

Continued gefitinib retreatment beyond progression in patients with advanced non-small cell lung cancer harboring sensitive *EGFR* mutations

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Abstract

Purpose: To evaluate the effectiveness and safety of gefitinib retreatment beyond disease progression in patients with advanced non-small cell lung cancer (NSCLC) with sensitive epidermal growth factor receptor (*EGFR*) mutations.

Methods: Data from patients with stage III/IV NSCLC were analyzed retrospectively. Patients with sensitive *EGFR* mutations received first-line treatment with gefitinib followed by retreatment with gefitinib after disease progression. Progression-free survival (PFS) after the first treatment (PFS-1) was defined as the time to progression or death using the Response Evaluation Criteria in Solid Tumors criteria (RECIST) v1.1 criteria. The second PFS (PFS-2) was defined as the interval between the first and second progressions, at the investigator's discretion. Toxicities were recorded in accordance with the National Cancer Institute (NCI)-Common Terminology Criteria (CTC) version 4.0.

Results: Sixteen patients aged 53 to 80 years (median 66 years) were included in the analysis. The median PFS-1 and PFS-2 were 10.0 months and 14.0 months, respectively. The median overall survival (OS) was 36.0 months. No toxicity of grade 3 or worse was observed.

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Conclusions: Our findings suggest that gefitinib retreatment beyond disease progression may be an effective and tolerable approach for NSCLC patients with sensitive *EGFR* mutations.

Keywords

Non-small cell lung cancer, gefitinib, retreatment, epidermal growth factor receptor, progression, mutation

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Introduction

Lung cancer is the leading cause of cancer-related death and continues to present a serious threat to public health.¹ Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and patients with sensitive epidermal growth factor receptor (*EGFR*) mutations can be treated effectively with tyrosine kinase inhibitors (TKIs), such as gefitinib.² However, resistance to TKIs inevitably occurs because of mechanisms such as T790M mutation and *MET* amplification.³ We previously^{4,5} showed that TKI retreatment beyond progression (TBP) could help to achieve long-term survival in selected patients. However, other studies^{6,7} have failed to support TBP, and its use thus remains controversial and the optimal therapeutic schedule for TBP remains undetermined. We, therefore, conducted a retrospective study to evaluate the effectiveness and safety of gefitinib retreatment in patients with NSCLC.

Patients and methods

Patients

This study was approved by the Ethics Committee of the People's Hospital of Bishan District, Chongqing, China, in 2014. After the patients provided informed consent, we retrospectively analyzed

patients with stage III/IV NSCLC with *EGFR* sensitive mutations treated with gefitinib at the People's Hospital of Bishan District of Chongqing City from August 2013 to November 2015. The inclusion criteria were as follows: histologically confirmed NSCLC; tumor biopsy tested for *EGFR* mutation; first-line treatment with oral gefitinib (250 mg/day); and first progression-free survival time (PFS-1) >3 months. We excluded patients who received chemotherapy alone or as combination therapy; however, radiotherapy for isolated lesions was permitted. After the first disease progression, which was defined in accordance with the Response Evaluation Criteria in Solid Tumors criteria (RECIST 1.1 version), retreatment with oral gefitinib 250 mg/day (TBP) was administered until a second progression, which was defined at the clinician's discretion. The patient's baseline characteristics (TNM stage, location, histopathology, genotype) were noted.

Follow-up

Follow-up was performed on a clinical basis, including head/chest/abdominal computed tomography (CT) and assessment of tumor biomarkers every 2 months for the first year and every 3 months thereafter. Follow-up data were updated in November 2015.

Effect and toxicity evaluation

The effect was evaluated 1 month after gefitinib treatment based on head/chest/abdominal CT and/or tumor biomarkers. Overall survival (OS) was calculated from the date of gefitinib initiation until the date of death or the date of last follow-up. The time to first progression-free survival (PFS-1) was defined in accordance with RECIST 1.1, and it was estimated from the date of gefitinib initiation to the time of RECIST failure; the time to second progression-free survival (PFS-2) was defined as the time interval between the first and second progressions, which was estimated from the date of gefitinib retreatment beyond RECIST progression to the date of death or last follow-up or second failure, based on the clinician's discretion. For survival calculations, patients who were alive at the end of the study period, who died from other causes, or who were lost to follow-up were censored. Treatment-related toxicities were recorded in accordance with the National Cancer Institute (NCI)-Common Terminology Criteria (CTC) version 4.0.

Statistical analysis

Survival curves were generated using the Kaplan–Meier method. Statistical analysis was performed using SPSS Statistics for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Sixteen patients were included in the analysis (Table 1). Most patients had adenocarcinoma. The most frequent sensitive mutations were 19DEL and L858R, and other mutations included L861Q and G719X. The median follow-up period was 24.0 months. All patients completed gefitinib treatment and retreatment. Five patients

Table 1. Clinical characteristics of the patients (n = 16).

Characteristic	Number of patients (%)
Age, years	
Median (range)	66 (53–80)
<65	7 (43.8)
≥65	9 (56.3)
Sex	
Male	7 (43.8)
Female	9 (56.3)
Location	
Left	6 (37.5)
Right	10 (62.5)
Pathology type	
Adenocarcinoma	14 (87.5)
Squamous cell carcinoma	1 (6.3)
Adenosquamous cell carcinoma	1 (6.3)
Clinical stage	
III	4 (25)
IV	12 (75)
Genotype	
L858R	6 (37.5)
19DEL	7 (43.8)
Other	3 (18.8)

(31.3%) also received radiotherapy for isolated lesions located in the lungs during the period of gefitinib retreatment.

Responses to gefitinib treatment

All patients were assessed for response to initial gefitinib treatment (Figure 1). Three patients (18.8%) showed complete response, 10 (62.5%) showed partial response, and three (18.8%) had stable disease. None experienced progressive disease. The overall response rate was 81%.

Follow-up

Follow-up was continued until November 2015. No patients were lost to follow-up. The 1- and 2-year OS rates were 100% and 75%, respectively. The median PFS-1 (Figure 2) was 10.0 (95% confidence interval [CI]: 6.1–13.9 months) and median PFS-2

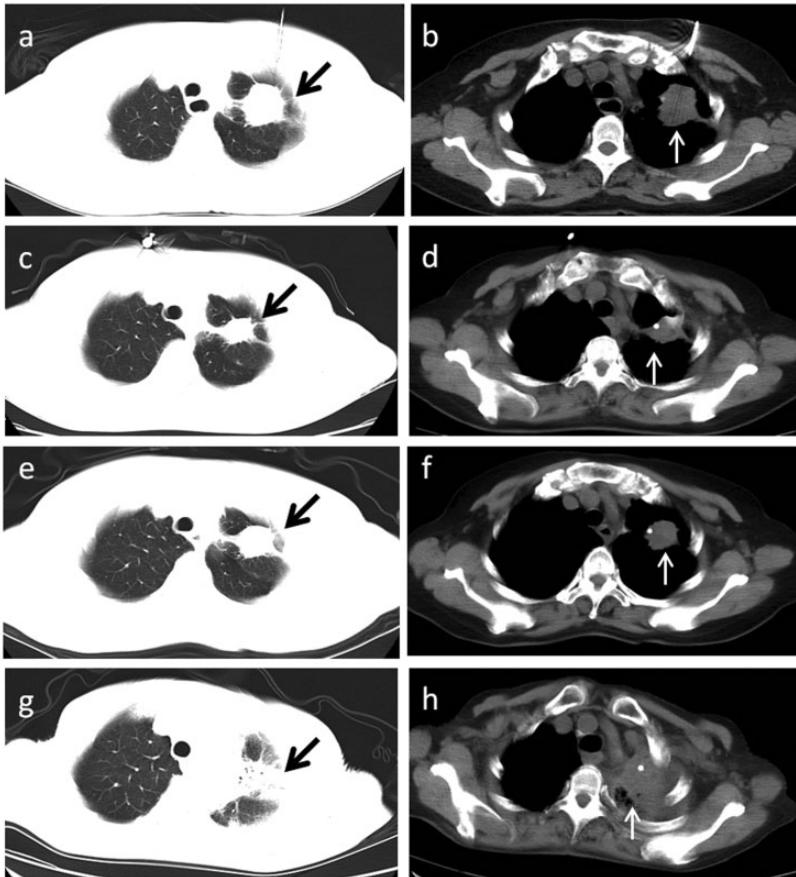


Figure 1. Representative computed tomography images with lung and mediastinal windows in a patient receiving gefitinib treatment and retreatment. A mass (arrow) in the upper-left lung (a, b) shrank following initial gefitinib treatment (c, d). It then enlarged again and the patient received gefitinib retreatment (e, f), after which it expanded slowly and remained well controlled (g, h).

(Figure 3) was 14.0 (95% CI: 8.8–19.2 months). Notably, after initial gefitinib failure, most patients (93.8%, 15/16) were diagnosed with local progression by CT-based evaluation (Figure 1). Only one patient had pleural effusion and a worse PFS-2 of 3.5 months. The median OS time was 36.0 months (95% CI: 17.3–54.7 months) (Figure 4).

Treatment-related toxicities

All the patients were evaluated for treatment-related toxicities. The side effects of gefitinib treatment and retreatment were

fatigue, diarrhea, rash, itching, and elevated transaminases, with rash being the most common toxicity, observed in 12 (75%) patients. Although these side effects were typically present, there were no toxicities of grade 3 or worse and no treatment-related deaths. Thus, gefitinib treatment and retreatment were shown to be tolerable.

Discussion

TBP is a potential therapeutic salvage treatment following initial TKI failure.^{4,5} In the

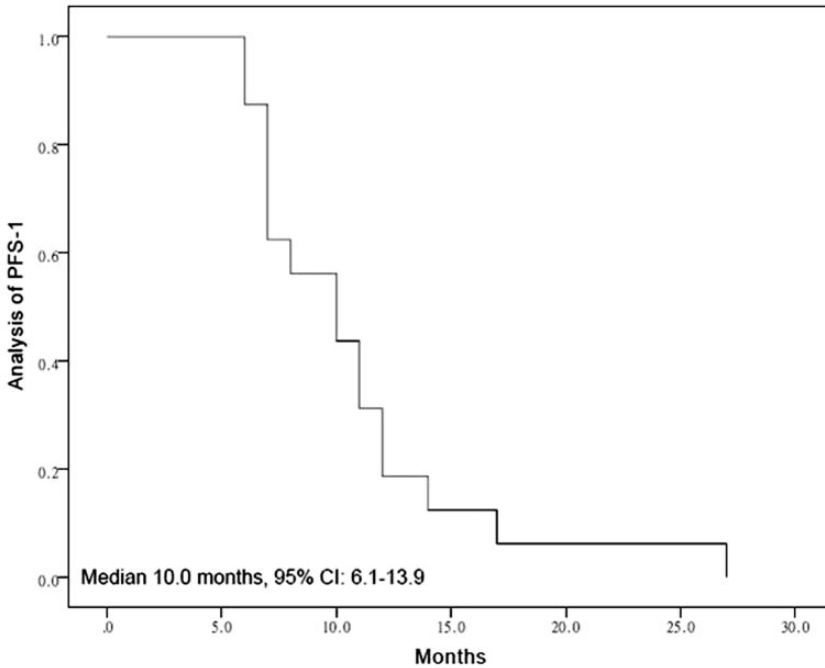


Figure 2. First progression-free survival (PFS-1) in patients with non-small cell lung cancer treated with gefitinib.
CI, confidence interval.

current study, we retrospectively analyzed 16 patients with advanced NSCLC and sensitive *EGFR* mutations who received TBP after the failure of first-line *EGFR*-TKI therapy. Adenocarcinoma (87.5%) was the dominant pathological type, and the most frequent genotypes were 19DEL (47.8%) and 21 exon L858R (37.5%). PFS following TKI retreatment has been reported to be positively correlated with the response to initial *EGFR*-TKI.⁸ The present study found a slightly better response to initial TKI treatment to previous reports,² with an overall response rate of 81%. TKI retreatment, thus, resulted in favorable outcomes. In our study, the 1- and 2-year OS rates were 100% and 75%, respectively, and the median PFS-2 was 14.0 months. However, the PFS-2 was worse in one patient with pleural effusion, suggesting that TBP should be administered with

caution in patients with complications such as pleural metastasis and effusion. In another study,⁹ “PFS-2” was defined as the time from first gefitinib dose to off-gefitinib progression, which was similar to PFS-1 plus PFS-2 in our study. Their median “PFS-2” of 27.7 months (95% CI, 21.6–33.9) was higher than the 24.0 months in the current study (PFS-1+PFS-2). This might have been due to the limited number of patients in the present study, which was only about one-third the number in the previous study. Despite the failure of the initial TKI treatment, cancer cell sensitivity to TKIs may not be lost, and TBP may, thus, still be able to control the disease.⁹ However, it has also been suggested that a long time interval after failure of initial TKI treatment is needed to restore *EGFR* sensitivity.¹⁰ In the current study, all the patients switched to gefitinib

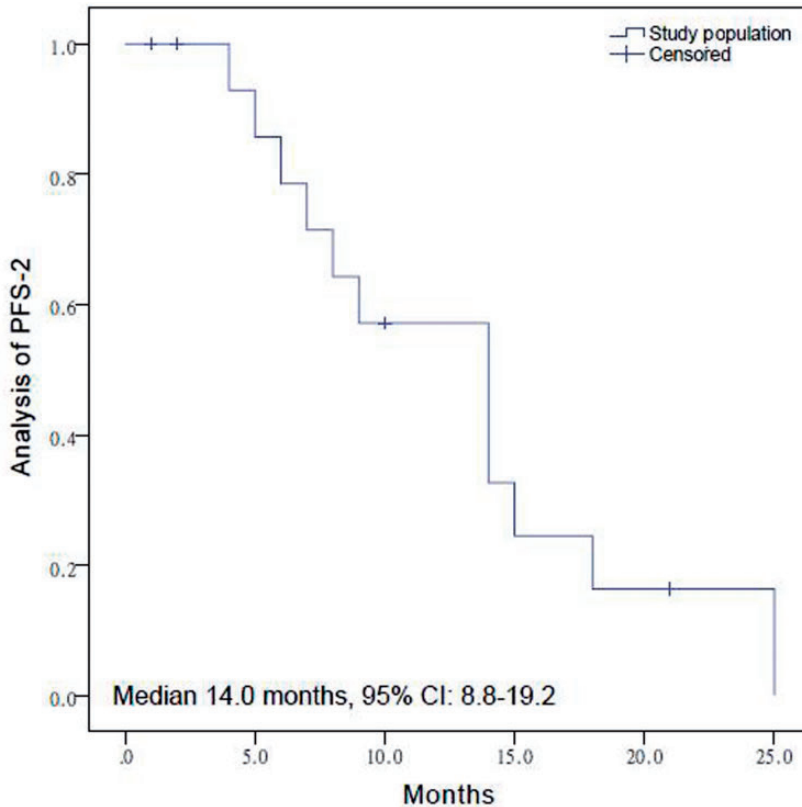


Figure 3. Second progression-free survival (PFS-2) in patients with non-small cell lung cancer treated with gefitinib.
CI, confidence interval.

retreatment alone with no intervening drug holiday, and the results still indicated that gefitinib retreatment might be safe and effective for controlling NSCLC after failure of first-line TKI treatment. NSCLC patients with the L858R *EGFR* mutation are less sensitive to EGFR-TKIs than patients with exon 19 deletion. However, the current study found no significant difference in response to initial treatment or TBP in relation to these genotypes.

Most recent studies have focused on the latest drugs and have ignored or underrated the benefits of reusing older ones. Third-generation EGFR-TKIs, such as osimertinib, have been reported to prolong median

PFS (mPFS) and OS (mOS) better than gefitinib/erlotinib (PFS: 18.9 vs. 10.2 months, OS: 38.6 vs. 31.8 months).¹¹ Moreover, the NEJ009 study¹² found that mPFS in patients receiving gefitinib plus chemotherapy was 20.0 months, which was similar to the 24.0 months (PFS-1+PFS-2) in the current study; this suggests that the benefit of gefitinib alone is equal to that of gefitinib plus chemotherapy. However, the mOS in their study was 52.0 months, which was higher than our mOS of 36.0 months. Overall, the present study found total mPFS and mOS times of 24.0 and 36.0 months, respectively, in patients who were treated with gefitinib, suggesting

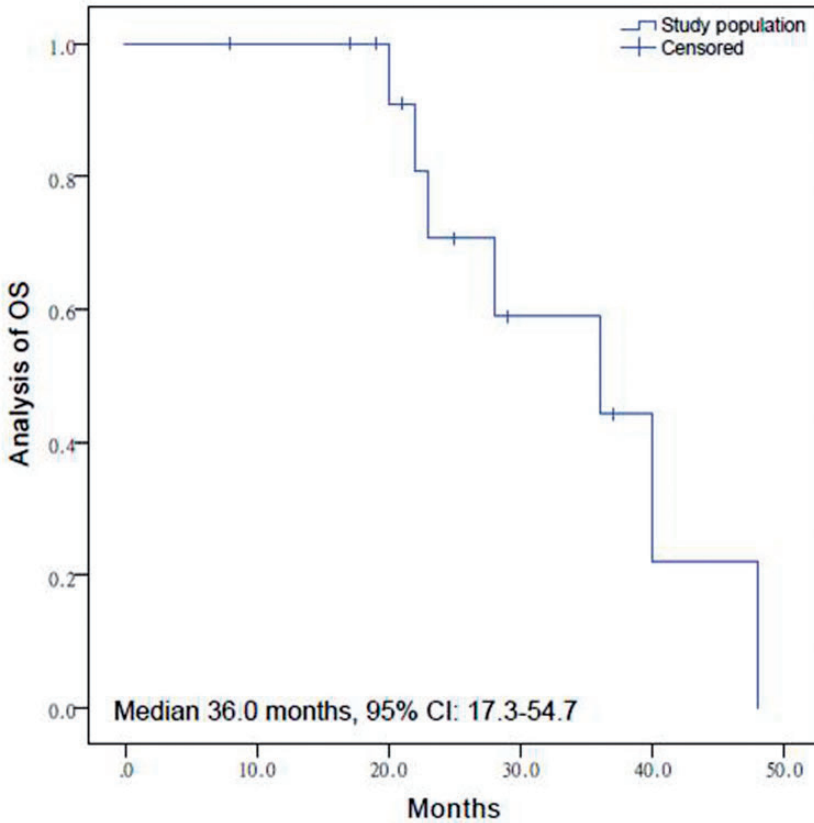


Figure 4. Overall survival (OS) in patients with non-small cell lung cancer treated with gefitinib. CI, confidence interval.

that initial gefitinib treatment plus TBP might contribute to long-term survival in selected patients.

This study had some limitations, including the small sample size, retrospective study design, and lack of investigation of the molecular mechanism of TKI resistance. Further prospective research is planned to address these questions.

Conclusion

The results of this study indicate that continued gefitinib retreatment beyond disease progression may produce favorable clinical outcomes in selected NSCLC patients, which suggests that it may be an alternative

treatment choice after failure of initial TKI treatment in patients with NSCLC who have sensitive *EGFR* mutations.

Author contributions

ZW and LS conceived the study, XJ and XL drafted the manuscript, and all other authors participated in its experimentation and revision of the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.


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Previous publication

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