Continuous Administration of EGFR-TKIs Following Radiotherapy after Disease Progression in Bone Lesions for Non-small Cell Lung Cancer

MINEHIKO INOMATA[1,2], TAKEHITO SHUKUYA[1,3], TOSHIAKI TAKAHASHI[1], AKIRA ONO[1], YUKIKO NAKAMURA[1], ASUKA TSUYA[1], HIROTSUGU KENMOTSU[1], TATEAKI NAITO[1], HARUYASU MURAKAMI[1], HIDEYUKI HARADA[4], MASAHIRO ENDO[5] and NOBUYUKI YAMAMOTO[1]

Divisions of [1]Thoracic Oncology, [4]Radiation Oncology, and [5]Diagnostic Radiology, Shizuoka Cancer Center, Suntou-gun, Shizuoka, Japan; [2]First Department of Internal Medicine, University of Toyama, Toyama-city, Toyama, Japan; [3]Department of Respiratory Medicine, Juntendo University, Bunkyou-ku, Tokyo, Japan

Abstract. *Background: There have been reports suggesting that continuous administration of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is advantageous for patients in which disease progression was observed after the establishment of clinical benefit from EGFR-TKIs. We retrospectively evaluated the clinical course of patients who received continuous administration of EGFR-TKIs after disease progression was detected solely in bone lesions. Patients and Methods: The medical records of patients administered gefitinib or erlotinib between 2002 and 2010 were reviewed. We evaluated the progression-free survival (PFS) and overall survival (OS) in patients who had bone metastases after the establishment of clinical benefit from EGFR-TKI and who received radiation therapy for the bone lesion and continuous treatment with EGFR-TKI. Results: Ten patients were enrolled in this study. The median PFS and OS were 88 days and 330 days, respectively. Furthermore, a longer duration from the start of first EGFR-TKI to detection of bone metastases (p=0.0049) was identified as being significantly associated with a longer PFS. Conclusion: Our data suggest that continuous administration of EGFR-TKI is a treatment option for patients with bone metastases who previously benefited from therapy with EGFR-TKI.*

Correspondence to: Takehito Shukuya, MD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-chou, Suntou-gun, Shizuoka, 411-8777, Japan. Tel: +81 559895222, Fax: +81 559895783, e-mail: tshukuya@juntendo.ac.jp

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The epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), represented by gefitinib and erlotinib, have exhibited marked antitumor activity for lung cancer harboring *EGFR* gene mutations, and tumors with deletion of exon 19 and point-mutation of exon 21 (L858R) are known to be especially sensitive to treatment with EGFR-TKIs (1-3). However, it is problematic that almost all of the cases that initially show marked regression of the tumor size eventually become resistant to EGFR-TKIs, and that the disease progresses after a median of about 10 months (1-4).

Trastuzumab, an anti-human epidermal growth factor receptor-2 (HER-2) monoclonal antibody, has demonstrated a benefit for patients with breast cancer overexpressing HER-2. Trastuzumab is empirically continued after disease progression is documented, and the benefit of continuous administration of trastuzumab has been suggested in retrospective studies (5, 6). Furthermore, the efficacy of continuous administration of EGFR-TKIs for patients with lung cancer has been also reported. For example, Riely *et al.* evaluated the changes in the tumor diameter and standardized uptake value (SUV) of 18-fluoro-2-deoxy-D-glucose (FDG) after the cessation of EGFR-TKIs in patients with acquired resistance to EGFR-TKIs. All of the patients were presented with a prior radiographic response to EGFR-TKIs or had an *EGFR* exon 19 deletion or an L858R mutation. An increase in the tumor diameter and SUV 3 weeks after the cessation of EGFR-TKIs and a decrease in the tumor diameter and SUV 3 weeks after restarting the EGFR-TKIs was documented (7). Furthermore, it was reported that in patients in whom isolated central nervous system (CNS) failure was detected after an initial response to EGFR-TKI, there was a median progression-free survival (PFS) of 80 days and overall survival (OS) of 403 days due to treatment with radiotherapy for brain metastases and continuous administration of an EGFR-TKI (8). Based on these findings, it has been

Table I. *Characteristics of the patients of this study.*

Gender	Age (year)	Smoking status	Histology	Mutation	PS	Prior regimen, n	TKI		BP	Response to first TKI	Second progression
							First	Second			
M	50	Former	AD	*Exon19del*	1	0	G	E	+	PR	Bone
F	77	Never	AD	Unknown	1	0	G	G	–	SD	Brain
F	36	Never	AD	Unknown	1	0	G	G	–	PR	Bone
F	79	Never	AD	None (Wild-type)	1	3	E	E	–	SD	Bone
F	57	Never	AD	Unknown	2	0	G	G	+	SD	Brain, bone
F	67	Never	AS	Unknown	2	1	G	G	–	PR	Brain, bone, lung
M	59	Former	AD	Unknown	2	2	E	E	–	SD	Lung
M	66	Former	AD	Unknown	3	1	G	G	–	SD	Brain
F	60	Never	AD	Unknown	1	0	G	G	–	PR	Bone
M	60	Former	AD	Unknown	1	3	E	E	+	PR	Censored

AD, adenocarcinoma; AS, adenosquamous cell carcinoma; BP, bisphosphonate; E, erlotinib; F, female; G, gefitinib; M, male; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor.

suggested that continuous administration of EGFR-TKIs might show considerable efficacy in patients in which disease progression, especially in CNS metastases, were observed after initial clinical benefit from EGFR-TKIs (8, 9).

In some cases, bone metastases are considered to be relatively resistant to systemic chemotherapy, probably due to issues related to drug penetration. For example, it was reported that penetration of some antibiotics into bone lesions are poor (10, 11). We hypothesized that the disease progression in bone lesions is probably due to incomplete penetration of the EGFR-TKIs into bone, rather than to acquired systemic resistance to EGFR-TKIs in some of the patients who showed a prior clinical response to EGFR-TKIs. Thus, these patients might benefit from continuous EGFR-TKI administration after radiation therapy for the bone metastases. We retrospectively evaluated the clinical course of patients who received continuous administration of EGFR-TKIs after disease progression in bone lesions.

Patients and Methods

Patient selection. The medical records of patients administered gefitinib or erlotinib between 2002 and 2010 were reviewed. The inclusion criteria were as follows: i) histological or cytological confirmation of non-small cell lung cancer; ii) objective clinical benefit (partial response, PR, or stable disease, SD, longer than ~6 months) from treatment with an EGFR-TKI; iii) determination of progressive disease (PD) in bone metastases only while on continuous treatment with an EGFR-TKI (gefitinib or erlotinib) within the previous 30 days; and iv) cases in which EGFR-TKIs were administered continuously or restarted after radiotherapy for bone metastases without other intervening systemic therapy. The clinical information, such as the histological diagnosis, performance status (PS) at the date of detection of bone metastases and the second disease progression, as well as systemic therapies given after second disease progression, were reviewed from the medical records.

Treatment methods. Patients with bone metastases after establishment of clinical benefit from EGFR-TKIs received radiation therapy for the bone metastases (20 Gy/5 fractions or 30 Gy/10 fractions). EGFR-TKIs were continuously administered, or were discontinued temporarily during radiation therapy and were restarted after the radiation treatments were completed. When EGFR-TKIs were restarted, the selection of EGFR-TKI (gefitinib or erlotinib) was determined by the physicians in charge of the patients.

Statistical analysis. Tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST ver 1.0) guideline. Survival curves were drawn by the Kaplan-Meier method to analyze PFS and OS of the patients. The PFS was calculated from the initiation of radiotherapy for bone metastases to the date of detection of any disease progression or the date of occurrence of death from any cause, and was censored at the date of the last visit for patients without documented disease progression. The OS was calculated from the initiation of radiotherapy to the date of death, and censored at the date of the last visit for those patients whose deaths could not be confirmed. We compared the PFS between patients with different demographic factors using a log-rank test. The statistical analysis was performed using the statistical package JMP 9.0.0 (SAS Institute, Cary, NC, USA).

Results

Two hundred and fifty-six patients with histological or cytological confirmation of the presence of advanced non-small cell lung cancer showed a response of PR or SD longer than 6 months to an EGFR-TKI. Out of 256 patients, 16 patients (6.3%) had PD in bone metastases only. Out of these 16 patients, 10 received radiotherapy for the bone metastases and continuous administration of EGFR-TKIs. Table I shows the characteristics of these patients. Their median (range) age was 60 (36 to 79) years. Nine patients were diagnosed with adenocarcinoma and one patient was diagnosed with adenosquamous cell carcinoma. Five patients were

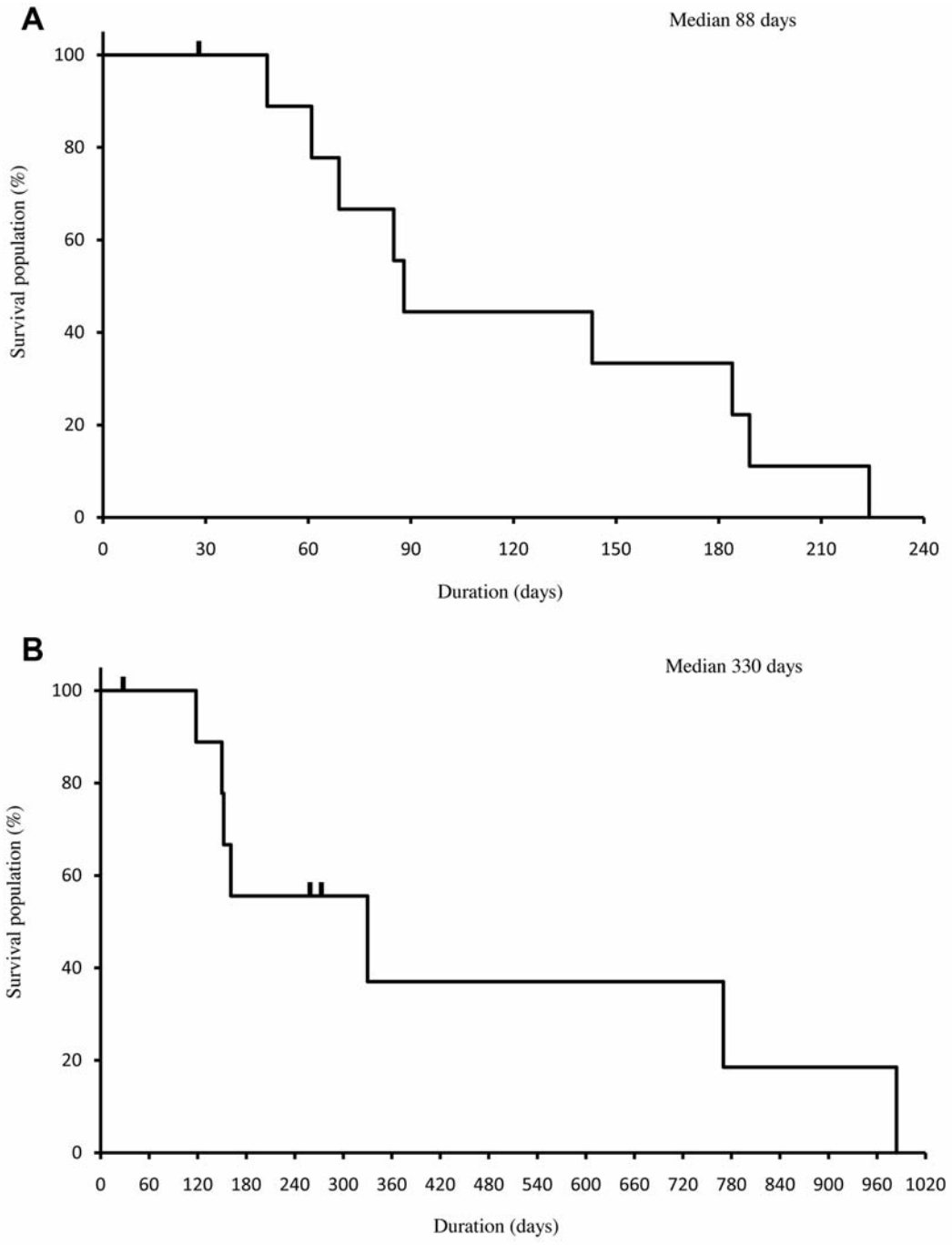

Figure 1. *The Kaplan-Meier curve for progression-free (A) and overall (B) survival is shown for the ten patients who had shown a prior response to an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) and received continuous administration of an EGFR-TKI after the detection of bone metastasis.*

administered EGFR-TKIs as first-line therapy. Wild-type *EGFR* was observed in tumor in one patient, but this case showed a response of SD longer than 6 months to treatment with the first EGFR-TKI. EGFR-TKIs were administered continuously during and after radiotherapy for three patients, and were ceased during radiotherapy and restarted after radiotherapy for seven patients.

The median PFS and OS were 88 days and 330 days, respectively (Figure 1). Table II shows the results of the univariate analysis of the PFS. A PS of 0 or 1 (p=0.048) and

Table II. *The results of the univariate analyses of the progression-free survival.*

		Median PFS (days)	95%CI	*p*-Value
Age				
<60	N=4	136	69-224	0.36
≥60	N=6	85	48-189	
Prior regimens				
<1	N=5	184	48-224	0.11
≥1	N=5	77	61-143	
Smoking history				
Former	N=4	69	61-224	0.73
Never	N=6	115.5	48-189	
PS				
<2	N=6	184	48-224	0.048
≥2	N=4	77	61-88	
Response to 1st TKI				
SD	N=5	88	61-89	0.56
PR	N=5	134.5	48-189	
Second TKI				
Gefitinib	N=6	86.5	48-189	0.38
Erlotinib	N=4	143	69-224	
Time to bone metastasis				
≥280	N=5	186.5	143-224	0.0049
<280	N=5	69	48-88	

PFS, progression free survival; PS, performance status; TKI, tyrosine kinase inhibitor.

a longer duration from the start of first EGFR-TKI to detection of bone metastasis (p=0.0049) were identified as being significantly associated with a longer PFS. Second disease progression was observed in nine out of the ten patients. Progression of the bone lesions was detected in six patients, brain or leptomeningeal metastases were detected in four, and growth of the primary lesion was noted in one patient. At the time of the second disease progression, the PS had deteriorated in four patients and maintained or improved in six patients. Four patients had a PS of 0 or 1, and five patients had a PS of 2 or more at the second disease progression. Patients with a PS of 2 or more received best supportive care, and four patients with a PS of 0 or 1 received further systemic therapy, including a cytotoxic agent or another EGFR-TKI.

One patient had lung infiltration 48 days after the initiation of radiation therapy to the upper arm, scapula, and cervical vertebrae (240 days after the start of gefitinib). Her bone lesions also exhibited obvious progression at the same time. Gefitinib was ceased because of the possible onset of interstitial lung disease associated with EGFR-TKIs. The patient died 161 days after the initiation of radiation therapy due to progression of lung cancer. There were no severe toxicities which required a change in treatment related to EGFR-TKIs for the other patients.

Discussion

The present study showed that the median PFS and OS in patients who received therapy with EGFR-TKIs continuously after the detection of bone metastases were 88 days and 330 days, respectively. Although we cannot compare the PFS between cases which received continuous administration of EGFR-TKIs and in which it ceased after radiotherapy due to the small number of patients, the observed PFS was comparable to the one shown in a previous study which reported the benefit of continuous administration of EGFR-TKIs after isolated CNS failure (8) and that of patients treated with pemetrexed or docetaxel as second-line chemotherapy (12). Furthermore, the median PFS was 186.5 days in patients whose bone metastases were detected later than 280 days from the start of EGFR-TKI treatment.

It has been suggested that EGFR-TKI penetration of the brain-blood barrier is incomplete (9, 13), and it was proposed that patients who experience only CNS relapse might not actually have systemic acquired resistance to EGFR-TKI therapy (14). Therefore, it can be hypothesized that continuous administration of EGFR-TKIs continues to have systemic effects after the progression in CNS was controlled by radiation therapy in the patients with isolated CNS failure. Similarly, the present study showed that patients with bone metastases can also benefit from continuous treatment with EGFR-TKI. Although there have been no reports about the delivery of EGFR-TKIs to bone lesions, we hypothesized that bone metastases may occur due to incomplete drug penetration into the bone, rather than to systemic acquired resistance to EGFR-TKIs in a subgroup of patients. Therefore, we believe that continuous treatment with an EGFR-TKI can confer systemic antitumor effects after radiation therapy for a bone lesion. In addition, in the present study, the PS was maintained or improved in six of the patients while they received EGFR-TKIs after the detection of bone metastases. Continuous therapy with EGFR-TKIs, in addition to radiotherapy, might contribute to the maintenance or improvement of the PS.

Our study has several limitations. The first limitation is clearly the small sample size. However, we consider the results of the present investigation worthwhile because cases showing disease progression only in bone lesion during treatment with an EGFR-TKI are not frequent, thus the results of our investigation might contribute to a better understanding of the clinical benefit of continuous treatment with an EGFR-TKI after disease progression. Secondly, the intervals between evaluations in the present study were not as closely monitored as those in a prospective study. However, all of the patients were evaluated approximately every two months by computed tomography, magnetic resonance imaging, bone scintigraphy or positron emission tomography.

Conclusion

We evaluated the clinical course of patients who showed disease progression in bone metastases after a prior response to EGFR-TKI and who received continuous administration of EGFR-TKIs after radiation therapy for the bone lesion(s). These patients had a median PFS of 88 days and a median OS of 330 days. A longer duration from the start of EGFR-TKI treatment to the detection of bone metastases, and a better PS appear to be predictors of a longer PFS, and the median PFS was 186.5 days in patients in whom bone metastases were detected later than 280 days from the start of EGFR-TKI therapy. These findings suggest that continuous administration of EGFR-TKIs is a feasible treatment option for patients with isolated bone metastases who initially showed a clinical benefit from EGFR-TKI treatment.

Conflict of Interest

All the Authors declare that they have no conflicts of interest.

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