Aim: c-Met amplification and T790M are both recognized as the common molecular mechanisms of acquired resistance (AR) to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in advanced non-small-cell lung cancer (NSCLC). It is not clear that c-Met overexpression could be as the biomarker for AR.

Methods: Advanced NSCLC patients with AR to EGFR TKIs were detected for c-Met overexpression by immunohistochemistry. ≥50% tumor cells with moderate to high intensity staining were defined as c-Met positive. The statuses of EGFR, ALK, KRAS and ROS1 were also tested.

Results: From January 2013 to April 2014, 80 advanced NSCLC patients with AR to gefitinib or erlotinib were enrolled prospectively. The frequency of c-Met overexpression was 28.8% (23/80), c-Met overexpression + T790M 12.5% (10/80), T790M 25.0% (20/80), small-cell lung cancer or squamous cell transformation 2.5% (2/80), KRAS mutation 1.3% (1/80), ROS1 fusion 1.3% (1/80) and unknown mechanism 28.8% (23/80), respectively. Fourteen c-Met overexpressed patients received gefitinib plus c-Met inhibitors. Among them 4 patients with c-Met overexpression only shown good response to crizotinib (2/3 cases achieving partial response [PR] and 1 with stable disease), another case shown PR to single agent axitinib and all got prominently clinical benefit. Among 10 with c-Met overexpression + T790M, 6 received combination of EGFR TKI and c-Met inhibitor and best response was progressive disease, even though one was treated with afatinib plus crizotinib.

Conclusions: c-Met overexpression could be as a biomarker for AR. Combination of EGFR TKIs and c-Met inhibitor is a good strategy to overcome AR for c-Met overexpressed patients, but not effective in c-Met/T790M-coexisting cases, for whom further investigations are warranted.

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