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Dramatic Response to Low-Dose Erlotinib of Epidermal Growth Factor Receptor Mutation-Positive Recurrent Non-small Cell Lung Cancer After Severe Cutaneous Toxicity

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Abstract: Erlotinib is increasingly being used for the treatment of non-small cell lung cancer. The recommended dose is 150 mg/day and no efficacy data is available for lower doses. We describe a case of dramatic tumor response to 50 mg erlotinib in a patient with EGFR mutation positive NSCLC who developed a severe rash on full dose erlotinib. Rash is known to correlate with response and survival in patients treated with erlotinib. Our case suggests that in the presence of rash, dose reductions to "subtherapeutic" levels remain effective and may prevent unnecessary early treatment termination.

Key Words: Non-small cell lung cancer (NSCLC), Erlotinib, Rash.

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The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib is approved for patients with non-small cell lung cancer (NSCLC) who have failed ≥1 platinum-based chemotherapy regimen. The standard dose is 150 mg/d. When severe or intolerable toxicity occurs, dose reductions to 100 mg/d are recommended. There are no data available on the efficacy of lower doses. We describe a case of impressive response of recurrent, EGFR mutation-positive NSCLC to erlotinib 50 mg/d.

CASE HISTORY

In June 2006, a 46-year-old Caucasian never-smoker presented with stage IIIb adenocarcinoma of the left upper lobe. She received six cycles of paclitaxel/carboplatin. In June 2007, she developed progressive disease with multiple liver, bone, and brain metastases. In view of the clinical characteristics predicting a good response, she started erlotinib 150 mg/d. However, because of a severe, grade 4 generalized papulopustular rash, treatment was discontinued after 7 days (Figure 1*A*). Subsequently, she completed six cycles of gemcitabine/cisplatin and four cycles of pemetrexed. In August 2008, a follow-up computed tomography (CT) scan showed new intrapulmonary and intracerebral metastases. Because of the lack of other alternatives, we again offered her erlotinib treatment but at a reduced dose (50 mg/d). This was well tolerated with toxicity limited to a grade 2 papulopustular rash on the face (Figure 1*B*). After 6 weeks of therapy, a CT scan showed marked response (Figure 2). Molecular analysis of a biopsy from a pleural metastasis demonstrated an EGFR L858R mutation in exon 21. The erlotinib steady-state plasma concentration was 0.352 μg/L. Cytochrome P450 (CYP) genotyping revealed no polymorphisms. Currently, she continues on this treatment regimen.

DISCUSSION

This is the first report of response to one third of the recommended dose of erlotinib. At 50 mg/d, the erlotinib steady-state plasma concentration was 0.352 μg/ml. This is significantly lower than the estimated 0.5 μg/ml needed for clinical efficacy.[1] Although erlotinib is metabolized by CYP enzymes, our patient neither had CYP polymorphisms nor was taking CYP-inducing comedications. Consistent with the clinical characteristics of female gender, a negative smoking history, and adenocarcinoma histology, an EGFR mutation in exon 21 was detected in a biopsy from a pleural metastasis. This mutation is associated with improved response to EGFR tyrosine kinase inhibitor therapy.[2]

Patients receiving EGFR inhibitors frequently develop the typical rash characterized by inflammatory papules and pustules demonstrated in our patient.[3] The presence and severity of this rash correlate with response and survival.[4,5] Our patient developed a severe, generalized erlotinib-induced rash at the standard dose of 150 mg/d. After treatment discontinuation, this resolved completely. On rechallenge with a lower dose, the rash reappeared but was mild and tolerable. Currently, studies are assessing whether dose escalation to rash improves outcome in patients who do not initially develop a rash. However, no studies are investigating the effect of dose reductions on antitumor efficacy in patients who develop a severe rash. Our case suggests that in patients with EGFR mutation-positive NSCLC who develop a high-grade rash, erlotinib dose reductions to "subtherapeutic" levels remain effective while improving the severity of the rash.

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Disclosure: The authors declare no conflict of interest.

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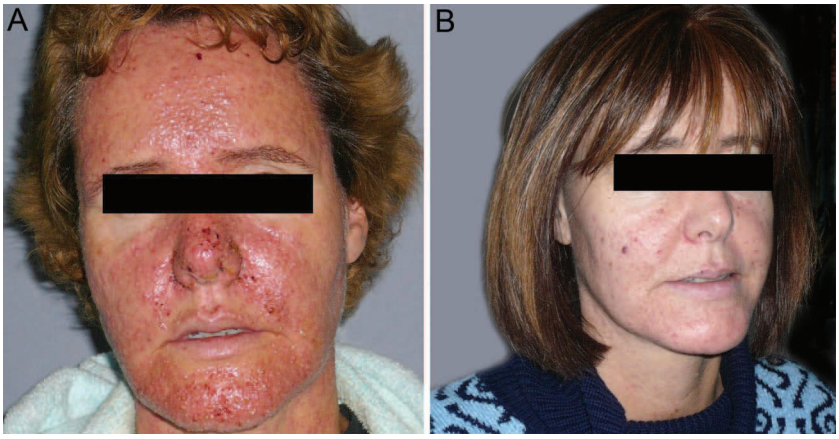

FIGURE 1. Photography images of the face show a severe (grade 4) erlotinib-induced papulopustular rash on erlotinib 150 mg/d (*A*), which improved to grade 2 on erlotinib 50 mg/d (*B*).

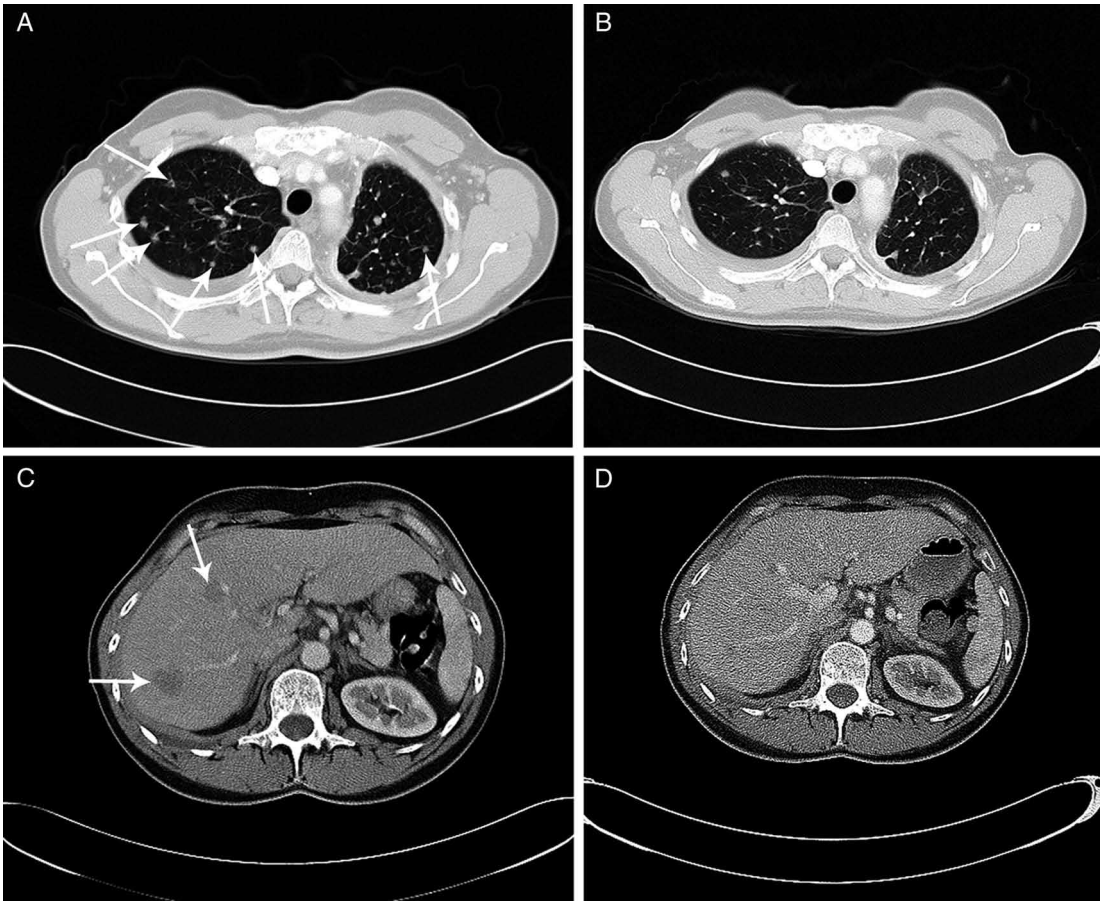

FIGURE 2. Radiologic images before and 6 weeks after erlotinib 50 mg/d. Axial, contrast-enhanced computed tomographic (CT) images of the lungs show a right-sided pleural effusion and multiple intrapulmonary metastases bilaterally (arrows) (*A*), which shrunk or disappeared after 6 weeks of treatment (*B*). Axial, contrast-enhanced CT images of the abdomen show two liver metastases (arrows) (*C*), which decreased significantly in size (*D*).

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