Can EGFR mutation status evolve with chemotherapy?

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Epidermal growth factor receptor (EGFR) inhibition by oral tyrosine kinase inhibitors (TKIs) and platinum-based chemotherapy are important treatment strategies for advanced non-small-cell lung cancer (NSCLC). However, a significant number of patients have tumors that are intrinsically resistant to chemotherapy and/or TKIs, and even those who respond initially eventually develop acquired resistance. There have been several studies to date trying to identify subsets of patients most likely to derive initial benefit from particular agents, the so-called "personalized medicine" approach. One major success occurred when several phase III clinical trials investigating oral EGFR TKIs in NSCLC demonstrated that somatic mutations in EGFR are important predictive biomarkers for tumor response to first-line TKIs (1,2). However, tumor response to second-line TKIs following platinum-based chemotherapy was less than response to first-line TKIs in patients with EGFR mutations, suggesting resistance mechanisms following treatment with chemotherapy (3,4). This discrepancy in the predictive value of EGFR mutations between first- and second-line treatments with TKIs could be due to various mechanisms that are yet to be answered.

In a recent article published in *Journal of Clinical Oncology* (5), Bai and colleagues have made an important contribution to understanding this discrepancy in the predictive value of EGFR mutations. The investigators studied three different cohorts: first, 264 patients with advanced NSCLC who received first-line chemotherapy with matched pre- and post-treatment plasma samples; second, 63 patients who underwent neoadjuvant chemotherapy with pre- and post-treatment tissue specimens; and third, 79 patients with advanced NSCLC who underwent palliative surgery. EGFR mutation status was determined in patients of all three cohorts. Bai and colleagues are to be congratulated for their extraordinary efforts to collect challenging tumor specimens, in particular, 79 samples from palliative resection. They report novel information that the rate of EGFR mutation decreased significantly following chemotherapy in both plasma and tumor tissue samples. In addition, a small number of patients, whose tumors were initially EGFR wild-type, were later determined to harbor EGFR mutations following chemotherapy. These findings could provide partial explanation for the inconsistency in the predictive value of EGFR mutations between first- and second-line TKIs. It is relatively uncommon for treating physicians to obtain additional biopsy at time of progression. Hence, based on their findings, patients who lose sensitizing EGFR mutations following chemotherapy may end up receiving TKIs in 2nd or 3rd line with suboptimal benefit. In the third cohort, Bai and colleagues report that 38% of the tumors demonstrated an intratumor heterogeneity of EGFR mutation. This is a provocative finding with several potential implications. As the authors state, EGFR mutation shift may be related to the heterogeneity of intratumoral EGFR mutation and variable sensitivities of EGFR-mutated and wild-type tumor cells to chemotherapy, as suggested by their finding that patients who achieved partial response to chemotherapy were more likely to have EGFR mutation shift than those who achieve stable disease or progressive disease.

A limitation of this report is in interpreting the findings from the first and second cohorts in that predictive value of post-chemotherapy EGFR mutation status in tumor response to 2nd or 3rd line TKIs is unknown. Bai and colleagues (5) state in the introduction that EGFR mutations were not associated with the outcomes of TKI treatment in the BR.21 trial (3) or in the ISEL (IRESSA Survival Evaluation in Lung Cancer) study (4), which

compared erlotinib or gefitinib with placebo in patients for whom platinum-based chemotherapy had failed. This may overstate the actual findings. For instance, in the BR.21 trial, the EGFR mutant patients had significantly increased response rate (27% *vs.* 7%) after TKIs, and while progression-free survival was not statistically significant, the hazard ratio was 0.55 with P-value of 0.12 compared to EGFR wild-type patients (6). For the ISEL study of gefitinib, EGFR mutation status correlated with response (37.5% *vs.* 2.6%), with insufficient patients for survival analysis (7). Similarly, with the INTEREST (The Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere) study, EGFR mutation status predicted response and PFS advantage of gefitinib over docetaxel (8). In short, EGFR mutation status from initial biopsy specimens does appear to offer potential predictive value for response to second-line TKIs. Demonstrating superiority of predictive value for post-chemotherapy over pre-chemotherapy EGFR mutation status would be necessary to validate the findings of Bai and colleagues.

Upon progression with first-line chemotherapy, tumor cells may acquire molecular changes that may render tumors resistant to subsequent lines of therapy (9). Alternating multiple agents with different mechanisms of action did not improve clinical outcome (10). Another potential mechanism for reduced tumor response to second-line TKIs following platinum-based chemotherapy may be due to broad reduction in membrane transporters for both chemotherapy and targeted therapy (11). A recent finding suggests that reduced tissue platinum concentration in NSCLC was significantly associated with reduced tumor shrinkage and decreased survival (12). Furthermore, the flattening of the NSCLC dose-response curve at higher platinum-based chemotherapy doses (13) suggest that one of the most important factors in chemotherapy resistance is deficiency of factors required for drug uptake such as the copper transporter CTR1 (in the case of platinums). CTR1 expression was significantly lower in tumors of patients who had received either chemotherapy or targeted therapies within the previous 3 months than in tumors of patients with a longer interval off therapy (14). The correlation with time from last chemotherapy or targeted therapy was stronger than the correlation with time from last cytotoxic therapy alone. This suggests that chemotherapy or targeted therapy may result in a broad reduction in membrane transporters and that this, in turn, may generate broad cross resistance. This could also explain why gefitinib maintenance after concurrent chemoradiation (cisplatin plus etoposide) was associated with significant decrease in overall survival but not in progression-free survival compared with placebo in stage III NSCLC (15). Cause of death in both arms was thought to be due to progression of disease. It may be possible that at time of progression, tumors of patients who had received both chemotherapy and gefitinib maintenance were more likely to have down-regulation of membrane transporters required for uptake of subsequent agents, resulting in decreased overall survival but not progression-free survival.

The finding that 38% of tumors in the study from Bai *et al.* demonstrated a mixture of EGFR-wild type and mutant foci implies that the results from routine EGFR mutation analysis clinicians use to make treatment decision may not be as precise as they are perceived to be. As a result, we raise the possibility that tumors with EGFR mutation shift following chemotherapy are more likely to harbor heterogeneous EGFR mutation status, and therefore are more susceptible to imprecise determination of EGFR mutational status. Their findings would have been strengthened if they were able to implement the analysis from the third cohort into the second cohort. Percent change in frequency of EGFR mutant foci in response to chemotherapy may have been a better endpoint to corroborate their conclusions. We, however, realize that it would be extremely difficult to examine multiple foci for EGFR mutation in pre-chemotherapy specimens prior to resection.

In this targeted-therapy era, we heavily rely on molecular test results from a single biopsy which likely represents a small focus of molecularly heterogeneous tumor. Their provocative finding from the third cohort provides at least a partial justification to pursue additional biopsy either at the same site or at a different site of metastasis when initial biopsy reveals EGFR-wild type but patients otherwise fit the characteristics that are frequently associated with EGFR-mutant tumors. Further investigation at a larger scale involving patients from the institutions of different countries is warranted.

In conclusion, there could be multiple reasons for reduced tumor response to second-line TKIs following platinum-based chemotherapy and discrepancy in the predictive value of EGFR mutations between first- and second-line treatments. Bai and colleagues reported influence of chemotherapy on EGFR mutation as a potential explanation through extensive tissue-based analysis. Further investigation in this area is necessary to develop an enhanced strategy for second-line treatment

and to determine optimal sequence of targeted agents and chemotherapy. Finally, rapid determination of EGFR mutation status at time of diagnosis prior to initiating first-line therapy may allow a majority of patients with EGFR mutations to receive TKIs in first-line setting. By this approach, we could avoid the potential problem with chemotherapy-induced EGFR mutation shift in second or third-line setting.

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