Erlotinib for Pretreated Squamous Cell Carcinoma of the Lung in Japanese Patients

Akito Hata1,*, Nobuyuki Katakami1, Kei Kunimasa2, Hiroshige Yoshioka2, Shiro Fujita1, Reiko Kaji1, Ryo Tachikawa3, Keisuke Tomii3, Yukihiro Imai1, Masahiro Iwasaku2 and Tadashi Ishida2

1Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, 2Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Okayama and 3Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan

*For reprints and all correspondence: Akito Hata, Division of Integrated Oncology, Institute of Biomedical Research and Innovation, 2-2, Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan. E-mail: a-hata@fbri.org

Received August 18, 2011; accepted October 10, 2011

Objective: Erlotinib has demonstrated survival benefit in patients with not only adenocarcinoma but also squamous cell carcinoma. Epidermal growth factor receptor-tyrosine kinase inhibitors are more effective in Asian populations, including the Japanese than in western populations. However, a higher incidence of interstitial lung disease has been reported as a fatal adverse event in the Japanese population. There is little data on erlotinib for Japanese patients with pretreated squamous cell carcinoma.

Methods: Between January 2004 and October 2010, we retrospectively evaluated the efficacy and toxicity of erlotinib administered as the first epidermal growth factor receptor-tyrosine kinase inhibitors for 41 Japanese patients with pretreated squamous cell carcinoma. Patients with pre-existing interstitial lung disease were carefully excluded by several examinations including high-resolution computed tomography.

Results: The response rate and disease control rate were 9.7% [95% confidence interval: 2.7–23.1%] and 43.9% (95% confidence interval: 28.5–60.2%), respectively. Median time to treatment failure and overall survival were 2.2 months (95% confidence interval: 1.0–2.8 months) and 11.0 months (95% confidence interval: 5.7–15.7 months), respectively. Interstitial lung disease (Grade 5) was observed in one (2.4%) patient. Patients with Grade 0–1 skin rashes vs. patients with Grades 2–3 exhibited disease control rates of 28 vs. 83% (P = 0.0017), and median time to treatment failure of 1.2 months vs. 3.4 months (P = 0.0099).

Conclusions: Erlotinib has moderate efficacy for pretreated squamous cell carcinoma in Japanese patients. A higher grade of skin rash was associated with clinical benefit. Careful exclusion of pre-existing interstitial lung disease can minimize the occurrence of interstitial lung disease.

Key words: squamous cell carcinoma – erlotinib – interstitial lung disease – rash

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide (1). Non-small cell lung cancer (NSCLC) accounts for ~80% of lung cancers, and the majority are already unresectable and metastatic upon their initial diagnosis. Systemic chemotherapies are the primary therapeutic option for these patients (2). Cytotoxic chemotherapies such as platinum-based regimens have been commonly administered, but the advancement of cytotoxic agents has reached a plateau. Currently, several molecular-targeted agents have been developed, and inhibition of epidermal growth factor receptor (EGFR) or vascular endothelial growth factor pathways...
can provide clinical benefit (3,4). Among these agents, erlotinib and gefitinib are oral EGFR-tyrosine kinase inhibitors (TKIs) widely used to treat patients with advanced or metastatic NSCLC. Somatic mutations in the EGFR gene have been identified in patients with radiographic responses to EGFR-TKIs (5,6), and recently the efficacy of up-front EGFR-TKIs has been demonstrated for patients harboring EGFR mutations in prospective randomized phase III trials (7–9). Initially, the efficacy of EGFR-TKIs was explored in pretreated patients of non-selected populations. In a placebo-controlled, randomized phase III trial, erlotinib demonstrated a survival benefit compared with the placebo (3). Conversely, gefitinib failed to demonstrate a survival benefit compared with the placebo (9). The efficacy of gefitinib seems to be mostly limited to patients with EGFR mutations (11). However, erlotinib demonstrated efficacy in patients with not only EGFR mutations but also squamous cell carcinoma (SCC), revealed in the subset analyses of BR.21 and SATURN trials (3,12).

Early investigations of EGFR-TKIs indicated several clinico-pathological factors that predict a better outcome, including gender (female), smoking status (never), ethnicity (east Asian including Japan) and histology (adenocarcinoma) (13,14). In the IDEAL 1 trial, Japanese patients appeared to have higher sensitivity to gefitinib than western patients (13). On the other hand, interstitial lung disease (ILD), known as a fatal adverse effect, was frequently observed in Japanese patients (13). Although a clinical benefit of EGFR-TKI therapy for Japanese patients can be expected, the occurrence of ILD should be carefully monitored. Most SCC patients are commonly male and current smokers, factors which significantly predict high incidence of ILD in gefitinib treatment (15). However, there is little data on the efficacy and safety of erlotinib for Japanese patients with pretreated SCC.

The aim of our study was to evaluate the efficacy of erlotinib in Japanese patients with SCC and investigate the incidence and grade of adverse events, particularly ILD.

PATIENTS AND METHODS

PATIENTS

Between January 2004 and October 2010, we analyzed 41 patients with pretreated lung SCC who had received erlotinib therapy as the first-TKI treatment (excluding cases who received re-administration of erlotinib) at our institutes. The results were retrospectively identified using case records and radiographic records. Patients had Eastern Cooperative Oncology Group performance status (PS) 0–3, with no severe organ dysfunction. We excluded patients suspected of having pre-existing ILD by several examinations: auscultation, blood laboratory tests (KL-6 and surfactant protein-D) and high-resolution computed tomography (CT) before initiation of erlotinib. Patients who reported never smoking in their lifetime were defined as never smokers. Those who had smoked within 1 year of the diagnosis were categorized as current smokers. The rest were considered former smokers. Written informed consent regarding erlotinib therapy was obtained from all patients.

TREATMENT METHODS

Patients received erlotinib initially at a dose of 150 mg/day. Dose reduction to 100, 75 or 50 mg/day and dose interruption were performed when intolerable toxicities were observed. Therapy was continued until disease progression, intolerable toxicity or patient withdrawal.

EVALUATION OF EFFICACY AND TOXICITY

Baseline evaluations including medical history, physical examinations and laboratory tests were performed. Evaluation of treatment response by CT scan was repeated every 4–8 weeks according to the Response Evaluation Criteria in Solid Tumors Committee (16). If a patient was documented to demonstrate a complete response (CR) or a partial response (PR), a confirmation was necessary after >4 weeks. Disease control was defined as the best tumor response of CR, PR or stable disease (SD) that was confirmed and sustained for at least 8 weeks. The response rate (RR) and disease control rate (DCR) were defined as CR + PR and CR + PR + SD ≥ 8 weeks, respectively. Time to treatment failure (TTF) was defined as the period from the start of treatment to the date when disease progression was observed or treatment was stopped. Overall survival (OS) was defined as the period from the start of erlotinib treatment to the date of death. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

EGFR MUTATIONAL ANALYSIS

In cases with available tissue or cytological specimens, we isolated tumor DNA from various specimens and the EGFR mutation status was analyzed before administration of erlotinib using the peptide nucleic acid (PNA)–locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp method, as previously reported (17).

STATISTICAL ANALYSIS

DCRs were compared between demographic factors using Fisher’s exact test or Spearman’s rank correlation. The survival distribution (TTF and OS) was estimated by the Kaplan–Meier method. TTF between Grade 0–1 and Grade 2–3 rash were compared using the log-rank test. P values <0.05 were considered statistically significant. Statistical
analysis was performed using JMP 7 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

Between January 2004 and October 2010, 41 patients with pretreated lung SCC who had received erlotinib therapy as first TKI (excluding cases who received re-administration of erlotinib) were retrospectively evaluated at our institutes. Table 1 lists patient characteristics. The median age was 68 (range, 47–84). The male gender was dominant (29 of 41, 71%). Most patients were ever smokers (35 of 41, 85%). Good PS (0/1) patients were dominant (34 of 41, 83%). Only one patient with adeno-SSC was included. Two patients harbored EGFR-sensitive mutations, both of them a deletional mutation in exon 19 (E746-A750).

TUMOR RESPONSE

Out of 41 patients, 4 had a PR and 14 had SD, yielding an overall RR of 9.7% [95% confidence interval (CI): 2.7–23.1%] and a DCR of 43.9% (95% CI: 28.5–60.2%). Two patients with EGFR mutations failed to respond to erlotinib.

Table 1. Patient characteristics (n = 41)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>68 (47–84)</td>
</tr>
<tr>
<td>Prior regimens, median (range)</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Former</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Current</td>
<td>23 (56)</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>34 (83)</td>
</tr>
<tr>
<td>2, 3</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>40 (98)</td>
</tr>
<tr>
<td>Adeno-squamous</td>
<td>1 (2)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Negative</td>
<td>32 (78)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (17)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

SURVIVAL

The median TTF was 2.2 months (95% CI: 1.0–2.8 months; Fig. 1a) and the median OS time was 11.0 months (95% CI: 5.7–15.7 months; Fig. 1b). A comparison of rash grades is shown in Fig. 2. The median TTF with Grade 0–1 rash was 1.2 months (95% CI: 0.8–2.2 months) and the median TTF with Grade 2–3 rash was 3.4 months (95% CI: 1.3–5.8 months; P = 0.0099).
TOXICITY PROFILE

Twenty-two (53.9%) skin rash, 14 (34.1%) diarrhea, 10 (24.4%) anorexia, 5 (12.2%) fatigue and 1 (2.4%) liver dysfunction were observed in total. Adverse events ≥Grade 3: 2 (4.9%) skin rash; 3 (7.3%) diarrhea; 3 (7.3%) anorexia; 1 (2.4%) fatigue and 0 (0%) liver dysfunction were confirmed. Interstitial lung disease was observed in one (2.4%) of 41 patients, and caused that patient’s death; this was the only treatment-related death. Non-hematological adverse events ≥Grade 3 were observed in 10 (30%) of 41 patients. Dose reduction or interruption due to adverse events was necessary in 19 (46.3%) of 41 patients.

ANALYSIS OF DISEASE CONTROL

Analysis of disease control is shown in Table 2. Using univariate analysis, skin rash was suggested as the only predictive factor for better disease control. The DCR of patients with Grade 0–1 rash was 28% (8 of 29; 95% CI: 13–47%) and that with Grade 2–3 rash was 83% (10 of 12; 95% CI: 52–98%; P = 0.0017).

CASE REPORT

We herein document two cases who achieved a PR to erlotinib.

CASE 1

A 69-year-old, never-smoking woman was diagnosed with metastatic poorly differentiated SCC of the lung (Supplementary data, Fig. S1). EGFR mutation analysis was not performed. She received cisplatin plus vinorelbine as the first-line chemotherapy and docetaxel as the second-line chemotherapy. Erlotinib was administered as the third-line chemotherapy and PR was achieved for 9.2 months (Fig. 3). Grade 1 rash and Grade 2 diarrhea were observed and dose reduction to 100 mg/day was performed.

CASE 2

A 63-year-old, currently smoking man was diagnosed with metastatic moderately differentiated SCC of the lung (Supplementary data, Fig. S2). The EGFR mutation status was wild-type. He received cisplatin plus S-1 as the first-line chemotherapy and docetaxel as the second-line chemotherapy. Erlotinib was administered as the third-line chemotherapy and PR was achieved for 8.2 months (Fig. 4). Grade 3 rash and paronychia were observed. Because of intolerable toxicities, erlotinib was interrupted, and a dose modification was needed.

DISCUSSION

In the present study, the RR, DCR, median TTF and median OS were 9.7%, 43.9%, 2.2 months and 11.0 months, respectively. In the pivotal phase III trial (BR.21) investigating erlotinib therapy for pretreated NSCLC, the RR, DCR, median progression-free survival (PFS) and median OS were 8.9%, 45.0%, 2.2 months and 6.7 months, respectively (3). These results are remarkably similar (except for OS; survival is commonly better in Japanese NSCLC patients) (10), and also comparable to results in a phase II trial for EGFR mutation-negative Japanese NSCLC. In the trial, the RR, DCR, median PFS and median OS were 3.3%, 60.0%, 2.1 months and 10.7 months, respectively (18). Similarly, Matsuura et al. (19) have reported the efficacy of erlotinib as third-line therapy in advanced NSCLC without EGFR mutations. In their report, the RR, DCR, median PFS and median OS were 15.0%, 55.0%, 2.1 months and 6.7 months, respectively. Although these results are moderate compared with results achieved by EGFR mutation-positive patients (7–9), erlotinib can exert a survival benefit even for patients with pretreated SCC, as demonstrated by the subset analyses of
the BR.21 and SATURN trials (3,12). In global, open-label, phase IV trials of erlotinib (Tarceva Lung Cancer Survival Treatment: TRUST study), similar efficacies of erlotinib for SCC were documented: RR, DCR, median PFS and median OS were 5.8%, 67.6%, 2.3–3.0 months and 5.0–9.4 months, respectively (20,21). On the other hand, except for erlotinib, docetaxel is considered the recommended regimen for pretreated SCC after failure of platinum doublets (2). Although there is no data limited to SCC, in a Japanese phase III trial comparing docetaxel with gefitinib, docetaxel suggested the efficacy and safety after first-line therapy. In the study, the RR, DCR, median PFS and median OS were 12.8%, 34.0%, 2.0 months and 14.0 months, respectively. The toxicities were well tolerated (22). These results are also similar to our present study regarding erlotinib. The reproducibility of these results suggests that erlotinib can be a treatment option for Japanese pretreated SCC patients if the risk of ILD is permissible.

Two patients with EGFR-sensitive mutations in our study failed to respond to erlotinib. Shukuya et al. (23) reported the efficacy of gefitinib for 27 SCC patients with EGFR-sensitive mutations and the RR, DCR and median PFS were 30%, 67% and 3.1 months, respectively. Their results and our cases suggest that EGFR-TKIs may be less effective in SCC with EGFR mutations than in adenocarcinoma with EGFR mutations. The reasons for these results are unclear. We speculate that intratumoral heterogeneity is one of the reasons. Travis et al. (24) have suggested that a complexity of adeno and squamous histologies are occasionally found in histological samples. PNA–LNA PCR clamp

**Figure 3.** Chest computed tomography scans of Case 1 show responses of multiple pulmonary metastases and the right adrenal metastasis (arrowhead): (a and b) before the initiation of erlotinib and (a’ and b’) 2 months after the initiation of erlotinib.

**Figure 4.** Chest computed tomography scans of Case 2 show responses of the primary tumor (arrowhead) and pulmonary metastases: (a and b) before the initiation of erlotinib and (a’ and b’) 3 months after the initiation of erlotinib.
method was used in EGFR mutational analysis of our data. It is a highly sensitive technique and may have detected a minor population of EGFR-mutated adeno-component in an EGFR wild-type SCC tumor. However, there is insufficient data to discuss the efficacy of EGFR-TKIs for SCC harboring EGFR-sensitive mutations at present and further research is needed.

As in previous studies, rash and diarrhea were frequently observed in our study. ILD is rarely observed in the Caucasian population, but it is a serious problem as a fatal adverse event in Japan. In our study, ILD was observed in one (2.4%) of 41 patients, and caused this patient’s death. In phase II studies of erlotinib therapy conducted in Japan, the incidences of ILD were reported as 6.5% (4 of 62), 2.5% (1 of 40) and 6.7% (2 of 30) (18,25,26). In a prospective epidemiologic cohort study on gefitinib, a higher incidence of ILD was significantly associated with the following factors: elderly, smoker, pre-existing ILD and poor PS (15,27). Among these factors, pre-existing ILD had the strongest relationship with the occurrence of ILD. Pre-existing ILD therefore should be ruled out before initiating EGFR-TKI treatment. We carefully performed several kinds of examinations to exclude cases suspected of pre-existing ILD before administration of erlotinib. Although male smokers were predominant, the incidence of ILD in our study was similar to or less than those in previous reports. Careful examinations to rule out ILD can improve the safety of erlotinib therapy even in a Japanese SCC population.

Our present study suggests that there are two patterns of SCC patients who can expect a response to erlotinib. The first pattern is a never-smoking female. As Shepherd et al. (3) documented in BR.21, being a never smoker, female, Asian and having adenocarcinoma were significant predictive factors for a higher response rate. Our Case 1 was a never-smoking female, but she was diagnosed with SCC. Histology revealed a poorly differentiated tumor; strict pathological diagnosis was difficult. We speculate that EGFR-mutated adenocarcinoma components may have been included and responded to the erlotinib. Additionally, the incidence of ILD is predicted to be extremely low in a never-smoking female. In terms of efficacy and safety, we can confidently administer erlotinib to a never-smoking female, even in patients with SCC. The second pattern comprises cases in which the patients develop a high-grade rash. Case 2 was a currently smoking male with moderately differentiated SCC. Grade 3 severe rash was confirmed and erlotinib was effective. Moreover, the remaining two patients of the four who obtained a PR were former smoking males, and both of exhibited rash >Grade 2. Rash grade has been shown to be strongly associated with a better outcome in erlotinib therapy (28). Even in an SCC, currently smoking male patient, clinical benefit from erlotinib can be expected in cases with a high grade of skin rash.

In our study, never or former smoking status and a good PS showed better trends to obtain disease control by univariate analysis, but these differences were not statistically significant, probably because of the small sample size. Skin rash was confirmed as the only predictive factor for better disease control. Moreover, the higher the severity of the rash, the longer the TTF. The significance of rash grade was proven despite the small sample size. Rash was thus suggested as a strong predictive factor for better outcome. Rash management is extremely important in erlotinib treatment.

In conclusion, erlotinib has moderate efficacy for pre-treated SCC in Japanese patients. Greater benefit can be expected in patients who develop a higher grade of skin rash. The incidence of ILD can be minimized by careful examinations to exclude pre-existing ILD. As our study is retrospective and the sample size is small, further prospective study is warranted to confirm the efficacy and safety of erlotinib (especially the incidence and severity of ILD) in Japanese SCC patients.

### Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

### Acknowledgements

We thank Mr. David Martin for writing support.

### Conflict of interest statement

None declared.

### References


