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ORIGINAL RESEARCH

The effectiveness of EGFR-TKIs against brain metastases in EGFR mutation-positive non-small-cell lung cancer

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Abstract: Brain metastases are usual in non-small-cell lung cancer (NSCLC) with poor prognosis and few available therapeutic options. This retrospective study aims to evaluate the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) against brain metastases from NSCLC harboring activating *EGFR* mutation. A total of 148 patients with brain metastases from *EGFR* mutation-positive NSCLC were analyzed retrospectively. The patients were orally given gefitinib (250 mg) or erlotinib (150 mg) once a day until intracranial disease progression, death, or intolerable side effects. A survival analysis was done using the Kaplan–Meier analysis and log-rank test. Objective response rate and disease control rate within brain lesions were 36.5% and 87.2%, respectively, with a median progression-free survival (PFS) and overall survival (OS) of 11.2 months (95% confidence interval [CI], 10.1–12.3) and 13.6 months (95% CI, 12.3–14.9), respectively. The patients' characteristics were not statistically associated with PFS and OS. EGFR-TKIs showed promising antitumor activity against brain metastases in NSCLC patients with activating *EGFR* mutation and might be the treatment choice in this clinical setting.

Keywords: brain metastases, non-small-cell lung cancer, mutation, EGFR inhibitors, targeted therapy

Introduction

Lung cancer is currently the most common cancer diagnosis and the leading cause of cancer-related death worldwide.[1] Brain metastasis is usual in non-small-cell lung cancer (NSCLC) and ~30%–50% patients may develop brain metastases at some point during their disease courses.[2,3] Few therapeutic options are available for brain metastases and the prognosis of NSCLC patients with brain metastasis is still poor. Brain metastasis has become a critical issue and more novel strategies are urgently needed.

The epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib have been proved to be effective in improving tumor response and increasing survival for advanced NSCLC.[4–9] Moreover, it has been found that activating *EGFR* mutations within the tyrosine kinase domain in NSCLC are highly associated with the sensitivity to EGFR-TKI treatment, which has emerged as an important predictor of response and survival benefit in NSCLC.[5,10–14] To date, EGFR-TKI has become the standard treatment option for NSCLC with activating *EGFR* mutation.

Since there are more effective molecular targeted agents in the treatment for some subsets of NSCLC compared to the conventional therapy, increasing attention has been paid to the potential role of EGFR-TKI in brain metastases from NSCLC in recent

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years. Nonetheless, brain metastases were usually considered as exclusion criteria in most previous clinical studies involving EGFR-TKI and accounts of its use in intracranial lesions are available only in a few case reports or some small studies with limited number of patients. Therefore, the role of EGFR-TKI in this setting still remains unclear. The purpose of this retrospective study was to further explore the antitumor efficacy of EGFR-TKI therapy against brain metastases from NSCLC harboring *EGFR* mutation.

Methods

Study design and patients

This study was approved by the Institutional Review Board of Shanghai Chest Hospital, which waived the need to obtain patient consent due to the retrospective nature of the study that had no potential benefit or harm to the patients. From January 2006 to June 2016, 1,076 NSCLC patients with brain metastases were screened in Shanghai Chest Hospital, 324 of whom once received the EGFR-TKI treatment for brain metastases. Inclusion criteria were as follows: 1) patients were pathologically diagnosed with lung adenocarcinoma harboring *EGFR* mutation in exon 19 or 21; 2) brain metastases were confirmed by contrast-enhanced magnetic resonance imaging (MRI); 3) the patients had extracranial diseases including primary lung tumor and other metastases; 4) there was at least one measurable lesion for both intracranial and extracranial diseases; 5) the patients received gefitinib or erlotinib therapy following failure in prior brain irradiation with or without chemotherapy; 6) the interval from the end of brain irradiation to the start of oral TKI was at least 4 weeks; 7) no patients received a target therapy before the occurrence of brain metastases; 8) radiotherapy, interventional therapy, and other local treatments were not administered during the EGFR-TKI therapy; and 9) the patients had complete follow-up data. Thus, a total of 148 patients were eligible for assessment in this study.

Baseline characteristics of the patients were retrieved from medical records within 4 weeks before the EGFR-TKI treatment, including age, sex, smoking history, an Eastern Cooperative Oncology Group performance status (ECGO PS), recursive portioning analysis (RPA) class, number of brain metastases, initial brain symptoms, type of prior brain irradiation, prior chemotherapy, *EGFR* mutation status, and kind of EGFR-TKI.

All patients were orally given gefitinib 250 mg or erlotinib 150 mg once a day until intracranial disease progression (morphologically confirmed intracranial disease progression or the deterioration of symptomatic brain metastases clinically), death, or unacceptable toxicity. Median time from the end of brain irradiation to the beginning of EGFR-TKI intake was 4.7 months (range, 1.4–29.3 months).

Response assessment and toxicity evaluation

Radiological images (MRI for intracranial diseases and computed tomography scan for extracranial diseases) were first taken 1 month after the beginning of EGFR-TKI intake and were routinely taken every 2 months or when clinically indicated thereafter.

Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), in accordance with the standard Response Evaluation Criteria in Solid Tumors (version 1.1).[15] The objective response rate (ORR) was defined as CR plus PR. The disease control rate (DCR) was defined as the best tumor response of CR, PR, or SD.

The toxicity of EGFR-TKI was evaluated by reviewing the documented medical records at each clinical visit. All toxicities, including skin rash, diarrhea, hepatotoxicity, and radiological evidence of interstitial pneumonitis, were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE3.0).[16]

Statistical methods

The progression-free survival (PFS) was measured from the first day of EGFR-TKI intake to the documented progression within brain, or death from any cause. The overall survival (OS) was determined from the first date of EGFR-TKI intake to the date of death from any cause, or the last survival follow-up. The last follow-up date was August 30, 2016.

SPSS software version 11.0 for Windows was used for the statistical analysis. Differences among response rates were analyzed by the chi-squared test. Actuarial progression and survival curves were calculated using the Kaplan–Meier method. The impact of the potential variables affecting PFS and OS was assessed by the univariate analysis with the log-rank test. The multivariate survival analysis was performed using the Cox proportional hazard method by entering all significant variables from the univariate analysis. Statistical significance was defined as $P<0.05$.

Results

Patient characteristics

The patients' baseline characteristics are summarized in Table 1, which include median age, 55 years (range, 28–77 years); 98 females and 50 males; 109 nonsmokers and 39 former or current smokers; 72 with PS 0–1 and 76 with PS 2–3; 99 with RPA class I–II and 49 with RPA class

Table 1 Patients' characteristics

Characteristic	N	%
Age (years), Median (range)	55 (28–77)	
<65	107	72.3
≥65	41	27.7
Sex		
Female	98	66.2
Male	50	33.8
Smoking history		
Never smokers	109	73.6
Former or current smokers	39	26.4
ECGO PS		
0–1	72	48.6
2–3	76	51.4
RPA class		
I–II	99	66.9
III	49	33.1
Number of metastases		
Single	51	34.5
Multiple	97	65.5
Initial brain symptoms		
Yes	101	68.2
No	47	31.8
Prior brain irradiation		
SRS only	37	25.0
SRS + WBRT	22	14.9
WBRT only	89	60.1
Prior chemotherapy		
Yes	123	83.1
No	25	16.9
EGFR mutation		
Exon 19	88	59.5
Exon 21	60	40.5
EGFR-TKI		
Gefitinib	95	60.8
Erlotinib	53	39.2

Abbreviations: ECGO PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; RPA, recursive portioning analysis; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

III; 97 with multiple intracranial lesions and 51 with a single intracranial lesion; 101 with metastatic brain symptoms and 47 without metastatic brain symptoms; 37 pretreated with stereotactic radiosurgery (SRS) only, 22 pretreated with SRS followed by whole-brain radiation therapy (WBRT), and 89 pretreated with WBRT only; 123 with prior chemotherapy and 25 without chemotherapy; 88 with in-frame deletion mutation in exons 19 and 60 with a point mutation (L858R) in exon 21; and 95 with oral gefitinib and 53 with oral erlotinib.

Response assessment and survival data

No patient achieved CR in the study. Among them, for intracranial diseases, 54 achieved PR, 75 obtained SD, and 19 had PD, yielding an ORR of 36.5% and a DCR of 87.2%; for extracranial diseases, 62 achieved PR, 72 obtained SD, and 14 had PD, yielding an ORR of 41.9% and a DCR of 90.5% (Table 2). The median PFS and OS of the entire series were 11.2 months (95% CI, 10.1–12.3) (Figure 1) and 13.6 months (95% CI, 12.3–14.9) (Figure 2), respectively. The patients' characteristics were not statistically associated with PFS and OS.

Table 2 Response of intracranial and extracranial diseases

	Intracranial response		Extracranial response	
	n	%	n	%
CR	0	0	0	0
PR	54	36.5	62	41.9
SD	75	50.7	72	48.6
PD	19	12.8	14	9.5

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The difference in the intracranial efficacy outcomes by the two EGFR-TKIs was also analyzed. Out of the 95 patients receiving gefitinib, there were 33 PRs and 49 SDs with a DCR of 86.3% while, out of the 53 patients receiving erlotinib, there were 21 PRs and 26 SDs with a DCR of 88.7% (P=0.813). There was no statistical difference in the median PFS (11.3 vs 10.8 months, P=0.2030) and OS (13.8 vs 13.5 months, P=0.3185) between the gefitinib and the erlotinib group (Table 3).

Toxicity

In the entire series, 105 patients (70.9%) had at least one type of drug-related toxicity. Rash was the most common side

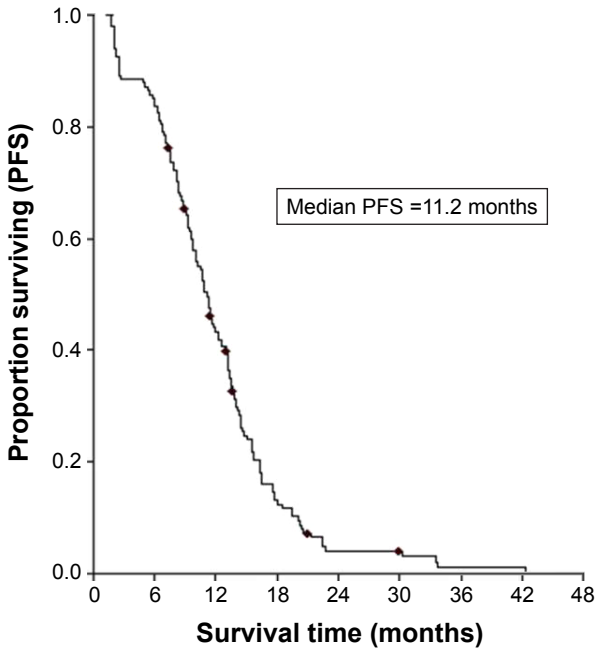

Figure 1 PFS of patients treated with EGFR-TKIs.
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival.

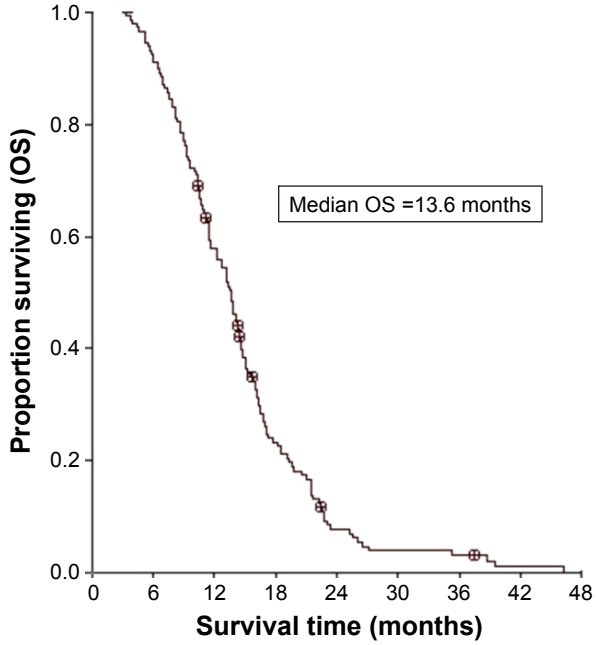

Figure 2 OS of patients treated with EGFR-TKIs.
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; OS, overall survival.

effect (62.8%), followed by diarrhea (38.5%), fatigue (27.7%), hepatotoxicity (20.9%), nausea (16.9%), and vomiting (4.7%). Most side effects were grade 1–2 and no interstitial lung disease events were encountered. Seventeen patients (11.5%) experienced grade 3–4 toxicities mainly including rash, hepatotoxicity, and diarrhea (eight with grade 3–4 rashes, six with grade 3 hepatotoxicity, and three with grade 3 diarrhea), 12 (8.1%) of whom required dose reduction (seven in the gefitinib group and five in the erlotinib group), which was sufficient to decrease the toxicity to grade 2. No patient stopped the EGFR-TKI treatment due to the side effects.

Discussion

The therapeutic efficacy of EGFR-TKI in NSCLC with activating *EGFR* mutation is now widely recognized. Recently, more interest has been shown in EGFR-TKI against brain metastases from NSCLC. However, data in this regard have mainly been limited to some individual case reports or small case series studies, in which the reported ORR (range, 69%–88%), DCR (range, 82%–100%), PFS (range, 6.6–14.5 months), and OS (range, 12.9–21.9 months) varied considerably.[17–23]

Table 3 Response of gefitinib and erlotinib against intracranial diseases and survival data

	Gefitinib		Erlotinib	
	n	%	n	%
CR	0	0	0	0
PR	33	34.7	21	39.6
SD	49	51.6	26	49.1
PD	13	13.7	6	11.3
MPFS (months)	11.3		10.8	
MOS (months)	13.8		13.5	

Abbreviations: CR, complete response; MOS, median overall survival; MPFS, median progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

In this study, ORR was 36.5% and DCR was 87.2% within the brain lesions, with a median PFS of 11.2 months and OS of 13.6 months, respectively. In contrast, the ORR of 36.5% within brain was lower than that reported by other authors while DCR, PFS, and OS were of similar magnitude to those mentioned above. The difference may be partly due to several reasons, such as the inclusion criteria of the study, the number of enrolled patients, the therapy timing in EGFR-TKI treatment lines, the examination method of *EGFR* mutation, and the patients' individual differences. Despite the relatively lower ORR within brain in this study, DCR, PFS, and OS were not inferior to previous reports. In our opinion, the emphasis of clinical evaluation of EGFR-TKI against brain lesions should be placed not only on short-term tumor response but also on long-term survival benefit. As we know, brain radiotherapy could improve the permeability of the blood brain–barrier (BBB) and help TKI cross the BBB.[24] This may be one of the reasons why the patients pretreated with brain irradiation could benefit from TKIs. Moreover, as the most important and favorable prognostic factor, the impact of activating *EGFR* mutation might have masked the influence of other variables in the statistical analysis. Thus, no significant differences in PFS and OS related to the patients' characteristics were detected in this study. Furthermore, EGFR-TKI was selected as a second- or third-line therapy for brain metastases in this study. This means that the patients lacked other effective options subsequently, in the case of disease progression after the TKI treatment. This may explain why PFS was almost the same as OS of the patients.

In addition to the EGFR-TKI efficacy within brain, the extracranial response was also evaluated in this study. The data showed that ORR and DCR in the intracranial and extracranial diseases were 36.5%, 87.2% and 41.9%, 90.5%, respectively. The efficacy of EGFR-TKI in intracranial lesions was paralleled by its efficacy in extracranial lesions, which confirms the results of some reports.[18,23] This indicates that the patients with activating *EGFR* mutation responding to EGFR-TKI within brain also responded in extracranial lesions. Unlike local therapies that induce intracranial response only, EGFR-TKI is active for both intracranial and extracranial lesions, which could definitely supplement the traditional treatment for brain metastases from NSCLC.

The tolerability of EGFR-TKI in patients with brain metastases has not been specifically addressed before. In this study, 105 patients (70.9%) experienced at least one type of drug-related toxicity, which were usually mild or moderate in intensity. Rash and diarrhea were the most common adverse events and no patient stopped the TKI therapy due to toxicity. Like those descriptions of drug-related side effects in earlier studies that excluded patients with brain metastases,[4,5,8,9] this study shows that both EGFR-TKIs are generally well tolerated in patients with brain metastases.

It might be expected that the *EGFR* mutation status would be discordant between primary tumors and brain metastases due to the heterogeneity of tumor cells.[25–28] In such a situation, the response discrepancy between intracranial and extracranial lesions may exit when EGFR-TKI is used.[29,30] It is debatable whether it is reasonable to use EGFR-TKI for brain metastases based on the *EGFR* mutation in lung tumor. In this study, all samples for the *EGFR* mutation analysis were obtained from primary lung tumors. Interestingly, the data from this study showed that the patients achieved an intracranial DCR of 87.2% with a similar extracranial DCR of 90.5% and most patients who had responses in intracranial lesions also attained responses in extracranial lesions. This finding supports the hypothesis that the *EGFR* mutation in lung tumors could be related to the EGFR-TKI response even in the presence of brain metastases.[17–23] It suggests the antitumor role of EGFR-TKI against brain metastases dependent on the *EGFR* mutation from lung tissue, while the *EGFR* status in brain lesions is not determined. In fact, considering that surgical resection on metastatic brain tumors can only be indicated for a limited number of patients,[31–33] it is impossible to get brain tumor tissues for the *EGFR* mutation analysis in most cases. In our view, it may be feasible in a clinical setting that the *EGFR* mutation status in lung tumor could be regarded as an indicator for EGFR-TKI against brain metastases. Of course, the relationship between *EGFR* mutation status of primary NSCLC and that of matched brain metastases should be further explored.

Gefitinib and erlotinib are the two frequently used EGFR-TKIs in the treatment for NSCLC. In a recently published randomized phase II study of gefitinib versus erlotinib in locally advanced, metastatic NSCLC patients following failure in previous first-line chemotherapy, both drugs demonstrated a comparable clinical activity with no significant difference in the response rate or PFS, and an acceptable safety profile.[34] It is of interest to compare the obtained results of gefitinib with those of erlotinib against brain metastases. In this study, there was no statistical difference in terms of ORR, DCR, PFS, and OS between the gefitinib and the erlotinib group. Moreover, a non-significant trend toward more severe skin toxicity and hepatotoxicity in patients treated with gefitinib or erlotinib was observed. As a result, it cannot be identified which TKI is superior or inferior, which is similar to some isolated reports.[18,35,36] Overall, the lack of clinical data available for distinct patient populations limited the conclusions of the assessment.

The major limitations of this study were its retrospective, nonrandomized design and single-institution study population. Although the efficacy and safety data from this study are promising, it is wise to take into consideration the limitations of this study when interpreting the results.

In conclusion, the results of this study suggest that EGFR-TKIs show a promising antitumor activity in treating brain metastases from NSCLC harboring activating *EGFR* mutations with an acceptable safety profile, meaning the EGFR-TKI therapy can be a novel option in this group of patients. Further randomized and prospective trials are warranted to validate the findings.

Author contribution

All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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