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CLINICAL–PATIENT STUDIES

# Erlotinib therapy in a patient with non-small-cell lung cancer and brain metastases

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**Abstract** Brain metastases are a common occurrence and a major cause of mortality in non-small-cell lung cancer, with few systemic treatment options. Although targeting epidermal growth factor receptor-associated tyrosine kinase with erlotinib and gefitinib results in durable responses in some patients, the activity of these drugs against brain metastases has been poorly documented. In particular, few reports have so far reported the activity of erlotinib in this setting. Here we report the case of a male Italian smoker with an adeno-carcinoma of the lung whose lung cancer and brain metastases have both responded to erlotinib.

**Keywords** Erlotinib · Brain metastases · Lung cancer

## Introduction

Brain metastases from non-small-cell lung cancer (NSCLC) are a challenging clinical problem because of the lack of effective therapies. Systemic chemotherapy is largely unsuccessful because drugs cannot effectively penetrate the blood–brain barrier and because NSCLC is normally only poorly to moderately sensitive to this treatment [1]; some patients can be handled with surgical resection or stereotactic radiosurgery, even if metastases are often multiple and median survival after whole brain radiotherapy is only 3–4 months [2]. The discovery that somatic mutations in the epidermal growth factor receptor (EGFR) gene occur in a subset of lung adeno-carcinomas and are associated with sensitivity to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, with impressive responses, has generated excitement among clinicians and researchers studying NSCLC [3]. Although activity of gefitinib against brain metastases in NSCLC has previously been demonstrated, there are no data demonstrating a survival benefit of use of gefitinib. To date, few reports have so far reported the activity of erlotinib in this setting. Here, we report the case of a male Italian smoker with an adeno-carcinoma of the lung whose lung cancer and brain metastases have both responded to erlotinib.

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## Case report

In January 2007, a 61-year-old male Italian smoker initially presented with generalized seizures. His physical performance status was good and examination was unremarkable. A brain MRI scan at presentation showed an enhancing lesion located along the left ventricular margins. A body CT scan the following day, showed a 3 × 3.7 cm mass in the left lower lobe of the lung. A core-needle biopsy obtained from the lung showed a moderately differentiated adeno-carcinoma, confirming diagnosis of stage IV non-small-cell lung cancer. He was initially treated with anti-convulsants and whole-brain radiotherapy (20 Gy in five fractions) after which he commenced first-line systemic chemotherapy with gemcitabine and carboplatin with palliative intent. Restaging after two cycles indicated both extra-cranial and intra-cranial progressive disease. (Figs. 1a, 2a, 3a) To assess epidermal growth factor receptor (EGFR) mutational status, a complementary DNA

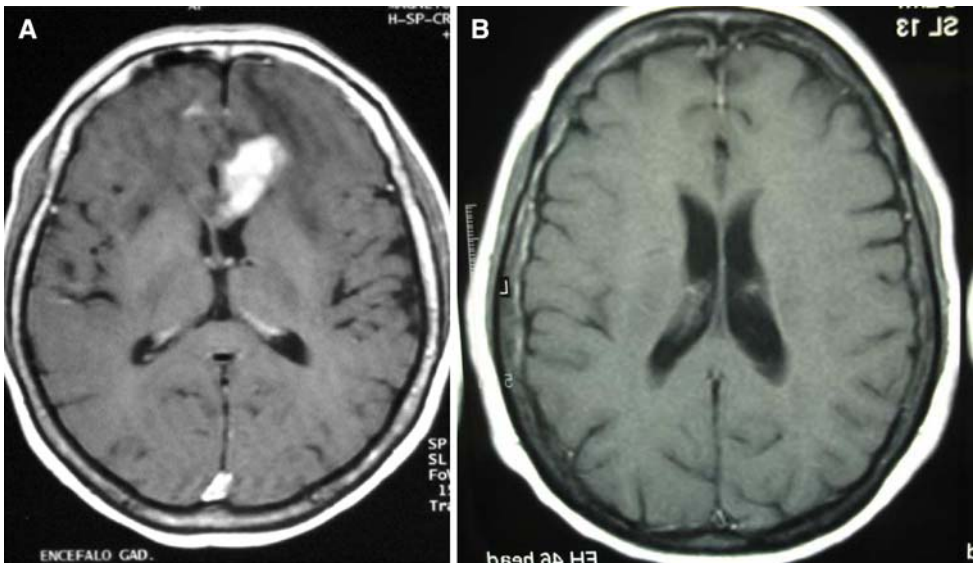


**Fig. 1** MRI studies before (**a**) and after (**b**) erlotinib therapy

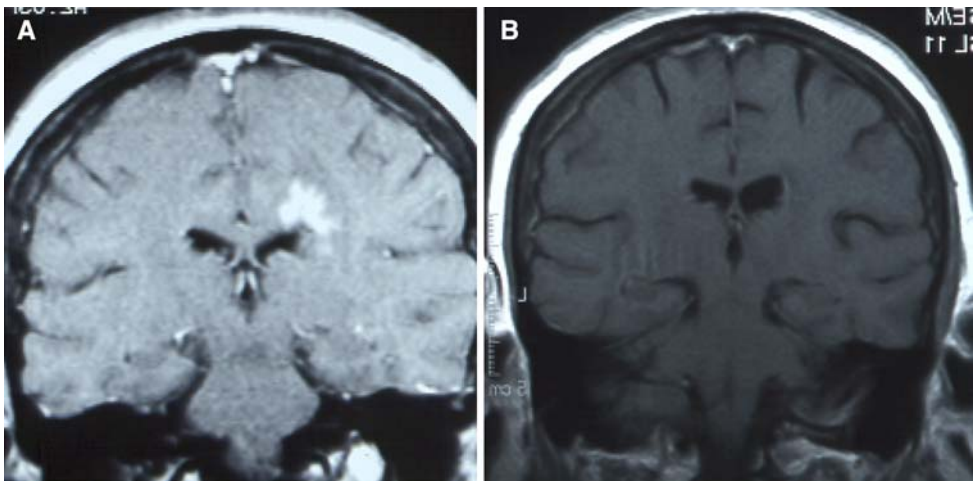


**Fig. 2** MRI studies before (**a**) and after (**b**) erlotinib therapy

sequencing from the core-needle biopsy obtained at presentation was performed, and a leucine-to-arginine substitution at amino acid 858 (L858R) was identified. He was prescribed oral erlotinib 150 mg daily. Within two weeks of starting the treatment his neurological symptoms resolved themselves and an MRI scan taken 8 weeks after starting erlotinib showed a complete response by brain metastases (Figs. 1b, 2b); furthermore, the chest CT scan showed that the mass in the left lung had nearly completely resolved itself (Fig. 3b). Eleven months after starting the treatment he remains clinically well on erlotinib without any chest-related or neurological symptoms except for a grade 1 skin rash.

## Discussion

The EGFR is a receptor tyrosine kinase of the Erb B receptor family that is abnormally activated in many epithelial tumours. The aberrant activation leads to enhanced proliferation which provides a strong rationale to target this receptor family. Somatic mutations in the EGFR have been detected in patients with NSCLC and are associated with sensitivity to treatment with gefitinib or erlotinib, which are adenosine triphosphate-competitive inhibitors of the receptor's tyrosine kinase. These mutations are more common in non-smokers, women, Asians, and patients with adeno-carcinoma, possibly explaining the association of these characteristics with response to treatment. The increased prevalence of mutations in Asians compared with North American and Western European patients is currently unexplained. EGFR mutations occur mainly in the first four exons of the gene encoding the tyrosine kinase domain (18–21) and are clustered around the ATP-binding pocket of the enzyme. About 90% of EGFR mutations are missense mutations resulting in leucine to arginine substitution at codon 858 (L858R) in exon 21 and small exon 19 in-frame deletions (LREA). Other

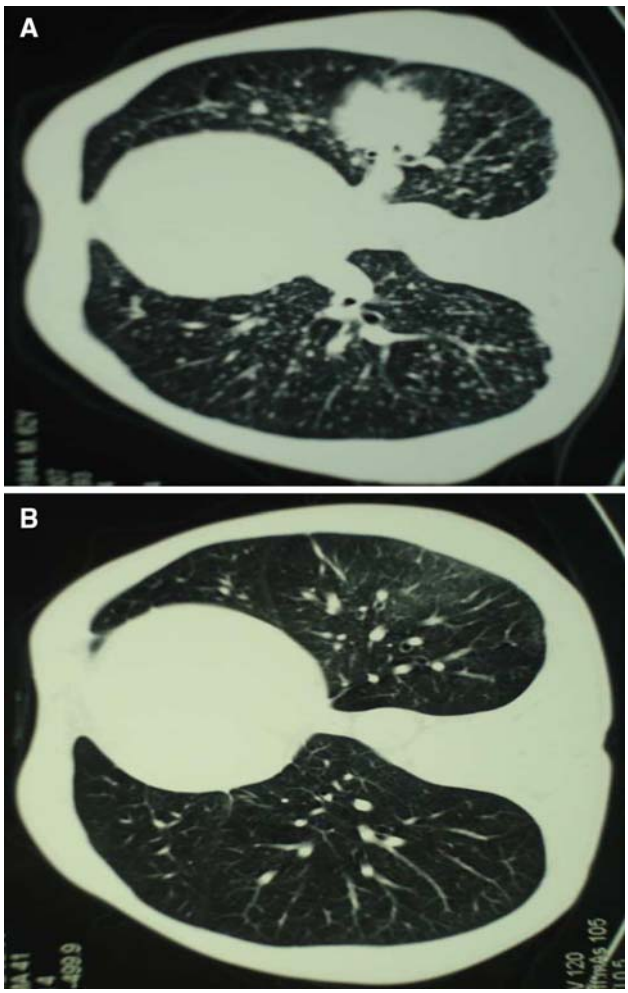


**Fig. 3** CT scans before (**a**) and after (**b**) erlotinib therapy

mutations occur at a lower frequency at codon 719, resulting in substitution of glycine with cysteine, alanine, or serine (G719X), and in exon 20 as in-frame insertion mutations. In-vitro studies with NSCLC cell lines have highlighted the fact that erlotinib and gefitinib-sensitizing mutations increase the kinase activity of EGFR, leading to increased and sustained phosphorylation of EGFR and hyperactivation of downstream pathways promoting both cell proliferation and survival. Unfortunately, despite the presence of activating EGFR mutations in their tumours, patients can fail to respond to TKIs and also those with an initial dramatic response develop acquired drug resistance after variable periods of time, because of additional genetic lesions [4].

Several studies have documented the effectiveness of gefitinib in the treatment of central nervous system metastasis of NSCLC. In a prospective study of 41 patients a partial response was observed in four patients (10%), with a median duration of 13.5 months [5]. Furthermore, in a retrospective study, Hotta reported that 7 out 14 patients with CNS metastasis had a partial response to gefitinib. Finally, another study reported three cases of NSCLC with CNS metastasis that harboured classic EGFR mutations which demonstrated a durable response to gefitinib [6].

To date, there have been only five reported cases of responses to brain metastases in NSCLC in patients receiving erlotinib. Three patients harboured L858R mutation while in two patients EGFR status was not assessed. [7–9] Our findings in a patient with metastatic NSCLC whose tumour carried the classic EGFR mutation L858R and who responded dramatically to erlotinib therapy are in agreement with the three reported cases, so we believe that erlotinib could be an appropriate option for front-line therapy in patients with NSCLC, L858R mutation, and CNS metastases for whom systemic chemotherapy might have little benefit.

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