Abstract. Aim: To evaluate the tolerability and efficacy of erlotinib treatment in advanced non-small cell lung cancer (NSCLC) patients who had previously experienced severe hepatotoxicity after gefitinib treatment. Patients and Methods: Twenty-five NSCLC patients with epidermal growth factor receptor (EGFR) mutation were initially treated with gefitinib (250 mg/day). However, 7 of these experienced severe hepatotoxicity. After recovery from hepatotoxicity, treatment was switched to erlotinib (150 mg/day) in all 7 patients. Toxicity and efficacy of erlotinib were analyzed. Results: None of the 7 patients reported severe hepatotoxicity with erlotinib despite gefitinib-induced severe hepatotoxicity. All patients achieved response with gefitinib or following erlotinib treatment. The response achieved with gefitinib was maintained after switching to erlotinib. Therefore, an excellent median progression-free survival of 372 days was achieved although gefitinib induced severe hepatotoxicity. Conclusion: Erlotinib treatment was efficient and well-tolerated in NSCLC patients with EGFR mutation, despite their severe hepatotoxicity with prior gefitinib treatment.

Lung cancer, despite being the world’s leading cause of cancer death (1), is often diagnosed at an advanced incurable stage. The disease is histologically divided into 2 groups, small-cell and non-small-cell lung cancer (NSCLC), each with different treatment strategies. One of the treatment options for advanced NSCLC is chemotherapy, which has been shown to improve quality of life and prolong survival (2). NSCLC patients who present with a good performance status and tolerate treatment-induced toxicity are often eligible for conventional chemotherapy. However, in the past decade, thanks to improved molecular biological understanding, the focus of clinical development of new pharmaceutical agents has shifted towards molecular-targeted agents, especially in NSCLC.

Gefitinib is a small-molecule drug targeting epidermal growth factor receptor (EGFR) tyrosine kinase. It is especially efficient in treating NSCLC with EGFR mutation (3, 4). In a phase III randomized clinical trial enrolling patients with chemotherapy-naïve stage IIIB or IV advanced NSCLC with EGFR mutation, gefitinib has been shown to double the progression-free survival (PFS) time compared to conventional chemotherapy such as the carboplatin- and-paclitaxel combination (5-7). Therefore, gefitinib is currently one of the standard chemotherapies for advanced NSCLC with EGFR mutation (8). Skin rash and diarrhea are the most frequently observed toxicities associated with gefitinib treatment. In a phase I clinical trial for gefitinib, diarrhea and hepatotoxicity were dose-limiting factors (9, 10). Additionally, in the same phase III trial mentioned above, severe hepatotoxicity involving elevated liver transaminase levels ≥ grade 3 according to the Common Terminology Criteria (CTC) for Advanced Events, Version 4.0 was observed in approximately 10-26% of patients receiving gefitinib treatment (5, 6, 7). Hepatotoxicity associated with gefitinib often necessitated discontinuation, dose reduction or permanent termination of treatment.

Erlotinib, on the other hand, is another EGFR tyrosine kinase inhibitor that has demonstrated significant superiority to traditional cytotoxic agents in chemotherapy-naïve, advanced NSCLC patients in a randomized phase III clinical trial (11, 12). Therefore, erlotinib has also been considered a first-line chemotherapy for advanced NSCLC patients with EGFR mutation. Hepatotoxicity induced by erlotinib has been observed in similar extent and frequency compared to gefitinib.

However, it is important to note that hepatotoxicity associated with erlotinib has been reported to be mechanistically independent of that induced by gefitinib (13, 14). Therefore, erlotinib might be an alternative treatment in cases of gefitinib-induced hepatotoxicity. In the present study, we aimed to evaluate tolerability and efficacy of...
erlotinib in \textit{EGFR} mutation-positive NSCLC patients who had previously experienced hepatotoxicity with gefitinib treatment.

\textbf{Patients and Methods}

\textit{Patients and treatment.} The present study included 25 patients with stage IIIB or IV advanced NSCLC treated at the Izumi City Hospital from September 2011 to August 2013. These patients were positive for \textit{EGFR} mutation and were treated with gefitinib as first-line chemotherapy for advanced NSCLC. Seven of these patients experienced severe hepatotoxicity, grade 4 elevated liver transaminase levels in one and with grade 3 elevated levels in six. Patients' characteristics including age, gender, histology, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, clinical stage, \textit{EGFR} mutation status, first-line treatment regimen and duration of gefitinib treatment are shown in Table I. With the exception of gefitinib treatment duration, background characteristics did not differ significantly between patients with gefitinib-induced hepatotoxicity and all included patients. Although all patients received gefitinib as first-line chemotherapy, the duration of gefitinib treatment was significantly shorter in those with gefitinib-induced hepatotoxicity, compared to all treated patients ($p=0.0331$).

\textit{Tolerability.} No severe hepatotoxicity associated with erlotinib was observed in any of the 7 patients with gefitinib-induced hepatotoxicity ($p<0.05$, Table II). Two patients treated with erlotinib had grade 1 elevated liver transaminase levels but did not require dose reduction. The maximum erlotinib treatment duration was 1,073 days with a median of 280 days, ranging from 28 to 1,073 days. Erlotinib treatment was terminated in 6 patients; due to disease

\begin{table}[h]
\centering
\caption{Baseline patient characteristics.}
\begin{tabular}{l|l|l}
\hline
\textbf{Characteristics} & \textbf{All patients treated with gefitinib (n=25)} & \textbf{Patients treated with erlotinib following gefitinib (n=7)} \\
\hline
Median age & 68 years (range, 38-87 years) & 69 years (range, 38-84 years) \\
Gender: Male/Female & 8 (32 %)/17 (68%) & 3 (42.9%)/4 (57.1 %) \\
Histology: Adenocarcinoma/NSCLC NOS & 23 (92%)/2 (8%) & 7 (100%)/0 (0%) \\
Smoking status: Never/Past usage/Current smoker & 22/3/0 & 0/0/0 \\
ECOG performance status: 0-1/2 & 20/5 & 6/1 \\
Clinical stage: IIIB/IV & 1/24 & 0/7 \\
\textit{EGFR} mutation status: Exon 19 deletion/Exon 21 mutation & 15 (60%)/10 (40%) & 4 (57%)/3 (43 %) \\
Initial chemotherapy & Gefitinib-alone (100%) & Gefitinib-alone (100%) \\
Duration of gefitinib treatment (Median)* & 200 days & 99 days \\
\hline
\end{tabular}
\footnotetext{*All patients treated with gefitinib vs. patients treated with erlotinib following gefitinib; log-rank test $p=0.0331$; hazard ratio, 0.2659; 95% confidence interval (CI), 0.0786-0.8992. NSCLC NOS, non-small cell lung cancer not otherwise specified; ECOG, eastern cooperative oncology group; \textit{EGFR}, epidermal growth factor receptor.}
\end{table}
progression in 5 and due to complication with interstitial pneumonia in 1. Four patients received erlotinib for a longer period of time than they did with gefitinib.

Skin rash was observed in all patients during gefitinib treatment although the symptoms were manageable without the need for dose modification (Table III). However, dose reduction was required in 4 patients during erlotinib treatment due to severe grade 3 rash or for cosmetic reasons. No other toxicity requiring dose reduction or discontinuation was observed during both gefitinib and erlotinib treatments except for a case of grade 2 interstitial pneumonia that occurred during erlotinib administration.

**Efficacy.** All patients achieved response with gefitinib or erlotinib treatment. After switching to erlotinib from gefitinib treatment, response continued for more than 10 weeks in all patients. Figure 1 shows the PFS curves from the first day of gefitinib treatment to the day of disease progression for all patients treated with gefitinib (n=25) and for patients treated with erlotinib following gefitinib-induced hepatotoxicity (n=7). Median PFS was 372 days in both groups. There was no significant difference on PFS between the 2 groups (hazard ratio, 1.074; 95% confidence interval (CI), 0.3689-3.127; p=0.8959).

### Table II. Summary of CTC hepatotoxicity grade and treatment duration in patients receiving gefitinib followed by erlotinib.

<table>
<thead>
<tr>
<th>Case</th>
<th>CTC grade of elevated liver transaminase levels during gefitinib treatment</th>
<th>Duration of gefitinib treatment (days)</th>
<th>CTC grade of elevated liver transaminase levels during erlotinib treatment</th>
<th>Duration of erlotinib treatment (days) and reason for termination (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-year-old, female EGFR Ex19 mutation</td>
<td>Grade 4</td>
<td>42</td>
<td>None</td>
<td>363, disease progression</td>
</tr>
<tr>
<td>84-year-old, female EGFR Ex19 mutation</td>
<td>Grade 3</td>
<td>39</td>
<td>None</td>
<td>395, treatment continued</td>
</tr>
<tr>
<td>38-year-old, female EGFR Ex19 mutation</td>
<td>Grade 3</td>
<td>99</td>
<td>None</td>
<td>280, disease progression</td>
</tr>
<tr>
<td>71-year-old, female EGFR Ex21 mutation</td>
<td>Grade 3</td>
<td>181</td>
<td>Grade 1</td>
<td>28, complicated with interstitial pneumonia</td>
</tr>
<tr>
<td>69-year-old, male EGFR Ex21 mutation</td>
<td>Grade 3</td>
<td>143</td>
<td>Grade 1</td>
<td>74, disease progression</td>
</tr>
<tr>
<td>76-year-old, male EGFR Ex19 mutation</td>
<td>Grade 3</td>
<td>553</td>
<td>Grade 1</td>
<td>1073, disease progression</td>
</tr>
<tr>
<td>65-year-old, male EGFR Ex19 mutation</td>
<td>Grade 3</td>
<td>98</td>
<td>None</td>
<td>78, disease progression</td>
</tr>
</tbody>
</table>

CTC, Common terminology criteria; EGFR, epidermal growth factor receptor.

### Table III. Grade of skin rash induced by either gefitinib or erlotinib.

<table>
<thead>
<tr>
<th>Case</th>
<th>Grade of skin rash with gefitinib</th>
<th>Grade of skin rash with erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-year-old, female</td>
<td>Grade 1</td>
<td>Grade 2, dose reduction required</td>
</tr>
<tr>
<td>84-year-old, female</td>
<td>Grade 1</td>
<td>Grade 3, dose reduction required</td>
</tr>
<tr>
<td>38-year-old, female</td>
<td>Grade 2</td>
<td>Grade 2, dose reduction required</td>
</tr>
<tr>
<td>71-year-old, female</td>
<td>Grade 1</td>
<td>Grade 1, erlotinib 150 mg/day</td>
</tr>
<tr>
<td>69-year-old, male</td>
<td>Grade 1</td>
<td>Grade 3, dose reduction required</td>
</tr>
<tr>
<td>76-year-old, male</td>
<td>Grade 1</td>
<td>Grade 1, erlotinib 150 mg/day</td>
</tr>
<tr>
<td>65-year-old, male</td>
<td>Grade 1</td>
<td>Grade 1, erlotinib 150 mg/day</td>
</tr>
</tbody>
</table>
Discussion

In the present study, we found that erlotinib was an efficient and well-tolerated treatment for *EGFR* mutation-positive NSCLC despite severe hepatotoxicity associated with precedent gefitinib treatment. Gefitinib induced severe hepatotoxicity in 28% of all NSCLC cases included in this study, similar to previously reported observations in other studies (5-7). In contrast, alternative treatment with erlotinib did not induce any severe hepatotoxicity among 7 NSCLC patients with gefitinib-induced hepatotoxicity. Even in 3 patients who continued to receive erlotinib for more than 1 year, hepatotoxicity was not observed. Although this result might be biased due to the limited sample size and retrospective nature of the study, our findings suggest that gefitinib- and erlotinib-induced hepatotoxicity might be of independent origin. Although no immunological examination or pharmacokinetic analysis of gefitinib or erlotinib was performed in this study, gefitinib has been reported to cause hepatotoxicity due to drug allergy (13). Since erlotinib has a different chemical structure from gefitinib, switching to erlotinib from gefitinib could prevent immunological cross-reaction. However, gefitinib-induced hepatotoxicity has also been associated with impaired metabolic pathway (14). More specifically, both gefitinib and erlotinib are mainly metabolized by CYP3A4, CYP3A5 and CYP1A1, whereas CYP2D6 is specifically involved in gefitinib metabolism. Thus, gefitinib-induced hepatotoxicity might be associated with CYP2D6 polymorphism. Further elucidating the mechanism of gefitinib-induced hepatotoxicity might ensure safer management.

In the present study, although gefitinib treatment resulted in partial response of all 7 patients, the median time-to-treatment failure of 99 days, due to severe hepatotoxicity, was disappointing. However, overall PFS in our study was similar to that previously reported (5-7), which could be explained by the ability of erlotinib to maintain response for a definite period, even after discontinuation of gefitinib treatment. *EGFR* tyrosine kinase inhibitor has been considered an indispensable drug, offering significantly prolonged survival in NSCLC patients with *EGFR* mutation (15). Safe administration of erlotinib in case of gefitinib-induced hepatotoxicity could contribute to improvement of prognosis compared to intermittent administration or termination of gefitinib.

Regarding toxicity other than hepatotoxicity, rash was more severe and frequently observed in erlotinib treatment compared to prior gefitinib treatment. Rash induced by gefitinib was mild and easily manageable without dose modification or discontinuation of gefitinib. In contrast, erlotinib treatment required dose reduction in more patients. However, rash induced by erlotinib was well-managed with recommended interventions or with dose modification (16). These results are in line with other reports that erlotinib is associated with more toxic and frequent rash compared to gefitinib (17).

The present treatment options for NSCLC with *EGFR* mutation include gefitinib, erlotinib and afatinib; with the latter being recently approved. The difference in efficacy among these drugs has not yet been elucidated (17). Therefore, these drugs should be chosen according to their toxicity profiles. Our results suggested that alternative usage of erlotinib is a safe and efficient treatment in case of hepatotoxicity induced by gefitinib.

Acknowledgements

The Authors would like to thank the medical team members for this study.

References


Received May 19, 2014
Revised July 1, 2014
Accepted July 2, 2014