Skeletal-related Events in Advanced Lung Adenocarcinoma Patients Evaluated *EGFR* Mutations

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Abstract

Background

The rate of lung cancer metastasis to the bone is high and skeletal-related events (SREs) decrease the quality of life in many patients. Recently, it was found that a subgroup of patients with non-small cell lung cancer (NSCLC) have specific mutations in the *EGFR (epidermal growth factor receptor)* gene. We assessed the SREs in advanced lung adenocarcinoma patients that evaluated *EGFR* mutations in whom bone metastasis was present.

Methods

We retrospectively investigated the clinical records of 377 patients with advanced NSCLC. Patients were evaluated for the presence of *EGFR* mutations, bone metastases, the incidence of SREs, and treatment history before the first SRE.

Results

A total of 78 patients who were evaluated for *EGFR* mutations had bone metastasis from lung adenocarcinoma. The most frequent site of bone metastasis was the spine (36.2%). SREs occurred in 37 patients (47.4%), the most common of which was bone radiotherapy (41.0%). Significant differences were not observed in the sites of bone metastases or the patterns of SREs between patients with and without *EGFR* mutations. The median time from bone metastasis to the first SRE was 5.8 months in all of the subjects, history of EGFR-tyrosine kinase inhibitor (TKI) treatment was significantly associated with longer median time to first SRE (14.2 months vs 1.3 months, $p<0.0001$), and the median time to first SRE of patients with PS 0-1 was longer (8.5 months vs 0.9 months, $p=0.0023$).

Conclusions

We found that SRE patterns have no difference between *EGFR* mutation positive and negative, and that the time from bone metastasis to the first SRE was longer in advanced lung

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adenocarcinoma patients with good PS and history of EGFR-TKI treatment.

Key Words: Bone metastasis; Skeletal-related event; *EGFR* mutation; Non-small cell lung cancer; Adenocarcinoma

Introduction

Lung cancer is the most common type of cancer and represents the leading cause of malignancy-related deaths worldwide[1]. Approximately 85% of all patients with lung cancer are diagnosed with non-small cell lung cancer (NSCLC) and half of those are adenocarcinoma.

Bone metastasis occurs in 30% to 40% of NSCLC patients and causes skeletal-related events (SREs)[2,3]. Bone pain, symptomatic pathologic fractures, spinal cord compression, and hypercalcemia of malignancy are common skeletal complications[2,3]. SREs decrease the quality of life in many patients during their clinical course due to the loss of mobility, independence, and social functioning[4], all of which have been shown to shorten survival[5].

A recent strategy for treating NSCLC focuses on the development of molecular-targeted therapies such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). These agents include erlotinib, gefitinib, and bevacizumab, which block angiogenesis. A subgroup of patients with NSCLC has specific mutations in the *EGFR* gene and these mutations correlate with the clinical responsiveness to EGFR-TKIs[6,7]. These agents have been effective in increasing progression-free survival[8-10] and in preventing SREs[11] and improving survival after bone metastasis[12].

However, the impact of *EGFR* mutation status in patients with bone metastasis from lung cancer is unknown. Therefore, we retrospectively evaluated the clinical predictive factors including *EGFR* mutations for SREs in patients with bone metastasis from advanced lung adenocarcinoma.

Patients and Methods

Study population

We retrospectively examined the clinical records of 377 patients who were histologically or cytologically diagnosed with NSCLC and were treated between January 2007 and December 2009 at Osaka City University Hospital. This study population consisted of patients who had inoperable stage Ⅲ or Ⅳ disease or who had postoperative recurrence. Among them, patients with bone metastasis during their clinical course were investigated in detail.

The TNM stage was evaluated using chest and abdominal computed tomography (CT), brain magnetic resonance image (MRI), bone scintigraphy, and/or positron emission tomography (PET)-CT. Tumor specimens were obtained during diagnostic or surgical procedures from patients with NSCLC. *EGFR* mutations were investigated with the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Bone metastasis was detected using bone scintigraphy, plain radiography, MRI, and/or biopsy. SREs included pathologic fractures, spinal cord compression, bone surgery, bone radiation therapy, or hypercalcemia of malignancy. SREs were evaluated from the time of bone metastasis diagnosis until May 2011. A history of cytotoxic chemotherapy, treatment with EGFR-TKIs, or bisphosphonates before the first SRE was confirmed.

Statistical analysis

The characteristics of the patients were compared using chi-squared tests. The time from bone metastasis to the first SRE was calculated and was analyzed using the Kaplan-Meier method, and differences were assessed by log-rank tests. Subsequent multivariate analyses were performed to detect the clinical factors that were significant in the univariate analysis using a Cox proportional hazard regression model. The results are reported in terms of hazard ratio and 95% confidence interval (CI). All analyses were 2-sided and p values less than 0.05 were considered statistically significant. The statistical analysis was performed with StatView 5.0 and JMP 9 software (SAS Institute, Inc., Cary, NC, USA).

Results

Patients

We sequentially investigated 377 patients with advanced NSCLC. The pathologic diagnosis was adenocarcinoma in 284 patients (75%). Among them, *EGFR* mutation status was evaluated in 193 patients whose tumor specimens were obtained during diagnostic or surgical procedures. Bone metastases were present in 78 (40%) of the 193 patients at the initial diagnosis or during the follow-up period (Fig. 1). Most of these 78 patients had a good performance status (PS) at the time of diagnosis of bone metastasis (PS 0/1 in 58 patients [74.4%]). The median age of these patients was 62.5 years (range, 34-85) and 41 of these cases (53%) were positive for *EGFR* mutations and 37 (47%) were negative. Cytotoxic chemotherapy and/or EGFR-TKIs were used to treat 69 of the 78 patients before their first SRE. Obvious differences were not observed in the characteristics of patients who were with or without SREs except for history of EGFR-TKI treatment before the first SRE (Table 1). The specific *EGFR* mutation sites were exon 18 G719S, exon 19 deletion, and exon 21 L858R in 7, 23, and 14 patients, respectively.

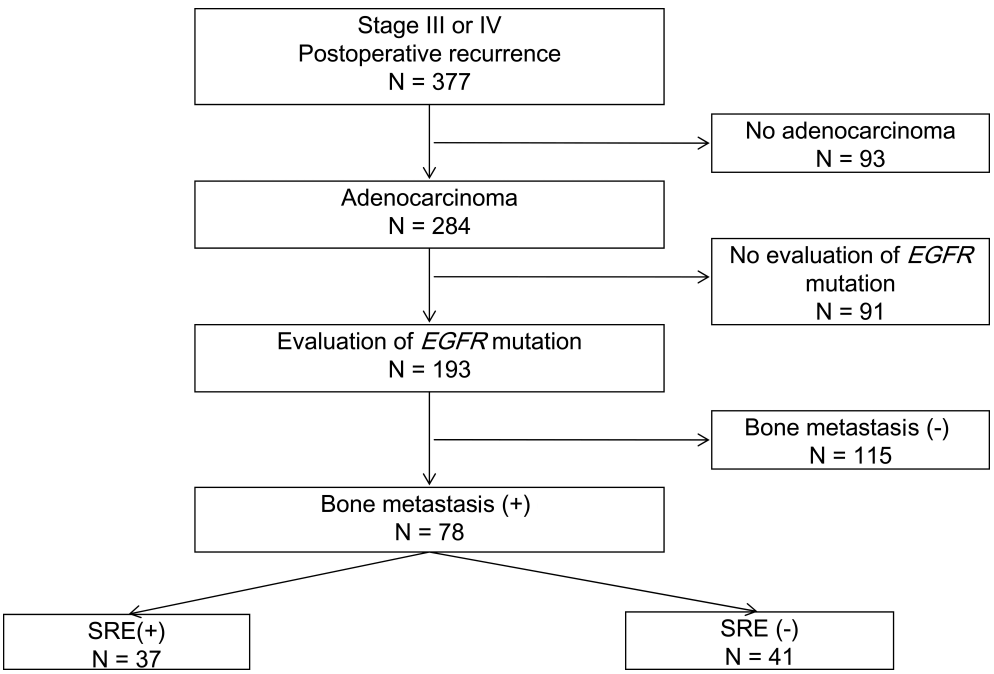

Figure 1. Incidence of bone metastasis and SRE events in patients with advanced lung adenocarcinoma, who were evaluated for *EGFR* mutations. SRE, skeletal-related event; and EGFR, epidermal growth factor receptor.

Table 1. Characteristics of patients with bone metastasis

Characteristic	No. of patients	Patients with SREs	Patients without SREs	p value[b]
		N (%)	N (%)	
Total	78	37 (47.4)	41 (52.6)	
Gender				
Male	47	21 (44.7)	26 (55.3)	0.5485
Female	31	16 (51.6)	15 (48.4)	
Age				
≧70 years	22	11 (50.0)	11 (50.0)	0.1073
<70 years	56	26 (46.4)	30 (53.6)	
Median (range)	62.5 (34-85)			
Smoking				
Former smoker	52	23 (44.2)	29 (55.8)	0.4227
Never smoked	26	14 (53.8)	12 (46.2)	
Performance status				
ECOG 0-1	57	25 (43.9)	32 (56.1)	0.2974
ECOG 2-3	21	12 (57.1)	9 (42.9)	
EGFR mutation				
Positive	41	17 (41.5)	24 (58.5)	0.2661
Negative	37	20 (54.1)	17 (45.9)	
Zoledronic acid treatment[a]				
Yes	17	10 (58.8)	7 (41.2)	0.2877
No	61	27 (44.3)	34 (55.7)	
EGFR-TKI treatment[a]				
Yes	39	13 (33.3)	26 (66.7)	0.0126
No	39	24 (61.5)	15 (38.5)	

[a]History of zoledronic acid treatment and EGFR-TKI treatment that were given before the first SRE.

[b]The analyses was performed by using the chi-square test.

NA, not available; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; and SRE, skeletal-related event.

Incidence of bone metastasis

A total of 78 patients were found to have bone metastasis during their clinical course. Among them, 54 patients (69%) had bone metastasis at the time of their initial lung adenocarcinoma diagnosis. *EGFR* mutations were present in 32 (59%) of the 54 patients. Many cases of bone metastasis involved multiple sites and the following 130 metastatic sites were recorded: 47 (36.2%) in the spine, 28 (21.5%) in the rib or clavicle, 24 (18.5%) in the pelvic bones, 15 (11.5%) in the extremities, 8 (6.2%) in the sternum, 5 (3.8%) in the skull, and 4 (3.1%) in the scapula. Of these sites, the proportions of patients who were *EGFR* mutation status positive/negative were 27/20 in the spine, 14/14 in the rib or clavicle, 16/8 in the pelvic bones, 10/5 in the extremities, 2/6 in the sternum, 3/2 in the skull, and 2/2 in the scapula.

Details of SREs

Among the 78 patients with bone metastasis, SREs occurred in a total of 37 (47.4%) after they were diagnosed with bone metastasis. SREs were found at the same day as diagnosis in 3 (8.1%) of the 37 patients, 1 of whom was *EGFR* mutation-positive and 2 of whom were *EGFR* mutation-negative. Multiple SREs were found in 9 of 37 patients (24.3%).

The SRE details were as follows: bone radiotherapy in 32 cases (41.0%), spinal cord compression in 8 cases (10.3%), pathologic fractures in 8 cases (10.3%), hypercalcemia in 2 cases (2.6%), and bone surgery in 2 cases (2.6%). For these patients, the proportions of patients who

were *EGFR* mutation positive/negative were as follows: bone radiotherapy in 15/17 cases, spinal cord compression in 3/5 cases, pathologic fractures in 5/3 cases, hypercalcemia in 1/1 case, and bone surgery in 1/1 case.

Bisphosphonate and systemic chemotherapy

Only 17 (21.8%) of the 78 patients with bone metastasis were given the bisphosphonate zoledronic acid before their SRE occurred and 7 of these 17 patients did not have SRE. Bisphosphonate use did not differ significantly between patients with or without SREs.

EGFR-TKIs such as gefitinib and erlotinib were used in 39 patients before their first SRE and 34 (87.2%) of these patients were *EGFR* mutation-positive. Systemic chemotherapy, including EGFR-TKI and/or cytotoxic agents, was used in 69 patients before their first SRE. Of these patients, 40 (58.0%) were *EGFR* mutation-positive.

Table 2. Analysis of clinical predictive factors for the time to first SRE

Clinical factors	Univariate[b]	Multivariate[c]	
	p	HR (95% CI)	p
Gender (Male/Female)	0.87	NA	
Age (≧70 years/＜70 years)	0.69	NA	
Smoking (Former/ Never)	0.65	NA	
Performance status (0-1/2-3)	0.008	0.30 (0.14-0.64)	0.002
EGFR mutation (Positive/ Negative)	0.003	1.97 (0.71-5.45)	0.19
Zoledronic acid treatment[a] (Yes/No)	0.20	NA	
EGFR-TKI treatment[a] (Yes/No)	＜0.0001	0.07 (0.02-0.26)	＜0.0001

[a]History of zoledronic acid treatment and EGFR-TKI treatment, that were given before the first SRE.

[b]The univariate analysis was performed using the Kaplan-Meier method and the log-rank test.

[c]The multivariate analysis was performed using the Cox proportional hazard model.

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, Hazard ratio; CI, confidence interval; NA, not applicable; and SRE, skeletal-related event.

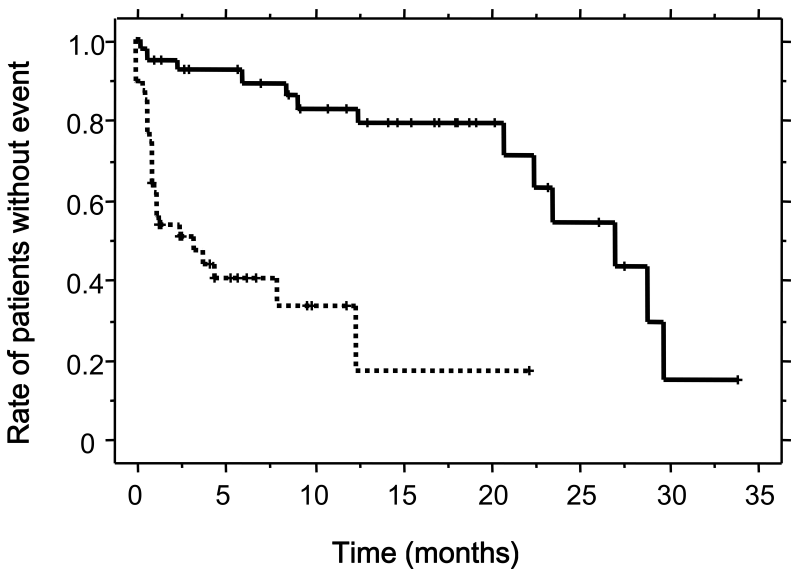

Figure 2. Time to first SRE in 78 patients who treated with or without EGFR-TKI (*solid lines* for History of EGFR-TKI treatment and *dashed lines* for No history of EGFR-TKI treatment). SRE, skeletal-related event; EGFR, epidermal growth factor receptor; and TKI, tyrosine kinase inhibitor.

Time to first SRE

The median time to the first SRE was 5.8 months (range, 0.0-33.9 months) in patients with bone metastasis.

Table 2 shows the analysis of clinical predictive factors for the time to first SRE. History of EGFR-TKI treatment was significantly associated with longer median time to first SRE compared without history of EGFR-TKI treatment (14.2 months vs 1.3 months, $p<0.0001$) (Fig. 2). The median time to first SRE of patients with PS 0-1 was longer than that of patients with PS 2-3 (8.5 months vs 0.9 months, $p=0.0023$).

Discussion

Progression-free survival was increased by EGFR-TKI treatment in patients with *EGFR* mutation[8-10] and prevention of SREs led to improved survival after bone metastases[5]. However, SREs in advanced lung cancer patients evaluated *EGFR* mutation is unknown. To our knowledge, this is the first assessment of SREs in patients with advanced lung adenocarcinoma who were examined for *EGFR* mutation status.

Bone metastasis occurred at a frequency of 40% during the clinical course and 69% of these cases had bone metastasis at the time of their initial lung adenocarcinoma diagnosis. These findings are similar to the data reported from a study conducted in the USA[2]. The most frequent sites of bone metastasis were the spine, ribs, and pelvic bones, which is similar to the data of several previous reports[5,11,12]. The most common SRE was bone radiotherapy (41.0%) in our study, as was found by Rosen et al[13]. We found no significant differences in the sites of bone metastasis and the patterns of SREs between the patients with and without *EGFR* mutations.

The median time to the first SRE was 5.8 months (176 days) in this study, which was low compared to the 8.9 months found in a study from Korea[11] and 7.7 months (236 days) for patients treated with a bisphosphonate (zoledronic acid, 4 mg) found by Rosen et al[13]. This discrepancy may be due to the fact that a small population of patients was treated with bisphosphonates in the present study. Several reports have shown that bisphosphonates have broad efficacy in the treatment of bone metastases from all malignancies, and bisphosphonate treatment has been recommended for lung cancer patients with bone metastasis to prevent and delay SREs[13-16].

In our study, the time from bone metastasis to the first SRE was longer in advanced lung adenocarcinoma patients with good PS and history of EGFR-TKI treatment. The median overall survival after bone metastasis tend to be longer in patients with history of EGFR-TKI treatment in this study [no history of EGFR-TKI treatment 6.7 (range 0.9-40.7) vs history of EGFR-TKI treatment 15.6 (range 1.0-40.1) months, $p=0.06$]. Tsuya et al reported that NSCLC patients with SREs had worse prognoses than those of patients without SREs[5]. On average, medical costs were higher per patient with an SRE compared with patients who did not experience SREs[17]. A recent report showed that overall survival was significantly longer among *EGFR*-mutated patients who were treated after EGFR-TKI approval[18]. Therefore, the prevention of SREs and the maintenance of quality of life are very important.

Normanno et al reported that EGFR-TKI inhibit the recruitment of osteoclasts in bone lesions by affecting the ability of human bone marrow stromal cells to induce osteoclast differentiation and activation[19]. Recent report suggested EGFR-TKI as small-molecule tyrosine kinase inhibitors of the EGFR intracellular domain is able to block the mechanism that the cross-talk

between the urokinase-type plasminogen activator/receptor (uPA/uPAR) system and the EGFR might sustain the ability of these highly metastatic cells to form bone metastasis[20]. Several reports have shown that treatment with EGFR-TKI was effective for bone metastasis from lung cancer[21-23]. Small-molecule tyrosine kinase inhibitors, EGFR-TKIs such as gefitinib and erlotinib inhibit plural kinase activation, so these might inhibit development of bone metastases by acting on unknown unique kinase other than the uPA/uPAR system and the EGFR. The limitations of the present study are retrospective study and small sample size. We could not elucidate that the *EGFR* mutation per se could prolong the time to SREs. It is difficult to perform the prospective clinical study to use placebo or EGFR-TKI in patients with *EGFR* mutation positive. They cannot divide in clinical setting. In univariate analysis of the present study *EGFR* mutation status is significant clinical predictive factor ($p<0.003$), however, in multivariate analysis it is not significant ($p=0.19$) (Table 2). The reason is the interaction between *EGFR* mutation status and the treatment of EGFR-TKI.

Future directions are in vitro study to demonstrate the difference of the mechanism of bone metastasis in *EGFR* mutation status and in clinical to demonstrate the improvement the SREs in *EGFR* mutated patients in addition bisphosphonate or denosumab to EGFR-TKI.

In conclusion, we found that SRE patterns have no difference between *EGFR* mutation positive and negative, and that the time from bone metastases to the first SRE was longer in advanced lung adenocarcinoma patients with good PS and history of EGFR-TKI treatment.

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