



ORIGINAL ARTICLE

Apatinib as maintenance therapy following standard first-line chemotherapy in extensive disease small cell lung cancer: A phase II single-arm trial

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Abstract

Background: There is a need for the development of therapies to delay cancer progression and prolong survival after initial chemotherapy for the treatment of small cell lung cancer (SCLC). Since apatinib has been found to exert promising effects on cancer patients after standard first-line chemotherapy, this study aimed to investigate apatinib as a maintenance treatment following first-line chemotherapy in extensive disease (ED)-SCLC.

Methods: The primary endpoints were overall survival (OS) and progression-free survival (PFS). The secondary endpoints included toxicity and safety. Apatinib (250 mg/day) was administered during the chemotherapy interval and as maintenance therapy after 4–6 cycles until the patient's disease progressed, the patient died, or became intolerant to the drug's toxicity.

Results: The patients who received apatinib maintenance treatment had a median PFS of 3.7 months (95% CI: 1.3–6.2 months). The median OS was 16.3 months (95% CI: 9.7–22.8 months). The objective response rate and disease control rate were 50.0% and 66.7%, respectively. Two patients required dose reduction due to adverse effects (AEs). The most common AEs included hypertension ($n = 4$, 33.3%) and hand-foot-skin reaction ($n = 2$, 16.7%). One patient developed diarrhea, while another patient developed hemoptysis. The most serious AE was intestinal obstruction.

Conclusions: Apatinib maintenance therapy showed promising efficacy and safety to extend the OS/PFS of patients with ED-SCLC, thus making it a potent therapeutic option in future clinical practice. Given the small sample size of this study, further studies with large sample sizes are needed to validate the findings of the present study.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for 15%–20% of the total number of lung cancers. It is a highly malignant tumor with relatively rapid disease progression and about two-thirds of patients are reported to have already had distant metastasis before its detection. Extensive disease (ED)-SCLC accounts for 60%–70% of all SCLC cases, with a 5-year survival rate of 1%.¹ For half a century, the standard treatment for ED-SCLC includes 4–6 cycles of chemotherapy with platinum and etoposide. Although patients are highly

sensitive to initial treatment, many patients relapse within 6 months of first-line chemotherapy and often do not respond to subsequent chemotherapy. Previous studies have reported that these regimens resulted in an objective response rate (ORR) and median overall survival (OS) of 73% and 8–10 months, respectively.^{2–4} Due to the unknown cell origin, complex tumor heterogeneity, and unclear pathogenesis and driver genes, the development of basic and clinical research on SCLC is slow. How to prolong survival after initial chemotherapy for SCLC remains an unmet clinical need.

Tumor angiogenesis is an important factor that affects tumor growth.⁵ Almost 80% of SCLC tissues express vascular endothelial growth factor (VEGF). In addition, antiangiogenesis studies on ED-SCLC have been tentatively explored,⁶ with bevacizumab being the most widely used antiangiogenic drug. CALGB30306 and E3501 are two early phase II single-arm clinical studies that have previously been reported to be effective and safe in SCLC.^{7,8} Subsequent studies, such as SALUTE and IFCT-0802, demonstrated that combined treatment with bevacizumab prolonged progression-free survival (PFS) but not OS.^{9,10} In 2015, Ready et al.¹¹ investigated the efficacy of sunitinib in the maintenance of ED-SCLC chemotherapy, demonstrating that the maintenance therapy extended PFS from 2.1 months to 3.7 months ($p = 0.02$) but was ineffective in terms of OS.¹¹ Two other clinical trials of pazopanib for second-line therapy for ED-SCLC showed that PFS was extended by nearly 2 months compared with placebo.^{12,13} The development of therapies to delay cancer progression and prolong survival after initial chemotherapy for SCLC remains an unmet clinical need.

Apatinib, a VEGF receptor 2 (VEGFR-2) inhibitor developed in China, competes for the ATP binding site of VEGFR-2 within cells and blocks the downstream signal transduction, thereby inhibiting tumor angiogenesis.^{14,15} Previous studies have demonstrated that apatinib has a notable antitumor activity with tolerable toxicity in several types of solid tumors, including SCLC.¹⁶ Apatinib has been approved for the treatment of advanced or metastatic chemorefractory gastric cancer in China.^{17,18} To date, two retrospective studies in China have evaluated apatinib as third- to fifth-line therapy and as maintenance therapy in patients with ED-SCLC, respectively. These studies suggested that apatinib has a promising activity and acceptable toxicity in patients with ES-SCLC.¹⁹ Moreover, studies have also demonstrated that apatinib exerts promising effects in cancer patients after first- and second-line chemotherapy. Therefore, we designed a prospective II clinical trial to study the clinical efficacy and toxicity of apatinib in maintenance therapy after standard first-line chemotherapy.

METHODS

Patient selection

A total of 12 patients with ED-SCLC were enrolled in the study from March 2017 to August 2018.

The inclusion criteria were: (1) diagnosis of SCLC by pathological biopsy, (2) imaging staging was extensive-stage (CT or PET-CT), (3) patients were aged between 18 and 70 years, (4) an ECOG score between 0 and 2, (5) the liver, kidney, and bone marrow function well, and (6) patients with brain metastasis must complete whole-brain radiotherapy four weeks or more before the first dose and without

clinical symptoms. The exclusion criteria were: (1) an ECOG score > 2 , (2) an estimated survival period less than 1 month, and (3) patients with other primary tumors. The design and acquisition of clinical case data of this study were approved by our cancer center and followed the ethical requirements.

Treatment

This study was approved by our institutional review board (approval no: 17-016/1270). In this prospective clinical study (clinical trial information: NCT03129698), the patients with SCLC received standard first-line chemotherapy as follows: cisplatin (75 mg/m^2) or carboplatin area under the curve of 4–5 on day one plus etoposide (100 mg/m^2 per day) on days 1–3 every 21 days for 4–6 cycles. Apatinib (250 mg/day per os q.d.) was administered as maintenance therapy after 4–6 cycles until the patient's disease progressed, the patient died, or became intolerant to the drug's toxicity. Reduction of apatinib should be done in the event of grade I–II adverse reactions and can given 250 mg per os q.o.d. Also, in the event of a serious adverse reaction, apatinib should be discontinued. The full analysis set (FAS) included patients who received at least one cycle of treatment. Efficacy was evaluated every two cycles (6 weeks).

Response and toxicity evaluation

Patients were followed up to observe the efficacy and side effects of the medication. Toxicity was evaluated and graded according to the NCI CTCAE3.0 (National Cancer Institute Common Toxicity Criteria version 3.0). Tumor shrinkage was assessed according to the RECIST1.1 (Response Evaluation Criteria in Solid Tumors guidelines version 1.1). All recorded evaluations were confirmed by independent evaluators. Evaluation procedures were performed at each cycle of treatment, including physical examination, measurement of vital signs, and complete blood count. The maintenance phase was evaluated monthly.

Study endpoint and follow-up

The primary endpoints of this study were PFS and OS. The secondary endpoints included ORR, disease control rate (DCR), 6-months PFS, 12-months OS, toxicity, and safety. All patients were followed up until disease progression or death. The longest follow-up period was observed as median PFS and median OS. Herein, PFS is defined as the time from the first day of treatment to the first confirmation of a patient's disease progression or death, while OS is defined as the time from the first day of treatment to death for any reason.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp.). The Kaplan–Meier method was used to create the survival curve, while the Cox proportional risk regression model was used to investigate the prognostic factors. *p*-values less than 0.05 were considered statistically significant.

TABLE 1 Baseline patient demographic and clinical characteristics (*n* = 12)

Characteristics		
Total	12	n (%)
Sex	Male	9 (75.00)
	Female	3 (25.00)
Smoking status	Never	2 (16.67)
	Former	10 (83.33)
Family history	No	6 (50.00)
	Yes	6 (50.00)
Lung lobe	Left	8 (66.67)
	Right	4 (33.33)
Pleural metastasis	No	10 (83.33)
	Yes	2 (16.67)
Liver metastases	No	9 (75.00)
	Yes	3 (25.00)
Bone metastases	No	7 (58.33)
	Yes	5 (41.67)
Brain metastases	No	11 (91.67)
	Yes	1 (8.33)
Radiation therapy	No	5 (41.67)
	Yes	7 (58.33)

RESULTS

Patient characteristics

A total of 12 patients with ED-SCLC were enrolled in this study to evaluate the efficacy and safety of apatinib from March 2017 to August 2018. The 12 patients comprised nine males and three females, with an average age of 56.4 years. Six patients had a family history, two patients had pleural metastasis, three patients had liver metastasis, and one patient had brain metastasis. Also, seven patients received thoracic radiotherapy, including five sequential thoracic radiotherapies and two concurrent chemoradiotherapies. Table 1 shows the demographics and baseline characteristics of the 12 patients.

Clinical outcomes

At data cutoff, 10 patients had died during the follow-up period until February 2021. The patients who received apatinib maintenance treatment exhibited a median PFS of 3.7 months (95% CI: 1.3–6.2 months, Figure 1). The median OS was 16.3 months (95% CI: 9.7–22.8 months, Figure 2). Of the 12 patients, two (16.7%) had partial response, four (33.3%) had complete response, two (16.7%) had stable disease, and four (33.3%) had progressive disease. The ORR and DCR were 50.0% and 66.7%, respectively.

Safety and toxicity

In this study, a total of five patients developed adverse events and were treated symptomatically. Among them, hand-foot skin reaction and hypertension were the most severe adverse events (Table 2). Other adverse events

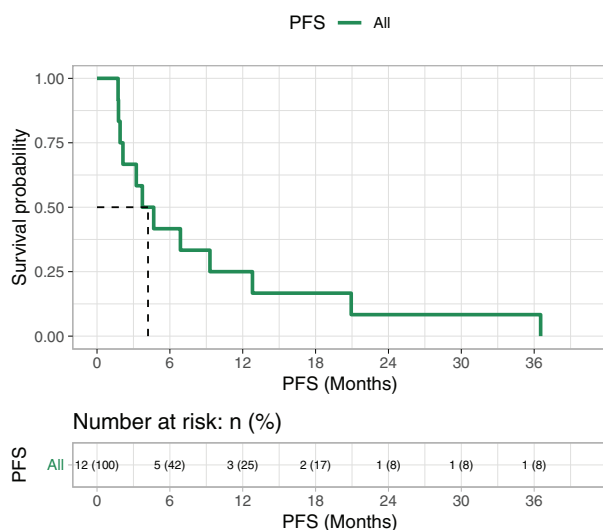


FIGURE 1 The PFS of all small cell lung cancer patients

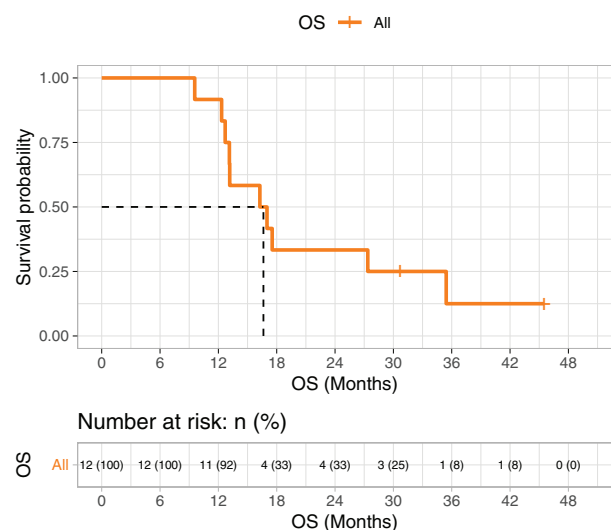


FIGURE 2 The OS of all small cell lung cancer patients

TABLE 2 Occurrence of adverse events

Adverse events	n (%)
Hand-foot skin reaction	2 (16.7%)
Hypertension	4 (33.3%)
Hemoptysis	1 (8.3%)
Diarrhea	1 (8.3%)
Intestinal obstruction	1 (8.3%)

included hemoptysis in one patient, diarrhea in one patient, and intestinal obstruction in one patient. There were no adverse events above grade III. When a patient developed hand and foot reactions, lotion application was prescribed. Antihypertensive therapy was administered for patients with hypertension. Patients with hemoptysis were orally administered Yunnan Baiyao capsules while patients with diarrhea were orally administered montmorillonite powder. The primary treatment approach for intussusceptions was fasting from food and water and administration of laxatives.

DISCUSSION

To the best of our knowledge, this is the first prospective phase II trial investigating apatinib as a maintenance treatment following standard first-line chemotherapy in ED-SCLC. Apatinib is a highly selective tyrosine kinase inhibitor of VEGFR-2; it exerts a promising antitumoral effect in various tumors. There is no standard protocol for the maintenance therapy of SCLC. Due to the high toxicity of chemotherapeutic drugs, we hypothesized that antiangiogenic agents may be useful as maintenance therapy. The results indicated that apatinib monotherapy yielded good efficacy, with an acceptable safety profile for patients with ED-SCLC, and can prolong the duration of clinical benefit in patients. In this study, patients who received apatinib maintenance treatment exhibited a median PFS and median OS of 3.7 months and 16.3 months, respectively. The ORR and DCR were 50.0% and 66.67%, respectively.

Previously, the expression of c-KIT was considered an important marker for the personalized medication of multi-target drugs. However, in recent years, c-KIT has been considered an important marker of tumor stem cells. Therefore, it is worthy to investigate whether the expression of c-KIT can inhibit the proliferation of tumor stem cells, thereby inhibiting tumor recurrence. Research on SCLC stem cells is also a hot topic. When the traditional side population (SP) cell method was used to screen tumor stem cells, it was found that CD56 and CD90 were highly expressed in the SP cells of SCLC cell lines and that the expressions of ABCG2, FGF1, IGF1, MYC, SOX1/2, and WNT1 signals were also increased.²⁰ Another study isolated SP cells from the SCLC cell line H446 and found that CD133 and ABCG2 may be characteristic markers of tumor stem cells in SCLC.²¹ Further studies have also found that CD133 is a marker of

SCLC stem cells; however, it is not always expressed in NSCLC.²² Of course, there are also contrary findings that CD133 alone is not enough to represent an SCLC stem cell marker²³ and that CD133 and CD87 cannot be fully used for the evaluation of SCLC stem cells.²⁴ Recent studies suggest that in the SCLC cell line H466, urokinase plasminogen activator receptor-positive (uPAR+) cells can form clonal spheres, while negative cells cannot. This suggests that uPAR (+) may be an important marker of SCLC stem cells.²⁵

Apatinib targets VEGFR-2, RET, platelet-derived growth factor- β (PDGFR- β), c-Src, and c-KIT.^{26,27} According to in vitro experiments, apatinib is an even more selective inhibitor of VEGFR-2 than sunitinib, with IC50s of 0.0011 M and 0.0051 M, respectively.²⁸ Apatinib can effectively inhibit the proliferation, migration, and tube formation of human umbilical vein endothelial cells. In addition, it can block the budding of rat aortic rings and inhibit the growth of several established human tumor xenograft models with little toxicity.²⁸ Previous studies have reported that apatinib can reverse the ATP-binding cassette transporter (ABC) subfamily B member 1 (MDR1/P-glycoprotein) and the ABC subfamily G member 2 (BCRP)-mediated multidrug resistance, which suggests the potential usefulness of combining apatinib with other chemotherapeutic drugs.^{26,29}

Based on the expression of high microvessel density and VEGF in nearly 80% of SCLC cases, angiogenesis is critical in SCLC.³⁰ In 2007, a phase II clinical trial of thalidomide as maintenance therapy for ED-SCLC indicated that the median survival from the time of initiation of chemotherapy was 12.8 months (95% CI: 10.1–15.8 months) and that the 1-year survival was 51.7% (95% CI: 32.5%–67.9%). When administered as maintenance therapy for ED-SCLC after initiation of chemotherapy, 200 mg of thalidomide per day was well-tolerated.

However, the subsequent phase III clinical study found that thalidomide combined with chemotherapy shortened patient survival and increased the risk of thrombosis.³¹ Moreover, studies on the application of imatinib and vandetanib in SCLC found that the addition of these drugs did not yield survival benefits.³² Another phase II study of sunitinib found that although the benefits of OS were not achieved, the use of sunitinib extended PFS (median PFS: 3.7 months vs. 2.8 months, median OS: 9 months vs. 6.9 months).¹¹ Other studies found that the use of apatinib in the treatment of ED-SCLC after two or more chemotherapy failures is effective and safe.^{33,34}

The results of this clinical study show that apatinib, as maintenance treatment following standard first-line chemotherapy, significantly improved OS and PFS in ED-SCLC patients compared with chemotherapy alone. The patients who received apatinib maintenance treatment exhibited a median PFS and OS of 3.7 months (range: 1.3–6.2 months) and 16.3 months (range: 9.7–22.8 months), respectively. A total of five patients developed adverse events and were treated symptomatically. Consistent with our study, Shi et al.³⁵ found that in the treatment of advanced NSCLC with apatinib, the incidence of adverse events, such as mainly

proteinuria, hypertension, and hand-foot syndromes, was higher in the apatinib group. Apatinib can prolong the patient's sustained clinical benefit. Antiangiogenic drugs have a higher risk of causing bleeding and hypertension; therefore, the benefits and risks need to be fully weighed.

Adverse events are often observed in cancer patients undergoing therapeutic treatment. Recently, several studies have shown that adverse events during target therapy, such as cetuximab and panitumumab in colorectal cancer,³⁶ cetuximab in advanced head and neck cancer,³⁷ sunitinib and sorafenib in metastatic renal cell carcinoma,³⁸ and sunitinib in metastatic renal cell carcinoma,³⁹ were associated with efficacy. In this study, patients with ED-SCLC had a lower probability of developing these adverse events. None of the five patients with adverse reactions stopped taking the drug. Since the poor treatment outcome was not related to adverse events, in addition to active supportive care in the future, a threshold for increasing the therapeutic dose can be set. However, it must be understood that increasing the therapeutic dose of apatinib may be a double-edged sword, since it may simultaneously increase the efficacy and worsen the OS/PFS. Thus, we will further explore and strengthen this aspect in future studies.

In the past few years, management of lung cancer tumors with very poor prognoses have only achieved minor therapeutic success. The main reason for the failure of most chemotherapy is the development of chemoresistance. Most lung cancer patients will eventually develop resistance to chemotherapeutic agents that they are administered, even those with a good initial response to treatment. In addition to the active efflux of the chemotherapeutic agent from tumor cells, the hypoxic tumor microenvironment and hypoxia-mediated upregulation of VEGF play an important role in hypervascularization, which entails the formation of new blood vessels to supply nutrient and oxygen for tumor progression and recurrence. Since several therapeutic drugs cannot increase OS after the failure of chemotherapy, VEGF targeting by apatinib can be combined with traditional treatment modalities to ensure maximum effectiveness. In order to reduce chemoresistance, continuous use of low doses of apatinib may inhibit VEGF-mediated angiogenesis, which is the basic mechanism of action of apatinib. In particular, apatinib has been reported to prevent multidrug resistance (MDR) of cancer cells against other conventional chemotherapeutic drugs by inhibiting ABCB1- and ABCG2-mediated drug export.²⁹ Increased accumulation of doxorubicin was found in the apatinib-treated MDR cells. In addition, the effect of apatinib on prolonging OS may be due to the promotion of tumor cell apoptosis and cell cycle arrest, which may also support the fact that apatinib can lead to a significant prolongation of OS and PFS in ED-SCLC patients.

There were a number of limitations in this study. First, the number of patients was small and there was no control. Second, SCLC is sensitive to radiotherapy. In the baseline patient characteristics, seven patients received radiotherapy or concurrent chemoradiotherapy. Adding radiotherapy and chemoradiotherapy could be a factor in prolonging PFS and

OS. Third, nowadays, combination therapy with chemotherapy plus an immune checkpoint inhibitor is a standard treatment modality for patients with ES-SCLC. No studies have been conducted on the effects of immunological agents combined with apatinib on patients during intermissions between immunotherapy and chemotherapy. Therefore, immunotherapy combined with apatinib as a maintenance treatment can be a follow-up research focus.

In conclusion, our study showed that apatinib is efficacious and highly safe for the treatment of patients with ED-SCLC. It can clinically extend patients' sustained duration, which can be further studied and applied in clinical practice. Because the sample size of this study was small, further studies with a larger sample size are needed in the future.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest that might be relevant to the content of this manuscript. The abstract of this paper was presented at the IASLC 2021 World Conference on Lung Cancer as a poster presentation. The poster's abstract was published in "Poster Abstracts" in *Journal of Thoracic Oncology*. <https://doi.org/10.1016/j.jtho.2021.08.674>.

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