Identification of a Novel Osimertinib-Sensitive Mutation, EGFR H773L, in a Chinese Patient With NSCLC

To the Editor:

EGFR mutations are key therapeutic driver mutations in NSCLC.1 The utilization of EGFR tyrosine kinase inhibitor (TKI) treatment largely relied on defined sensitive EGFR mutations (e.g., L858R); therefore, identifying novel, sensitive mutations has great therapeutic importance. Here, we present a patient with stage IV NSCLC with novel EGFR H773L mutation who obtained remarkable benefit from osimertinib treatment.

A 62-year-old woman was admitted to our hospital with complaints of irregular coughing and blood in sputum in June 2018. Computed tomography and whole-body bone scans revealed a lesion in the right lung and bone metastasis (Fig. 1A and B). Transbronchoscopic needle aspiration biopsy of lymph nodes yielded a diagnosis of NSCLC (Fig. 1C). Stage IV (T1bN2M1) NSCLC was thus diagnosed in the patient.

Next-generation sequencing was conducted, but only one unknown mutation—EGFR H773L—was identified. The patient thus received standard chemotherapy with pemetrexed plus cisplatin from July 2018. Unfortunately, the disease progressed quickly after two cycles of chemotherapy. A new lesion in the right lung and bilateral pleural and pericardial effusions were observed. The patient, considering her chemotherapy-insensitive status, received osimertinib (80 mg once a day) from August 19, 2018, on providing full consent. Soon, partial response was obtained within 1 month (Fig. 1D). The patient continued osimertinib treatment until 10 months later, when the right lower lung lesion progressed and the bilateral pleural and pericardial effusions in addition to the enlarged lymph nodes in the mediastinum and right hilum reappeared. Disease progression was thus considered.

In this case, the patient who failed chemotherapy obtained a considerable benefit from osimertinib with the progression-free survival exceeding 10 months. Conversely, the median overall survival of patients with stage IV NSCLC with bone metastasis is only 5 months and is even worse after chemotherapy failure.2 To our knowledge, this is the first report of a patient with NSCLC with EGFR H773L mutation who responded well to osimertinib.

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Osimertinib is a third-generation EGFR-TKI and has recently been approved as a first-line TKI regardless of its T790M status, with significantly prolonged progression-free survival (18.9 versus 10.2 mos) compared with standard TKIs. However, its application has been restricted to patients with "sensitive EGFR mutations." The challenge of precise utilization of EGFR-TKI is in identifying novel sensitive EGFR mutations similar to identifying other sensitive mutations in the past.

The H773L mutation is located in the kinase domain of EGFR. Mutations within this domain such as L858R and 19del usually lead to constitutive EGFR activation and promote oncogenesis. We believe that H773L shares a similar mechanism and is an EGFR-activating oncogenic mutation because osimertinib could only inhibit EGFR harboring activating mutations without affecting wild-type EGFR. Notably, it was reported that a patient with H773L/V774M cis mutation responded to osimertinib in combination with bevacizumab. However, whether osimertinib or bevacizumab and whether V774M or H773L contributed to that response was unclear. Our case suggests that H773L is an osimertinib-sensitive mutation. This finding would extend our knowledge and the beneficiaries of EGFR-TKIs. Nevertheless, more studies are needed for better understanding.

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**Figure 1.** (A) Computed tomography scan of the right lung. (B) Bone metastasis revealed by whole-body bone scanning. (C) Hematoxylin and eosin staining of the lymph node sample obtained from transbronchoscopic needle aspiration biopsy. (D) Computed tomography results indicating tumor response during osimertinib treatment.
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