EGFR Tyrosine Kinase Inhibitors Prolong Overall Survival in *EGFR* Mutated Non-Small-Cell Lung Cancer Patients with Postsurgical Recurrence

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Abstract: It is indisputable that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) prolong progression-free survival in non-small-cell lung cancer (NSCLC) patients with *EGFR* mutations better than cytotoxic chemotherapy. However, it is unclear whether EGFR-TKIs prolong the overall survival of NSCLC patients, especially in those with postsurgical recurrence. We retrospectively examined 304 NSCLC patients with known *EGFR* mutational status (excluding those with squamous cell carcinoma), who had undergone pulmonary resection and experienced postsurgical recurrence. Of these patients, 137 carried *EGFR* mutations and 167 did not. Of the 137 patients with *EGFR* mutations, 83 were treated with EGFR-TKIs for their recurrent disease, and 32 of the 167 patients without *EGFR* mutations were treated with EGFR-TKIs. Postsurgical survival was divided into two parts: recurrence-free survival (RFS) and postrecurrence survival (PRS), and these were compared between the subgroups with a multivariate analysis, adjusted for baseline clinical characteristics. There was no significant difference in RFS between patients with *EGFR* mutations and those without (*P* = 0.88). PRS was also similar in these two subgroups when we excluded patients who had been treated with EGFR-TKIs (*P* = 0.64). In patients with EGFR mutations, PRS was significantly longer in those who were treated with EGFR-TKIs than in those who were not given EGFR-TKIs (*P* = 0.04). However, among patients without *EGFR* mutations, PRS was similar in patients who had and had not been treated with EGFR-TKIs (*P* = 0.87). In conclusion, among NSCLC patients with postsurgical recurrence, EGFR-TKIs prolonged PRS in those with *EGFR* mutations.

Keywords: Molecular target therapy, biomarker analysis, prognostic factor, predictive factor, gefitinib, erlotinib, pulmonary resection, postsurgical recurrence-free survival (RFS), postrecurrence survival (PRS).

1. INTRODUCTION

Preclinical and clinical studies have shown that non-small-cell lung cancers (NSCLCs) with epidermal growth factor receptor gene (*EGFR*) mutations are exquisitely sensitive to orally available EGFR tyrosine kinase inhibitors (EGFR-TKIs; gefitinib and erlotinib) [1-3]. Four recent phase III trials have shown that the progression-free survival (PFS) of patients with advanced NSCLC treated with these EGFR-TKIs was longer than that of patients treated with platinum-based chemotherapy when the patients had *EGFR* mutations [4-7].

However, in the WJTOG3405 study, which included a large number of patients with postsurgical recurrence (n = 71; 41%), postsurgical recurrence itself was a better prognostic factor than stage IIIB/IV disease (hazards ratio [HR] 0.433, *P* < 0.0001) [4]. In the subgroup analysis of the WJTOG3405 study, PFS was

significantly longer in the gefitinib group than in the chemotherapy group of patients with stage IIIB/IV disease (n = 101; median PFS, 8.4 vs 5.4 months, respectively; *P* < 0.0001), but this difference was not statistically significant in patients with postsurgical recurrence (n = 71; median PFS, 13.7 vs 8.1 months, respectively; *P* = 0.069). The PFS curves for the two subgroups also differed: the curves for the gefitinib and chemotherapy groups in the postsurgical recurrence subgroup overlapped during the first six months, whereas the curves for the stage IIIB/IV subgroup were clearly separated during this period. These results indicate that the baseline characteristics and response to treatment of NSCLC patients with postsurgical recurrence may differ from those with advanced disease.

Overall survival (OS), rather than PFS, has been regarded as the gold standard measure for evaluating the clinical benefit of antitumor therapies. The NEJ002 and WJTOG3405 studies both failed to show the clinical benefit of gefitinib on overall survival [4, 8], probably because of the high crossover rate. To establish whether EGFR-TKIs improve OS in NSCLC patients, Takano *et al.* performed a historical

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comparison of lung adenocarcinoma patients treated before and after gefitinib approval in Japan [9]. They demonstrated that OS was significantly longer among *EGFR*-mutant patients treated after gefitinib approval compared with those treated before it, whereas no improvement in survival was observed in patients without *EGFR* mutations. However, their patient cohort consisted predominantly of patients with advanced lung adenocarcinomas (76% and 59% of patients treated before and after gefitinib approval, respectively), rather than those with postsurgical recurrence.

Therefore, it remains unclear whether EGFR-TKIs can prolong OS in NSCLC patients with postsurgical recurrence. To address this question, we performed a retrospective analysis of NSCLC patients with a known *EGFR* mutational status, comparing those who were treated with EGFR-TKIs and those who were not.

2. PATIENTS AND METHODS

2.1. Study Population and Procedures

We analyzed 375 Japanese NSCLC patients (excluding those with squamous cell carcinoma) who had undergone pulmonary resection at the Department of Thoracic Surgery, Aichi Cancer Center Hospital, between May 2000 and December 2008, and who had experienced a recurrence by September 2011. All the patients gave their written informed consent to their participation and the appropriate approval was obtained in advance from our institutional review board.

In this cohort, samples from 304 patients were available for *EGFR* mutational analysis and those patients were included in the study. Complete clinical data including sex, age, pathological diagnosis, pathological stage (7th edition), date of surgery, date of relapse, date of death were obtained from medical records and reviewed by the physicians. *EGFR* mutational analysis was performed as previously reported [10]. *EGFR* mutations were detected in 137 patients, and 83 of those patients were treated with EGFR-TKI monotherapy (gefitinib, 65 patients; erlotinib, six patients; and both, 12 patients) at any line of the treatment. Of the 167 patients without *EGFR* mutations, 32 were treated with EGFR-TKI monotherapy (gefitinib, 27 patients; erlotinib, five patients). Further details of the clinical and pathological characteristics of the patients are shown in Table **1**. No significant clinicopathological differences were observed between the patients who were or were not treated with EGFR-TKIs in both the mutant *EGFR* and wild-type *EGFR* subgroups.

2.2. Clinical Outcomes and Statistical Analysis

Postsurgical survival was divided into two parts: postsurgical recurrence-free survival (RFS) and postrecurrence survival (PRS). RFS was defined as the time from pulmonary resection to the detection of recurrence. PRS was defined as the time from the recognition of recurrence to death. Patients without a known date of death were censored at the time of the last follow-up.

Table 1: Patient Characteristics

Characteristics	No. Patients					
	With EGFR mutation (n = 137)			Without EGFR mutation (n = 167)		
	TKI treated (n = 83)	TKI naïve (n = 54)	*P* value	TKI treated (n = 32)	TKI naïve (n = 135)	*P* value
Sex						
Male/female	39/44	25/29	0.94	19/13	96/39	0.20
Age (Years)						
$\leq 59/60\text{-}69/ \geq 70$	28/38/17	17/21/16	0.46	15/12/5	48/46/41	0.22
Smoking (PY)						
Never/ $\leq 20/ \leq 40/ \geq 41$	50/10/9/14	31/8/9/6	0.89	13/1/8/10	28/13/29/65	0.06
Pathological-Stage at surgery						
I/II/III -IV	21/14/48	23/9/22	0.09	13/4/15	44/32/59	0.36
Histology						
AD/non-AD	78/5	54/0	0.07	29/3	107/28	0.14

Notes: PY, smoking status (pack-years); AD, adenocarcinoma; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

A χ^2 test was used to compare proportions. Differences in RFS or PRS of the two groups were compared with multivariate analyses using the Cox proportional hazards modeling technique, with adjustments made for the baseline clinical characteristics: sex, age, smoking history, pathological stage, and histology. All statistical analyses were performed with StatView version 5.01 (SAS Institute). Significance was set at $P < 0.05$.

3. RESULTS

3.1. No Significant Differences in RFS between Subgroups

We first compared the RFS of patients with and without *EGFR* mutations, and identified no significant difference (HR = 0.98; 95% confidence interval [CI], 0.76–1.27; $P = 0.88$).

We then compared the RFS of patients treated with and without EGFR-TKIs to confirm that the baseline potential of these two subgroups was similar. In both patients with and those without *EGFR* mutations, we observed no significant difference in RFS between those who had been treated with EGFR-TKIs and those

who had not, i.e., HR for EGFR-TKI-treated patients was 1.05 in patients with *EGFR* mutations ($P = 0.78$; Table **2**) and 1.19 in those without *EGFR* mutations ($P = 0.43$; Table **3**).

3.2. Treatment with EGFR-TKIs Prolonged PRS in Patients with *EGFR* Mutations But Not in Those without *EGFR* Mutations

We compared the PRS of the subgroups. In the analysis of all 304 patients, the patients with *EGFR* mutations survived longer than those without *EGFR* mutations (HR = 0.63; 95% CI, 0.47–0.86; $P < 0.01$).

To examine the effect of EGFR-TKIs on PRS, we divided the patients into those with *EGFR* mutations and those without *EGFR* mutations, because the efficacy of these drugs is strongly influenced by the presence of *EGFR* mutations. In patients with *EGFR* mutations, PRS was significantly longer in those who had been treated with EGFR-TKIs (HR = 0.60; 95% CI, 0.36–0.97; $P = 0.04$; Table **2**). In contrast, in patients without *EGFR* mutations, PRS was similar in patients who had been treated with EGFR-TKIs and those who had not (HR = 0.96; 95% CI, 0.62–1.49; $P = 0.87$; Table **3**).

Table 2: Multivariate Analysis of Postsurgical Recurrence-Free Survival and Postrecurrence Survival in Patients with *EGFR* Mutations

Characteristics	Postsurgical recurrence-free survival			Postrecurrence survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Female vs male	0.80	0.47–1.36	0.41	1.07	0.62–1.83	0.82
Age (years)						
60–69 vs ≤ 59	0.74	0.49–1.14	0.17	0.76	0.44–1.30	0.31
≥ 70 vs ≤ 59	0.80	0.48–1.32	0.37	1.89	1.04–3.45	0.04
Smoking (PY)						
≤ 20 vs never	1.03	0.52–2.04	0.93	0.87	0.41–1.85	0.72
21–40 vs never	0.78	0.40–1.52	0.46	0.54	0.22–1.34	0.18
≥ 41 vs never	1.03	0.54–1.95	0.93	1.50	0.79–2.84	0.21
Pathological-Stage						
II vs I	2.00	1.13–3.52	0.02	2.10	1.07–4.12	0.03
III–IV vs I	2.52	1.65–3.87	< 0.01	1.92	1.09–3.37	0.02
Histology						
non-AD vs AD	2.79	1.05–7.41	0.04	1.12	0.34–3.69	0.85
TKI treatment						
Yes vs no	1.05	0.72–1.54	0.78	0.60	0.36–0.97	0.04

Notes: PY, smoking status (pack-years); AD, adenocarcinoma; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

Table 3: **Multivariate Analysis of Postsurgical Recurrence-Free Survival and Postrecurrence Survival in Patients without *EGFR* Mutations**

Characteristics	Postsurgical recurrence-free survival			Postrecurrence survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Female vs male	1.08	0.66–1.79	0.41	1.44	0.80–2.57	0.22
Age (years)						
60–69 vs ≤ 59	0.94	0.64–1.37	0.75	0.93	0.60–1.43	0.73
≥ 70 vs ≤ 59	1.07	0.72–1.59	0.74	0.98	0.62–1.57	0.94
Smoking (PY)						
≤ 20 vs never	2.08	1.08–3.99	0.03	1.30	0.61–2.76	0.49
21–40 vs never	1.09	0.61–1.94	0.78	1.74	0.90–3.33	0.10
≥ 41 vs never	1.08	0.60–1.94	0.79	1.84	0.95–3.54	0.07
Pathological-Stage						
II vs I	1.40	0.86–2.27	0.17	1.43	0.83–2.48	0.20
III–IV vs I	2.18	1.49–3.18	< 0.01	1.99	1.28–3.09	< 0.01
Histology						
non-AD vs AD	1.60	1.01–2.54	0.04	1.82	1.11–2.99	0.02
TKI treatment						
Yes vs no	1.19	0.77–1.84	0.43	0.96	0.62–1.49	0.87

Notes: PY, smoking status (pack-years); AD, adenocarcinoma; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

3.3. PRS Was Similar in Patients with and without *EGFR* Mutations in the Absence of EGFR-TKIs

Our results indicated that EGFR-TKIs prolonged PRS in patients with *EGFR* mutations but not in those without *EGFR* mutations. To determine whether patients with *EGFR* mutations live longer than those without *EGFR* mutations, even in the absence of EGFR-TKIs, we excluded patients who had been treated with EGFR-TKIs. The analysis of 189 patients (54 patients with and 135 patients without *EGFR* mutations) showed that RFS was similar in both subgroups (HR for patients with *EGFR* mutations was 0.92; 95% CI, 0.63–1.33; *P* = 0.64). PRS was also similar in these two subgroups (HR for patients with *EGFR* mutations was 0.89; 95% CI, 0.56–1.41; *P* = 0.62).

4. DISCUSSION

In this study, we identified two important trends in NSCLC patients with postsurgical recurrence. First, *EGFR* mutational status was not a prognostic factor in patients with postsurgical recurrence. This finding is based on two results: i) RFS was similar in patients with and without *EGFR* mutations; and ii) PRS was

also similar in these two subgroups if we excluded patients who had been treated with EGFR-TKIs. This is consistent with several retrospective analyses of patients with early-stage NSCLC, which have shown that the presence of *EGFR* mutations was associated with a favorable prognosis for OS in univariate analyses but not after adjustments were made for the patients' backgrounds [10-12]. For instance, in our previous analysis of lung adenocarcinoma patients who had undergone potentially curative pulmonary resection, disease stage (*P* < 0.0001) and smoking status (*P* = 0.0310) were independent prognostic factors for postsurgical survival, but the mutational status of any gene was not (*EGFR*, *P* = 0.3225; *KRAS*, *P* = 0.8500; *TP53*, *P* = 0.3191) [10].

Another finding of this study was that the PRS of NSCLC patients with *EGFR* mutations was significantly longer in patients who were given EGFR-TKIs than in those who were not. This result may have been considered as a foregone conclusion, but our analysis is important in establishing the ultimate clinical benefit of EGFR-TKIs in patients with *EGFR* mutations who experience postsurgical recurrence.

The PRS of NSCLC patients without *EGFR* mutations was similar in patients who were and were

not treated with EGFR-TKIs. However, it is unclear whether this result can be attributed to the failure of EGFR-TKIs to confer a clinical benefit on NSCLC patients without *EGFR* mutations or to the small sample size, which may have failed to detect small differences. Until now, two subset analyses of phase III studies have demonstrated the clinical benefit of erlotinib in NSCLC patients without *EGFR* mutations [13, 14], whereas no such data have been reported for gefitinib. In our cohort, only five of the 167 NSCLC patients without *EGFR* mutations had received erlotinib. Analysis of a larger sample of patients treated with erlotinib may conclude whether NSCLC patients without *EGFR* mutations will benefit from EGFR-TKIs or not.

The present study was our second attempt to establish the clinical benefit of EGFR-TKIs on OS in patients who experienced postsurgical recurrence. We previously compared 81 patients who had been treated with gefitinib with 81 patients matched for sex, age, pathological stage, and smoking status who were not given EGFR-TKIs [15]. In that study, we used a matching method to exclude selection bias for EGFR-TKI treatment, but that method yielded a small patient sample and an uneven distribution of *EGFR* mutational status across the treatment groups. Therefore, in this study, we analyzed a large number of patients, dividing these patients according to their *EGFR* mutational status, and clearly identified the clinical benefit of EGFR-TKIs in NSCLC patients with *EGFR* mutations but not in those without *EGFR* mutations.

In conclusion, our results indicate that the presence of *EGFR* mutations is not a prognostic factor for NSCLC patients with postsurgical recurrence. However, EGFR-TKIs prolonged PRS in NSCLC patients with *EGFR* mutations, but not in those without *EGFR* mutations.

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DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

REFERENCES

[1]   Lynch TJ, Bell DW, Sordella R, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129-39.
http://dx.doi.org/10.1056/NEJMoa040938

[2]   Paez JG, Janne PA, Lee JC, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-500.
http://dx.doi.org/10.1126/science.1099314

[3]   Mitsudomi T, Kosaka T, Endoh H, *et al.* Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol 2005; 23: 2513-20.
http://dx.doi.org/10.1200/JCO.2005.00.992

[4]   Mitsudomi T, Morita S, Yatabe Y, *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121-8.
http://dx.doi.org/10.1016/S1470-2045(09)70364-X

[5]   Maemondo M, Inoue A, Kobayashi K, *et al.* Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-8.
http://dx.doi.org/10.1056/NEJMoa0909530

[6]   Zhou C, Wu YL, Chen G, *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735-42.
http://dx.doi.org/10.1016/S1470-2045(11)70184-X

[7]   Rosell R, Carcereny E, Gervais R, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13(3): 239-46.

[8]   Inoue A, Kobayashi K, Maemondo M, *et al.* Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations. J Clin Oncol 2011; 29(suppl): abstr 7519.

[9]   Takano T, Fukui T, Ohe Y, *et al.* EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. J Clin Oncol 2008; 26: 5589-95.
http://dx.doi.org/10.1200/JCO.2008.16.7254

[10]   Kosaka T, Yatabe Y, Onozato R, Kuwano H, Mitsudomi T. Prognostic implication of EGFR, KRAS, and TP53 gene mutations in a large cohort of Japanese patients with surgically treated lung adenocarcinoma. J Thorac Oncol 2009; 4: 22-9.
http://dx.doi.org/10.1097/JTO.0b013e3181914111

[11]   Sasaki H, Shimizu S, Endo K, *et al.* EGFR and erbB2 mutation status in Japanese lung cancer patients. Int J Cancer 2006; 118: 180-4.
http://dx.doi.org/10.1002/ijc.21301

[12]   Marks JL, Broderick S, Zhou Q, *et al.* Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. J Thorac Oncol 2008; 3: 111-6.
http://dx.doi.org/10.1097/JTO.0b013e318160c607

[13]   Zhu CQ, da Cunha Santos G, Ding K, *et al.* Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008; 26: 4268-75.
http://dx.doi.org/10.1200/JCO.2007.14.8924

[14]   Cappuzzo F, Ciuleanu T, Stelmakh L, *et al.* Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010; 11: 521-9.
http://dx.doi.org/10.1016/S1470-2045(10)70112-1

[15]   Katayama T, Matsuo K, Kosaka T, Sueda T, Yatabe Y, Mitsudomi T. Effect of gefitinib on the survival of patients with recurrence of lung adenocarcinoma after surgery: a retrospective case-matching cohort study. Surg Oncol 2010; 19: e144-9.
http://dx.doi.org/10.1016/j.suronc.2010.07.002