Potential resistance mechanisms revealed primary resistance to crizotinib in ROS1+ non-small cell lung cancer using next generation sequencing: A multicenter study

Q. Zhang1, C. Xu1, W. Wang2, W. Zhuang3, Z. Song2, Y. Zhu4, Y. Chen1, G. Chen1, M. Fang5, T. Lu5, Y. Song3
1Pathology, Fujian Cancer Hospital, Fuzhou, China, 2Chemotherapy, Zhejiang Cancer Hospital, Hangzhou, China, 3Medical Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China, 4Thoracic Disease Center, Zhejiang Rongjun Hospital, Jiaxing, China, 5Respiratory Medicine, Jinling Hospital, Nanjing, China

Background: Crizotinib have greatly improved the prognosis of ROS1+ lung adenocarcinoma. However, approximately 5% to 10% of patients with ROS1+ non-small-cell lung cancer (NSCLC) have primary resistance to crizotinib treatment. The underlying mechanism is unknown.

Methods: We screened 2617 patients with NSCLC for ROS1 fusion. Among them, 23 patients received crizotinib treatment, and a total of 20 patients with stage IIIb-IV ROS1+ NSCLC were undergoing tumor biopsies or blood withdrawing by the time of primary or acquiring resistance to crizotinib, in including 4 formalin-fixed paraffin-embedded (FFPE) samples, 13 serum samples and 3 serous effusions. We used targeted NGS to detect genes status of patients.

Results: Among 23 patients treated with crizotinib, 73.9% (17/23) developed acquired resistance, and 13.04% (3/23) had primary resistance. Using the specimens at the baseline, there was 1 (33.3%) patient with PTEN mutation, and 1 (33.3%) patient with KIT mutation. Median PFS was significantly shorter in patients with primary resistance than those with acquired resistance (2.5 vs. 14.5 months, P < 0.001).

Conclusions: BCL2L11 loss, PTEN mutation, and KIT mutation might contribute to molecular mechanisms of primary resistance to crizotinib in ROS1+ NSCLC. Further investigations are warranted to overcome these primary resistances.

Legal entity responsible for the study: Quxia Zhang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.