Clinical utility of erlotinib for the treatment of non-small-cell lung cancer in Japanese patients: current evidence

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Abstract: Gefitinib, an epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI), has been approved in Japan for the treatment of patients with advanced non-small-cell lung cancer (NSCLC) based on Phase II clinical trials since 2002. Erlotinib, another EGFR-TKI, was also approved a few years thereafter. In 2004, activating mutations in the EGFR gene were discovered to be a predictive biomarker for EGFR-TKI treatment, and gefitinib, which is not effective for patients with EGFR wild-type NSCLC, has since been used only in patients with EGFR-mutated NSCLC. In contrast, erlotinib is potentially effective for the treatment of EGFR wild-type NSCLC. Similar to gefitinib, erlotinib is also effective for EGFR-mutated NSCLC and has been used as an initial treatment for patients with advanced EGFR-mutated NSCLC. Both gefitinib and erlotinib can be used in a Japanese clinical setting. The approved daily dose of erlotinib (150 mg) is equal to the maximum tolerated dose of erlotinib. In contrast, the daily dose of gefitinib has been set at 250 mg, which is approximately one-third of the maximum tolerated dose of gefitinib. Accordingly, a higher serum concentration can be achieved using erlotinib, compared with gefitinib. This advantage can be applied to the treatment of central nervous system metastases (brain metastasis and carcinomatous meningitis), the treatment of which is complicated by the difficulty drugs have penetrating the blood–brain barrier. Although patients with EGFR-mutated NSCLC respond dramatically to EGFR-TKIs, some patients have a poor response and the majority eventually undergo disease progression. To overcome such resistance, several novel treatment strategies, such as combination therapy and next-generation EGFR-TKIs, have been attempted.

Keywords: non-small-cell lung cancer, epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib, EGFR mutation

Introduction

Lung cancer is the leading cause of cancer-related death in the developed world.1 Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and despite recent advances in therapy for advanced NSCLC, its prognosis remains very poor.2 For most individuals with advanced NSCLC, cytotoxic chemotherapy is the mainstay of treatment based on moderate improvement in survival. However, the outcome of chemotherapy in such patients has reached a plateau in terms of the response rate (25%–35%) and overall survival (OS; 8–10 months).3,4 Epidermal growth factor receptor (EGFR) is recognized as an important molecular target in cancer therapy.5 Phase II trials using the EGFR-tyrosine kinase inhibitor (EGFR-TKI) gefitinib (Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2; IDEAL1 and 2) have shown favorable outcomes.6,7 In Japanese patients, especially, the response rate...
was approximately 30%. Based on these results, the use of gefitinib was approved in Japan prior to its approval in other countries. A larger Phase III trial (Iressa Survival Evaluation in Lung Cancer; ISEL), however, showed no superiority of gefitinib to best supportive care (median OS 5.6 months for gefitinib versus 5.1 months for best supportive care, hazard ratio [HR] 0.89, \( P=0.087 \)). In this trial, however, gefitinib seemed to result in an improvement in survival among never-smokers and Asians, as has been reported in previous Phase II trials.\(^6\)\(^-\)\(^8\) In addition, somatic-activating mutations of the EGFR gene (EGFR mutations) were discovered to be oncogenic driver mutations in NSCLC in 2004, and patients with NSCLC harboring EGFR mutations generally responded to EGFR-TKIs.\(^9\)\(^-\)\(^11\) In the Iressa Pan-Asia Study (IPASS), however, patients with EGFR wild-type NSCLC rarely responded to gefitinib.\(^12\)\(^,\)\(^13\) Therefore, gefitinib is now used only for EGFR-mutated NSCLC. In contrast to gefitinib, erlotinib – another EGFR-TKI – was shown to be superior to best supportive care in a large Phase III trial (BR.21) (median progression-free survival [PFS] 2.2 months for erlotinib versus 1.8 months for a placebo, HR 0.61, \( P=0.001 \); median OS 6.7 months versus 4.7 months, HR 0.70, \( P=0.001 \)).\(^14\) The results of several trials seemed to suggest that erlotinib was effective not only for EGFR-mutated NSCLC, but also for EGFR wild-type NSCLC. Here, this review summarizes erlotinib treatment in the Japanese clinical setting, where both gefitinib and erlotinib can be used as EGFR-TKIs.

Structure and EGFR inhibitory activity of erlotinib

The discovery that 4-anilinoquinazolines exhibit EGFR inhibitory activity led to the development of EGFR-TKIs.\(^15\) Nanomolar concentrations of the quinazoline erlotinib ([6,7-bis{2-methoxy-ethoxy}-quinazolin-4-yl]-[3-ethylphenyl]) amine (Figure 1) inhibit the activity of purified EGFR-TK and EGFR autophosphorylation in intact tumor cells, with 50% inhibitory concentration values of 2 nmol/L and 20 nmol/L, respectively.\(^16\) Erlotinib is 1,000-fold more potent against EGFR-TK than most other human kinases, including c-Src and insulin receptor TK.\(^16\)

Erlotinib for EGFR-mutated NSCLC

In 2004, three groups in the US reported the landmark findings that a subset of NSCLC patients harbor activating mutations of \(EGFR^{9\)–\(^11\) and that tumors positive for such mutations are highly sensitive to EGFR-TKIs, such as gefitinib and erlotinib. Indeed, most NSCLC patients who experienced a marked response to EGFR-TKIs were found to harbor EGFR mutations. EGFR mutations are present predominantly among women, never-smokers, individuals with adenocarcinoma, and those of East Asian ethnicity. The prevalence of EGFR mutations is approximately 20%–40% among East Asians and 10% among Caucasians.\(^17\)\(^-\)\(^22\) The most common EGFR mutations in patients with NSCLC include short in-frame deletions in exon 19 and a specific point mutation in exon 21 at codon 858. Both mutations account for approximately 80%–90% of the EGFR mutations that were detected. Several studies have revealed that EGFR-TKIs are more effective against NSCLCs with an EGFR exon 19 deletion mutation compared with those with an exon 21 L858R mutation.\(^23\)\(^-\)\(^25\) Other less commonly detected sensitizing EGFR mutations include the G719A/C/S and S720F mutations in exons 18, the L861Q/R mutations in exon 21, and the V765A, T783A, and S768I mutations in exon 20. In contrast, less commonly detected primary resistant EGFR mutations include various insertion mutations in exon 20.\(^21\)\(^,\)\(^22\)\(^,\)\(^26\)

At first, \(EGFR^{\text{mutational}}\) analyses were performed using direct sequencing. However, the clinical specimens that are used to diagnose lung cancers (ie, sputum, pleural effusion, bronchial washing, and surgically resected tissue) contain numerous normal cells. Thus, a method capable of detecting \(EGFR\) mutations within a large background of wild-type \(EGFR\) genes was required. Therefore, highly sensitive polymerase chain reaction (PCR) methods, such as PCR-Invader® (Hologic, Inc., Bedford, MA, USA), peptide nucleic acid-locked nucleic acid PCR clamp, Cycleave® PCR (Takara Bio Inc., Kyoto, Japan), and the Scorpion amplification refractory mutation system (Roche Diagnostics, Basel, Switzerland), have become widely used in the Japanese clinical setting.\(^9\)\(^,\)\(^27\)\(^-\)\(^30\) Both the sensitivities and the specificities of these assays are higher than 90%, and formalin-fixed paraffin-embedded tissue, bronchofiberscopic brushing cytology, and pleural effusion cytology samples can be analyzed using these methods.\(^31\) In Japan, these highly sensitive methods have been widely introduced into clinical
settings. Therefore, the Japanese treatment guidelines recommend that NSCLC, especially non-squamous cell lung cancer, be first analyzed for EGFR mutations before deciding upon an appropriate treatment.

In prior clinical trials of EGFR-TKIs, such as the ISEL and BR.21 trials, the patients were not selected. Since the IPASS trial, however, patients participating in such clinical trials have been selected according to their EGFR mutation status. Therefore, the current evidence is based on such selected trials. Three large Phase III trials comparing erlotinib and cytotoxic platinum doublet standard chemotherapy as first-line treatments for patients with EGFR-mutated NSCLC (OPTIMAL, European Tarceva versus Chemotherapy [EURTAC], and ENSURE) revealed that erlotinib was superior as a first-line treatment in terms of PFS (Table 1). In addition, erlotinib was associated with an improved quality of life, compared with chemotherapy. In the OPTIMAL and EURTAC trials, however, no significant difference in overall survival was observed between the erlotinib group and the chemotherapy group because of the potential impact of crossover (Table 1). A recent Japanese Phase III trial directly comparing gefitinib and erlotinib to demonstrate noninferiority of gefitinib to erlotinib in terms of PFS resulted in a negative study, but no significant difference in PFS was seen between gefitinib and erlotinib for the treatment of patients with EGFR-mutated NSCLC (median PFS 8.9 months versus 10.1 months, P=0.532; median OS 32.0 months versus 26.6 months, P=0.111). A subset analysis revealed a prolongation of the PFS in the erlotinib arm, compared with the gefitinib arm, in patients aged <65 years (HR 1.357, P=0.032). The detailed results of this study might help to decide which drug should be used.

**Erlotinib for EGFR wild-type NSCLC**

The BR.21 trial demonstrated that erlotinib is superior to best supportive care for the treatment of patients with EGFR wild-type NSCLC, including squamous cell cancer, as analyzed using direct sequencing. Japanese Phase II trials have demonstrated that the use of erlotinib for pretreated patients with EGFR wild-type NSCLC seems to have a modest activity (Table 3). Among Caucasians, who are expected to have a lower frequency of EGFR mutations, no significant difference in the time to progression (median 3.0 months versus 3.9 months, P=0.195) or the OS (median 10.1 months versus 8.2 months, P=0.986) was observed between pemetrexed and erlotinib as a second-line or third-line treatment. Furthermore, among patients with squamous cell cancer, which rarely harbors EGFR mutations, those who received erlotinib had a significantly longer median time to progression (2.5 months versus 4.1 months, P=0.006). A systematic review has shown a significant benefit of erlotinib in patients with EGFR wild-type NSCLC. However, a randomized trial comparing erlotinib and docetaxel as second-line treatments for EGFR wild-type NSCLC (TArcvea Italian Lung Optimization tRial; TAILOR) has demonstrated that docetaxel is more effective than erlotinib (median PFS 2.9 months for docetaxel versus 2.4 months for erlotinib, HR 0.71, P=0.02; median OS 8.2 months versus 5.4 months, HR 0.73, P=0.05). Similarly, a Japanese randomized Phase III trial of erlotinib versus docetaxel as a first-line treatment for patients with EGFR-mutated non-small-cell lung cancer was associated with an improved quality of life, compared with chemotherapy. In Japan, Phase II trials examining first-line and second-line or third-line erlotinib treatment for EGFR-mutated NSCLC have demonstrated similar favorable results (Table 2). Based on these findings, erlotinib has been approved as a first-line treatment for EGFR-mutated NSCLC, and the Japanese treatment guidelines recommend gefitinib or erlotinib monotherapy for patients with EGFR-mutated NSCLC. A recent Japanese Phase III trial directly comparing gefitinib and erlotinib to demonstrate that noninferiority of gefitinib to erlotinib in terms of PFS resulted in a negative study, but no significant difference in PFS was seen between gefitinib and erlotinib for the treatment of patients with EGFR-mutated NSCLC (median PFS 8.9 months versus 10.1 months, P=0.532; median OS 32.0 months versus 26.6 months, P=0.111). A subset analysis revealed a prolongation of the PFS in the erlotinib arm, compared with the gefitinib arm, in patients aged <65 years (HR 1.357, P=0.032). The detailed results of this study might help to decide which drug should be used.

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**Table 1 Phase III studies of erlotinib versus chemotherapy as a first-line treatment for patients with EGFR-mutated non-small-cell lung cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Treatment (number of patients)</th>
<th>EGFR mutational analyses</th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMAL</td>
<td>People's Republic of China</td>
<td>Erlotinib (82) versus CBDCA plus GEM (72)</td>
<td>Exon 19 deletion or L858R, PCR-based direct sequencing performed at central laboratory</td>
<td>83 versus 36, P&lt;0.0001</td>
<td>13.1 versus 4.6, HR 0.16, P&lt;0.0001</td>
<td>28.9 versus 22.7, HR 1.04, P=0.69</td>
<td>22</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Europe</td>
<td>Erlotinib (86) versus CBDCA/CDDP plus DOC/GEM (87)</td>
<td>Exon 19 deletion or L858R, Sanger sequencing confirmed using clamp or TaqMan assay</td>
<td>58 versus 15, P&lt;0.0001</td>
<td>9.7 versus 5.2, HR 0.34, P&lt;0.0001</td>
<td>19.3 versus 19.5, HR 1.04, P=0.87</td>
<td>23</td>
</tr>
<tr>
<td>ENSURE</td>
<td>People's Republic of China</td>
<td>Erlotinib (110) versus CDDP plus GEM (107)</td>
<td>Exon 19 deletion or L858R, PCR-based direct sequencing performed at central laboratory</td>
<td>63 versus 34, P=0.0001</td>
<td>11.0 versus 5.5, HR 0.33, P&lt;0.0001</td>
<td>NA</td>
<td>24</td>
</tr>
</tbody>
</table>

**Abbreviations:** CBDCA, carboplatin; CDDP, cisplatin; DOC, docetaxel; OPTAC, European Tarceva versus Chemotherapy; GEM, gemcitabine; HR, hazard ratio; NA, not available; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; EGFR, epidermal growth factor receptor.
second- or third-line therapy (Docetaxel and Erlotinib Lung Cancer Trial; DELTA) demonstrated that erlotinib was inferior to docetaxel in an EGFR wild-type subpopulation (median PFS 1.3 months for erlotinib versus 2.9 months for docetaxel, HR 1.452, \( P = 0.010 \) (Table 3). Therefore, Japanese clinicians do not use erlotinib prior to docetaxel in patients with EGFR wild-type NSCLC.

A Phase II trial examining erlotinib in Japanese patients with EGFR wild-type NSCLC with a never or light smoking history resulted in a favorable response rate of 15.2%. EGFR mutations are predominant among never-smokers and individuals of East Asian ethnicity. Despite the use of highly sensitive methods to detect EGFR mutations, false-negative results sometimes occur in patients with EGFR-mutated NSCLC; therefore, such patients could be included in this study. In addition, a novel biomarker predicting the efficacy of erlotinib in patients with EGFR wild-type NSCLC (ie, a ligand of EGFR; amphiregulin) may exist, and this procedure should be further performed.

### Erlotinib for NSCLC unsuitable for chemotherapy

A previous report has indicated that patients with EGFR-mutated NSCLC and an extremely poor performance status might benefit from gefitinib. In contrast, a Phase III trial of erlotinib versus a placebo for patients with advanced NSCLC unsuitable for chemotherapy (TOPICAL) has demonstrated that the median OS period was similar between the two groups (3.7 months for erlotinib versus 3.6 months for the placebo, HR 0.94, \( P = 0.46 \)). In this trial, the study population was not selected for patients with EGFR-mutated NSCLC. Patients who develop a first-cycle rash might benefit from erlotinib, whereas those who do not develop a rash after 28 days are likely to have a shorter survival period. Although the number was very small (n=17), all the patients with EGFR mutations who were assigned to the erlotinib arm developed a rash. If the patients had been selected as they would have been for gefitinib treatment, they might have benefited from the erlotinib treatment. In Japan, however, based on the results of a previous study and the Japanese treatment guidelines, clinicians usually use gefitinib for selected patients.

### Maintenance therapy

Maintenance therapy, which is defined as “any treatment that is given to keep cancer from progressing after it has been successfully controlled by the appropriate first-line therapy”, has become an established paradigm for the treatment of patients with advanced NSCLC. The rationale for this strategy is that continuous treatment can delay disease progression and improve survival. Nowadays, various agents have been applied in maintenance regimens, such as bevacizumab, pemetrexed, and erlotinib for switching or continuous maintenance therapy. A Phase III study of erlotinib as a maintenance treatment in patients with non-progressive disease after first-line chemotherapy (Sequential Tarceva in Unresectable NSCLC; SATURN) has confirmed the
efficacy and safety of erlotinib. The median PFS and OS were significantly longer with erlotinib treatment than with a placebo (median PFS 12.3 weeks versus 11.1 weeks, HR 0.71, \(P=0.0001\); median OS 12.0 versus 11.0 months, HR 0.81, \(P=0.0088\)). A biomarker analysis showed that patients with *EGFR* mutations exhibited a significantly greater PFS benefit from maintenance erlotinib (HR 0.10, \(P=0.0001\)) compared with those with *EGFR* wild-type tumors (HR 0.780, \(P=0.018\); treatment-by-mutation interaction \(P=0.001\)). However, the *EGFR* mutation status did not predict an OS benefit. In Japan, maintenance therapy with erlotinib is not recommended by the Japanese treatment guidelines and is not generally performed because many patients have *EGFR* mutations and careful clinical follow-up allows most patients to receive second-line or higher treatment.

### Combination regimens containing erlotinib

Although patients with *EGFR*-mutated NSCLC dramatically respond to EGFR-TKIs and can have a long PFS, they cannot be cured. Therefore, to achieve a longer survival period, combination regimens of chemotherapy and EGFR-TKIs have been tried. Even though previous Phase III studies in unselected populations have shown that the concurrent combination of chemotherapy and erlotinib did not improve survival compared with chemotherapy alone, sequential intercalated combination regimens of chemotherapy and erlotinib (First-line Asian Sequential Tarceva And Chemotherapy Trial; FASTACT) have been shown to enable a significant improvement in responses and PFS, especially in patients with adenocarcinoma. One explanation for this lack of efficacy with a concurrent combination is that G1 cell cycle arrest caused by EGFR-TKIs might reduce the cell cycle phase-dependent activity of chemotherapy. In contrast, preclinical data showed that the sequential administration of EGFR-TKIs after chemotherapy might be effective. To confirm this finding, FASTACT-2 was started in Asian countries. In this Phase III trial, patients with untreated advanced NSCLC were randomly assigned to receive six cycles of gemcitabine plus platinum with intercalated erlotinib (chemotherapy plus erlotinib; 150 mg/day on days 15–28, orally) or a placebo orally (chemotherapy plus placebo) every 4 weeks. All the patients in the placebo group were offered second-line erlotinib at the time of progression. The PFS was significantly prolonged with chemotherapy plus erlotinib versus chemotherapy plus placebo (median PFS 7.6 months versus 6.0 months, HR 0.57, \(P=0.0001\)). The median OS period for the patients in the chemotherapy plus erlotinib group and those in the chemotherapy plus placebo group was 18.3 months and 15.2 months, respectively (HR 0.79, \(P=0.0420\)). A statistically significant treatment benefit was observed in patients with *EGFR* mutations (median PFS 16.8 months versus 6.9 months, HR 0.25, \(P=0.0001\); median OS 31.4 months versus 20.6 months, HR 0.48, \(P=0.0092\)). However, no significant difference in either the median PFS or the OS was observed in patients with *EGFR* wild-type NSCLC in the chemotherapy plus erlotinib group versus those in the chemotherapy plus placebo group. In Japan, a Phase II trial of gefitinib and inserted cisplatin plus docetaxel in selected patients with *EGFR* mutations has revealed favorable outcomes (median PFS 19.5 months; median OS 48 months). At present, a large Phase III trial in selected patients with *EGFR* mutations is being planned.

A Phase III trial of bevacizumab, an antiangiogenic agent, plus erlotinib versus erlotinib alone in advanced NSCLC after the failure of standard first-line chemotherapy (Bevacizumab/Tarceva [BeTa] trial) has shown that the addition of bevacizumab to erlotinib does not improve survival (median OS 9.3 months versus 9.2 months, HR 0.97, \(P=0.758\)). Interestingly, the improvement of OS was more prominent among patients with *EGFR*-mutated NSCLC (HR 0.44) than among those with *EGFR* wild-type NSCLC (HR 1.11). In Japan, a similar randomized trial examining bevacizumab plus erlotinib as a first-line treatment in selected patients with *EGFR* mutations has demonstrated favorable results (median PFS 16.0 months for bevacizumab versus 9.7 months for control, HR 0.54, \(P=0.0015\)).

### Beyond progression

In view of the nature of EGFR-TKI-resistant tumors and disease flare after the withdrawal of EGFR-TKIs, several strategies have been developed to overcome acquired resistance, including switching to cytotoxic therapies or irreversible EGFR-TKIs in combination with other signal inhibitors, local therapy, or cytotoxic therapies. Nevertheless, the best treatment mode remains unclear.

A few clinical trials investigating treatment strategies after EGFR-TKI failure are ongoing, including a Phase II Study of Continued Erlotinib Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients with *EGFR* Mutation-Positive NSCLC (ASPIRATION) and A Study of Iressa Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone (IMPRESS). More importantly, deeper molecular characterization of the primary
tumor or metastases using a rebiopsy should be recommended for the further exploration of optimal treatment strategies after patients acquire resistance to EGFR-TKIs.\textsuperscript{75-77}

\section*{Difference between gefitinib and erlotinib}

The discovery that 4-anilinoquinazolines exhibit EGFR inhibitory activity led to the development of gefitinib and erlotinib,\textsuperscript{15} and both of these drugs can be used in Japan. Although erlotinib seems to have a slightly broader spectrum of kinase inhibition and to have a slightly stronger EGFR inhibitory activity in several \textit{EGFR} mutations than gefitinib,\textsuperscript{78,79} both drugs are essentially EGFR-specific TKIs. The most prominent difference between these two drugs is the dose setting. The approved daily dose of erlotinib (150 mg) is equal to the maximum tolerated dose of erlotinib. In contrast, the daily dose of gefitinib has been set at 250 mg, which is approximately one-third of the maximum tolerated dose of gefitinib.\textsuperscript{80-83} This difference seems to have several influences, especially on central nervous system (CNS) lesion and adverse events.

In general, patients with CNS metastases suffer from a deterioration of their performance status and therefore do not have a long survival time. The primary treatment for CNS metastases in patients with NSCLC has traditionally consisted of whole-brain radiotherapy, surgery, or radiosurgery, while systemic chemotherapy has been thought to play a limited role because of the belief that the brain is a site of pharmacological sanctuary.\textsuperscript{84-86} However, several studies have documented the effectiveness of EGFR-TKIs\textsuperscript{87} for the treatment of CNS metastases of NSCLC. In addition, previous studies suggest that a higher cerebrospinal fluid concentration can be achieved with erlotinib than with gefitinib because of the dose setting; thus, erlotinib might be more effective for the treatment of CNS metastases, especially leptomeningeal metastases.\textsuperscript{87-89} The CNS is a common site of recurrence, possibly because of the poor penetration of chemotherapeutic agents into the CNS.\textsuperscript{90} Therefore, considering the higher cerebrospinal fluid concentration of erlotinib, patients may achieve a longer PFS with erlotinib treatment than with gefitinib treatment. Indeed, one pooled analysis has shown such results.\textsuperscript{91}

Considering the dose setting, many adverse events, including rash and diarrhea, seem to occur more frequently in patients treated with erlotinib than with gefitinib (Table 4). However, hepatotoxicity seems to occur relatively frequently in patients treated with gefitinib (Table 4). Several reports have indicated that patients with hepatotoxicity after gefitinib can subsequently be treated with erlotinib without experiencing hepatotoxicity.\textsuperscript{82,83} This result might arise because of the difference in metabolic enzymes that are affected.\textsuperscript{35} In addition, interstitial lung disease is one of the most serious adverse events associated with EGFR-TKIs, and there seems to be no significant difference in the frequency of interstitial lung disease between the two drugs.\textsuperscript{87,94-96} Hepatotoxicity and interstitial lung disease, both of which are often associated with drug discontinuation, seem to occur independent of the dose setting. A recent Phase III trial directly comparing gefitinib and erlotinib demonstrated similar results.\textsuperscript{38}

\section*{Conclusion}

The outcome of cytotoxic chemotherapy for NSCLC had reached a plateau, but the discovery of \textit{EGFR} mutations in 2004 opened a new era of personalized treatment for NSCLC. Subsequently, \textit{EML4–ALK}, a novel driver oncogene, was found in 2007.\textsuperscript{76} Crizotinib, the first clinically available anaplastic lymphoma kinase TKI, appeared to be more effective (compared with standard chemotherapy) in NSCLC patients harboring \textit{EML4–ALK}.\textsuperscript{98} The introduction of these molecular targeted drugs into a clinical setting was followed by the identification of genetic changes that give rise to NSCLC and has been accompanied by appropriate patient selection.

Treatment with erlotinib therapy can dramatically delay disease progression and is well tolerated in patients harboring activating \textit{EGFR} mutations. Although erlotinib also has a mild efficacy for \textit{EGFR} wild-type NSCLC, \textit{EGFR} mutation is the strongest predictive biomarker for its efficacy, and mutations are more common in the Asian (including Japanese) population. In Japan, both gefitinib and erlotinib can be used as EGFR-TKIs. Furthermore, afatinib, an irreversible EGFR-TKI, can also be used, and this novel drug seems to

\begin{table}[h]
\centering
\caption{Comparison of adverse events between gefitinib and erlotinib treatment in Japanese patients}
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Study & Drug & Number of patients & Treatment line & Rash (Grade $\geq$3) & Diarrhea (Grade $\geq$3) & Hepatotoxicity (Grade $\geq$3) & Reference \\
\hline
WJTOG3405 (Phase III) & Gefitinib & 86 & First line & 85.1% (2.3%) & 54.0% (1.1%) & 70.1% (27.6%) & 2.3% (1.16%) & 82 \\
NEJ002 (Phase III) & Gefitinib & 114 & First line & 71.1% (5.3%) & 34.2% (0.9%) & 55.3% (26.3%) & 5.3% (0.88%) & 83 \\
JO22903 (Phase II) & Erlotinib & 102 & First line & 83% (14%) & 81% (1%) & 33% (8%) & 4.85% (1.94%) & 27 \\
\hline
\end{tabular}
\end{table}

\textbf{Abbreviation:} ILD, interstitial lung disease.
have a significant effect on NSCLCs harboring an EGFR exon 19 deletion. Thus, clinicians should use each of these drugs in appropriate settings.

Acquired resistance, including EGFR secondary mutations (T790M and other rare mutations), MET gene amplification, PTEN gene downregulation, high-level hepatocyte growth factor expression, epithelial–mesenchymal transition, and conversion to small cell lung cancer continues to restrict the durable long-term outcomes of erlotinib. Further efforts are needed to explore new strategies to improve the efficacy of erlotinib treatment in all settings and to overcome drug resistance.

Disclosure
The authors report no conflicts of interest in this work.

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