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ORIGINAL ARTICLE

Apatinib monotherapy for advanced non-small cell lung cancer after the failure of chemotherapy or other targeted therapy

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Abstract

Background: Apatinib, a small-molecule inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), has proven to be effective and safe for treating patients with advanced gastric cancer after second-line chemotherapy failure. As VEGFR-2 targeted therapy has made encouraging progress for the treatment of a broad range of malignancies, we explored the efficacy and safety of apatinib for the treatment of advanced non-small cell lung cancer after the failure of chemotherapy or other targeted therapy.

Methods: We retrospectively analyzed the data of 34 patients (11 with squamous carcinoma and 23 with adenocarcinoma) who were treated with apatinib alone in a daily oral dose of 250 mg in the second-line or third-line setting from January 2016 to July 2017. The primary endpoint was progression-free survival (PFS).

Results: *EGFR* mutation or amplification was detected in 15 patients. The median PFS of the whole group was four months (95% confidence interval 0.3–7.7). A partial response was observed in 2 patients (5.88%) and stable disease in 19 (55.88%). The disease control rate was 61.76%. Common side effects of apatinib were hypertension (n = 12), hand-foot syndrome (n = 8), and proteinuria (n = 5), which accounted for 35.30%, 23.53%, and 14.71%, respectively, and no grade 3/4 adverse reactions occurred. Apatinib toxicity was controllable and tolerable.

Conclusions: Apatinib appears to be effective and safe for advanced non-small cell lung cancer after the failure of chemotherapy or other targeted therapy.

Introduction

Lung cancer is the most common cancer with the highest mortality in men worldwide and has become the leading cause of cancer death among women in developed countries in recent years.[1] In China, non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer cases.[2] The leading cause of cancer death among both men and women is cancer of the lung and bronchus, for which the 2015 age-standardized mortality rate in China was 733.3 per 100 000 (509.3 per 100 000 in men and 224.0 per 100 000 in women).[3] Patients with NSCLC are usually diagnosed at advanced stage. For advanced NSCLC patients with or without *EGFR* mutations, EGFR-tyrosine kinase inhibitors (TKIs) and chemotherapy are recommended as first-line treatment, respectively.[4–10] After the failure of first-line therapy, second or third-line treatment does not currently yield acceptable progression-free-survival (PFS) or overall survival (OS).[11–13] Third-generation EGFR-TKIs were not available in mainland China at the beginning of our research.

Vascular endothelial growth factor (VEGF) could stimulate angiogenesis, regulate vascular permeability, and

inhibit apoptosis in endothelial cells.[14] Bevacizumab, a humanized anti-VEGF monoclonal antibody, specifically binds to the VEGF-A protein, thereby inhibiting the process of angiogenesis. It has been recommended as first-line therapy for lung adenocarcinoma in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Apatinib is a novel oral TKI that selectively inhibits VEGF receptor 2 (VEGFR-2), thus exerting an antiangiogenic effect and repressing tumor growth.[14,15] Apatinib may be useful in circumventing multiple drug resistance (MDR) to other conventional chemotherapy drugs by inhibiting the transport function of ABCB1 and ABCG2-mediated MDR.[16] Based on the results of two clinical trials, apatinib has been recommended to treat chemotherapy-refractory patients with metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction.[17,18]

In this study, we evaluated the efficacy and toxicity of apatinib in advanced NSCLC patients after the failure of chemotherapy or EGFR-TKI therapy.

Methods

Patient selection

The data of 34 patients with stage IV or recurrent NSCLC treated from 28 January 2016 to 15 July 2017 were retrospectively analyzed. Patients were eligible if they had been histologically or cytologically diagnosed with lung squamous carcinoma or adenocarcinoma with confirmed *EGFR* mutations or *ALK* rearrangement; and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. All histological diagnoses of NSCLC were made according to 2015 World Health Organization histopathological criteria. Tumors were classified according to the seventh edition American Joint Committee on Cancer Staging System.

The Ethics Committee of the Guangdong Association Study of Thoracic Oncology approved the study and all participants signed informed consent.

Treatment

Patients were treated with apatinib alone in daily oral dose of 250 mg after the failure of previous therapy: patients with *EGFR* mutations received apatinib after EGFR-TKI therapy or EGFR-TKI therapy followed by chemotherapy; patients with wild-type *EGFR* received apatinib after first or second-line chemotherapy. The treatment cycle was 28 days, during which time patients took apatinib every day until disease progression or intolerable adverse events (AEs) occurred. No radiotherapy or other local therapy was offered during apatinib treatment.

Response and toxicity evaluation

Magnetic resonance imaging (MRI) or computed tomography (CT) scans of measurable lesions were assessed at the end of the first cycle, then every two cycles or earlier when significant signs of progression appeared. Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate tumor responses to apatinib. Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the addition of objective response and stabilization rates (CR + PR + SD). Blood pressure was checked weekly, blood counts and urinalysis were performed biweekly, and hepatic and renal function tests were performed monthly. Toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria version 4.0 (CTC4.0).

Statistical methods

Progression-free survival was defined as the duration from the first date of apatinib administration to documented progression or mortality from any cause. Survival analysis was conducted using the Kaplan–Meier method and compared using a log-rank test. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The median follow-up period was 11.4 months (range: 2.3–17.8). Follow-ups were conducted up to 15 July 2017.

Results

Patient characteristics

Thirteen patients were male and 21 were female. Ten had a smoking history and 24 had never smoked. Eleven patients had squamous carcinoma and 23 had adenocarcinoma. Twelve patients were detected as *EGFR* mutation positive (7 with deletions in exon 19, 4 with L858R in exon 21, 1 with L861Q in exon 21); three via fluorescence in situ hybridization as *EGFR*-positive. No patients had *ALK* fusion gene rearrangements. Twenty-one patients were in stage IV and 13 were recurrent after radical surgery. Seventeen patients received apatinib as second-line therapy and 17 as third-line treatment. Nine patients had a PS of 0, 22 had a PS of 1, and 3 had a PS of 2. The patient characteristics are listed in Table 1.

Response to treatment

The median PFS (mPFS) of the whole patient sample was four months (95% confidence interval [CI] 0.3–7.7) (Fig 1). Among the 34 patients, PR was observed in 2 patients (5.88%) and SD in 19 (55.88%) (Fig 2). The DCR was 61.76%. No significant correlation existed between PFS and gender ($P = 0.45$), age ($P = 0.20$), PS ($P = 0.72$), smoking

Table 1 Baseline patient characteristics (n = 34)

Characteristic	No. of patients (%)
Age	
Median (range), years	55 (30–74)
> 60	11 (32.35%)
≤ 60	23 (67.65%)
Gender	
Female	21 (61.76%)
Male	13 (38.24%)
PS	
0	9 (26.47%)
1	22 (64.71%)
2	3 (8.82%)
Smoking status	
Ever	12 (35.29%)
Never	22 (64.71%)
Pathology	
Adenocarcinoma	23 (67.65%)
Squamous cell carcinoma	11 (32.35%)
EGFR status	
Mutation	12 (35.29%)
Amplification	3 (8.82%)
Wild-type	19 (55.88%)
Line of apatinib therapy	
2	17 (50%)
3	17 (50%)

PS, performance status.

status (P = 0. 68), pathological subtype (P = 0.79), *EGFR* mutation status (P = 0.59), stage (P = 0.29), or line of therapy (P = 0.13). The results of univariate analysis are detailed in Table 2.

Tumor response was evaluated according to the diameter of both measurable and unmeasurable lesions. Five patients had unmeasurable lesions (pleural effusion with pleural nodules or with lung lesions that were difficult to measure).

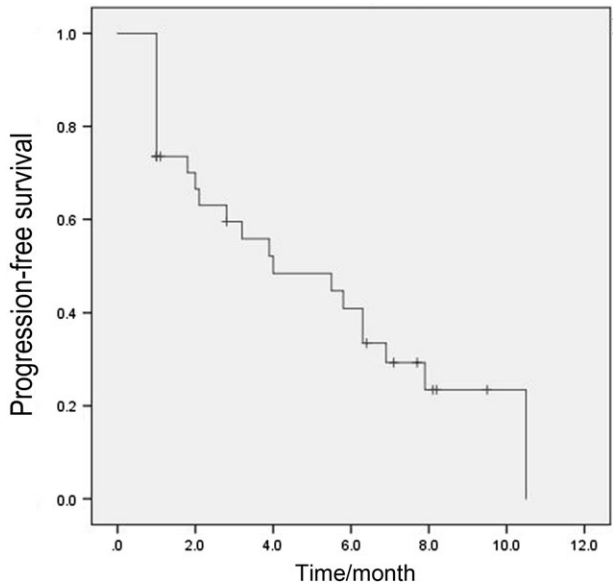

Figure 1 Kaplan–Meier estimates of progression-free survival.

Safety and toxicity

The common side effects of apatinib were hypertension (n = 12), hand-foot syndrome (n = 8), proteinuria (n = 5), and fatigue (n = 4), which accounted for 35.30%, 23.53%, 14.71%, and 11.76%. No grade 3/4 adverse reactions occurred. Six of the patients did not experience any AEs during the research period. No hematologic, liver, or renal toxicities were observed. No patients withdrew as a result of AEs. The adverse events are listed in Table 3.

Discussion

Our results show that 250 mg daily apatinib for advanced NSCLC is effective and safe. EGFR-TKI therapy is recommended as first-line treatment or as second-line setting after chemotherapy for advanced NSCLC patients with *EGFR* mutations. Platinum-based doublet chemotherapy is recommended as first-line treatment and single-agent chemotherapy as second-line treatment for patients with wild-type *EGFR* and *ALK*-negative tumors. Zhang *et al.* conducted a phase II trial to determine whether apatinib could improve PFS compared to a placebo in patients with advanced non-squamous NSCLC who had failed two lines of therapy.[19] Ninety patients were randomized to apatinib 750 mg until disease progression or unacceptable toxicity. The trial showed that apatinib has a substantial clinical effect without severe additional AEs in patients with advanced NSCLC. Some of the patients in our sample declined chemotherapy as second-line treatment after EGFR-TKIs or chemotherapy. Third generation EGFR-TKIs were not available in mainland China at the beginning of our follow-up; therefore, we administered apatinib as second-line treatment for these patients.

Progression-free survival in our patient sample was four months and the DCR was 61.76%. Maruyama *et al.* reported better mPFS (2 months) than PFS (1.4 months) of second and third-line docetaxel in a phase III clinical trial.[13] The mPFS in our study was 6.3 months in the second-line setting, which was superior to those reported in two phase III clinical trials.[11,12] In the CTONG0806 study, pemetrexed was administered as second-line treatment in advanced non-squamous NSCLC patients with wild-type *EGFR* and the mPFS was 4.8 months.[11] The ETOP study showed an mPFS of 4.1 months in advanced squamous cell NSCLC patients treated with docetaxel as second-line setting.[12] In our patient sample, the mPFS in squamous cell NSCLC patients was 5.5 months (95% CI 0–12.7) and in adenocarcinoma NSCLC patients 6.3 months (95% CI 0–12.8) as a second-line setting. These

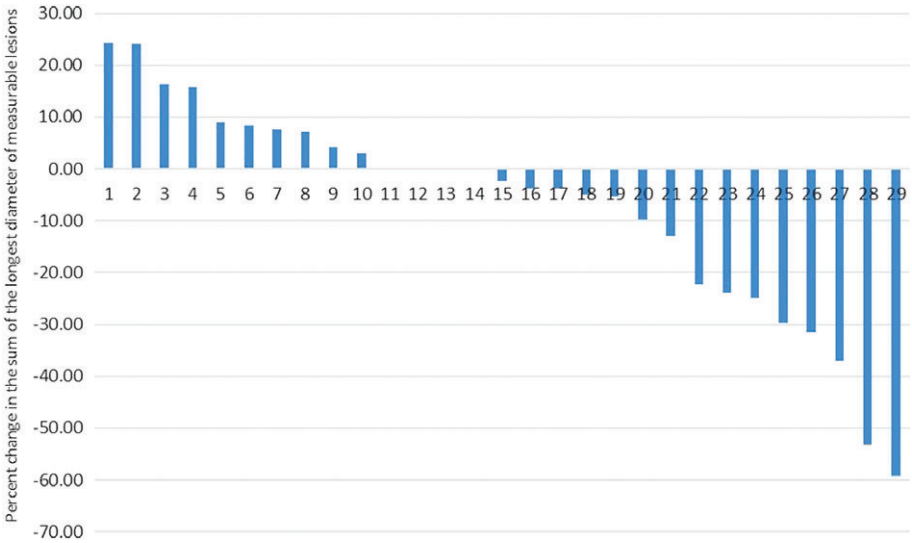

Figure 2 Waterfall plot of measurable lesion response.

Table 2 Univariate analysis of PFS

Characteristic	mPFS	95% CI	*P*
Gender			0.446
Male	3.2	0.1–6.3	
Female	5.8	3.4–8.1	
Age, years			0.203
> 60	3.2	0.0–6.7	
≤ 60	4	0.0–9.8	
PS			0.726
0	6.3	3.1–9.5	
1	2.8	0.0–6.1	
2	7.9	0.4–15.4	
Line of therapy			0.134
2	6.3	2–10.6	
3	3.9	0.9–6.9	
Smoking status			0.682
Ever	3.2	2.1–4.3	
Never	5.8	2.0–9.6	
Histology			0.789
Adenocarcinoma	4	0.5–7.5	
Squamous cell	2.1	0–6.8	
EGFR status			0.843
Mutation	4	1.2–6.7	
Amplification	6.3	†	
Wild-type	5.5	0.8–10.2	

†Only three patients harbored *EGFR* amplification and one did not arrive at the endpoint. CI, confidence interval; mPFS, median progression-free-survival; PS, performance status.

Table 3 Apatinib-related adverse events

	No. of adverse events		
Type of adverse event	Grade 1	Grade 2	Percentage (%)
Hypertension	9	3	35.30
Hand-foot syndrome	5	3	23.53
Proteinuria	3	2	14.71
Fatigue	1	3	11.76

results show that apatinib might have similar or even better efficacy than single-agent chemotherapy as second-line treatment in advanced NSCLC. In recent research, apatinib was administered at a dose of 500 mg in third-line or further settings for advanced NSCLC.[20] The median PFS was 4.2 months and the DCR was 61.9%, which was consistent with our results.

Li *et al.* used apatinib in a third-line setting for patients with metastatic gastric cancer at a dose of 850 mg once daily or 425 mg twice daily.[17] The incidence of hypertension, proteinuria, and hand-foot syndrome was 40.43%, 27.66%, and 25.53% in the 850 mg once daily and 39.13%, 34.78%, and 45.65% in the 425 mg twice-daily groups, respectively. Grade 3 to 4 hand-foot syndrome and hypertension occurred in more than 10% of patients. Hu *et al.* recommend a dose of apatinib 500 mg/day rather than 750 mg/day for pretreated patients with metastatic triple-negative breast cancer, because of the toxicity associated with the higher dose.[21] At a dosage of 500 mg/day, the incidence of hypertension, proteinuria, and hand-foot syndrome was 64.4%, 52.6%, and 49.2%, respectively. The AEs observed in our patient sample included hypertension, proteinuria, and hand-foot syndrome. We observed more mild to moderate AEs at a dose of 250 mg compared to the 500 mg used by Song *et al.*[20] Zeng *et al.* reported results of four advanced lung adenocarcinoma patients with *KRAS* mutations treated with apatinib at a dose of 250 mg/d.[22] Only one patient showed grade 1 hoarseness and hemoptysis. Our results indicate that 250 mg/d might be an optional dosage in advanced NSCLC patients. However, further large-scale clinical trials are needed to verify the most suitable dosage of apatinib.

The major limitations of the present study are its small sample size and its retrospective nature. In addition, we observed cavities in the tumor after the administration of

apatinib in three patients. As there are currently no evaluation criteria for tumor cavities, we evaluated the tumor diameter ignoring the cavity. During anti-angiogenesis therapy, patients with advanced lung cancer commonly developed cavitation in their lung lesions.[23] A cavernous tumor response could be assessed by volume assessment for target lesions or fluorodeoxyglucose metabolism.[24,25] We expect that evaluation criteria for tumor cavities is forthcoming. Although the dose of 250 mg apatinib in a second-line setting adopted in this study is not widely recommended, the safety and efficacy observed were promising.

Based on our results, it will be interesting to view further research of apatinib combined with chemotherapy in a first-line setting for advanced NSCLC.

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Disclosure

No authors report any conflict of interest.

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