A Dilemma on Re-biopsy in the Era of Precision Cancer Therapy

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Molecular targeted therapy and immune-checkpoint therapy have evolutionally changed cancer drug therapy. Consequently, the survival of patients with cancer harboring a molecular target has dramatically improved. Tissue sampling for analyzing the molecular targets before starting therapy is the bottom line in an era of personalized or precision medicine. For example, the first step of the algorithm for decision-making in treating patients with non-small cell lung cancer (NSCLC) is to detect either an epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutation (1). This step is not so difficult because the mutations are examined using tissue samples for the normal pathological diagnosis of cancer. Recent advancements in molecular targeted therapy for NSCLC, however, are now demanding more precise analyses.

Patients with NSCLC harboring the *EGFR* mutation mostly enjoy a long progression free survival-time while being treated with an *EGFR*-tyrosine kinase inhibitor (TKI). Nevertheless, the cancer normally becomes resistant to *EGFR*-TKIs within a couple of years. The secondary mutation of T790M on *EGFR* in 49% and the transformation to small cell lung carcinoma (SCLC) in 14% constitute a part of this resistance mechanism (2). New generation *EGFR*-TKIs which are specifically effective for T790M mutated *EGFR* are expected to become available soon. Diagnosing SCLC transformation is also clinically important because the disease is sensitive for specific chemotherapy. The resistance mechanism to *ALK*-TKIs includes an acquired mutation in *EGFR* (3) that is sensitive to *EGFR*-TKIs. In addition, an evolutionary development of immune-checkpoint therapy for cancer has prompted the possible need to evaluate the PD-L1 expression at the time of cancer recurrence in patients with NSCLC (4). Therefore, when NSCLC with an *EGFR* or *ALK* mutation becomes resistant to an *EGFR*-TKI or an *ALK*-TKI, respectively, or possibly when any NSCLC be-

comes resistant to any first-line chemotherapy, then tissue sampling to elucidate the resistance mechanism and evaluate the PD-L1 expression at the time of tumor recurrence by means of a re-biopsy is required.

The re-biopsy, however, in patients with advanced and relapsed lung cancer is often technically difficult to perform, and it is also associated with some significant risk in such patients. Although a re-biopsy is still not a common procedure in the current practice, physicians treating lung cancer are required to overcome the problem of re-biopsy before the new generation *EGFR*-TKIs will be approved.

An important case report published in this issue of *Internal Medicine* raised an additional issue associated with re-biopsy. Taniguchi et al. reported a patient who had lung adenocarcinoma with an *ALK* translocation (5). The patient was treated with chemoradiotherapy followed by consolidation chemotherapy, and thereafter the cancer was surgically resected. Nevertheless, the cancer unfortunately recurred at 15 months after surgery, and the recurred cancer was re-biopsied to clarify the type of recurrence. *ALK* expression assessed by immunohistochemistry (IHC) was positive at the first diagnosis of cancer and at the recurrence after surgery, but it was negative at the time of surgery, that is, at the time chemoradiotherapy was completed, while it was fluorescence *in situ* hybridization (FISH) positive for *ALK* translocation throughout the entire clinical course. Such a conditional alteration in the mutated *ALK* expression according to cytotoxic chemotherapy sounds reasonable, whereas this new finding should be seen as a warning to physicians who are responsible for diagnosing the molecular targets of cancer. Currently, *ALK* translocation is diagnosed by any of three methods, IHC, FISH or reverse-transcriptase polymerase chain reactions, with the first two methods being covered by the Japanese health insurance system. The guidelines of the Japanese Lung Cancer Society place IHC testing

above FISH testing, because of the technical difficulties and high cost of FISH (6). As shown by Taniguchi et al., if IHC testing could be performed at the completion of cytotoxic chemotherapy, an algorithm prioritizing IHC over FISH would fail to detect the *ALK* fusion gene. An acquired decrease in HER2 expression in breast cancer due to chemotherapy is also demonstrated in preclinical and clinical situations (7-9). PD-L1 expression in cancer is also considered to be a dynamic marker. It is therefore necessary to elucidate the optimal timing and the best methods for performing re-biopsy to achieve the best therapeutic outcome and to lower the patients' burden. While the goal of precision medicine is to achieve a better outcome, it increases the burden on patients since it requires that they undergo painful re-biopsies, while also increasing the stress on physicians due to the need to perform sophisticated re-biopsies.

Author's disclosure of potential Conflicts of Interest (COI).

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