

ORIGINAL ARTICLE

Clinical investigation of the efficacy and toxicity of apatinib (YN968D1) in stage III/IV non-small cell lung cancer after second-line chemotherapy treatment: A retrospective study

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Keywords

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Abstract

Background: This study was designed to assess the clinical efficacy and toxicity of apatinib (YN968D1) as third or subsequent-line treatment for stage III/IV non-small cell lung cancer (NSCLC).

Methods: A total of 100 patients with advanced NSCLC who were treated with apatinib at a daily dose of 250/425/500 mg at Shandong Cancer Hospital from January 2016 to June 2018 were enrolled in our study. The objective response, disease control, and median progression-free survival rates were reviewed and evaluated. Univariate and multivariate analyses were performed to determine the prognostic factors. The main adverse events were evaluated per the Common Terminology Criteria for Adverse Events version 4.0.

Results: All patients were assessable for response. No complete responses were observed, 11 patients achieved a partial response, and 56 showed stable disease. The objective response rate was 11.0%, the disease control rate was 67.0%, and the median progression-free survival was 2.93 months (95% confidence interval 2.07–3.87). In Cox regression analysis, the Eastern Cooperative Oncology Group performance status score (hazard ratio 1.799; $P < 0.05$) and smoking history (hazard ratio 1.958; $P < 0.05$) were predictive indicators for apatinib treatment efficacy. Treatment-related adverse events were tolerated, predictable, reversible, and controllable.

Conclusion: Apatinib was found to be both effective and safe in advanced NSCLC patients without a genetic driver mutation who experienced progression after two or more lines of chemotherapy treatment.

Introduction

Lung cancer, which poses a great threat to public health, is the most common malignancy and the leading cause of cancer-related death worldwide.¹ Non-small cell lung cancer (NSCLC) is the most common subtype, accounting for 80–85% of lung cancer cases.² As symptoms of early NSCLC are usually atypical and go unnoticed, nearly 75–80% patients are diagnosed at an advanced stage (III/IV),³ with an associated five-year survival rate of 15%.⁴

Currently, multidisciplinary treatment strategies for stage III/IV NSCLC include radiotherapy, chemotherapy, molecular targeted therapy, antiangiogenic therapy,

immunotherapy, and traditional Chinese herbal medicine.^{5–9} According to the National Comprehensive Cancer Network (NCCN) guidelines, standard first and second-line treatment regimens are recommended for NSCLC patients without genetic driver mutations. However, no standard regimens have yet been recommended for third or subsequent-line treatment.¹⁰ Therefore, it is imperative to explore effective and safe treatment options for patients who fail second-line chemotherapy.^{11,12}

Angiogenesis, which is mainly mediated by the vascular endothelial growth factor (VEGF) pathway, is crucial for tumor growth, proliferation, progression, and

metastasis.^{13,14} In 1971, Folkman was the first to hypothesize the potential therapeutic benefit of targeting tumor angiogenesis.¹⁵ Proteins in the VEGF family are key regulators of normal and tumor angiogenesis and provide promising targets for anticancer therapies.^{16,17} In recent years, antiangiogenic therapy has become increasingly popular in cancer treatment and has demonstrated potential benefits.^{18,19} Antiangiogenic agents include bevacizumab, ombrabulin, axitinib, ramucirumab, linifanib, cediranib, bavituximab, pazopanib, motesanib, vandetanib, nintedanib, and sunitinib. Among these agents, bevacizumab,^{20–22} ramucirumab,²³ nintedanib,²⁴ and endostar²⁵ have been approved for the treatment of advanced NSCLC.

Apatinib (YN968D1) is a novel oral small molecule tyrosine kinase inhibitor (TKI)²⁶ that selectively inhibits VEGF receptor-2 (VEGFR-2) and blocks the signaling pathway downstream of VEGF binding, thus strongly inhibiting tumor angiogenesis.²⁷ Apatinib was approved and accepted as a subsequent-line treatment for advanced or metastatic chemorefractory gastric cancer by the China State Food and Drug Administration (cFDA) in October 2014.^{27,28} Clinical studies have shown its satisfactory safety, tolerability, and efficacy in various types of solid tumors,²⁶ including breast cancer,²⁹ hepatocellular carcinoma³⁰ and sarcomas.³¹ In addition, preclinical evidence³² and preliminary clinical research³³ have shown the efficacy of apatinib in colon cancer. Furthermore, in a multicenter, placebo-controlled, phase II trial conducted in China, apatinib proved a promising treatment for patients with advanced nonsquamous NSCLC who had undergone two previous treatment regimens.³⁴ A phase III clinical trial of apatinib in patients with NSCLC is ongoing. Some studies have also revealed that apatinib has a certain therapeutic effect and safety in patients with advanced NSCLC refractory to multiline treatments.^{35,36}

In this retrospective study, we investigated the efficacy and toxicity of apatinib for stage III/IV NSCLC after second-line chemotherapy treatment.

Methods

Patients

We retrospectively analyzed the records of 100 patients with advanced NSCLC administered apatinib treatment from January 2016 to June 2018 at Shandong Cancer Hospital, China. Inclusion criteria were as follows: (i) age at diagnosis between 18 and 85 years, (ii) the presence of pathologically or cytologically confirmed advanced NSCLC (stage III or IV), (iii) a prior lack of response or intolerance to at least two lines of chemotherapy, (iv) the presence of at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors

(RECIST), (v) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and (vi) sufficient main organ function. Patients with small cell lung cancer, uncontrolled hypertension, a bleeding tendency or ischemic cardiovascular disease, severe liver and kidney dysfunction; who were pregnant or lactating; or who had previously received other VEGFR-2 TKIs (previous anti-VEGF antibody treatment was permitted), were excluded from the study. Only patients who had finished at least one cycle of apatinib therapy for which the efficacy was evaluated were included in this study (one treatment cycle was 28 days long). A total of 100 patients were enrolled (Table 1).

To preserve patient confidentiality and privacy, patient data were de-identified before analysis. Because of the retrospective design and the patient anonymization protocol, the ethics committee of the Cancer Hospital, Chinese Academy of Medical Sciences approved the study and determined that informed consent was not required. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 1 Baseline characteristics of patients

Characteristics	Patients (n = 100) (%)
Gender	
Male	57 (57.0)
Female	43 (43.0)
Age (years)	
Median	59
> 60	47 (47.0)
≤ 60	53 (53.0)
Smoking history	
Never	60 (60.0)
Former or current	40 (40.0)
ECOG PS	
0–1	76 (76.0)
2	24 (24.0)
Pathological diagnosis	
Adenocarcinoma	68 (68.0)
Squamous cell carcinoma	26 (26.0)
Others	6 (6.0)
Clinical stage	
III	23 (23.0)
IV	77 (77.0)
EGFR mutation status	
Sensitive mutation	17(17.0)
Wild type	38(38.0)
Untested	45(45.0)
Line of apatinib	
Third line	42(42.0)
Further line	58(58.0)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment methods

Apatinib mesylate (Jiangsu Hengrui Medicine, Jiangsu, China) was initiated by the oral administration of a dosage ranging from 250 mg to 500 mg once a day as determined by the doctor, according to the patient's ECOG PS. No other chemotherapy was administered during apatinib treatment, while brain radiotherapy was allowed for patients with brain metastases. Patients were required to take apatinib with warm water 30 minutes after a meal, keeping the daily medication time as consistent as possible. One treatment cycle was 28 days long, and tolerance was assessed two weeks later. If obvious adverse events (AEs) occurred, dose reduction was deemed necessary; the attending physician recommended the final dose based on an assessment of each patient's clinical status and treatment tolerance. Treatment was continued until disease progression, development of an unacceptable serious toxic effect, death, or any other reason.

Evaluation of efficacy and adverse events

Computed tomography (CT) scans were obtained before commencing apatinib treatment to assess the tumor every one or two cycles during the treatment or for early evaluation when significant signs of tumor progression appeared. The short-term efficacy was assessed according to RECIST version 1.1 and was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR was defined as the complete disappearance of all visible lesions. PR was defined as a 30% reduction in the sum of the longest diameter of tumor lesions. SD was defined as a response between PR and PD. PD was defined as a 20% increase in the longest diameter of tumor lesions or the development of new lesions. The objective response rate (ORR) represented the percentage of patients with a CR or PR, and the disease control rate (DCR) was defined as the percentage of patients with a CR, a PR, or SD. The progression-free survival (PFS) duration was calculated from the date of apatinib treatment to the date of tumor progression or death from any cause. If disease progression was not observed, the PFS was defined as the time to the last date the patient was confirmed without disease progression. The overall survival (OS) duration was defined from date of initial apatinib treatment to death. Adverse events (AEs) were divided into grades 0–IV according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; the higher the grade, the worse the adverse reaction.

Follow-up visits

Telephone and outpatient follow-up approaches were adopted, at which time adverse reactions, changes in

condition, and patient death was recorded. Patients were observed until PD, death, or the end of the study. The last follow-up date in this study was 22 June 2018.

Statistical analysis

SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The median PFS duration was calculated using the Kaplan–Meier method, the plots were generated using GraphPad Prism 7.0 (GraphPad, La Jolla, CA, USA), and the survival curves were compared by a log-rank test. Factors with $P < 0.05$ in univariate analysis were assessed by a Cox regression model. Cox proportional hazards regression models were used to estimate hazard ratios (HRs). A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 100 patients with advanced NSCLC were included in this study. The main demographic and clinical characteristics of the 100 patients are shown in Table 1.

All patients received at least two lines of chemotherapy. The study included 57 men and 43 women, with a median age of 59 years (range: 25–82). Most patients had a favorable ECOG PS (0–1) and did not have a history of smoking. A total of 68 patients had adenocarcinoma, 26 patients had squamous cell carcinoma, and 6 patients had other pathological diagnoses (except small cell lung cancer). *EGFR* mutation status was wild type in 38, mutated in 17, and untested in 45 patients. Twenty-three patients were in stage III, and 77 were in stage IV. Forty-two patients received apatinib as third-line therapy and 58, as a subsequent-line treatment.

Initial dosage and adjustment

The treatment administration and dosage modification profiles are listed in Table 2. Thirty-five patients were initially administered and then maintained at a dosage of

Table 2 Treatment administration and dose modification

Treatments of apatinib	Total
Initial dosage, mg/day	
500	53
425	12
250	35
Modification of dosage, mg/day	
425 → 250	1
500 → 250	2

250 mg. Of the 53 patients who were initially administered a dosage of 500 mg/day, two required a dosage reduction to 250 mg; of the 12 who were initially administered a dosage of 425 mg/day, one required a dosage reduction and was maintained at 250 mg. The common causes of dosage reduction in these patients included hypertension, proteinuria, vomiting, and fatigue.

Efficacy

All patients were administered at least one cycle of apatinib and were followed up until June 2018. None achieved a CR, 11 achieved a PR, 56 reached a stage of SD, and 33 suffered PD. The ORR and DCR were 11.0% and 67.0%, respectively. The median PFS with apatinib treatment was 2.93 months (95% confidence interval [CI] 2.33–3.52), and the median OS was not reached (Fig 1). Examples of follow-up CT images after apatinib therapy in a 51-year-old woman with adenocarcinoma are shown in Figure 2. The disease was controlled successfully, with a PFS of

6.7 months. In addition, this patient tolerated apatinib well, with a satisfactory quality of life.

The median PFS for the 68 patients with adenocarcinoma was 2.97 months (95% CI 2.07–3.87), and the ORR and DCR were 10.3% and 67.6%, respectively. The median PFS for the 26 patients with squamous cell carcinoma was 2.57 months (95% CI 1.66–3.48), and the ORR and DCR were 15.4% and 69.2%, respectively. No significant differences were observed between these two groups ($P > 0.05$) (Fig 1).

In univariate analysis, the absence of a history of smoking was associated with longer PFS ($P < 0.05$). In addition, the results showed that the PFS of patients with an ECOG PS of 0–1 was significantly prolonged compared to that of patients with an ECOG PS of 2 ($P < 0.05$) (Table 3, Fig 1). The results of the Cox regression analysis showed that the ECOG PS score (HR 1.799; $P < 0.05$) and a smoking history (HR 1.958; $P < 0.05$) were predictive indicators for apatinib treatment efficacy. Additionally, we found that age, gender, *EGFR* mutation status, line of apatinib treatment, and AEs were not risk factors for shorter PFS.

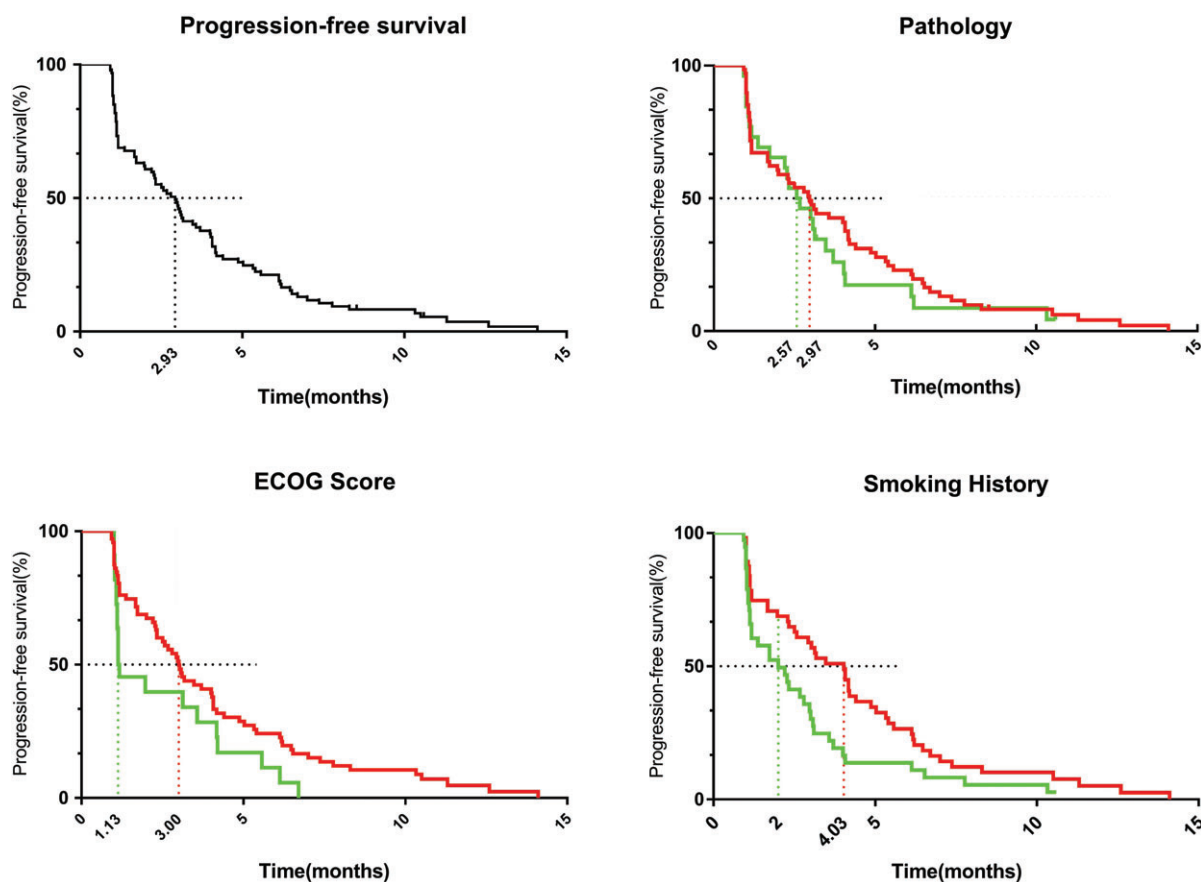


Figure 1 The median progression-free survival of patients with advanced non-small cell lung cancer after apatinib treatment. (—) Adenocarcinoma, (—) squamous cell carcinoma, (—) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, (—) ECOG PS 2, (—) never, (—) former or current.

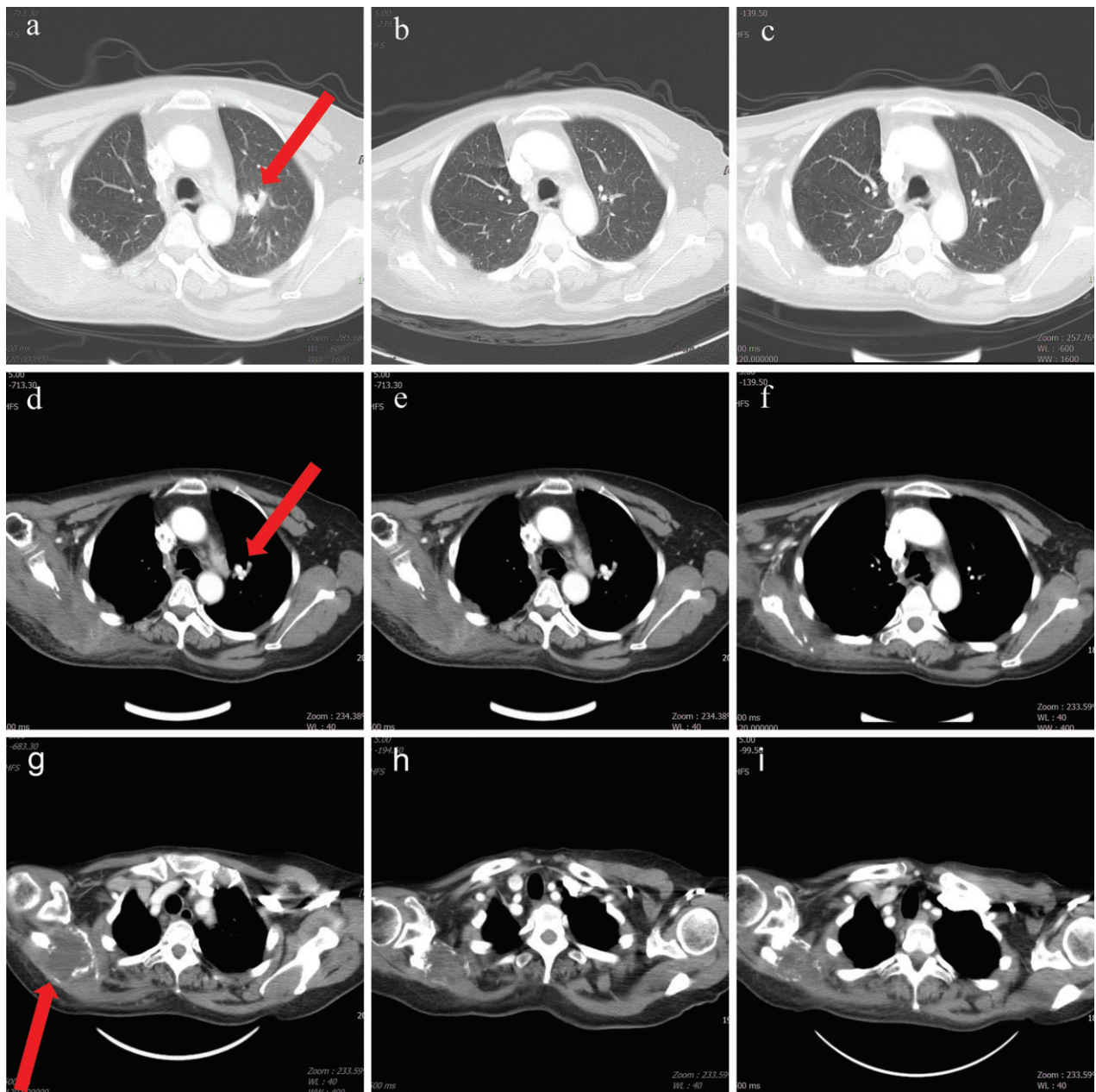


Figure 2 Computed tomography scans (a,d,g) before (31 October 2017), (b,e,h) one month after (4 December 2017) and (c,f,i) four months after (13 March 2018) apatinib treatment.

Safety

No grade 4 AEs were observed in our study. The treatment-related AEs, which mainly manifested as hypertension (53%), hand-foot reaction (47%), proteinuria (41%), fatigue (21%), anorexia (19%), and hematologic toxicity (15%), were acceptable and manageable. The main treatment-related AEs are summarized in Table 4.

Discussion

Lung cancer is the main cause of cancer-related death worldwide; it has long been the most common cancer and the leading cause of cancer-related death in China.³⁷ For NSCLC patients that do not harbor a genetic driver mutation, anticancer treatment after second-line chemotherapy is indicated if the ECOG PS is satisfactory. However, alternative third or subsequent-line therapeutic regimens are

Table 3 Univariate analysis of PFS

	PFS	95% CI	P
Gender			0.486
Male	2.67	1.67–3.67	
Female	3.17	1.04–5.29	
Age (years)			0.943
> 60	2.97	2.16–3.70	
≤ 60	2.93	1.99–3.96	
Smoking history			0.023
Never	3.47	2.37–4.58	
Former or current	2.00	0.92–3.08	
ECOG PS			0.014
0–1	3.00	2.62–3.33	
2	1.13	1.05–1.21	
Pathological diagnosis			0.352
Adenocarcinoma	2.97	2.07–3.87	
Squamous cell carcinoma	2.57	1.66–3.48	
Others	1.13	0.00–3.46	
Clinical stage			0.450
III	3.10	1.60–4.60	
IV	2.67	1.77–3.58	
EGFR mutation status			0.452
Sensitive mutation	2.00	0.82–3.18	
Wild type	3.13	2.43–3.83	
Untested	2.57	1.87–3.27	
Line of apatinib			0.228
Third-line	2.33	1.25–3.41	
Further-line	3.13	2.22–4.05	
Initial dosage, mg/day			0.161
500	3.17	1.99–4.35	
425	2.80	1.72–3.88	
250	1.73	0.44–3.02	

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

Table 4 Treatment-related adverse events

Adverse event	Grade 1–2	Grade 3	Total
Hypertension	44	9	53
Hand-foot syndrome	36	11	47
Proteinuria	34	7	41
Fatigue	20	1	21
Mucositis	12	0	12
Diarrhea	10	1	11
Anorexia	18	1	19
Bone marrow suppression	11	3	14
Hematologic toxicity	12	3	15
Nausea	3	0	3
Vomiting	2	0	2

limited, and the efficacy is generally unsatisfactory. Therefore, patients require newer, safer, and more effective treatments. Angiogenesis is closely related to tumor growth, proliferation, progression, and metastasis; it supplies necessary oxygen, growth factors, and nutrients. Thus, angiogenesis is generally considered an attractive target in cancer therapy.^{38–40} VEGF plays an important role in angiogenesis;

VEGFRs are TKIs that are the key regulators of this process.^{17,41} The VEGFR family is composed of multiple TKIs, such as VEGFR-1, VEGFR-2, VEGFR-3, and the VEGFR co-receptors neuropilin 1 and 2.⁴² Among these receptors, VEGFR-2 is the major mediator of the mitogenic, angiogenic, and permeability-enhancing effects of VEGF.⁴³ Thus, inhibition of VEGFR-2 might be a promising strategy for inhibiting tumor angiogenesis.^{44,45}

Apatinib, also known as YN968D1, is a small molecule TKI that mainly targets VEGFR-2 through the intracellular ATP-binding site that inhibits all VEGF-stimulated endothelial cell migration and proliferation, decreases tumor microvascular density, and promotes apoptosis.^{46–48} On 17 October 17, 2014, apatinib was approved by the cFDA as a third or subsequent-line therapy for advanced or metastatic chemo-refractory gastric cancer.⁴⁹ Both preclinical and clinical studies have shown that apatinib has promising efficacy, convenient oral administration methods, and manageable AEs in the treatment of a variety of solid tumors.^{26,32,33,50}

The efficacy of apatinib as a second or subsequent-line therapy in patients with advanced NSCLC has been investigated in several studies.^{26,51–53} In a phase II multicenter, randomized, placebo-controlled trial for the treatment of advanced non-squamous NSCLC after two previous treatment regimens (nct01270386),⁵⁴ the cohort was randomly divided into two groups (observation vs. placebo) in a 2:1 ratio. The observation group received apatinib at a dosage of 750 mg/day until PD or unacceptable toxicity occurred. The results showed that the median PFS in the observation group was better than that in the placebo group (4.1 vs. 1.9 months, respectively; HR 0.278; $P < 0.001$). Furthermore, apatinib provided significantly greater efficacy than the placebo in terms of both the response rate (12.2% vs. 0%, respectively; $P < 0.02$) and the DCR (68.9% vs. 24.4%, respectively; $P < 0.0001$). In addition, many case reports have revealed that apatinib is a promising therapeutic measure.^{55,56}

Our study was designed to observe the clinical efficacy and toxicity of apatinib as a third or subsequent-line treatment for stage III/IV NSCLC. A total of 11 patients achieved a PR, and 56 showed SD according to RECIST version 1.1. The ORR was 11.0%, and the DCR was 67.0%; these values are consistent with those reported in the phase II multicenter, randomized, placebo-controlled trial (ORR 12.2%, DCR 68.9%). The median PFS in our study was 2.93 months, which was shorter than that reported in the phase II multicenter, randomized, placebo-controlled trial (4.7 months) and in the phase II open-label NSCLC trials (4.0 months). We consider that our result may be related to the greater number of patients in fourth and subsequent-line settings. These differences highlight the gap between randomized controlled trials and actual

clinical practice.⁵⁷ In our study, the mean OS could not be calculated; thus, further exploration with long-term follow-up is needed. However, our data support the potential usefulness of apatinib in treating advanced NSCLC patients after second-line chemotherapy. Furthermore, the usefulness of apatinib as a first or second-line treatment in patients that do not harbor a genetic driver mutation is worth further exploration.

In clinical practice and in most clinical studies, apatinib has mainly been used in patients with adenocarcinoma.^{55,56} However, the subgroup analysis in our study indicated no significant difference in the PFS duration between patients with adenocarcinoma and those with squamous cell carcinoma; these results indicate a therapeutic approach for patients with advanced squamous cell lung cancer. A small prospective single-arm study ($n = 7$ efficacy-evaluable patients) and retrospective single-center studies ($n = 11$ efficacy-evaluable patients) reported similar results.⁵² The dual blockade of both the *EGFR* and *VEGFR* pathways has been reported to provide an additive and even a synergistic anticancer therapeutic strategy.⁵⁸ Therefore, the therapeutic efficacy of the combination of apatinib and other targeted drugs in patients harboring *EGFR* mutation requires further exploration. Moreover, in our study, univariate Cox regression analysis showed that smoking history and ECOG PS were risk factors for shorter PFS. A better therapeutic effect of apatinib could be achieved in patients without a history of smoking or with an ECOG PS of 0–1.

Apatinib has consistently demonstrated manageable toxicity at daily doses of 250 mg to 850 mg.⁵⁰ In the phase I study of apatinib, the maximum tolerated dosage was 850 mg once daily, and the recommended dosage was 750 mg.²⁶ The data did not indicate any safety or pharmacokinetic differences between genders. However, in many clinical trials, a lower apatinib dosage was used (typically 500 mg once daily).⁵² Furthermore, the appropriate dosage of apatinib in NSCLC treatment is unknown. The initial dosages of apatinib used in our study were 500 mg/day in 53 patients, 425 mg/day in 12 patients, and 250 mg/day in 35 patients. Research has attempted to define the safe and effective dosage of apatinib, but further exploration in additional large-sample, multicenter, randomized controlled prospective studies is required.

Regarding the safety of apatinib, hypertension, hand-foot syndrome, and proteinuria are the most common AEs previously reported in clinical trials.^{57,59} Other common hematologic toxicities include neutropenia, leukopenia, thrombocytopenia, and anemia; non-hematologic toxicities include elevated transaminase levels, fatigue, bleeding, diarrhea, and increased alkaline phosphatase levels.³³ In our study, the observed treatment-related AEs, which mainly manifested as hypertension (53%), hand-foot reaction (47%), proteinuria (41%), fatigue (21%), anorexia (19%),

and hematologic toxicity (15%), were moderate and controllable; the severity of these AEs was similar to or better than those observed in a previous study. We certainly need to consider several questions: First, what measures should be taken for patients who experience grade 3 AEs? Second, if patients demonstrate fairly good tolerance for apatinib, does the dose need to be adjusted upward? Moreover, the determination of an optimized dose range of apatinib that balances toxicity with efficacy needs further exploration.

In conclusion, our study indicated that apatinib was both effective and safe after failure of second-line chemotherapy treatment in advanced NSCLC patients without genetic driver mutations. Because of its easy administration, better compliance, mild toxicity, improved outcomes, and reasonable price, apatinib could be a therapeutic option for advanced NSCLC. However, the efficacy of apatinib needs to be further verified in additional large-sample, multicenter, randomized controlled prospective studies.

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Disclosure

No authors report any conflict of interest.

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