Review Article

Strategy for Epidermal Growth Factor Receptor-mutated Non-small Cell Lung Cancer using Epidermal Growth Factor Receptor- Tyrosine Kinase Inhibitors

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Abstract

Somatic-activating mutations of the epidermal growth factor receptor (EGFR), including exon 19 deletion mutation and L858R point mutation, have been associated with dramatic tumor responses and favorable clinical outcomes using first-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib for advanced non-small cell lung cancer (NSCLC). Despite the high efficacy of these reversible, small, targeted molecular agents in patients with activating EGFR mutations in NSCLC, all responders eventually acquire resistance. EGFR T790M increases the affinity of mutant EGFRs for adenosine triphosphate, which is the most common mechanism of acquired resistance to first-generation EGFR-TKIs. Second-generation irreversible EGFR-TKIs, including afatinib and dacomitinib, may overcome for NSCLC through acquired resistance to first-generation EGFR-TKIs. In this review, we will discuss the optimal treatment strategy for NSCLC using EGFR-TKIs.

ABBREVIATIONS

EGFR-TKIs: Epidermal growth factor receptor-tyrosine-kinase inhibitors; NSCLC: Non-small cell lung cancer; RR: Response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; RECIST: Response evaluation criteria in solid tumors; AE: Adverse event

INTRODUCTION

In the last decade, first-generation quinazoline reversible epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib, were clinically effective in treating lung cancer patients harboring activating EGFR mutations [1,2]. Despite the high efficacy of first-generation EGFR-TKIs, a majority of responders will develop resistance to these agents. EGFR T790M mutation is a gatekeeper mutation responsible for secondary resistance to EGFR-TKIs [3]. Second-generation EGFR-TKIs, including afatinib and dacomitinib, are irreversible pan-HER inhibitors that are proven to be efficacious for non-small cell lung cancer (NSCLC) with activating EGFR and EGFR T790M mutations in vivo [4,5]. This short review discusses strategies for treating patients harboring activating EGFR mutations using EGFR-TKIs.

EGFR-TKIs as front-line therapy for EGFR-mutated NSCLC

Four randomized phase III trials showed that first-generation EGFR-TKIs as front-line therapy for activating EGFR-mutated advanced NSCLC demonstrated a higher response rate (RR) and significantly longer progression-free survival (PFS) than standard platinum-doublet chemotherapy [6-9]. Afatinib, a second-generation EGFR-TKI, binds irreversibly to both HER1 (EGFR) and HER2 kinases [10]. In the LUX-Lung 3 and LUX-Lung 6 studies, afatinib treatment resulted in a significantly longer PFS and RR than standard platinum-doublet chemotherapy in patients with activating EGFR-mutated NSCLC [11,12]. Although these trials met the primary endpoint of longer PFS with EGFR-TKI treatment, no statistically significant overall survival
(OS) was documented, probably because of the crossover to alternative treatments.

**Should EGFR-TKIs be administered as front- or second-line treatment?**

Six randomized phase III trials showed that EGFR-TKIs and standard platinum-doublet chemotherapy used as front-line therapy had similar RRs and PFSs for EGFR-mutated NSCLC. Only the NEJ 002 study showed that EGFR-TKI as second-line therapy had a lower RR of 59% compared with the 74% attained by the use of gefitinib as front-line therapy. Rosell et al. reported that erlotinib as second-line therapy and erlotinib as front-line therapy showed similar RR (77% vs. 74%), PFS (13 months vs. 14 months), and OS (28 months vs. 27 months) [2]. Considering these results, any treatment line may be acceptable for EGFR-TKI administration. However, the difference in the PFSs after the use of EGFR-TKIs as front-line or second-line therapy in the same study population was not evaluated in these six trials.

**Would first or second generation EGFR-TKIs be better for activating EGFR-mutated NSCLC?**

In previous phase III studies comparing the efficacies of first-generation EGFR-TKIs and standard platinum-doublet chemotherapy, higher RRs (60–80%) and longer PFSs (9–13 months) were documented for EGFR-mutated NSCLC. The second-generation EGFR TIs, including afatinib and dacomitinib, which are pan-HER inhibitors, have increased efficacy through prolonged inhibition of EGFR signaling. These second-generation EGFR-TKIs potentially improve PFS in patients with EGFR-mutated NSCLC because they have higher biological activity than first-generation EGFR-TKIs, and may overcome the progression of lung tumors with acquired resistance to first-generation EGFR-TKIs [3,4].

In the LUX-Lung 3 [11] and LUX-Lung 6 [12] trials, the RR and PFS after afatinib treatment were 61% and 13.6 months and 67% and 11.0 months, respectively. In a randomized Phase II study comparing treatments with dacomitinib and erlotinib in pretreated patients with advanced NSCLC, the median PFS was 7.4 months after treatment with dacomitinib and erlotinib in a small subgroup of patients (n = 30) with activating EGFR mutations (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.18–1.18; P = 0.098) [13]. Kris et al. reported at the annual 2012 ASCO meeting that among 46 EGFR-mutated patients, the RR and PFS after dacomitinib treatment were 74% and 18.2 months (95% CI: 12.8–23.8 months), respectively [14].

A considerable number of severe treatment-related toxicities have been documented in previous studies after treatment with second-generation EGFR-TKIs. Table 2 shows EGFR-TKI-related severe toxicity (grade ≥3) in randomized phase III trials comparing the efficacy of EGFR-TKIs with that of standard chemotherapy in patients with EGFR-mutated NSCLC. Severe toxicities associated with dermatosis, including dry skin and

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
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<tr>
<td></td>
<td>CDDP+TXT</td>
<td>86</td>
<td>32</td>
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</tr>
<tr>
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<td>36</td>
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<tr>
<td>EURTAC [9]</td>
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<td>86</td>
<td>58</td>
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</tr>
<tr>
<td></td>
<td>Platinum + TXT/GEM</td>
<td>87</td>
<td>15</td>
<td>5.2</td>
<td>18.8</td>
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<tr>
<td></td>
<td>HR = 0.37</td>
<td>P &lt; 0.001</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP/PEM</td>
<td>104</td>
<td>22</td>
<td>6.9</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>HR = 0.47</td>
<td>P = 0.001</td>
<td></td>
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<td></td>
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<tr>
<td>Lux-Lung 6 [12]</td>
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<td>242</td>
<td>67</td>
<td>11.0</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>CDDP/GEM</td>
<td>122</td>
<td>23</td>
<td>5.6</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>HR = 0.28</td>
<td>P &lt; 0.001</td>
<td></td>
<td>NE</td>
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</table>

**Table 1:** Randomized phase III trials comparing EGFR-TKIs to platinum-based combination chemotherapy as first-line treatment for EGFR-mutated NSCLC.

**Abbreviations:** EGFR-TKIs: Epidermal growth factor receptor–tyrosine kinase inhibitors; NSCLC: Non-small cell lung cancer; PFS: Progression-Free survival; OS: Overall survival; CDDP: Cisplatin; TXT: Docetaxel; CBDCA: Carboplatin; PTX: Paclitaxel; GEM: Gemcitabine; PEM: Pemetrexed; GEM: Gemcitabine; HR: Hazard ratio; NS: Not significant; NE: Not evaluated; NR: Not reached

Asami et al. (2014)
Email: kazu.tazoe@nifty.com
The JBR-26 study involves comparison of the efficacy of dacomitinib available in this study.

No data on the direct or indirect comparison of the treatment efficacy of first-generation and second-generation EGFR-TKIs for EGFR-mutated NSCLC are available. LUX-Lung 7 is an ongoing phase Ib trial that compares the efficacies of the front-line treatment with afatinib and gefitinib in patients with activating EGFR-mutated advanced NSCLC (NCT01466660).

EGFR-TKIs after failure of first-generation EGFR-TKIs

Despite the high efficacy of first-generation EGFR-TKIs in patients with EGFR-mutated NSCLC, the disease condition in all responders eventually progresses due to development of resistance. In patients treated with first-generation EGFR-TKIs, secondary resistance EGFR T790M mutation, which increases the affinity of the kinase for ATP, is determined to be responsible for approximately half of the resistance in NSCLC [3,15].

At the time of confirmation of disease progression in patients harboring EGFR-mutations, it is unclear whether EGFR-TKIs should be switched to another therapy based on the response evaluation criteria in solid tumors (RECIST). Based on retrospective studies, some researchers have reported that continuation of first-generation EGFR-TKI treatment beyond progressive disease may prolong survival in patients with activating EGFR mutations [16,17]. The IMPRESS study is an ongoing trial that compares the efficacy of gefitinib in addition to chemotherapy after progression with that of chemotherapy alone in patients with activating EGFR-mutated NSCLC (NCT01544179).

Although second-generation EGFR-TKIs potentially have the potency to retard lung tumor progression with acquired resistance to first-generation EGFR-TKIs, the LUX-Lung 1 (18) and LUX-Lung 4 (19) trials showed that patients with acquired resistance to first-generation EGFR-TKIs failed to meet the primary RR endpoints, particularly those with lung tumors with EGFR T790M mutation; the RR reported in the two studies was only 7% and 8% lower than the expected values. A phase II study of dacomitinib treatment in advanced NSCLC patients with wild-type KRAS in whom chemotherapy and erlotinib treatment failed showed an RR of 5% with stable disease at 56% [20]. However, no molecular information on activating EGFR mutations was available in this study.

There are two ongoing phase III trials on dacomitinib. The JBR-26 study involves comparison of the efficacy of dacomitinib with that of a placebo in advanced NSCLC patients in whom treatment with chemotherapy and first-generation EGFR-TKIs failed (NCT01000025). The ARCHER study involves the comparison of the efficacy of dacomitinib with that of erlotinib in a similar patient population (NCT01360554). However, these trials on dacomitinib were not limited to patients harboring activating EGFR mutations.

Combination of EGFR-TKI and chemotherapy or targeted molecular agents for EGFR-mutated NSCLC

The CALGB 30406 randomized phase II trial studied the efficacy of erlotinib alone or in combination with carboplatin and paclitaxel in advanced lung adenocarcinoma patients with no smoking history or with a non-chronic smoking history. Among patients in the study harboring activating EGFR mutations, the PFS and OS with erlotinib monotherapy and combined erlotinib and chemotherapy was 15.7 months and 17.2 months, and 31.3 months and 39.0 months, respectively [21]. The small sample size of patients with EGFR mutations may have contributed to the lack of a statistically significant difference in survival time between treatment groups.

Shukuya et al. reported that gefitinib and chemotherapy were reasonable treatment option in a gefitinib responder after therapeutic failure [22]. In the retrospective study, RR, PFS, and OS were 13%, 4.3 months, and 8.1 months, respectively. The ongoing LUX-Lung 5 phase III trial compares the efficacy of chemotherapy administered after afatinib in patients with advanced NSCLC in whom treatment with first-generation EGFR-TKIs failed (NCT01085136).

Cetuximab is a monoclonal antibody that binds competitively with high affinity to the extracellular domain of the EGFR receptor. Cetuximab showed minimal activity in few patients with acquired resistance to first-generation EGFR-TKIs [23]. The combination of afatinib and cetuximab caused shrinkage of a mouse xenograft with EGFR T790M NSCLC [24]. Although neither afatinib nor cetuximab could significantly inhibit lung tumor progression, the combination of afatinib and cetuximab resulted in disease regression. A phase Ib study on the efficacy of the combination of afatinib and cetuximab showed a partial response in nearly 30% of patients who developed secondary resistance to the EGFR T790M mutation [25].

Bevacizumab is a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor -A, which is a chemical signal that stimulates the growth of new blood vessels. A previous phase III study comparing the efficacy

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Table 2: Severe toxicity (grade ≥3 ) profile of EGFR-TKIs for EGFR-mutated NSCLC.

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<tbody>
<tr>
<td>Rash</td>
<td>gefitinib</td>
<td>gefitinib</td>
<td>erlotinib</td>
<td>erlotinib</td>
<td>afatinib</td>
<td>dacomitinib</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>5.3%</td>
<td>2%</td>
<td>13%</td>
<td>16.2%</td>
<td>17%</td>
</tr>
<tr>
<td>Elevated Transaminase</td>
<td>14%</td>
<td>26.3</td>
<td>4%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>0.9%</td>
<td>1%</td>
<td>5%</td>
<td>14.4%</td>
<td>14%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
<td>2.6%</td>
<td>0%</td>
<td>0%</td>
<td>1.3%</td>
<td>-</td>
</tr>
<tr>
<td>ILD</td>
<td>2.3%</td>
<td>2.6%</td>
<td>0%</td>
<td>1%</td>
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<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: NSCLC: Non-Small Cell Lung Cancer; ILD: Interstitial Lung Disease
of erlotinib plus bevacizumab with that of erlotinib monotherapy in advanced NSCLC patients, in whom treatment with first-line standard chemotherapy failed, showed that the primary OS endpoint of the study was not met [26]. Although OS with erlotinib plus bevacizumab was not prolonged compared with that after erlotinib treatment, patients treated with this combination therapy showed significantly longer PFS than those treated with erlotinib monotherapy (3.4 months [95% CI, 1.4–8.4 months] vs. 1.7 months [95% CI, 1.3–4.1 months]; HR, 0.62; 95% CI, 0.52–0.75) [27]. Grade 5 adverse events (AEs) developed in 6% of patients treated with erlotinib plus bevacizumab and 4% in patients treated with erlotinib. The ATLAS study is a randomized, double-blind, placebo-controlled phase IIIB trial comparing the efficacy of bevacizumab with or without erlotinib after completion of chemotherapy plus bevacizumab as front-line therapy in patients with advanced NSCLC [28]. Although a significantly longer PFS was noted in patients treated with bevacizumab plus erlotinib (4.8 months vs. 3.7 months; HR, 0.71; 95% CI, 0.58–0.86; P < 0.001); no significant difference was observed in OS for both treatment groups. As for toxicity, severe AEs, including grades 3 and 4 toxicities (mainly rash and diarrhea), occurred more frequently in patients treated with bevacizumab plus erlotinib. However, the incidence of AEs leading to discontinuation of the therapy was similar in both treatment arms. Molecular aspect of activating EGFR mutations was not available in these two trials. The Innovations trial is a randomized phase II study comparing the efficacy of erlotinib plus bevacizumab with that of chemotherapy as front-line treatment in patients with non-squamous cell NSCLC [29]. Among patients (n = 224) enrolled in this study, EGFR mutations were detected in 32 patients (20 in the erlotinib plus bevacizumab arm, 12 in the chemotherapy arm). The RR and PFS in each group was 25% and 4.4 months in the erlotinib plus bevacizumab arm and 17% and 5.7 months in the chemotherapy arm. A phase II trial comparing the efficacies of erlotinib plus bevacizumab and erlotinib monotherapy in advanced NSCLC patients with activating EGFR mutation to assess PFS is ongoing (NCT01532089).

**DISCUSSION AND CONCLUSION**

Results from previous randomized phase III trials of first-generation and second-generation EGFR-TKIs indicate that front-line EGFR-TKI treatment may be optimal for advanced EGFR-mutated NSCLC. While considerable data supported the use of EGFR-TKIs as a front-line treatment, data supporting the use of EGFR-TKIs in chemoradiotherapy patients with activating EGFR mutations are lacking. However, no prospective studies comparing the treatment efficacy of EGFR-TKIs for activating EGFR-mutated NSCLC in chemonaive and chemoradiotherapy patients have been performed. Furthermore, data defining the most appropriate indication for EGFR-TKI administration are insufficient. Owing to insufficient evidence, it is unclear if EGFR-TKIs should be administered in chemonaive patients with activating EGFR-mutated NSCLC. EGFR-TKIs play a key role in patients harboring EGFR mutations, and non-administration of these agents could adversely affect survival. Thus, physicians should consider the risk to survival when choosing whether to administer EGFR-TKIs as a front-line therapy in patients harboring activating EGFR mutations.

Considering the data already mentioned, standard chemotherapy, first or second generation EGFR-TKIs, and EGFR-TKI plus chemotherapy may optimal front-line treatments (Figure 1). Compared with first-generation EGFR-TKIs, severe treatment-related toxicities might develop in patients treated with second-generation EGFR-TKIs and combined EGFR-TKI and chemotherapy. The efficacy of these treatments as front-line therapy should be validated further with respect to response, survival, and quality of life, and the toxicities should be compared with those of first-generation EGFR-TKIs. While previous studies have shown the efficacy of EGFR-TKI plus bevacizumab in chemoradiotherapy patients with NSCLC, data supporting this combination therapy as front-line treatment are unavailable.

Among first-generation EGFR-TKIs, it is unclear whether gefitinib or erlotinib is the more appropriate agent for initial EGFR-TKI therapy. Erlotinib has higher biological activity compared with gefitinib [30,31]. Some researchers reported the efficacy of erlotinib administered after failure of gefitinib treatment [32,33]. Erlotinib is a potentially appropriate agent after failure of gefitinib treatment. A prospective study comparing the efficacies of gefitinib with erlotinib as initial EGFR-TKI treatment in patients harboring activating EGFR mutations may be warranted.

To the best our knowledge, efficacy data supporting the use of first-generation EGFR-TKI as treatment after failure of second-generation EGFR-TKI treatment are lacking. Considering the biological activities of second-generation EGFR-TKIs, treatment with second-generation EGFR-TKIs after failure of first-generation EGFR-TKI treatment may be optimal for EGFR-mutated NSCLC. Combined second-generation EGFR-TKIs and other targeted molecular agents may be more effective than a single agent. Recently, a study of the combined treatment with an EGFR-TKI and Met inhibitor suggested showed that this combination treatment might be useful in patients with pre-existing high MET expression [34]. Amplification of MET has been detected in nearly 20% of lung tumors with acquired resistance to first-generation EGFR-TKIs by activating the HER3/ERBB3 pathway resulting in secondary KRAS amplification [35–37]. Previous studies have demonstrated the efficacy of combination therapy using erlotinib plus bevacizumab as second-line treatment in patients with advanced NSCLC. This treatment regimen may potentially be more useful than erlotinib monotherapy in patients in whom gefitinib treatment failed. Future studies should focus on the efficacy of combination therapies consisting of EGFR-TKIs and other signaling pathway inhibitors after failure of first-generation EGFR-TKI treatment.

![Figure 1](Front-line treatment option in patients with activating EGFR mutation.)
It is unclear when EGFR-TKIs therapy should be discontinued for patients who to the treatment. Treatment switched based on the RECIST criteria may not reflect survival for responders to EGFR-TKI treatment. New criteria, which would influence survival, should be established. Jackman et al. proposed new guidelines for EGFR-TKI responders that define acquired resistance to EGFR-TKIs [38]. Continuation therapy of EGFR-TKIs in addition to chemotherapy beyond disease progression may be reasonable treatment option because of inhibit rapidly tumor progression due to discontinuation of the therapy. Furthermore, additional chemotherapy would reduce acquired resistance of lung cancer cell to EGFR-TKIs.

In conclusion, second-generation EGFR-TKIs have a potentially greater effect on activating EGFR-mutated NSCLC compared with first-generation EGFR-TKIs. Furthermore, the efficacy of combination therapy with EGFR-TKI and chemotherapy or other targeted molecular agents may be superior to that of EGFR-TKI monotherapy. Although second-generation EGFR-TKIs and combination treatment regimens may potentially be more beneficial for patients with activating EGFR mutations, severe treatment-related toxicities may occur more frequently compared with EGFR-TKI monotherapy. Future studies on these regimens, especially as front-line treatment, will need to be validated with respect to survival advantage with acceptable toxicities. Treatment strategy after failure of first-generation EGFR-TKIs needs to be established immediately. Figure 2 shows prospective trials of continuation first-generation EGFR-TKIs beyond progressive disease in addition to chemotherapy are ongoing.

ACKNOWLEDGEMENTS

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REFERENCES


