

Title:

Efficacy of increased-dose erlotinib for central nervous system metastases in non-small cell lung cancer patients with epidermal growth factor receptor mutation

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Abstract

Purpose Recent reports indicate that refractory central nervous system (CNS) metastases of non-small cell lung cancer (NSCLC) are improved by high-dose gefitinib or erlotinib administration. We describe a Japanese female with NSCLC and CNS metastases who was resistant to 75 mg daily erlotinib, but the metastases were improved by 150 mg daily erlotinib. We investigated the plasma and CSF concentrations of erlotinib at each dose as well as the correlation between the plasma and CSF concentrations of erlotinib.

Methods Including this patient, we administered 150 mg erlotinib daily to nine NSCLC patients with CNS metastases and measured the plasma and CSF concentrations just before administration on day 8. The concentrations were determined using high-performance liquid chromatography with ultraviolet detection.

Results The plasma and CSF concentrations of erlotinib at a dose of 75 mg were 433 nM and 14 nM, respectively. The plasma and CSF concentrations of erlotinib at a dose of 150 mg were increased to 1117 nM and 44 nM, respectively. The mean $\pm$ standard deviation of CSF concentrations and penetration rates were 106 ± 59 nM and $4.5 \pm 1.5\%$, respectively. There was a good correlation ($R^2 = 0.84$) between plasma and CSF concentrations ($P = 0.0005$).

Conclusions This study indicates that CSF concentrations of erlotinib depend on its plasma concentration. As seen in this patient, high CSF concentrations of erlotinib can be achieved by high-dose administration, and this finding suggests the efficacy of high-dose administration, especially to refractory CNS metastases of NSCLC patients.

Keywords

Non-small cell lung cancer; epidermal growth factor receptor; tyrosine kinase inhibitor; erlotinib; central nervous system metastasis; cerebrospinal fluid

Introduction

Patients with non-small cell lung cancer (NSCLC) who have somatic activating mutations of the epidermal growth factor receptor (EGFR) gene (*EGFR* mutations) generally respond to EGFR-tyrosine kinase inhibitors (EGFR-TKIs; e.g., gefitinib and erlotinib) [1,2]. Nevertheless, the majority of these patients experience eventual disease progression, despite an initial dramatic response to treatment. The central nervous system (CNS) is a common site of recurrence, which is thought to be due to penetration of the agents into the CNS [3,4]. A previous report described refractory CNS metastases of NSCLC that were improved by high-dose gefitinib [5]. Several cases in which CNS metastases resistant to gefitinib were improved by erlotinib have been also reported [6]. In addition, in several articles, intermittent, high-dose erlotinib improved CNS metastases that were resistant to continuous, normal-dose erlotinib [7-9]. These challenges are based on the hypothesis that high cerebrospinal fluid (CSF) concentrations may be achieved by high-dose administration of EGFR-TKIs, with higher CSF concentrations achieved by erlotinib compared with gefitinib. We previously reported the CSF concentrations of erlotinib and its penetration rates in four NSCLC patients with CNS metastases [10]. In this article, we describe a Japanese female with NSCLC and *EGFR* mutation having CNS metastases that are resistant to 75 mg daily erlotinib. The metastases were subsequently improved by 150 mg daily erlotinib. We investigated the plasma and CSF concentrations of erlotinib at each dose. Furthermore, including previous data, we investigated the correlation between plasma and CSF concentrations.

Patients and methods

Patients

A 66-year-old Japanese female was diagnosed with advanced lung adenocarcinoma and *EGFR* mutation (L858R) 3 years prior. Erlotinib had been administered as fourth line of treatment. Before the initiation of erlotinib, the patient had no CNS metastases. Although partial response (PR) was achieved, the erlotinib dose was reduced from 150 mg daily to 75 mg daily due to grade 3 fatigue. After progression-free survival (PFS) of 12 months, the patient experienced recurrent CNS metastases. The plasma and CSF concentrations of erlotinib just before administration of the 75-mg dose were 433 nM and 14 nM, respectively. The patient received whole-brain radiotherapy (WBRT), but the CNS metastases did not improve (Fig. 1A). The dose was subsequently increased to 150 mg daily; the plasma and CSF concentrations just before administration of erlotinib on day 8 erlotinib were 1,117 nM and 44 nM, respectively. Four weeks after initiation of 150 mg administration of erlotinib, CNS metastases improved (Fig. 1B).

We previously reported the plasma and CSF concentrations of four NSCLC patients with CNS metastases (cases 1-4) [10]. In addition to these patients, we investigated the plasma and CSF concentrations of four other NSCLC patients with CNS metastases (cases 5-8) (Table 1).

Methods

Blood and CSF samples were obtained just before administration of 150 mg erlotinib on day 8 when steady-state plasma concentrations of erlotinib were assumed to be achieved. Plasma and CSF concentrations of erlotinib were determined using high-performance liquid chromatography with ultraviolet detection as previously reported [11]. Before the collection of samples and analysis, we obtained written informed consent from all patients.

Statistical analysis

Linear regression was performed on the data in Figure 2 by fitting a straight line. The R^2 value was used to measure the strength of the relationship between the plasma and CSF concentrations of erlotinib. The 150 mg daily erlotinib data from this 66 year-old Japanese female patient were analyzed, and the 75 mg daily erlotinib data were excluded. Linear regression analysis, performed by using JMP 8 software (SAS Institute, Cary, NC, USA), was two-tailed, and P values less than 0.05 were considered statistically significant.

Results

The clinical characteristics of all patients ($n=9$) are summarized in Table 1. In CNS lesions, 7 of the 9 patients achieved PR (78%) and 5 of the 6 patients with *EGFR* mutations achieved PR (83%). Gefitinib was administered to three patients prior to erlotinib therapy; these patients achieved PR but had CNS recurrence after a long PFS of more than 6 months. Two of these three patients achieved PR after erlotinib therapy in spite of gefitinib resistance.

The plasma and CSF concentrations are summarized in Table 2. The mean $\pm$ standard deviation (SD) of CSF concentrations and penetration rates were 106 ± 59 nM and $4.5 \pm 1.5\%$, respectively. As seen in Figure 2, there was a good correlation ($R^2 = 0.84$) between plasma and CSF concentrations ($P = 0.0005$).

Discussion

This study demonstrated that there is a good correlation ($R^2 = 0.84$) between plasma and CSF concentrations of erlotinib ($P = 0.0005$), which indicates that high CSF concentrations can be achieved by high plasma concentrations. That is, high CSF concentrations can be achieved by high-dose erlotinib administration. CNS metastases of the 66-year-old Japanese female patient responded to 150 mg daily erlotinib despite resistance to 75 mg daily erlotinib, likely because of higher CSF concentrations. There are several reports based on the hypothesis that high CSF concentrations may be achieved by high-dose erlotinib administration [5-9], and our study supports this hypothesis.

The mean $\pm$ SD of CSF penetration rates were $4.5 \pm 1.5\%$ and this result was similar to that of recent another study [12]. However, the rates of our study were ranged from 3.2 to 7.7% and those of another study ranged from 2.5% to 13.3%, which indicates that there seem to be difference in the penetration rate among individuals. Recently, it has been reported that some transporters restrict brain penetration of erlotinib [13,14]. Polymorphisms of these transporters can be associated with this individual difference of the penetration rate.

Since systemic chemotherapy is thought to play a limited role in CNS metastases because of the belief that the brain is a pharmacological sanctuary, patients with NSCLC who showed initial good responses to EGFR-TKIs often had recurrent CNS metastases. Considering CSF concentrations, high-dose EGFR-TKIs can be effective for such refractory metastases. Furthermore, the association between CNS responses/recurrence and CSF concentrations should be investigated in the future.

Table 1. Patient characteristics

Case	Age (yr)	Sex	PS	Histology	<i>EGFR</i> gene	Smoking status	Previous chemotherapy regimen	Previous gefitinib (length of PFS)	Previous WBRT
1	59	F	3	Ad	NE	Never	3	Yes (10 months)	Yes
2	82	F	4	Ad	Wild type	Never	0	No	No
3	70	F	3	Ad	Wild type	Never	1	No	Yes
4	86	F	3	Ad	Ex 21; L858R	Never	1	Yes (7 months)	No
5	67	F	1	Ad	Ex 21; L858R	Never	1	No	No
6	72	M	0	Ad	Ex 21; L858R	Former	1	No	No
7	81	M	1	Ad	Ex 19 deletion	Former	1	Yes (46 months)	Yes
8	85	F	2	Ad	Ex 21; L858R	Never	1	No	Yes
*	66	F	1	Ad	Ex 21; L858R	Never	3	No	Yes

PS, performance status; *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; WBRT, whole-brain radiotherapy; F, female; M, male; Ad, adenocarcinoma; NE, not evaluated; Never, never-smoker; Former, former-smoker; *, 66-year-old Japanese female patient in this study.

Table 2. Plasma and cerebrospinal fluid concentrations of erlotinib, and central nervous system metastases response

Case	Plasma concentration (nM)	CSF concentration (nM)	Penetration rate (%)	CNS response¶
1	2082	98	4.7	Partial response
2	4059	202	5.0	Stable disease
3	4922	156	3.2	Partial response
4	544	42	7.7	Stable disease
5	2575	98	3.8	Partial response
6	1314	47	3.5	Partial response
7	1886	98	5.2	Partial response
8	5376	172	3.2	Partial response
* (75 mg erlotinib)	433	14	3.3	Progressive disease
* (150 mg erlotinib)	1117	44	3.9	Partial response
Mean ± SD¶¶	2653 ± 1734	106 ± 59	4.5 ± 1.5	

CSF, cerebrospinal fluid; CNS, central nervous system; *, 66-year-old Japanese female patient in this study; SD, standard deviation; ¶Responses were assessed by magnetic resonance imagings with use of the Response Evaluation Criteria in Solid Tumor version 1.1. ¶¶We analyzed the mean ± SD from all data except for the data from the 66-year-old Japanese female patient at a dose of 75 mg erlotinib.

Conflicts of interest

We declare that we have no potential conflict of interest related to this article.

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References

1. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304:1497-1500.
2. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350:2129-2139.
3. Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, Abrey LE (2005) High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer* 103:2344-2348.
4. Lee YJ, Choi HJ, Kim SK, Chang J, Moon JW, Park IK, Kim JH, Cho BC (2010) Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with nonsmall-cell lung cancer. *Cancer* 116:1336-1343.
5. Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borrás AM, Bailey C, de Jong F, Jänne PA, Johnson BE (2006) Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol* 24:4517-4520.
6. Katayama T, Shimizu J, Suda K, Onozato R, Fukui T, Ito S, Hatooka S, Sueda T, Hida T, Yatabe Y, Mitsudomi T (2009) Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. *J Thorac Oncol* 4:1415-1419.
7. Dhruva N, Socinski MA (2009) Carcinomatous meningitis in non-small-cell lung cancer: response to high-dose erlotinib. *J Clin Oncol* 27:31-32.
8. Clarke JL, Pao W, Wu N, Miller VA, Lassman AB (2010) High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. *J Neurooncol* 99:283-286.
9. Hata A, Kaji R, Fujita S, Katakami N (2011) High-dose Erlotinib for Refractory Brain Metastases in a Patient with Relapsed Non-small Cell Lung Cancer. *J Thorac Oncol* 6:653-654.
10. Togashi Y, Masago K, Fukudo M, Terada T, Fujita S, Irida K, Sakamori Y, Kim YH, Mio T, Inui K, Mishima M (2010) Cerebrospinal fluid concentration of erlotinib and its active metabolite OSI-420 in patients with central nervous system metastases of non-small cell lung cancer. *J Thorac Oncol* 5:950-955.

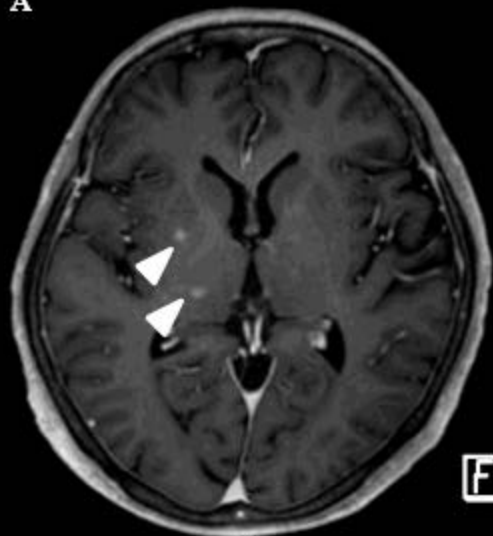
11. Zhang W, Siu LL, Moore MJ, Chen EX (2005) Simultaneous determination of OSI-774 and its major metabolite OSI-420 in human plasma by using HPLC with UV detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 814:143-147.
12. Masuda T, Hattori N, Hamada A, Iwamoto H, Ohshimo S, Kanehara M, Ishikawa N, Fujitaka K, Haruta Y, Murai H, Kohno N (2011) Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. *Cancer Chemother Pharmacol* 67:1465-1469.
13. Elmeligy MA, Carcaboso AM, Tagen M, Bai F, Stewart CF (2011) Role of ATP-binding cassette and solute carrier transporters in erlotinib CNS penetration and intracellular accumulation. *Clin Cancer Res* 17:89-99.
14. de Vries NA, Buckle T, Zhao J, Beijnen JH, Schellens JH, van Tellingen O (2010) Restricted brain penetration of the tyrosine kinase inhibitor erlotinib due to the drug transporters P-gp and BCRP. *Invest New Drugs* [Epub ahead of print].

Figure legends

Figure 1. Brain magnetic resonance imaging (MRI) in the 66-year-old Japanese female patient. A: Brain MRI after whole-brain radiotherapy demonstrated stable brain metastases (arrowheads). At this point, 75 mg daily erlotinib was administered. B: Four weeks after initiation of 150 mg daily erlotinib, the metastases were improved (arrowheads).

Figure 2. Correlation between plasma concentrations and cerebrospinal fluid (CSF) concentrations of erlotinib. A good correlation ($R^2 = 0.84$) was demonstrated ($P = 0.0005$).

A



B

