Association between EGFR-TKI Resistance and Efficacy of Radiotherapy for Brain Metastases from *EGFR*-mutant Lung Adenocarcinoma

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Abstract. *Aim: To clarify how patients with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma with acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs) respond to radiotherapy (RT) for brain metastases. Patients and Methods: Forty-seven patients were divided into the following three groups: a TKI-naïve group with EGFR mutation (n=11), a TKI-resistant group with EGFR mutation (n=10), and an EGFR-wild-type group (n=26). Patients received stereotactic RT (n=23) or whole-brain RT (n=24). Results: The response rate for patients with TKI-resistant tumor at three months after RT tended to be lower (11%) than that of those who were TKI-naïve (82%, p=0.006) and for patients with wild-type EGFR (48%, p=0.10). On univariate analysis, central nervous system progression-free and overall survival were significantly shorter for patients with TKI-resistant tumors than for those who were TKI-naïve (p=0.018 and p=0.005, respectively). Multivariate analysis showed that TKI resistance was an independent predictor of poorer overall survival (p=0.011). Conclusion: Acquired resistance to TKIs appears to be associated with low efficacy of brain RT.*

Non-small cell lung cancer (NSCLC) is one of the most frequent causes of cancer-related mortality worldwide. Approximately 20-40% of patients with NSCLC develop brain metastases during the course of their disease and their prognosis is generally poor. Over the past decade, the development of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, has dramatically improved the prognosis of patients with *EGFR*-mutant NSCLC. However, even in the era of targeted-therapy, management of brain metastases persists as an important issue. TKIs have been reported to show efficacy against brain metastases from NSCLC (1). Nevertheless, the majority of patients with *EGFR*-mutant disease finally develop tolerance to TKIs despite an initial dramatic response to treatment (2). Furthermore, the central nervous system (CNS) is frequently the initial failure site after clinical benefit from TKIs (3, 4). Therefore, even in the era of targeted-therapy, radiotherapy (RT) for brain metastases is considered to be a viable treatment option in *EGFR*-mutant cases, especially in those which develop acquired resistance to TKIs.

With regard to RT for brain metastases, efficacy for *EGFR*-mutant NSCLC compared with *EGFR*-wild-type NSCLC has been reported (5-7). Pre-clinical studies demonstrating that *EGFR*-mutant NSCLC cells exhibit characteristics of a radiosensitive phenotype support this finding (8). On the other hand, little is known about how *EGFR*-mutant NSCLC with acquired resistance to TKIs responds to RT. Recent pre-clinical studies have revealed that acquired resistance to EGFR inhibitors is associated with cross-resistance to RT (9, 10). However, it is not clear how patients with *EGFR*-mutant disease with acquired resistance to TKIs respond to RT for brain metastases. To clarify this question, we assessed the response to RT and survival of patients with brain metastases from lung adenocarcinoma.

Patients and Methods

Patients. This retrospective analysis was approved by the Institutional Review Board of the Kitakyushu Municipal Medical Center. Between July 2008 and October 2011, 53 consecutive

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patients with histologically-proven lung adenocarcinoma received RT for brain metastases at our hospital. All brain metastases were diagnosed on gadolinium-enhanced magnetic resonance imaging (MRI), and none of the cases had history of prior brain RT. Patients who were treated with whole-brain radiotherapy (WBRT) or stereotactic radiotherapy (SRT) were eligible for the present study. Other eligibility requirements were known *EGFR* mutation status and no evidence of leptomeningeal metastases. Because intracranial biopsy is not easy and in many cases cannot be performed at all, *EGFR* mutation testing was performed on either the primary tumor or other metastatic sites using the Cycleave polymerase chain reaction technique and fragment analysis (11). Of the 53 patients who underwent RT, four patients with unknown *EGFR* mutation status and two with leptomeningeal metastases were excluded. Therefore, a total of 47 patients were enrolled in this study.

Twenty-one out of 47 patients (45%) had *EGFR* mutations (11 patients with *exon 21 L858R* point mutation; nine patients with *exon 19* deletions; one patient with *exon 18 G719X*). Patients in this study were divided into the following three groups according to *EGFR* mutation status and acquired resistance to TKIs: a TKI-naïve group with *EGFR* mutation, a TKI-resistant group with EGFR mutation, and an *EGFR* wild-type group. TKI-naïve patients were defined as those with no history of TKI administration before the starting date of RT. TKI-resistant patients who experienced disease progression after initial benefit from TKIs were defined as those with progressive or newly-diagnosed brain metastases while on continuous treatment with TKIs, or those with brain metastases found during salvage chemotherapy. This TKI-resistant definition was adopted based on a previous report on acquired resistance to TKIs (2). Consequently, the 47 eligible patients were classified as follows: TKI-naïve group, 11 patients; TKI-resistant group, 10 patients; and *EGFR*-wild-type group, 26 patients.

The RT method was determined clinically based on the characteristics of the brain metastases. The standard treatment of WBRT in this study consisted of an isocentric dose of 30 to 35 Gy in 10 to 14 fractions (2.5 to 3 Gy per fraction) to the whole brain using a Siemens Oncor linear accelerator (Siemens Healthcare, Erlangen, Germany). SRT was performed using an Accuknife (DiREX Inc., Tokyo, Japan) detachable micro-multileaf collimator connected to a linear accelerator. The planning target volume (PTV) for SRT was generated with a margin of 2 mm around the target. The dose covering 95% of the PTV in this study was 20 to 30 Gy in two to three fractions (10 to 13 Gy per fraction). A biological effective dose assuming an α/β-ratio of 10 Gy for tumor cell kill was 59.8-60 Gy in patients treated with SRT, and 39-43.8 Gy in patients treated with WBRT, respectively. Steroids and osmotic diuretic agents were administered at the discretion of the physician according to the clinical signs and symptoms.

Response evaluation. MRI was routinely performed three months after treatment and every three to six months thereafter, or whenever intracranial disease progression was suspected. Using gadolinium-enhanced T1-weighted images at three months after treatment, RT responders were defined as those who exhibited a complete response or partial response according to the revised Response Evaluation Criteria in Solid Tumors (12), whereas non-responders exhibited stable or progressive disease.

CNS disease progression was defined as local disease progression or the appearance of new intracranial lesions. CNS progression-free survival (PFS) was calculated from the starting date of RT to the first observation of CNS disease progression on MRI or death. Overall survival (OS) was also calculated from the first day of RT. Patients who were not deceased were censored at the date of last contact.

The RT response rate at three months after treatment, CNS-PFS and OS were evaluated in the three groups.

The following prognostic factors recorded on the first day of RT were also analyzed: patient age (<65 *vs.* ≥65 years); gender; Karnofsky performance status (KPS) (≤70% *vs.* ≥80%); the number of brain metastases (1,2 *vs.* ≥3); the largest diameter of brain metastases (<15 mm *vs.* ≥15 mm); RT method (WBRT *vs.* SRT); the presence of extracranial metastases; and the status of extracranial disease (progressive *vs.* stable). Extracranial disease was estimated within at least one month before RT. The association of RT efficacy with the recursive partitioning analysis (RPA) prognostic classification system (13) was not analyzed, because only three patients (one TKI-naïve patient and two *EGFR* wild-type patients) in this study were in a better prognostic classification RPA class 1 (patients with KPS ≥70, <65 years of age with controlled primary and no extracranial metastases). Receipt of TKIs was also not analyzed as a prognostic factor because it would be highly colinear with *EGFR* mutation status and acquired resistance to TKIs.

Statistical analysis. Categorical variables, including the patient characteristics and RT response rate were compared using Fisher's exact test. Survival was estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Multivariable analysis was carried out by the Cox regression model to identify independent variables predictive of OS. Two-sided *p*-values of less than 0.05 were considered significant. All analyses were performed using JMP 9.0 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics. A total of 47 patients with lung adenocarcinoma who underwent *EGFR* screening and received RT for brain metastases were identified. All *EGFR*-mutant patients were administered TKIs (gefitinib or erlotinib) at some point during the course of their disease. In place of TKIs, three out of 11 TKI-naïve patients (27%), eight out of 10 TKI-resistant patients (80%), and 10 out of 26 *EGFR*-wild-type patients (38%) received chemotherapy before brain RT. SRT was performed in 23 patients (49%). All patients except one with 1-2 brain metastases (17 patients) underwent SRT. No patient in this study underwent an SRT boost following WBRT. The patients' characteristics recorded on the first day of RT are listed in Table I according to the presence or absence of acquired resistance to TKIs. The proportion of females was higher in the TKI-naïve and the TKI-resistant group compared with the *EGFR* wild-type group (p=0.038 and p=0.079, respectively). The proportion of patients with stable extracranial disease was higher in the TKI-resistant group than the *EGFR*-wild-type group (p=0.039). There were no significant differences in the other patient characteristics among the three groups.

Table I. *Patients' characteristics*.

Variable	TKI-naïve n=11, n (%)		TKI-resistant n=10, n (%)		*EGFR*-wild-type n=26, n (%)		*p*-Value*
Age							
<65 years	5	(45%)	2	(20%)	14	(54%)	
≥65 years	6	(55%)	8	(80%)	12	(56%)	
Gender							0.038†
Male	5	(45%)	5	(50%)	22	(85%)	0.079‡
Female	6	(55%)	5	(50%)	4	(15%)	
KPS							
≥70	9	(82%)	8	(80%)	19	(73%)	
<70	2	(18%)	2	(20%)	7	(27%)	
Number of brain metastases							
≤2	4	(36%)	3	(30%)	11	(42%)	
≥3	7	(64%)	7	(70%)	15	(58%)	
Maximum size of brain metastases							
<15 mm	7	(64%)	5	(50%)	11	(42%)	
≥15 mm	4	(36%)	5	(50%)	15	(58%)	
Brain RT method							
SRT	6	(55%)	3	(30%)	14	(54%)	
WBRT	5	(45%)	7	(70%)	12	(46%)	
Presence of extracranial metastases							
Yes	6	(55%)	6	(60%)	17	(65%)	
No	5	(45%)	4	(40%)	9	(35%)	
Status of extracranial disease							0.039‡
Progressive	9	(82%)	6	(60%)	24	(92%)	
Stable	2	(18%)	4	(40%)	2	(8%)	

TKI: Tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; KPS: Karnofsky performance status; RT: radiotherapy; SRT: stereotactic radiotherapy; WBRT: whole-brain radiotherapy. *By Fisher's exact test. Comparison between the †TKI-naïve and the *EGFR* wild-type group, and ‡TKI-resistant and the *EGFR*-wild-type group.

Correlation of RT response and acquired resistance to TKIs. MRI was not available for four patients who had died of primary disease progression within three months after RT (one TKI-resistant patient with *EGFR* mutation in *exon 18 G719X*, and three patients with wild-type *EGFR*). None of these four patients showed neurological deficits after brain RT. Therefore, after excluding these four patients without MRI, 43 out of 47 patients were evaluated for RT response. The association between the RT response rate and acquired resistance to TKIs is shown in Figure 1. Among the nine evaluable TKI-resistant patients, only one who received SRT for single-brain metastasis was classified as an RT responder (11%). The RT response rate of the TKI-resistant group tended to be lower than that of both the TKI-naïve (p=0.006) and *EGFR*-wild-type group (p=0.10). Eight of out 11 TKI-naïve patients (73%) received continuous TKIs during or following RT at the time of evaluation. Among the remaining three patients without TKIs, one was classified as a non-responder. Furthermore, with regard to the response rate to each RT method, there was no significant difference between SRT and WBRT (55% *vs*. 43%, p=0.55).

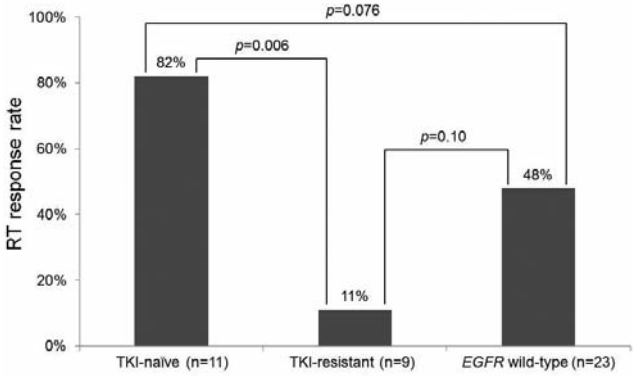

Figure 1. *Correlation of response rate to radiotherapy (RT) and acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).*

Correlation of CNS-PFS and acquired resistance to TKIs. Thirty-two out of 47 patients (68%) had died by the end of follow-up. Thirty-one patients had died of disease progression. The median follow-up of the 47 patients was 7.9 months (range=0.9-33.5 months), and 53% (25 out of 47) experienced progressive CNS disease diagnosed on MRI. Five patients had died of CNS progression by the end of follow-up.

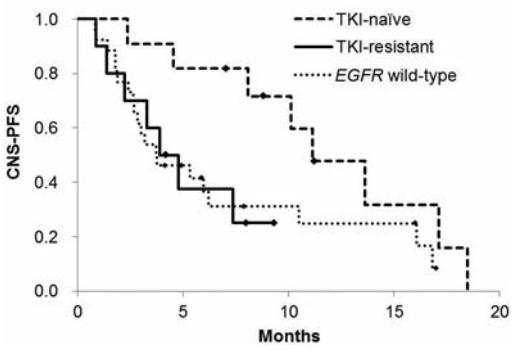

Figure 2. *Central nervous system progression-free survival (CNS-PFS) according to acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).*

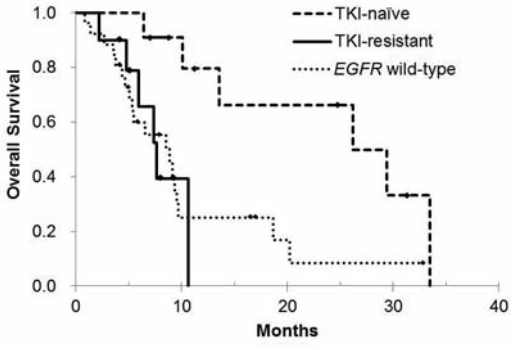

Figure 3. *Overall Survival according to acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).*

The association of CNS-PFS with acquired resistance to TKIs is shown in Figure 2. The median CNS-PFS for the TKI-resistant group was 4.3 months, whereas those for the TKI-naïve and *EGFR* wild-type groups were 11.1 and 3.8 months, respectively. On univariate analysis, CNS-PFS duration for the TKI-resistant and EGFR-wild-type groups were significantly shorter compared with those of the TKI-naïve group (p=0.018 and p=0.048, respectively). On the other hand, no significant difference in CNS-PFS was observed between the TKI-resistant and the *EGFR* wild-type group.

Correlation of OS and acquired resistance to TKIs. The median OS for the TKI-resistant group was 7.6 months, whereas those for the TKI-naïve and *EGFR* wild-type groups were 26.2 and 8.9 months, respectively. The association of OS with acquired resistance to TKIs is shown in Figure 3 and Table II. On univariate analysis, the duration of OS for the TKI-resistant and *EGFR*-wild-type groups were significantly shorter than that for the TKI-naïve group (p=0.005 and p=0.006, respectively). As in the analysis of CNS-PFS, no significant difference was observed between the TKI-resistant and the *EGFR*-wild-type group. With regard to other prognostic factors, female patients and patients with better KPS had significantly better OS (p=0.002 and p=0.004, respectively). Patients without extracranial metastases also survived longer (p=0.058). Multivariate analysis showed that both TKI-resistance [hazard ratio (HR)=5.67; 95% confidence interval (CI)=1.49-23.16; p=0.011] and harboring the *EGFR* wild-type gene (HR=3.19; 95% CI=1.17-10.49; p=0.022), were independent predictors of worse OS compared with the TKI-naïve group. Female sex (HR=0.31; 95% CI=0.10-0.82; p=0.017) was also an independent predictor of better survival. Better KPS tended to be associated with better OS (HR=0.42; 95% CI=0.18-1.02; p=0.054).

Discussion

In the current report we have demonstrated that acquired resistance to TKIs appears to be associated with low efficacy of RT for brain metastases from *EGFR*-mutant lung adenocarcinoma. Recent retrospective studies have reported that *EGFR*-mutant NSCLC exhibits better efficacy of brain RT than dose *EGFR* wild-type (5-7). However, our findings suggested that low RT efficacy for patients with *EGFR*-mutant lung adenocarcinoma with acquired resistance to TKIs seems to be similar to the efficacy in those with wild-type *EGFR*. Recent pre-clinical studies demonstrating an association between acquired resistance to TKIs and cross-resistance to radiation support the results of our study (9, 10). By contrast, the RT response rate and survival for TKI-naïve patients were significantly better in our study. However, these results do not simply indicate the marked radiosensitization of TKI-naïve patients with *EGFR* mutation, because approximately 70% of the TKI-naïve patients were receiving TKIs at the time of evaluation.

The relationship between *EGFR* mutation status and RT response has been investigated in several pre-clinical studies. Das *et al*. have shown that *EGFR*-mutant NSCLC cells are many times more sensitive to radiation compared with the *EGFR* wild-type NSCLC cells *in vitro* (8). *EGFR*-mutant NSCLC cells exhibited delays in the repair of radiation-induced DNA double-strand breaks. Furthermore, the capacity of EGFR inhibitors (both TKIs and anti-EGFR antibody) to enhance the antitumor activity of radiation has been reported (14-16). On the other hand, little is known about how *EGFR*-mutant NSCLC with acquired resistance to TKIs responds to radiation. Various mechanisms of acquired resistance to TKIs have been reported, such as secondary threonine-to-methionine mutation at codon 790 in exon 20 of the *EGFR* gene, MET amplification, and overexpression of hepatocyte growth factor (17). However, only a few studies have focused on the relationship between

Table II. *Correlation of overall survival (OS) and patients' characteristics (n=47).*

Variable	Median OS (months)	Univariate analysis *p*-Value*	Multivariate analysis *p*-Value†
Acquired resistance to TKIs			
TKI-naïve	26.2		
TKI-resistant	7.6	0.005‡	0.011‡
EGFR-wild-type	8.9	0.006§	0.022§
		0.85#	
Age		0.65	
<65 years	10.6		
≥65 years	8.9		
Gender		0.002	0.017
Male	8.5		
Female	33.5		
KPS		0.004	0.054
≥70	13.6		
<70	7.3		
Number of brain metastases		0.78	
≤2	8.9		
≥3	9.6		
Maximum size of brain metastases		0.29	
<15 mm	10.1		
≥15 mm	8.9		
Brain RT method		0.78	
SRT	8.9		
WBRT	9.7		
Presence of extracranial metastases		0.058	0.19
Yes	9.4		
No	9.6		
Status of extracranial disease		0.48	
Progressive	9.4		
Stable	16.9		

TKI: Tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; KPS: Karnofsky performance status; RT: radiotherapy; SRT: stereotactic radiotherapy; WBRT: whole-brain radiotherapy. *By log-rank test; †By cox regression test. Comparison between the ‡TKI-naïve and the TKI-resistant group, §TKI-naïve and the *EGFR* wild-type group, and #TKI-resistant and the EGFR wild-type group.

acquired resistance to TKIs and RT response. Using human head and neck squamous cell carcinoma tumor cells with acquired resistance to TKIs and anti-EGFR antibody, Benavente *et al*. revealed that acquired resistance to EGFR inhibitors is associated with cross-resistance to radiation (9). More recently, Huang *et al*. demonstrated one possible mechanism of this cross-resistance by utilizing NSCLC cells *in vitro* and *in vivo* (10). They found a robust loss of p53 in both TKI-resistant cells and anti-EGFR antibody-resistant cells. In addition, they have suggested that p53 plays a central role in regulating acquired resistance to EGFR inhibitors and radiation *via* regulation of cell-cycle arrest, apoptosis, and DNA damage repair.

With regard to RT efficacy for brain metastases, recent retrospective studies have reported that patients with *EGFR*-mutant disease exhibit a higher response compared with patients harboring wild-type *EGFR*. Gow *et al*. reported on 63 lung adenocarcinoma patients with brain metastases, all of whom were treated with WBRT (5). Forty-six of their patients had *EGFR* mutations, but the proportion of TKI-resistant patients was not described. They found that *EGFR*-mutant patients had higher response rates based on the clinical symptoms and steroid dose. The RT responders had a significantly better OS. Eichler *et al*. reported on 93 patients with brain metastases from NSCLC, the majority of whom were initially treated with WBRT (6). Forty-one of these patients had an *EGFR* mutation and 12 of them received TKIs prior to diagnosis of brain metastases. However, the proportion of TKI-resistant patients was also not available in this study. They found that among the 42 MRI-evaluable patients, the WBRT response rates were higher in those with *EGFR*-mutant disease than in those with EGFR wild-type disease (p=0.23), but the timing of MRI evaluation was not given. They also showed that *EGFR* mutation was an independent predictor of OS. Lee *et al*. reported on 43 patients with brain metastases from NSCLC, all of whom received WBRT (30-40 Gy) with or without a local boost up to 50-60 Gy. (7). Thirty of these patients had

an *EGFR* mutation. The brain RT response was assessed by MRI or computed tomography. They demonstrated that *EGFR*-mutant patients exhibited higher response and had longer intracranial radiological PFS, whereas the RT dose did not significantly affect the brain RT response and intracranial radiological PFS. In the present study, we analyzed RT efficacy with a focus not only on *EGFR* mutation status, but also on acquired resistance to TKIs. In contrast to previous studies in which RT was shown to be highly effective against *EGFR*-mutant NSCLC, our TKI-resistant patients exhibited a low RT response (Figure 1) and survival (Figures 2 and 3). Our findings imply that EGFR-mutant patients with acquired resistance to TKIs exhibit low RT efficacy, which seems to be similar to the efficacy in patients with wild-type *EGFR*.

In addition, we found that the female sex was independently associated with better OS. Previous studies have demonstrated that female sex was a favorable prognostic factor in patients with brain metastases from lung cancer. Consistent with previous studies (7, 13, 18), we found that KPS was an important prognostic factor for OS. Moreover, as reported by Gow *et al*. (5), patients without extracranial metastases survived significantly longer, but this finding was not seen on the multivariate analysis of the present study. The relatively small sample size in our study might have masked such a relationship.

There are several limitations inherent to our study. Firstly, this is a retrospective single-institution study and is susceptible to selection bias. Secondly, *EGFR* mutation analysis was not performed on metastatic tissue from brain. The discordance of *EGFR* mutation status in primary and metastatic sites has been reported to reach 27%, as previously described (19); the lack of availability and safety of intracranial biopsy makes use of the primary status a reasonable surrogate. Finally, the RT method was not uniform in this study. The majority of patients with one or two brain metastases received SRT. However, the proportion of patients treated with a particular RT method (SRT or WBRT) and the number of brain metastases did not significantly differ among the three groups. Moreover, no single-RT method significantly correlated with better RT response rate or longer survival.

In conclusion, to our knowledge, this is the first study to focus on how patients with *EGFR*-mutant disease and acquired resistance to TKIs respond to RT for brain metastases from lung adenocarcinoma. In contrast to previous studies indicating that RT is highly effective against *EGFR*-mutant NSCLC, our findings suggest that acquired resistance to TKIs appears to be associated with low RT efficacy. This low efficacy seems to be similar to the efficacy in patients with wild-type *EGFR*. Further studies are needed to confirm and overcome this low RT efficacy against *EGFR*-mutant NSCLC with acquired resistance to TKIs.

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