Emergence of EGFR G724S After Progression on Osimertinib Responded to Afatinib Monotherapy

To the Editor:
EGFR G724S/19del has been reported to induce resistance to osimertinib and retain sensitivity to afatinib in vitro studies.1,2 Afatinib activity in EGFR G724S/19del mutant patients hasn’t been reported yet. Herein, we report that emergence of EGFR G724S after progression on osimertinib responded to afatinib monotherapy.

A 55-year-old Chinese female never-smoker referred to a local hospital for repetitive cough in February 2017. Computed tomography (CT) scan of the chest revealed a pulmonary mass in the left lobe and multiple metastatic lesions in the left pleura. Brain metastasis was observed through cerebral magnetic resonance image. Biopsy on lung tissue and subsequent targeted next-generation sequencing (NGS) led to the diagnosis of lung adenocarcinoma with EGFR E746_S752delinsV, an EGFR exon 19 deletion mutation (EGFR 19del). Then the patient started erlotinib 100 mg daily as first-line therapy since March 1, 2017, and achieved partial response (PR). She experienced progressive disease due to enlarged lung mass after 1 year. Thereafter, the patient was treated with chemotherapy consisting of carboplatin and pemetrexed. Although pulmonary stability was observed during chemotherapy, the patient ultimately experienced progressive brain metastasis. Repeated NGS on blood only detected an EGFR 19del mutation. Then the patient started osimertinib 80 mg because of brain progression. However, CT scan after 3 months of osimertinib treatment revealed enlarged lung mass and increased pleural lesions, resulting in disease progression again (Fig. 1A).

Pleural effusion drainage and follow-up NGS confirmed the emergence of EGFR G724S with pre-existing EGFR 19del. Considering that preclinical studies have shown that EGFR G724S/19del could induce resistance to osimertinib and retain sensitivity to afatinib, the patient was treated with afatinib 40 mg daily since June 5, 2019.1,2 CT scan after 1 month showed obvious shrinkage in lung mass and pleural lesions, contributing to PR. The patient complained of grade 2 skin toxicity and afatinib was reduced to 30 mg daily. Stable lung lesions were shown through CT scan after 3 months of afatinib treatment, leading to a confirmed PR (Fig. 1A). The patient reported feeling better after

Figure 1. Radiologic images and depiction of the patient’s clinical course. A, Clinical response to osimertinib and afatinib therapy at different time. B, Treatment history and genomic results during the patient’s clinical course. PD, progressive disease; PR, partial response.
afatinib reduction. The patient continued on afatinib 30 mg daily up to now (September 26, 2019, the cutoff day), with a progression-free survival of more than 3.8 months.

Although the combination of afatinib 20 mg and osimertinib 80 mg has been used to treat a patient with EGFR G724S/19del and achieved disease control, the patient experienced progressive disease rapidly. Whether afatinib monotherapy could retain sensitivity with standard dose in EGFR G724S/19del mutant patients remains unclear. To the best of our knowledge, this case is the first to elicit clinical response of afatinib monotherapy in EGFR G724S/19del adenocarcinoma after progression on osimertinib. Despite afatinib reduction due to intolerable rash, continued response was still observed.

In conclusion, this case showed promising antitumor activity of afatinib in EGFR G724S/19del mutant NSCLC patients after resistance to osimertinib, providing a clinical strategy for such a subset of patients.

Wenfeng Fang, MD, PhD
Yihua Huang, MD
Jiadi Gan, MD
Qiufan Zheng, MD
Li Zhang, MD
Department of Medical Oncology
State Key Laboratory of Oncology in South China

Collaborative Innovation Center for Cancer Medicine
Sun Yat-sen University Cancer Center
Guangzhou, China

Acknowledgments
Supported by National Key R&D Program of China (2016YFC0905500, 2016YFC0905503), Chinese National Natural Science Foundation Project (81972556, 81772476, 81602005, 81872499, and 81702283), Science and Technology Program of Guangdong (2017B020227001), Science and Technology Program of Guangzhou (201607020031, 201704020072), and CSCO-Hengrui Cancer Research Fund (Y-HR2016-113).

References

A 76-year-old man was admitted to the Affiliated Wuxi People’s Hospital of Nanjing Medical University with left lower lung occupation for 1 month. A chest computed tomography scan revealed the existence of an eccentric cavity with speculation sign in the lower lobe of his left lung.

After thoracoscopic radical resection of lower left lung cancer, stage IIb lung adenocarcinoma was diagnosed from surgical pathology. The specimen was then subjected to NGS analysis, and a novel intergenic region between TMED2 and ALK fusion was identified (Fig. 1).

The fusion of TMED2-ALK included exons 3-4 of TMED2 and exons 20-29 of ALK, and the complete kinase structure of ALK protein was retained. Split signal was observed with a frequency of 74% in fluorescence in situ hybridization (FISH) image and immunohistochemistry (IHC) staining indicated a weakly ALK protein expression (>5%) (Fig. 2). ALK-positive was considered.

Although several ALK inhibitors have been approved for the treatment of lung cancer patients with ALK-positive cases, the tumor response is heterogeneous.1,4 One