Editorial

BRAF Mutations and Resistance of Non-Small Cell Lung Cancer to *BRAF*-Targeted Therapies Using Liquid Biopsy

Ming Li[1], Xiaoying Zhang[2]

[1]Department of Nursing, Zhangqiu People's Hospital of Jinan City, Jinan, China, [2]Department of Geriatrics, Qilu Hospital of Shandong University, Jinan, China

Corresponding author: Xiaoying Zhang, MD. Department of Geriatrics, Qilu Hospital of Shandong University, Jinan, China. E-mail: zhangxiaoying@qiluhospital.com

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Lung cancer is the most frequently diagnosed and fatal cancer worldwide.[1] The 5-year overall survival rate of patients with any type of lung cancer in developing countries, including the Chinese mainland, is markedly lower than that of patients with other leading cancers.[2] Non-small cell lung cancer (NSCLC) is the main subtype of lung cancer and accounts for approximately 80%–85% of all lung cancers.[3] *BRAF* is one of the most important genes implicated in NSCLC. The mutations that activate *BRAF* can activate constitutive kinases and thereby trigger downstream signaling pathways related to cancer cell proliferation.[4] Approximately 2%–3% of patients with NSCLC develop *BRAF*-activating mutations.[5] In these patients, the response rates (RRs) to *BRAF* inhibitor monotherapy were 33%–42%.[6,7] The co-administration of *BRAF* inhibitor and trametinib increases the RR to 64%.[8] Therefore, both the U.S. Food and Drug Administration and European Medicines Agency have approved the combination therapy of *BRAF* inhibitor and trametinib for the treatment of *BRAF*-mutant metastatic NSCLC. Although *BRAF* inhibitors have achieved encouraging therapeutic effects, they are effective only temporarily as almost all patients develop resistance to the treatment within a few months.[6,8] Many molecular mechanisms of drug resistance in cancer cells have been discovered, including changes in drug transporter expression, influences of tumor microenvironment, and pathological transition.[9,10] Moreover, the resistance mechanisms of *BRAF*-targeted therapy in patients with NSCLC are poorly understood; this restricts the development and application of related targeted therapeutic strategies.

Currently, liquid biopsy has been extensively used in cancers to detect cancer mutations, monitor therapeutic responses, detect cancer recurrences, predict patient outcomes, and identify drug resistance mechanisms.[11,12] Indeed, cancer mutations detected in the plasma have been used to determine the potential molecular mechanisms of drug resistance of metastatic NSCLC.[13,14] In a recent prospective study, Ortiz-Cuaran *et al*.[15] assessed the clinical utility of circulating tumor DNA-targeted sequencing in identifying *BRAF* mutations and *BRAF*-targeted therapy resistance-associated genomic alterations in patients with advanced *BRAF*-mutant NSCLC.

In this study, we enrolled 78 patients with *BRAF*-mutant metastatic NSCLC from 27 centers in France. A total of 208 blood samples were collected from the participants, including 47 (22.6%) from patients who had never undergone *BRAF*-targeted therapy, 115 (55.3%) from those under treatment and without disease progression, and 46 (22.1%) from those with disease progression while

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receiving *BRAF*-targeted therapy. The circulating tumor DNA isolated from the blood samples was examined by InVisionFirst®-Lung assay. The potential effects of the circulating tumor DNA alterations were predicted by *in silico* structural modeling. Moreover, *BRAF* V600E mutation was found in the circulating tumor DNAs from 35 (74.5%) patients with NSCLC who also had never undergone *BRAF*-targeted therapy. The *BRAF* mutation was determined to be associated with the signal transducers and protein kinases of MAPK and/or PI3K signaling pathways in 10 (29%) samples. In addition, *BRAF* mutations in the circulating tumor DNA detected during disease progression and at the first radiographic evaluation under treatment were associated with poor overall survival. Furthermore, we identified resistance-associated driver genomic alterations to either *BRAF*-targeted monotherapy or *BRAF/MEK* combination targeted therapy in 46% of patients. These resistance-associated genomic alterations included mutations that activate MAPK and PI3K signaling pathway effectors and alterations in genes such as *IDH1*, *U2AF1*, and *CTNNB1.*

The present study findings revealed that circulating tumor DNA-targeted sequencing is an accurate and efficient method in identifying *BRAF*-activating mutations upon diagnosis, monitoring patient response upon receipt of *BRAF*-targeted therapy, and identifying the molecular mechanisms of *BRAF*-targeted therapy resistance in patients with *BRAF*-mutant NSCLC. Moreover, consistent with previous findings, the resistance mechanism critical in *BRAF*-targeted monotherapy or *BRAF/MEK* combination targeted therapy implicates MAPK signaling pathway reactivation. This study has several limitations. First, the heterogeneity of blood sample collection and treatment regimens might have influenced the data interpretation of survival analyses. Second, the patient cohort with resistance to *BRAF*-targeted therapy was relatively small. Therefore, a larger prospective patient cohort is necessary to validate the observations of this study. Third, the DNA samples from the white blood cells of the enrolled patients were not sequenced; thus, potential false-positive mutations caused by clonal hematopoiesis cannot be ruled out. Fourth, we did not characterize *in vitro* and *in vivo* the potential resistance effectors found in patients with NSCLC who also received *BRAF*-targeted therapy and did not provide suggestions or methods in overcoming challenges in therapy resistance. Despite these limitations, this study provides useful information that would help oncologists understand the pathophysiology of *BRAF*-mutant NSCLC and promote the development of successful *BRAF*-targeted therapeutic strategies for patients with *BRAF*-mutant NSCLC.

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Conflicts of interest

There are no conflicts of interest.

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