Erlotinib Accumulation in Brain Metastases from Non-small Cell Lung Cancer: Visualization by Positron Emission Tomography in a Patient Harboring a Mutation in the Epidermal Growth Factor Receptor

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Introduction: Drugs directed toward the epidermal growth factor receptor (EGFR), such as erlotinib (Tarceva®) and gefitinib (Iressa®), are used for the treatment of patients with advanced non-small cell lung cancer (NSCLC), including patients with brain metastases. However, whether erlotinib actually enters into brain metastases has not been adequately elucidated. In this study, we investigated the accumulation of [^{11}C]-erlotinib by positron emission tomography (PET) combined with computed tomography (CT) and magnetic resonance imaging (MRI).

Methods: A 32-year-old patient with NSCLC and multiple brain metastases was treated with first-line erlotinib. EGFR mutations were determined by analyzing a fine-needle lung tumor biopsy taken before the treatment. A PET/CT of the brain with [^{11}C]-erlotinib was performed during treatment, and a MRI of the head and a CT of the chest were performed pre- and posttreatment.

Results: The primary lung tumor displayed an erlotinib-sensitizing exon 19 deletion in the EGFR gene, and [^{11}C]-erlotinib PET/CT showed accumulation in the brain metastases. Posttreatment MRI and CT demonstrated regression of both brain metastases and primary lung tumor.

Conclusion: Our data demonstrated that erlotinib accumulated in brain metastases in a NSCLC patient who responded to the treatment.

Key Words: NSCLC, EGFR mutation, Erlotinib, Brain metastases, PET.

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Epidermal growth factor receptor (EGFR) represents an attractive target for treatment of many epithelial cancers due to its role in tumorgenesis, proliferation, and prognosis.[1] Tyrosine kinase inhibitors (TKI) targeting the EGFR, such as erlotinib (Tarceva®) and gefitinib (Iressa®), are used for treatment of patients with advanced non-small cell lung cancer (NSCLC), either as first-line treatment of patients harboring an EGFR mutation or as second-/third-line treatment after platinum-based doublet chemotherapy.[2,3] Dramatic responses to the treatment have been observed in patients with specific EGFR mutations in the ATP-binding domain of the EGFR protein. Most frequently, a deletion in exon 19 and a point mutation in exon 21 (L858R) are encountered, and both are associated with TKI sensitivity.[4,5]

Patients presenting with symptomatic brain metastases and meningeal carcinomatosis have a poor prognosis, with a median survival of 4 to 11 weeks.[6] The standard treatment is whole-brain radiotherapy, but the clinical benefit is questionable. Intravenous chemotherapy is of limited effect due to poor penetration of the chemotherapeutic drugs into the brain tissue and cerebrospinal fluid.[6,7] Intrathecal chemotherapy has no clear effect in patients with solid tumors but severely reduces quality of life due to side effects.[8]

Recently, several case reports have reported clinical and objective responses of brain metastases in patients with NSCLC after treatment with erlotinib or gefitinib.[9–11] However, the ability of these drugs to accumulate in brain metastases has, to our knowledge, not previously been studied.

Employing dynamic positron emission tomography (PET)/computed tomography (CT) with [^{11}C]-erlotinib, we investigated whether erlotinib accumulated in brain metastases of a patient with NSCLC harboring an EGFR mutation.

CASE REPORT

A 32-year-old Chinese woman was hospitalized because of severe nausea, vomiting, headache, and multiple convulsions. She had no medical history and had never smoked. On admission, she had a performance status (World Health Organization) of 4 (bedridden and completely disabled).

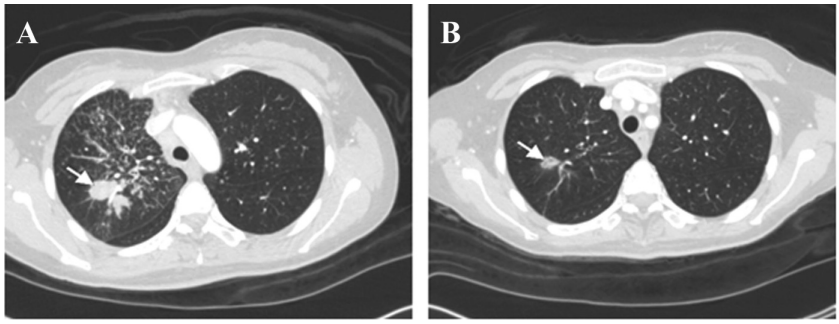

FIGURE 1. Computed tomography of the chest before (*A*) and 3 weeks after start of treatment with erlotinib (*B*) of a 32-year-old woman diagnosed with non-small cell lung cancer with brain metastases who harbored an exon 19 mutation. Arrows indicate the tumor sites.

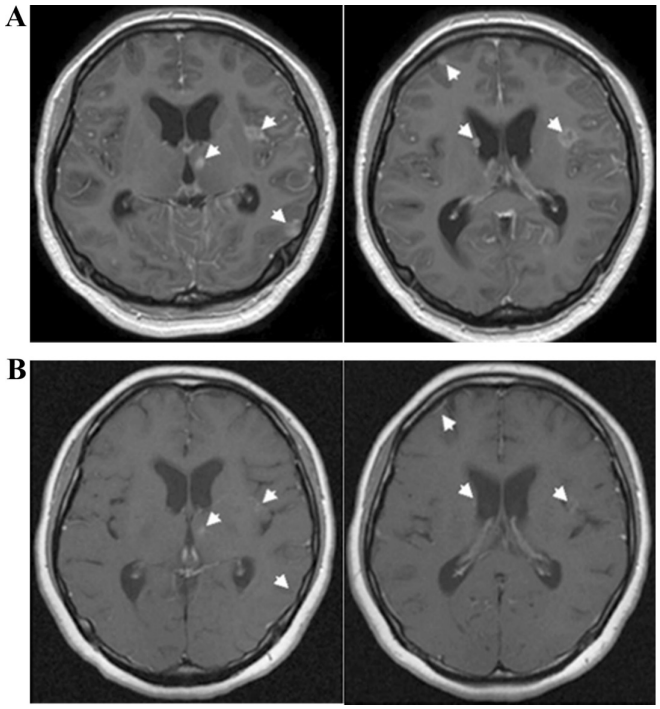

FIGURE 2. Two axial magnetic resonance imaging of the brain before (*A*) and 3 weeks after start of treatment (*B*) of a 32-year-old woman diagnosed with non-small cell lung cancer and brain metastases harboring an exon 19 mutation. Arrows indicate positions of brain metastases.

The patient was diagnosed as having NSCLC (Figure 1*A*), multiple brain metastases, and meningeal carcinomatosis visualized by magnetic resonance imaging (MRI) (Figure 2*A*). Oral administration of 150 mg erlotinib daily was chosen as first-line treatment. No radiotherapy was given. Within 2 weeks, the patient became fully oriented and regained her ability to walk and feed herself, although she still suffered from nausea and impaired vision. MRI 3 weeks after the start of treatment showed a nearly complete remission of the brain metastases and no signs of meningeal carcinomatosis (Figure 2*B* compared with Figure 2*A*), and CT of her chest showed a marked reduction of the mass initially observed in the lung (Figure 1*B* compared with Figure 1*A*). New scans after 11 weeks confirmed the results.

Because of a severe grade 4 generalized papulopustular rash, the dose of erlotinib was reduced to 50 mg daily 2 weeks after the start of the treatment. Continuing on this dose, the patient remained in remission for 10.5 months before progression of the disease, and she died 11.5 months after the start of the treatment. The patient had not received other antineoplastic treatments nor was radiotherapy given at any time.

The patient gave informed consent, and the study was approved by the Ethics Committee (M-20080012, M-20080050) and the Danish Medicines Agency (2512-96464). The study was conducted according to the declarations of Helsinki.

METHODS

PET Study

Accumulation of erlotinib in the brain metastases was assessed 8 months after the start of erlotinib treatment by PET/CT using [^{11}C]-erlotinib, a novel PET tracer developed by our group.[12] Before the PET/CT study, the patient did not take the drug for 7 days, thereby minimizing competition between the binding of unlabeled and labeled erlotinib to receptor sites on the tumor cells.

Imaging was performed using an advanced PET/CT imaging system, Siemens Biograph 64 (Siemens AG, Erlangen, Germany) (Memon et al., unpublished data, 2011). A low-dose CT acquisition of the head and thorax was performed before administration of the tracer for attenuation correction and anatomical references.

[^{11}C]-Erlotinib (433 MBq) was administered intravenously, followed by dynamic PET recording of the brain for 60 minutes using list-mode acquisition. Images were reconstructed by an attenuation-weighted ordered-subsets expectation maximization algorithm (3 iterations, 21 subsets) followed by a postreconstruction smoothing Gaussian filter (3-mm full width at half maximum). PET images were coregistered with gadolinium-enhanced T1-weighted MR images.

Mutation Analysis

A fine-needle aspiration biopsy of the lung tumor tissue was removed 2 weeks before the start of treatment. Mutation analysis of exon 19 of the EGFR gene by the Sanger sequencing technique was performed.

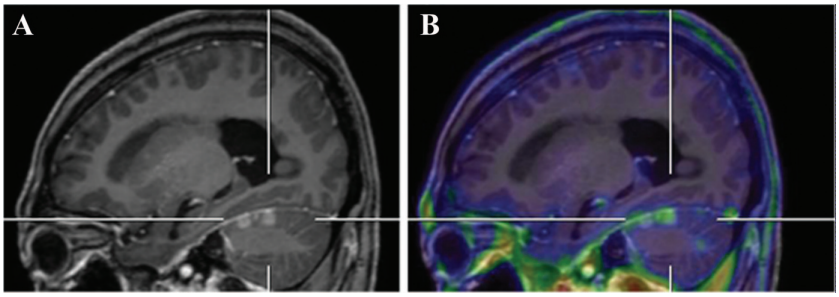

FIGURE 3. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) (*A*) coregistered with [^{11}C]-erlotinib positron emission tomography (PET) (sum image, 5–60 minutes after tracer administration) (*B*) of a 32-year-old woman diagnosed with non-small cell lung cancer and brain metastases harboring an exon 19 mutation. The selected MRI image shows two metastatic lesions in the cerebellum. The [^{11}C]-erlotinib PET image shows abnormal accumulation in focal areas corresponding to the two lesions on the MRI scan. Note the absence of [^{11}C]-erlotinib accumulation in normal brain tissue.

RESULTS

PET Study

The PET images showed increased ^{11}C activity in brain foci corresponding to MRI foci, with increased contrast accumulation indicating tumor nodules (Figure 3). Uptake in muscle tissue and meninges was also observed. The ^{11}C activity in the cerebral cortex was very low, making delineation of tumor tissue from normal brain tissue easy (Figure 3); tumor-to-cortex ratios up to 10:1 were observed.

Mutation Analysis

The mutation analysis revealed an exon 19 deletion (delL747-P753insS) in the EGFR gene.

DISCUSSION

Using ^{11}C-erlotinib PET/CT images combined with MR images, we demonstrated erlotinib accumulation in metastatic lesions in the brain of a patient with NSCLC harboring a deletion in exon 19 of the EGFR gene. Moreover, treatment with erlotinib as monotherapy was followed by a reduction in size of both the brain metastases and the primary lung tumor.

Dynamic PET recording showed continued ^{11}C-erlotinib accumulation during the 60-minute study period, indicating binding to receptors on the tumor cells. Interestingly, no accumulation was seen elsewhere in the cortex.

The finding of erlotinib accumulation in brain metastases is in accord with the dramatic response of this drug on the brain metastases both in our patient and in previously described patients.[9,11] There is increasing evidence that most patients with partial or complete responses to erlotinib or gefitinib have a somatic mutation in the EGFR possibly because the binding affinity of erlotinib to a mutated receptor is much higher than for a nonmutated receptor.[13] This could explain the clinical observation that a dose as low as one-third of the recommended dose was sufficient to maintain remission in our patient and other patients.[14]

A small Korean study ($N = 23$) reported the use of a TKI targeting the EGFR in the first-line treatment of lung cancer patients with brain metastases.[15] This study, which included only never-smokers (known to have a high probability of harboring EGFR mutations) with nonsymptomatic brain metastasis, demonstrated a MRI-detected intracranial response rate of 73.9%, according to RECIST.

In conclusion, our study showed a beneficial effect of erlotinib in a patient with highly symptomatic brain metastases and demonstrated erlotinib accumulation in the metastatic lesions.

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