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ORIGINAL ARTICLE

Apatinib for chemotherapy-refractory extensive-stage SCLC: a retrospective study

Hui Li[1] · Jian Zeng[2] · Xiangyu Jin[1] · Xinmin Yu[1] · Guoming Zhou[3] · Wei Hong[1]

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Abstract

Purpose There is no standard treatment strategy for patients with extensive-stage small cell lung cancer (SCLC) who have failed two or more prior chemotherapeutic regimens. In this study, we retrospectively evaluated the efficacy and safety of apatinib in patients with extensive-stage SCLC after failure of more than second-line chemotherapy.

Methods A study group comprised of 22 patients with extensive-stage SCLC after failure of more than two prior chemotherapeutic regimens was given apatinib orally at an initial dose of 500 mg daily until disease progression or unacceptable toxicity. This study was analyzed according to the National Cancer Institute Common Toxicity Criteria for adverse events (AEs) and Response Evaluation Criteria in Solid Tumors (RECIST) for response assessment.

Results Between August 30, 2015, and May 26, 2017, 22 patients were enrolled for evaluating the efficacy and safety of apatinib. Among them, 12/22 (54.5%) underwent dose reduction during treatment. Up to July 31, 2018, the median progression-free survival rate was 135.0 days [95% confidence interval (CI) 63.8–206.2]. According to the RECIST criteria, the disease control rate (DCR) was 86.4%, 19/22 [comprised of partial response (PR) 18.2%, 4/22; and stable disease (SD) 68.2%, 15/22 patients]. The most frequent AEs were hand–foot syndrome (45.5%, 10/22), secondary hypertension (45.5%, 10/22) and fatigue (40.9%, 9/22). The primary grade 3 or 4 toxicities were hypertension (22.7%, 5/22), hand–foot syndrome (13.6%, 3/22), and proteinuria (9.1%, 2/22).

Conclusions Apatinib exhibits modest activity and acceptable toxicity for patients with heavily pretreated extensive-stage SCLC.

Keywords Apatinib · Small cell lung cancer · Chemotherapy refractory · Efficacy · Safety

Introduction

Lung cancer is the most common malignancy in the world and is especially prevalent in China, with 733,300 newly diagnosed cases and 610,200 cancer deaths predicted in 2015 [1]. As a highly aggressive and lethal malignancy, small cell lung cancer (SCLC) accounts for approximately 15% of newly diagnosed lung cancer cases, and almost two-thirds of patients present with extensive disease (ED) at diagnosis [2]. Despite the fact that SCLC is highly sensitive to systemic chemotherapy, resulting in dramatic responses, the majority of patients have a high recurrence and eventually die from systemic metastases [3]. A combination of platinum and etoposide is the gold standard chemotherapy in current first-line treatment for SCLC [4] After relapse, standard second-line therapies such as irinotecan and topotecan only modestly improve the outcomes, and the overall survival (OS) for patients with ED is less than 1 year [5–7]. Moreover, for patients with ED-stage SCLC who experience progression with two or more lines of chemotherapy, there are still no standard treatment strategies. Over the past decades, little progress has been made with no new drugs approved. Therefore, the development of more effective novel strategies for chemotherapy-refractory SCLC is an unmet need.

Hui Li and Jian Zeng are co-first authors.

✉ Wei Hong
hongweizjcc@126.com

[1] Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou 310022, China

[2] Department of Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China

[3] Department of Laboratory Medicines, Zhejiang Cancer Hospital, Hangzhou 310022, China

Angiogenesis is recognized as one of the major hallmarks of tumor progression and metastasis, which was defined by Weinberg and Hanahan as a conceptual framework [8]. In SCLC, angiogenesis plays a key role not only in the formation of neovessels but also in growth, invasion and metastases. VEGF levels have been positively associated with microvessel density, which was confirmed as an independent prognostic factor in SCLC patients [9, 10]. As a core component of the angiogenesis, the VEGF pathway is active in SCLC. Salven et al. suggested that the VEGF levels and tumor stage may be independent prognostic factors in untreated SCLC patients [11], and VEGF was confirmed as a prognostic factor in SCLC in a systematic review and meta-analysis by Zhan et al. [12]. In addition, human SCLC cell lines express functional VEGFR2/3 (vascular endothelial growth factor receptor) and PDGFR-β (platelet-derived growth factor receptor), indicating that VEGF/VEGFR is an autocrine growth regulator in SCLC [13, 14].

The inhibition of angiogenesis has shown modest efficacy as an approach toward restraining several solid human cancers, including non-small cell lung cancer (NSCLC). However, for SCLC, several anti-angiogenic agent, such as bevacizumab [15–18], sunitinb [19, 20], thalidomide [21, 22], aflibercept [23], vandetanib [24], cediranib [25], sorafenib [26], pazopanib [27] and rovalpituzumab-tesirine [28], have been tested in clinical trials as a second-line therapy strategy. Unfortunately, the results were disappointing, and due to their limited efficacy, none of them has received regulatory approval. Additionally, Han et al. conducted a Phase II study on nintedanib, an oral multi-target tyrosine kinase inhibitor that targets VEGFR-1/2/3, FGFR-1/2/3 and PDGFRα/β, in SCLC patients who exhibited progression after one or two prior rounds of chemotherapy or chemo/radiotherapy [29]. The overall response rate (ORR) was 5%, the median progression-free survival (PFS) was 1.0 month, and the OS was 9.8 months. Thus, ninedanib also only exhibited limited activity owing to unfulfilled criteria in relapsed or refractory SCLC [4].

Apatinib is an oral tyrosine kinase inhibitor that specifically targets VEGFR-2. In preclinical models, apatinib inhibited the in vitro proliferation, migration and tube formation of HUVECs (human umbilical vein endothelial cells) and blocked rat aortic budding. In addition, apatinib presented statistically significant inhibition in established human lung, colon and gastric tumor xenograft models [4, 29]. Clinical activity of apatinib has been described in phase II or III studies of gastric cancer [29], breast cancer (non-triple-negative breast cancer and triple-negative) [30], non-squamous NSCLC and hepatocellular carcinoma. Furthermore, a recent study suggests that 250 mg per day of apatinib may have some utility as maintenance therapy for ED-stage SCLC when administered after induction therapy [31]. Given its promising activity and acceptable toxicity profile, we retrospectively assessed the efficacy and safety of apatinib for patients with ED-SCLC after the failure of second- or third-line chemotherapy.

Materials and methods

Data collection

Between August 30, 2015, and May 26, 2017, patients with SCLC who were diagnosed and treated with chemotherapy at Zhejiang Cancer Hospital consented to have their data available for research. SCLC was diagnosed by experienced pathologists who assessed the disease according to the American Joint Committee on Cancer classification. Patients with ED-SCLC who had progressed after treatment with at least two lines chemotherapy were eligible for inclusion in the study. Patients who had progressed more than 3 months after completing first-line treatment were considered "sensitive relapse" patients; patients who exhibited progressive disease (PD) within 3 months were considered "refractory relapse"; and patients, who did not respond or relapsed during first-line chemotherapy, were considered "resistant". All patients displayed measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1); had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than or equal to 2; had adequate hepatic, renal and hematologic function; had normal thyroid function; and were at least 18 years of age. Baseline characteristics were obtained from their clinical files, including sex, age, ECOG PS, numbers of previous chemotherapy lines and relapse pattern after first-line chemotherapy therapy. Chest and abdominal CT scans and brain MRIs were performed for all patients who showed metastatic disease at initial evaluation before beginning oral apatinib. The responses to apatinib were evaluated after the first month of oral apatinib and every two subsequent months after the first evaluation until the disease progressed, and were recorded as complete response (CR) or partial response (PR). PD was evaluated according to RECIST criteria, and the PFS after administration of apatinib was calculated. Toxicities were scored according to the National Cancer Institute Common Toxicity Criteria, version 4.0 for reporting results of cancer treatment. A dose reduction to 250 mg daily was allowed for up to 3 weeks for grade 3 and grade 4 toxicities even after symptomatic treatment.

Statistical analyses

The PFS time was calculated by the Kaplan–Meier method. All statistical calculations were performed with SPSS 22.0 for Windows (Chicago, IL). Two-sided P values of <0.05 were considered to represent statistical significance.

Ethics statement

All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Results

Patient characteristics

Data were extracted for 30 patients with ED-SCLC who had been treated from August 30, 2015, to May 26, 2017, at Zhejiang Cancer Hospital. Among the patients, 22 who had received at least 1 cycle of apatinib were available for efficacy and safety evaluation. The baseline characteristics of the evaluated patients are listed in Table 1. The median age was 58 years (range 39–73), and the majority of patients (90.9%, 20/22) were male. Thirteen patients (59.1%, 13/22) had an ECOG PS of 0 or 1. Twelve patients (54.5%, 12/22) had received two prior chemotherapy regimens, and ten patients (45.5%, 10/22) had received three or more lines of chemotherapy. Fourteen patients (63.6%, 14/22) exhibited resistant or refractory relapse after first-line chemotherapy and eight patients (36.4%, 8/22) were sensitive to the first-line chemotherapy.

Apatinib delivery

Nineteen patients (19/22, 86.4%) received two or more cycles of apatinib at a dose of 500 mg daily. Up to July 31, 2018, no patients (0%, 0/22) remained on treatment. For 21 patients (95.5%), the reason for treatment discontinuation was PD during treatment. Twelve of 22 patients (54.5%) required a 50% dose reduction because of grade 3 or 4 toxicities, and only one patient (4.5%) discontinued treatment because of third-degree fatigue even after the dose was reduced to 250 mg (Table 2).

Table 1 Baseline characteristics of patients

Characteristics	Number of patients	%
Age (years)		
Median (range)	58 (39–73)	
Gender		
Male	20	90.9
Female	2	9.1
ECOG PS		
0–1	13	59.1
2	9	40.9
Prior therapy numbers		
Two	12	54.5
Three or more	10	45.5%
Relapse pattern		
Sensitive	8	36.4
Resistant or refractory	14	63.6

ECOG PS Eastern Cooperative Oncology Group performance status

Toxicity evaluation

All patients who received at least one cycle of treatment were assessed for toxicity. The results were reported as the maximum toxicity experienced during the treatment. As shown in Table 3, the most frequent treatment-related adverse events (AEs) were hand–foot syndrome (45.5%, 10/22), secondary hypertension (45.5%, 10/22) and fatigue (40.9%, 9/22). The main grade 3 or 4 toxicities were hypertension (22.7%, 5/22), hand–foot syndrome (13.6%, 3/22), and proteinuria (9.1%, 2/22). Most AEs were mild and manageable. There were no treatment-related deaths.

Response and survival

Up to July 31, 2018, a total of 22 patients were evaluable for response. As shown in Table 4, 4 of the 22 patients (18.2%, 4/22) presented a PR, 15 of 22 patients 68.2%, 15/22) exhibited stable disease (SD) and 3 patients (13.6%, 4/22) showed PD. Among the fifteen patients with SD, nine patients (60.0%, 9/15) showed some degree of tumor shrinkage (Fig. 1). The disease control rate (DCR, including CR, PR and SD patients) was 86.4% (19/22) and the ORR (including CR and PR) was 18.2% (4/22). Among eight patients with sensitive relapse after first-line chemotherapy, one (12.5%, 1/8) showed a PR, six (75.0%, 6/8) showed SD and one (12.5%, 1/8) showed PD. The ORR was 12.5% (1/8) and the DCR was 87.5% (7/8). Among patients who were resistant or refractory after first-line chemotherapy, three (21.4%, 3/14) presented a PR; nine patients (64.3%, 9/14) exhibited SD and two patients (14.3%, 2/14) showed PD. The ORR was 21.4% (3/14), and the DCR was 85.7%

Table 2 Treatment delivery and patient disposition

	Number of patients	%
Treatment status		
Discontinued	22	100.0
Continued	0	0.0
Discontinuation reason		
PD	21	95.5
Unacceptable toxicity	1	4.5
Dose reduction		
Reduction to 250 mg/day	12	54.5

PD progressive disease

Table 3 Adverse event

AE	Grade 1 (*n*, %)	Grade 2 (*n*, %)	Grade 3 (*n*, %)	All grades (*n*, %)
Hypertension	4 (18.2%)	1 (4.5%)	5 (22.7%)	10 (45.5%)
Skin rash	1 (4.5%)	1 (4.5%)	1 (4.5%)	3 (13.6%)
Diarrhea	2 (9.1%)	2 (9.1%)	0 (0.0%)	4 (18.2%)
Fatigue	6 (27.3%)	2 (9.1%)	1 (4.5%)	9 (40.9%)
Mucositis	3 (13.6%)	1 (4.5%)	1 (4.5%)	5 (22.7%)
Anorexia	4 (18.2%)	1 (4.5%)	0 (0.0%)	5 (22.7%)
Hand–foot syndrome	3 (13.6%)	4 (18.2%)	3 (13.6%)	10 (45.5%)
Leukopenia	1 (4.5%)	1 (4.5%)	0 (0.0%)	2 (9.1%)
Neuropenia	1 (4.5%)	1 (4.5%)	0 (0.0%)	2 (9.1%)
Anemia	3 (13.6%)	0 (0.0%)	0 (0.0%)	3 (13.6%)
Thrombocytopenia	3 (13.6%)	0 (0.0%)	0 (0.0%)	3 (13.6%)
ALT elevation	2 (9.1%)	0 (0.0%)	0 (0.0%)	2 (9.1%)
AST elevation	3 (13.6%)	0 (0.0%)	0 (0.0%)	3 (13.6%)
Bilirubin elevation	4 (18.2%)	0 (0.0%)	0 (0.0%)	4 (18.2%)
Proteinuria	1 (4.5%)	3 (13.6%)	2 (9.1%)	6 (27.3%)
Creatinine elevation	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.5%)

AE adverse events

Table 4 Objective response results

	Whole patients (*n*, %) *n* = 22	Sensitive patients (*n*, %) *n* = 8	Resistant or refratory patients (*n*, %) *n* = 14
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	4 (18.2%)	1 (12.5%)	3 (21.4%)
SD	15 (68.2%)	6 (75.0%)	9 (64.3%)
PD	3 (13.6%)	1 (12.5%)	2 (14.3%)
ORR	4 (18.2%)	1 (12.5%)	3 (21.4%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* overall response rate

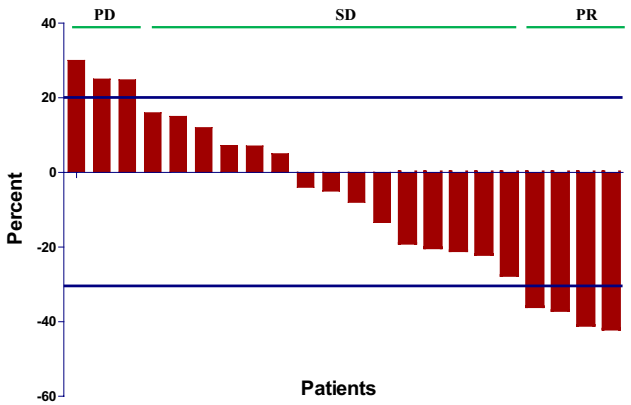

Fig. 1 The effect of treatment with apatinib in patients with extensive-stage SCLC after the failure of second- or third-line chemotherapy. Among twenty-two patients who received apatinib treatment, four patients (18.2%, 4/22) presented a PR, fifteen patients (68.2%, 15/22) exhibited SD and three patients (13.6%, 4/22) showed PD. Among the fifteen patients with SD, nine patients (60.0%, 9/15) showed some degree of tumor shrinkage

(12/14). The median PFS was 135.0 days [95% confidence interval (CI) 63.8–206.2] (Fig. 2a), whereas the median OS had not been reached. The median PFS of patients with sensitive relapse after first-line chemotherapy was 122.0 days (95% CI 0.0–291.1). For the patients who were resistant or refractory after first-line chemotherapy, the median PFS was 135.0 days (95% CI 48.8–221.2), and there were no significant differences in these subgroups ($P = 0.13$), suggesting the specific activity of apatinib in SCLL compared to the conventional chemotherapy (Fig. 2b).

Discussion

Although there is substantial biologic rationale for targeting angiogenesis in SCLC, few clinical trials have yielded positive results. There are only three ongoing clinical trials registered on clinicaltrials.gov that investigate anti-angiogenesis agents in SCLC, which raises questions as to whether angiogenesis-targeting therapy is effective for SCLC. Here, we retrospectively evaluated the tyrosine kinase inhibitor apatinib as a treatment for ED-SCLC patients who experienced progression with two or more lines of chemotherapy. Apatinib exhibits modest activity and acceptable toxicity for patients with heavily pretreated extensive-stage SCLC.

For almost 30 years, combination chemotherapies of etoposide with a platinum salt (either cisplatin or carboplatin) have been widely accepted as the gold standard chemotherapy regimen in SCLC [4]. However, most patients with SCLC relapse within 1 year of initial treatment, regardless of the high response rate (RR) to first-line chemotherapy [32]. Several chemotherapeutic agents, including irinotecan

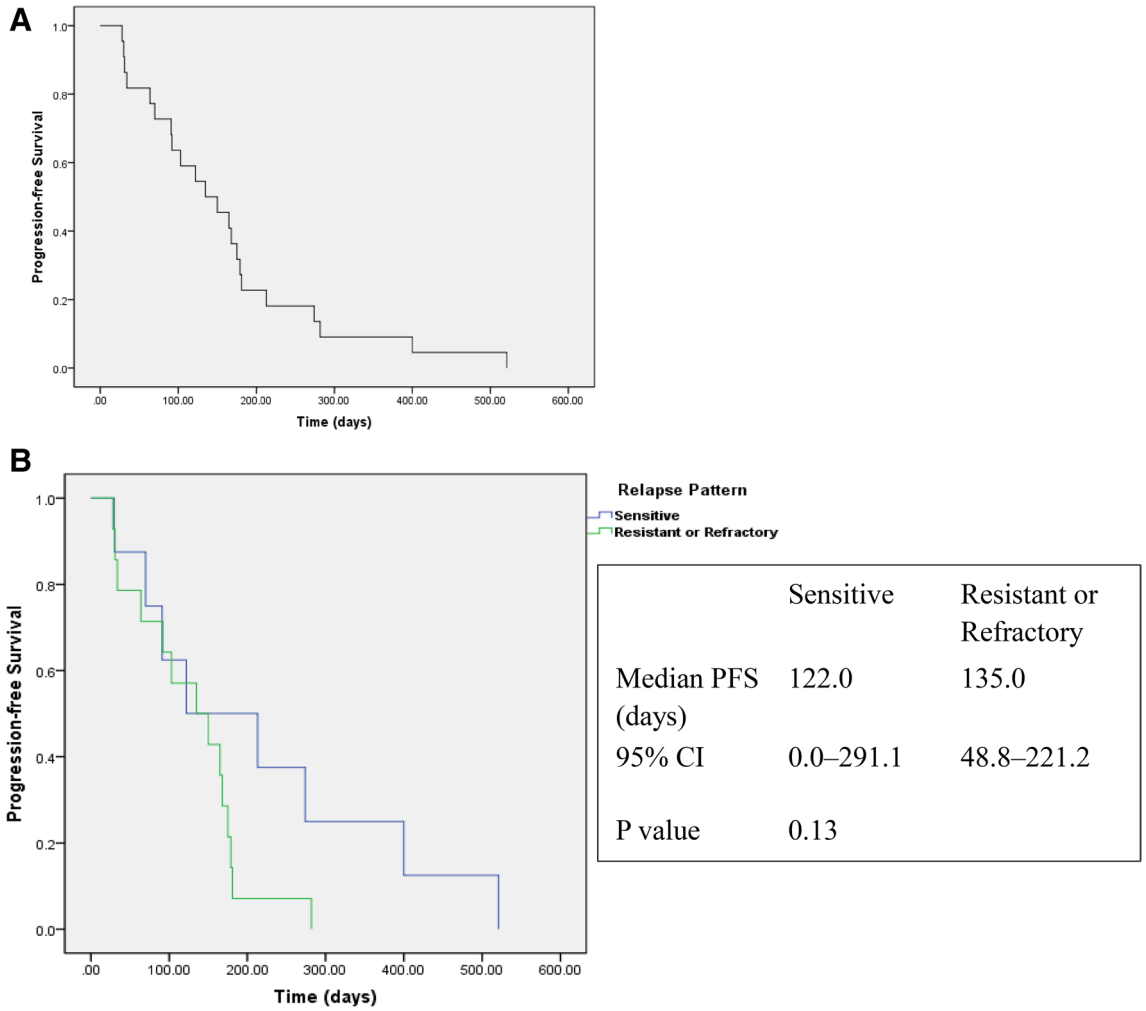

Fig. 2 Kaplan–Meier survival curve of progression-free survival for patients treated with apatinib as third-line therapy. A total of 22 patients were evaluated until July 31, 2018. The median PFS was 135.0 days (95% CI 63.8–206.2)

and topotecan paclitaxel, have shown activity in the second-line setting of SCLC, depending on the response to first-line chemotherapy [categorized as sensitive (time to progression > 3 months), resistant (time to progression ≤ 3 months) or refractory (progression during first-line therapy)]. Topotecan showed times to progression of 13.3 weeks, which places it barely in the sensitive range [5, 6]. Therefore, for patients with a second relapse, subsequent lines of therapy regimens are needed. However, there is little evidence to guide treatment decisions, and until recently, only a few studies have investigated the efficacy of third-line chemotherapy in SCLC.

De Jong et al. and Lebeau et al. analyzed the efficacy of third-line chemotherapy in SCLC at a single institution [33, 34]. In the former study, 191 patients were treated for SCLC over an 8.5-year period, with only 35 patients (18.3%) who had received a third-line of chemotherapy. The RR was 26% and the median OS was 5 months [33]. The study by Lebeau et al. included 35 patients who were being treated with a combination of lomustine, etoposide and cyclophosphamide in the third-line setting [34]. The RR was 31% and the median OS was 4.4 months [34]. In a small single-arm study by Park et al., the toxicity and efficacy of paclitaxel with ifosfamide were assessed in the third or more lines setting for 35 South Korean patients with SCLC, among whom 26 (26/75, 74%) received third-line chemotherapy [35]. The authors reported that the RR was 20% without CR [35]. Furthermore, Igawa et al. investigated the safety and efficacy of amrubicin in 27 Japanse patients who had received one or two lines of chemotherapy to identify the optimal dose [36]. Fourteen (14/27, 51.9%) patients received treatment in the third-line setting, and the cumulative RR was 14%. For the entire study cohort (second line and third line), the median OS was 9.2 months. However, the authors did not report data for the 14 patients who received amrubicin in a third-line

setting [36]. Recently, apatinib was shown to have some potential efficacy as maintenance therapy after induction therapy [31], which suggests that it may also be useful for third-line treatment. In our study, the DCR was 86.4% (19/22) without CR and the median PFS was 103.0 days, indicating a potential survival benefit from apatinib as a third-line treatment strategy in SCLC.

The AE and toxicity profiles observed in our study were similar to those from previous clinical trials of apatinib. The most frequently observed AEs of apatinib in our study were hand–foot syndrome (45.5%, 10/22), secondary hypertension (45.5%, 10/22) and fatigue (40.9%, 9/22). As a result, 54.5% of the patients (12 of 22) received a 50% dose reduction. After the dose reduction and symptomatic treatment, most patients tolerated apatinib treatment. Only one patient (1/22, 4.5%) interrupted the apatinib treatment owing to unacceptable toxicity even with the dose reduction or supportive treatment. The possible mechanism of apatinib-induced hypertension is thought to be downregulation of nitric oxide synthase caused by inhibition of VEGFR in arterial endothelial cells. However, using angiotensin receptor blocker with or without calcium antagonists, hypertension may be able to be controlled. Furthermore, hand–foot syndrome can be well tolerated after dose reduction [37]. Therefore, given the manageable toxicity profile, apatinib could be considered as a potential option for patients with ED-SCLC who have undergone multiple rounds of chemotherapy, though further studies may be needed to optimize the dosing regimen according to the comprehensive situation of each patient.

The lack of predictive biomarkers is still a challenge for assessing the efficacy of anti-angiogenic strategies. A few of biomarkers have been proposed, such as VEGF levels, treatment-related hypertension and functional imaging [38], but none has accurately predicted the response to angiogenesis inhibitors. In our studies, the treatment-related AEs were not associated with the efficacy of apatinib, and it is, therefore, unclear how apatinib may function to inhibit SCLC progression. Considering the modest activity of apatinib in the treatment of SCLC compared to previous anti-angiogenesis strategies with little or no activity, we speculate that the efficacy of apatinib may contribute to the inhibition of the growth of cancer stem cells, which are thought to be major contributors to the chemotherapy-resistance and aggressive phenotype of SCLC [39]. Apatinib may target pro-angiogenic molecules other than VEGFR2, which still needs further investigation. This study was also limited by the different forms of previous therapy that the patients had, which may have introduced some variability into the results. Furthermore, our study is limited by its size and the fact that it was performed retrospectively. A larger prospective study will be required to confirm the efficacy and safety of apatinib as a third-line treatment for SCLC.

Conclusion

In this single-center retrospective study, apatinib exhibited modest activity and acceptable toxicity for heavily pretreated patients with ED-SCLC. Further investigation is needed to better define the safety benefits of apatinib in patients previously treated for SCLC. In addition, identification of the appropriate dose and underlying mechanism of apatinib needs to be further explored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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