Clinical Impact of Switching to a Second EGFR-TKI After a Severe AE Related to a First EGFR-TKI in EGFR-mutated NSCLC

Masayuki Takeda1, Isamu Okamoto1,*, Junji Tsurutani1, Naoki Oiso2, Akira Kawada2 and Kazuhiko Nakagawa1

1Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka and 2Department of Dermatology, Kinki University Faculty of Medicine, Osaka, Japan

*For reprints and all correspondence: Isamu Okamoto, Department of Medical Oncology, Kinki University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. E-mail: chi-okamoto@dotd.med.kindai.ac.jp

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Objective: Somatic mutations in the epidermal growth factor receptor gene are associated with a therapeutic response to epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib and erlotinib in patients with non-small cell lung cancer. Although the safety profile of these drugs is favorable, a small proportion of patients with EGFR mutation-positive non-small cell lung cancer must discontinue treatment because of adverse events such as interstitial lung disease and hepatotoxicity. Subsequent chemotherapy has not been optimized in such patients.

Methods: We performed a retrospective analysis of EGFR mutation-positive non-small cell lung cancer patients who received both gefitinib and erlotinib at our institution. Patients received the second epidermal growth factor receptor-tyrosine kinase inhibitor after experiencing an adverse event or progressive disease on the first epidermal growth factor receptor-tyrosine kinase inhibitor.

Results: We identified 14 patients who received both gefitinib and erlotinib in the course of their treatment. Three patients initially treated with gefitinib and two with erlotinib discontinued epidermal growth factor receptor-tyrosine kinase inhibitor therapy because of severe non-hematologic toxicity (one because of gefitinib-induced interstitial lung disease, one because of erlotinib-induced lupus erythematosus-like eruption and three because of hepatotoxicity). All five of these patients were able successfully to continue therapy with the second epidermal growth factor receptor-tyrosine kinase inhibitor with no evidence of a recurrent adverse event. Progression-free survival was significantly longer in these five patients than in the nine patients who discontinued treatment with the first epidermal growth factor receptor-tyrosine kinase inhibitor because of disease progression.

Conclusions: EGFR mutation-positive non-small cell lung cancer patients who discontinue treatment with a first epidermal growth factor receptor-tyrosine kinase inhibitor because of an adverse event benefit substantially from switching to a second epidermal growth factor receptor-tyrosine kinase inhibitor before the development of drug resistance.

Key words: non-small cell lung cancer – epidermal growth factor receptor – tyrosine kinase inhibitor – adverse events

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INTRODUCTION

Targeted therapies are undergoing active development as a means to improve treatment efficacy in selected patient populations. Small-molecule tyrosine kinase inhibitors (TKIs) that target the epidermal growth factor receptor (EGFR), such as gefitinib and erlotinib, are the first targeted drugs to enter the clinical use for the treatment of non-small cell lung cancer (NSCLC). Somatic mutations in the EGFR gene are associated with the therapeutic response to EGFR-TKIs in patients with advanced NSCLC. Indeed, retrospective and prospective trials have confirmed that the response rate to gefitinib or erlotinib in patients with EGFR mutations is ~70–80% (1,2). Moreover, recently completed randomized Phase III studies showed that first-line gefitinib treatment resulted in an improved progression-free survival (PFS) compared with standard chemotherapy in patients with advanced NSCLC who were selected on the basis of the presence of EGFR mutations (3,4), suggesting that more patients with EGFR mutation-positive tumors will now receive EGFR-TKIs.

Erlotinib and gefitinib share the same mechanism of action and exhibit highly similar side effect profiles, and a rule for drug selection between the two EGFR-TKIs has not been established. In the case of EGFR mutation-positive NSCLC, a study found no clinical evidence for the efficacy of erlotinib after disease progression on gefitinib (5), but the role for administration of a second EGFR-TKI after failure of treatment with a first such drug in EGFR mutation-positive patients warrants further investigation. EGFR-TKIs are generally well tolerated, with skin rash and diarrhea being the most common adverse events (AEs) of treatment. However, a small proportion (up to 14%) of NSCLC patients with EGFR mutations discontinue EGFR-TKI treatment as a result of more serious AEs such as interstitial lung disease (ILD) or hepatotoxicity (6–10). Moreover, subsequent chemotherapy has not been optimized in such patients. It would therefore be desirable if there were a role for treatment with a second EGFR-TKI after discontinuation of a first such drug as a result of a drug-related AE. We have now performed a retrospective study of the primary objective of assessing the efficacy of a second EGFR-TKI after failure of treatment with a first EGFR-TKI because of the development of a drug-related AE.

PATIENTS AND METHODS

Patients

All lung cancer patients diagnosed at Kinki University Hospital between September 2002 and April 2010 were reviewed. Criteria for the use of a patient’s data included signed informed consent for EGFR mutation analysis, a diagnosis of Stage IIIb or IV or recurrent NSCLC with a proven EGFR mutation, and exposure to both gefitinib and erlotinib. Gefitinib at an initial dose of 250 mg/day or erlotinib at a starting dose of 150 mg/day also must have been given as the first EGFR-TKI therapy. Treatment response was determined on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All toxicities were graded according to National Cancer Institute common toxicity (NCI-CTC) criteria (v4.0). The institutional review board approved our study protocol with the condition that the study be disclosed publicly, according to the Ethical Guidelines for Human Genome Research published by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labor and Welfare, and the Ministry of Economy, Trade and Industry of Japan.

EGFR Mutation Analysis

EGFR mutations that confer sensitivity to EGFR-TKIs were identified either by the Scorpion Amplified Refractory Mutation System (ARMS) method, by the PCR-Invader method (BML, Tokyo, Japan) or by the peptide nucleic acid–locked nucleic acid polymerase chain reaction clamp method (Mitsubishi Chemical Medience, Tokyo, Japan).

Statistical Analysis

Time to treatment failure was assessed from the first day of EGFR-TKI administration to the day of objective disease progression, death or withdrawal of treatment because of an AE. PFS was calculated from the date of EGFR-TKI treatment onset to that of radiographic tumor progression or death. Patients without documented disease progression at the time of the final analysis were evaluated on the basis of the date they were last known to be alive or of their last objective tumor assessment. The probability of survival as a function of time was estimated with the Kaplan–Meier method.

RESULTS

Patient Characteristics

Fifty-five patients with NSCLC who harbored EGFR mutations were treated with EGFR-TKIs during the study period. Five (9%) of the 55 patients discontinued EGFR-TKI therapy because of treatment-related AEs, and all five of these individuals subsequently received a second EGFR-TKI. The remaining 50 patients continued EGFR-TKI treatment until disease progression without discontinuation for unacceptable toxicity. Nine of these 50 individuals subsequently received a second EGFR-TKI based on the attending physician’s decisions. We thus identified 14 EGFR mutation-positive patients who received both gefitinib and erlotinib in the course of their treatment. The patient characteristics and clinical outcome of those 14 patients are summarized in Table 1. Among 14 patients who discontinued first EGFR-TKI therapy, none of the patients except Patient 3 had interruption and resume of first EGFR-TKI administration. In the remaining 41 patients, none had interruption and resume of first EGFR-TKI administration.
Clinical impact of switching to a second EGFR-TKI

A brief description of the five patients for whom an EGFR-TKI-related AE led to discontinuation of the treatment follows.

Patient 1 was treated with gefitinib (250 mg/day) as a second-line chemotherapy. After 3 weeks of gefitinib treatment, a chest computed tomography scan revealed extensive bilateral ground-glass opacities throughout both lungs, consistent with a diagnosis of gefitinib-induced Grade 4 ILD (Fig. 1). Discontinuation of gefitinib and initiation of high-dose methylprednisolone treatment resulted in improvement in the chest radiological findings. Four months after discontinuation of gefitinib, the patient received erlotinib (150 mg daily) and the patient continued this treatment for 4.4 months until disease progression with no recurrence of ILD.

Patients 2 and 3 received gefitinib (250 mg daily) as a first-line therapy. Their serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased up to 599 U/l (Grade 3) and 519 U/l (Grade 3) in Patient 2, and 226 U/l (Grade 3) and 1035 U/l (Grade 4) for ALT, and erlotinib was permanently discontinued. Treatment with gefitinib (250 mg/day) was started 16.7 months after the withdrawal of erlotinib, and the patient continued this treatment for 4.4 months until disease progression with no evidence of recurrent hepatic toxicity.

Finally, Patient 5 received erlotinib (150 mg daily) as a third-line therapy. After 2 weeks of erlotinib treatment, she manifested fever, multiple erythematous patches over her upper chest and upper limbs, and prominent butterfly-shaped plaque erythema over her malar eminences that was categorized as lupus erythematosus-like eruption (Grade 3). A skin biopsy specimen from the upper chest revealed superficial perivascular dermatitis with a vacuolar change consistent with a diagnosis of Grade 4 ILD.

Table 1. Characteristics and clinical course of EGFR mutation-positive non-small cell lung cancer patients receiving both gefitinib and erlotinib

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Histology</th>
<th>TKI sequence (lines of treatment)</th>
<th>EGFR mutation</th>
<th>Reasons for discontinuation (AEs are graded according to the CTCAE v4.0)</th>
<th>Best response to 1st TKI</th>
<th>TTF of 1st TKI (months)</th>
<th>Interval between TKIs (months)</th>
<th>Best response to 2nd TKI</th>
<th>PFS for 2nd TKI (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>62</td>
<td>Ad</td>
<td>G (2) → E (3)</td>
<td>E19del</td>
<td>ILD (Gr. 4)</td>
<td>NE</td>
<td>0.8</td>
<td>4.0</td>
<td>SD</td>
<td>2.5</td>
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<tr>
<td>2</td>
<td>F</td>
<td>66</td>
<td>Ad</td>
<td>G (1) → E (2)</td>
<td>E19del</td>
<td>Hepatotoxicity (Gr. 4)</td>
<td>PR</td>
<td>7.5</td>
<td>1.6</td>
<td>PR</td>
<td>11.7</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>63</td>
<td>Ad</td>
<td>G (1) → E (2)</td>
<td>L858R</td>
<td>Hepatotoxicity (Gr. 3)</td>
<td>SD</td>
<td>13.4</td>
<td>0.9</td>
<td>SD</td>
<td>4.2*</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>53</td>
<td>Ad</td>
<td>E (2) → G (4)</td>
<td>E19del</td>
<td>Hepatotoxicity (Gr. 4)</td>
<td>NE</td>
<td>1.4</td>
<td>16.7</td>
<td>SD</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>71</td>
<td>Ad</td>
<td>E (4) → G (5)</td>
<td>L858R</td>
<td>Atypical rash (Gr. 3)</td>
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<td>0.5</td>
<td>0.2</td>
<td>PR</td>
<td>10.0*</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>61</td>
<td>Ad</td>
<td>G (2) → E (3)</td>
<td>L858R</td>
<td>PD</td>
<td>CR</td>
<td>68.9</td>
<td>0.0</td>
<td>SD</td>
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<td>7</td>
<td>F</td>
<td>76</td>
<td>Ad</td>
<td>G (2) → E (7)</td>
<td>E19del</td>
<td>PD</td>
<td>PR</td>
<td>16.1</td>
<td>45.0</td>
<td>PD</td>
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<tr>
<td>8</td>
<td>F</td>
<td>70</td>
<td>Ad</td>
<td>G (1) → E (2)</td>
<td>L858R</td>
<td>PD</td>
<td>PR</td>
<td>20.4</td>
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<td>9</td>
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<td>Ad</td>
<td>G (1) → E (2)</td>
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<td>PD</td>
<td>PR</td>
<td>15.6</td>
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<tr>
<td>10</td>
<td>F</td>
<td>58</td>
<td>Ad</td>
<td>G (2) → E (3)</td>
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<td>0.0</td>
<td>SD</td>
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<td>11</td>
<td>F</td>
<td>71</td>
<td>Ad</td>
<td>G (1) → E (2)</td>
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<td>PD</td>
<td>NE</td>
<td>2.4</td>
<td>0.0</td>
<td>PD</td>
<td>1.1</td>
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<tr>
<td>12</td>
<td>F</td>
<td>71</td>
<td>Ad</td>
<td>G (3) → E (5)</td>
<td>L858R</td>
<td>PD</td>
<td>PR</td>
<td>8.2</td>
<td>12.4</td>
<td>SD</td>
<td>4.0</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>61</td>
<td>AdSq</td>
<td>G (1) → E (2)</td>
<td>L858R</td>
<td>PD</td>
<td>SD</td>
<td>5.3</td>
<td>2.9</td>
<td>PD</td>
<td>2.2</td>
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<tr>
<td>14</td>
<td>M</td>
<td>63</td>
<td>Ad</td>
<td>E (4) → G (5)</td>
<td>E19del</td>
<td>PD</td>
<td>PR</td>
<td>14.0</td>
<td>0.8</td>
<td>PD</td>
<td>1.5</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor gene; TKI, tyrosine kinase inhibitor; AEs, adverse events; TTF, time to treatment failure; PFS, progression-free survival; Ad, adenocarcinoma; G, gefitinib; E, erlotinib; E19del, exon-19 deletion; ILD, interstitial lung disease; Gr., grade; NE, not evaluable; SD, stable disease; PR, partial response; PD, progressive disease; CR, complete response; AdSq, adenosquamous cell carcinoma.

*Patients have continued the second EGFR-TKI, and latest follow-up data were collected on 1 August 2011.
*Patient 4 received erlotinib followed by docetaxel.
*Patient 7 received several systemic chemotherapy regimens, including docetaxel, gefitinib, gemcitabine, S-1, gefitinib rechallenge, gemcitabine rechallenge and erlotinib.
*Patient 12 received gefitinib followed by docetaxel.
with interface dermatitis, including erythema multiforme, toxic epidermal necrolysis, fixed drug eruption, lupus erythematosus or graft-versus-host disease. A drug lymphocyte stimulation test yielded a strong positive result for erlotinib, suggesting that the atypical rashes were attributable to an allergic reaction to erlotinib rather than to dose-dependent toxicity. Erlotinib treatment was immediately discontinued, and the skin lesions resolved within 1 week with the application of topical corticosteroids. The patient was started on treatment with gefitinib (250 mg daily), which she has continued for 10.0 months with no evidence of disease progression or recurrent skin toxicity at her last follow-up.

SAFETY AND Efficacy OF Treatment WITH A Second EGFR-TKI

Responses could be evaluated in all 14 patients who received a second EGFR-TKI after the failure of treatment with the first EGFR-TKI (Table 1). No patient discontinued treatment with the second EGFR-TKI as the result of a drug-related AE. All five patients who discontinued treatment with the first EGFR-TKI because of an AE (AE group) achieved disease control [two with a partial response (PR) and three with stable disease (SD)] with the second EGFR-TKI. Of the nine patients who discontinued the first EGFR-TKI because of disease progression (PD group), none achieved a PR and four individuals had SD after treatment with the second EGFR-TKI. The Kaplan–Meier curves for PFS are shown in Fig. 2. The median PFS after the onset of treatment with the second EGFR-TKI was 11.7 and 2.0 months in the AE group and in the PD group, respectively (Fig. 2).

DISCUSSION

Mutations of EGFR have been identified in tumor specimens from patients with NSCLC who respond to EGFR-TKI treatment. Several prospective studies of EGFR-TKI treatment in EGFR mutation-positive NSCLC patients have revealed that reasons for discontinuation of such treatment include non-hematologic AEs such as ILD and hepatitis, with the frequency of treatment withdrawal as a result of these events being 0–14% (6–10). However, subsequent chemotherapy has not been optimized for EGFR mutation-positive patients who discontinue EGFR-TKI treatment because of AEs, and limited information exists with regard to the long-term efficacy and safety of treatment with a second EGFR-TKI in such patients. In the present study, among 55 EGFR mutation-positive NSCLC patients who had received EGFR-TKIs, 5 individuals (9%) discontinued initial EGFR-TKI treatment as a result of the development of non-hematologic AEs, with the precise reasons for treatment discontinuation being similar to those described in previous studies. All five patients who discontinued treatment with the first EGFR-TKI because of drug-related toxicity were able to continue treatment with a second EGFR-TKI with no evidence of recurrent AEs.

The toxicity profile of erlotinib is highly similar to that of gefitinib, with acneiform rash and diarrhea being the most common side effects (11,12). These side effects are typically mild to moderate, easily managed and reversible. However,
previous studies have shown that ILD and hepatotoxicity are the major causes of permanent discontinuation of gefitinib treatment for patients harboring EGFR mutations (6–10). We have now shown that erlotinib is an effective and well-tolerated treatment option for EGFR mutation-positive NSCLC patients for whom gefitinib has been discontinued because of severe gefitinib-induced hepatotoxicity. We also found that it was safe to administer gefitinib after discontinuation of erlotinib because of drug-related hepatotoxicity, although no studies have described the safety and efficacy of gefitinib treatment after discontinuation of erlotinib. Erlotinib and gefitinib share a common chemical backbone including a 4-anilinoquinazoline base structure, but they differ in the substituents attached to the quinazoline and anilino rings. Minor differences in the chemical structures of these compounds may thus influence their associated AEs. There have been case reports of successful rechallenge with erlotinib after the development of gefitinib-induced ILD (13). Consistent with these cases, we were able to successfully manage patients who had previously developed gefitinib-induced ILD with a full dose of erlotinib. Given that EGFR-TKI-induced ILD has a high associated mortality, we cannot recommend the routine use of second EGFR-TKI in this setting.

A previous study of erlotinib administration after failure of gefitinib treatment in EGFR mutation-positive NSCLC patients found that most patients did not exhibit a radiographic response (5). Our data also show that none of the patients who discontinued treatment with the first EGFR-TKI because of disease progression achieved an objective tumor response to the second EGFR-TKI, with the median PFS after the onset of treatment with the second EGFR-TKI for these patients being only 2.0 months. These findings are consistent with preclinical data showing that the growth of EGFR mutation-positive NSCLC cells with a secondary T790M mutation of EGFR or with MET amplification, the two most common mechanisms of EGFR-TKI resistance, is not inhibited in vitro by clinically achievable concentrations of gefitinib or erlotinib (14–17). Together, these observations thus do not support the routine use of a second EGFR-TKI after disease progression during treatment with a first EGFR-TKI in EGFR mutation-positive NSCLC patients. In contrast, patients who discontinue treatment with a first EGFR-TKI because of a severe AE would still be expected to benefit substantially from ‘switching’ to a second EGFR-TKI before the development of resistance, assuming that such patients continue to receive the second EGFR-TKI with no evidence of recurrent toxicity. Although the number of patients with available data is small in the present study, the median PFS of 11.7 months after the onset of treatment with the second EGFR-TKI in the AE group would be considered promising.

In conclusion, treatment with a second EGFR-TKI is an effective and well-tolerated option for EGFR mutation-positive NSCLC patients for whom treatment with a first EGFR-TKI has been discontinued because of the development of a severe AE. Our results of this retrospective study are limited by the small sample at single institution. Therefore, further evidence from large cohort studies is warranted. Given the remaining potential for the development of adverse reactions, we suggest that a careful assessment of clinical symptoms and radiographic findings as well as informed consent are warranted in this setting.

Conflict of interest statement
Isamu Okamoto and Kazuhiro Nakagawa received honoraria from Chugai pharmaceuticals and AstraZeneca.

References

