Does osimertinib treatment discriminate young patients?

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Osimertinib (AZD9291 or TAGRISSO™) is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) developed to overcome T790M-induced resistance, which accounts for approximately 60% of resistant cases after 1st generation EGFR-TKI treatment. Beyond T790M mutation, osimertinib also selectively and irreversibly inhibits EGFR harboring the common “sensitive” mutations such as 19del and L858R. Osimertinib is now an FDA-approved drug for non-small cell lung cancer (NSCLC) patients with activating EGFR mutations (first-line) or those who have become resistant to the 1st generation EGFR-TKIs (e.g., erlotinib) through the T790M mutation (second-line). Despite its recognized efficacy, all patients unavoidably develop resistance to osimertinib, resulting in eventual treatment failure in the clinic (1,2).

Lung cancer is a deadly disease that affects both male and female adults with comparable chance. It has been suggested that young NSCLC patients have distinctive clinicopathologic characteristics and survival outcomes compared to older patients (3,4). However, it is unclear whether age impacts the outcomes of NSCLC treatment with osimertinib. Early studies with 1st and 2nd generation EGFR-TKIs generated inconsistent results regarding the impact of age on therapeutic outcomes. While some studies showed no difference in the efficacy and safety of EGFR-TKIs between elderly and younger patients (5,6), one retrospective study showed that EGFR-TKI exhibited poor efficacy in patients >75 years of age (7). However, another study reported that the efficacy of 1st and 2nd generation EGFR-TKIs was better in elderly patients with NSCLC than in those aged <50 years (8).

Kato et al. (9) recently reported a study that specifically assessed the impact of age, in addition to ECOG-PS and other clinical variables, on outcomes of patients with EGFR T790M mutant NSCLC who received osimertinib treatment. This study enrolled a total of 31 patients, including 8 young (<65 years) and 23 elderly (≥65 years) patients. The interesting finding is that the progression-free survival was significantly shorter in young patients than in elderly patients [3.5 vs. 6.4 months, P=0.041; hazard ratio (HR), 2.41]. The overall survival of the young patients also tended to be shorter than that of the elderly patients (5.3 vs. 19.4 months, P=0.067; HR, 2.58). By multivariate analysis, beyond ECOG-PS, age was another independent predictor of osimertinib efficacy, while other clinical characteristics and patterns of disease progression showed no difference between the young and elderly patients.

That age may impact the outcomes of T790M positive NSCLC patients receiving osimertinib as a second-line treatment is clearly an interesting finding with potential significance in guiding osimertinib application in the clinic. However, there were several major limitations of this study, including it being conducted at a single center, the retrospective study design and the small sample size. Among the 31 patients enrolled, there were only 8...
young patients (9). Therefore, further validation studies including retrospective and prospective study designs with large cohorts of patients are definitely needed. Given that osimertinib has been approved for the treatment of NSCLC patients with activating EGFR mutations as a first-line treatment in the US, it will also be interesting to explore whether the finding of age as an independent predictor of osimertinib efficacy in this study also holds true for osimertinib as a first-line treatment option.

Another interesting question is why younger patients have poorer outcomes than elderly patients after osimertinib treatment. If the findings in this study can be validated, it will be critical to understand the mechanism accounting for the poor prognosis of young patients receiving osimertinib treatment. The potential impact of differences in tissue or serum T790M levels between young and elderly patients on osimertinib outcomes should be considered but were not reported in the current study. Beyond T790M mutation, there are other EGFR-independent mechanisms that may affect cancer cell response to osimertinib, such c-MET amplification and Ras/MEK/ERK signaling activation (10,11). Given that c-MET amplification and T790M mutation can concurrently occur in EGFR mutant NSCLC tissues relapsed from first generation EGFR-TKI treatment (12), whether these receptor-independent resistance mechanisms contribute to the poor prognosis of young patients receiving osimertinib treatment needs investigation. The study by Kato et al. included 14 patients with brain metastasis. There were more patients with brain metastasis in the younger patient group (5/8; 62.5%) than in the elderly patient group (9/23; 39.1%). It is unclear whether these patients received local brain radiotherapy before or after osimertinib treatment. These factors need to be considered as well.

Overall, the finding that younger patients with EGFR T790M mutant NSCLC have poorer response to osimertinib treatment is intriguing. However, this finding needs further validation in larger cohorts of patients with consideration of other additional variable factors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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