A Prospective Study of Apatinib in Patients with Extensive-Stage Small Cell Lung Cancer After Failure of Two or More Lines of Chemotherapy

YUTAO LIU, a XINGSHENG HU, a JUN JIANG, b LIN YANG, c SHENGYU ZHOU, a PENG LIU, a JUNLING LI, a YAN WANG, a XUEZHI HAO, a YUANKAI SHI a

aDepartment of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, People’s Republic of China; bDepartment of Radiology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People’s Republic of China; cDepartment of Pathology, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People’s Republic of China

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Apatinib • Small cell lung cancer • Third-line treatment • Subsequent-line treatment

ABSTRACT

Background. Because of rapid disease progression and lack of optimal treatment strategies beyond the second-line, the prognosis of patients with extensive-stage (ES) small cell lung cancer (SCLC) still remains depressing. Alternative treatment strategies are required to improve their prognosis. In this prospective clinical study, we aimed to evaluate the feasibility of single-agent apatinib, a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor, as a treatment option for patients with ES-SCLC after failure of at least two prior chemotherapy regimens.

Materials and Methods. Twenty-two patients with ES-SCLC treated with 500 mg single-agent apatinib as subsequent-line regimen in our institution from November 2016 to August 2018 were enrolled in the study. The primary end-point was progression-free survival (PFS). The secondary end-points included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs).

Results. Clinical outcomes included partial response in 3 patients (13.6%), stable disease in 18 patients (81.8%), and disease progression in 1 patient (4.5%), with an ORR of 13.6% and DCR of 95.5%. The median PFS and OS were 5.4 and 10.0 months, respectively. Apatinib demonstrated a manageable toxicity profile, with grade I–III secondary hypertension and proteinuria as the most common AEs. No grade IV and V AEs were observed among the patients. Multivariate analysis revealed secondary hypertension as an independent predictor of OS ($p = .047$); however, the association became insignificant after Q correction ($p = .455$).

Conclusions. Apatinib was safe and effective in the management of patients with ES-SCLC and can be considered as a treatment option after failure of at least two prior chemotherapy regimens. ClinicalTrials.gov identifier. NCT02995187

The Oncologist 2020;25:e833–e842

Implications for Practice: This study indicated the acceptable toxicity profile and promising efficacy of apatinib in the management of patients with extensive-stage small cell lung cancer after failure from at least two prior chemotherapy regimens. Secondary hypertension can be a potential prognostic factor for apatinib treatment.

INTRODUCTION

Small cell lung cancer (SCLC) represents 15% of all lung cancers. Although rare cases involving never-smokers were reported, a majority of the patients with SCLC are elderly men who are current or past smokers and have various...
pulmonary, cardiovascular, and metabolic comorbidities [1]. Because of its aggressive clinical course, 60%–70% of the patients with SCLC exhibit regional and distal metastasis at diagnosis [2]. Hence, prognosis remains very poor, with a 5-year survival rate of less than 7% [3] and median survival of only 2–4 months in untreated patients with extensive-stage (ES) SCLC [1]. Combination chemotherapy is an essential treatment modality in patients with ES-SCLC, with 4–6 cycles of etoposide or irinotecan plus platinum-containing chemotherapy as the standard regimen [1, 4–6]. Patients with ES-SCLC treated with front-line combination chemotherapy have response rates between 60% and 70% and median overall survival between 9 and 11 months [5–7]. In addition, the significantly longer survival outcomes for patients with ES-SCLC receiving a combination of chemotherapies and atezolizumab, an immunotherapy agent, as front-line therapy as compared with chemotherapy alone resulted in its recent approval by the US Food and Drug Administration [8]. Despite remarkable response to initial treatment, a majority of patients will eventually relapse with a disease that is relatively resistant to subsequent treatment [2, 5]. Generally, clinical response to subsequent lines of therapy is low and primarily associated with the duration of response from the initial treatment, whereas better response to subsequent lines of therapy (response rate of ~25%) was observed in patients whose disease relapsed later than 3 months than in those whose disease relapsed within 3 months (response rate of <10%) [2, 5, 6]. The median survival with subsequent lines of therapy is only between 4 and 5 months [6]. Currently, topotecan remains the only approved drug for patients with SCLC in the second-line setting. However, after failure from second-line chemotherapy, the clinical management of patients with ES-SCLC remains limited and controversial. Recently, in line with their growing use in other solid tumors, immune checkpoint inhibitors, particularly nivolumab monotherapy, have also benefitted previously treated patients with ES-SCLC, resulting in its recent approval as a standard treatment in the third-line setting [9].

Consistent with other malignancies, angiogenesis is also essential in the tumor progression of SCLC. The protein expression of vascular endothelial growth factor (VEGF), one of the essential growth factors in angiogenesis, has been reported to be correlated with the prognosis of patients with SCLC [10]. Thus, the inhibition of the components of the VEGF signaling pathway is an attractive treatment option for patients with SCLC. A meta-analysis including three randomized control trials and six single-arm trials regarding the use of bevacizumab, a widely used anti-VEGF monoclonal antibody, in combination with chemotherapy as first-line therapy demonstrated no significant improvement in survival outcomes in ES-SCLC [11]. Despite no significant survival benefit reported by two prior clinical trials [12, 13], a more recent phase III clinical study reported an acceptable toxicity profile and significant improvement in progression-free survival (PFS) and overall survival (OS) of patients treated with bevacizumab, a VEGF-A monoclonal antibody, in addition to cisplatin and etoposide as front-line therapy [14]. Moreover, patients with ES-SCLC receiving bevacizumab in the second-line setting demonstrated a median PFS of 2.7–4 months and median OS of 6.3–7.4 months [11]. Conversely, apatinib, a selective small molecule inhibitor of VEGF-receptor-2 tyrosine kinase, has been proven to be safe and effective for the treatment, particularly after failure from second-line chemotherapy, of a broad range of advanced solid tumors, including gastric, non-small cell lung, breast, gynecological, and thyroid cancers, hepatocellular carcinoma, and sarcomas [15, 16]. Considering not only the limited improvement in survival outcome brought about by combination therapies in patients with SCLC but also the potential for overlapping or cumulative toxicities from prior chemotherapy regimens, single-agent therapy is an attractive treatment option for the treatment of relapsed SCLC [17]. The efficacy and safety of 250 mg apatinib as maintenance treatment after front-line etoposide and platinum-based combination in Chinese patients with ES-SCLC was revealed by a recent retrospective study [18]. However, no information on the efficacy of apatinib monotherapy in the third-line or subsequent-line setting in patients with ES-SCLC has yet been reported. In this prospective study, we aimed to evaluate the clinical responses and survival outcomes of Chinese patients with ES-SCLC treated with single-agent apatinib after failure from at least two prior chemotherapy regimens.

Subject, Materials, and Methods

Patient Recruitment (Inclusion and Exclusion Criteria)

A total of 27 Chinese patients were diagnosed with ES-SCLC from our institution between November 2016 and August 2018 (Fig. 1). The extent of the disease was classified according to the two-stage classification scheme of the Veterans Administration Lung Group, wherein extensive-stage disease is defined as disease beyond the ipsilateral hemithorax, including the presence of malignant pleural or pericardial effusion or hematogenous metastases [6]. Patients aged 18 to 75 years, with small cell lung carcinoma histology, measurable disease (at least one single-path measurable lesion with longest diameter of ≥10 mm measured by spiral computed tomography [CT]), and metastatic disease, who recurred or failed from at least two prior chemotherapy regimens and Eastern Cooperative Oncology Group (ECOG) performance score (PS) of at least 2 were recruited in the study. Patient exclusion criteria included (a) non-small cell lung carcinoma histology; (b) previous therapy with VEGF inhibitors; (c) allergy to any ingredients of apatinib mesylate; (d) presence of necrotizing tumors; (e) presence of clinical symptoms of brain or meningeal metastasis; (f) uncontrolled hypertension (i.e., systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, despite optimal drug treatment); (g) suffering from severe cardiovascular disease, myocardial ischemia, or myocardial infarction above grade II, poorly controlled arrhythmias (including men with QTc interval ≥450 milliseconds, women ≥470 milliseconds) according to New York Heart Association criteria, grades III to IV insufficient function, or cardiac color, Doppler ultrasound examination indicating left ventricular ejection fraction <50%; (h) events of venous and/or venous thrombosis occurring within the first 12 months of apatinib treatment such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, cerebral infarction), deep vein thrombosis, and pulmonary embolism; (i) abnormal blood coagulation (international normalized ratio >1.5 or prothrombin...
time > upper limit of normal [ULN] + 4 seconds or activated partial thromboplastin time >1.5 ULN) with bleeding tendency, or a clear tendency to hemorrhage (i.e., gastrointestinal bleeding, hemorrhagic stomach ulcer, or basal fecal occult blood) or undergoing thrombolytic or anticoagulant therapy; (j) major surgery or severe traumatic injury, fracture, or ulcer within 4 weeks prior to apatinib treatment; and (k) clinically significant sputum or daily hemoptysis greater than half a teaspoon (2.5 mL) or more within 2 months prior to apatinib treatment. Four patients did not fulfill the inclusion criteria and another patient did not consent to participate in the clinical study. A total of 22 patients with ES-SCLC were recruited for the study. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is illustrated in Figure 1. Written informed consent was provided by all the patients. The study was approved by the Review Board of Cancer Hospital, Chinese Academy of Medical Sciences (No. 16-163/1242) and conducted in accordance with the Declaration of Helsinki.

Treatment Schedule
Apatinib mesylate was orally administered at a dose of 500 mg once daily on a 28-day cycle until the evaluation of disease progression (PD) or the occurrence of unacceptable toxicity. Dosage reduction to either 425 mg or 250 mg once daily was permitted based on the evaluation of toxicities. Dosage re-escalation was permitted. No other chemotherapy was administered during the period of apatinib treatment, whereas brain radiotherapy was allowed for cases with brain metastasis.

Evaluation of Treatment Response and Adverse Events
Treatment response was evaluated using RECIST version 1.1 [19, 20] by investigator assessment using CT or magnetic resonance imaging scans. Evaluation of treatment response was performed after 1 cycle (28 days) and every 2 cycles (56 days) thereafter until treatment termination. Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0.3) standards. The severity of the adverse symptoms was further classified into grades I–V, with grade I as mild, grades III–IV as moderate toxicity, and grade V as death. Treatment failure was defined as (a) evaluation of PD during or after the last treatment evidenced by imaging or clinical progression, and (b) withdrawal from treatment because of intolerance of AEs (i.e., grade ≥IV hematological toxicity or grade ≥II nonhematologic toxicity or grade ≥II heart, liver, kidney, and other major organs). ECOG PS score, blood, and urine routine tests were performed prior to and every cycle of apatinib treatment until treatment termination.

Statistical Data Analysis
The primary endpoint of this study was PFS. The secondary endpoints included OS, objective response rate (ORR), disease control rate (DCR), and AE. ORR was defined as the proportion of patients who achieved complete response (CR) and partial response (PR). DCR was defined as the proportion of patients who achieved CR, PR, and stable disease (SD) and maintained the treatment response for at least 4 weeks. PFS was defined from the start of apatinib treatment until the date of detection of disease progression, death, or day of the last follow-up. OS was defined from the start of apatinib treatment to the date of death or last follow-up day. All the statistical data were analyzed using R software. Survival analyses were estimated using the Kaplan-Meier method with log-rank statistics. Multivariate Cox proportional hazards regression was employed to assess the association between clinical variables and survival outcome. Data were adjusted with gender and age. Statistical significance was defined as p values <.05 in all statistical analysis.

To compute the sample size, we considered the lower limit (3.01 months; 12.9 weeks) of the time to progression reported for second-line topotecan treatment in ES-SCLC [21], our...
sample size computations showed that under a power \((1 - \beta)\) of 0.8, a sample size of 21 patients is sufficient to achieve 80% probability in attaining a PFS of longer than 12.9 weeks for our cohort treated in the third line and beyond.

**RESULTS**

**Patient Characteristics**

Our cohort consisted of 22 patients diagnosed with ES-SCLC. The median age was 56 years, ranging from 36 to 70 years. A majority of the patients were male (77%, 17/22). Primary tumors were equally distributed on the left and right (50%, 11/22) lobes of the lungs, with a median baseline tumor diameter of 53.5 mm, ranging from 15.5 to 190.0 mm. Fifty-nine percent (59, 13/22) of the patients had between one to two sites of metastasis, whereas the remaining 41% (9/22) of the patients had between three to five sites of metastasis. Extensive lymph node involvement was detected in a majority of the patients (86%, 19/22). Other organ metastasis detected among the patients included brain \((n = 6)\), bone \((n = 4)\), lung \((n = 5)\), liver \((n = 4)\), adrenal gland \((n = 3)\), peritoneum and abdominal cavity \((n = 3)\), esophagus and pericardium \((n = 2)\), and kidney \((n = 1)\). A majority (64%, 14/22) received apatinib as third-line treatment, whereas 23% (5/22) and 14% (3/22) received it as fourth- or fifth-line treatment.

© 2020 The Authors.
*The Oncologist* published by Wiley Periodicals, Inc. on behalf of AlphaMed Press.
treatment, respectively. Table 1 summarizes the patient characteristics of the cohort.

**Best Response of the Patients**

The clinical responses of each of the patient in the cohort were assessed based on RECIST v.1.1 criteria at 28 days after initiating apatinib treatment and every 56 days thereafter until treatment failure. PR was achieved by three (13.6%) patients and stable disease was exhibited by 18 (81.8%) patients. Hence, the ORR and DCR of the cohort was 13.6% (95% confidence interval [CI], 2.9%–34.9%) and 95.5% (95% CI, 77.2%–99.9%), respectively. Only a patient (4.5%) who received third-line apatinib did not benefit from the treatment and had PD. Among the 14 patients who received apatinib as third-line treatment, PR and SD were achieved by 1 and 12 patients, respectively. Moreover, among the five patients who received apatinib as fourth-line treatment, two and three patients exhibited PR and SD, respectively. Meanwhile, all three patients who received apatinib as fifth-line treatment achieved SD as best response. Based on the waterfall plot analysis, the range of maximum tumor reduction achieved with apatinib treatment of the cohort was between $-53.9\%$ and $-1.1\%$ (Fig. 2). Among the 18 patients who achieved SD, 4 patients achieved between 22.8% and 28.6% reduction in tumor diameter, whereas 2 patients had 15.5% and 16.0% increase in their tumor diameter (Fig. 2).
Survival Outcome

We further analyzed the survival outcome of the cohort. The PFS and OS from the start of the apatinib monotherapy were evaluated. Based on the Kaplan-Meier estimation and log-rank test, the median PFS of the cohort was 5.4 months (95% CI, 2.9–7.2; Fig. 3A), whereas the median OS was 10.0 months (95% CI, 4.2–17.1; Fig. 3B).

Among the patients who received apatinib as third-line treatment, the median PFS and OS were 4.6 months (95% CI, 2.7–7.2) and 11.0 months (95% CI, 3.0 to upper limit not applicable [NA]), respectively. Patients who received apatinib as fourth-line treatment had median PFS and OS of 5.15 months (95% CI, 1.8 to NA) and 6.2 months (95% CI, 1.3 to NA), respectively, and patients who received apatinib as fifth-line treatment had median PFS and OS of 5.4 months (95% CI, 5.4 to NA) and 10.0 months (95% CI, 6.3 to NA), respectively.

Evaluation of Adverse Events

Because our cohort consisted of patients who have received at least two prior chemotherapy regimens with the potential occurrence of overlapping or cumulative toxicities, we then evaluated the safety profile of apatinib treatment in our cohort. A median of four adverse events, ranging from one to nine events, was observed among the 21 evaluable patients. Secondary hypertension and proteinuria were the two most common adverse events, with an incidence of 57% (12/21) and 48% (10/21), respectively. Grade III

Table 2. Possible treatment-related AEs observed among the 21 evaluable apatinib-treated patients with extensive-stage small cell lung cancer

| Adverse events | Grade I | Grade II | Grade III | Total, n (%) |
|----------------|---------|----------|-----------|--------------|
| **Nonhematological AEs** | | | | |
| Secondary hypertension | 6 | 5 | 1 | 12 (57) |
| Proteinuria | 6 | 2 | 2 | 10 (48) |
| Oral mucositis | 6 | 0 | 0 | 6 (29) |
| Hand-foot syndrome | 2 | 2 | 0 | 4 (19) |
| Other skin reactions such as rash, skin ulcerations | 4 | 0 | 0 | 4 (19) |
| Anorexia | 2 | 0 | 0 | 2 (10) |
| Nausea | 2 | 3 | 0 | 5 (24) |
| Vomiting | 0 | 1 | 0 | 1 (5) |
| Acid reflux | 2 | 0 | 0 | 2 (10) |
| Diarrhea | 1 | 2 | 0 | 3 (14) |
| Fecal occult blood | 2 | 0 | 0 | 2 (10) |
| Fatigue | 0 | 1 | 0 | 1 (5) |
| Elevated serum aspartate aminotransferase levels | 6 | 0 | 0 | 6 (29) |
| Elevated serum alkaline phosphatase levels | 2 | 0 | 0 | 2 (10) |
| Elevated serum lactate dehydrogenase levels | 1 | 0 | 0 | 1 (5) |
| Hyperbilirubinemia | 4 | 0 | 0 | 4 (19) |
| **Hematological AEs** | | | | |
| Leukopenia | 3 | 1 | 0 | 4 (19) |
| Thrombocytopenia | 1 | 1 | 0 | 2 (10) |
| Anemia | 2 | 1 | 0 | 3 (14) |
| Neutropenia | 2 | 0 | 0 | 2 (10) |

Abbreviation: AE, adverse event.

Figure 4. Treatment duration in months of each patient based on the line of apatinib therapy received. The treatment duration is indicated for each patient, the cross after the duration denotes the last-day of follow-up. Single asterisks denote the 7 patients who discontinued treatment due to adverse events. The number of “#” symbols denotes the grade of secondary hypertension experienced by the patient.
adverse events were only observed in three (14%) patients with either hypertension (n = 1) or proteinuria (n = 2). Except for these three patients, all the other patients experienced grade I–II adverse events. No grade IV and fatal adverse events were observed. Hematological toxicities observed in the cohort included leukopenia (n = 4), anemia (n = 3), thrombocytopenia (n = 2), and neutropenia (n = 2). Other nonhematological adverse events observed included oral mucositis (n = 6), elevated serum aspartate aminotransferase levels (n = 6), nausea (n = 5), hand-foot syndrome (n = 4), other skin reactions (n = 4), hyperbilirubinemia (n = 4), diarrhea (n = 3), anorexia (n = 2), fecal occult blood (n = 2), acid reflux (n = 2), elevated serum alkaline phosphatase levels (n = 2), elevated serum lactate dehydrogenase levels (n = 1), vomiting (n = 1), and fatigue (n = 1). Table 2 summarizes the adverse events observed in the cohort.

Treatment Tolerance and Dosage Adjustments
The median duration of apatinib treatment was 4.5 months, ranging from 0.9 to 18.0 months (Fig. 4). A total of 13 patients continued apatinib treatment until evaluation of PD from either enlargement of the primary lesion (n = 5) or development of new lesions or metastasis (n = 8). Seven (32%) patients had to discontinue the treatment because of adverse events, including grade III secondary hypertension (n = 1), grade II–III proteinuria (II, n = 1; III, n = 2), grade II leukopenia (n = 1), grade II nausea and vomiting (n = 1, patient 22), and heart discomfort (n = 1, patient 10). The only patient who did not benefit from apatinib treatment had tumor enlargement of 73.9% and terminated the treatment because of grade II nausea and vomiting for a total of 2.9 months of apatinib intake. A patient who received apatinib as fifth-line treatment discontinued apatinib treatment after 2.3 months because of nontreatment-related injury that required surgical intervention, but metastasis to the adrenal gland was shortly detected resulting in a PFS of 3.0 months. Only one patient was lost to follow-up.

Among all the patients, 36.4% (8/22) continued receiving apatinib at a dose of 500 mg daily as third- (n = 6), fourth- (n = 1), and fifth-line (n = 1) treatment. From an initial dose of 500 mg, dosage was reduced to 250 mg and re-escalated to 500 mg in two (9%) patients receiving apatinib as third-line treatment. Because of certain adverse events, the initial dose of 500 mg was reduced to 425 mg and 250 mg in a total of three (13.6%) and five (22.7%) patients, respectively. Prior to dose reduction, treatment was interrupted in three (13.6%) patients with a median interruption duration of seven days.

Furthermore, statistical analysis did not reveal any association between the number of adverse events encountered by the patient and variables including dosage adjustments (p = .09), the cause of treatment failure (disease progression or toxicity from adverse events, p = .17), and line of apatinib treatment (p = .94).

These data demonstrate that apatinib as third- and subsequent-line monotherapy in patients with ES-SCLC was well tolerated and has a manageable safety profile.

Multivariate Analysis
To understand the association between the clinical variables and survival outcomes, we performed Cox multivariate regression analysis. Table 3 summarizes the results of the analysis. Based on the analysis, third-line apatinib was correlated with better PFS compared with apatinib use beyond third line (p = .044). Other clinical variables such as gender, the presence of metastasis, and the number of prior lines of treatment were not associated with survival outcome. Interestingly, among the adverse events, the occurrence of secondary hypertension was significantly associated with longer OS (p = .047); however, this association became insignificant.

Table 3. Multivariate analysis between clinical variables and survival outcomes

| Clinical variables          | Progression-free survival | Overall survival |
|----------------------------|---------------------------|-----------------|
|                            | HR (95% CI)               | p value         | HR (95% CI)               | p value         |
| Age                        |                           | .12             | 0.36 (0.044–2.9)          | .34             |
| Gender                     |                           | .25             | 2 (0.64–6.0)              | .24             |
| Clinical outcomea          |                           | .044            | 2 (0.64–6.0)              | .24             |
| Total number of metastasis |                           | .70             | 1.5 (0.51–4.3)            | .46             |
| Bone metastasis (n = 4)    | 1.2 (0.23–6.4)            | .83             | 1.9 (0.38–9.7)            | .43             |
| Brain metastasis (n = 6)   | 0.5 (0.13–1.9)            | .31             | 0.45 (0.12–1.7)           | .25             |
| Liver metastasis (n = 4)   | 1.8 (0.36–9)              | .47             | 1.4 (0.29–6.9)            | .67             |
| Lung metastasis (n = 5)    | 1.6 (0.49–5)              | .45             | 1.4 (0.44–4.6)            | .55             |
| Lymph node metastasis (n = 19) | 3.3 (0.38–28)           | .28             | 1.8 (0.23–15)             | .57             |
| Hypertension as AEa (n = 12) | 0.25 (0.06–1.1)         | .065            | 0.22 (0.05–0.98)          | .047            |
| Proteinuria as AE (n = 10) | 0.5 (0.16–1.6)            | .25             | 0.32 (0.084–1.2)          | .096            |
| Dose reduction             | 0.63 (0.19–2.1)           | .46             | 0.54 (0.16–1.8)           | .32             |

*p values in bold (<.05) are statistically significant.
Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio.
after Q-correction (p = .455). These data suggest that hypertension in response to apatinib treatment is potentially predictive of prognosis; however, a larger cohort is required to further confirm this finding.

**DISCUSSION**

Despite the remarkable response to initial therapy in patients with ES-SCLC, responses are not durable, with only about 4–5 months of median PFS [5, 8]. Because of rapid disease progression, limited treatment options, and clinical benefit from subsequent lines of therapy after failure from initial chemotherapy, the prognosis of patients with ES-SCLC remains depressing. Hence, alternative treatment regimens, particularly in the later-line setting, are needed to be continuously explored and evaluated to improve the survival outcomes of these patients. Our single-arm, single-institution, phase II clinical trial explored the clinical outcomes of patients with ES-SCLC to apatinib monotherapy after failure from at least two prior lines of chemotherapy. Our study met all its primary and secondary endpoints, revealing the efficacy and safety of apatinib mesylate monotherapy in 22 patients with ES-SCLC previously treated and whose disease relapsed from at least two lines of chemotherapy regimen. The ORR and DCR in this cohort was 13.6% (PR, n = 3) and 95.5% (PR, n = 3; SD, n = 18), respectively. The clinical outcomes included 3 PRs, 18 SDs, and 1 PDs. The median PFS and OS of the cohort were 5.4 and 10.0 months, respectively. The survival benefits observed in our cohort are remarkably similar to survival outcomes from patients on first-line chemotherapy regimen with or without immunotherapy [5, 8] or even better than patients treated with bevacizumab, another antiangiogenic agent, in the second-line setting [11]. Numerous studies have observed that treatment response to subsequent lines of therapy concomitantly declines as treatment lines progress and was considered to be dependent from the duration of response from prior lines of treatment, whereas better responses to subsequent lines of therapy (response rate of ~25%) were observed in patients whose disease relapsed later than 3 months than in patients whose disease relapsed within 3 months (response rate of <10%) [2, 5, 6]. Although we observed some benefit with apatinib monotherapy in the third line and beyond, this study was underpowered for OS and should be validated in a phase III study with adequate power and a control group to detect potential OS benefit. To the best of our knowledge, this is the first registered and completed clinical trial that investigated the feasibility of antiangiogenic inhibitor monotherapy after failure from at least two prior lines of chemotherapy in patients with ES-SCLC.

Currently, topotecan remains as the only second-line treatment approved for patients with SCLC. Clinical studies have demonstrated a response rate between 10% and 40% and a median survival of 6.1 months with topotecan treatment after failure with etoposide and platinum-based combination regimen [2, 17, 21–24]. However, treatment with third line and beyond in SCLC has been considered anecdotal [25], possibly related to ES-SCLC being diagnosed in mostly elderly patients, with an approximate age of diagnosis between 65 and 70 years [6, 17]. Age has been considered as a positive prognostic factor in ES-SCLC, wherein younger patients diagnosed with ES-SCLC had better clinical outcomes than older patients; however, because of rapid disease progression, only about 6%–18% of the patients with ES-SCLC could live to receive third-line treatment and beyond [25, 26]. Consistent with the earlier reports on third-line chemotherapy use in patients with SCLC [25, 26], the treatment responses we have observed among our patients are due to the inclusion of relatively younger patients (median age of 56, ranging from 36 to 70) with better ECOGPS scores in our cohort. One of the first reports on the efficacy of third-line chemotherapy among 35 patients, including 17 patients with ES-SCLC, with median age of 58, had ORR of 26% and median OS of 5.0 months [25]. Another retrospective analysis of third-line chemotherapy in 120 patients with SCLC, including 72 with ES-SCLC, revealed an ORR of 18% (all partial responses) and median OS of 4.7 months [26]. In addition to standard chemotherapy, immune checkpoint inhibitors including nivolumab and pembrolizumab have been explored as treatment options in the third-line setting or beyond and have led to significant improvements in clinical outcomes of patients with SCLC [9, 27]. In contrast to these studies, our study administered small molecule tyrosine kinase inhibitor that has a different mechanism of action as compared with either immunotherapeutic or chemotherapeutic agents. An initial dose of 500 mg once daily of apatinib in third- or subsequent-line treatment of patients with advanced gastric cancer was reported to have better clinical benefit with lower toxicities than a dose of 850 mg (PFS, 4.6 vs. 2.2 months; OS, 6.8 vs. 4.0 months) [28]. In addition, apatinib monotherapy at a dose of 500 mg as third-line treatment of patients with non-small cell lung cancer (NSCLC) was effective and safe, revealing an ORR of 8%, DCR of 68%, and median PFS of 5.2 months [29]. The most common grade 1 or 2 adverse events reported from the apatinib monotherapy in patients with NSCLC included hypertension (72%), hand-foot-skin reaction (24%), fatigue (24%), and abnormal liver function (20%) [29]. Consistently, in our present study, apatinib treatment at a dose of 500 mg once daily had an acceptable safety profile, with only mild to moderate severity of toxicity observed among the patients. Secondary hypertension was the most common treatment-related adverse event, with an incidence rate of 57%, which was managed accordingly with blood pressure lowering medications. Hypertension is one of the common side effects associated with anti-VEGF therapy and is being proposed as a predictive and prognostic biomarker for the efficacy of VEGF treatment [30–32]. It has been reported that the risk of disease progression and death among patients with metastatic renal cell carcinoma who developed VEGF inhibitor-induced hypertension was lower than those who had normal blood pressure [32]. Consistently, multivariate analysis from our cohort revealed treatment-associated hypertension as an independent predictor of overall survival (p = .047, hazard ratio, 0.22; 95% CI, 0.05–0.98); however, the application of Q-correction resulted in a statistically insignificant difference due to a limited sample size. These
data further suggest that the occurrence of hypertension in response to apatinib was positively correlated with prognosis and could potentially serve as a prognostic biomarker among apatinib-treated patients with ES-SCLC; however, a larger cohort is recommended to further investigate this correlation.

**CONCLUSION**

Overall, our findings demonstrate the safety and efficacy of apatinib monotherapy at a dose of 500 mg once daily in Chinese patients with ES-SCLC who failed at least two prior chemotherapy regimens. Hence, apatinib monotherapy can be considered as a treatment option for patients with ES-SCLC in the similar setting. Because our present prospective study is an exploratory single-arm clinical trial, our conclusion is severely limited by the small number of patients and the lack of a standard group for comparison. A well-designed multicenter clinical trial with a larger cohort is necessary to confirm our findings.

**ACKNOWLEDGMENTS**

The authors would like to acknowledge Qiaolin Kang, Xuan Lin, and Dr. Analyn Ang Lizaso of Burning Rock Biotech for their valuable contribution in the statistical analysis, data interpretation, and manuscript preparation. We would also like to thank Bin Shan for his assistance in the statistical analysis. Finally, we would like to extend our gratitude to all the patients who participated in this study and their families, the investigators, study coordinators, operation staff, and the whole project team who worked on this study.

This work is supported by grants from the Hengru Oncology Research Grant of Beijing Xisike Clinical Oncology Research Foundation (grant Y-HR2017-005) and Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) (grant 2016-I2M-1-001).

**REFERENCES**

1. van Meerbeeck JP, Fennell DA, De Ruyscher DK. Small-cell lung cancer. Lancet 2011; 378:1741–1755.
2. Schneider BJ. Management of recurrent small cell lung cancer. J Natl Compr Canc Netw 2008;6:323–331.
3. Karachalios N, Pilotto S, Lazari C et al. Cellular and molecular biology of small cell lung cancer: An overview. Transl Lung Cancer Res 2016; 5:2–15.
4. Jiang J, Liang X, Zhou X et al. A meta-analysis of randomized controlled trials comparing irinotecan/platinum with etoposide/platinum in patients with previously untreated extensive-stage small cell lung cancer. J Thorac Oncol 2010; 5:867–873.
5. Simon GR, Wagner H; American College of Chest Physicians. Small cell lung cancer. Chest 2003;123(suppl):259S–271S.
6. Kalemkerian GP, Akerley W, Bogner P et al. Small cell lung cancer. J Natl Compr Canc Netw 2013;11:78–98.
7. Simon M, Argris A, Murren JR. Progress in the therapy of small cell lung cancer. Crit Rev Oncol Hematol 2004;49:119–133.
8. Horn L, Mansfield AS, Szczesna A et al; Impower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220–2229.
9. Ready N, Farago AF, de Braud F et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Clin 2019;14:237–244.
10. Lucchi M, Mussi A, Fontanini G et al. Small cell lung carcinoma (SCLC): The angiogenic phenomenon. Eur J Cardiothorac Surg 2002;21:1105–1110.
11. Zhu YJ, Zhang HB, Liu YH et al. Meta-analysis of the role of bevacizumab in extensive stage small cell lung cancer. Oncol Lett 2017;14:655–664.
12. Spigel DR, Townley PM, Waterhouse DM et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small lung cancer: Results from the SALUTE trial. J Clin Oncol 2011; 29:2215–2222.
13. Pujol JL, Lavole A, Quoix E et al. Randomized phase II–III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: Results from the ICF-0802 trial. Ann Oncol 2015;26:908–914.
14. Tiseo M, Boni L, Ambrosio F et al. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: The GOIRC-AIFA FARM6PMFJM Trial. J Clin Oncol 2017;35:1281–1287.
15. Scott LJ. Apatinib: A review in advanced gastric cancer and other advanced cancers. Drugs 2018;78:747–758.
16. Tian S, Quan H, Xie C et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci 2011;102:1374–1380.
17. Garst J. Topotecan: An evolving option in the treatment of relapsed small cell lung cancer. Ther Clin Risk Manag 2007;3:1087–1095.
18. Gandara DR, Paul SM, Kowatzetz M et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med 2018;24:1441–1448.
19. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
20. Schwartz LH, Littere S, de Vries E et al. RECIST 1.1—Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132–137.
21. O’Brien ME, Ciuleanu TE, Tsekov H et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 2006;24:5441–5447.
22. von Pawel J, Schiller JH, Shepherd FA et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:659–667.
23. Ardizzoni A. Topotecan in the treatment of recurrent small cell lung cancer: An update. The Oncologist 2004;9(suppl 6):4–13.
24. Eckardt JR, von Pawel J, Pujol JL et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 2007;25:2086–2092.
25. de Jong WK, ten Hacken NH, Groen HJ. Third-line chemotherapy for small cell lung cancer. Lung Cancer 2006;52:339–342.
26. Simos D, Sajjady G, Sergi M et al. Third-line chemotherapy in small-cell lung cancer: An international analysis. Clin Lung Cancer 2014;15:110–118.
27. Ott PA, Eilez E, Hiret S et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823–3829.
28. Deng W, Qin S, Li J et al. Initial dose of apatinib in Chinese patients with chemotherapy-refractory advanced or metastatic cancer. Transl Lung Cancer Res 2016;5:224–233.
adenocarcinoma of stomach or gastroesophageal junction in third- or later-line setting: 500 mg or 850 mg? J Clin Oncol 2018;36:35a.

29. Xu J, Liu X, Yang S et al. Clinical response to apatinib monotherapy in advanced non-small cell lung cancer. Asia Pac J Clin Oncol 2018;14:264–269.

30. Scartozzi M, Gallizia E, Chiorrini S et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol 2009;20:227–230.

31. Mir O, Ropert S, Alexandre J et al. Hypertension as a surrogate marker for the activity of anti-VEGF agents. Ann Oncol 2009;20:967–970.

32. Rini BI, Cohen DP, Lu DR et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2011;103:763–773.