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ORIGINAL ARTICLE

# An observational study of apatinib mesylate in treating advanced non-small cell lung cancer with unknown driving gene(s)

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## Summary

***Purpose:*** *To investigate the efficacy and safety of apatinib mesylate (AM) in treating advanced non-small cell lung cancer (aNSCLC) with wild or unknown epidermal growth factor receptor (w/nEGFR).*

***Methods:*** *A total of 34 w/nEGFR -aNSCLC patients who failed chemotherapy from August 2015 to April 2017 were administered orally AM (425 mg/d) as primary treatment and observed their progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR), as well as related adverse events.*

***Results:*** *Efficacy was evaluable in 30 cases, with median PFS (mPFS) 3.75 months (95% CI 0.648-6.852), ORR 20%, and DCR 73.33%. The main adverse reactions included hypertension (52.94%), hand-foot syndrome (52.94%), proteinuria (44.12%), and fatigue (41.18%); no drug-related death occurred. The efficacy correlation analysis showed that Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (p=0.008) combined with chemotherapy (p=0.009) were the factors that extended PFS, and combined chemotherapy (p=0.040, HR=3.052, 95% CI 1.052-8.858) was an independent prognostic factor.*

***Conclusions:*** *AM has good therapeutic efficacy in treating aNSCLC patients after chemotherapy failure. The side effects can be controlled and it is worth testing it in large-scale clinical studies.*

***Key words:*** *apatinib, non-small cell lung cancer, anti-angiogenesis, clinical efficacy*

## Introduction

With the advent of the era of precision medicine, precision treatment against non-small cell lung cancer (NSCLC) has also been developed. For example, NSCLC patients sensitive to mutation of epidermal growth factor receptor (EGFR) have achieved 3-year fold raise of overall survival after therapy with tyrosine kinase inhibitor (TKI) combined with chemotherapy [1]. However, for patients with negative or unknown EGFR mutation, platin-containing two-drug combination chemotherapy has been used as a standard treatment against aNSCLC for nearly 20 years, and even if pemetrexed has significant efficacy against non-squamous NSCLC, and is used as a standard first-line chemotherapy when combined with platin compounds against advanced lung adenocarcinoma, the median overall survival is only 5.3 months [2]. Numerous studies have shown that traditional chemotherapy has reached a therapeutic plateau [3-5], so looking for more effective treatments con-

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stitutes an urgent need. Related research is being carried out, revealing that antiangiogenesis therapy is one of the hot spots [6].

In 1971, Folkman put forward the idea that "tumor growth depends on the formation of blood vessels" [7]. Later, vascular endothelial growth factor (VEGF) and its receptor (VEGFR) were discovered. Studies have shown that VEGF or VEGFR are highly expressed in many tumor tissues including NSCLC. Therefore, antiangiogenesis therapy has become a hot spot in NSCLC targeted therapy. Antiangiogenic drugs can be divided into two categories according to their target sites: (1) acting on VEGF ligand, such as bevacizumab; and (2) acting on receptors (VEGFR), such as ramucirumab. ECOG4599 study [8] and Avail study [9] have confirmed that bevacizumab combined with paclitaxel and carboplatin can significantly prolong PFS, so it was approved by the Food and Drug Administration (FDA) in 2006 to combine with chemotherapy for first-line treatment against non-squamous aNSCLC [10]. In addition, based on the results of REVEL study [11], ramucirumab was also approved in 2014 for treating metastatic NSCLC. However, there is no effective target drug against aNSCLC or lung cancers with other pathological types.

AM, a new oral small-molecule angiogenesis inhibitor developed independently in China (Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China), was approved by China Food and Drug Administration (CFDA) in October 2014 for the treatment of advanced gastric adenocarcinoma or gastric-esophageal junction adenocarcinoma [12]. Studies have found that AM also exhibits significant inhibitory effect on the proliferation of lung cancer, liver cancer, or many other tumor cells [13,14], but it's still in experimental stage to be used for the treatment of other malignancies. This study observed the outcomes of AM in treating 34 aNSCLC patients after chemotherapy failure.

## Methods

*General information*

A total of 34 w/nEGFR-aNSCLC patients who were treated with platinum-based combination chemotherapy at the Department of Oncology, Kailuan General Hospital and Tangshan Workers' Hospital, from August 2015 to April 2017 were enrolled. Patient gender included 19 males (55.88%) and 15 females (44.1%), with median age 58 years (range 34-78). Tumor types: 23 cases of adenocarcinoma, 8 cases of squamous cell carcinoma, and 3 cases of other types (1 case of adenosquamous carcinoma, and the rest two cases of poorly differentiated cancer); ECOG performance status (PS) score: 0-1 in 24 cases and 2 in 10 cases. The specific situations are shown in Table 1.

**Table 1.** Clinicopathological characteristics

| *Characteristics* | *n (%)* |
|---|---|
| Gender | |
| Male | 19 (55.88) |
| Female | 15 (44.12) |
| Age, years | |
| <60 | 20 (58.82) |
| ≥60 | 14 (41.18) |
| ECOG PS | |
| 0-1 | 24 (70.59) |
| 2 | 10 (29.41) |
| Pathological type | |
| Adenocarcinoma | 23 (67.65) |
| Squamous cell | 8 (23.53) |
| Others | 3 (8.82) |
| Number of metastatic sites | |
| 0-2 | 27 (79.41) |
| ≥3 | 7 (20.59) |
| Brain metastasis | |
| Yes | 8 (23.53) |
| No | 26 (76.47) |
| Combined with chemotherapy | |
| Yes | 11 (32.35) |
| No | 23 (67.65) |

Patient inclusion criteria: >18 years old without gender limitations; ECOG PS score: 0-2; underwent at least platin-containing first-line two-drug combination chemotherapy while the disease still progressed; with expected survival ≥3 months; without unexpected surgery within 1 month; without unhealed wound in the body; blood routine tests: absolute neutrophil count (ANC) ≥1.5×10$^9$/L, hemoglobin (Hb) ≥9 g/dL, platelet count (PLT) ≥100×; blood biochemistry: alanine transarninase (ALT) ≤2.5× the upper limit of normal (ULN), aspartate aminotransferase (AST) ≤2.5× ULN, serum total bilirubin (TBIL) ≤1.5× ULN, serum creatinine (Scr) ≤1.5× ULN, normal coagulation; normal electrocardiogram (ECG); normal blood pressure or satisfactory controlled with drugs; did not participate in other clinical research projects. This study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Tangshan Workers' Hospital. Written informed consent was obtained from all participants.

*Treatment protocol*

All the patients signed informed consent for voluntary oral administration of AM; the dose was 425 mg/day, and whether to combine it with chemotherapy or not was left to each patient's decision. A new chemotherapy protocol was decided or adjusted by physicians according to the specific circumstances.

*Observation indexes*

Each patient's blood pressure was monitored every day during medication, together with testing blood and

serum tests and urine evaluation every week. Initial imaging assessment was performed after 28-day treatment, followed by re-assessment every two months until disease progression (including death) or appearance of intolerable adverse reactions.

*Follow-up and efficacy evaluation*

The evaluation of short-term efficacy was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST1.1 version) and was divided into complete remission (CR), partial remission (PR), disease stability (SD), and disease progression (PD). At the same time, adverse events (AE) were evaluated using the National Cancer Institute Common Toxicity Criteria version 4.0 (NCI-CTC 4.0). AE included all the adverse events associated with AM. In this study, we observed and assessed the patient PFS and related AE. The primary PFS endpoint was defined as the time interval from the first-time administration of AM to any recorded tumor progression or death from any reason. Secondary endpoints included the ORR and DCR. ORR was defined as the sum of patients with CR and PR and DCR was defined as the sum of patients with CR, PR and SD.

*Statistics*

The data were processed using SPSS17.0 statistical software (SPSS Inc., Chicago, IL, USA). Survival analysis was performed by the Kaplan-Meier method and log-rank test was used to compare differences between groups. Furthermore, survival analysis was performed in relation to selected clinical factors using the Cox multivariate regression model to determine the effective independent predictors. A p value ≤0.05 was considered statistically significant.

## Results

*Short-term efficacy*

The follow-up lasted until April 2017, and among the 34 patients, 30 could be evaluated for efficacy, while 4 patients withdrew due to intolerance or other AE. The median PFS was 3.75 months (95% CI 0.961-6.59), and the overall survival is shown in Figure 1A. Statistics of remission rate: CR:0 case (0%), PR: 6 cases (20.00%), SD: 16 cases (53.33%), and PD: 7 cases (23.33%); the total ORR was 20% and the DCR 73.33%.

*Adverse events*

According to the standards in NCI-CTC version 4.0, hypertension, hand-foot syndrome, proteinuria, or fatigue were the main treatment-related AE (Table 2).

*Relationships among baseline features, drug efficacy and clinical prognosis*

Overall survival is shown in Figure 1A. Log-rank test was performed to reveal the differences in PFS with different baseline features, which were as follows: Patients with ECOG PS 0-1 exhibited significantly prolonged PFS (p=0.008) (median PFS: 6.43 months in patients with ECOG 0-1, 95% CI: 1.151-11.709 months, and 1.79 months in patients with ECOG 2, 95% CI: 0.132-3.448 months; Figure 1B).

**Table 2.** Treatment-related adverse events

| *Adverse events* | *Grade 1-2* | *Grade 3-4* | *n (%)* |
|---|---|---|---|
| Hypertension | 3 | 15 | 18 (52.94) |
| Hand-foot syndrome | 13 | 5 | 18 (52.94) |
| Proteinuria | 13 | 2 | 15 (44.12) |
| Fatigue | 13 | 1 | 14 (41.18) |
| Whiteness of skin | 8 | 1 | 9 (26.47) |
| Nausea, vomiting | 8 | 0 | 8 (23.53) |
| Mucositis | 7 | 0 | 7 (20.59) |
| Diarrhea | 4 | 1 | 5 (14.71) |
| Bleeding | 5 | 0 | 5 (14.71) |
| Thrombocytopenia | 3 | 2 | 5 (14.71) |
| Anorexia | 4 | 0 | 4 (11.76) |
| Bilirubin increase | 2 | 0 | 2 (5.88) |
| Leukopenia | 2 | 0 | 2 (5.88) |

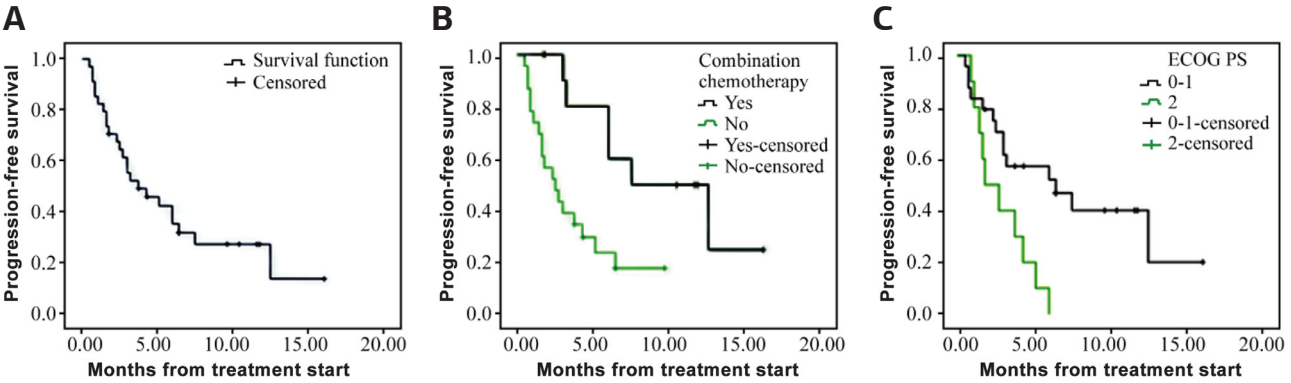


**Figure 1. A:** PFS of the whole group (n=30); **B:** Impact of ECOG score on efficacy. PFS: 7.50 months vs 2.50 months, p=0.009; **C:** Impact of chemotherapy on efficacy. PFS: 6.43 months vs 1.79 months, p=0.008.

The patients administered combined chemotherapy showed prolonged PFS (p=0.008) (median PFS: 7.50 months in patients with combined chemotherapy, 95% CI:1.745-13.255 months, and 2.50 months in patients without combined chemotherapy (95% CI: 1.060-3.940 months; Figure 1C).

No significant differences in PFS were noticed according to gender (p=0.281), age (≥60 years;p=0.403), pathological type (p=0.072), number of metastatic sites ≥3 (p=0.485), or existence of brain metastasis (p=0.378).

Brain metastasis in relation to ECOG PS were assessed by multivariate Cox regression analysis and showed that combination with chemotherapy was an independent predictor for prolonged PFS (p=0.040), and could reduce the risk of death (HR=3.052, 95% CI: 1.052-8.858).

## Discussion

AM is a new generation small molecule that inhibits the vascular endothelial growth factor receptor-2 (VEGFR-2). This molecule was developed in China, and selectively blocks the signal transduction, thus inhibiting tumor growth [15-17]. Its efficacy and safety in phase II and III clinical trials showed good results [12,18].

The primary objective of this study was to assess the short-term efficacy and safety of AM in treating w/nEGFR-aNSCLC patients who failed chemotherapy. The median PFS in this study reached 3.5 months, the overall ORR reached 20%, and DCR was up to 73.33%. A randomized, controlled, double-blind, multicenter phase II clinical study about non-squamous NSCLC enrolled 135 patients (CSC Annual Report, 2012) [13], and the results showed that the median PFS in the AM group was significantly increased compared with the placebo group (4.7 vs 1.9 months; HR=0.278; 95% CI: 0.170-0.455; p<0.001), together with ORR 12.2% and DCR 68.9%. In recent years, there have been a number of successful treatment cases of AM against NSCLC, and the PFS achieved was up to 6 months [18-21], but no large-scale clinical studies have been performed so far. We speculate that antiangiogenic drugs may play an important role in the inhibition of tumor neovascularization, but they have no obvious effect in the already formed blood vessels. Therefore, the clinical efficacy of these drugs is mainly manifested in stable disease.

Objectively speaking, the incidence of adverse reactions to AM is relatively high.

In a phase III clinical trial for advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction, the recommended oral dose of AM was 850 mg/d, but dose-related toxicities did happen, like hand-foot reaction, proteinuria and hypertension [12]. In a phase II clinical trial against breast cancer, oral administration of 750 mg/d AM was recommended but a dose-related death occurred due to bronchopulmonary hemorrhage [22]. Therefore, AM dose of 425mg/d was used in this study, and AE occurred in ≥10% of the patients including hypertension, hand-foot syndrome, proteinuria, fatigue, nausea, vomiting, mucositis, diarrhea, or bleeding, of which higher-than-level 3 AE was mainly hypertension. Fortunately, most AE cases were mild to moderate and no AE-associated death occurred. This was similar to the results of an early-phase II clinical trial [18].

In efficacy-correlation of this study revealed that good physical conditions (ECOG PS 0-1) and combining with chemotherapy are more helpful in prolonging PFS, suggesting that early application or combination with chemotherapy may be more effective in exploiting AM's advantages. In the present study no statistical significance appeared between different pathological types, number of metastatic sites, and existence of brain metastasis, suggesting that the application of AM is not limited by these factors.

Naturally, due to the limited sample size, certain bias is inevitable, so we'll conduct more extensive clinical studies for confirmation of the present results. In conclusion, this study was based on clinical practice and revealed that AM has good efficacy and controllable safety against advanced lung cancer.

## Conflict of interests

The authors declare no conflict of interests.

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