Three Cases of Long-Lasting Tumor Control with Erlotinib after Progression with Gefitinib in Advanced Non-Small Cell Lung Cancer

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Introduction: We report the cases of three patients with advanced non-small cell lung cancer responding to erlotinib after progression under gefitinib treatment.

Methods: Three never-smoker women with advanced lung adenocarcinoma, two pretreated with chemotherapy and with gefitinib and one with gefitinib alone, received erlotinib in a daily dose of 150 mg. All three patients had disease progression and had achieved tumor control with gefitinib.

Results: The first patient achieved partial response of lung lesions, the second had partial response of brain lesions and stable disease of lung and bone disease, and the third had partial response of brain lesions and stable disease of lung disease. At the time of this analysis, all three patients were still receiving treatment with erlotinib with no evidence of treatment failure after more than 13, 13, and 7 months, respectively. Erlotinib was generally well tolerated, with grade 1 skin toxicity recorded in two patients.

Conclusions: Erlotinib may be effective in patients with non-small cell lung cancer who were previously and successfully treated with gefitinib. However, careful selection of these patients is needed.

Key Words: Erlotinib, Gefitinib, Non-small cell lung cancer.

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The epidermal growth factor receptor (EGFR) is a transmembrane receptor found primarily on cells of epithelial origin. Autophosphorilation of its intracellular domain initiates a cascade of events leading to cell proliferation. EGFR is commonly expressed at a high level in a variety of solid tumors, and it has been implicated in the control of cell survival, proliferation, metastasis, and angiogenesis.[1] Gefitinib and erlotinib are two orally available EGFR tyrosine kinase inhibitors (EGFR-TKIs). Two large phase II trials of gefitinib monotherapy have been conducted among patients with advanced non-small cell lung cancer (NSCLC) that progressed after one or more chemotherapy regimens. In these two studies, named IDEAL 1 and 2 (Iressa Dose Evaluation in Advanced Lung cancer), gefitinib was demonstrated to be active and well tolerated.[2,3] However, very recently, Thatcher et al. reported a phase III trial (ISEL) comparing gefitinib with best supportive care among patients with advanced NSCLC who had received one or two prior chemotherapy regimens.[4] In 1692 patients, a difference between gefitinib and placebo was reported, although this did not reach a statistical significance in the overall population (5.6 vs 5.1 months; HR, 0.89; 95% CI, 0.78–1.03; $p = 0.11$). Pre-planned subgroup analyses suggested survival benefits for gefitinib and placebo among patients of Asian origin and patients who never smoked, respectively. In a phase III, randomized, placebo-controlled trial, erlotinib prolonged survival (6.7 vs 4.7 months for erlotinib vs placebo; $p = 0.001$) among patients with NSCLC after first- or second-line chemotherapy.[5] The analysis of quality of life and time to deterioration of patients reported symptoms showed statistically and clinically meaningful benefit for patients randomized to erlotinib.[6] Tsao et al. used tumor biopsy samples from participants in the afore-mentioned trial to investigate whether responsiveness to erlotinib and its impact on survival were associated with expression by the tumor of EGFR and EGFR gene amplification and mutations.[7] In multivariate analyses adenocarcinoma ($p = 0.01$), never having smoked ($p < 0.01$) and expression of EGFR ($p = 0.03$) were associated with an objective response.

Somatic mutations in the EGFR have been identified among patients with advanced NSCLC who achieve dramatic clinical and radiographic response to the EGFR-TKIs gefitinib and erlotinib.[8,9] These mutations in EGFR are found more frequently in patients with adenocarcinomas, never-smokers, patients of Asian ethnicity, and women—the same populations that are most likely to have a clinical response when treated with EGFR-TKIs. Retrospective studies comparing the outcomes of patients with and without EGFR mutations treated with EGFR-TKIs show a significant clinical benefit of EGFR-TKIs among patients with EGFR mutations.[10]

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Comparative data between erlotinib and gefitinib or evidences on cross-resistance do not exist, as it is unknown whether some patients who do not respond to erlotinib can benefit from gefitinib and vice versa. In this article, we report three cases of long-lasting tumor control with erlotinib after disease progression during gefitinib therapy in advanced NSCLC.

PATIENTS AND METHODS

All three patients received erlotinib once daily at the dose of 150 mg. Patient characteristics are summarized in Table 1. Patients were women aged 67, 38, and 50 years. All three patients were never-smoker whose histology was adenocarcinoma. Two patients received chemotherapy before gefitinib (one pretreated with cisplatin plus vinorelbine and then by gemcitabine, and one with cisplatin plus gemcitabine and then by carboplatin plus paclitaxel). One patient never received chemotherapy because of liver cirrhosis. Two patients had brain metastasis. All three patients received gefitinib just before therapy with erlotinib: two reported stable disease and one partial response. During gefitinib therapy, the first patient progressed on lung, whereas the second and third progressed on lung and brain. In particular, new lesions appeared in all three cases. Only fine-needle ago-biopsies with cytological examinations were available for these three patients. Thus, mutational analysis was not performed.

RESULTS

At the time of this analysis, all the three patients are still on treatment with erlotinib with no evidence of treatment failure after more than 13, 13, and 7 months. Patient 1 achieved partial response, and Patients 2 and 3 achieved stable disease. Specifically, Patient 1 achieved partial response on lung lesions (Figure 1), Patient 2 achieved partial response on brain lesions (Figure 2) and stable disease on lung and bone lesions, and Patient 3 achieved partial response on brain lesions and stable disease on lung lesions. All three patients experienced symptomatic improvement in cerebral and extracerebral symptoms while receiving treatment. Erlotinib was generally well tolerated, with grade 1 skin toxicity recorded in two cases.

DISCUSSION

In our series, we found three cases of long-lasting tumor control with erlotinib after disease progression with gefitinib in the treatment of advanced NSCLC. One patient achieved partial response, and two patients achieved stable disease. All three patients had adenocarcinomas, were women and never-smokers, and had previously achieved tumor control with gefitinib. Thus, we described clinical cases of patients selected by clinical predictive factors of response.

Garfeld recently reported the case of an elderly patient, male and former smoker, with advanced NSCLC (cell type not specified) that responded to erlotinib after an immediate failure to gefitinib therapy.[11] This case is very interesting but different from our cases because gefitinib did not achieve tumor control as in our cases and because the patient described by Garfeld represents the NSCLC patient population with lower response rates to EGFR inhibitors (male, non-adenocarcinoma, and former smoker). On the contrary, Choong et al. recently described the case of a 70-year-old Japanese-American woman who had never smoked with advanced NSCLC.[12] Whereas during treatment with erlotinib she progressed, developing leptomeningeal carcinomatosis, and she achieved tumor response to gefitinib. The authors also performed a mutational analysis and found in this tumor a novel double L858R + E884K somatic mutation of the EGFR.

Differential activity between gefitinib and erlotinib is unknown. Somatic mutations in the EGFR have been detected among patients with NSCLC (especially those with adenocarcinoma and never-smokers) and are associated with sensitivity to treatment with gefitinib or erlotinib, but the relationship between different mutations and the activity of

TABLE 1. Patient Characteristics, Response, and Toxicity

	Case 1	Case 2	Case 3
Age	67	38	50
Sex	Female	Female	Female
Prior smoking history	Never smoker	Never smoker	Never smoker
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
EGFR status	Unknown	Unknown	Unknown
Stage	IV	IV	IV
Disease sites	Lung	Lung, bone, brain	Lung, brain
Number of previous chemotherapies	0	2	2
Response to gefitinib	Stable disease for 18 months	Stable disease for 12 months	Stable disease for 24 months
Progression status of gefitinib	New lung lesions	New lung and brain lesions	New lung and brain lesions
Response to erlotinib	Partial response	Stable disease	Stable disease
Brain		Partial response	Partial response
Extracranial disease	Partial response (lung)	Stable disease (lung and bone)	Stable disease (lung)
Duration of response	13+	13+	7+
Toxicity			
Site (grade)	Skin (1)		Skin (1)

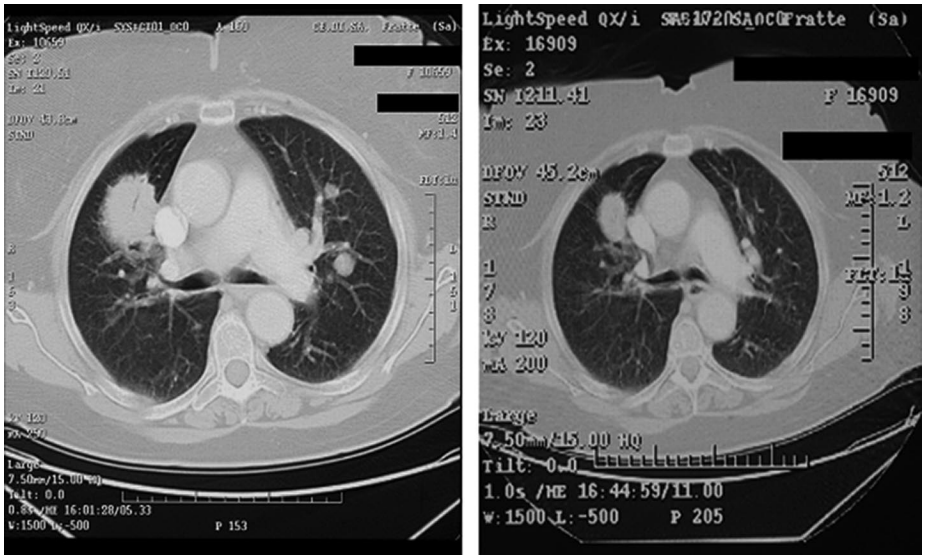

FIGURE 1. Patient 1 achieved partial response on lung lesions after erlotinib therapy (*left*, baseline).

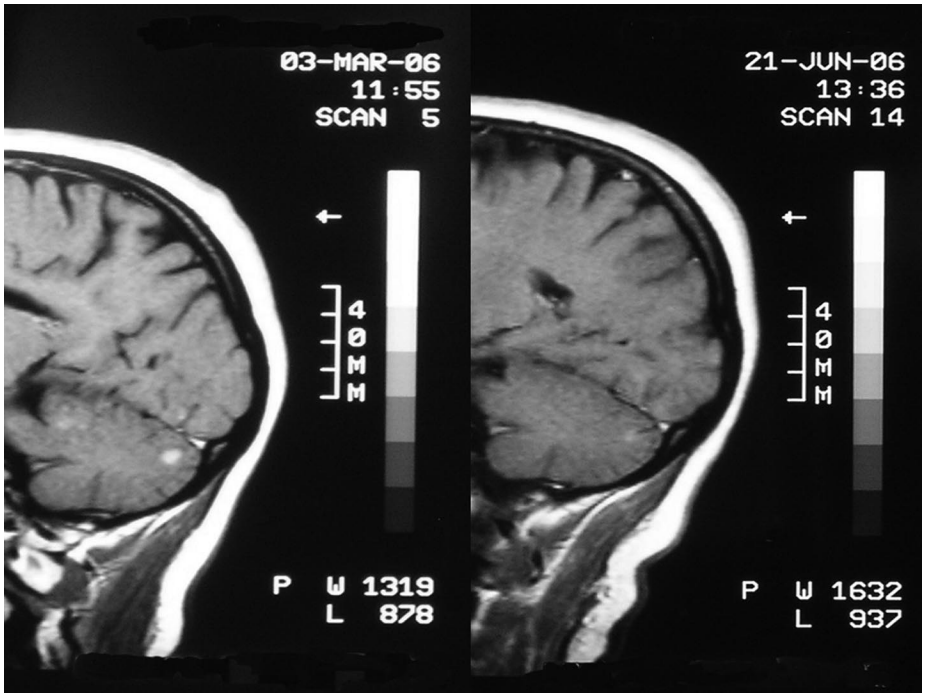

FIGURE 2. Patient 2 achieved partial response on brain lesions after erlotinib therapy (*left*, baseline).

the two EGFR-TKIs has not yet been deeply studied. Some common somatic mutations in EGFR, including deletion mutations in exon 19 and leucine-to-arginine substitution at amino acid position 858 (L858R) in exon 21, have been examined for their ability to predict sensitivity to gefitinib or erlotinib.[8,9] However, reports have shown that the threonine-to-methionine substitution at amino acid position 790 (T790M) in exon 20 is related to gefitinib resistance.[13] Some studies have indicated that high copy numbers of the EGFR gene may be a more effective molecular predictor to responsiveness and prolonged survival among patients treated with EGFR-TKIs.[14] Tokumo et al. recently described two patients with NSCLC with the L858R mutation who did not respond to gefitinib.[15] Patient 1 harbored both the T790M and L858R mutations, and fluorescence in situ hybridization showed EGFR gene amplification. Patient 2 harbored both the L858R and aspartic acid-to-tyrosine substitution at amino acid position 761 in exon 19 of EGFR mutations and had a high polysomy status for EGFR. In these two patients, tumors showed resistance to gefitinib treatment despite the presence of EGFR L858R mutation and increased copy number. Jackman et al. recently explored the relationship between the two most common types of somatic EGFR mutations, exon 19 deletions and the L858R point mutation, and outcomes of patients after treatment with gefitinib or erlotinib.[16] In 36 patients, those with an exon 19 deletion had a significantly

longer overall survival compared with patients with an L858R mutation (38 vs 17 months; $p = 0.04$), and a trend toward higher response rate (73% vs 50%). Interestingly, we also noted a difference in response rate for patients treated with gefitinib compared with erlotinib (18 of 23 [78%] vs 3 of 9 [33%]; $p = 0.04$]. However, the number of patients available in this analysis is not sufficient for definitive conclusions on differential activity between gefitinib and erlotinib. Pooling of greater numbers of patients and completion of prospective trials are needed to further define the predictive and prognostic roles of different EGFR mutations with respect to treatment with gefitinib, erlotinib, and other EGFR inhibitors.

In conclusion, our three cases demonstrate that erlotinib may be effective among patients with NSCLC previously and successfully treated with gefitinib. However, a careful selection of these patients is needed, and candidates for this switch are only to be found among never-smokers. The search for patients who do not respond to erlotinib but who respond to gefitinib or vice versa would also be useful for clinical practice. Only a detailed correlation between molecular analysis of somatic mutations of EGFR and clinical outcomes of the two EGFR-TKIs may clarify how to select patients with NSCLC with gefitinib-resistant and erlotinib-sensitive disease and vice versa.

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