Editorial

Does osimertinib treatment discriminate young patients?

Cheng Ji[1], Chongke Zhong[2], Shi-Yong Sun[3]

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou 215006, China; [2]Department of Epidemiology, School of Public Health and Jiangsu Key Laboratory of Preventive and Translational Medicine of Geriatric Diseases, Medical College of Soochow University, Suzhou 215123, China; [3]Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Center, Atlanta, GA, USA

Correspondence to: Dr. Cheng Ji. Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou 215006, China. Email: jicheng_suda@163.com; Dr. Shi-Yong Sun. Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Center, Atlanta, GA 30047, USA. Email: ssun@emory.edu.

Comment on: Kato Y, Hosomi Y, Watanabe K, *et al.* Impact of clinical features on the efficacy of osimertinib therapy in patients with T790M-positive non-small cell lung cancer and acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. J Thorac Dis 2019;11:2350-60.

Submitted Aug 09, 2019. Accepted for publication Aug 22, 2019.
doi: 10.21037/jtd.2019.08.118
View this article at: http://dx.doi.org/10.21037/jtd.2019.08.118

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.

Acknowledgments

We thank Dr. Anthea Hammond at Emory University for editing the manuscript.

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.

References

1. Govindan R. Overcoming resistance to targeted therapy for lung cancer. N Engl J Med 2015;372:1760-1.
2. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:841-9.
3. Liu M, Cai X, Yu W, et al. Clinical significance of age at diagnosis among young non-small cell lung cancer patients under 40 years old: a population-based study. Oncotarget 2015;6:44963-70.
4. Liu B, Quan X, Xu C, et al. Lung cancer in young adults aged 35 years or younger: A full-scale analysis and review. J Cancer 2019;10:3553-9.
5. Goto K, Nishio M, Yamamoto N, et al. A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). Lung Cancer 2013;82:109-14.
6. Roviello G, Zanotti L, Cappelletti MR, et al. Are EGFR tyrosine kinase inhibitors effective in elderly patients with EGFR-mutated non-small cell lung cancer? Clin Exp Med 2018;18:15-20.
7. Okamoto I, Morita S, Tashiro N, et al. Real world treatment and outcomes in EGFR mutation-positive non-small cell lung cancer: Long-term follow-up of a large patient cohort. Lung Cancer 2018;117:14-9.
8. Wu SG, Chang YL, Yu CJ, et al. Lung adenocarcinoma patients of young age have lower EGFR mutation rate and poorer efficacy of EGFR tyrosine kinase inhibitors. ERJ Open Res 2017. doi: 10.1183/23120541.00092-2016.
9. Kato Y, Hosomi Y, Watanabe K, et al. Impact of clinical features on the efficacy of osimertinib therapy in patients with T790M-positive non-small cell lung cancer and acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. J Thorac Dis 2019;11:2350-60.
10. Shi P, Oh YT, Zhang G, et al. Met gene amplification and protein hyperactivation is a mechanism of resistance to both first and third generation EGFR inhibitors in lung cancer treatment. Cancer Lett 2016;380:494-504.

11. Eberlein CA, Stetson D, Markovets AA, et al. Acquired Resistance to the Mutant-Selective EGFR Inhibitor AZD9291 Is Associated with Increased Dependence on RAS Signaling in Preclinical Models. Cancer Res 2015;75:2489-500.
12. Suda K, Murakami I, Katayama T, et al. Reciprocal and complementary role of MET amplification and EGFR T790M mutation in acquired resistance to kinase inhibitors in lung cancer. Clin Cancer Res 2010;16:5489-98.

Cite this article as: Ji C, Zhong C, Sun SY. Does osimertinib treatment discriminate young patients? J Thorac Dis 2019;11(Suppl 15):S1852-S1854. doi: 10.21037/jtd.2019.08.118

