Oncology and Translational Medicine
DOI 10.1007/s10330-016-0198-8

December 2016, Vol. 2, No. 6, P268–P274

ORIGINAL ARTICLE

Icotinib, an EGFR-TKI, for the treatment of brain metastases in non-small cell lung cancer: a retrospective study

Qunhui Wang, Hua Zheng (Co-first author) (✉), Ying Hu, Baohua Lu, Fanbin Hu, Hongmei Zhang, Baolan Li (✉)

Department of Oncology, Beijing Chest Hospital, Capital Medical University, Beijing 101149, China

Abstract

Objective Treatment of brain metastases from non-small cell lung cancer (NSCLC) is a challenge because of the poor prognosis. Icotinib is a new type of oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) used in the treatment of advanced NSCLC. The aim of this study was to evaluate the efficacy of icotinib in NSCLC patients with brain metastasis.

Methods This study reviewed records of 51 NSCLC patients with brain metastases who took icotinib 125 mg, 3 times a day. Response rate, progression free survival, and overall survival were analyzed. SPSS software version 17.0 was used for univariate analysis, and Cox regression analysis to analyze factors affecting survival.

Results Thirty-six cases had partial response, 6 cases had stable disease, and 10 cases had progressive disease. In 31 cases, EGFR gene mutation test were performed. EGFR was mutated in 26 cases and was with wild-type in 5 cases. In patients with EGFR mutations, 23 patients responded to icotinib [the disease control rate (DCR) was 88.5%], significantly higher than in patients with wild-type EGFR (1 patient, DCR 20%) (P = 0.005). The overall median progression-free survival (PFS) was 7.6 months. PFS was longer in the patients with EGFR mutations than in those with wild type EGFR (7.8 months vs 1.2 months, P = 0.03). The overall median overall survival (OS) time was 10.7 months. OS was longer in patients with EGFR mutations than in those with wild type EGFR (15.1 months vs 6.7 months, P = 0.003). The main side effects of the treatment were skin rash and diarrhea; no stage 3 or 4 toxic effects occurred. Univariate analysis demonstrated that OS was related to sex, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, and EGFR mutation. Multivariate analysis showed that OS was independently related to sex, ECOG PS, and EGFR mutations.

Conclusion Icotinib has a favorable effect on NSCLC patients with brain metastases harboring EGFR mutations. Icotinib can be a new choice of treatment for brain metastases in patients with NSCLC harboring EGFR mutations.

Received: 4 August 2016
Revised: 4 September 2016
Accepted: 25 September 2016

Key words: non-small cell lung cancer (NSCLC); brain metastases; icotinib; epidermal growth factor receptor (EGFR)

Lung cancer is the most common type of cancer and is the leading cause of cancer death in China [1]. Non-small cell lung cancer (NSCLC) cases constitute approximately 80% of all lung cancer cases [2]. NSCLC is the most common type of cancer with brain metastases and at least 25–40% of patients develop brain metastases at some point during their disease [3].

The prognosis of NSCLC patients with brain metastasis is poor with a median overall survival (OS) of less than 3 months without treatment [4]. The quality of life of these patients is also very poor [5]. The standard treatment options for patients with brain metastasis include surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or a combination of these [6].

✉ Correspondence to: Hua Zheng, Email: zhenghua022@sina.com; Baolan Li, Email: libaolan1109@163.com

Chemotherapy has not been a standard treatment for these patients because drugs cannot penetrate the blood-brain barrier effectively. However, chemotherapy is an option for NSCLC with brain metastasis, with reports of response rates of 15–30% and an OS of 6–8 months [7–9].

Recent studies showed the effectiveness of pemetrexed treatment in NSCLC patients with brain metastasis [10–12]. Bevacizumab, the most widely used drug in anti-angiogenic therapy, has also been shown to improve response rates, progression-free survival (PFS), and OS compared to chemotherapy alone in NSCLC patients with brain metastasis [9]. However, because of concerns about tumor-related intracranial hemorrhage [13], the use of bevacizumab to treat NSCLC patients with brain metastasis has remained limited.

In the last 10 years, several clinical studies showed EGFR-tyrosine kinase inhibitor (TKI) significantly prolonged PFS and OS of advanced NSCLC patients with sensitive EGFR mutations [14–16] and it is used for the treatment of patients with brain metastases [17–22]. Most of these reports are about gefitinib and erlotinib, both known to cross the blood-brain barrier [23–24].

Icotinib is a new type of oral EGFR-TKI developed in China (Conmana, Zhejiang Beta Pharma, China). A phase III trial (ICOGEN) [25] demonstrated that icotinib was non-inferior to gefitinib in terms of PFS in NSCLC patients and this result led icotinib to be approved by the China Food and Drug Administration in August 2011. Icotinib was reported to have a beneficial effect on brain metastases of NSCLC in some case reports [26–27].

The aim of this study is to evaluate the efficacy of icotinib in NSCLC patients with brain metastases.

Materials and methods

Patients

This study enrolled 51 consecutive NSCLC patients with a confirmed pathological diagnosis, advanced stage (IIIb or IV), brain metastasis, and received icotinib treatment at the Beijing Chest Hospital between October 2011 and April 2014. The brain metastasis was confirmed using magnetic resonance imaging or computed tomography. The patients' information was collected, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), pathology, smoking history, neurological symptoms, numbers of brain metastasis foci, presence of an EGFR mutation, and previous treatment. All patients took icotinib 125 mg, 3 times a day, until their disease progressed, death, or the development of unacceptable toxic effects. This retrospective study obeyed all the rules and regulations of clinical studies with respect to human subject protection and was approved by the independent ethics committee.

Assessments

Tumor assessment was performed within 2 weeks before icotinib treatment and first reassessed after 4 weeks of medication. Afterward, an assessment was performed every 2 months during treatment according to the Response.

Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which is divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Adverse reactions were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) once a week during treatment and then every 8 weeks at follow-up visits.

Progression-free survival (PFS) was calculated as the duration of time from the start of icotinib to progression of the disease. OS was calculated as the duration of time from the start of icotinib to date of death. EGFR mutations were detected by the use of an amplification refractory mutation system or Sanger sequencing.

Statistical analysis

All data were analyzed using SPSS (Chicago, IL, USA) version 17.0. Baseline characteristics between groups were compared using the Chi-square test or Fisher's exact test. The Kaplan–Meier method and log-rank test were used for survival analysis. The Cox regression model was used to identify independent prognostic factors. A *P*-value of 0.05 was considered to be statistically significant.

Follow-up

All patients were followed up until December 31, 2014 and during this time period 37 patients died, 12 survived, and 2 cases were lost.

Results

Baseline characteristics

A total of 51 cases were analyzed. The detailed patients' characteristics were summarized in Table 1. The ages ranged from 34 to 78 years old, and the median age was 59 years old. There were 22 (43.1%) men and 29 (56.9%) women. Thirty (58.8%) cases were ECOG PS score 0–1, while 21 (41.2%) cases were 2–3. There were 17 (33.3%) smokers and 34 (66.7%) non-smokers. The majority of patients had adenocarcinoma (48 cases, 94.1%), and 3 cases (5.9%) were non-adenocarcinoma. Twenty-six (51%) cases had EGFR mutations, among them 19 (37.3%) cases harboring exon 19 deletion mutations and 7 (13.7%) cases with L858R mutations. Five (9.8%) cases had wild type EGFR and 20 (39.2%) cases were unknown. Twenty-eight (54.9%) cases were concomitantly treated for brain metastases with icotinib and WBRT while the other 23 (45.1%) cases used icotinib alone to control their disease. The numbers of cases using icotinib for first-line,

Table 1 Characteristics of the cases

Features	*n*	%
Sex		
Male	22	43.1
Female	29	56.9
Median age (years)		
> 65	13	25.5
≤ 65	38	74.5
ECOG PS		
0–1	30	58.8
2–3	21	41.2
Smoking history		
Never smoked	34	66.7
Former smoker	17	33.3
Histologic feature		
Adenocarcinoma	48	94.1
Other	3	5.9
Neurological symptom		
Yes	31	60.8
No	20	39.2
Number of brain metastasis		
Single	10	19.6
Multiple	41	80.4
EGFR mutation		
Wild type	5	9.8
Exon 19 deletion	19	37.3
L858R	7	13.7
Unknown	20	39.2
Icotinib treatment		
First line	19	37.3
Second line	20	39.2
Third line	8	15.7
Fourth line	4	7.8
WBRT		
Yes	28	54.9
No	23	45.1

second-line, third-line, and fourth line treatment were 19 (37.3%), 20 (39.2%), 8 (15.7%), and 4 (7.8%), respectively.

Efficacy

Among all 51 cases, for the brain metastatic lesion, 35 (68.6%) cases had a PR, 6 (11.8%) cases SD, and 10 (19.6%) cases PD, and no CR case was observed. The objective response rate (ORR) was 35 (68.6%) and the disease control rate (DCR) was 41 (80.4%) in the entire population. Among EGFR mutated cases, the ORR was 21 (80.8%) and the DCR was 23 (88.5%). There was 1 patient with EGFR wild type who showed PR. The difference in DCR between the group with EGFR mutated and wild type was statistically significant (P = 0.005). DCR had no correlation with sex, age, smoking status, ECOG PS, number of brain metastases (single or multiple), radiotherapy used or not, which line of icotinib was used, and having neurological symptoms or not (P > 0.05).

Survival

The overall median PFS was 7.6 months. Univariate analysis showed that PFS for patients with EGFR mutations was 7.8 months vs 1.2 months for EGFR wild type (P = 0.03). Women had a PFS of 8.3 months vs 5.2 months for men (P = 0.02). PFS for patients with 19 exon deletion mutations was significantly longer than wild type (8.1 months vs 1.2 months, P = 0.03). PFS of patients with an L858R mutation was longer than for wild type, but the difference was not statistically significant (4.6 months vs 1.2 months, P = 0.61). However, age, smoking status, number of brain metastases, WBRT, neurological symptoms, and which line for use of icotinib were not significant (P > 0.05). ECOG PS had a close to significant influence on PFS (P = 0.06; Table 2).

The median OS was 10.7 months. OS for patients with EGFR mutations was 15.1 months vs 6.7 months for EGFR wild type (P = 0.003). Women had an OS of 15.6 months vs 8.3 months for men (P = 0.001). OS of patients with exon 19 deletion mutations was statistically significantly longer than wild type (15.6 months vs 6.7 months, P = 0.004). OS of patients with L858R mutations was not significantly longer than wild type (10.3 months vs 6.7 months, P = 0.082). ECOG PS was significantly correlated with OS (P = 0.01). However, OS was not significantly related to age, number of brain metastases, WBRT, neurological symptoms, or the line of icotinib use (P > 0.05; Table 2).

Multivariate analysis showed that EGFR gene mutation (P = 0.002), sex (P = 0.018), and ECOG PS (P = 0.013) were independently correlated with OS.

Safety

The most common toxic effects of icotinib treatment were diarrhea and skin rashes. There were no stage 3 or 4 toxic events.

Discussion

The survival time for patients receiving therapy is limited and brain metastasis from NSCLC is still a challenge. The treatment options for patients with brain metastasis include surgery, WBRT, SRS, or a combination of these [6]. Encouragingly, with the development of molecular biology, targeted therapy has become an important tool in the treatment of NSCLC through studies such as IPASS, OPTIMAL, NEJ002, WJTOG3405, EURTAC, LUX-Lung 3, and LUX-Lung 6 [14, 15, 28–32]. These studies showed that ORR can reach 60–80% and the median PFS can be 8–13 months with few toxic effects after targeted therapy. Additionally, EGFR-TKIs have a favorable efficacy on brain metastasis in advanced NSCLC patients harboring EGFR sensitive mutations [17–22]. These EGFR-TKIs can achieve a median PFS of 6.6–14.5 months and a median OS of 8–20 months in patients with brain

Table 2 Univariate analysis of PFS and OS to icotinib for NSCLC

	Median PFS (month)	95% CI	*P*	Median OS (month)	95% CI	*P*
Sex			0.02			0.001
Male	5.2	2.7–7.3		8.3	2.0–13.9	
Female	8.3	6.3–9.7		15.6	6.0–23.9	
Age (years)			0.59			0.92
> 65	8.2	3.5–12.5		8.4	2.9–13.0	
≤ 65	7.0	5.2–8.8		10.2	7.2–12.8	
ECOG PS			0.06			0.01
0–1	7.8	5.8–10.2		15.6	10.1–19.9	
2–3	5.4	3.9–6.0		7.8	4.4–9.6	
Smoking history			0.12			0.03
Never smoked	5.2	3.7–6.3		8.4	4.1–11.9	
Former smoker	7.1	5.6–8.4		13.5	8.2–17.7	
Neurological symptom			0.23			0.38
Yes	5.2	2.0–7.9		8.4	3.8–12.1	
No	7.1	4.5–9.5		12.2	8.6–15.3	
Number of BM			0.48			0.29
Single	7.5	0–15.3		20.6	12.2–27.5	
Multiple	7.2	4.9–9.0		10.3	8.8–11.2	
EGFR mutation			0.03			0.003
Wild type	1.2			6.7	0–14.6	
Mutated	7.8	4.1–9.9		15.1	10–19.1	
Exon 19-del	8.1	4.5–11.4	0.03	15.6	8.6–21.4	0.004
L858R	4.6	1.4–6.6	0.61	10.3	3.8–16.2	0.082
WBRT			0.79			0.54
Yes	6.1	2.5–9.5		13.4	9.1–16.9	
No	7.0	4.6–9.3		10.6	6.8–13.1	
Icotinib treatment			0.89			0.46
First line	7.1	5.6–8.4		10.2	4.3–15.6	
Second line	7.0	4.5–9.5		12.6	8.4–15.6	
Third line	2.8	0–7.2		8.8	2.8–13.1	
Fourth line	1.0			2.4		

metastasis from advanced NSCLC. Most of these reports are on gefitinib and erlotinib, which are known to cross the blood-brain barrier [23–24]. Icotinib is a new type of oral EGFR-TKI developed in China. A randomized, double-blind, multicenter, controlled, and head-to-head (icotinib vs gefitinib) phase III trial of icotinib (ICOGEN) demonstrated that icotinib was non-inferior to gefitinib in terms of PFS (7.8 months vs 5.3 months, $P = 0.32$) and OS (20.9 months vs 20.2 months, $P = 0.76$) in NSCLC patients with mutated EGFR [25]. Patients harboring active EGFR mutations have a better response to icotinib than those without EGFR mutations. Additionally, icotinib has shown a higher liposolubility and can pass through the blood brain barrier easier as compared with gefitinib [33].

Previous reports showed that icotinib has a good effect on brain metastasis [26–27] and leptomeningeal carcinomatosis [34] in NSCLC. Additionally, Icotinib shows efficacy in preventing brain metastases [33]. In the current study, 51 patients with advanced NSCLC with brain metastases received icotinib treatment. The overall median PFS was 7.6 months and OS was 10.7 month. PFS and OS for patients with EGFR mutations were significantly longer than those with EGFR wild type. The ORR and DCR among patients with EGFR mutations were also significantly higher than those with EGFR wild type. These results indicated that icotinib has good efficacy for NSCLC patients with brain metastases harboring EGFR mutations.

For the different EGFR mutations, PFS and OS in patients with exon 19 deletions were significantly longer than those with EGFR wild type (8.1 months vs 1.2 months, $P = 0.03$ and 15.6 months vs 6.7 months, $P = 0.004$). However, PFS and OS in patients with L858R mutations were not statistically different than those with EGFR wild type (4.6 months vs 1.2 months, $P = 0.61$ and 10.3 months vs 6.7 months, $P = 0.082$). It appears that survival in patients with exon 19 deletions is different compared with that in patients with L858 mutations.

Similar results have been reported in LUX-Lung 3 and LUX-Lung 6 [35]. Yang found that OS was significantly

longer for patients with deletion 19-positive tumors in the afatinib group than in the chemotherapy group in both trials. In LUX-Lung 3 the OS was 33.3 months vs 21.1 months, $P = 0.0015$ and in LUX-Lung 6, it was 31.4 months vs 18.4 months, $P = 0.023$. In contrast, there were no significant differences in the OS of different treatment groups of patients with EGFR L858R-positive tumors in either trial. In LUX-Lung 3, the OS was 27.6 months vs 40.3 months, $P = 0.29$), and in LUX-Lung 6 it was 19.6 months vs 24.3 months, $P = 0.34$). Therefore, we speculate that EGFR deletion 19-positive disease might be different from L858R-positive disease. Further study is needed to confirm this conclusion.

This study did not show that icotinib plus concomitant WBRT had a higher response rate to brain metastasis than icotinib alone. Moreover, PFS or OS was not improved using WBRT compared to icotinib alone in the treatment of brain metastases from NSCLC. A phase Ⅱ study indicated that the combination of icotinib and WBRT was well-tolerated and median PFS was 7.0 months [36]. This is similar to our results, but it was a single-arm study and therefore whether patients can benefit from the combination of icotinib with WBRT is still unknown.

Whether concomitant WBRT with EGFR-TKI is beneficial for NSCLC patients is still unclear. A retrospective study showed that gefitinib plus concomitant WBRT had a higher response rate of brain metastases and significant improvement in time to progression (10.6 vs 6.57 months, $P < 0.001$) and OS (23.40 vs 14.83 months, $P = 0.002$) compared with gefitinib alone in the treatment of brain metastases from NSCLC [37].

Van reported that radiation therapy might disrupt the blood-brain barrier [38] and the addition of WBRT might increase the concentration of gefitinib in the CNS. However, a prospective phase 3 trial showed that the addition of temozolomide or erlotinib to WBRT plus SRS in NSCLC patients with 1 to 3 brain metastases did not improve survival and possibly had a deleterious effect [39]. Further studies are needed to harmonize targeted therapy and WBRT in NSCLC patients with brain metastases harboring EGFR mutations.

We conducted univariate analysis and found that patients' PFS and OS were related to EGFR mutation status, sex, and ECOG PS. Among EGFR mutated patients, the disease progressed in 3 patients after administration of icotinib. All these patients had adenocarcinoma and two harbored deletions in exon 19 and one had a L858R mutation. We found that one patient had elevated carcinoembryonic antigen (CEA), neuron-specific enolase, and pro-gastrin-releasing peptide levels; one had elevated CEA and CYFRA 21-1 levels; the other patient's tumor markers were normal but his brain lesion progressed, while he had stable disease in his lung lesion. We concluded that tumor heterogeneity affects the response to icotinib.

Tanaka [40] found that EGFR-mutated NSCLC patients with a high CYFRA 21-1 level have significantly shorter PFS than those with normal CYFRA 21-1 level. The authors speculated that the serum CYFRA 21-1 level was associated with the proportion of squamous component in the NSCLC. There are also reports [41–43] on heterogeneity between the primary lesion and metastatic lesion, with a discrepancy that can vary from 6.3%–26.9%. These findings indicated that heterogeneity influences the efficacy of EGFR-TKIs. Therefore, we speculated that there may be small cell lung cancer components in the metastatic lesion in the first patient, squamous components in the second patient, and differences between the primary and metastatic lesions in the third patient.

The most common adverse events of icotinib in NSCLC with brain metastases were rash and diarrhea, and no patients had grade 3 or 4 toxic effects. This result is consistent with those of previous studies on icotinib use [25, 44] and confirms the safety and good quality of life with icotinib treatment.

In summary, icotinib shows favorable efficacy in NSCLC patients with brain metastases harboring EGFR mutations. Icotinib was well tolerated and patients showed significantly improved survival. The effect of icotinib may be different between patients with exon 19 deletions and L858R mutations. Concomitant WBRT did not show any beneficial effect and further prospective studies are needed to optimize treatment strategies. Moreover, tumor heterogeneity can influence the efficacy of EGFR-TKIs.

References

1. Chen W, Zheng R, Zeng H, *et al*. Annual report on status of cancer in China, 2011. Chin J Cancer Res, 2015, 27: 2–12.
2. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. CA Cancer J Clin, 2011, 61: 69–90.
3. D'Antonio C, Passaro A, Gori B, *et al*. Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies. Ther Adv Med Oncol, 2014, 6: 101–114.
4. Nussbaum ES, Djalilian HR, Cho KH, *et al*. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer, 1996, 78: 1781–1788.
5. Tsao MN, Lloyd N, Wong RK, *et al*. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev, 2012, 4: Cd003869.
6. Welsh JW, Komaki R, Amini A, *et al*. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. J Clin Oncol, 2013, 31: 895–902.
7. Moscetti L, Nelli F, Felici A, *et al*. Up-front chemotherapy and radiation treatment in newly diagnosed nonsmall cell lung cancer with brain metastases: survey by Outcome Research Network for Evaluation of Treatment Results in Oncology. Cancer, 2007, 109 : 274–281.

8. Postmus PE, Smit EF. Chemotherapy for brain metastases of lung cancer: a review. Ann Oncol, 1999, 10: 753–759.
9. Tang N, Guo J, Zhang Q, *et al*. Greater efficacy of chemotherapy plus bevacizumab compared to chemo- and targeted therapy alone on non-small cell lung cancer patients with brain metastasis. Oncotarget, 2016, 7: 3635-3644.
10. Bearz A, Garassino I, Tiseo M, *et al*. Activity of Pemetrexed on brain metastases from Non-Small Cell Lung Cancer. Lung Cancer, 2010, 68: 264–268.
11. Raizer JJ, Rademaker A, Evens AM, *et al*. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. Cancer, 2012, 118: 3743–3748.
12. Dai H, Chen Y, Elmquist WF. Distribution of the novel antifolate pemetrexed to the brain. J Pharmacol Exp Ther, 2005, 315: 222–229.
13. Gordon MS, Margolin K, Talpaz M, *et al*. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol, 2001, 19: 843–850.
14. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med, 2009, 361: 947–957.
15. 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: 735–742.
16. Wu YL, Zhou C, Liam CK, *et al*. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol, 2015, 26: 1883–1889.
17. Kim JE, Lee DH, Choi Y, *et al*. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer, 2009, 65: 351–354.
18. Park SJ, KimHT, Lee DH, *et al*. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21mutation. Lung Cancer, 2012, 77: 556–560.
19. Iuchi T, Shingyoji M, Sakaida T, *et al*. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer, 2013, 82: 282–287.
20. Song Z, Zhang Y. Gefitinib and erlotinib for non-small cell lung cancer patients who fail to respond to radiotherapy for brain metastases. J Clin Neurosci, 2014, 21: 591–595.
21. Fan Y, Xu X, Xie C. EGFR-TKI therapy for patients with brain metastases from non-small-cell lung cancer: a pooled analysis of published data. Onco Targets Ther, 2014, 7: 2075–2084.
22. Porta R, Sánchez-Torres JM, Paz-Ares L, *et al*. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J, 2011, 37: 624–631.
23. Fukuhara T, Saijo Y, Sakakibara T, *et al*. Successful treatment of carcinomatous meningitis with gefitinib in a patient with lung adenocarcinoma harboring a mutated EGF receptor gene. Tohoku J ExpMed, 2008, 214: 359–363.
24. Togashi Y, Masago K, Fukudo M, *et al*. Cerebrospinal fluid concentration of erlotinib and its active metabolite OSI-420 in patients with central nervous system metastases of non-small cell lung cancer. J Thorac Oncol, 2010, 5: 950–955.
25. Shi Y, Zhang L, Liu X, *et al*. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol, 2013, 14: 953–961.
26. Zheng H, Wang Q, Shi H, *et al*. Favorable response to icotinib in a lung cancer patient with a special mutation at exon 19 of epidermal growth factor receptor. Thorac Cancer, 2014, 5: 358-361.
27. Zhang Y, Tang H, Li J, *et al*. An active treatment of lung adenocarcinoma cancer with brain metastases: icotinib. Oncol Targets Ther, 2015, 8: 1351–1354.
28. Inoue A, Kobayashi K, Maemondo M, *et al*. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol, 2013, 24: 54–59.
29. Mitsudomi T, Morita S, Yatabe Y, *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol, 2010, 11: 121–128.
30. Rosell R, Carcereny E, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol, 2012, 13: 239–246.
31. Yang JC, Hirsh V, Schuler M, *et al*. Symptom control and quality of life in LUX-Lung 3: a Phase III study of afatinib or cisplatin/pemetrexed with advanced lung adenocarcinoma with mutations. J Clin Oncol, 2013, 31: 3342–3350.
32. Wu YL, Zhou C, Hu CP, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol, 2014, 15: 213–222.
33. Zhao X, Zhu G, Chen H, *et al*. Efficacy of icotinib versus traditional chemotherapy as first-line treatment for preventing brain metastasis from advanced lung adenocarcinoma in patients with epidermal growth factor receptor-sensitive mutation. J Cancer Res Ther, 2014, 10 Suppl: C155–C159.
34. Gong L, Xiong M, Huang Z, *et al*. Icotinib might be effective for the treatment of leptomeningeal carcinomatosis in non-small cell lung cancer with sensitive EGFR mutations. Lung Cancer, 2015, 89: 268–273.
35. Yang JC, Wu YL, Schuler M, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol, 2015, 16: 141–151.
36. Fan Y, Huang Z, Fang L, *et al*. A phase II study of icotinib and whole-brain radiotherapy in Chinese patients with brain metastases from non-small cell lung cancer. Cancer Chemother Pharmacol, 2015, 76: 517–523.
37. Zeng YD, Zhang L, Liao H, *et al*. Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: a retrospective study. Asian Pac J Cancer Prev, 2012, 13: 909–914.
38. van Vulpen M, Kal HB, Taphoorn MJ, *et al*. Changes in blood-brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? (Review). Oncol Rep, 2002, 9: 683–688.
39. Sperduto PW, Wang M, Robins HI, *et al*. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group

0320. Int J Radiat Oncol Biol Phys, 2013, 85: 1312–1318.
40. Tanaka K, Hata A, Kaji R, *et al*. Cytokeratin 19 fragment predicts the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitor in non-small-cell lung cancer harboring EGFR mutation. J Thorac Oncol, 2013, 8: 892–898.
41. Gow CH, Chang YL, Hsu YC, *et al*. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol, 2009, 20: 696–702.
42. Schmid K, Oehl N, Wrba F, *et al*. EGFR/KRAS/BRAF mutations in primary lung adenocarcinomas and corresponding locoregional lymph node metastases. Clin Cancer Res, 2009, 15: 4554–4560.
43. Sun L, Zhang Q, Luan H, *et al*. Comparison of KRAS and EGFR gene status between primary non-small cell lung cancer and local lymph node metastases: implications for clinical practice. J Exp Clin Cancer Res, 2011, 30: 30.
44. Tan F, Gu A, Zhang Y, *et al*. Safety and efficacy results of a phase IV, open-label, multicenter, safety-monitoring study of icotinib in treating advanced non-small cell lung cancer (NSCLC): ISAFE study. Proc Am Soc Clin Oncol, 2013, 31: e19161.

DOI 10.1007/s10330-016-0198-8
Cite this article as: Wang QH, Zheng H, Hu Y, *et al*. Icotinib, an EGFR-TKI, for the treatment of brain metastases in non-small cell lung cancer: a retrospective study. Oncol Transl Med, 2016, 2: 268–274.