Editorial

Recent advances in the development of mutant-selective EGFR inhibitors for non-small cell lung cancer patients with EGFR-TKI resistance

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Over the last decade, first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI) (erlotinib and gefitinib) for the treatment of advanced non-small cell lung cancer (NSCLC), especially adenocarcinoma, have demonstrated remarkable advances and leaded to improvement in patients' survival time, either progression-free survival or overall survival. EGFR-TKI therapies also provided a superior quality of life in specific patient populations (1). Erlotinib and gefitinib are orally administered small molecules that reversibly target the EGFR tyrosine kinase domain and interfere with tumor growth. Activating *EGFR* mutations, such as exon 19 deletion and exon 21 L858R point mutation, have been associated with dramatic responses to first-generation EGFR-TKIs. Their side effects like dose-dependent skin rash and diarrhea are usually mild to moderate. However, patients receiving first-generation EGFR-TKIs will eventually experience disease progression because of acquired resistance. *EGFR* T790M mutation was identified in more than half of patients with resistance to gefitinib or erlotinib, and it was the most common mechanism of acquired resistance. At present, there is no standard targeted therapy for patients with EGFR-TKI resistance (1).

The second-generation EGFR-TKIs, including afatinib and dacomitinib, were developed as irreversible pan-HER (human epidermal growth factor receptor) inhibitors which may interfere with the EGFR signal transduction pathway more completely compared with the first-generation EGFR-TKIs (2). They are effective in NSCLC with activating *EGFR* mutation, and also have ability to overcome T790M activity in preclinical models. Nevertheless, the irreversible second-generation EGFR-TKIs as monotherapy failed to overcome T790M activity in NSCLC patients with acquired resistance to gefitinib or erlotinib, because the drug concentrations to inhibit T790M *in vitro* could not be achieved in patients as a result of nonselective wild-type EGFR inhibition-related toxicity. Dual EGFR inhibition with afatinib and cetuximab in NSCLC patients with acquired resistance to EGFR-TKIs has demonstrated a 29% response rate in T790M mutation-positive NSCLC, but this therapy is associated with a significant degree of cutaneous and gastrointestinal toxicities (2). Therefore, in order to pursue better therapies for overcoming T790M-mediated resistance and sparing wild-type EGFR, the third-generation EGFR-TKIs were developed to target T790M and classic *EGFR* mutation while sparing wild-type EGFR.

The third-generation EGFR-TKIs, including AZD9291, CO-1686, and HM61713, are oral, irreversible, mutant-selective EGFR inhibitors that target T790M and have low affinity for wild-type EGFR, while remaining effective against classic *EGFR* mutations. In the recent preliminary reports, the response rates of AZD9291, CO-1686, and HM61713 in patients with T790M mutation were 64%, 58%, and 29%, respectively (3-5). AZD9291 demonstrated promising efficacy against T790M-positive tumors. A multicenter phase I trial of AZD9291 recruited 199 patients, including Asian and Caucasian NSCLC patients with *EGFR* mutation and acquired resistance to EGFR-TKIs (3). This

study revealed an overall response rate of 51% (91/177 patients). In the subgroup of 132 patients with T790M mutation status, the overall response rates were 64% (95% CI: 53-74%) in 89 T790M-positive patients and 23% (95% CI: 12-39%) in 43 T790M-negative patients. Better efficacy was observed in the T790M-positive than -negative tumors. A 96% disease control rate (85/89 patients) was revealed in T790M-positive patients. The longest duration of response was reported to be more than 8 months, but the median duration of response is still pending. The efficacy of AZD9291 to overcome T790M-mediated resistance was demonstrated to be better than that of second-generation EGFR-TKIs.

AZD9291 was designed with reduced affinity for wild-type EGFR. Because of sparing wild-type EGFR in the skin and gut cells, the common side effects, such as skin rash and diarrhea, were milder and fewer than first-generation EGFR-TKIs. No dose-limiting toxicities at 20 to 240 mg/day were discovered in the recent trial (3). The most common drug-related adverse events in the study of AZD9291 were low-grade diarrhea (30%), skin rash (24%), and nausea (17%). The most concerning toxicity was interstitial lung disease (ILD)-like events, and five ILD-like events were reported. All of them responded to treatment, and were resolved without fatalities.

In a recent study, another third-generation EGFR-TKI, CO-1686, also demonstrated considerably lower rates of common EGFR toxcicities, including low-grade diarrhea (22%) and rash (4%), compared with first-generation EGFR-TKIs (4). In addition, the skin toxicity of CO-1686 is also milder and fewer than AZD9291. However, CTCAE grade 3 hyperglycemia in 22% of patients, and prolonged QT corrected (QTc) interval in 7% of patients were observed. Unlike CO-1686, the study of AZD9291 revealed no significant aberration of blood glucose or QTc interval (3). Therefore, AZD9291 treatment in NSCLC patients with diabetes mellitus may be better than CO-1686 when considering the side effect of hyperglycemia.

The third-generation EGFR-TKIs targeting *EGFR*-mutated tumors while sparing wild-type EGFR provide higher efficacy against T790M-positive tumors, and at the same time, they have demonstrated fewer toxicities and good tolerability. However, the efficacy of these third-generation TKIs compared with first-generation TKIs in treatment-naïve *EGFR*-mutated NSCLC is still not clear, nor is the treatment for T790M-negative tumors in patients with acquired EGFR-TKI resistance. Further investigations are ongoing to determine the relevant clinical benefit of these mutant-selective, third-generation EGFR-TKIs, and their role in the first-line setting or treatment for TKI-resistant lung cancer.

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