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CASE REPORT

Response to second-line erlotinib in an *EGFR* mutation-negative patient with non-small-cell lung cancer: make no assumptions

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ABSTRACT

Erlotinib—an oral tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR)—has commonly been used as a therapeutic option in metastatic non-small-cell lung cancer (NSCLC) patients in the second- or third-line treatment setting. A mutation in the *EGFR* gene (*EGFR* M+) confers an increased response to this class of drugs. In the first-line setting, use of TKIs is restricted to patients having a mutation. The importance of this biomarker has been questioned in subsequent treatment lines.

Here, we report a case showing a positive response to erlotinib treatment in the second-line setting. The patient, an elderly male smoker with stage IV NSCLC, had a tumour that was *EGFR* mutation-negative (wild-type *EGFR*). Based on this clinical case, we discuss the controversy concerning the need for, and impact of, testing for *EGFR* mutation after first-line treatment.

KEY WORDS

Non-small-cell lung cancer, gefitinib, erlotinib, *EGFR* mutation

1. CASE REPORT

In January 2010, a 71-year-old white man presented with progressive dyspnea on exertion and cough. His past medical history was notable for severe chronic obstructive pulmonary disease and a 50 pack–year history of smoking.

Computed tomography (CT) imaging of the patient's chest showed two well-defined lesions in the posterior segment of the right upper lobe. A bronchoscopy was positive for adenocarcinoma. Imaging by combined positron-emission tomography (PET)–CT showed intense fluorodeoxyglucose activity in the right upper-lobe nodule adjacent to the major fissure and in a smaller, superior lesion. Extensive fluorodeoxyglucose activity was also evident within the hilar and mediastinal lymph nodes.

The patient was subsequently treated with palliative radiation therapy at a dose of 20 Gy in 5 fractions to encompass his central chest disease.

At the time of his initial medical oncology consultation, the patient declined chemotherapy and thus was tested for the *EGFR* mutation through the AstraZeneca Pharmaceuticals Open Access Program. He was found to be *EGFR* mutation-negative (wild-type *EGFR*). Chemotherapy was offered again, and the patient accepted the recommendation. Palliative chemotherapy with first-line gemcitabine–cisplatin was started on May 16, 2010. On CT imaging of the chest after 3 cycles of chemotherapy, the patient was found to have a partial response. He completed a total of 4 cycles of chemotherapy on July 11, 2010.

Chest imaging by CT on July 23, 2010, 2 weeks after completion of chemotherapy, revealed that the right upper-lobe nodule adjacent to the major fissure measured 4.0×2.8 cm (lesion 1, Figure 1), and the smaller, superior lesion measured 3.0×1.5 cm (lesion 2, Figure 2). Also, a new nodularity measuring 2.0×1.7 cm (lesion 3, Figure 3) was now evident anterior to the superior margin of the larger nodule.

Second-line therapy with erlotinib was initiated. The patient was also enrolled in an ongoing clinical trial to prospectively examine skin rash. He was randomized to arm 1 (treatment with prophylactic oral minocycline 150 mg for 4 weeks).

The patient received his first dose of erlotinib (150 mg daily) on August 24, 2010. On day 18 of erlotinib therapy, he developed a grade 3 rash (severe, extensive, and painful) on his face and neck (Figure 4). Erlotinib and minocycline were both stopped for 2 weeks. Dose-reduced (100 mg) daily erlotinib was then restarted on October 4, 2010. The rash improved to grade 1 when seen in follow-up on November 30, 2010 (Figure 5). During subsequent visits, the rash on the patient's face and neck further improved, and the erlotinib dose was increased to 150 mg in January 2011.

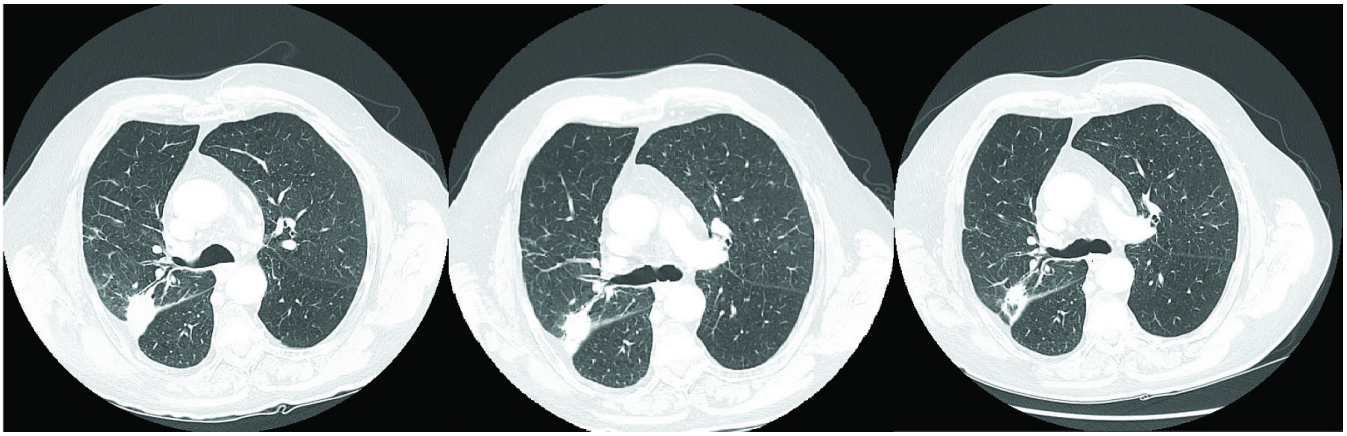

FIGURE 1 Axial computed tomography images showing lesion 1. Left to right: July 23, 2010: 4.0×2.8 cm; October 26, 2010: 3.5×2.5 cm; February 11, 2011: 3.4×2.5 cm.

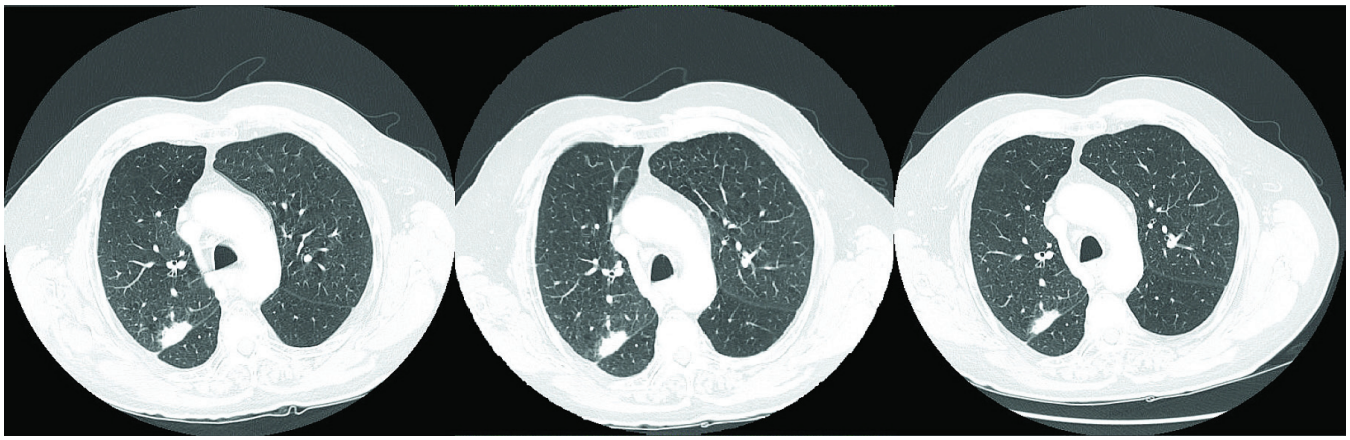

FIGURE 2 Axial computed tomography images showing lesion 2. Left to right: July 23, 2010: 3.0×1.5 cm; October 26, 2010: 2.8×1.5 cm; February 11, 2011: 2.7×1.0 cm.

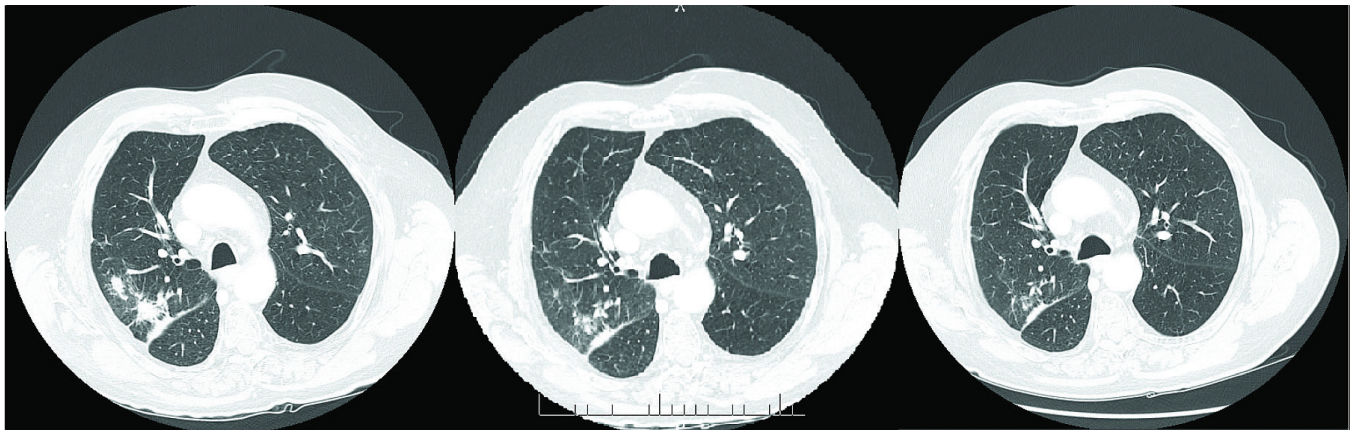

FIGURE 3 Axial computed tomography images showing lesion 3. Left to right: July 23, 2010: 2.0×1.7 cm; October 26, 2010: no longer measurable; February 11, 2011: further resolution.

Follow-up CT imaging of the patient's chest on October 26, 2010, showed that all 3 lesions had decreased in size. Lesion 1 now measured 3.5×2.5 cm (Figure 1); lesion 2 measured 2.8×1.5 cm (Figure 2); and lesion 3 was no longer measurable (Figure 3). Subsequent CT imaging of the chest on February 11, 2011, showed that, compared with the initial CT images acquired on July 23, 2010, the 3 lesions in the right upper lobe had achieved a partial response per the Response Evaluation Criteria in Solid Tumors. Lesion 1 measured 3.4×2.5 cm; lesion 2 measured 2.7×1.0 cm; and lesion 3 showed further resolution (Figures 1–3).

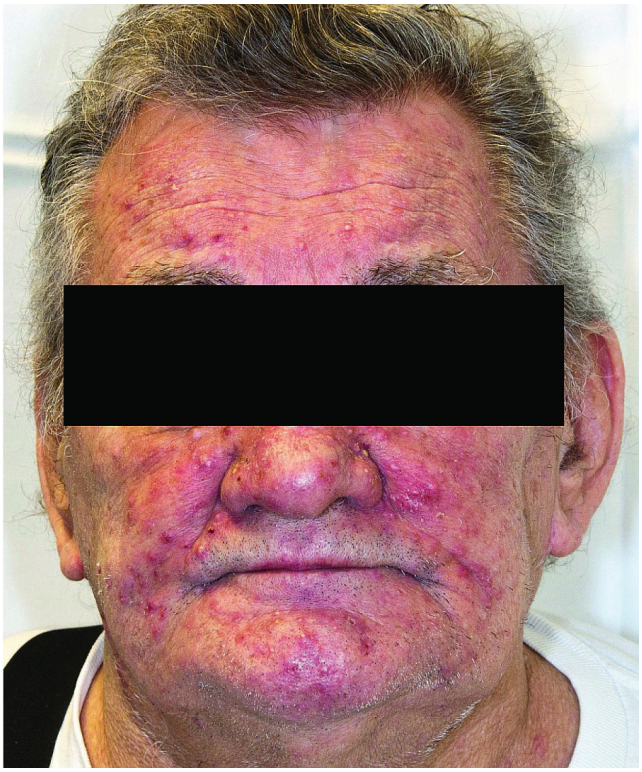

FIGURE 4 *Grade 3 rash, November 1, 2010.*

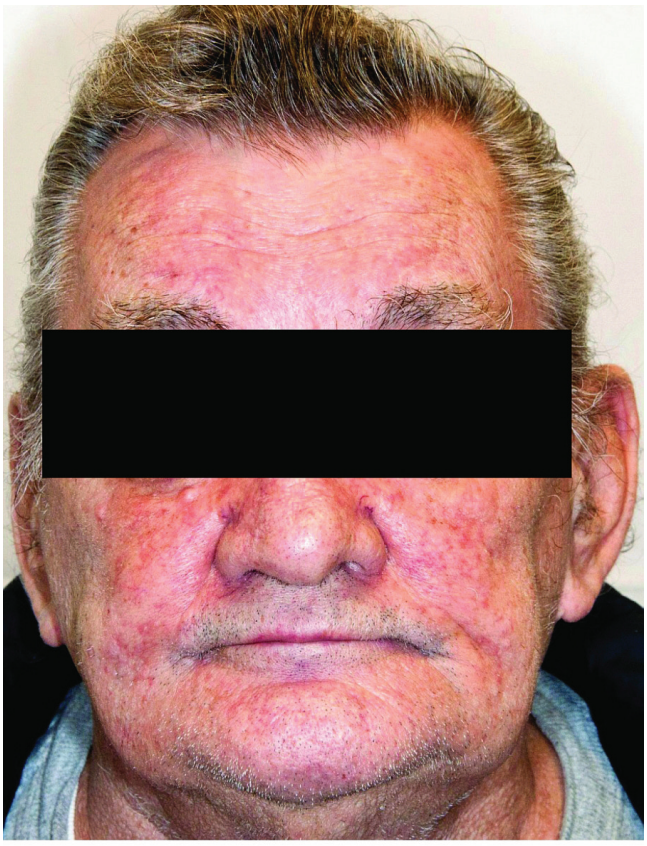

FIGURE 5 *Grade 1 rash, November 30, 2010.*

At the time of writing, the patient was still taking erlotinib and continuing to experience symptomatic benefit.

2. DISCUSSION

Over the last several years, the development of molecularly targeted therapeutic agents has changed the outcome of advanced NSCLC. The EGFR is a member of the Erb family of cell membrane receptors, which play a major role in cell growth, differentiation, and survival [1]. Non-small-cell lung cancer is one of the epithelial cancers associated with high levels of EGFR expression [1]. Gefitinib and erlotinib are two low molecular weight TKIs that have been approved for the treatment of advanced NSCLC [1].

A side effect specific to this class of agents is the development of a rash primarily on the face, neck, and upper torso, which occurs after 1 week of treatment, which reaches maximum intensity after 2–3 weeks, and which affects 50%–75% of patients [2–4]. Multiple trials of EGFR inhibitors across different tumour types have confirmed a relationship for the incidence and severity of rash with both response and survival [5,6]. It appears that patients who develop worse rashes from this class of drugs show more benefit.

Nonetheless, the strongest predictor of response to TKIs reported in the literature is alteration of the *EGFR* gene (deletion in exon 19 and missense mutation in exon 21) [7–9]. There is evidence that *EGFR* mutation testing should be a prerequisite for first-line treatment of advanced NSCLC with gefitinib; a reduction in survival is observed in patients with wild-type *EGFR* who are given gefitinib. In the second line or in subsequent lines of therapy, the need for *EGFR* mutation testing in advanced NSCLC remains unclear.

The trial called IPASS (Iressa Pan-Asia Study) provides strong evidence for testing for *EGFR* in the first-line setting [10]. Most patients were nonsmokers or light smokers, had adenocarcinoma histology, were of Asian ethnicity, and were women. Patients with stage IV NSCLC were randomized to chemotherapy or gefitinib. In a subgroup of patients who tested positive for the *EGFR* mutation (*EGFR* M+) and were treated with gefitinib, the objective response rate was 71.2% compared with 1.1% in the mutation-negative subgroup ($p = 0.001$). In addition, among the patients who were *EGFR* M+ treated with gefitinib, progression-free survival (PFS) was significantly longer than it was among patients who received carboplatin–paclitaxel [hazard ratio (HR): 0.48; 95% confidence interval (CI): 0.36 to 0.64; $p < 0.001$]. Patients who tested negative for the mutation had a significantly longer PFS if treated with carboplatin–paclitaxel (HR: 2.85 for gefitinib; 95% CI: 2.05 to 3.98; $p < 0.001$) [10].

The IPASS trial led to the approval in Canada of gefitinib in the first-line setting for patients with non-squamous metastatic NSCLC whose tumours tested positive for the *EGFR* mutation. After that approval,

AstraZeneca Pharmaceuticals initiated an Open Access Program in Canada for both mutational testing and gefitinib access. Centralized testing was set up in 5 laboratories that had first to prove quality assurance to meet Health Canada standards.

In INTEREST (Iressa Non-Small Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere), a randomized phase III trial, the qualitative difference in response seen in the first line was not demonstrated in second-line settings [11]. In INTEREST, patients were randomized to receive gefitinib or docetaxel. The analysis showed that survival and response were similar for gefitinib and docetaxel, with no statistically significant differences between the treatments in the *EGFR* mutation-negative patients. Consequently, there was no harm to the patients who were negative for *EGFR* mutation and who received gefitinib [11].

The NCIC trial BR.21 was designed to examine the benefit of erlotinib after progression on first-line chemotherapy. Patients with locally advanced and metastatic NSCLC who relapsed after first- or second-line chemotherapy were randomized to treatment with erlotinib or to placebo. Treatment with erlotinib improved PFS (HR: 0.61; $p < 0.001$) [4]. Erlotinib was then approved in Canada for the treatment of patients with metastatic NSCLC after failure of first- or second-line chemotherapy. Exploratory analysis revealed an increased benefit in patients who shared certain clinical characteristics—namely, female sex, nonsmoking status, Asian ethnicity, and adenocarcinoma histology [12].

More recently, the SATURN (Sequential Tarceva in Unresectable NSCLC) trial investigated the effect on PFS of erlotinib as maintenance therapy in patients with non-progressing disease after first-line platinum-doublet chemotherapy [13]. That trial provided strong evidence that *EGFR* mutational testing should not be done in settings after first-line chemotherapy. Compared with placebo, erlotinib resulted in significantly prolonged PFS in all analyzable patients regardless of *EGFR* status (12.3 weeks vs. 11.1 weeks for placebo; HR: 0.71; 95% CI: 0.62 to 0.82; $p < 0.0001$). A PFS benefit was observed in both *EGFR* mutation-positive (HR: 0.10; $p < 0.0001$) and wild-type *EGFR* patients (HR: 0.78; $p = 0.0185$). A greater benefit from erlotinib was noted in *EGFR* mutation-positive tumours, but both groups benefited. The secondary endpoint was overall survival, which was prolonged with erlotinib (median overall survival: 12.0 months vs. 11.0 months with placebo; HR: 0.81; 95% CI: 0.70 to 0.95; $p = 0.0088$). Compared with placebo, erlotinib resulted in improved PFS in all patient subgroups regardless of sex, ethnic origin, histology, or smoking status [13].

3. CONCLUSIONS

In the second-line, third-line, or maintenance settings, it appears that treatment with a TKI benefits all patients in terms of PFS and overall survival, regardless of *EGFR* mutation status or patient characteristics. Possible explanations include a change in mutational status after platinum-containing chemotherapy regimens. More likely, another pathway supersedes to make the patient's tumour more sensitive to an epidermal growth factor inhibitor, thus producing a benefit in stabilization or response, and (more importantly) survival. Clearly, our understanding of the epidermal growth factor pathway, its drivers and inhibitors, needs further study.

In the present case report, the patient's response and grade of rash were surprising because his clinical characteristics did not correlate with those of patients known to respond or benefit. Indeed, his *EGFR* mutational test was negative. It is anticipated that this patient will achieve a survival benefit, because PFS in the NCIC's BR.21 was 2.2 months in the erlotinib group, and our patient has already exceeded that duration, having been on active therapy with erlotinib for 6 months at the time of writing.

Make no assumptions. A TKI should be strongly considered for all patients in the second-line, third-line, or maintenance setting, including those patients who are *EGFR* mutation-negative and who may not have the clinical predictors of outcome previously reported in the literature.

4. CONFLICT OF INTEREST DISCLOSURES

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