NSCLC, metastatic

DE NOVO MET OVEREXPRESSION COEXISTING WITH ONCOGENIC DRIVERS IN ADVANCED NON-SMALL-CELL LUNG CANCER

N.N. Lou1, J. Yang2, X. Zhang3, H. Chen3, Y. Wu4
1Division of Pulmonary Oncology, Cancer Center, Guangdong Lung Cancer Institute, Guangzhou, CHINA
2Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Guangzhou, CHINA
3Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangdong Lung Cancer Institute, Guangdong, CHINA
4Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) & Guangdong Academy of Medical Sciences, Guangzhou, CHINA

Aim: There were many driver genes in non-small-cell lung cancer (NSCLC), such as EGFR and ALK. De novo MET amplification coexisting with EGFR mutation is recognized as intrinsic resistance to EGFR tyrosine kinase inhibitors (EGFR TKIs), in which ≥50% tumor cells with moderate to high intensity staining were defined as MET positive, and MET amplification by fluorescence in situ hybridization (FISH). Meanwhile, EGFR and KRAS mutations were detected by DNA sequencing, and ALK rearrangements were also detected by FISH.

Methods: We screened 195 consecutive patients with advanced NSCLC for the presence of de novo MET overexpression by immunohistochemical (IHC), in which ≥50% tumor cells with moderate to high intensity staining were defined as MET positive, and MET amplification by fluorescence in situ hybridization (FISH). Meanwhile, EGFR and KRAS mutations were detected by DNA sequencing, and ALK rearrangements were also detected by FISH.

Results: The frequency of de novo MET overexpression was 32.8% (64/195) in advanced NSCLC. The overall frequency was 36.0% (23/64) for de novo MET overexpression coexisting with EGFR mutations (n = 14), ALK rearrangements (n = 6) and KRAS mutations (n = 3). Seven patients with concurrent de novo MET overexpression and EGFR mutations were treated with first-line EGFR-TKIs (gefitinib or icotinib), with the response rate of 71.4% (5/7). Among them, one developed intrinsic resistance to icotinib, but achieved partial response after taking third-line crizotinib. One patient had primary resistance to first-line crizotinib. Five patients with concomitant de novo MET overexpression and ALK rearrangements were treated with crizotinib, with the response rate of 80% (4/5). The frequency of MET amplification was 13.6% (3/22) in patients with de novo MET overexpression. Among 2 with concurrent MET amplification and EGFR mutations, one responded to first-line gefitinib, but the other had stable disease. Dramatic response was observed in one with concomitant MET amplification and KRAS mutations, when treated with crizotinib.

Conclusions: De novo MET overexpression or MET amplification could coexist with other oncogenic drivers in a small subgroup of NSCLC. Advanced NSCLC with such co-alterations could have diverse responses to EGFR-TKIs and crizotinib.

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