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High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer

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Abstract

Leptomeningeal metastases (LM) occur in 5–10% of patients with solid tumors and are associated with a dismal prognosis. We describe LM from lung adenocarcinoma harboring a mutation in the epidermal growth factor receptor (EGFR) gene that confers sensitivity to the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib and gefitinib. The CSF concentration of EGFR-TKIs achieved by standard daily dosing may be insufficient for therapeutic effect. However, intermittent (pulsatile) high dose administration (1000–1500 mg/week) achieves a higher CSF concentration than standard dosing, and successfully controlled LM in this patient.

Keywords

Leptomeningeal metastases; EGFR; Lung cancer; Erlotinib

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Introduction

Leptomeningeal metastases (LM) affect 5–10% of patients with solid tumors; untreated, median survival is 1–2 months [1]. We describe a patient with LM from non-small cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) kinase domain mutation that confers exquisite sensitivity to the EGFR tyrosine kinase inhibitors erlotinib and gefitinib [2]. Such mutations occur in 10% (USA) to 25% (Asia) of NSCLCs [2]. However, secondary mutations during therapy lead to acquired resistance [2]. A recent case report highlighted that central nervous system (CNS) metastases do not always harbor resistance mutations [3], suggesting retained erlotinib/gefitinib sensitivity if therapeutic drug concentrations are achieved. We induced sustained control of LM harboring an EGFR tyrosine kinase inhibitor (TKI) sensitizing mutation without an acquired resistance mutation with high-dose weekly erlotinib following progression on standard daily dosing. Such “pulsatile” therapy is tolerable [4] and may achieve therapeutic cerebrospinal fluid (CSF) erlotinib concentrations.

Methods

Patients

All patients provided informed consent for molecular tumor analysis on an Institutional Review Board approved protocol at Memorial Sloan-Kettering Cancer Center.

Pharmacokinetic data

Plasma or CSF samples (obtained from another patient) were analyzed at various time points after dosing of erlotinib. To assess the level of erlotinib in blood or CSF, frozen samples were thawed at ambient temperature and extracted with a solvent mixture of methanol and acetonitrile (1/4, v/v). The sample solutions were placed at −20°C for approximately 1 h and then centrifuged at 1000*g* for 10 min. The supernatants were transferred to a 96-well plate and loaded into an autosampler (model SILHTC, Shimadzu, Columbia, Maryland) for high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) analysis. HPLC was then used to separate erlotinib from any potential interference and measured by MS/MS detection method. Calibration curves were determined for erlotinib to permit conversion of peak areas to the drug amounts against external reference standards. The tandem MS/MS detector (Model ABI/Sciex API 4000, Applied Biosystem, Foster City, California) permitted verification of peak identity as well as a quantitative assessment of the compounds in the samples.

Mutational analyses

EGFR mutational analyses were performed as published [8].

Case

A 54-year-old woman with stage IV NSCLC was treated with carboplatin and paclitaxel without disease response. Molecular analysis of tumor tissue was unavailable at that time. However, her demographic profile (Asian, minimal smoking history, non-small cell histology) predicted her disease would harbor EGFR TKI sensitive cells [2]. Therefore, she then initiated standard daily dosing of erlotinib (150 mg) and her disease responded. Twenty-eight months later, she acquired resistance to erlotinib with progression of disease systemically. Following further progression through an experimental angiogenesis inhibitor, she initiated pemetrexed and resumed standard dose erlotinib. After initial response, 11 months later, her disease again progressed. DNA was extracted from biopsy of a progressing

lung lesion and examined using established techniques for analysis of *EGFR* mutations [5]. Direct sequencing of exons 18–21 encoding the kinase domain of EGFR revealed the L858R mutation associated with EGFR TKI sensitivity (Fig. 1) [2]. It also demonstrated the T790M mutation associated with acquired EGFR TKI resistance (Fig. 1) [2].

She also developed headaches and there was a high clinical suspicion of CNS metastases despite negative imaging (not shown). She refused a lumbar puncture. She initiated empiric temozolomide plus standard dose erlotinib (150 mg daily) for presumed CNS disease, but after one cycle her headaches worsened, and she developed nausea and vomiting concerning for CNS metastases with associated raised intracranial pressure. Magnetic resonance imaging (MRI) of the brain now demonstrated LM (Fig. 2) confirmed by CSF cytology (not shown). By direct sequencing, DNA from CSF cells harbored L858R predicting EGFR TKI sensitivity (Fig. 3, left panel) but not the T790M resistance mutation (data not shown). Because the result for T790M was negative in this sample, we performed a more sensitive fluorescence detection PCR-based assay that takes advantage of a PCR restriction fragment length polymorphism generated by the specific missense mutation (Fig. 3, right panel, arrow, positive control) [6]. That result was also negative, as only the wild type peak was detected (Fig. 3, right panel, bottom). Therefore, we hypothesized that the LM remained sensitive to an EGFR TKI if sufficiently high concentrations of drug could be achieved in the CSF.

The erlotinib concentration required to inhibit growth of cell lines harboring L858R by 50% (IC_{50}) is 100 nM (nM) [2]. Standard dose erlotinib (150 mg daily) achieves 3000 nM in plasma [7], but CSF concentrations of EGFR TKIs are as low as 1% plasma levels below the IC_{50} [3, 8]. Increasing the daily dose of gefitinib to enhance CSF penetration has been an effective strategy [3], but gefitinib is no longer available in the United States following failure in phase III NSCLC trials. An analogous increase of the daily erlotinib dose above 150–200 mg daily induces unacceptable toxicity. However, weekly high-dose erlotinib up to 2000 mg is tolerable [4].

Pharmacokinetic analysis of CSF from another patient with NSCLC LM (not shown) treated with 1500 mg erlotinib weekly demonstrated a peak plasma concentration of 11,300 nM with a concurrent CSF concentration of 130 nM. Therefore, such high dose weekly administration of erlotinib achieved a CSF concentration exceeding the IC_{50}.

Therefore, to increase CSF penetrance over standard daily erlotinib dosing in this patient, we initiated high-dose weekly erlotinib at 1000 mg then 1200 mg; persistent nausea precluded higher doses. Pharmacokinetic analysis was not undertaken in this patient. After 1 month there was a partial radiographic response of LM on brain MRI (Fig. 2b) and after 2 months in the cauda equina (not shown). However, hydrocephalus and persistent symptoms referable to increased intracranial pressure led to a VP shunt and whole-brain radiation therapy, after which she resumed treatment with 1500 mg weekly erlotinib. One month later, progressive intra-thoracic disease led to initiation of cetixumab and erlotinib was continued but changed to low dose (100 mg) daily. She survived 14 months following the diagnosis of CNS disease.

Discussion

Patients with *EGFR* mutant lung cancer taking EGFR TKIs may develop LM because of inadequate drug penetration into the CSF through a relatively intact blood-brain barrier, rather than from secondary resistance mutations, despite the concurrent acquisition of resistance mutations outside the CNS [3]. This phenomenon may reflect EGFR independence. However, another explanation is the lack of selective pressure on EGFR-

dependent tumor cells during inadequate CSF drug exposure [3]. High-dose weekly erlotinib administration is tolerable [4]. Moreover, such “pulsatile” kinase inhibition induces cancer cell apoptosis as effectively as chronic inhibition [9].

The *EGFR* kinase domain mutations that confers sensitivity to the EGFR TKIs erlotinib and gefitinib [2] occur in 10% (USA) to 25% (Asia) of NSCLCs as either multi-nucleotide in-frame deletions in exon 19 or single missense mutations in exon 21 such as L858R [2]. However, secondary mutations during therapy, such as T790M, lead to acquired TKI resistance [2]. LM may not harbor resistance mutations [3], suggesting retained TKI sensitivity if therapeutic drug concentrations are achieved in CSF. Others have reported a case of leptomeningeal NSCLC that responded empirically to erlotinib 600 mg every 4 days, but without mutational or pharmacokinetic analysis [10]. We induced sustained control of LM harboring L858R but not T790M with high-dose weekly erlotinib and whole brain radiotherapy following progression on standard daily dosing. Such “pulsatile” therapy is tolerable [4] and, as we demonstrate here via analysis of CSF from a similarly-dosed patient, achieves therapeutic CSF erlotinib concentrations. Improved outcome for LM from NSCLC may be achieved by strategies that yield higher CSF levels of EGFR TKIs, either through increased daily dosing [3], pulsatile dosing described here and elsewhere [10], or new formulations of existing EGFR TKIs that penetrate the blood-brain barrier more effectively or can be administered intrathecally.

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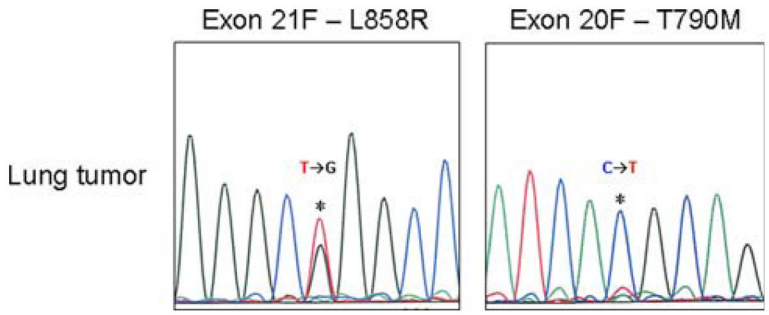

Fig. 1.

Direct forward (F) sequencing chromatograms of *EGFR* exons 18–21, encoding the kinase domain, using DNA extracted from a progressing lung lesion (clinically acquired resistance to erlotinib). The tumor contained a T → G change at nucleotide 2573 (*left* panel, *asterisked black peak*) resulting in the EGFR TKI sensitizing mutation in exon 21 substituting arginine (R) for leucine (L) at amino acid position 858 (L858R). It also contained the C → T change (*right* panel, *asterisked small red peak*) at nucleotide 2369, resulting in the exon 20 mutation substituting methionine (M) for threonine (T) at amino acid position 790 (T790M) that engenders acquired resistance to EGFR TKIs molecularly

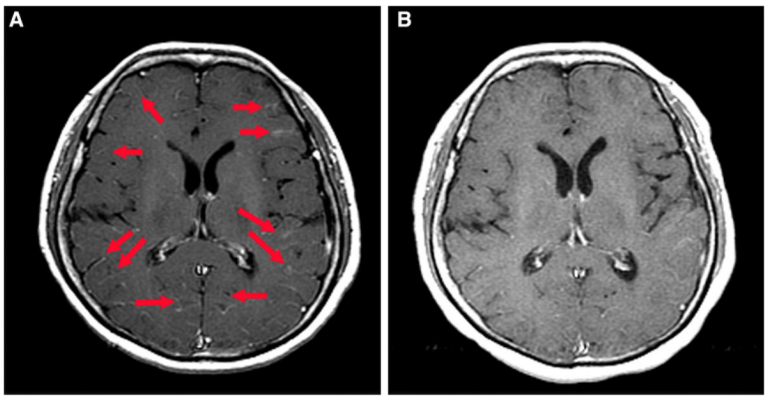

Fig. 2.
Gadolinium-enhanced brain MRI at diagnosis of LM (**a**, *arrows*), and showing partial response after 1 month of pulsatile erlotinib (**b**)

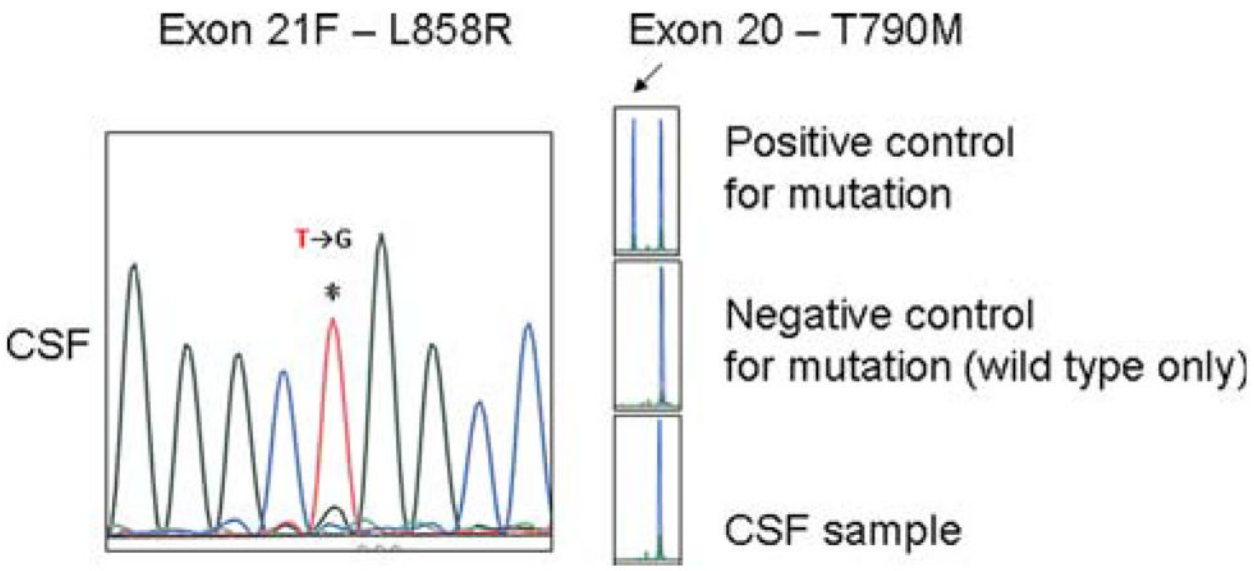

Fig. 3.

Direct forward (F) sequencing chromatogram of DNA from leptomeningeal tumor cells demonstrated L858R (*left* panel, mutant *black peak with asterisk*) but not T790M (not shown). Therefore, a more sensitive T790M assay was performed (*right* panel) which also did not detect the acquired resistance mutation