Editorial

The impact of age and performance status on the efficacy of osimertinib in patients with EGFR T790M-positive non-small cell lung cancer

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The last decade has seen remarkable advances in the treatment of non-small cell lung cancer (NSCLC), especially targeted therapy. Since the efficacy of gefitinib [the first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)] for patients with advanced lung adenocarcinoma was proven 10 years ago (1), many recent works have shown that EGFR-TKIs exhibit better treatment efficacies than platinum-based chemotherapy in patients with NSCLCs harboring EGFR mutations (2-4). However, although 1st or 2nd-generation EGFR-TKIs such as erlotinib, gefitinib, or afatinib are superior to conventional chemotherapy, disease progression and EGFR-TKI-resistance usually develop within 1–2 years of treatment (1-4).

Osimertinib is a 3rd-generation EGFR-TKI that irreversibly inhibits both EGFR-TKI sensitizing mutations and Thr790Met (T790M) mutation but exhibits less activity against the wild-type protein (5). The AURA trial series showed that osimertinib was remarkably effective in patients with NSCLC patients with acquired EGFR T790M mutations which developed after previous treatment of 1st or 2nd-generation of EGFR-TKIs (6). AURA 3 study revealed that the median progression-free survival (mPFS) of patients given osimertinib was significantly longer than that of patients given platinum plus pemetrexed (10.1 *vs.* 4.4 months) (7). The objective response rate (ORR) was also significantly higher in the former patients (71% *vs.* 31%). Even in patients with central nervous system (CNS) metastases, osimertinib afforded a longer mPFS than did platinum plus pemetrexed (8.5 *vs.* 4.2 months) (7). Osimertinib is less active toward wild-type than mutant EGFR (8), but the drug also exhibits higher-level CNS penetration and activity than do previous-generation EGFR-TKIs (9,10).

In the FLAURA study, osimertinib was more efficacious than 1st or 2nd-generation EGFR-TKIs when used as first-line treatment for the patients with advanced NSCLC who were positive for EGFR mutation. The mPFS afforded by first-line osimertinib was significantly longer than that associated with first-line 1st-generation EGFR-TKIs (18.9 *vs.* 10.2 months) (11). Osimertinib not only prolonged the mPFS but also overall survival (OS). In a very recent report on OS in the FLAURA, patients who received first-line osimertinib exhibited a longer median OS than did those who received 1st-generation EGFR-TKIs (38.6 *vs.* 31.8 months) (12). The safety profile of osimertinib was similar to those of other EGFR-TKIs (11,12).

As human life expectancy increases, the average age of lung cancer patients also increases. The incidence of lung cancer increases with age, being highest among those aged ≥75 years (13,14). Therefore, physicians are encountering increasing numbers of older NSCLC patients of poor performance status. Kato *et al*. explored how clinical characteristics affected the efficacy of osimertinib

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therapy in patients with NSCLC harboring T790M EGFR mutation and acquired resistance to prior EGFR-TKIs (15). The study enrolled 31 patients of whom eight were categorized as younger patients (<65 years) and 23 were categorized as older patients (≥65 years). Other clinical characteristics (sex, smoking history, previous therapies, type of EGFR mutation, and CNS metastasis status) did not differ significantly between the groups. The PFS was significantly shorter in younger patients in comparison with older patients (3.5 *vs.* 6.4 months, P=0.041) and the OS tended to be shorter in younger patients in comparison with older patients (5.3 *vs.* 19.4 months, P=0.067). The PFS (9.1 *vs.* 5.5 months; P=0.071; HR, 0.38) was shorter in patients with poor Eastern Co-operative Oncology Group performance status (ECOG-PS) in comparison with those with good ECOS-PS. On multivariable analysis, ECOG-PS and age remained as independent predictors of the efficacy of osimertinib. The authors concluded that younger age and poor performance status were associated with the lower efficacy of osimertinib in patients with T790M-positive NSCLC. The association between poor performance status and lower efficacy is understandable. However, the association between younger age and poor performance status is debatable. In previous studies, older patients exhibited higher EGFR-TKI response rates and longer OS (16,17). Wu *et al*. found that age ≤50 years was associated with a poor response to EGFR-TKI. However, in the analysis of BR.21 trial, age did not significantly affect the response rate, PFS, or OS associated with erlotinib treatment (18). The inconsistencies may be attributable to differences in study design, the small sample sizes, and the use of different EGFR-TKIs and definitions of young age.

Previous studies showed that none of age, body weight, gender, or ethnicity exerted a clinically relevant effect on pharmacological clearance/exposure of 1st or 2nd-generation EGFR-TKIs (19-21). A pharmacokinetic study of osimertinib found that none of age, sex, or smoking status affected the pharmacokinetics (22). However, age would affect the response to EGFR-TKIs. Older patients are more likely than younger patients to have comorbidities and, thus, to take other drugs. Concurrent medications may affect the pharmacokinetics of EGFR-TKIs (21), elevating the plasma level of osimertinib. Notably, the cited work found more adverse events in older patients, perhaps associated with the higher plasma level of osimertinib (15). The work did not discuss comorbidities, concurrent medications, or plasma osimertinib levels. Another study is needed to explore associations between age, concurrent medications, osimertinib plasma concentration, and the osimertinib response.

In addition, younger patients may have fewer uncommon EGFR mutations than older patients (23). Uncommon EGFR mutations include mutations other than the exon 19 del and L858R mutations. One retrospective study found that young, Asian NSCLC patients had fewer EGFR mutations, but the types thereof were more uncommon (23). Two uncommon or compound mutations were detected only in older patients (thus, in no young patients); the presence of uncommon mutations, therefore, did not explain the poor response to osimertinib among young patients of the cited work (15). However, it is possible that other genetic changes might exist in young patients more commonly than in older patients, and that these might compromise the efficacy of EGFR-TKIs. A recent study found that the molecular features of lung adenocarcinomas in patients aged ≤35 years differed from those of older patients (24).

Although the cited authors addressed the impact of age on the response to osimertinib in patients with EGFR T790M-positive NSCLCs, it may be too early to conclude that younger age predicts poor osimertinib efficacy. Further in-depth genetic analysis and measurement of osimertinib plasma concentrations are needed.

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Footnote

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