revise in 2013) and Good Clinical Practice Guidelines. All patients provided written informed consent.

Procedures

All patients received oral apatinib (at a dose of 250 mg, administered once daily on each day of a 28-day cycle) combined with oral etoposide (at a dose of 50 mg daily on days 1–21 of a 28-day cycle) treatment. Treatment was administered until the disease progressed, or the patient withdrew, developed intolerable toxicity, or died. Given the anti-tumor efficacy of apatinib at the dose of 250 mg and etoposide at the dose of 50 mg once daily, dose reductions were not permitted in our study. However, if uncontrollable adverse events occurred, dose interruption was allowed. In the event of a grade III or IV toxicity, treatment was delayed until the patient had recovered to grade I or better before resumption at the same dose. Repeated dose interruptions were permitted if the intolerable adverse events recurred.

Measurable lesions were assessed and documented prior to treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) was used to assess tumor response according to RECIST 1.1 following each treatment cycle of apatinib combined with etoposide until disease progression was confirmed. Enhanced CT scans of the chest and upper abdomen were necessary after every cycle, and enhanced CT scans of the lower abdomen and pelvis or enhanced brain MRI were performed if related lesions were documented or new-onset associated symptoms occurred. As well as routine physical, urine, and stool examinations, the patients also underwent hematology, serum chemistry, vital signs, ECOG PS, 12-lead electrocardiogram, and blood pressure assessments after every cycle. In addition, routine blood monitoring was conducted weekly during treatment and 1 week before the start of treatment. If electrocardiography showed abnormal signs, myocardial enzymes were measured. Adverse events were evaluated and documented continuously throughout treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v.4.0). The survival status of the patients was followed up every 3 months during treatment.

Outcomes

The primary endpoint was PFS, which was defined as the interval from the randomization date until the date of first documented progression or any-cause mortality. The secondary endpoints included OS, objective response rate (ORR), and safety. OS was defined as the interval from the randomization date until the date of any-cause mortality. The ORR was defined as the proportion of patients who achieved a complete response (CR) and partial response (PR) according to the RECIST evaluation criteria, version 1.1. Treatment safety was evaluated based on the occurrence of adverse events, with the severity of these events graded

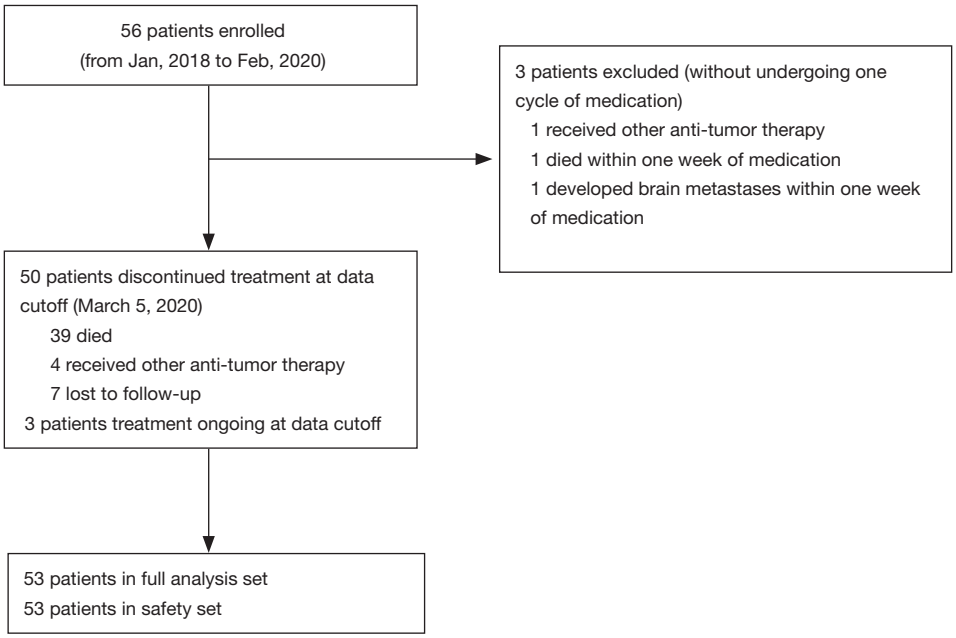

Figure 1 Trial profile. Three patients without undergoing one cycle of medication were excluded.

according to the NCI-CTCAE v.4.0.

Statistical analyses

PFS of 2 months was considered to be a clinically meaningful threshold for this study. Using Fisher's one-sided exact test in the PASS 11 software, we determined that a sample size of 37 patients would provide at least 80% power and, at most, a 5% probability of making a type I error. Taking a 20% drop-out rate into consideration, we planned to enroll 50 patients.

Kaplan-Meier curves were used to analyze PFS and OS. All statistical analyses were two-sided, and $P<0.05$ indicated a statistically significant difference. All statistical analysis was performed with SPSS for Windows Version 23.0 (IBM, Chicago, IL, USA).

Results

Patient characteristics

Between January 2018 and February 2020, 56 patients with relapsed or refractory ES-SCLC from 11 Chinese medical centers were enrolled into our trial. Each patient was administered at least one dose of the combination treatment of oral apatinib plus etoposide. Three patients were excluded: one case died within the first cycle of treatment due to rapid disease progression; one case developed brain metastasis after 1 week of medication; and one case discontinued the treatment plan after 1 week of medication. Eventually, 53 patients who received the protocol treatment without any major protocol violations were included in the full analysis set, which comprised the per-protocol set and the safety analysis set (*Figure 1*).

Baseline characteristics of the 53 patients included in the full analysis set are listed in *Table 1*. These patients had a median age of 57 years (range, 30–77 years), and 40 (40/53; 75.5%) patients were male. In the full analysis set, 26 patients (26/53, 49.06%) were over the age of 60 years, and 45 patients (45/53, 84.9%) had a smoking history. Fourteen (14/53, 26.4%), 10 (10/53, 18.9%), and 10 (10/53, 18.9%) patients presented with metastases of the bone, liver, and brain, respectively. Thirty-three patients (33/53, 62.3%) had received 2 prior lines of treatment, while 20 patients (20/53, 37.7%) had received ≥3 prior lines of treatment.

Efficacy evaluation

As of March 5, 2020, 44 (83.0%) of 53 patients had experienced disease progression events (9 patients had incomplete post-baseline efficacy assessments). Thirty-nine

Table 1 Baseline patient characteristics

Characteristics	All treated patients (n=53)
Sex, n (%)	
Male	40 (75.5)
Female	13 (24.5)
Age (years), n (%)	
Median [range]	57 [30–77]
<60	27 (50.9)
≥60	26 (49.1)
ECOG performance status, n (%)	
0–1	49 (92.5)
2	4 (7.5)
Smoking history, n (%)	
Yes	45 (84.9)
No	8 (15.1)
Previous lines of treatment, n (%)	
2	33 (62.3)
≥3	20 (37.7)
Brain metastases, n (%)	
Yes	10 (18.9)
No	43 (81.1)
Liver metastases, n (%)	
Yes	10 (18.9)
No	43 (81.1)
Bone metastases, n (%)	
Yes	14 (26.4)
No	39 (73.6)

ECOG, Eastern Cooperative Oncology Group.

(73.6%) of the 53 patients had died, 7 had survived, and 7 had been lost to follow-up; 3 of the surviving patients are still receiving the treatment. The best response was PR in 11 patients (21.0 %) and SD in 37 patients (70%) (*Figure 2*). The ORR was recorded for 11 (20.8%) of 53 patients, with PR recorded in each case. The full analysis set had a median PFS reaching 3.0 months (95% CI, 2.1–3.9), and 3 (5.7%) of the 53 patients did not experience disease progression, with a PFS of 19.2, 9.2, and 4.9 months, respectively, as of the cutoff date. At the cutoff date, the median OS was 5.0 months (95% CI, 3.6–6.4) (*Figure 3*). The OS rate was

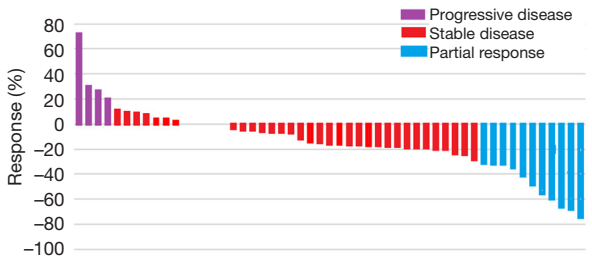

Figure 2 Waterfall plot showing the best response in target lesion size in 53 patients who had at least one post-baseline efficacy assessment. Five patients had 0% change from baseline. The color indicates the type of response.

40.1% (95% CI, 26.2–54) and 18.4% (95% CI, 4.7–32.1) at 6 and 12 months, respectively.

Adverse events

Toxicity is an important aspect of cancer treatment strategies. A previous study showed that apatinib at a dose of 750 mg once a day resulted in substantial toxicities in a cohort of breast cancer patients. Most of the patients experienced toxicities of grade III or worse, which led to a dose delay with dose reduction (20). However, in previous studies, a low dose of apatinib (250 mg daily) as a monotherapy or combination therapy has shown tolerable or controllable toxicity in numerous cancers (21,22). In this phase II study, we evaluated the safety of apatinib (250 mg once daily) plus etoposide capsules (50 mg once daily). The most common grade I or II adverse events observed in our study were anemia [17 (24.5%)], leukopenia [16 (30.2%)], fatigue [15 (28.3%)], nausea [13 (24.5%)], proteinuria [10 (18.9%)], vomiting [10 (18.9%)], hand-foot syndrome [9 (17%)], thrombocytopenia [9 (17%)], and hypertension [8 (15.1%)] (*Table 2*). No treatment-related deaths or unexpected toxicities occurred.

Severe adverse events were observed in three patients. One patient had anemia with a hemoglobin concentration of 5.4 g/dL and was transferred to hospital for a blood transfusion; this event was possibly related to the etoposide capsules. One patient had neutropenia with an absolute neutrophil count of 300 cells per μL, which could possibly be attributed to the etoposide capsules. Another patient developed massive ascites as a result of disease progression.

Dose interruption was required by 11 patients due to intolerable toxicity including 8 patients with grade III or VI leukopenia, 1 patient with anemia, 1 patient with impaired

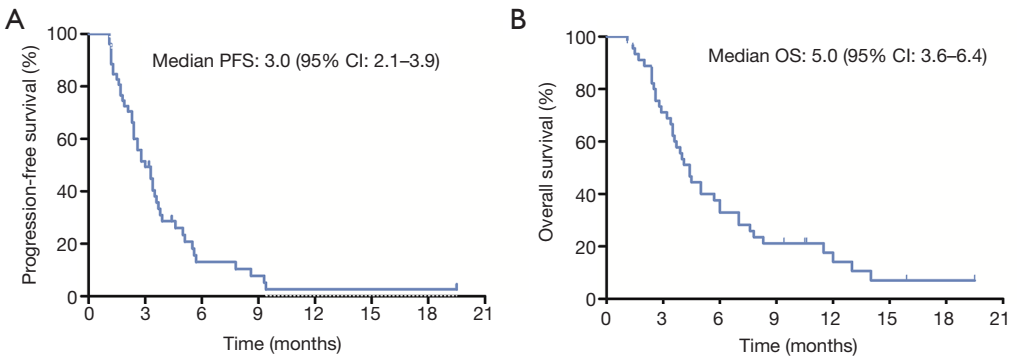

Figure 3 Kaplan-Meier curve for PFS in patients with at least one post-baseline efficacy assessment (n=53). Estimation of the PFS of patients with ES-SCLC treated with apatinib plus etoposide capsules (A). Estimation of the OS of patients with ES-SCLC treated with apatinib plus etoposide capsules (B).

liver function, and 1 patient with mucositis. Treatment was resumed at the same dosage after recovery to grade I or better.

Discussion

As a highly aggressive lung cancer, SCLC is defined by poor differentiation, rapid tumor growth, and poor survival outcome (23). Generally, SCLC is divided into limited and extensive stages depending on the extent of the disease. The International Association for the Study of Lung Cancer (IASLC) defines limited-stage patients as those without distant metastasis, and extensive-stage patients as those with distant metastatic sites (24). ES-SCLC makes up 60–70% of all SCLCs and has a survival rate of only 1% at 5 years after diagnosis (25). Despite the extreme sensitivity SCLC shows to initial treatment with chemotherapy or radiotherapy, drug resistance eventually occurs, and most patients progress rapidly or relapse, which has remained an immense treatment challenge, despite the arrival of immunotherapy in recent years (23,26,27).

In the past 30 years, etoposide combined with platinum has become broadly recognized as the first-line gold standard of chemotherapy for SCLC (23). Although SCLC is highly sensitive to chemotherapy, most patients develop recurrence or metastasis within 1 year after receiving the initial treatment. According to the duration time after first-line chemotherapy, the disease is classified into three categories: sensitive type (tumor response lasting 90 days or longer), resistant type (recurrence within 90 days of completing primary therapy), or refractory type (progression during the first-line chemotherapy) (28,29). While some chemotherapeutics such as irinotecan, topotecan, and paclitaxel have exhibited anti-tumor activity in the second-line treatment of SCLC, their efficacy is mainly dependent on the patient's response to first-line chemotherapy and is still unsatisfactory, with toxic reactions including severe neutropenia and anemia (29). For patients who suffer relapse after second-line treatment, follow-up treatment strategies are limited.

Apatinib is a small-molecule TKI that can suppress the activity of VEGFR-2 to decrease cell proliferation and induce apoptosis. It has been shown to exert an anti-tumor effect in numerous solid tumors, including SCLC (14,30-32). Etoposide, an inhibitor of topoisomerase II, has demonstrated anti-cancer activity both in untreated and pretreated patients with ES-SCLC (33). Additionally, in a phase II, single-arm, prospective study, oral apatinib combined with etoposide capsules showed promising efficacy and reasonable toxicity in patients with ovarian tumors that were resistant or refractory to platinum (19). However, concern remains over the use of this combination regimen in ES-SCLC.

As far as we are aware, ours is the first evaluative study on the efficacy and safety of apatinib plus etoposide capsules in patients with relapsed or refractory ES-SCLC. This study reached all of its primary and secondary endpoints, and demonstrated considerable efficacy and reasonable safety of apatinib plus etoposide capsules in the 53 patients enrolled. An objective response was observed in almost 21% of cases. The median PFS reached 3.0 months (95% CI, 2.1–3.9), and the median OS reached 5.0 months (95% CI, 3.6–6.4). Moreover, this combination treatment had manageable toxicity. As apatinib and etoposide are orally administrated,

Table 2 Possible treatment-related adverse events in the safety population

Adverse events	Grade (%)		
	Grade I–II	Grade III	Grade IV
Hematological			
Leukopenia	16 (30.2)	6 (11.3)	2 (3.8)
Anemia	17 (32.1)	4 (7.4)	0
Thrombocytopenia	9 (17.0)	2 (3.8)	1 (3.9)
Neutropenia	12 (22.6)	5 (9.4)	2 (3.8)
Lymphopenia	2 (3.8)	0	0
Non-hematological			
Fatigue	15 (28.3)	0	0
Nausea	13 (24.5)	1 (1.9)	0
Vomiting	10 (18.9)	1 (1.9)	0
Proteinuria	10 (18.9)	0	0
Hand-foot syndrome	9 (17.0)	2 (3.8)	0
Hypertension	8 (15.1)	1 (1.9)	0
Hypokalemia	7 (13.2)	0	0
Hyponatremia	4 (7.5)	0	2 (3.8)
Increased AST	5 (9.4)	2 (3.8)	0
Increased ALT	6 (11.3)	0	0
Hyperbilirubinemia	6 (11.3)	1 (1.9)	0
Hypoalbuminemia	3 (5.7)	0	0
Increased LDH	1 (1.9)	0	0
Anorexia	5 (9.4)	0	0
Diarrhea	2 (3.8)	0	0
Cough	2 (3.8)	0	0
Mucositis	2 (3.8)	1 (1.9)	0
Hoarseness	5 (9.4)	0	0
Gingival hemorrhage	2 (3.8)	0	0
Alopecia	1 (1.9)	0	0
Pain	2 (3.8)	0	0
Rash	2 (3.8)	0	0
Pruritus	1 (1.9)	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

intravenous transfusion or frequent hospital admission is not necessary; thus, this regimen may be conveniently administrated and economically beneficial for patients. Also, in most ES-SCLC patients, death occurs rapidly after disease progression in the third or further line setting, which means that oral medication might be more suitable for those receiving palliative therapy, especially during the COVID-19 pandemic, as it removes the need for frequent hospital visits (34).

According to the published reports, fatigue, hypertension, proteinuria, and hand-foot syndrome are the most frequently reported adverse events related to apatinib. These adverse events were also observed in our study, with patients experiencing fatigue (28.3%), proteinuria (18.9%), hand-foot syndrome (17%), and hypertension (15.1%), and most cases were grade I or II. Hoarseness was observed in 5 patients (9.4%) in our study, which was considered to be related to the use of apatinib. Hand-foot syndrome (3.8%), hypertension (1.9%), and mucositis (1.9%) were the main grade III or IV adverse events associated with apatinib, and leukopenia (15.1%), neutropenia (13.2%), and anemia (7.4%) were the leading hematological toxicities resulting from etoposide. Grade IV hyponatremia was observed in two patients in our study and was possibly disease-related. All adverse events were tolerable after symptomatic and supportive treatment, and no serious adverse events, such as interstitial pneumonia, occurred. Previous studies have also reported that the toxicity of VEGFR-TKIs acts as a predictive biomarker of the therapeutic effect; however, in this study, no significant relationship was observed between adverse events and PFS or OS.

Nivolumab or pembrolizumab is approved by Food and Drug Administration (FDA) as a third- or later-line therapy for patients with ES-SCLC. In the CheckMate 032 study evaluating the efficacy and safety of third- or later-line nivolumab monotherapy treatment, an ORR of 11.9% was observed in 71.6% of ES-SCLC patients receiving third-line treatment; the median PFS and OS were 1.4 months and 5.6 months, respectively; and the OS rate at 12 months was 28.3% (35). In the KEYNOTE-028 study, 50% of patients with ES-SCLC and a tumor cell, immune infiltrate and stromal summative programmed death ligand-1 status combined positive score (CPS) of ≥1% received pembrolizumab as the third line of treatment. The ORR for the entire cohort was 33%. The median PFS and OS were 1.9 and 9.7 months, respectively. The 12-month PFS and OS were 23.8% and 37.7%, respectively. The phase II TRINITY study evaluated the efficacy and safety of rovalpituzumab tesirine as a third- or further-line therapy for patients with ES-SCLC and delta-like 3 protein expression. For the entire cohort, the ORR was 12.4% and the median OS was 5.6 months. However, grade III–V adverse events were observed in 63% of patients (36).

Anlotinib is a novel multi-target inhibitor of tumor angiogenesis and growth that is approved as a third-line treatment for ES-SCLC by the Chinese Food and Drug Administration (CFDA) (37). In the ALTER1202 study, the median PFS of the anlotinib group exceeded that of the placebo group (4.3 *vs.* 0.7 months, HR =0.19, P<0.0001). The median OS in the anlotinib group reached 7.3 months, compared with 4.9 months in the placebo group (1).

The results of a retrospective study designed to investigate the efficacy of paclitaxel as the third-line chemotherapy for SCLC showed that the median PFS and OS were 2.5 and 5.9 months, respectively, and the incidence of grade III or IV neutropenia and thrombocytopenia was 20% and 10%, respectively.

In summary, the survival benefits observed in our data are comparable to those reported by previous studies of patients with ES-SCLC in the third- or further-line setting. Our findings suggest that apatinib with oral etoposide is effective with good tolerability and could potentially serve as a third- or further-line therapy for patients with ES-SCLC. However, we acknowledge that our study is a single-arm clinical trial and lacks a control group for comparison; therefore, selection bias cannot be ruled out. Nevertheless, our study demonstrated the efficacy and safety of low-dose apatinib combined with oral etoposide as a third- or further-line treatment for patients with ES-SCLC. Our results offer a manageable and feasible treatment strategy for ES-SCLC patients who have been heavily pretreated and provides further evidence for the clinical usage of the combination of low-dose apatinib and etoposide in ES-SCLC. Furthermore, apatinib and etoposide capsules can be taken orally and do not require intravenous access or hospitalization; therefore, they may offer a useful, convenient, and compassionate treatment option for patients and their families in the palliative setting.

Conclusions

Overall, the present analysis has demonstrated that the administration of apatinib combined with orally administrated etoposide as a third- or further-line treatment exhibited promising survival benefits in patients with ES-SCLC. Considering its encouraging efficacy and reasonable

toxicity, apatinib with oral etoposide may provide a more economical and convenient treatment alternative for patients with ES-SCLC in a similar setting. However, our findings are limited by the small sample size and lack of control subjects; confirmation in a well-designed phase III clinical trial is necessary.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/tlcr-20-1235

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-1235). The authors have no conflicts of interest to declare.

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. The independent ethics committee of Henan Cancer Hospital of Zhengzhou University granted approval for this study, which was carried out in adherence to the Declaration of Helsinki (as revise in 2013) and Good Clinical Practice Guidelines. All patients provided written informed consent.

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