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Low-dose apatinib monotherapy in advanced chemotherapy-refractory small cell lung cancer: a case series and literature review

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Abstract

The therapeutic regimen for small cell lung cancer (SCLC) has changed little in the past several decades. Apatinib is a small molecule inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase. Apatinib has demonstrated efficacy against advanced gastric cancer and breast cancer, and recent studies have also reported its successful use in non-SCLC; however, its efficacy in SCLC remains unclear. In this study, we used apatinib as salvage therapy for chemotherapy-refractory SCLC. Five male patients with advanced SCLC were administered oral apatinib (250 mg/day) as 2nd- to 4th-line treatment. One patient showed a partial response to apatinib, one showed stable disease, and three patients showed progressive disease. The progression-free survival durations in the patients with stable disease and partial response were 1.5 and 3 months, respectively. Only three patients showed adverse effects, including mild hypertension, vomiting, and hand–foot syndrome, respectively, all of which were manageable. Apatinib might thus be a salvage option in patients with advanced SCLC after chemotherapy.

Keywords

Vascular endothelial growth factor receptor, apatinib, small cell lung cancer, salvage therapy, safety, survival

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Introduction

Small cell lung cancer (SCLC) accounts for 11% of all lung cancers, and is characterized by rapid growth, high aggressiveness,

and widespread metastasis.[1] Although SCLC is sensitive to initial chemoradiotherapy, long-term survivors are rare. The 5-year survival rate of these patients remains low (<7%), and most patients survive for no more than 1 year after diagnosis.[2] The therapeutic regimen for SCLC has not changed significantly in the past several decades, and studies investigating other chemotherapeutic drugs, molecular targeted drugs, and maintenance chemotherapy have resulted in little improvement.[3,4]

Angiogenesis is a crucial hallmark of tumor growth, development, and metastasis. Vascular endothelial growth factor (VEGF) signaling promotes angiogenesis via activating the VEGF receptor (VEGFR), and is thus a critical target of cancer treatment.[5,6] Agents targeting VEGF or VEGFR have demonstrated efficacy in solid tumors, including non-SCLC (NSCLC);[5,6] however, their role in SCLC remains controversial.[7–11] A previous study indicated that the addition of bevacizumab to cisplatin and etoposide in patients with extensive SCLC improved progression-free survival (PFS) and overall survival,[10] but a subsequent report suggested that the addition of bevacizumab to paclitaxel did not improve outcomes in patients with relapsed chemosensitive SCLC.[11] Evidence for the use of anti-angiogenesis drugs for SCLC thus remains unclear.

Apatinib is an oral small-molecule inhibitor of VEGFR-2, with proven efficacy in patients with advanced breast and gastric cancers.[12,13] Recent studies have also shown its efficacy in patients with NSCLC.[14–17] We previously reported that low-dose apatinib (250 mg/day) monotherapy resulted in similar PFS to higher-dose apatinib (500–750 mg/day) in patients with NSCLC,[16,17] and was associated with fewer adverse effects in these studies. In a recent case report, apatinib (425 mg/day) combined with pneumonectomy and/or radiotherapy was used in two patients with relapsed SCLC,[18,19] and two other studies also reported on the use of apatinib as maintenance therapy in patients with stable SCLC after induction chemotherapy.[20,21] Another report used higher-dose apatinib (500 mg/day) in patients with extensive SCLC.[22] However, there is currently no evidence for the use of low-dose apatinib as monotherapy in patients with advanced SCLC after failure of chemotherapy.

We therefore determined the efficacy and safety of low-dose apatinib (250 mg/day) in patients with advanced chemotherapy-refractory SCLC.

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All procedures were carried out according to the guidelines of the Science Council of China and approved by the Research Ethics Committee of Soochow University. Informed consent was obtained from all participants. Three patients had extensive and two had limited SCLC. All patients had pathologically diagnosed SCLC based on transbronchial lung biopsy.

Tumor responses were evaluated every month according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) using chest computed tomography. Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). All adverse effects were also recorded.

The baseline characteristics of the patients are shown in Table 1. All patients received 1st-line platinum-based doublet chemotherapy (platinum and etoposide), with oral apatinib (250 mg/day) as salvage therapy when the disease progressed after 1st- to 3rd-line chemotherapy. Three patients also received lung radiotherapy after 1st-line chemotherapy and one patient received prophylactic craniocerebral radiation.

One month after apatinib monotherapy (Table 1 and Figure 1), one patient showed

Table 1. Characteristics of five patients with small cell lung cancer treated with apatinib.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	60	64	61	64	71
Sex	Male	Male	Male	Male	Male
Stage	Extensive	Extensive	Limited	Limited	Extensive
Performance score	2	2	2	3	3
Drug treatment					
1st-line	Plat+Etop (PD)	Plat+Etop (PR)	Plat+Etop (SD)	Plat+Etop (PR)	Plat+Etop (SD)
PFS1	–	12 months	5 months	9 months	4 months
2nd-line	Irinotecan (PR)	Irinotecan (PD)	Carb+Doc (PD)	Apatinib (PD)	Topotecan (PD)
PFS2	8 months	–	–		–
3rd-line	Docetaxel (PD)	Apatinib (PD)	Irinotecan (PD)		Apatinib (PD)
PFS3	–		–		
4th-line	Apatinib (PR)		Apatinib (SD)		
PFS4	3 months		1.5 months		
Other treatments		Lung radiotherapy and prophylactic craniocerebral radiotherapy	Lung radiotherapy		Lung radiotherapy
Apatinib PFS	3 months	–	1.5 months	–	–
Adverse effects	Hand-foot syndrome	–	Hypertension	Vomiting	–

Plat, platinum; Carb, carboplatin; Etop, etoposide; Doc, docetaxel; SD, stable disease; PD, progressive disease; PR, partial response.

PR (4th-line), one patient showed SD (4th-line), and three patients showed PD (2nd- to 3rd-line). The final PFS durations of the two patients with partial response and stable disease were 1.5 and 3 months, respectively. One patient each developed manageable hypertension and vomiting, respectively, and one patient developed grade 2 hand–foot syndrome.

Discussion

There are currently few available drugs for the treatment of patients with SCLC following disease progression after platinum-based chemotherapy. Most patients in the present report received anti-VEGFR2 treatment as 3rd- to 4th-line salvage therapy, except for one patient who received apatinib as 2nd-line treatment because of a poor performance score (3-4). Although anti-VEGF/VEGFR drugs have demonstrated efficacy in patients with advanced NSCLC, there is little evidence for their use in SCLC. The current results support the use of anti-VEGFR treatment as salvage therapy in patients with advanced SCLC. However, further studies are needed to confirm the clinical value of anti-VEGF drugs in SCLC.

We previously showed that low-dose (250 mg/day) apatinib had similar efficacy and fewer adverse reactions to higher-dose apatinib.[16,17] The current results also suggested that a lower dose might be a potential option in patients with advanced SCLC. Two recent reports described the use of apatinib combined with pneumonectomy or/and radiotherapy in two patients with relapsed SCLC,[18,19] while other studies reported on the use of apatinib as maintenance therapy in patients with stable SCLC after induction chemotherapy.[20,21] Low-dose apatinib might thus be a possible therapeutic choice in patients with advanced SCLC. However, further large-

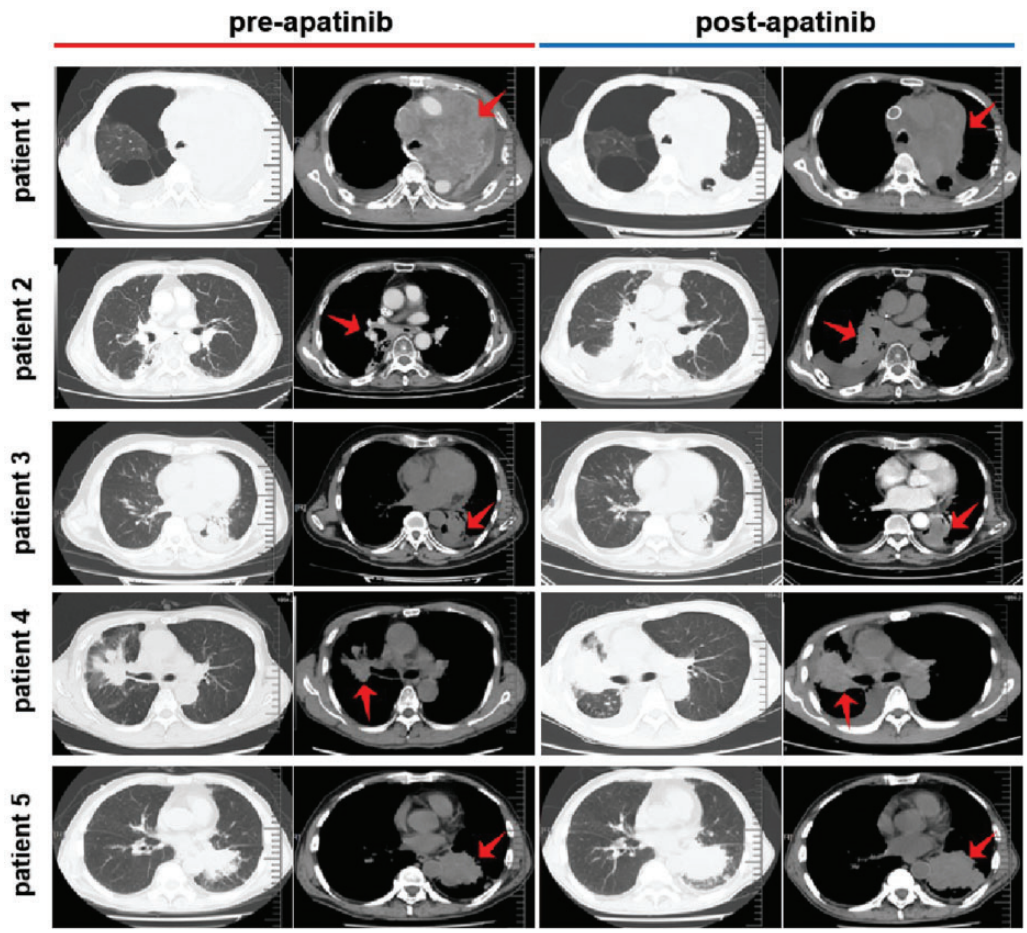

Figure 1. Computed tomography scans in five patients before and after apatinib monotherapy. Red arrows indicate tumor mass.

scale randomized controlled trials are needed to confirm this. Interestingly, two of the current patients achieved PR or SD after apatinib as 4th-line treatment, and the other patients developed PD after apatinib as 2nd- to 3rd-line treatment. However, this did not mean that apatinib was more effective as 4th-line compared with 2nd-line treatment. Furthermore, the efficacy of low-dose apatinib in other cancers is currently unclear.

This study provides additional information to previous studies. First, apatinib was used as salvage therapy in our study, rather than as maintenance treatment following induction chemotherapy. Furthermore, all patients in our study experienced PD before apatinib administration, rather than being in a stable stage. Second, we used an initial dose of apatinib of 250 mg/day, which was lower than the doses used in most previous studies (500–850 mg/day). We also previously showed that lower-dose apatinib resulted in similar PFS to a higher dose, but with fewer adverse effects.[16,17] This

was also indicated in two recent studies of lower-dose apatinib in patients with stable SCLC after induction chemotherapy.[20,21] Another report also indicated that >50% of patients required a dose reduction because of grade 3 or 4 toxicities at an initial dose of 500 mg/day.[22] However, the optimal dose of apatinib in SCLC remains unknown. Third, we used apatinib monotherapy in this study rather than combined with pneumonectomy, chemotherapy, or radiotherapy, and there is currently no information on the use of apatinib in combination with chemotherapy or radiotherapy in SCLC.

In conclusion, this report indicated that a low dose of apatinib (250 mg/day) might be an option for salvage treatment in patients with advanced SCLC. However, further studies are needed to determine the optimal dose and to establish the efficacy of apatinib combined with chemotherapy or radiotherapy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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