Editorial

Following the crumbs: from tissue samples, to pharmacogenomics, to NSCLC therapy

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Lung cancer is still the leading cause of death in the United States and worldwide (1). The 5-year survival rate is still only 14% implying the need for new treatments (2). According to the National Cancer Institute Office of Cancer Genomics, for the facilitation of personalized cancer medicine (PCM), based on genetic aberrations which exist in human malignancies, three goals have been established; first, enhancement of the understanding of the molecular mechanisms of cancer; second, the acceleration of genomic science and technology development; and third, translation of genomic data to improve cancer prevention, early detection, diagnosis, and treatment (3).

Thus, it is a fact that molecular profiling has been added in the evolving treatment of lung cancer and has been considered for predicting response to selected therapies. Besides, 85% of all lung cancers are categorized as non-small cell lung cancer (NSCLC) confirming the importance of understanding the molecular profile of this type of lung cancer (4). It is known that clinical research in the treatment of NSCLC concerns two goals, cytotoxic agents such as platinum compounds and tubulin inhibitors and targeted agents by interrupting the signaling pathways responsible for cell proliferation and survival. Furthermore, the identification of mutations and aberrations that concern NSCLC molecular pathways has enabled a personalized medicine approach to treatment.

Epidermal growth factor receptor (EGFR) signaling is one of the major targets of NSCLC treatment, considering that EGFR overexpression is found in approximately 40-80% of the patients (5). Several research groups identified EGFR gene mutations as predictive factors for drug sensitivity (6-8). EGFR mutations have been identified in larger numbers in Asians, women, non-smokers, and patients with adenocarcinoma, groups. These populations match the highly gefitinib-sensitive clinical subset (9).

Moreover, EGFR which has been clinically investigated for more than a decade, activates 2 major pathways in solid tumors, the RAS/RAF/MEK/MARK and the PI3K/AKT/mTOR pathway, which induce cancer cell proliferation, cell growth, invasion, metastatic spread, apoptosis, and tumor angiogenesis (10).

More specifically, EGFR tyrosine kinase inhibitors target the intracellular tyrosine kinase (TK) domain of EGFR, blocking the downstream signaling of the receptor (10). These include gefitinib (Iressa_; AstraZeneca, Wilmington, DE), erlotinib (Tarceva_; Genentech, South San Francisco, CA), which have been established as first-line therapy for NSCLC patients whose tumors harbor an EGF receptor gene mutation, including exon 19 deletion and exon 21 L858R (11). Although plenty clinical trials showed good response rates and PFS (12,13) in NSCLC patients with EGFR mutations, acquired resistance in these patients responsive to EGFR-TKIs is a major clinical problem (14). Moreover, an anti-EGFR monoclonal antibody, cetuximab (chimeric human-mouse anti-EGFR) (15) has been used in several clinical trials resulting in good tolerability (16).

Recently, acquired resistance has been reported to include mechanisms such as secondary mutation of the EGFR gene, amplification of the MET gene, and overexpression of hepatocyte growth factor (HGF) (14). Moreover, a meta-analysis of studies in advanced NSCLC demonstrated that k-RAS mutations are highly specific negative predictors of response (de-novo resistance) to single-agent EGFR TKIs (17). However, other groups reported that the clinical usefulness of

KRAS mutation as a selection marker either for EGFR-TKIs or cetuximab sensitivity in NSCLC is limited (18,19).

As a result novel compounds have been developed such as irreversible EGFR-TKIs to overcome resistance. These new pharmaceutical agents bind irreversibly to EGFR tyrosine kinase and include neratinib or HKI-272, PF00299804, and afatinib or BIBW 2992 which are currently being evaluated in clinical development for NSCLC (20).

Other studies in Phase I and Phase II trials have demonstrated the use of anti-EGFR TKIs in combination with radiation or concurrent chemoradiation for stage III NSCLC to be feasible but still remains to be further determined (21-23).

The PI3K/AKT/mTOR pathway includes Akt, one of the most frequently activated protein kinases in human cancer (24). Drugs interfering with the mTor pathway includes rapamycin (sirolimus), cell cycle inhibitor (CCI)-779 (temsirolimus) and RAD001 (everolimus) (25). Although mTOR inhibitors such as everolimus in combination with EGFR inhibitors appear to be well tolerated, with some evidence suggesting antitumor activity (26), optimization of the therapeutic impact of mTOR inhibitors still remain to be clarified when reliable predictive factors will be identified. In addition, another study indicated that transient blockade of PI3K/Akt pathway might overcome EGFR TKIs resistance and restore sensitivity to agents well tolerated, thereby providing clinical benefit (27).

Another active research field in NSCLC is the discovery of therapies that target angiogenesis. Vascular endothelial growth factor (VEGF) pathway includes monoclonal antibodies against VEGF such as bevacizumab which has been approved for the treatment of metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel and showed increased survival (28), VEGF receptors such as aflibercept and also small molecule TKIs such as sunitinib and sorafenib that target the TK domain of VEGF receptor (29). There are also other agents that are under clinical development concerning the antiangiogenic patway. Predictive biomarkers of response to antiangiogenic therapy and the mechanisms of resistance to these agents are still under investigation. The latest goal of the researchers is the evaluation of antiangiogenics in combination with radiotherapy. Data do not support the combination of bevacizumab and radiation (30).

Other targets include MET oncogene or EML4-ALK (anaplastic lymphoma kinase) fusion which is a rare abnormality, appeared in 4-5% of NSCLC patients (31). The Met and ALK inhibitor crizotinib in the first-in-man phase I study in patients with EML4-ALK fusion showed good tolerability with rapid, durable responses (32).

At this point EGFR gene mutations used as predictive factors is the best accomplishment achieved so far by the researchers. Their efforts are focused on identifying other molecular signatures that could be predictive of response. Indeed, targeted therapies have revolutionized the area of NSCLC treatment. Pharmacogenetics and pharmacogenomics will be ultimately leading to drug prescription based on a patient's individual genetic and molecular profile.

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