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LETTER TO THE EDITOR

Subsequent brain metastasis responses to epidermal growth factor receptor tyrosine kinase inhibitors in a patient with non-small-cell lung cancer

KEYWORDS
Non-small-cell lung cancer;
Lung adenocarcinoma;
Brain metastasis;
Epidermal growth factor receptor mutation;
Receptor tyrosine kinase inhibitor;
Erlotinib;
Gefitinib

Summary In response to the paper by Popat et al. ''Recurrent responses to non-small-cell lung cancer brain metastases with erlotinib'', we wish to report a similar case and to provide comments. A 32-year-old Chinese never-smoker female presented a primary lung adenocarcinoma with brain metastasis and three subsequent responses to EGFR tyrosine kinase inhibitors (gefitinib and erlotinib). Direct sequencing of *epidermal growth factor receptor* (*EGFR*) gene exons 18 to 21 and *K-ras* gene was performed on tissue obtained from initial biopsies and post-chemotherapy surgical specimens. An *EGFR* exon 21 L858R point mutation was identified on pre- and post-chemotherapy samples. *K-ras* mutations and *EGFR* exon 20 T790M point mutations were not detected. Moreover, EGFR protein overexpression was observed by immunohistochemistry as well as *EGFR* gene high polysomy by fluorescent in situ hybridization. These case suggest that re-challenging patients with NSCLC several times with EGFR-TKI should be considered when progressive disease is observed under chemotherapy. However, we do not yet know whether this option should be considered in light of tumor molecular evaluation, or whether it should be proposed to patients who experienced a clinical response after a first administration.

In response to the paper by Popat et al. ''Recurrent responses to non-small-cell lung cancer brain metastases with erlotinib'' [1], we wish to report a similar case and to provide comments.

A 32-year-old Chinese never-smoker female presented with a primary lung adenocarcinoma (CK7+/CK20—/TTF1+). There was no extra-thoracic extension. Surgery was ruled out because of proven pleural invasion by thoracoscopy. Cisplatin and gemcitabin followed by paclitaxel were given. Disease stabilization was observed after each regimen of chemotherapy. Because of the patient's young age and nearly complete metabolic response on fluorodeoxyglucose PET-scan, a right pleuropneumonectomy was performed. Five months later, the patient presented brain metastases without extracerebral relapse, and was primarily treated by 30 Gy whole-brain irradiation. Gefitinib (250 mg daily) was then started. It appears that gefitinib in the first instance was not given for relapse of brain metastases after radiotherapy but was given for consolidation of response to radiotherapy. A significant decrease of brain metastases compared with post-irradiation brain CT (Fig. 1A and B) was observed and maintained for 10 months. This response is probably related to gefitinib, even if we could not exclude also an delayed effect from radiotherapy. Since brain metastases relapsed, gefitinib was withdrawn and pemetrexed started. However, brain metastases rapidly progressed on chemotherapy (Fig. 1C) and it was decided to treat the patient with erlotinib (150 mg/daily). One month later, an objective response was again observed in brain metastases (Fig. 1D), but disease progressed with the occurrence of a single bone metastasis. Erlotinib was continued and bone metastasis controlled by palliative irradiation. After a 5-month-partial response of brain metastases, erlotinib was discontinued and vinorelbine started for new brain progression. Since brain metastases continued to progress after 4 weeks of chemotherapy (Fig. 1E), the patient was re-treated by erlotinib (150 mg/daily) and exhibited a third brain metastases response during a 2-month period (Fig. 1F). Although erlotinib was pursued, the patient died from left lung and bone disease progression.

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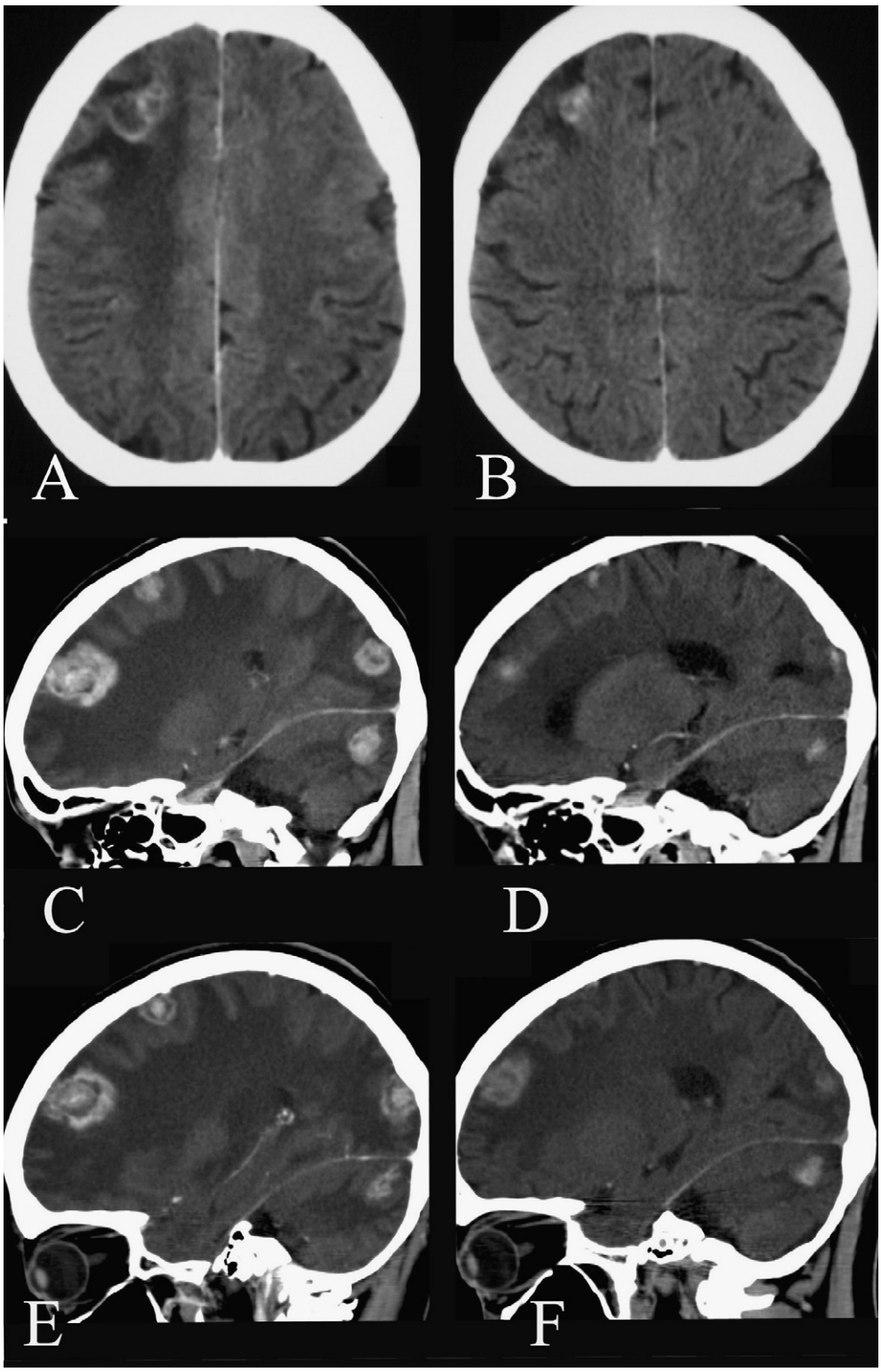

Fig. 1 Serial enhanced brain CT-scan. (A) Axial CT-scan slice, post-irradiation and before the treatment by gefitinib, shows right frontal localization of metastases surrounding by edema. (B) Axial CT-scan slice, during treatment by gefitinib, shows clearly the decreasing of metastases enhancement and edema. (C) Sagittal CT-scan slice, after pemetrexed and before erlotinib, shows progression of metastases and worsening of the edema. (D) Sagittal CT-scan slice, during treatment by erlotinib, shows the disappearance of contrast enhancement of right frontal metastases and persistence of low density of the white matter without mass effect. (E) Sagittal CT-scan slice, after vinorelbine and before re-challenge with erlotinib, shows appearance of metastases and worsening of the edema with mass effect. (F) Sagittal CT-scan slice, during second treatment by erlotinib, shows the decrease of contrast enhancement of right frontal metastases and persistence of low density of the white matter without mass effect.