



Efficacy, safety and prognostic factors analysis of first-line icotinib treatment in advanced non-small cell lung cancer patients with mutated EGFR

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Background: This study aimed to evaluate the efficacy, safety and prognostic factors of icotinib as first-line treatment in advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR)-sensitive mutation.

Methods: A total of 152 advanced NSCLC patients with EGFR-sensitive mutation underwent first-line icotinib treatment were retrospectively reviewed in this cohort study. Icotinib was given orally three times daily at 125 mg dose. Scorpion amplification refractory mutation system kit was used for EGFR mutation detection. The median follow-up duration was 15.0 (range: 1.0–44.0) months, and the last follow-up date was 2016/12/31.

Results: The complete response (CR), partial response (PR), objective response rate (ORR), stable disease (SD) and progressive disease (PD) rates were 4% (N=6), 67.8% (N=103), 71.8% (N=109), 23.7% (N=36) and 4.6% (N=7) respectively. Median progression-free survival (PFS) and overall survival (OS) were 14.0 months (95% CI: 12.7–15.3 months) and 33.0 months (95% CI: 24.9–41.1 months) respectively. Multivariate logistic analysis indicated smoking history (P=0.013) was statistically correlated with non-ORR achievement, while EGFR mutation 19del (P=0.001) was statistically associated with ORR achievement. No factor could predict PFS or OS. As to safety profiles, there were 66 (43.4%), 35 (23.0%), 10 (6.6%), 9 (5.9%), 9 (5.9%), 4 (2.6%) and 3 (2.0%) patients appeared rash, diarrhea, abnormal liver function, paronychia, oral ulcer, fatigue and poor appetite, and most adverse events (AEs) were in mild grade.

Conclusions: First-line icotinib treatment was efficient and well tolerated in patients with advanced NSCLC harboring EGFR mutations, and smoking history was negatively while EGFR mutation 19del was positively correlated with ORR achievement.

Keywords: Advanced; efficacy; epidermal growth factor receptor mutation (EGFR mutation); first-line; icotinib; non-small cell lung cancer (NSCLC); prognostic factors

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Introduction

Lung cancer is the most frequently diagnosed cancer and the most common cause of cancer-related deaths, which seriously threatens human health and life (1). According to 2015 cancer statistics, estimated 733,000 new cases and 610,000 deaths due to lung cancer occurred in China (2). Lung cancer is mainly classified into two subtypes, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which account for approximately 15% and 85% of all lung cancer respectively (3). Among these, more than 65% patients with NSCLC at the first diagnosis are in advanced stage or with metastatic disease, and the 5-year overall survival (OS) rate is only 15% (4). For these patients, conventional chemotherapy is one of the most frequently used treatments and could provide a modest survival advantage, while its response rate among these advanced NSCLC patients is still less than 40%, suggesting that the efficacy of conventional chemotherapy might reach the therapeutic plateau (5-7).

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is recognized as the first-line therapy for NSCLC patients with active sensitizing EGFR mutation due to its superior efficacy over than conventional chemotherapy (8,9). Currently, gefitinib, erlotinib and afatinib, as three common EGFR TKIs, have established their values in NSCLC patients with EGFR-sensitive mutation, particularly exon 19 deletions and exon 21 L858R mutations (10,11). Icotinib, acting as another novel, orally administered, reversible small-molecule EGFR-TKI, is designed and patented by Beta Pharma (Zhejiang, China), which is approved by the State Food and Drug Administration of China for advanced NSCLC patients with EGFR mutation based on phase III of ICOGEN trial (12,13). Several previous studies have proven that icotinib contributes to good efficacy in advanced NSCLC patients as second-line treatment (14). Although there are several retrospective studies in China, while the sample sizes in most studies are relatively small, which are less than 50 cases, and few study with larger samples to confirm the effects of icotinib as first-line treatment in advanced NSCLC patients has been found (5,15). In the current study, we recruited 152 advanced NSCLC patients with EGFR mutation, and the purpose was to evaluate the efficacy, safety and prognostic factors of icotinib as first-line treatment in advanced NSCLC patients with EGFR-sensitive mutation.

Methods

Patients

A total of 152 advanced NSCLC patients with EGFR-sensitive mutation underwent first-line icotinib treatment at Shanghai Chest Hospital, Shanghai Jiao Tong University between November 2011 to November 2016 were retrospectively reviewed in this cohort study. The inclusion criteria were: (I) confirmed diagnosis of NSCLC with EGFR mutation by cytopathology and histopathology analysis; (II) patients received first-line icotinib treatment (patients did not receive surgery, chemotherapy, radiotherapy or any other treatments before icotinib administration); (III) patients were in stage IIIb and stage IV, who could not undergo surgery; (IV) more than one measurable lesion based on Response Evaluation Criteria in Solid Tumors 1.1 (RECIST, version 1.1) (16). The exclusion criteria were: (I) secondary lung cancer patients; (II) previous lung severe infection or transplantation; (III) complicated with severe underlying cardiopulmonary diseases, a history of interstitial lung disease or severe gastrointestinal disorders influencing drug absorption; (IV) lacked one of the following basic data including age, gender, smoking history, EGFR mutation type, TNM stage, brain metastasis status, treatment response evaluation.

This study was approved by Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University. The number of ethical approval was KS1034. The written informed consents or oral agreements (with recording) were required from all patients or their guardians.

Detection of EGFR mutation

Scorpion amplification refractory mutation system (ARMS) kit (Qiagen, Venlo, the Netherlands) was used for EGFR mutation detection. EGFR sensitive mutations was defined as exon 19 deletions and exon 21 L858R mutations.

Treatment

Icotinib was given orally three times daily at 125 mg dose until tumor progression or intolerable drug toxicity, with no other systematic anticancer treatments such as chemotherapy and anticancer herbal therapy. If PD occurred, patients could further receive repeated icotinib treatment (if it was beneficial after evaluation), patients who were younger than 75 years old and with generally good

Table 1 Characteristics of 152 advanced NSCLC patients with EGFR mutation

Characteristics	Patients (N=152), n/%
Age (years)	63.35±11.29
Gender (male/female)	62/90
Smoke	48 (31.6)
ECOG performance status	
0	40 (26.3)
1	68 (44.7)
2	31 (20.4)
3	13 (8.6)
EGFR mutation type	
19del	84 (55.3)
21L858R	68 (44.7)
Stage	
IIIb	23 (15.1)
IV	129 (84.9)
Brain metastasis	28 (18.4)

Data was presented as mean ± standard deviation or count (%). NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

conditions would further receive chemotherapy and patients who were older than 75 years old or with poor conditions (performance status score ≥ 2) would further received optimum supportive treatment.

Treatment response and adverse events (AEs) assessments

Baseline evaluation of all patients was completed within 1 week before treatment. The assessment included chest computed tomography (CT) scan, abdominal CT scan, Brain CT scan or magnetic resonance imaging (MRI) of the brain and whole body bone scan. RECIST criteria (version 1.1) was used to assess the treatment response as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as CR plus PR. The radiological evaluation was performed by two independent oncologists and when controversial results existed, a third oncologist was invited to vote. Generally, the treatment response was evaluated at 1–2 months after icotinib treatment. AEs were assessed according to the National

Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Follow ups

Patients were followed up 1–2 months after icotinib treatment, then regularly followed up according to patients' willing and disease condition. Due to medicine controls in China, every patient could be issued with 4-week dose of icotinib, thus, these NSCLC patients would come to Outpatient Clinic of the hospital to get more icotinib every 4 weeks. At this time, each patient would receive blood test, liver and kidney function examinations as well as tumor markers examinations. Meanwhile, imaging examination (CT scan) was performed every 8 weeks. The median follow-up duration was 15.0 (range: 1.0–44.0) months, and the last follow-up date was 2016/12/31. Progression-free survival (PFS) was calculated from the time of icotinib administration to documented progression or death from any cause. OS was calculated from the time of icotinib administration until the date of death from any causes.

Statistics

Statistics was performed using SPSS 24.0 (SPSS Inc., USA) and 2010 office software (Microsoft, USA). Data was presented as mean ± standard deviation or count (%). Kaplan-Meier (K-M) curves were performed to assess PFS and OS after first-line icotinib treatment. Factors affecting ORR achievement were determined by univariate logistic regression analysis, while all factors with P value no more than 0.1 were further detected by multivariate logistic regression analysis. Factors affecting PFS and OS were determined by univariate Cox's analysis. P value <0.05 was considered significant.

Results

Baseline characteristics

As listed in *Table 1*, mean age of 152 advanced NSCLC patients with EGFR mutation was 63.35±11.29 years. Males and females were 62 and 90 respectively. There were 48 (31.6%) patients with smoking history. As to EGFR mutation type, the numbers of patients with 19del and 21L858R were 84 (55.3%) and 68 (44.7%) respectively. Twenty-three (15.1%) patients were in stage IIIb and 129 (84.9%) patients were in stage IV. Twenty-eight (18.4%)

patients were complicated with brain metastasis.

Treatment response after first-line icotinib treatment

After first-line icotinib treatment, the rates of CR and PR were 4.0% (N=6), 67.8% (N=103), and the rate of ORR, which was the combination of CR and PR, was 71.8% (N=109). In addition, the rates of SD and PD rates were 23.7% (N=36) and 4.6% (N=7) respectively (Table 2).

PFS and OS after first-line icotinib treatment

Median PFS was 14.0 months (95% CI: 12.7–15.3 months),

Parameters	Patients (N=152), n/%
CR	6 (4.0)
PR	103 (67.8)
SD	36 (23.7)
PD	7 (4.6)
ORR	109 (71.8)
DCR	145 (95.4)

Data were presented as count (%). CR, complete response; PR, partial response; SD, stable disease; PD, progress disease; ORR, objective response rate; DCR, disease control rate.

and the rates of 1-year and 2-year PFS were 53.9% and 21.7% respectively (Figure 1A). As to OS, median OS was 33.0 months (95% CI: 24.9–41.1 months), and the rates of 1-year and 2-year OS were 65.8% and 28.3% respectively (Figure 1B).

Factors influencing ORR achievement

Factors affecting ORR achievement were assessed by logistic regression model analysis, which suggested that smoking history (P=0.005) was associated with a lower possibility for ORR achievement, while EGFR mutation 19del (P=0.001) were correlated with a higher possibility for ORR achievement (Table 3). All factors with a P value ≤ 0.1 in univariate logistic model were further analyzed by multivariate logistic regression model, which indicated smoking history (P=0.013) was statistically correlated with non-ORR achievement, while EGFR mutation 19del (P=0.001) was statistically associated with ORR achievement in advanced NSCLC patients with EGFR mutation after first-line icotinib treatment.

Factors influencing PFS

Univariate Cox's proportional hazards regression model analysis was performed to evaluate factors influencing PFS, as presented in Table 4, which revealed that no factor (all P>0.05) could predict PFS in advanced NSCLC patients

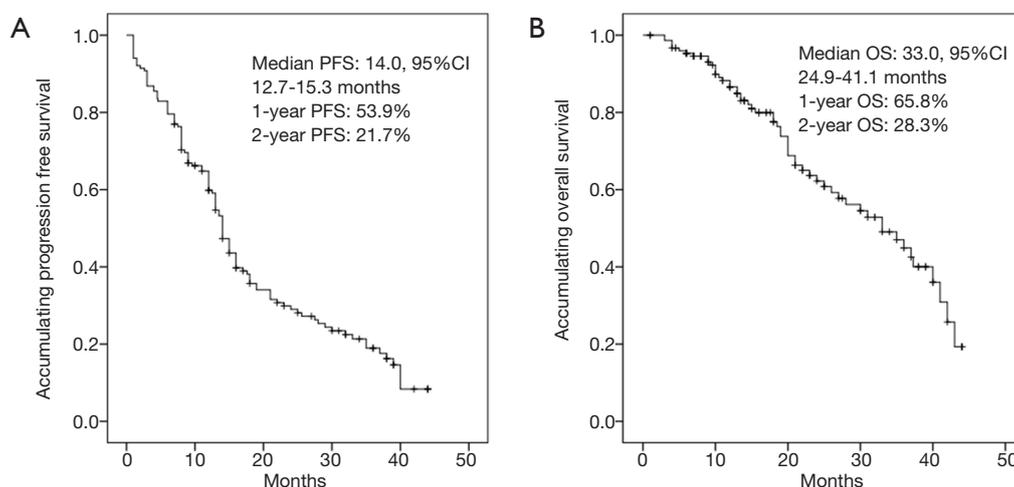


Figure 1 PFS and OS after first-line icotinib treatment. (A) PFS after first-line icotinib treatment, median PFS was 14.0 months (95% CI: 12.7–15.3 months), and 1-year and 2-year PFS rates were 53.9% and 21.7% respectively; (B) OS after first-line icotinib treatment; median OS was 33.0 months (95% CI: 24.9–41.1 months), 1-year and 2-year OS rates were 65.8% and 28.3% respectively. Kaplan-Meier curves were used to evaluate PFS and OS. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Table 3 Factors influencing ORR achievement by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age ≥70 years	0.106	0.548	0.265–1.135	–	–	–
Male	0.368	0.721	0.353–1.470	–	–	–
Smoke	0.005	0.345	0.165–0.723	0.013	0.378	0.175–0.817
EGFR mutation 19del (vs. 21L858R)	0.001	3.718	1.759–7.859	0.001	3.476	1.618–7.465
Stage IIIb (vs. IV)	0.215	2.058	0.657–6.448	–	–	–
Brain metastasis	0.617	0.798	0.329–1.934	–	–	–

Data was presented as P value, OR and 95% CI. Factors affecting ORR achievement were determined by univariate logistic regression analysis, while all factors with P value no more than 0.1 were further detected by multivariate logistic regression analysis. P value <0.05 was considered significant. ORR, objective response rate; OR, odds ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.

Table 4 Factors influencing PFS by Cox's regression model analysis

Parameters	Univariate Cox's regression		
	P value	HR	95% CI
Age ≥70 years	0.333	1.208	0.824–1.770
Male	0.610	1.100	0.762–1.590
Smoke	0.161	1.314	0.897–1.925
EGFR mutation 19del (vs. 21L858R)	0.890	1.026	0.709–1.486
Stage IIIb (vs. IV)	0.061	0.603	0.355–1.024
Brain metastasis	0.657	1.114	0.693–1.790

Data was presented as P value, HR and 95% CI. Factors affecting PFS were determined by univariate Cox's proportional hazards regression model analysis, while no factor with P below 0.1 was discovered, thus multivariate Cox's proportional hazards regression model analysis was not performed. P value <0.05 was considered significant. PFS, progression-free survival; HR, hazards ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.

with EGFR mutation after first-line icotinib treatment. Due to all factors with $P > 0.1$ in univariate Cox's proportional hazards regression model analysis, multivariate Cox's proportional hazards regression analysis was not performed.

Factors influencing OS

Factors affecting OS was determined by univariate Cox's proportional hazards regression model analysis (Table 5). No factor (All $P > 0.05$) could be predictive factor for OS in advanced NSCLC patients with EGFR mutation after first-line icotinib treatment. Owing to no factor with $P < 0.1$ in univariate Cox's proportional hazards regression model analysis, multivariate Cox's proportional hazards regression analysis was not performed.

Safety profiles by first-line icotinib treatment

There were 66 (43.4%), 35 (23.0%), 10 (6.6%), 9 (5.9%), 9 (5.9%), 4 (2.6%) and 3 (2.0%) patients appearing rash, diarrhea, abnormal liver function, paronychia, oral ulcer, fatigue and poor appetite (Table 6). Most adverse events were of grade 1, except for 2 (1.3%) cases of grade 3 rash, and 2 (1.3%) cases of grade 2 diarrhea.

Correlation of metastasis types with treatment response

In the present study, there were 29 patients with CNS metastasis, and 1 case achieved CR and 19 cases achieved ORR. In addition, we further performed chi-square test to compare the CR rate and ORR rate between brain metastasis patients and others, and found there was no

Table 5 Factors influencing OS by Cox's regression model analysis

Parameters	Univariate Cox's regression		
	P value	HR	95% CI
Age \geq 70 years	0.217	1.397	0.822–2.375
Male	0.966	1.012	0.594–1.723
Smoke	0.445	1.240	0.715–2.151
EGFR mutation 19del (vs. 21L858R)	0.485	0.828	0.487–1.407
Stage IIIb (vs. IV)	0.233	0.643	0.311–1.329
Brain metastasis	0.884	0.948	0.459–1.955

Data was presented as P value, HR and 95% CI. Factors affecting OS were determined by univariate Cox's proportional hazards regression model analysis, while no factor with P below 0.1 was discovered, thus multivariate Cox's proportional hazards regression model analysis was not performed. P value <0.05 was considered significant. OS, overall survival; HR, hazards ratio; CI, confidence interval; EGFR, epidermal growth factor receptor.

Table 6 Safety profiles by first-line icotinib treatment

Adverse events	Total (n/%)	Grade 1 (n/%)	Grade 2 (n/%)	Grade 3 (n/%)
Rash	66 (43.4)	64 (42.1)	0 (0.0)	2 (1.3)
Diarrhea	35 (23.0)	33 (21.7)	2 (1.3)	0 (0.0)
Abnormal liver function	10 (6.6)	10 (6.6)	0 (0.0)	0 (0.0)
Paronychia	9 (5.9)	9 (5.9)	0 (0.0)	0 (0.0)
Oral ulcer	9 (5.9)	9 (5.9)	0 (0.0)	0 (0.0)
Fatigue	4 (2.6)	4 (2.6)	0 (0.0)	0 (0.0)
Poor appetite	3 (2.0)	3 (2.0)	0 (0.0)	0 (0.0)

Data was presented as count (%).

Table 7 Correlation of metastasis types with treatment response

Items	Metastasis (n/%)	Brain metastasis (n/%)	Others (n/%)	P value
CR	6 (4.7)	1 (3.6)	5 (4.0)	0.910
ORR	90 (69.8)	19 (67.9)	90 (72.6)	0.616

Data were presented as count (%). Comparison of the CR rate and ORR rate between brain metastasis patients and others were determined by chi-square test. P value <0.05 was considered significant. CR, complete response; ORR, objective response rate

difference in CR rate ($P=0.910$) and ORR rate ($P=0.616$) between brain metastasis patients and others (*Table 7*).

Discussion

In the present study, we observed that: (I) first-line icotinib treatment achieved CR of 4% and ORR of 71.8% respectively in advanced NSCLC patients with EGFR-

sensitive mutation received first-line icotinib treatment. Median PFS of 14.0 months (95% CI: 12.7–15.3 months) and OS of 33.0 months (95% CI: 24.9–41.1 months) were observed. (II) Smoking history was statistically correlated with non-ORR achievement, while EGFR mutation 19del ($P=0.001$) was statistically associated with ORR achievement. No factor affecting PFS and OS was observed. (III) After first-line icotinib treatment, rash, diarrhea and

abnormal liver function were common AEs, and most AEs were in mild grade, suggesting that first-line icotinib treatment was well tolerated.

NSCLC is one of most complicated malignancies, and more than 50% NSCLC patients in China have been identified with EGFR mutation, which is one of multi-function transmembrane glycoproteins and involves in the process of cell proliferation, differentiation, migration, invasiveness, angiogenesis and adhesiveness, thereby its mutation might contribute to tumor growth and progress (17). According to a larger number of previous studies, EGFR TKI plays a critical role in the antitumor effects among NSCLC patients with EGFR mutation by binding to tyrosine kinase to control EGFR enzymatic activity and repress signal conduction, subsequently decreasing the growth of tumor cell (18). As a novel target EGFR TKI, icotinib is the first Chinese small molecular targeted antineoplastic drug, which has similar chemistry structure and working mechanism with gefitinib and erlotinib (19). However, compared to these two popular EGFR-TKI, icotinib may have more advantages as follows: (I) it has better capability to penetrate cytomembrane and blood brain barrier (BBB) by lipid solubility (19); (II) it has better selectivity and competitiveness to bind to kinases, thereby effectively blocking signal conduction (5); (III) it could be metabolized by various enzymes, including CYP2C19, CYP3A4, and CYP2E1, thereby reducing drug accumulation and decreasing toxicity (13,20).

Accumulating studies have investigated the efficacy of EGFR-TKI in NSCLC patients, suggesting that EGFR-TKI is optimal choice as the first-line therapy in advanced NSCLC patients, particular in patients with EGFR-mutation (6,9). A clinical trial, OPTIMAL compares the efficacy of erlotinib and chemotherapy and illustrates that CR of 2% and ORR of 83% in erlotinib group are higher than CR of 0% and ORR of 36% in control group (21). Based on ICOGEN trial, a phase III trial, which compared icotinib with gefitinib in second-line therapy, indicates that icotinib achieved ORR of 27.6%, which is similar to gefitinib group with ORR of 27.2% (13). Moreover, a previous study found that first-line icotinib treatment achieved CR of 0.0% and ORR of 62.9% among advanced NSCLC with EGFR-sensitive mutation, and there were only 35 patients enrolled in this previous study and the sample size was relatively small, thereby lacking statistical power (5). In the present study, we enrolled a larger sample size with 152 advanced NSCLC patients with EGFR-sensitive mutation and assessed the treatment response of

first-line icotinib treatment, which revealed that the rates of CR and ORR were 4% and 71.8% respectively, which was higher compared to ICOGEN and OPTIMAL trials. The possible reasons were that: (I) all patients enrolled in our study were with EGFR-sensitive mutation, who might have better response to EGFR TKIs, including icotinib; (II) icotinib is applied as first-line treatment in advanced NSCLC patients with EGFR-sensitive mutation in this study.

In the current study, we also observed that median PFS and OS were 14.0 months (95% CI: 12.7–15.3 months) and 33.0 months (95% CI: 24.9–41.1 months) respectively. The survival duration of patients treated with icotinib in our study was relatively long compared to gefitinib and erlotinib in NSCLC patients with EGFR mutation in several clinical trials: in OPTIMAL trials, median PFS is 13.1 months (95% CI: 10.58–16.53 months); in LUX-lung 3 trials, median PFS is 13.6 months for afatinib and 6.0 months for chemotherapy (HR, 0.47; 95% CI, 0.34–0.65; $P=0.001$); in LUX-lung 6 trial, PFS is prolonged in patients received afatinib compared to patients received gemcitabine or patients received cisplatin (median PFS 11.0 *vs.* 5.6 months, HR =0.28; $P<0.0001$) (21,22). In addition, a respective study recruited 49 NSCLC patients with wild-type or with EGFR mutation, which showed that the PFS was 9.5 months (95% CI: 7.9–11.0 months) and 8.5 months (95% CI: 6.5–10.5 months) in patients treated with first-line and second-line/further-line icotinib respectively (15). Also, a randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin as first-line treatment in NSCLC patients discloses that the median PFS and OS are 4.7 months (95% CI: 4.4–5.0 months) and 11.7 months (95% CI, 8.6–14.8 months) in the Pem-Cis arm, and 4.4 months (95% CI, 3.7–5.1 months) and 13.3 months (95% CI, 8.1–18.5 months) in the Doc-Cis arm (23). Another interesting previous study suggested that the median PFS and OS were 11.0 months (95% CI: 10.2–11.8 months) and 21.0 months (95% CI: 20.1–21.9 months) respectively in NSCLC patients with EGFR mutation received first-line icotinib treatment (5). Therefore, these results suggest that first-line icotinib treatment is efficient in advanced NSCLC patients with EGFR-sensitive mutation. The possible reasons for better survival duration in this study were that: (I) all patients enrolled in this study were with EGFR-sensitive mutation, who might have better response to EGFR TKIs, including icotinib, and icotinib is applied as first-line treatment in these patients; (II) if PD occurred, some of them would

receive repeated icotinib treatment if it was beneficial after evaluation, some of them would receive icotinib treatment with a higher dose, and others would receive further treatment such as chemotherapy, third-generation EGFR-TKIs and optimum supportive treatment, thereby prolonging survival duration in advanced NSCLC patients with EGFR-sensitive mutation.

In the current study, we also observed that smoking history was statistically correlated with non-ORR achievement in advanced NSCLC patients with EGFR mutation received first-line icotinib treatment. This might result from that smoking history is negatively associated with EGFR mutation, thereby improving efficacy of icotinib (24). Moreover, the results of this study showed that EGFR mutation 19del was statistically associated with ORR achievement in advanced NSCLC patients with EGFR mutation received first-line icotinib treatment, which had the similar trend with the results of a meta-analysis, which assesses clinical efficacy of icotinib in lung cancer patients with different EGFR mutation status and discloses that compared to EGFR L858R patients, EGFR 19Del patients treated with icotinib have better ORRs, and it is a useful biomarker to assess the efficacy of icotinib in advanced NSCLC patients (14). However, no factor affecting PFS and OS was observed in the current study, the possible reasons were as follows: (I) sample size was relatively small in this study, thus the influence of extremum may lead to the excursion of efficacy in subgroups; (II) the follow-up duration was short, and the median value was only 15.0 (range: 1.0–44.0) months; (III) all the patients enrolled in this study were in TNM stage IIIb and IV, While the prognosis of NCLC patients was greatly affected by TNM stage, thus the influence of other factors would be reduced relatively.

With respect to safety, most common AEs including rash, diarrhea and pain have been reported in NSCLC patients, and most AEs were with mild grade (5,13). In accordance of these studies, we also observed that icotinib with related AEs mainly involved rash, diarrhea and abnormal liver function and the most AEs were in mild grade. In addition, there was no severe drug toxicity, such as myelosuppression. Therefore, it suggested that icotinib was well tolerated in advanced NSCLC patients with EGFR-sensitive mutation.

There were still patients who needed further treatment (patients were SD or PD). To these patients, nearly half of them received the secondary tissue biopsy or liquid biopsy as evidence for further treatments, including repeated icotinib treatment, chemotherapy, third-generation EGFR-TKIs, optimum supportive treatment or other treatments,

suggesting that if PD occurred, patients treated with first-line icotinib therapy still could receive further treatment.

Despite the interesting results reported, there were still some limitations existing in this study. Firstly, it was a retrospective study and all patients enrolled were from eastern China, thus, a cross-regional study with larger sample size is necessary. Secondly, follow-up duration was relatively short, the potential long-term efficacy of icotinib as first-line therapy in advanced NSCLC patients with EGFR-sensitive mutation is needed to be addressed in further study.

In conclusion, first-line icotinib treatment was efficient and well tolerated in patients with advanced NSCLC harboring EGFR mutations, and smoking history was negatively while EGFR mutation 19del was positively correlated with ORR achievement.

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Footnote

Conflict of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.05.30>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University. The number of ethical approval was KS1034. The written informed consents or oral agreements (with recording) were required from all patients or their guardians.

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