Commentary

Epidermal growth factor receptor-tyrosine kinase inhibitors, which is the best choice?

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For the treatment of epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC), we have typically used an EGFR-tyrosine kinase inhibitor (EGFR-TKI), gefitinib or erlotinib (1-4). In addition, recent clinical trials have revealed the efficacy of afatinib as an irreversible blocker of the ErbB family (5,6). The effect of afatinib on overall survival of patients with EGFR common mutation-positive [exon 19 deletion (del19), exon 21 L858R point mutation (L858R)] lung adenocarcinoma through an analysis of data from two open-label, randomized, phase III trials has been reported (7). Overall survival for EGFR common mutation-positive NSCLC patients treated with afatinib was significantly longer than for those treated with chemotherapy. In particular, overall survival for del19-positive NSCLC patients was apparently longer in the afatinib group than in the chemotherapy group. Since gefitinib or erlotinib was used in the chemotherapy group as an EGFR-TKI, these results lead us to consider which EGFR-TKI is the best choice for EGFR mutation-positive NSCLC as a first-line treatment.

Recently, Park and colleagues reported the LUX-Lung7 study, a phase 2B, open-label, randomized, controlled trial to compare afatinib with gefitinib as first-line treatment in EGFR common mutation-positive NSCLC, where the target sample size was 316, and the same sample size was set for each group. The objective of this study was to demonstrate the superiority of afatinib over gefitinib in terms of improvement in progression-free survival, time-to-treatment failure, and overall survival. Originally, the primary outcomes were progression-free survival and disease control at 12 months; however, the protocol was updated to include time-to-treatment failure and overall survival in the primary outcomes, and disease control became a secondary endpoint. The results showed that progression-free survival [median 11.0 months (95% CI, 10.6–12.9) with afatinib *vs.* 10.9 months (95% CI, 9.1–11.5) with gefitinib; hazard ratio (HR) =0.73 (95% CI, 0.57–0.95); P=0.017] and TTF [median 13.7 months (95% CI, 11.9–15.0) with afatinib *vs.* 11.5 months (95% CI, 10.1–13.1) with gefitinib; HR =0.73 (95% CI, 0.58–0.92); P=0.0073] were significantly longer with afatinib than with gefitinib. Interestingly, progression-free survival by mutation types showed no significant difference, but it was better with afatinib than with gefitinib. Because the sample size of the LUX-Lung 7 trial was larger than many previous randomized, phase III trials, and the PFS data of the LUX-Lung 7 trial were similar to previous trials (1,2,5,6), this phase 2B trial data was thought to be reliable. Therefore, given the results of this phase IIB trial, afatinib may be a better choice for common EGFR mutation-positive NSCLC patients.

In contrast, the American Society of Clinical Oncology (ASCO) proposed defining clinically meaningful outcomes for clinical trials (8). Although PFS is a commonly used end point, the working groups each preferred to use overall survival as the primary measure of clinically meaningful outcome. For NSCLC, the recommendations for improvement over current overall survival and progression-free survival that would be clinically meaningful were 3.25 to 4 months and 4 months, respectively. The PFS difference

between afatinib and gefitinib in this phase 2B trial was significant, but it was not meaningful in the light of the ASCO recommendation. Furthermore, overall survival in this phase 2B trial is not yet established. In addition, the usefulness according to the EGFR common mutation type is not confirmed; therefore, it is too early to decide between afatinib and gefitinib with respect to superiority and inferiority.

The estimation of time-to-treatment failure is very interesting. In selected EGFR mutation-positive NSCLC patients, continuous therapy with EGFR-TKI beyond radiological progression in the absence of clinical deterioration or in the case of oligometastasis that is locally controlled with radiotherapy, such as central nervous system metastasis, may be an option in clinical practice. Although time-to-treatment failure was significantly improved with afatinib over gefitinib, indicating that afatinib might confer additional clinical benefit, it is not possible to compare, because previous trials have not estimated time-to-treatment failure.

The frequency and severity of adverse events were also reported. The most frequent drug-related grade 3 or worse adverse events in patients given afatinib were diarrhea, rash or acne, and fatigue, and in patients given gefitinib, they were increased ALT/AST concentration and rash or acne. The profile of adverse events for afatinib or gefitinib is similar to that of previous reports (5,6,9). Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and 7 (4%) in the gefitinib group. Ten (6%) patients in each group discontinued treatment due to drug-related adverse events. Fifteen (9%) fatal adverse events occurred in the afatinib group, with 10 (6%) in the gefitinib group. Though dose reductions due to adverse events were undertaken more with afatinib (42%) than with gefitinib (2%), both EGFR-TKIs demonstrated a manageable safety profile.

Taking this phase IIB trial and previous phase III trials together, afatinib is better than gefitinib with respect to progression-free survival. However, whether the effect of afatinib is different according to the EGFR common mutation type or how superior afatinib is to gefitinib is still not clear. The usefulness of gefitinib for EGFR mutation-positive NSCLC patients who are elderly or have poor performance status has been investigated, but it has not yet been investigated for afatinib (10). Therefore, it is better to choose the EGFR-TKI based on safety and background of the NSCLC patients.

The EGFR T790M point mutation (T790M) is the most common mechanism of drug resistance to EGFR-TKIs in EGFR mutation-positive NSCLC patients (11). Afatinib has been shown to be effective in preclinical models against EGFR T790M mutation-positive NSCLC, and the efficacy of combining afatinib and the anti-EGFR antibody cetuximab has been reported (12,13). Recently a new-generation EGFR-TKI that is selective for the EGFR T790M resistance mutation has been developed (14); however, when is the best time to use an EGFR T790M-selective EGFR-TKI, that is as first-line, second-line, or later lines, remains unclear. When resistance develops to one inhibitor, repeat biopsy can provide critical information as to whether sequential therapy with a different inhibitor may be effective. The sequence of EGFR-TKI therapy, including combination therapy, still needs to be determined.

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Footnote

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