Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Efficacy of Icotinib treatment in patients with stage IIIb/IV non-small cell lung cancer

Na Qin*, Xinjie Yang*, Quan Zhang, Xi Li, Hui Zhang, Jialin Lv, Yuhua Wu, Jinghui Wang & Shucai Zhang

Department of Medical Oncology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing, China

Keywords
EGFR mutation; Icotinib; non-small cell lung cancer; targeted therapy.

Correspondence
Shucai Zhang, Department of Medical Oncology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing 101149, China.
Tel: +86 10 89509324
Fax: +86 10 80507685
Email: zhangshucai6304@aliyun.com

*Co-first authors. Na Qin and Xinjie Yang contributed equally to this work.

Received: 10 November 2013; accepted 26 November 2013.

doi: 10.1111/1759-7714.12085

Abstract

Background: To evaluate the efficacy and safety of Icotinib – an orally administered, highly potent selective inhibitor of epidermal growth factor receptor (EGFR) and its active mutations, in the treatment of patients with advanced non-small cell lung cancer (NSCLC).

Methods: A total of 101 patients with stage IIIb/IV NSCLC were treated with 125 mg Icotinib three times a day until disease progression or intolerable toxicity. Response rate was evaluated using response evaluation criteria in solid tumors and progression-free survival (PFS) was collected.

Results: The overall response rate (ORR) and disease control rate (DCR) were 37.6% (38/101) and 79.2% (80/101), respectively. The median PFS was 6.5 months. Multivariate analysis showed that female gender ($P = 0.048$, 95% confidence interval [CI] 1.010–6.016) and occurrence of rash ($P = 0.002$, 95% CI 1.667–9.809) were the independent predictive factors for ORR, while a performance status (PS) score of 0–1 ($P = 0.001$, 95% CI 0.024–0.402) and rash ($P = 0.042$, 95% CI 1.089–76.557) were the independent predictive factors for DCR. In addition, PS scores of 0–1 ($P < 0.001$, 95% CI 0.135–0.509), and non-smoking ($P = 0.017$, 95% CI 0.342–0.900) were found to be independent influencing factors for PFS. Moreover, patients with EGFR mutations had better PFS than patients with wild type EGFR, while patients with EGFR exon 19 deletion had better survival than those with EGFR exon 21 mutation. The most common adverse effects of Icotinib were rash (35.6%) and diarrhea (17.8%), which was tolerable.

Conclusion: Treatment of stage IIIb/IV NSCLC patients with Icotinib was effective and tolerable, specifically in patients with EGFR mutation.

Introduction

Lung cancer is still the leading cause of cancer-related death in the world,[1] although a decreasing trend in incidence has been observed in a number of Western countries, such as the USA. However, in China, the morbidity and mortality associated with lung cancer are still on the rise.[2] Histologically, lung cancer can mainly be classified as small cell lung cancer and non-small cell lung cancer (NSCLC), which have relatively different risk factors and treatment options.[3] NSCLC accounts for 80% of all lung cancers,[4] and most patients with NSCLC have locally advanced or metastatic disease at the time of diagnosis.[5] Thus, for these patients, the opportunity for a curable surgery has passed, and chemotherapy and radiotherapy are not effective in the treatment of NSCLC.[6–8] Recently, targeted therapy based on the targeting of specific genes or gene pathways in tumor cells has emerged. Various molecular targeting strategies have been introduced for treatment of different human cancers. Targeting epidermal growth factor receptor (EGFR) using EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, is one such strategy that is being used to treat advanced NSCLC. Several clinical studies have confirmed that patients with EGFR mutation have benefited from such treatments.[9–12] These results have encouraged the development of more such target agents for cancer therapy. Icotinib is one such agent, an orally administered, highly potent selective inhibitor of EGFR and its active mutations, independently developed in China

and approved by the State Food and Drug Administration in June 2011 for treatment of NSCLC.[13] Similar efficacy and better safety spectrum was observed between Icotinib versus gefitinib treatment in a multi-center, randomized, double-blind, double-dummy, parallel controlled phase III study in patients with locally advanced or metastatic NSCLC previously treated with one or more lines of chemotherapy (Intensive Computing for Genetic-Neuroimaging [ICOGEN]).[14] Thus, in this retrospective study, we further evaluated clinical efficacy, progression-free survival (PFS), and side effects of Icotinib treatment in a total of 101 patients with stage IIIb/IV NSCLC. We also analyzed EGFR gene mutations in a subset of patients for its association with Icotinib treatment efficacy.

Subjects and methods

Patients

In this study, we retrospectively analyzed data of 101 patients with advanced stage NSCLC who received Icotinib at the Beijing Chest Hospital between March 2009 and June 2012. These patients were histopathologically or cytologically confirmed to have had stage IIIb/IV NSCLC according to the American Joint Committee on Cancer Tumor Node Metastasis staging system, 7th edition.[15] The patients had adequate hematological, hepatic, and renal functions to be eligible to receive Icotinib treatment. The exclusion criteria included non-standard treatments, absence of measurable tumor lesion, or previous treatment with an EFGR-TKI. Our Institutional Review Board approved this study and all subjects provided written informed consent. These patients received Icotinib (Conmana, Zhejiang Betapharma Co., Ltd., Zhejiang, China), 125 mg three times a day. Efficacy of the treatment was assessed one month after treatment and followed up every two months until progressive disease or intolerable toxicity. The treatment period ranged between one and 41 months.

Evaluation of clinical response to Icotinib treatment

All patients received routine blood, hepatic, and renal function tests, chest computed tomography (CT), head CT or magnetic resonance imaging (MRI), bone scan, and performance status (PS) scoring before, during, and after treatment. Imaging examinations were performed one month after treatment, and every two months thereafter. The short-term response was assessed by using response evaluation criteria in solid tumors (RECIST) 1.1[16] and recorded as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The overall response rate (ORR) included CR and PR, and the disease control rate (DCR) included CR, PR, or SD. PFS was defined as the time from the initial treatment to progressive disease or death from any cause. Those patients who had not progressed or died by the data cut-off date were censored at the date of last tumor assessment. The severity of toxicities was graded 1–5 by NCI-CTCAE V 3.0.

Detection of epidermal growth factor receptor (EGFR) mutation

A subset of tumor samples was subjected to detection of EGFR mutations and all samples were obtained before Icotinib treatment. A total of 46 tumor tissue samples were assessed for EGFR mutation using liquid chip technology[17] and DNA sequencing.

Statistical analysis

Data were analyzed using SPSS 16.0 software (SPSS, Chicago, IL). A Chi-square test was performed to test intergroup comparisons. The Kaplan-Meier method was used to evaluate PFS. A log-rank test was used to determine survival differences with different baseline characteristics and treatment responses. The Cox proportional hazards regression model was used to identify independent factors associated with TKI outcomes. $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients with stage IIIb/IV non-small cell lung cancer (NSCLC)

In this study, we retrospectively analyzed 101 patients with advanced NSCLC who received Icotinib treatment from March 2009 to June 2012 (see Table 1). Among them, 45 were male and 56 were female. A total of 91 patients had adenocarcinomas, seven had squamous cell carcinomas, and three patients presented with other NSCLC. Of 101 patients, 35 (34.7%) received Icotinib as first-line treatment, 34 (33.7%) as second-line treatment, and 32 (31.7%) as third- or later-line treatment.

Response and survival of patients following Icotinib treatment

Of the 101 patients enrolled in this study, no patients experienced CR. However, 38 (37.6%) exhibited PR, and 42 (41.6%) had SD, accounting for 37.6% ORR and 79.2% DCR. The ORR was observed to be significantly higher in females, non-smokers, those with PS scores of 0–1, and in those with the occurrence/presence of rash (Table 2), while the DCR was significantly higher in patients who were

Table 1 Clinical characteristics of these 101 patients with non-small cell lung cancer (NSCLC)

Clinical characteristics	*n* (%)
Age, median (range)	62 (35–86)
Gender	
Male	45 (44.6)
Female	56 (55.4)
Pathological type	
Adenocarcinoma	91 (90.1)
Squamous	7 (6.9)
Other non-small cell	3 (3.0)
TNM staging	
IIIb	3 (3.0)
IV	98 (97.0)
Smoking status	
Smoker	40 (39.6)
Non-smoker	61 (60.4)
PS score	
0–1	53 (52.5)
2	31 (30.7)
3–4	17 (16.8)
Line of treatment	
First	35 (34.7)
Second	34 (33.7)
Third and later	32 (31.7)

PS, performance status; TNM, tumor node metastasis.

non-smokers, those with PS scores of 0–1, and occurrence of rash (Table 2). However, age of patients, pathological type, and occurrence of diarrhea after treatment were not significantly associated with a response to Icotinib treatment (Table 2). Multivariate logistic regression analysis showed that female gender ($P = 0.048$, 95% CI 1.010–6.016) and the occurrence of rash ($P = 0.002$, 95%CI 1.667–9.809) were independent predictive factors for ORR, while PS scores of 0–1 ($P = 0.001$, 95% CI 0.024–0.402) and rash ($P = 0.042$, 95% CI 1.089–76.557) were independent predictive factors for DCR.

The final follow-up of these patients was on 30 November 2012 and it was recorded that 71 (70.3 %) had PD or had died of the disease. Statistical analysis showed that the median PFS was 6.5 months (ranged between one and 41 months, 95% CI 3.513-9.487). The PFS was better in those patients with PS scores of 0–1 (10.8 months, 95% CI 4.898–16.702, $P < 0.001$), non-smokers (8.7 months, 95% CI 4.594–12.806, $P = 0.005$), and those with the occurrence/presence of rash during treatment (13.0 months, 95% CI 6.642–19.358, $P = 0.008$) (Figs 1, 2). Duration of PFS was not associated with gender, age, histological type of tumor, clinical stage or treatment line (Table 2). Multivariate Cox regression analysis showed that PS scores of 0–1 ($P < 0.001$, 95% CI 0.135–0.509) and non-smokers ($P = 0.017$, 95% CI 0.342–0.900) were independent influencing factors for PFS.

Association between EGFR mutations and Icotinib treatment related progression-free survival (PFS)

In this study, we also analyzed EGFR mutation status in a subset (46/101) of patients. Of 46 patients with stage IV NSCLC, 35 patients had EGFR mutations and 11 patients had wild type EGFR; 27 (58.7%) were female, 41 (89.1%) had adenocarcinoma, 29 (63.0%) were non-smokers, 23 (50.0%) patients had a PS score of 0–1, and 15 (32.6%) patients received Icotinib as the first-line treatment. EGFR mutations were observed mostly in patients with adenocarcinoma ($n = 32$, 69.6%), but were found in three patients with squamous-cell carcinoma. As for the type of EGFR mutations, 22 patients had deletion of EGFR exon 19, 13 patients had a mutation of EGFR exon 21 L858R, and one case had mutations of EGFR exon 21 L858R and T790M. We then analyzed the association between EGFR mutation status and type with responses to Icotinib treatment. A significant ($P < 0.001$) difference was observed between EGFR mutation positive and EGFR wild type patients with reference to ORR (57.1% vs. 9.1%), DCR (94.3% vs. 45.5%) and PFS (11.0 months vs. 1.0 month), indicating that patients with EGFR mutation had a favorable clinical response to Icotinib treatment.

Furthermore, univariate analysis demonstrated that non-smoker ($P = 0.004$) and EGFR mutation patients ($P = 0.005$) had favorable ORR. Non-smokers ($P = 0.038$), first- or second-line treatment group ($P = 0.017$), those with PS scores of 0–1 ($P = 0.004$), EGFR mutation positive patients ($P = 0.001$), and those with the occurrence/presence of rash ($P = 0.037$) had better DCR. Age of patients, gender, pathological type, and occurrence of diarrhea did not affect clinical responses to Icotinib treatment. Multivariate analysis showed that non-smoking ($P = 0.011$, 95% CI 0.012–0.555) and the presence of EGFR exon 19 deletion ($P = 0.016$, 95% CI 0.004–0.554) were independent factors for ORR.

Until the last follow-up on 30 November 2012, there were 30 patients (65.2%) whose disease had progressed or had died of the disease. The median PFS of patients with EGFR mutation and wild type was 11 months and one month, respectively ($P < 0.001$) as shown in Figure 3. As indicated in Figure 4, the median PFS of patients with EGFR exon 19 deletion and those with EGFR exon 21 mutation was found to be 15.1 months and 6.5 months, respectively ($P = 0.011$). Multivariate analysis showed that EGFR exon 19 deletion was an independent factor to predict PFS following Icotinib treatment ($P = 0.031$, 95% CI 1.094–6.853).

Side effects of Icotinib treatment of patients with stage IIIb/IV NSCLC

The most common adverse effects observed in this study included rash, diarrhea, and elevated aminotransferase. It was

Table 2 Association of clinicopathological factors with Icotinib treatment efficacy and progress-free survival of these 101 non-small cell lung cancer (NSCLC) patients

	ORR		DCR		PFS	
Clinical characteristic	*n* (%)	*P*	*n* (%)	*P*	Months	*P*
Gender						
Male	12 (26.7)	0.042	32 (71.1)	0.072	3.0	0.054
Female	26 (46.4)		48 (85.7)		8.7	
Age						
< 70 years	28 (37.8)	0.941	57 (77.0)	0.371	6.5	0.465
≥ 70 years	10 (37.0)		23 (85.2)		8.9	
Pathological type						
Adenocarcinoma	35 (38.5)	0.511	71 (78.0)	1.000	7.3	0.332
Squamous	3 (42.9)		6 (85.7)		2.5	
Non-small cell	0 (0.0)		3 (100.0)		3.0	
TNM staging						
IIIb	1 (33.3)	1.000	3 (100.0)	1.000	18.5	0.440
IV	37 (37.8)		77 (78.6)		6.5	
Smoking history						
Smoker	10 (25.0)	0.034	27 (67.5)	0.019	3.0	0.005
Non-smoker	28 (45.9)		53 (86.9)		8.7	
PS score						
0–1	25 (47.2)	0.031	48 (90.6)	0.000	10.8	0.000
2	11 (35.5)		26 (83.9)		5.0	
3–4	2 (11.8)		6 (35.3)		1.0	
Line of treatment						
First	15 (42.9)	0.079	28 (80.0)	0.148	8.7	0.270
Second	16 (47.1)		30 (88.2)		7.5	
Third and later	7 (21.9)		22 (68.8)		3.0	
Rash						
Present	21 (58.3)	0.001	35 (97.2)	0.001	13.0	0.008
Absent	17 (26.2)		45 (69.2)		3.1	
Diarrhea						
Present	8 (44.4)	0.510	17 (94.4)	0.110	11.0	0.454
Absent	30 (36.1)		63 (75.9)		5.0	

DCR, disease control rate; ORR, overall response rate; PFS, progression-free survival; PS, performance status; TNM, tumor node metastasis.

noted that 48/101 (47.5%) patients experienced adverse reactions associated with Icotinib treatment. Specifically, 36 (35.6%) patients had rash (35 had grade 1–2, one had grade 3 rash); 18 (17.8%) had diarrhea (15 had grade 1, three had grade 2); four (4.0%) had grade 1–2 elevated aminotransferase; two (2.0%) showed gastric discomfort and itches; three (3.0%) had paronychia; one had a grade 1 oral ulcer and another had grade 1 desquamation. However, these adverse reactions did not result in the discontinuation of Icotinib treatment.

Discussion

Icotinib hydrochloride is an EGFR-TKI with a novel molecular structure, independently developed in China, which has similar activity as gefitinib and erlotinib. The Chinese State Food and Drug Administration have approved Icotinib for clinical use. A previous phase I/IIa clinical study showed that Icotinib was efficacious with an acceptable safety spectrum in the treatment of advanced NSCLC, which reported that the DCR was 78.1%, the ORR was 29.2%, and the most common toxicities were rash (34%) and diarrhea (11%).[18] In addition, a multi-center, randomized, double-blind, double-dummy, parallel controlled phase III study of Icotinib versus gefitinib in patients with locally advanced or metastatic NSCLC previously treated with one or more lines of chemotherapy (ICOGEN)[14] was reported at the 2011 American Society of Clinical Oncology (ASCO) annual meeting in Chicago, IL, USA. The data showed a median PSF of 137 days in the Icotinib treatment group compared to 102 days in the gefitinib treatment group, while time to progression (TTP) was 156 days in the Icotinib group versus 111 days in gefitinib group. However, the overall response was comparable between Icotinib and gefitinib groups, with the ORR 27.6% versus 27.2%, and DCR 75.4% versus 74.9%, respectively. With regard to the safety issue, the overall adverse reactions with Icotinib were 60.5%, which was significantly lower than that of gefitinib at 70.4%. Specifically, the rate of rash was

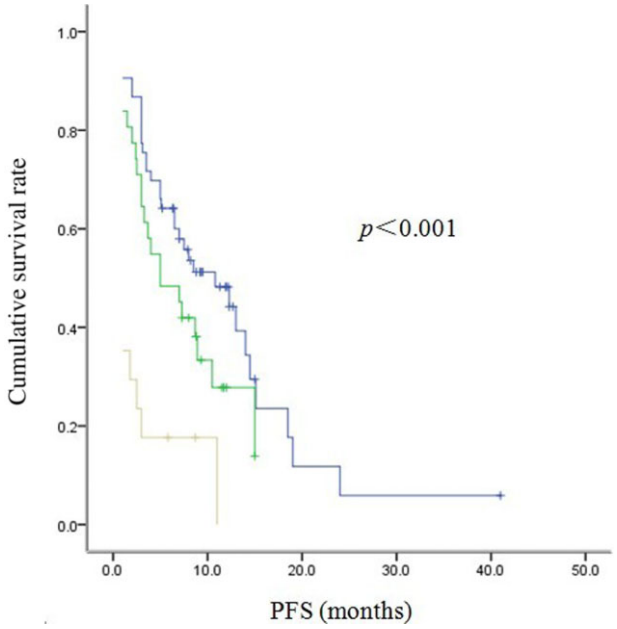

Figure 1 Progress-free survival (PFS) of non-small cell lung cancer (NSCLC) patients with different performance status after Icotinib treatment. ⎍, 0,1; ⎍, 2; ⎍, 3,4; +, 0,1-censored; +, 2-censored; +, 3,4-censored.

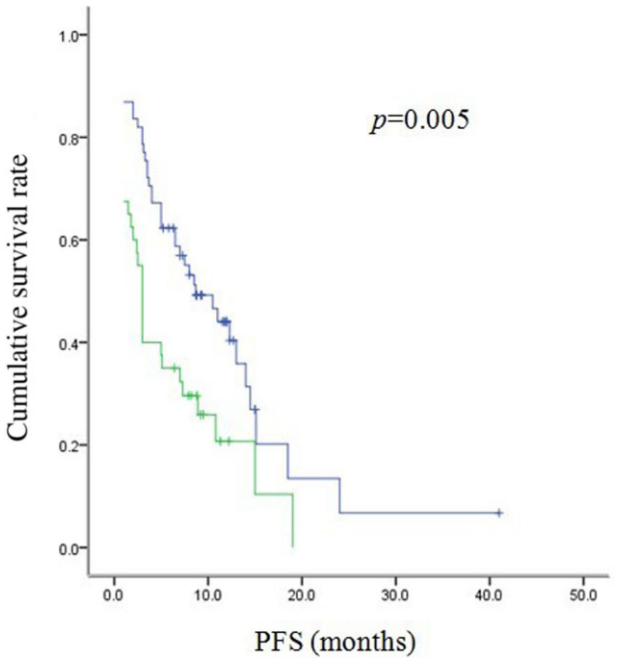

Figure 2 Progress-free survival (PFS) of non-small cell lung cancer (NSCLC) patients based on tobacco smoking status after Icotinib treatment. ⎍, no; ⎍, yes; +, no-censored; +, yes-censored.

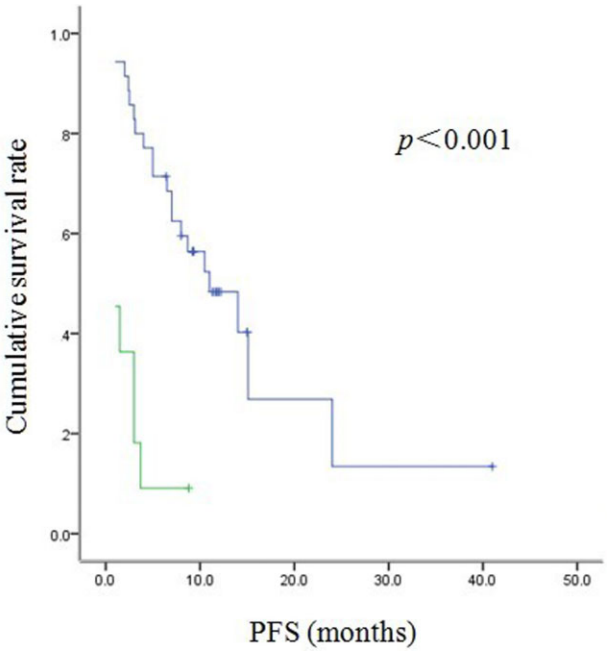

Figure 3 Progress-free survival (PFS) of non-small cell lung cancer (NSCLC) patients based on epidermal growth factor receptor (EGFR) mutation status. ⎍, positive; ⎍, wild; +, positive-censored; +, wild-censored.

40% versus 49.2% and diarrhea was 18.5% versus 27.6%, in Icotinib and gefitinib, respectively, indicating that Icotinib was safer, with fewer side effects than gefitinib. Survival data from an ICOGEN study was reported at the 2012 American Society of Clinical Oncology (ASCO) annual meeting. The overall survival was 13.3 months for the Icotinib group versus 13.9 months for the gefitinib group (95% CI 0.79–1.02, $P = 0.109$).[19]

In the current study, we further investigated the clinical efficacy and side effects of Icotinib on patients with stage IIIb/IV NSCLC and found that Icotinib treatment had an ORR of 37.6% and a DCR of 79.2%, which are higher than those in the ICOGEN study.[14] The difference may be associated with the distinct general characteristics of the clinically selected patients; there was a relatively higher proportion of adenocarcinoma, female, non-smoker, and patients with EGFR mutation, at 90.1%, 55.4%, 60.4%, and 34.7%, respectively. Multivariate Cox regression analysis demonstrated that female patients or those patients who experienced rash were associated with higher ORR, while patients with PS scores of 0–1, and those patients who experienced rash had higher DCR. These data were in accordance with a previous study.[20] Patients with lung squamous cell carcinoma displayed higher ORR than adenocarcinoma patients, which was related to higher EGFR mutation rates in squamous-cell carcinoma patients (42.9%; 3/7), than that in adenocarcinoma patients

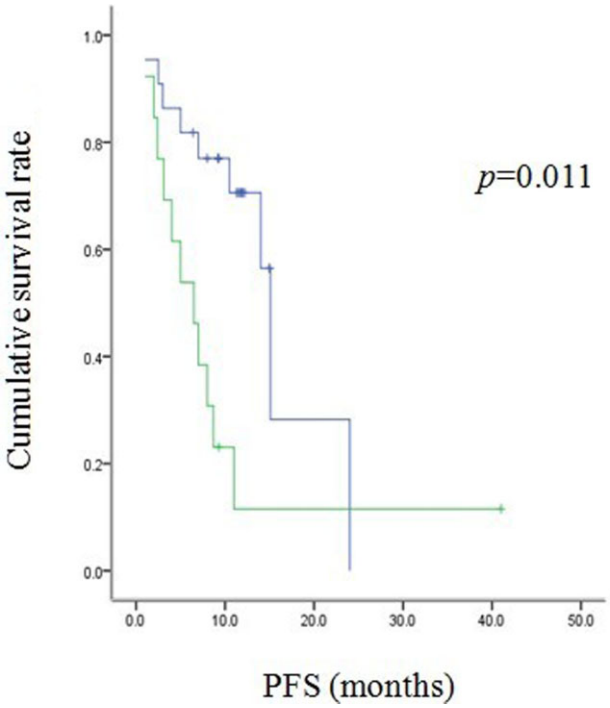

Figure 4 Progress-free survival (PFS) of non-small cell lung cancer (NSCLC) patients with different epidermal growth factor receptor (EGFR) mutations. ⎍, 19; ⎍, 21; +, 19-censored; +, 21-censored.

(35.2%; 32/91). However, because of the limited sample size of this subgroup, further study is needed to confirm our current data.

Furthermore, our current data showed a better efficacy of Icotinib, including ORR, DCR, and PFS, in the first- and second-line treatment than that of multiple-line treatment, which may be a result of a higher wild type EGFR ratio in the multiple-line subgroup. With similar baseline characteristics, especially with similar EGFR mutation status, Icotinib was a favorable option for patients with advanced NSCLC regardless of first-line, second-line or multiple-line treatment. A series of clinical trials showed patients with EGFR mutation exhibited favorable clinical response to EGFR-TKIs compared to those with wild type EGFR.[11,12] In the ICOGEN study, the ORR of patients with mutated and wild type EGFR status were 59.3% and 5.1%, respectively, and the PFS of patients with mutated and wild type EGFR were 7.8 and 2.3 months, respectively.[14,19] In the current study, the ORR of patients with mutated (57.1%) and wild type EGFR (9.1%) was similar to those observed in the ICOGEN study.[14] However, our current study showed that the PFS of patients with wild type was only one month, shorter than that of the IPASS study of 1.5 months,[11] and the ICOGEN study of 2.3 months.[19] This may be because the current study included more cases with wild type EGFR, a higher number of PS scores of 3, or in third-line or multiline treatments.

In addition, in our current study, we performed a subgroup analysis of EGFR mutations and found that out of 46 patients, there were 22 patients with EGFR exon 19 deletion and 13 patients with EGFR exon 21 L858R mutation. The PFS of patients with EGFR exon 19 deletion was longer than that of those with EGFR exon 21 L858R mutation (15.1 months vs. 6.5 months; $P = 0.011$). These observations were consistent with those reported by Jackman DM *et al*.[21] Although the number of patients was limited in the current study, we found that 13 of 22 patients with EGFR exon 19 deletion had stable disease or better up to the last follow-up, whereas only two of 13 patients with EGFR exon 21 L858R mutation had stable disease or better. Moreover, one patient with EGFR exon 21 L858R mutation had 41 months of PFS and is still being treated with Icotinib. Thus, further study is required to investigate the effects of Icotinib on patients with EGFR exon 21 L858R mutation.

Our current study showed that the most common adverse reactions were rash and diarrhea, with incidences of 35.6% (36/101) and 17.8% (18/101), respectively, and most were grade 1–2, similar to those observations made in previous studies, indicating that Icotinib is safe to be used in clinics. According to the Tarceva Lung Cancer Survival Treatment (TRUST) study,[22] the PFS of patients without rash was only eight weeks, compared with 18 weeks ($P < 0.0001$) in patients who experienced rash. Similarly, our current study showed that patients with the occurrence of rash had longer PFS (13.0 months vs. 3.1 months, $P = 0.008$), indicating that the appearance of rash is a predictive factor for efficacy.

Conclusion

Our current study further confirmed that Icotinib is effective and safe in the treatment of patients with advanced NSCLC, especially in patients with EFGR exon 19 deletion mutation and regardless of first-line, second-line or multiple-line treatment.

Acknowledgments

On the completion of my thesis, I should like to express my deepest gratitude to all those whose kindness and advice have made this work possible.

Disclosure

No authors report any conflict of interest.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. (Published erratum appears in CA Cancer J Clin 2011; 61: 134.) *CA Cancer J Clin* 2011; **61**: 69–90.

2 Chen W, Zhang S, Zou X. [Estimation and projection of lung cancer incidence and mortality in China.] *Zhongguo Fei Ai Za Zhi* 2010; **13**: 488–93. (In Chinese.)
3 Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. *In Collaboration with Pathologists from 14 Courtiers: World Health Organization International Histological Classification of Tumours: Histological Typing of Lung and Pleural Tumors. Edition 3*. Springer, Berlin, Germany 1999.
4 Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995; **311**: 899–909.
5 Fossella FV, DeVore R, Kerr RN *et al*. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. (Published erratum appears in J Clin Oncol 2004; 22: 209.) *J Clin Oncol* 2000; **18**: 2354–62.
6 Cufer T, Ovcaricek T, O'Brien ME. Systemic therapy of advanced non-small cell lung cancer: major-developments of the last 5-years. *Eur J Cancer* 2013; **49**: 1216–25.
7 Schiller JH, Harrington D, Belani CP *et al*. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**: 92–8.
8 Salama JK, Vokes EE. New radiotherapy and chemoradiotherapy approaches for non-small-cell lung cancer. *J Clin Oncol* 2013; **31**: 1029–38.
9 Shepherd FA, Rodrigues Pereira J, Ciuleanu T *et al*. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**: 123–32.
10 Hirsch FR, Varella-Garcia M, Bunn PA Jr *et al*. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24**: 5034–42.
11 Mok TS, Wu YL, Thongprasert S *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.
12 Zhou C, Wu YL, Chen G *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.
13 Tan F, Wang Y, Yuan X *et al*. Targeted therapy for non-small-cell lung cancer using EGFR-TKIs. *Chin J New Drugs* 2011; **20**: 1594–601. (In Chinese.)
14 Sun Y, Shi Y, Zhang L *et al*. A randomized, double blind phase III study of icotinib versus gefitinib in patients with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy (ICOGEN). 2011 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2011; **29** (Suppl): Absract 7522.
15 Goldstraw P, Crowley J, Chansky K *et al*. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumors. (Published erratum appears in J Thoracic Oncol 2007; 2: 985.) *J Thoracic Oncol* 2007; **2**: 706–14.
16 Eisenhauer EA, Therasse P, Bogaerts J *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
17 Zhang L, Yang H, Zhao Y *et al*. Detection of EGFR somatic mutations in non-small cell lung cancer (NSCLC) using a novel mutant-enriched liquidchip (MEL) technology. *Curr Drug Metab* 2012; **13**: 1007–11.
18 Tan F, Zhang L, Zhao Q *et al*. Pharmacology and clinical evaluation of icotinib hydrochloride. *Chin J New Drugs* 2009; **18**: 1691–700. (In Chinese.)
19 Sun Y, Shi Y, Zhang L *et al*. Final overall survival and updated biomarker analysis results from the randomized phase III ICOGEN trial. 2012 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2012; **30** (Suppl): Abstract 7559.
20 Jackman DM, Yeap BY, Lindeman NI *et al*. Phase II clinical trial of chemotherapy-naive patients ≥70 years of age treated with erlotinib for advanced non-small cell lung cancer. *J Clin Oncol* 2007; **25**: 760–6.
21 Jackman DM, Miller VA, Cioffredi LA *et al*. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009; **15**: 5267–73.
22 Heigener DF, Wu YL, van Zandwijk N, Mali P, Horwood K, Reck M. Second-line erlotinib in patients with advanced non-small-cell lung cancer: subgroup analyses from the TRUST study. *Lung Cancer* 2011; **74**: 274–9.

