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ORIGINAL PAPER

Comparison of adverse events and efficacy between gefitinib and erlotinib in patients with non-small-cell lung cancer: a retrospective analysis

Tsukasa Yoshida · Kazuhiko Yamada · Koichi Azuma · Akihiko Kawahara · Hideyuki Abe · Satoshi Hattori · Fumie Yamashita · Yoshiaki Zaizen · Masayoshi Kage · Tomoaki Hoshino

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Abstract Previous studies have demonstrated that both gefitinib and erlotinib are markedly effective for the treatment of non-small-cell lung cancer (NSCLC) with somatic activating mutations of the epidermal growth factor receptor gene (*EGFR-mt*). These agents are considered to act on EGFR through the same mechanism. However, the efficacy of these agents against *EGFR* wild-type (*-wt*) NSCLC remains unclear, and the frequency of adverse events (AEs) appears to differ between them at each approved dose. Here, we conducted a retrospective analysis of AEs and drug efficacy in patients with NSCLC whose *EGFR* mutation status had been confirmed and who all received 250 mg gefitinib or 150 mg erlotinib once daily. The erlotinib group ($n = 35$) had more AEs, including rash, fatigue, stomatitis, anorexia and constipation. On the other hand, liver dysfunction and nail change were more frequent in the gefitinib group ($n = 107$). AEs of ≥grade 2, including rash, fatigue and nausea, were more frequent in the erlotinib group. The erlotinib group also showed more of a tendency to require dose reduction due to AEs. With regard to treatment efficacy for patients with *EGFR-wt*, there was no significant difference in progression-free survival between the two drug groups. However, this study has several limitations as of the nature of retrospective design; our data suggest that gefitinib and erlotinib might have almost equal efficacy for patients with *EGFR-wt* NSCLC, as is the case for patients with *EGFR-mt* tumors, although erlotinib appears to have higher toxicity than gefitinib at each approved dose.

Keywords Gefitinib · Erlotinib · Adverse event · Efficacy · Comparison

T. Yoshida · K. Yamada (✉) · K. Azuma · F. Yamashita · Y. Zaizen · T. Hoshino
Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume City, Fukuoka 830-0011, Japan
e-mail: kayamada@med.kurume-u.ac.jp

A. Kawahara · H. Abe · M. Kage
Department of Diagnostic Pathology, Kurume University Hospital, Fukuoka, Japan

S. Hattori
Biostatistics Center, Kurume University, Fukuoka, Japan

Introduction

The epidermal growth factor receptor (EGFR) is recognized as an important molecular target in cancer therapy. Somatic activating mutations of the *EGFR* gene (*EGFR-mt*) have been identified as a major determinant of the clinical response to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib in patients with non-small-cell lung cancer (NSCLC) [1, 2]. Four phase III trials of gefitinib or erlotinib in patients with NSCLC harboring *EGFR* mutations have been conducted. These demonstrated a higher response rate of around 75 % and a longer progression-free survival time (PFS) of approximately 10 months than for patients who received platinum-based agents as for first-line chemotherapy [3–6]. Meanwhile, for patients with the wild-type *EGFR* (*EGFR-wt*), the survival impact of EGFR-TKIs has been unclear. The IRESSA Pan-Asia Study (IPASS) demonstrated that patients with *EGFR-wt* NSCLC were unlikely to benefit from gefitinib, with a response rate of only 1.1 % and a median PFS (mPFS) of less than 2 months [7]. Despite this great difference in response to gefitinib between patients with and without *EGFR-mt*, subgroup analysis in the BR21 trial demonstrated that the survival impact of erlotinib did not differ significantly according to *EGFR* mutation status,

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the hazard ratios for erlotinib over placebo being 0.55 ($p = 0.1217$) and 0.74 ($p = 0.0924$) in patients with and without *EGFR-mt*, respectively [8]. In addition, although the characteristic toxicities of EGFR-TKIs can include rash, diarrhea, liver dysfunction and interstitial lung disease (ILD), the frequencies of these toxicities seem to differ.

Both gefitinib and erlotinib were developed as EGFR tyrosine kinase-inhibiting agents, and there are no clear reasons why their efficacy, especially in patients with *EGFR-wt* NSCLC, and the frequency of their toxicities should differ. In addition, no prospective studies have yet compared gefitinib and erlotinib for adverse events (AEs) and efficacy, irrespective of *EGFR* mutation status. Therefore, we performed a retrospective investigation of differences in AEs and efficacy between gefitinib and erlotinib in patients with NSCLC.

Patients and methods

Study population

Two hundred and six consecutive Japanese patients with advanced or recurrent NSCLC who started treatment with 250 mg gefitinib or 150 mg erlotinib once daily between September 2002 and March 2011 at Kurume University Hospital were retrospectively screened. Among these patients, tumor specimens from 142 were available for detection of *EGFR* mutations, and these patients were enrolled in the study. The gefitinib group included patients treated with gefitinib only and patients who had been treated with gefitinib prior to erlotinib. The erlotinib group included patients treated with erlotinib only; none had been treated with erlotinib prior to gefitinib.

Clinical information about each case was obtained from the medical records; the parameters included gender, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor histology, stage, smoking status and the number of prior chemotherapy courses. AEs were assessed according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The criteria for dose reduction or discontinuation of the drugs were determined according to the previous reports [8, 9]. Tumor response was examined by computed tomography and evaluated using the Response Evaluation Criteria for Solid Tumors version 1.0 (RECIST v1.0). For *EGFR* mutation analysis, the peptic nucleic acid-locked nucleic acid (PNA-LNA) polymerase chain reaction (PCR) clamp method was adopted, using protocols described previously [10]. Specific PNA-LNA probe sets for two mutation sites, exon 19 (delE746-A750) and exon 21 (L858R), were developed, and these covered >90 % of *EGFR* mutations reported previously in Japan [11].

This study was approved by the institutional review board at the Kurume University.

Statistical analysis

Patient characteristics were compared between the gefitinib and erlotinib groups by using Fisher's exact test.

PFS was defined as the duration from the date of initiation of gefitinib or erlotinib treatment to that of disease progression or death from any cause. The survival functions for PFS were estimated by the Kaplan–Meier method, and survival differences between patients with *EGFR-mt* and those with *EGFR-wt* were compared by the log-rank test. Efficacy for patients with *EGFR-wt* was compared between the gefitinib and erlotinib groups as follows. The objective response rate was defined as the proportion of the complete response (CR) or the partial response (PR). The objective response rate and the Pearson–Cropper confidence interval were calculated for each group, and comparison between the groups was made by Fisher's exact test. Logistic regression analysis was also performed for comparison of the two groups adjusting for factors that were significantly unbalanced between the two groups. The comparison of survival functions was made by using the Kaplan–Meier method and log-rank test. Cox regression analysis was also performed for comparison adjusting for factors that were significantly unbalanced between the two groups.

To compare frequencies of AEs between the gefitinib and erlotinib groups, we applied Fisher's exact test. In addition, we conducted logistic regression analysis to compare the frequencies of AEs, adjusting for factors that were significantly unbalanced between the two groups. All tests were two-sided, and differences at $p < 0.05$ were considered statistically significant. Statistical analysis was performed with R version 2.90 and SAS version 9.2 software (SAS Institute, Cary, NC).

Results

Patient characteristics

Among the total of 142 patients, 107 were included in the gefitinib group and 35 in the erlotinib group. The clinical characteristics of the patients overall are summarized in Table 1. Eighty-three percent of patients had adenocarcinoma, and almost all of the patients had a good PS (0 or 1). In this series, 60 (42 %) of 142 patients had developed postoperative recurrence, and 103 (73 %) of them were treated with EGFR-TKI as a first- or second-line treatment. *EGFR* mutations were detected in approximately half of the subjects (49 %). The gefitinib group had significantly

Table 1 Patients' characteristics (all patients)

Characteristics	Total ($N = 142$)	Gefitinib ($N = 107$)	Erlotinib ($N = 35$)	p value*
Age (years)				
Median (range)	65 (33–82)	64 (33–82)	67 (35–78)	0.561
≥65	74	54	20	
<65	68	53	15	
Gender				
Male	58	34	24	<0.001
Female	84	73	11	
Histology				
Adenocarcinoma	119	95	24	0.008
Non-adenocarcinoma	23	13	11	
Smoking status				
Never smoker	79	68	11	<0.001
Smoker	63	39	24	
Performance status				
0–1	134	101	33	1
2–3	8	6	2	
Stage				
III or IV	82	51	31	0.003
Recurrent	60	56	4	
Treatment line				
1st or 2nd	103	83	20	0.028
3rd or 4th	39	24	15	
EGFR mutation status				
Positive	70	64	6	<0.001
(L858R/exon 19 del)	(38/32)	(34/30)	(4/2)	
Negative	72	43	29	

*Determined by Fisher's exact test

higher proportions of women, adenocarcinoma and never-smokers. As is generally known, these factors were significantly associated with *EGFR-mt*. In our investigated population, female gender (Fisher's exact test, $p = 0.011$), adenocarcinoma (Fisher's exact test, $p = 0.022$) and having never smoked (Fisher's exact test, $p = 0.004$) were significantly associated with *EGFR-mt*. Reflecting this, the gefitinib group included a significantly higher proportion of patients with *EGFR-mt*. In addition, in comparison with erlotinib, gefitinib was administered significantly more often to patients with postoperative recurrence and as an early treatment.

Adverse events

All patients in this study were included in the analysis of AEs. Comparisons of AEs between the gefitinib and erlotinib groups are summarized in Table 2. Major AEs seen in both groups were rash, fatigue, diarrhea and anorexia, which were similar to those observed in the previous studies. Fisher's exact test (unadjusted analysis) showed that rash, fatigue, stomatitis and anorexia were more frequent in the erlotinib group. On the other hand, the frequencies of diarrhea and nail change were higher in the gefitinib group. Logistic regression analysis (adjusted analysis) revealed that the frequencies of rash, stomatitis, constipation and anorexia were significantly higher in the erlotinib group. Liver dysfunction and interstitial lung disease (ILD) appeared to be more frequent in the gefitinib group, but not to a significant degree. The erlotinib group also had a tendency to require dose reduction due to AEs. We also compared the frequency of AEs of ≥grade 2. This revealed that rash was the main reason for dose reduction (data not shown) in a significantly higher proportion of patients in the erlotinib group. One treatment-related death occurred due to ILD in the gefitinib group (Table 3).

Efficacy analysis

PFS curves for the patients with *EGFR-mt* and *EGFR-wt* are displayed in Fig. 1. The mPFS was 8.2 months in the *EGFR-mt* group and 2.0 months in the *EGFR-wt* group. We also analyzed the response rate and PFS only for the patients with *EGFR-wt*. The characteristics of patients in this subgroup are summarized in Table 4. Unlike the characteristics of the patients as a whole, there was no

Table 2 Adverse events (all grade)

AE	Frequencies		Fisher's exact test	Adjusted analysis			
	Gefitinib	Erlotinib	*p* value	*p* value	OR	95 % CI	
Rash	67 (62.6 %)	33 (94.3 %)	<0.0001	<0.0001	0.04	0.009	0.189
Fatigue	32 (29.9 %)	21 (60.0 %)	0.0023	0.0708	0.404	0.151	1.08
Stomatitis	4 (3.7 %)	6 (17.1 %)	0.0148	0.0111	0.099	0.016	0.589
Nausea	8 (7.5 %)	5 (14.3 %)	0.3081	0.1375	0.325	0.074	1.432
Diarrhea	39 (36.4 %)	6 (17.1 %)	0.0373	0.2899	1.82	0.6	5.519
Constipation	0 (0.0 %)	2 (5.7 %)	0.0594	0.011	0.007	<0.001	0.321
Anorexia	9 (8.4 %)	13 (37.1 %)	<0.0001	0.0412	0.304	0.097	0.954
Weight loss	1 (0.9 %)	2 (5.7 %)	0.1503	0.2065	0.264	0.033	2.084
Liver dysfunction	14 (13.1 %)	2 (5.7 %)	0.3575	0.6366	0.671	0.128	3.509
ILD	8 (7.5 %)	0 (0.0 %)	0.1999	0.101	9.886	0.639	152.857
Epistaxis	1 (0.9 %)	0 (0.0 %)	1	0.3786	0.275	0.016	4.861
HFSR	4 (3.7 %)	4 (11.4 %)	0.1027	0.0936	0.242	0.046	1.27
INR increased	0 (0.0 %)	1 (2.9 %)	0.2465	0.076	0.081	0.005	1.301
Dry mouth	3 (2.8 %)	0 (0.0 %)	1	0.5794	2.189	0.137	34.976
Nail change	17 (15.9 %)	1 (2.9 %)	0.0449	0.2478	2.887	0.478	17.426
Pneumonia	0 (0.0 %)	1 (2.9 %)	0.2465	0.3344	0.32	0.032	3.238
Dose reduction due to AEs	15 (14.0 %)	9 (25.7 %)	0.1233	0.1573	0.425	0.13	1.391

ILD interstitial lung disease, *HFSR* hand–foot skin reaction

Table 3 Adverse events (≥grade 2)

AE	Frequencies		Fisher's exact test	Adjusted analysis			
	Gefitinib	Erlotinib	*p* value	*p* value	OR	95 % CI	
Rash	35 (32.7 %)	23 (65.7 %)	<0.0001	0.0013	0.179	0.063	0.51
Fatigue	7 (6.5 %)	10 (28.6 %)	0.0014	0.2891	0.518	0.154	1.747
Stomatitis	1 (0.9 %)	1 (2.9 %)	0.4335	0.7834	0.738	0.085	6.411
Nausea	1 (0.9 %)	3 (8.6 %)	0.0464	0.232	0.319	0.049	2.077
Diarrhea	16 (15.0 %)	5 (14.3 %)	1	0.672	0.757	0.209	2.74
Constipation	0 (0.0 %)	0 (0.0 %)					
Anorexia	3 (2.8 %)	4 (11.4 %)	0.0625	0.3781	0.479	0.093	2.46
Weight loss	0 (0.0 %)	1 (2.9 %)	0.2465	0.265	0.236	0.019	2.99
Liver dysfunction	11 (10.3 %)	1 (2.9 %)	0.2939	0.902	0.887	0.132	5.962
ILD	6 (5.6 %)	0 (0.0 %)	0.3362	0.1217	8.224	0.57	118.586
Epistaxis	0 (0.0 %)	0 (0.0 %)					
HFSR	4 (3.7 %)	3 (8.6 %)	0.3636	0.3382	0.444	0.084	2.338
INR increased	0 (0.0 %)	1 (2.9 %)	0.2465	0.076	0.081	0.005	1.301
Dry mouth	0 (0.0 %)	0 (0.0 %)					
Nail change	3 (2.8 %)	0 (0.0 %)	1	0.5085	0.399	0.026	6.088
Pneumonia	0 (0.0 %)	1 (2.9 %)	0.2465	0.3344	0.32	0.032	3.238

ILD interstitial lung disease, *HFSR* hand–foot skin reaction

difference in histology or smoking status between the two groups.

Objective response rates in the gefitinib and erlotinib groups were 13/43 = 30 % (95 % confidence interval [CI] 17–46 %) and 2/29 = 7 % (95 % CI 0–23 %), respectively. The *p* value of Fisher's exact test for comparison between the two groups was 0.079. The *p* value for comparison by the logistic regression adjusting for gender, smoking status, stage and treatment line, which were unbalanced between the groups, was also 0.079 with the odds ratio of the erlotinib

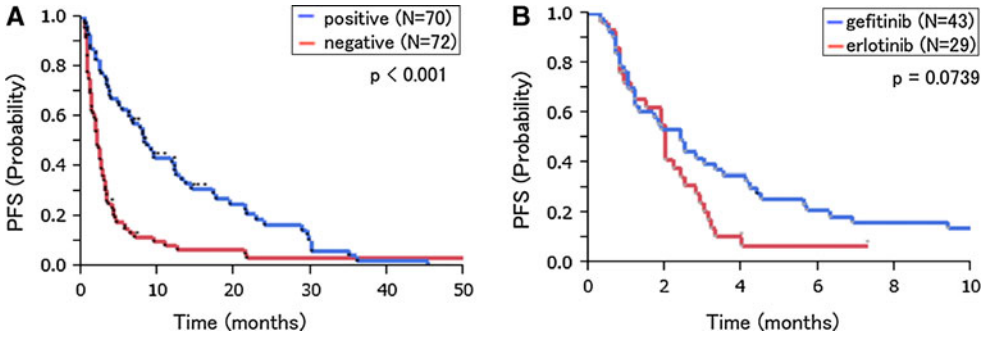

Fig. 1 **a** Progression-free survival according to *EGFR* mutation status. **b** Progression-free survival in patients with *EGFR-wt* according to treatment groups

Table 4 Patients' characteristics (patients with *EGFR-wt*)

Characteristics	Gefitinib ($N = 43$)	Erlotinib ($N = 29$)	p value*
Age (years)			
Median (range)	62 (38–82)	65 (35–78)	0.626
≥65	16	13	
<65	27	16	
Gender			
Male	17	20	0.018
Female	26	19	
Histology			
Adenocarcinoma	35	20	0.265
Non-adenocarcinoma	8	9	
Smoking status			
Never smoker	23	9	0.09
Smoker	20	20	
Performance status			
0–1	39	27	1
2–3	4	2	
Stage			
III or IV	18	25	<0.001
Recurrent	25	4	
Treatment line			
1st or 2nd	33	15	0.041
3rd or 4th	10	14	

*Determined by Fisher's exact test

group relative to the gefitinib group was 0.179 (95 % CI 0.026–1.223), although the difference was not statistically significant.

Forty-two (98 %) patients in the gefitinib group and 27 (93 %) in the erlotinib group suffered disease progression or had died by the data cutoff point. The mPFS in the gefitinib and erlotinib groups were 2.4 months (95 % CI 1.2–3.5 months) and 2.0 months (95 % CI 1.1–2.5 months), respectively (Fig. 1). The difference of PFS between the two groups was not statistically significant ($p = 0.076$). We also compared PFS between the two groups adjusting for gender, smoking status, stage and treatment line, and results are presented in Table 5. By adjusting for these variables, the p value for comparison of the treatment was far from the 5 % significant level ($p = 0.758$) with the hazard ratio of 1.116 (95 % CI 0.556–2.241).

Table 5 Cox regression analysis for comparison of PFS in patients with *EGFR-wt*

	p value	HR	95 % CI	
Treatment (erlotinib/gefitinib)	0.751	1.116	0.567	2.197
Gender (female/male)	0.225	0.577	0.237	1.404
Smoking status (never/smoker)	0.077	0.454	0.19	1.088
Stage (III or IV/recurrent)	0.909	0.965	0.522	1.784
Treatment line (1st or 2nd/3rd or 4th)	0.794	0.928	0.53	1.625

Discussion

On the basis of four phase III trials reported previously, it is now widely recognized that EGFR-TKIs are the most important agents for the treatment of patients with NSCLC who have *EGFR* mutations [3–6]. These trials, and several other studies of EGFR-TKIs [8, 9], have established that gefitinib at 250 mg once daily or erlotinib at 150 mg once daily have similar toxicity profiles and are both generally well tolerated. However, it has been unclear whether their degrees of toxicity are actually equivalent, and also whether they have equal efficacy for patients with NSCLC.

In this retrospective study, we found that AEs characteristic of EGFR-TKI, especially rash, occurred more frequently in the erlotinib group than in the gefitinib group and that the need for dose reduction due to AEs also seemed to be more frequent in the erlotinib group. One of the reasons may be the difference in the approved doses of the two agents. Administration of erlotinib at its maximum-tolerated and approved dose of 150 mg once daily resulted in a steady-state plasma trough concentration that was approximately 3.5 times that for gefitinib administered at its approved dose of 250 mg once daily (approximately

one-third of the maximum-tolerated dose) [12, 13]. Therefore, there is a possibility that the toxicities of erlotinib are dose-related. In our study, most patients who required dose reduction due to AEs were able to continue treatment with manageable toxicities. Furthermore, some studies have shown that low-dose erlotinib (25 or 50 mg) has minimal toxicities, but with a response rate and survival benefit almost equal to those achieved with a 150-mg dose [14, 15]. On the other hand, several AEs, including liver dysfunction and ILD, were observed more frequently in the gefitinib group, although not to a significant degree. Consequently, other factors may affect the toxicities of these agents. For example, it was recently reported that for gefitinib, cytochrome P450 (CYP) genotype polymorphisms, especially *CYP2D6*, were closely related to the frequency of toxicities such as liver dysfunction [16, 17]. Drug allergy may also be involved in some types of toxicity. Thus, various complex mechanisms could be implicated in the development of toxicities associated with each agent.

In relation to drug efficacy, we analyzed the response rate and PFS among patients with *EGFR-wt* only, as gefitinib and erlotinib are well known to induce a marked response and long PFS in patients with *EGFR-mt* tumors. Furthermore, no previous prospective study has compared the efficacy of the two agents directly in patients with *EGFR-wt* NSCLC. Our study showed that the mPFS for patients with *EGFR-wt* overall was 2 months (95 % CI 1.6–2.5 months), being comparable with the previous reports, and that there was no significant difference in PFS between the gefitinib and erlotinib groups. In addition, PFS adjusted for several variables also did not differ significantly between the two groups, although the sample size was small. Therefore, it is suggested that 250 mg gefitinib and 150 mg erlotinib might have almost equal efficacy in patients with *EGFR-wt* NSCLC, irrespective of the issue of whether or not EGFR-TKIs are indicated for such patients.

The limitations of our study included a small sample size, heterogeneity of the treatment timing or regimens, and its retrospective design. As shown in Tables 1 and 4, several biases were inherent to the patient population we studied. Therefore, a prospective well-designed study will be needed to validate our results. Currently, a phase III trial of gefitinib versus erlotinib for patients with previously treated lung adenocarcinoma is ongoing [18].

In conclusion, although this study was retrospective, we demonstrated that 150 mg erlotinib once daily was associated with more AEs characteristic of EGFR-TKIs than 250 mg gefitinib once daily, although the efficacies of these agents at the respective approved doses may not differ. If the toxicity of erlotinib is affected by its dose, then a comparison between 250 mg gefitinib and low-dose erlotinib is warranted.

Conflict of interest None declared.

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