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% (IC50) 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 IC50 [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 IC50.
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.