Original Article

A retrospective study of low-dose apatinib combined with S-1 in patients with advanced non-small cell lung cancer

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Background: The current regimens for advanced non-small cell lung cancer (NSCLC) patients are deficient due to failings in standard treatments. This retrospective study aimed to assess the efficacy and safety of low-dose apatinib in combination with S-1 therapy in a NSCLC setting.

Methods: In this retrospective study, advanced NSCLC patients who failed standard treatment in Changzhou Cancer Hospital of Soochow University were screened for eligibility. Progression-free survival (PFS) was set as the primary endpoint. Overall response rate (ORR), disease control rate (DCR), overall survival (OS), and the safety profile were considered to be the secondary endpoints.

Results: A total of 31 eligible patients were included. The median PFS (mPFS) was 102 days (95% CI: 57–147 days). ORR was achieved in 7 patients (22.6%; 95% CI: 11.1–38.2%) and DCR was maintained in 23 patients (74.2%; 95% CI: 58.2–86.5%). The median OS (mOS) was 422 days (95% CI: 148–696 days). Patients with a history of smoking tended to have a shorter OS without significant differences (HR =4.105, 95% CI: 0.874–19.288, P=0.074). Treatment-related grade III toxicity was observed in 5 patients (16%) and common grade I or II adverse events (AEs) were fatigue (42%), hypertension (32%), and hand-foot-skin reaction (23%).

Conclusions: Combination of low-dose apatinib and S-1 could be an effective and tolerable choice for advanced NSCLC patients who are unable to benefit from standard treatment; however, further exploration in larger clinical trials is needed.

Keywords: Non-small cell lung cancer (NSCLC); apatinib; S-1; combination therapy

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignancies worldwide. According to the 2015 China Cancer Surveys (1), NSCLC was the leading cause of cancer-related death with a poor outcome of a 16.1% five-year survival rate (2). NSCLC is the main pathological type of lung cancer, accounting for about 85% of all patients (3). Platinum-based chemotherapy and the continued emergence of targeted therapy and immunotherapy drugs have brought more treatment options for advanced NSCLC (4). However, these drugs are only approved for first or second-line treatment, and the guidelines of NSCLC still lack a recommended third-

line or beyond drug (3).

In the tumor microenvironment, neo-angiogenesis promotes cancer cells growth and metastasis, and this process depends on the activation of vascular endothelial growth factor (VEGF) signaling pathway (5). Bevacizumab (6) and ramucirumab (7), two kinds of monoclonal antibodies which inhibit VEGF signaling pathway, showed clinical benefit in advanced NSCLC as the first or second-line treatment. Anlotinib, another anti-angiogenic drug, also showed that it could significantly improve the progression-free survival (PFS) and overall survival (OS) rate compared with the placebo group in the third-line treatment of advanced NSCLC (8), suggesting anti-angiogenic drugs have tremendous clinical value for advanced NSCLC failing from multi-lines of therapies.

Apatinib, one novel tyrosine kinase inhibitor targeting VEGFR-2, inhibits the proliferation, migration, and neovascularization of endothelial cells. The usage of apatinib showed clinical benefits for advanced gastric cancer and breast cancer patients experiencing multiple lines of therapies (9,10). Efficacy of apatinib for advanced NSCLC patients who failed from second-line treatment was investigated in one phase II study, and the result showed that the apatinib group obtained a longer mPFS compared with the placebo group (11). In recent years, increasing clinical trials have reported the potential benefits of apatinib in advanced NSCLC patients after multi-line therapies (12-14). However, patients who received apatinib monotherapy with a higher dose faced more drug toxicity.

S-1, one compound preparation consisting of tegafur, gimeracil, and oteracil potassium, also demonstrated a notable treatment effect for lung cancer, including in the third-line of therapy (15-19). In addressing the clinical benefits of apatinib and S-1 single-drug therapy in lung cancer, we designed this retrospective study to further assess the efficacy and safety of low-dose apatinib combined with S-1 in advanced NSCLC patients failing from standard treatment. As far as we know, this was the first clinical trial to study the clinical value and safety of low-dose apatinib combined with S-1 treatment in this NSCLC setting.

Methods

Study design and participants

This retrospective study enrolled advanced NSCLC patients meeting the inclusion and exclusion criteria in Changzhou Cancer Hospital of Soochow University from August 2016 to March 2018.

Enrollment criteria included the following conditions: aged between 18 and 75 years; pathologically confirmed NSCLC; patients with EGFR-sensitive mutations treated by first or third generation EGFR-TKI until resistance or intolerance occurred; received low-dose apatinib combined with S-1 capsules after failure of standard treatment (apatinib 250 mg once daily; S-1 capsules 40–60 mg twice daily, days 1–14, one cycle repeated every 3 weeks, dosage depends on the patients' surface area); patients with extracranial measurable lesions; an Eastern Cooperative Oncology Group (ECOG) performance status score 0–2; asymptomatic CNS metastases; and informed consent. Patients were excluded for the following conditions: clinical symptoms of brain metastases or meningeal metastasis.

Efficacy and safety assessments

PFS was set as the primary endpoint, and overall response rate (ORR), disease control rate (DCR), OS, and safety were the secondary endpoints. PFS was measured from the time of treatment initiation to clinical or radiographic progression or death. OS was defined as the length of time from the random assignment to death or last contact. Tumor response was assessed according to the response evaluation criteria in solid tumors 1.1 (RECIST1.1). Safety assessments consisted of recording protocol-defined adverse events (AEs) and serious AEs (SAEs), which were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The presentation of categorical variables and continuous variables were expressed by statistical description: a percentage or mean ± standard deviation, respectively. The Cox proportional hazards model assessed univariate and multivariate analysis. The Kaplan-Meier method was used to estimate PFS and OS. For all analyses, P value <0.05 was considered statistically significant, and a confidence interval of 95% was used (95% CI). The SPSS22.0 software (SPSS, Inc., Chicago, IL, USA) was carried out for statistical analysis.

Results

Patient demographics

From August 2016 to March 2018, 31 advanced NSCLC patients were eligible as per inclusion and exclusion criteria.

Table 1 Patients demographics and clinical characteristic

Characteristic	All patients (n=31)
Gender	
Male	25
Female	6
Age, mean ± SD, years	60±8
Pathological diagnosis	
Adenocarcinoma	21
Squamous cell carcinoma	10
Smoking	
Yes	20
No	11
ECOG PS	
0–1	9
2	22
EGFR mutation	
Yes	7
No	24
Treatment line	
Second line	6
Third line or above	25
CNS metastatic	
Yes	6
No	25

CNS, central nervous system.

The baseline characteristics of the study enrolled patients are summarized in *Table 1*. The mean age of the study population was 60±8 years. Nineteen percent (6/31) and 81% (25/31) of patients were female and male, respectively. The percentage of pathological diagnosis of lung squamous cell and adenocarcinoma was 32% (10/31) and 68% (21/31), respectively. At the baseline, 23% (7/31) patients carried EGFR-sensitive mutations, and brain metastases accounted for 19% (6/31). Nineteen percent of (6/31) the patients experienced a second-line treatment. For patients with driver gene mutations (EGFR/ALK), the period of receiving the first-line treatment to the time administered by apatinib combined with S-1 therapy was 502±66 days. For patients without driver gene mutations (EGFR/ALK), the period in lung adenocarcinoma patients was 337±141 days, and in lung squamous carcinoma patients the period was 258±135 days.

Efficacy

All 31 patients were included in the analysis set. The mPFS was 102 days (95% CI: 57–147 days, *Figure 1*), and the mOS was 422 days (95% CI: 148–696 days, *Figure 1*). Tumor response in study patients is summarized in *Table 2*. ORR was achieved in 7 (22.6%; 95% CI: 11.1–38.2%) patients, and DCR was maintained in 23 patients (74.2%; 95% CI: 58.2–86.5%). In patients with lung adenocarcinoma, mPFS in the EGFR mutation group and wild type group was 73 and 78 days, respectively (P=0.708), and mOS in the EGFR mutation group and wild type group was 425 and 422 days, respectively (P=0.776). The clinical benefit of

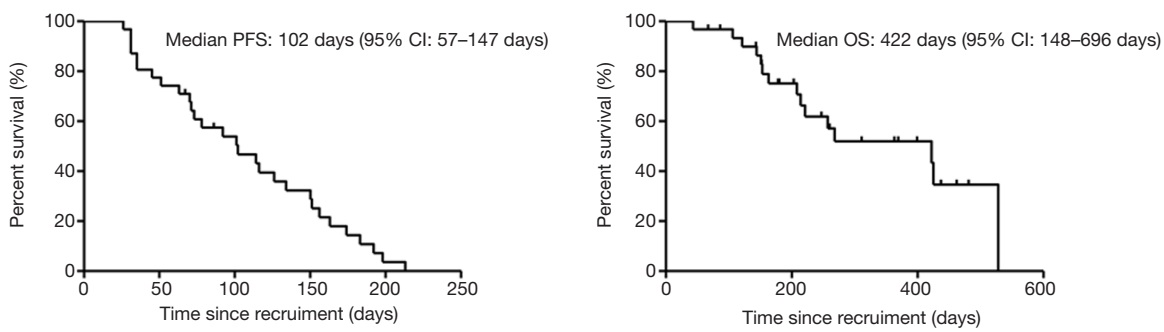

Figure 1 Kaplan-Meier curves of PFS and OS for low-dose apatinib combined with S-1 treatment in patients with advanced non-small cell lung cancer. PFS, progression-free survival; OS, overall survival.

Table 2 Responses assessed per RECIST version 1.1

Tumor response	Low-dose apatinib combined with S-1 (N=31)
Objective response, n (%; 95% CI)	22.6% (95% CI: 11.1–38.2%)
Disease control rate, n (%; 95% CI)	74.2% (95% CI: 58.2–86.5%)
Best overall response, n (%)	
Complete response	0
Partial response	7 (22.6)
Stable disease	16 (51.6)
Progressive disease	8 (25.8)

RECIST, response evaluation criteria in solid tumors.

study combination therapy was observed irrespective of sex, age, ECOG PS, EGFR mutation status, treatment line, and the presence of brain metastases. Patients with a history of smoking tended to have a shorter mOS without significant differences (HR =4.105, 95% CI: 0.874–19.288, P=0.074, *Table 3*).

Safety

At the data cutoff, AEs of any grade occurred in 94% of patients (29/31). AEs is summarized in *Table 4*. Most of the patients were tolerant, and the common grade I and grade II toxicity were fatigue (42%), hypertension (32%), and hand-foot-skin reaction (23%), consistent with reported observations (9,11). Grade III toxicity included hypertension, myelosuppression, fatigue and hand-foot-skin reaction, which occurred in 16% of patients (5/31), and disease symptoms were controlled after corresponding treatments. No cases of treatment-related death occurred until the end of the study period.

Discussion

The growth of tumor cells depended on oxygen and nutrients supplied by the tumor angiogenesis (20), and VEGF signaling pathway played an important role in neovascularization (21-23). To our knowledge, VEGFR-2, one member of the VEGFR family (mainly including VEGFR-1, VEGFR-2, VEGFR-3), was considered to be the most relevant factor associated with tumor angiogenesis (24). Apatinib could destroy the interaction between VEGF-A and VEGFR-2, and inhibit the VEGF signaling pathway (25,26). Our study indicated that low-dose apatinib combined with S-1 provided effective clinical outcomes and reliable safety in advanced NSCLC patients after standard treatment failure.

One meta-analysis demonstrated that anti-angiogenic tyrosinase inhibitors plus chemotherapy could significantly improve ORR and mPFS when compared with the chemotherapy alone group for advanced NSCLC (27). In our study, the ORR in the overall assessable patients was 22.6%, while the ORR in one previous phase II trial of apatinib monotherapy in patients with advanced non-squamous NSCLC was only 12.2% (11), indicating that low-dose apatinib combined with S-1 therapy might achieve higher response rate. Recently, one study explored the clinical efficiency of apatinib (the dosage from 250 to 750 mg per day) in advanced non-squamous NSCLC after multi-lines treatments, and the mOS was 7.4 months (95% CI: 1.3–13.5) (28). Compared with this study, the mOS in our trial was 422 days (95% CI: 148–696), which showed a longer survival time. Apatinib could reverse ABCB1 and ABCG2-mediated multidrug resistance (MDR) by inhibiting their transport function, resulting in an elevated concentration of antitumor drugs in tumor cells (29). This finding may provide one possible explanation for the better anti-tumor effect of combination therapy.

Several studies explored the predictive factors useful for selecting a sub-population that was more suitable for apatinib therapy. Early anti-angiogenesis-related AEs, protein expression level of phosphorylated VEGFR2 (p-VEGFR2), and hypertension were significantly related to patients' outcome and considered as potential predictive factors of apatinib therapy (30,31). Our study showed that patients with a history of smoking tended to have shorter mOS without significant differences (HR =4.105, 95% CI: 0.874–19.288, P=0.074). Due to the small sample size of the study, larger studies are needed to identify whether it is a potential marker.

The adverse event profiles were manageable for apatinib combined with S-1 therapy, and the incidence of grade III or VI was lower than a high dose of apatinib monotherapy (28). All patients were tolerant without any serious adverse reactions, and fatigue, hypertension, and hand-foot-skin reaction were the common grade I or II AEs.

There were some limitations in our study. As a retrospective study, the interpretations of the results are limited. The small sample size could have contributed to unavoidable selection bias, or measurement bias might

Table 3 Prognostic factors for PFS and OS analyzed by univariate and multivariate Cox regression model

Variable	PFS			OS					
	Univariate Cox regression model			Univariate Cox regression model			Multivariate Cox regression mode		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Sex (male *vs.* female)	1.194	0.446–3.197	0.724	1.894	0.418–8.585	0.408			
Age (≥65 *vs.* <65)	0.724	0.329–1.591	0.421	2.961	0.943–9.300	0.063	2.109	0.649–6.858	0.215
Smoking (yes *vs.* No)	1.663	0.714–3.876	0.238	4.567	1.008–20.696	0.049	4.105	0.874–19.288	0.074
ECOG (2 *vs.* 0–1)	1.379	0.544–3.496	0.498	0.95	0.296–3.047	0.931			
Pathological type (lung squamous cell *vs.* adenocarcinoma)	1.842	0.800–4.241	0.151	0.487	0.167–1.415	0.186	0.515	0.168–1.575	0.245
EGFR mutation status (mutation *vs.* wildtype)	1.028	0.410–2.573	0.953	0.938	0.257–3.418	0.922			
CNS metastatic (yes *vs.* no)	1.626	0.639–4.138	0.307	0.946	0.260–3.447	0.933			
Treatment line (third-line *vs.* second-line)	1.072	0.404–2.842	0.889	0.419	0.129–1.367	0.419			

PFS, progression-free survival; OS, overall survival; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

Table 4 Adverse events in the safety population

Event	Low-dose apatinib combined with S-1 (N=31)			
	Grade I–II	Grade III	Grade IV	Grade V
Hypertension	10 (32%)	1 (3%)	0	0
Myelosuppression	5 (16%)	3 (10%)	0	0
Mucositis	1 (3%)	0	0	0
Fatigue	13 (42%)	1 (3%)	0	0
Hand-foot-skin reaction	7 (23%)	2 (6%)	0	0
Hemoptysis	3(10%)	0	0	0
Hoarseness	2 (6%)	0	0	0
Appetite decreases	2 (6%)	0	0	0
Proteinuria	1(3%)	0	0	0
Oral ulcer	1 (3%)	0	0	0
Epistaxis	1 (3%)	0	0	0
Thrombocytopenia	0	0	0	0
Constipation	0	0	0	0

have weakened the relative reliability and validity of our conclusions.

In conclusion, low-dose apatinib combined with S-1 therapy obtained effective clinical benefits and was tolerable in advanced NSCLC patients who failed from standard treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Ethics Committee of Changzhou Cancer Hospital of Soochow University approved this study (approval number: 2017SY-005-01). All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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