TARGETED THERAPIES

Evolve and ... surrender!

Lung cancer, and in particular non-small cell-lung carcinoma (NSCLC), is the leading cause of cancer-related deaths in the world. NSCLC is generally insensitive to chemotherapy, whereas small cell-lung carcinoma (SCLC) usually responds better to both chemotherapy and radiation. In the past decade, advances in the development of targeted therapies have allowed patients with NSCLC who harbor mutations in *EGFR* to benefit from the efficacy of treatment with tyrosine kinase inhibitors (TKI), such as erlotinib and gefitinib. Unfortunately, and despite a remarkable and durable initial response, most patients develop resistance to the therapy within the first year. “This has been frustrating for patients and treating oncologists alike” explains Lecia Sequist.

Patients who develop acquired resistance to EGFR TKIs often display two other gene alterations: amplification of the *MET* gene and a second-site mutation in *EGFR* of the threonine residue at position 790—T790M. These mutations are respectively found in 20% and 50% of EGFR-mutant tumors with acquired resistance to TKIs.

“Our group has been integrally involved in the EGFR mutation story as it has unfolded” affirms Sequist. To further understand the mechanisms behind the acquisition of resistance to TKIs, Sequist and her collaborators compared tumor specimens from patients with NSCLC before treatment with biopsy tumor samples obtained at the time these patients acquired resistance to therapy. During an average of 30 months from the time of diagnosis, the researchers obtained 37 tumor samples from patients with activating mutations in *EGFR* who had been successfully treated with gefitinib or erlotinib for a median duration of 14 months until development of resistance. The pre-treatment and post-resistance samples were analyzed for genetic alterations using a genotyping assay and

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fluorescence *in situ* hybridization (FISH). All of the resistant samples retained the original pre-resistant mutation in *EGFR*, 49% of the patients acquired the secondary mutation T790M and 5% of the patients developed amplification of *MET*. The researchers also observed another mutation that had previously only been identified *in vitro*: 5% of the patients showed mutations in the gene encoding for one of the subunits of PI3 kinase (*PIK3CA*).

Perhaps more surprising was the finding—when analyzing the histology of the resistant samples—that five of the tumors had evolved from adenocarcinomas to the more responsive subset, SCLC. Of these five patients, four of them underwent chemotherapy to which three patients responded favorably.

A transition from an epithelial cell phenotype to a more invasive and aggressive mesenchymal phenotype (epithelial–mesenchymal transition, EMT) has been associated with EGFR-TKI acquired resistance in lung adenocarcinoma. Thus, Sequist and collaborators sought to investigate whether this could be the resistance mechanism behind those samples that did not show the classic T790M mutation, mutations in *MET* or *PIK3CA*. Three of these seven tumors, showed EMT at the time when resistance appeared.

Finally, to study the evolution of the tumors during the course of the treatment,

the researchers obtained biopsies from three patients for a period of 2 years. After 8 months of treatment with erlotinib, one of the patients became resistant by developing an acquired T790M mutation, which was undetectable when the treatment was withdrawn for 10 months. At that point, treatment with erlotinib was reintroduced and the patient had a second response. A second patient had a very similar clinical course with gain and loss of the T790M mutation that was detected in several biopsies.

These results show how the phenotypic and genotypic characteristics of tumors change with continued selective pressure from drugs and highlight the importance of continuous assessment of tumors to identify the best treatment options for patients: “we plan to broaden our program of repeat biopsies and expand it to other types of targeted therapy and other cancers ... We hope that other groups will also pursue these questions and that treating oncologists will talk to their patients in more detail about the possible benefits of undergoing repeat biopsies during the course of cancer therapy” concludes Sequist.

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