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Apatinib is effective as third-line and more treatment of advanced metastatic non-small-cell lung cancer

A retrospective analysis in a real-world setting

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Abstract

No standard methods are recommended for patients with advanced metastatic non-small-cell lung cancer (NSCLC) experiencing progression after 2 or more lines treatment now. The aim of this retrospective study was to assess the efficacy and safety of apatinib in metastatic NSCLC patients after second-line or more treatments failure in a real-world setting.

A total of 52 advanced NSCLC patients who experienced progression after second-line and more treatments and received apatinib from March 2016 to February 2018 were retrospectively reviewed. Patients were treated with oral apatinib 500 mg QD (take the medicine once a day), every 4 weeks for a cycle. Responding and stable patients continued the treatment until progression or intolerable toxicity. The overall survival (OS), progression-free survival (PFS), objective remission rate (ORR) and disease control rate (DCR), and side effects of the drug were collected and reviewed.

The ORR and the DCR were 6.9% and 67.4%. The median PFS and median OS of all patients were 3.8 months and 5.8 months, respectively. The Eastern Cooperative Oncology Group score was the independent influencing factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens (PFS: hazard ratio [HR] = 4.446, 95% confidence interval [CI]: 1.185–16.678, $P = .027$ and OS: HR = 8.149, 95% CI: 1.173–56.596, $P = .034$). The most common adverse events apatinib-related included hypertension (19.2%), hand-foot syndrome (11.5%), and mucous membrane reaction (17.3%). And treatment-related grade 3/4 toxicities were low.

Apatinib showed favorable efficacy and safety and could be a treatment option in patients with advanced NSCLC experiencing progression after second-line and more treatment.

Abbreviations: CR = complete response, DCR = disease control rate, ECOG = Eastern Cooperative Oncology Group, ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = endothelial growth factor recepter, NSCLC = non-small-cell lung cancer, ORR = objective remission rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, RECIST = response evaluation criteria in solid tumor, SD = stable disease, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

Keywords: anti-angiogenic drugs, apatinib, non-small cell lung cancer, targeted therapies, vascular endothelial growth factor receptor

Editor: Giandomenico Roviello.

This study was supported by a grant from Natural Science Foundation of Chongqing municipal science and technology commission, China (2013jcyjA10125); and a foundation of Young and Middle-age High-level Medical Reserved Personnel Training of Chongqing, China. All the funding source had no involvement in the study.

The authors have no conflicts of interest to disclose.

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How to cite this article: Leng J, Li DR, Huang LM, Ji XH, Wang DL. Apatinib is effective as third-line and more treatment of advanced metastatic non-small-cell lung cancer. Medicine 2019;98:36(e16967).

Received: 27 February 2019 / Received in final form: 12 July 2019 / Accepted: 5 August 2019

http://dx.doi.org/10.1097/MD.0000000000016967

1. Introduction

Lung cancer is one of the most common malignancies and the leading cause of cancer-related death in the world and China. Non-small cell lung cancer (NSCLC) has the highest incidence, accounting for over 80% of lung cancer patients. As the early symptoms are not obvious, the vast majority of lung cancer patients have been diagnosed at the advanced stages.[1] Despite the significant progress with the targeted and immunotherapeutic agents in the treatment of advanced NSCLC over the last decade, there is no standard treatment for patients with advanced metastatic NSCLC experiencing progression after 2 or more lines of standard treatment. Currently, Clinical trials or palliative care are generally recommended by the guidelines. For these patients with acceptable Eastern Cooperative Oncology Group (ECOG) scores, whether antiangiogenic drugs with definite curative effect and small side effect could be an option is widespread concerned.

Vascular endothelial growth factor (VEGF) family proteins are the most important cytokines that induce tumor angiogenesis.[2] The VEGF family consist of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor. VEGF-A can increase vascular permeability and promote

angiogenesis.[3] VEGF-B forms a dimer with VEGF-A to exert its effect.[4] The transmembrane receptors required for VEGF family signaling include Flt-1 (VEGFR-1), KDR (VEGFR-2), Flt-4 (VEGFR-3), Neuropilin-1, and Neuropilin-2.[5] Transmembrane receptors have an intrinsic tyrosine kinase activity. VEGF stimulates downstream signal transduction by binding to tyrosine kinases of transmembrane receptors and promotes proliferation, mitosis, differentiation, and migration of endothelial cells to form new vascular cavities.[6]

As a new target in the treatment of cancer, antiangiogenic drugs have been actively investigated in tumor.[7] Bevacizumab, a recombinant humanized monoclonal antibody against VEGF, is the first antiangiogenic drug approved by the Food and Drug Administration, which is now widely used in the treatment for cancer. Clinical evidence from ECOG 4599[8] and AVAIL[9] had laid the foundation for bevacizumab combined with standard chemotherapy as first-line therapy for NSCLC compared with standard chemotherapy alone, patients with advanced NSCLC had higher response rates and prolonged time to progression when treated with bevacizumab combined with standard chemotherapy.

Apatinib (HengRui Pharmaceutical Co, Ltd, Lianyungang, People's Republic of China), is a novel small molecule tyrosine kinase inhibitor which was approved in China in 2014. Apatinibbinds to the VEGFR-2 ATP binding site and selectively inhibits the phosphorylation of VEGFR-2 and tumor angiogenesis.[10,11] Based on the a promising phase III study in Chinese gastric cancer patients,[12] apatinib had been admitted as a standard third line treatment for advanced gastric cancer in China. Apatinib has also been used in some small clinical practice or case report and has some potential efficacy as a salvage treatment for other advanced metastatic tumor such as breast cancer, esophageal cancer.[13–16] However, there is no standard on the selection of case and treatment timing for patients with apatinib in solid tumor.

In this study, we retrospectively evaluated the efficacy and the safety profiles of apatinib in advanced NSCLC patients who had failed with second-line or more treatments in our medical center in a real-world treatment patterns. Clinicopathologic factors associated with prognosis were also concerned.

2. Material and methods

2.1. Patient selection

All the patients were treated in Chongqing University Cancer Hospital between March 2016 and February 2018. Fifty-two advanced NSCLC patients who experienced progression after second-line and more treatments and received apatinib were included. The study protocol was approved by the Ethics Committee of Chongqing University Cancer Hospital. All participants provided informed consent before treatment.

Data were collected from the medical records and radiographic imaging records included gender, age, smoking history, histology, endothelial growth factor recepter (EGFR) mutation type, ECOG performance status, previous treatment, response, adverse events, and survival data. Inclusion criteria included: pathologically diagnosed or recurrent stage IV NSCLC; ECOG 0 to 2; at least 1 radiologically measurable lesion did not receiving local treatments such as radiotherapy and freezing; progression after previously second-line and above standard treatments, including molecular targeted therapy according to gene mutations and/or platinum-based chemotherapy and/or radiotherapy; no other active antitumor treatments were offered during the period of apatinib treatment; no history of severe heart disease, and liver and kidney function and bone marrow hematopoiesis are normal. The main exclusion criterion was patients with uncontrolled blood pressure with medication (>140/90 mm Hg) and with those with bleeding tendency and receiving thrombolytics or anticoagulants.

2.2. Treatment regimen

Patients were treated with oral apatinib at a daily dose of 500 mg, every 4 weeks for 1 treatment cycle. Dose reduction (250 mg QD) was allowed for drug-related toxicity. Re-evaluating computed tomography (CT) scans will be carried out after 2 cycles of treatment. Responding and stable patients continued the treatment until progression or unacceptable toxicity. Follow-up time was until the death of the patient or the end of the study.

2.3. Responses and toxicity assessments

The size of measurable lesions was determined by CT scan every 2 cycles. The tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1 criteria.[17] Tumor efficacy was evaluated included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective remission rate (ORR) was defined as the percentage of CR and PR. The disease control rate (DCR) was defined as the percentage of CR and PR and SD. In addition, toxicities were assessed by the National Cancer Institute Common Toxicity Criteria version 4.0.

2.4. Follow-ups

Progression-free survival (PFS) was defined as the period between the first date of apatinib treatment and the date of progression. Overall survival (OS) was defined as the period from the first date of apatinib treatment to death or the study ending. Follow-ups were conducted up to February 28, 2018. And the median follow-up period was 11.3 month (2.9–21 m).

2.5. Statistical analysis

Data analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL). The Kaplan–Meier method was performed to survival analysis for PFS and OS. The multivariate Cox regression model was used to estimate the treatment hazard ratios. Differences with a 2-sided *P*-value of $<.05$ were considered statistically significant.

3. Results

3.1. Patients characteristics

A total of 52 patients retrospectively were collected. The patient's general information collection included gender, age, and pathological types, smoking status, EGFR mutations, ECOG scores, and prior treatment. Among them, 44 were male and 8 were female with a median age of 61 years (with the range of 32–77 years). According to their gene sensitizing gene mutations, all of them had received targeted treatment and/or platinum-based chemotherapy and/or radiotherapy before. Detection of *EGFR* gene by tissue had shown 6 of 8 patients

Table 1

Characteristics of the study population.

Characteristic	Number of patients	Percentage (%)
Gender		
Male	44	84.6
Female	8	15.4
Age		
<65 yr	33	63.5
≥65 yr	19	36.5
Histology		
Adenocarcinoma	32	61.5
Squamous cell carcinoma	20	38.5
Smoking history		
Yes	41	78.8
No	11	21.2
EGFR mutation		
Mutation	8	15.4
Wide type	26	50
Unknown	18	34.6
ECOGPS		
0–1	43	82.7
2	9	17.3
Previous treatment		
Targeted therapy + chemotherapy	5	9.6
targeted therapy + chemotherapy + radiotherapy	5	9.6
Chemotherapy	17	32.7
Chemotherapy + radiotherapy	25	48.1

ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth factor receptor.

were deletion of exon 19, while 1 was L858R in exon 21 and 1 was mutations in exon 20. And 43 patients had a PS of ECOG 0 or 1 and 9 patients had a PS of 2. The patients' characteristics are summarized in Table 1.

3.2. Survival and response

Nine of the 52 patients were not eligible for evaluation of the efficacy. Among these 9 patients, 7 patients could not follow-up. Another 2 patients stopped treatment after 2 weeks due to the sudden hemoptysis. A total of 43 patients were evaluated for efficacy. A total of 3 patients (6.9%) achieved PRs with an ORR of 6.9%. Twenty-six patients (60.5%) archived a SD status and 14 patients (32.6%) archived PD with a DCR of 67.4%.

The median progression-free survival (PFS) and median OS of all patients treated with apatinib as third-line or more were 3.8 months and 5.8 months, respectively (Figs. 1 and 2).

Cox method was used for the univariate analysis of 43 patients with advanced NSCLC experiencing progression after 2 or more lines of treatment. Cox univariate analysis showed that ECOG score affected the PFS and OS of apatini treated advanced NSCLC patients who failed above second line. Patients with ECOG 0–1 scores had prolonged PFS compared with ECOG 2 patients (3.9 months vs 2.1 months, respectively, $P = .029$). And patients with ECPG 01 scores also had longer OS than that of ECOG 2 (6.4 months vs 4.1 months, $P = 0.046$). The gender, age, smoking status, pathology type and EGFR status of the patients were not the predictors of PFS and OS (Table 2).

The multivariate analysis also showed that the ECOG score was the independent factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens (PFS: hazard ratio [HR] = 4.446, 95% confidence interval [CI]: 1.185–16.678, $P = .027$; OS: HR = 8.149, 95% CI: 1.173–56.596, $P = .034$). The results are listed in Table 3.

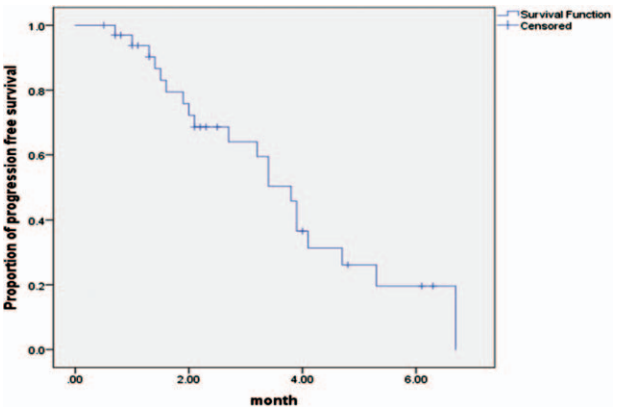

Figure 1. Progression-free survival curve of patients with apatinib treatment in advanced NSCLC who failed with second-line or more treatments. NSCLC = nonsmall cell lung cancer.

3.3. Adverse events

The most common treatment-related adverse events of all levels were as follows: hypertension 19.2% (10/52), hand-foot syndrome 11.5% (6/52), gastrointestinal reactions 13.5% (7/52), mucous membrane reaction 17.3% (9/52), myelosuppression 3.8% (2/52), palpitation 5.8% (3/52), hemoptysis 3.8% (2/52), proteinuria 1.9% (1/52). Treatment-related adverse events of grade 3 accounted for 13.5%, including hypertension (n = 2), of which 1 case considered mild cerebral hemorrhage, palpitations (n = 2), hemoptysis (n = 2), thrombocytopenia (n = 1). The symptoms related to treatment-related adverse events of grade 3 were quickly reduced and recovered after a dose reduction and symptomatic treatment in time. Dose reduce were not needed for these grade I-II adverse events and the symptoms could be controlled well. There were no drug-related serious adverse

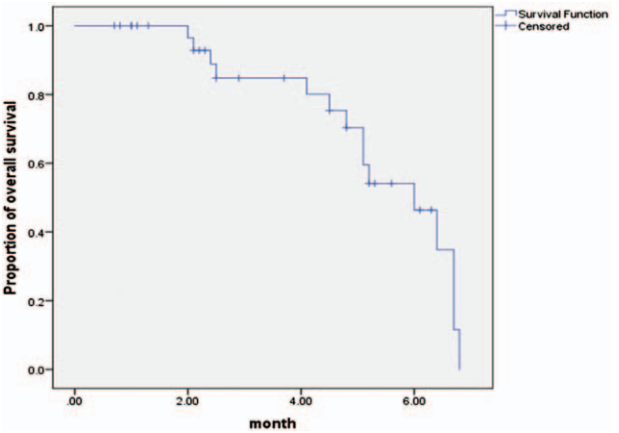

Figure 2. Overall survival curve of patients with apatinib treatment in advanced NSCLC who failed with second-line or more treatments. NSCLC = nonsmall cell lung cancer.

Table 2

Univariate analysis of progression-free survival and overall survival.

		PFS				OS			
Factors	**n**	**Median PFS**	**HR**	**95% CI**	***P***	**Median OS**	**HR**	**95% CI**	***P***
Gender									
Male	36	3.8				6.0			
Female	7	2.7	0.906	0.299–2.747	.861	6.7	0.909	0.251–3.295	.884
Age									
<65 yr	28	3.8				6.0			
≥65 yr	15	2.0	0.795	0.274–2.304	.672	6.7	0.984	0.306–3.163	.978
Pathological types									
Adenocarcinoma	27	3.4				5.1			
Squamous cell carcinoma	16	3.8	1.017	0.397–2.603	.972	6.0	0.806	0.267–2.431	.702
Smoking history									
Yes	34	3.8				6.0			
No	9	3.2	0.843	0.302–2.352	.744	6.7	0.653	0.195–2.184	.489
EGFR mutations									
Yes	8	4.1				5.1			
Wild type	22	2.7	1.411	0.384–5.189	.605	6.0	1.619	0.330–7.948	.553
Unknown	13	3.9	1.519	0.375–6.157	.559	5.2	1.632	0.312–8.536	.562
ECOG PS									
0–1	35	3.9				6.4			
2	8	2.1	3.605	1.140–11.397	.029	4.1	4.043	1.024–15.963	.046

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth factor receptor, HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

Table 3

Multivariate analysis of progression-free survival and overall survival.

	PFS			OS		
Factors	**HR**	***P***	**95% CI**	**HR**	***P***	**95% CI**
Gender	0.579	.644	0.057–5.871	1.440	.795	0.092–22.484
Age	0.814	.781	0.190–3.478	1.048	.961	0.164–6.681
Pathological types	1.157	.806	0.361–3.713	0.488	.345	0.110–2.166
Smoking history	2.177	.578	0.140–3.769	0.287	.422	0.014–6.032
EGFR mutations		.631			.931	
Wild type	2.485	.388	0.315–19.613	0.776	.851	0.055–10.877
Unknown	3.004	.343	0.310–29.117	1.066	.965	0.064–17.764
ECOG PS	4.446	.027	1.185–16.678	8.149	.034	1.173–56.596

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth factor receptor, HR = hazard ratio, PFS = progression-free survival.

reactions occurred in this study. The side effects are listed in Table 4.

4. Discussion

In 1971, Professor Folkman proposed the theory of "starving tumors." The theory was that tumors need New blood vessels to provide rich nutrition and nutrients. By blocking the blood supply of tumors, tumor lesions could be no more than 2 to 3 mm.[18] VEGF is a key mediator with neovascularization and the expression of VEGF in tumor is closely related to the early recurrence, metastasis and the prognosis of the tumor.

The family of VEGF and their receptors (vascular endothelial growth factor receptor [VEGFR]) were overexpressed on the surface of malignant tumors.[19] VEGFR-2 is the most important VEGFR and it is mainly expressed on the surface of vascular endothelial cells and bone marrow-derived endothelial cells.[20] Increased VEGFR-2 gene copy number was found in NSCLC tumor tissue.[21,13] The overexpression of VEGFs and VEGFRs plays an important role in the survival of patients with NSCLC.[13]

Although a few angiogenesis inhibitors such as bevacizumab combined with chemotherapy have shown improved OS or PFS in patients with lung, breast, renal, hepatic, and colon cancers,

Table 4

Adverse effects of apatinib.

Adverse effects	Hypertension	Hand-foot syndrome	Gastrointestinal reactions	Mucosal reaction	Myelosuppression	Palpitation	Hemoptysis	Proteinuria
I-II	8	6	7	9	1	1	0	1
III-IV	2	0	0	0	1	2	2	0
n	10	6	7	9	2	3	2	1
%	19.20%	11.50%	13.50%	17.30%	3.80%	5.80%	3.80%	1.90%

agents in angiogenesis alone had shown limited clinical value in metastatic NSCLC cancer.

Apatinib, one of the latest oral small-molecule angiogenesis inhibitors, selectively inhibits VEGFR-2, which may inhibit VEGF-stimulated endothelial cell migration and proliferation and decrease tumor growth and metastasis.[10,11] Li[12] had reported a randomized, placebo-controlled phase III study of Apatinib in Chinese gastric cancer patients. Two hundred seventy three advanced gastric cancer patients after second-line failure were randomly assigned to receive 850 mg of apatinib and placebo in 2:1 ratio. Patients with apatinib had a significantly prolong the median OS compared with those treated with placebo (6.5 months vs 4.7 months, $P = .0149$). The study in breast cancer patients who used apatinib as the salvage treatment also had similar prolonged PFS and OS (3.3 months for PFS and 10.7 months for OS).[13]

For advanced NSCLC patients who have failed after second-line or more radiochemotherapy or targeted treatment, no definitive chemotherapeutic regimen has been recommended now. New treatment strategy is urgently needed especially for these who had a better performance status (PS). Song[22] analyzed the efficacy of apatinib as a salvage treatment in 42 advanced NSCLC patients. Apatinib was approved effective in patients who were unresponsive to standard pretreatment before. In our study, the objective response rate and he DCR of apatinib were consistent with the previous study in the Chinese population. Our analysis revealed the median PFS was 3.8 months and the median OS was 5.8 months after Apatinib administration. These data suggest that the advanced NSCLC patient could acquire longer benefit from Apatinib treatment after second-line or more.

In our study, Cox univariate analysis showed that ECOG score affected the PFS and OS of apatinib treated advanced NSCLC above second lines. The gender, age, smoking status, pathology type and EGFR status of the patients were not the predictors of PFS and OS. In order to eliminate confounding factors, this study continued to use the cox proportional regression risk model for multivariate analysis. The multivariate analysis also showed that the ECOG score was the independent factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens. Apatinib maybe a treatment choice for these NSCLC patients who had a better PS. For various reasons, half of our patients did not undergo mutation gene detection during their course of disease. The multivariate analysis showed that previous treatments and EGFR mutation weren't the independent factor of PFS and OS for the patients.

The adverse events of apatinib especially III-IV grade side effects in different studies might be caused by the different dose and different cancer. The recommended dose for apatinib is 850 mg. While many trials had found the daily apatinib dose of 500 mg could have the similar efficacy as those of high dose while decrease the grade 3/4 toxicities significantly.[13] One of a small retrospective study[23] had reported a daily dose of 250 mg of apatinib was safe and effective in the treatment of NSCLC. In our center, a common recommended dose of 500 mg was used for more lines treated solid cancer patients considering the efficacy. And the majority of our patients were also willing to accept this dose for cost-effectiveness reasons too. Previous studies have found that the most common adverse events of apatinib were hypertension, hand-foot skin reactions, and proteinuria,[22–25] although some case report showed gastrointestinal hemorrhage and perforation during apatinib treatment.[26] Most of studies had supported that the adverse events of apatinib were dose-dependent and grade 3 to 4 side effects had found rare in low dosage.[22–25] In our study, apatinib-related grade 3 toxicities occurred in 13.5% patients, which were lower than that in gastric carcinoma patients.[12] The symptoms of III-IV grade side effects hypertension could be well controlled by drug suspension or dose reduction and symptomatic treatment. In our study, the common hematologic toxicities related to apatinib were mild. The toxicities of apatinib are similar to or better than those of other antiangiogenic drugs such as Bevacizumab[8,9,27] or rh-endostatin.[28] It seems that apatinib was safe in comparison with other antiangiogenic agents, especially lower than that in chemotherapeutics.[29–31] This means apatinib maybe a promising alternative therapy for patients who had undergone more lines treatments.

In summary, our current real-life setting study data provides a valuable real-life evidence regarding treatments received apatinib in advanced NSCLC patients after more lines treatment. The major limitations of this study were retrospective nature and a small sample size. Compared with prospective studies, there may be potential biases in the selection of possible cases and may affect the conclusions in retrospective study. Even Statistical analysis was used to reduce unmeasured confounding factors, the small number of patients still limited in its ability to provide better conclusion. More prospective study with a chemotherapy or palliative treatment control group will give us a more credible conclusion. There are many questions should be answer in apatinib treatment in NSCLC. What is the appropriate cases for apatinib treatment and when is the best time to use apatinib in advanced NSCLC patients? Could the combination of apatinib and chemotherapy improve the benefit in NSCLC patients? To answer these questions, more clinical studies will needed; and furthermore, these questions can be offered for clinical treatment. In addition, the dose of 500 mg apatinib adopted in this study was not widely recommended. Hence, the most suitable dosage is needed be verified by further prospective large-scale studies. However, without prospective clinical studies in the literature, since our patients chose apatinib treatment randomly, our conclusion may be deemed as meaningful and closer to a real-world setting.

Author contributions

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Supervision: Dong-Lin Wang.
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Writing – review and editing: Dai-Rong Li, Jiao Leng.

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