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
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

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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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