Efficacy of Erlotinib for Brain and Leptomeningeal Metastases in Patients with Lung Adenocarcinoma Who Showed Initial Good Response to Gefitinib

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Introduction: The efficacy of high-dose (1250 mg/d) gefitinib for the treatment of leptomeningeal metastasis in a patient with lung cancer harboring a mutation in the epidermal growth factor receptor (EGFR) gene was previously reported. We speculate that erlotinib, instead of high dose of gefitinib, may be also effective for the treatment of central nervous system (CNS) lesions, as trough serum concentration of erlotinib is nine times higher than that of gefitinib.

Patients and Methods: Patients with lung cancer in whom CNS lesions developed after an initial good response to gefitinib for extra CNS lesions were enrolled in the study. Tumor response, performance status, neurologic symptoms, and survival were retrospectively evaluated.

Results: All seven patients had *EGFR* mutations in their primary tumors except one patient. The median interval between gefitinib withdrawal and erlotinib administration was 5 days. Three patients showed partial response, three had stable disease, and one had progressive disease. Performance status and symptoms improved in five patients. The overall survival from the initiation of erlotinib treatment ranged from 15 to 530 days (median, 88 days).

Conclusions: Erlotinib was a reasonable option for the treatment of CNS diseases that appeared after a good initial response of extra CNS disease to gefitinib.

Key Words: Lung cancer, Brain metastasis, EGFR-TKI, BBB, CNS.

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Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) have been widely used for the treatment of patients with non-small cell lung cancer (NSCLC). Somatic activating mutations of the tyrosine kinase domain of the *EGFR* gene are highly associated with sensitivity of NSCLC to EGFR TKIs.[1–4] Nevertheless, the disease in the majority of these patients eventually progresses, despite an initial dramatic response to treatment, after a median of about 10 months.[5,6] The central nervous system (CNS), e.g., the brain or the leptomeninges, is a common site for metastasis of NSCLC. Patients with CNS metastasis in general suffer from deterioration of performance status (PS) and therefore do not have a long-survival time. Although the recent advent of radiosurgery techniques confers better local control of brain metastases, currently there is no efficient method of treatment for leptomeningeal metastases.

High-dose gefitinib (1250 mg/d) was reportedly effective for the treatment of leptomeningeal metastasis in a patient with lung cancer harboring an *EGFR* mutation.[7] In this study, the gefitinib concentration in the cerebrospinal fluid (CSF) was 6.2 nM at a dose of 500 mg daily, whereas it was 39 nM at a dose of 1250 mg daily, with a serum concentration of 3730 nM. On the other hand, the median IC_{50} value of cell lines that carry an activating mutation of the *EGFR* gene is 90 nM.[8] This difference in concentration between the serum and the CSF is thought to be associated with the blood–brain barrier (BBB).

Erlotinib is also an anilinoquinazoline compound that specifically inhibits EGFR tyrosine kinase, similarly to the action of gefitinib. Its dose was set at 150 mg daily, which equals to the maximum tolerated dose (MTD) of this drug. Trough serum concentration of erlotinib (administered at 150 mg/d) is 3.5 μM that is nine times higher than that of gefitinib (0.4 μM) administered at the usual dose of 250 mg/d,[9–13] approximately one third of the MTD of gefitinib (700 mg/d).

Prompted by these observations, we speculated that erlotinib, instead of a high dose of gefitinib, may also be effective for the treatment of CNS lesions in patients with NSCLC harboring *EGFR* mutations who showed an initial good response to gefitinib. We report the response of brain and leptomeningeal metastases to erlotinib in seven of these patients.

PATIENTS AND METHODS

Patients

The records of 43 patients with NSCLC that was pathologically diagnosed and treated with erlotinib at our institution between April 2005 and September 2008 were retrospectively reviewed in this study. We identified those who had been treated with erlotinib for CNS lesions that developed after an initial good response of their extra CNS lesions to gefitinib. This study was approved by the institutional review board of the Aichi Cancer Center Hospital, and written informed consent for genetic analysis was obtained for each patient at the time of diagnosis or operation.

Treatment and Response Evaluation

Medical records, serum carcinoembryonic antigen (CEA) levels, chest radiograph, chest–abdominal computed tomography scan, brain magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) were retrospectively reviewed. Erlotinib of 150 mg daily were administered to the patients until progressive disease. They all had previously received 250 mg gefitinib daily. Treatment response was evaluated according to the RECIST. Because of retrospective nature of this study, strict application of RECIST was impossible. Nevertheless, we defined tumor response when the long axis of the target lesion shrank by more than 30%.

Mutational Analysis

We extracted RNA or DNA from tumor samples and analyzed *EGFR* mutations as previously reported.[5,14] Briefly, we performed direct sequencing of the product of the reverse transcription polymerase chain reaction of exons 18 to 21 of the *EGFR* gene.

RESULTS

We identified seven patients who met our criteria. Patient characteristics and clinical courses are summarized in Table 1. There were five women and two men, and their ages ranged from 58 to 81 years (median, 61 years). We confirmed the presence of *EGFR* mutations in the primary tumors of all patients, with the exception of one patient, for whom a tumor specimen was not available. Four patients had a deletion mutation in exon 19, and two had a point mutation in exon 21 (L858R). Six patients had been locally pretreated with whole brain radiation therapy or radiosurgery, before disease progression in CNS.

Disease outside of the CNS was initially controlled by gefitinib monotherapy in all seven patients. The median duration of gefitinib administration was 310 days (range, 113–1211 days), and all patients showed progressive disease in their CNS; four patients exhibited disease progression in the CNS, and the other three patients developed new symptomatic brain or leptomeningeal metastases associated with deterioration of PS. Disease outside of CNS had been under

TABLE 1. Clinical Characteristics of Patients

Case	Age/ Sex	Histology	EGFR Mutation	Initial Metastatic Sites	Initial Response of Extra CNS Lesions to G	TTF to G, d	CNS Disease After G	Neurological Symptoms
1	81/M	Adeno	X19del	Brain, bone	CR	275	PD (new LMM)	Dysmnesia, gait disorder
2	63/F	Adeno	X19del	Lung, skin, Med LN	PR	516	PD (new brain)	Consciousness disorder
3	58/F	Adeno	L858R	Brain, lung	SD	113	PD (new LMM)	Headache, postural disorder
4	60/F	Adeno	X19del	Brain, bone	SD	1211	PD (new LMM)	Syncope, polyopia
5	64/M	Adeno	NA	Brain, lung	PR	192	PD	Consciousness disorder, gait disorder
6	60/F	Adeno	L858R	Brain, bone	NA	242	PD	Dysmnesia, gait disorder
7	61/F	Adeno	X19del	Bone, Med LN	CR	382	PD (new LMM)	Headache, vomiting

G, gefitinib; E, erlotinib; Med LN, mediastinal lymph nodes; TTF, time to treatment failure; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NA, not available; LMM, leptmeningeal metastasis.

TABLE 2. Erlotinib Treatment in Patients with CNS Involvement

Case	Interval Between G and E, d	Response of CNS Lesions to E	Change of PS	Metastasis-Related Neurological Symptoms	CEA Level, ng/ml	Interval Between E Start and Death, d	Adverse Effects
1	35	PR	4 → 4	Improved	43.6 → 11.5	178	Rash, FN
2	2	SD	3 → 1	Improved	451.0 → 7.1	247	Rash
3	47	SD	4 → 3	Improved	67.0 → 47.6	60	—
4	5	PR	1 → 1	Improved	3429.5 → 1294.5	530	Rash, diarrhea
5	2	PR	3 → 2	Improved	NA	88	Rash
6	8	SD	4 → 4	Progress	17.4 → 9.5	15	—
7	1	NA	3 → 4	Progress	136.7 → 110.8	23	—

G, gefitinib; E, erlotinib; CNS, central nervous system; PS, performance status; CEA, carcinoembryonic antigen; PR, partial response; SD, stable disease; NA, not available; FN, febrile neutropenia.

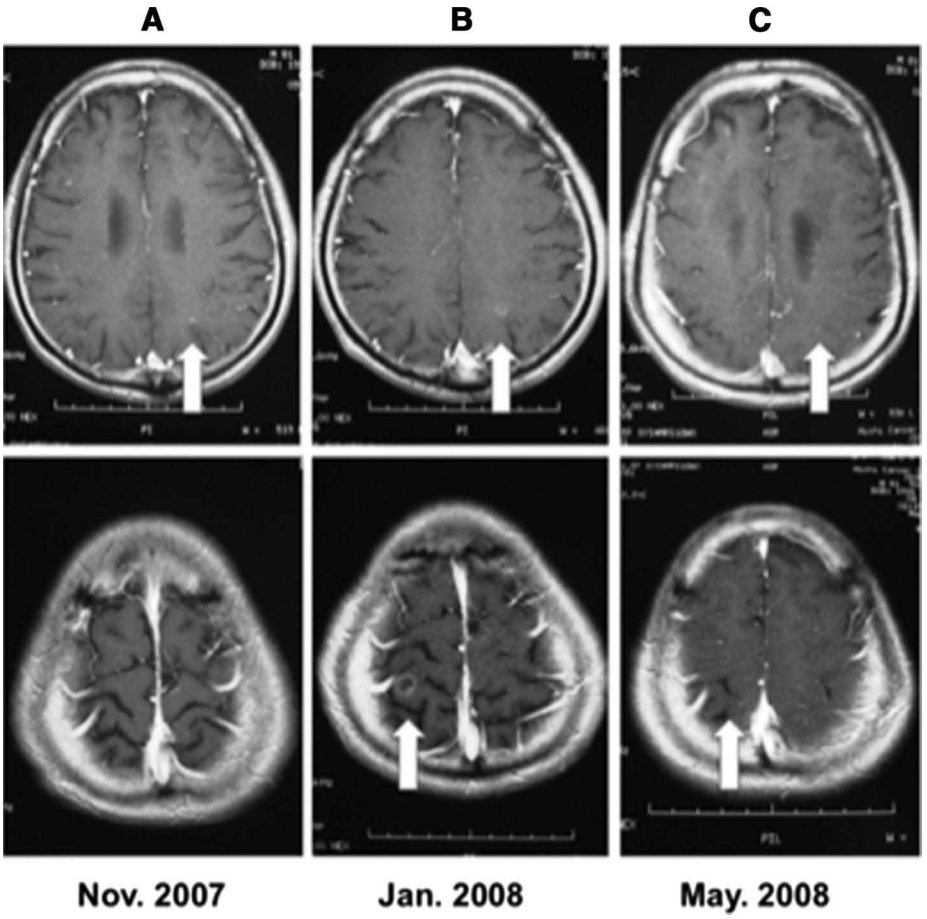

FIGURE 1. Contrast-enhanced T1-weighted magnetic resonance imaging (MRI) of the brain of patient 1. *A*, MRI study performed 8 months after initiation of gefitinib. A small nodule was in the occipital lobe (arrow), but no lesions were recognized in parietal lobe. *B*, The occipital lesion increased in size, and a new lesion appeared in parietal lobe in January 2008. *C*, The brain metastases shrunk 4 months after the initiation of erlotinib therapy.

good control in all patients during gefitinib therapy. Gefitinib was replaced with erlotinib without interposition of other drugs. The duration of drug holiday ranged from 1 to 47 days (median, 5 days). The PS in most patients at the initial erlotinib administration was 3 or 4.

Using RECIST, we found that three patients showed partial response, three patients remained stable disease, and diagnostic imaging was not available for one patient (Table 2). PS and metastasis-related neurologic symptoms improved in five patients, whereas the remaining two patients had disease progression. We confirmed that the CEA levels were reduced in six patients after erlotinib administration, with the exception of one patient, for whom information on CEA level was not available.

EGFR mutation analysis performed in a CSF sample from the patient 7 before erlotinib treatment revealed a point mutation in exon 20 (T790M), which is regarded as a resistant mutation[15,16] in addition to an exon 19 deletion mutation. Her disease progressed rapidly, even after replacement of gefitinib with erlotinib, and she died 23 days after the drug switch.

Case Report of Patient 1

The patient was an 81-year-old man who underwent left upper lobectomy in August 2006. The tissue sample of his primary tumor carried a deletion mutation in exon 19 of the *EGFR* gene. Nevertheless, his serum CEA level was 13.9 ng/ml in March 2007. Although he was asymptomatic, his brain MRI and PET scan revealed multiple metastases in the brain and bone. We treated him with 250 mg of gefitinib daily because he was elderly and had an *EGFR* mutation. The serum CEA level had decreased to 6.3 ng/ml in May 2007. We discontinued gefitinib treatment because of headache and general fatigue at December 25, 2007. Although the PET and computed tomography scans revealed remarkable improvement of bone metastasis, the brain MRI revealed the presence of new brain metastases (Figure 1*A*, *B*) and new leptomeningeal metastasis, and the serum CEA level increased to 43.6 ng/ml in January 2008. Dysmnesia and gait disorder became apparent, which escalated him to PS 4. Because of a difficulty in swallowing, enteral nutrient and a daily dose of 150 mg of erlotinib dissolved in water were administered via a nasogastric tube from January 30. His dysmnesia improved within 1 month after the initiation of erlotinib treatment. MRI revealed a remarkable improvement of brain metastasis in May 2008 (Figure 1*C*). His serum CEA level decreased to 11.3 ng/ml in June 2008. He continued to take erlotinib for 178 days until he died of pulmonary lymphangiosis on July 28, 2008.

DISCUSSION

In this study, we showed that erlotinib elicited tumor responses and improvement of PS in three of seven patients

who developed CNS lesions after an initial good response of extra CNS lesions to gefitinib. Neurologic symptoms and serum CEA level improved in five of seven and six of six patients, respectively. In addition, brain MRI revealed partial response in three patients.

Gefitinib and erlotinib are similar anilinoquinazoline compounds. Although it seems that erlotinib has a slightly broader spectrum of kinase inhibition than gefitinib,[17] they are essentially EGFR-specific TKIs. The most prominent difference between these two drugs is the dose setting. Although the approved daily dose of erlotinib (i.e., 150 mg/d) is equal to the MTD, the daily dose of gefitinib was set at 250 mg/d, because response and survival were not different between 250 and 500 mg of gefitinib in two phase II trials.[18,19] This difference of dose setting is reflected in the differences observed in their serum concentration. The C_{max} and area under the curve were 2120 ng/ml and 38,420 ng/h/ml for a dose of erlotinib of 150 mg daily,[12] and 307 and 5041 ng/h/ml for a dose of gefitinib of 225 mg daily,[13] respectively. The administration of 700 mg of gefitinib resulted in Cmax and area under the curve of 2146 ng/ml and 36.077 ng/h/ml,[13] respectively. Nevertheless, several reports revealed an unsatisfactory disease control by erlotinib after gefitinib failure, with response rates ranging from 9.5 to 14%.[20,21] This can be explained by the fact that the 2 common mechanisms of acquired resistance to EGFR-TKI, i.e., T790M secondary mutation and *MET* gene amplification, are both refractory to gefitinib and to erlotinib.[22]

Animal studies revealed that the delivery of gefitinib to the CNS of normal mice is hindered by the BBB.[23] It is possible that gefitinib may not have free access to the brain in human,[24] as another small, low-molecular weight TKI, imatinib, is shown to have limited brain penetration.[25] Hence, the CSF concentration of gefitinib is usually much lower than that observed in the serum.[23] Although there are several reports that gefitinib is effective for the treatment of brain metastases of several tumors,[24,26–31] these observations are thought to be dependent on a combination of the degree of disruption of the BBB caused by tumor invasion[32] and a sensitivity of cancer cells to the drug. Thus, dose escalation is thought to be a reasonable strategy to circumvent the EGFR-TKI-sensitive tumor cells that are present in the CNS.

In this study, we used 150 mg of erlotinib instead of 1250 mg of gefitinib. Even after a very short interval, erlotinib conferred appreciable and meaningful clinical responses, which included the improvement of the level of consciousness. While preparing this manuscript, Yi et al.[33] reported that treatment of elrotinib or an increased dose of gefitinib is an effective therapeutic option for selected patient with NSCLC and leptomenigeal metastasis. This response can be explained as follows; tumor cells in the CNS had not previously been exposed to gefitinib and, therefore, did not need to develop a resistance mechanism, thus remaining sensitive to erlotinib which traversed the BBB because of its relatively higher serum concentration compared with that of gefitinib. In the case reported by Jackman et al., the tumors of the lung, liver, and intestine had a T790M mutation, in addition to the exon 19 deletion, while the T790M mutation was not detected in the postmortem CNS tumor specimens. Relatively short survival of patient 1 despite that the CNS lesions responded well to erlotinib can be interpreted as follows; gefitinib had reached to the extra CNS lesions and acquired resistance to TKI such as T790M had already developed. Therefore, even erlotinib could not control the extra CNS lesions despite improvement of brain metastasis.

In patient 7, tumor cells of the CSF had a T790M mutation after gefitinib treatment and before erlotinib administration. Her disease progressed rapidly, even after the switch to erlotinib treatment, and the patient died 23 days after the initiation of erlotinib administration, as could be expected. In this case, we speculate that gefitinib could reach the CNS, where it was able to control tumor cells for a while initially. Nevertheless, the resistant clone carrying the T790M mutation eventually developed during the 382 days of gefitinib administration.

In conclusion, we report the effectiveness of erlotinib for the treatment of CNS lesions after gefitinib failure. This situation is relatively common in Japan, because there was an interval of over 5 years between the approval of gefitinib and erlotinib in our country.

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