Lung cancer is the leading cause of cancer death in the world. Before the era of targeted therapy, platinum-based doublet chemotherapy was the first-line therapy of choice for patients with metastatic non-small-cell lung cancer (NSCLC). It was during 2004 that tumor epidermal growth factor receptor (EGFR) activating mutations were found to be responsible for the responsiveness of NSCLC to EGFR tyrosine kinase inhibitor (TKI) treatment (1,2). The frequency of EGFR mutations in NSCLC has ranged from 5-30%, depending on the population studied (1-3). Lung cancer patients with tumor EGFR activating mutations have a more favorable prognosis than those without (1,4).

In current clinical practice, EGFR-TKI is the first-line treatment of choice for metastatic NSCLC patients with tumor EGFR mutation. Every effort should be exercised to ascertain the EGFR mutation status prior to initiating systemic treatment for advanced NSCLC patients (5). With regard to second-line TKIs following platinum-based chemotherapy, its tumor response rate was less than first-line TKIs in patients with EGFR mutations. The change of EGFR mutation status during disease course may partially explain the difference in the predictive value of EGFR mutation between first- and second-line TKIs treatment.

First-line chemotherapy may have influence on status of EGFR mutations, and thus, EGFR mutation status collected from the initial specimens for diagnosis might be inadequate for predicting efficacy of EGFR-TKI treatment after first-line chemotherapy. Intratumoral heterogeneity in the initial single tumor biopsy specimen could also lead to misinterpretation of the tumor EGFR mutation status and difficulty in making precise treatment decision. Many investigators used plasma EGFR mutation obtained from peripheral blood samples to represent the post-chemotherapy EGFR mutation status. However, many studies revealed that plasma EGFR mutation could not completely represent EGFR mutation status in the tumor tissue. There could be many reasons for the change of EGFR mutation status after chemotherapy. Influence of chemotherapy on EGFR mutation status may be one of the explanations for this phenomenon. Intratumoral heterogeneity also plays an important role in diversity of tumor EGFR mutation status. Further studies will be necessary to explain the mechanisms of chemotherapy-induced EGFR mutation change.

Keywords: Non-small-cell lung cancer (NSCLC); chemotherapy; epidermal growth factor receptor (EGFR); intratumoral heterogeneity

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change of *EGFR* mutation status during disease course may partially explain this difference. A recent study by Bai *et al.* revealed that first-line chemotherapy may significantly reduce both plasma and tumor *EGFR* mutation frequency in NSCLC patients. Among 264 patients with advanced NSCLC, plasma *EGFR* mutations were detected in 34.5% (91 of 264) of plasma samples collected before 2 cycles of platinum-based first line chemotherapy, but in only 23.1% (61 of 264) of plasma samples after treatment. Among 20.5% (54 of 264) of patients had changed *EGFR* mutation status from mutated type to wild type (9,10). Bai and colleagues also analyzed pre- and post-treatment tumor tissue specimens in 63 patients who received neoadjuvant chemotherapy and surgical resection of tumor. Among 19% (12 of 63) of patients, *EGFR* mutation status changed from mutated type to wild type (9). Disappearance of activated *EGFR* mutation in malignant pleural effusion after treatment with chemotherapy and *EGFR* TKIs in a Japanese woman has also been reported by Honda *et al.* (11). More recently, a study by Wang *et al.* also revealed the influence of chemotherapy on *EGFR* status. They investigated the presence of *EGFR* exon 20 mutation in plasma samples from 273 patients with NSCLC after platinum-based combined chemotherapy, and the results showed 28.21% of exon 20 mutation. The data suggested that the chemotherapy may induce *EGFR*-TKI resistant mutation at *EGFR* exon 20 in NSCLC patients, but it is also possible that mutation can exist before treatment as *de novo* exon 20 mutation contributing to *EGFR*-TKI resistance (12-15). Therefore, first-line chemotherapy may have influence on status of *EGFR* mutations, and thus, *EGFR* mutation status collected from the initial specimens for diagnosis might be inadequate for predicting efficacy of *EGFR*-TKI treatment after first-line chemotherapy.

In clinical practice, it is often difficult to acquire tumor biopsy specimens for evaluating *EGFR* mutation status after chemotherapy in advanced NSCLC patients. Many investigators used plasma *EGFR* mutation obtained from peripheral blood samples to represent the post-chemotherapy *EGFR* mutation status. A study by Bai and colleagues (16) revealed high correlation between the mutations detected in blood samples and the corresponding tumor specimens among 230 NSCLC patients (P<0.001, correlation index, 0.74). They also found that approximately 80% of tumor *EGFR* mutations were detected by *EGFR* mutation analysis derived from circulating free DNA. However, it has also been reported that inconsistency of *EGFR* mutation status between peripheral blood specimens and tumor biopsy specimens exists. Goto *et al.* analyzed *EGFR* mutation status by tumor tissue-derived DNA and circulating free DNA from blood samples of 233 Japanese patients in the IPASS (IRESSA Pan-Asia study) study. The results showed that *EGFR* mutation accessed by circulating free DNA yielded a high false negative rate (56.9%) (17). Although *EGFR* mutation analysis by using peripheral blood sample was relative non-invasive and practical method, its high false negative rate may lead to underestimation of tumor *EGFR* mutation rate. Thus, *EGFR* mutation status derived from blood samples could not completely represent *EGFR* mutation status in the tumor tissue.

In the study by Bai and colleagues (16), they also found that 7% (16 of 230) patients with *EGFR* mutations derived from plasma circulating free DNA had no detectable *EGFR* mutations in the matched primary tumors. It may be due to inadequate tumor sample size, insufficient sensitivity of *EGFR* mutation detecting method, or missing the *EGFR* mutation foci in the tumor during biopsy process. Therefore, *EGFR* mutation status derived from small tumor specimens may not completely represent the whole tumor genomics landscape.

In current clinical scenario, the *EGFR* mutation status was mostly determined by tumor tissue collected from the initial diagnostic biopsy. Although the general consensus is that the growth of cancer cells is clonal, there is more and more evidence for the existence of intratumoral heterogeneity. In the study by Bai and colleagues (9), *EGFR* mutation analysis in tumor foci microdissected from 79 NSCLC patients who had received palliative surgery was performed. The results revealed that approximately 38% (30 of 79) of tumors contained a mixture of *EGFR* mutated and wild-type foci. The proportion of *EGFR*-mutated cells was ranging from 7.69% to 90%. Similar results were also reported by Tomonaga *et al.* (18) and Taniguchi *et al.* (19). Intratumoral heterogeneity can lead to misinterpretation of the tumor *EGFR* mutation status from single tumor biopsy specimen and difficulty in making precise treatment decision (20). Tumor genetic heterogeneity is complex and often leads to failure of treatment, even in lung cancer patients with treatable activating driver oncogenes such as *EGFR* mutation (5).

In conclusion, the change of *EGFR* mutation status after chemotherapy was found by many investigators. Influence of chemotherapy on *EGFR* mutation status may be one of the explanations for this phenomenon. Intratumoral heterogeneity also plays an important role in diversity of tumor *EGFR* mutation status. Further investigations in this
area will be necessary to elucidate the pathophysiologic mechanisms of chemotherapy-induced EGFR mutation change and develop better treatment strategy in order to provide the optimal therapy for each patient.

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