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Personalized Therapy for Lung Cancer

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The past decade has seen an enormous advancement in the therapy for lung cancer, predominantly seen in adenocarcinoma, ranging from the introduction of histology-based drugs to the discovery of targetable mutations. These events have led to a personalized therapeutic approach with the delivery of drugs that target specific oncogenic pathways active in a given tumor with the intent of acquiring the best response rate. The discovery of sensitizing mutation in the epidermal growth factor receptor gene as the basis for clinical response to tyrosine kinase inhibitors led to a systematic search for other molecular targets in lung cancer. Currently, there are several molecular alterations that can be targeted by experimental drugs. These new discoveries would not be possible without a parallel technological evolution in diagnostic molecular pathology. Next-generation sequencing (NGS) is a technology that allows for the evaluation of multiple molecular alterations in the same sample using a small amount of tissue. Selective evaluation of targeted cancer genes, instead of whole-genome evaluation, is the approach that is best suited to enter clinical practice. This technology allows for the detection of most molecular alteration with a single test, thus saving tissue for future discoveries. The use of NGS is expected to increase and gain importance in clinical and experimental approaches, since it can be used as a diagnostic tool as well as for new discoveries. The technique may also help us elucidate the interplay of several genes and their alteration in the mechanism of drug response and resistance. CHEST 2014; 146(6):1649-1657

ABBREVIATIONS: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; FISH = fluorescence in situ hybridization; MET = mesenchymal epithelial transition; NGS = next-generation sequencing; SQCC = squamous cell carcinoma; TKI = tyrosine kinase inhibitor

Personalized medicine is defined by the National Cancer Institute as a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. Therefore, personalized therapy in lung cancer takes into consideration specific characteristics of the tumor to prescribe the best treatment plan. In the last decade, there has been a major change from the empirical treatment in lung cancer, where one drug fits all, to a biomarker-based therapy.[1,2]

Personalized therapy in lung cancer starts with the histologic diagnosis. Most of the advances in lung cancer targeted therapy occurred in adenocarcinoma. Bevacizumab and pemetrexed have been shown to be an effective treatment of adenocarcinoma but not squamous cell carcinoma (SQCC)

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because of severe drug-associated toxicity and lack of drug activity in the latter.[3,4] More importantly, targetable mutations are more commonly identified in adenocarcinomas. Currently, there are two types of molecular target therapies approved by the US Food and Drug Administration for the treatment of pulmonary adenocarcinoma. These are erlotinib/gefitinib, and more recently afatinib, for tumors that carry mutations in the tyrosine kinase domain of *EGFR* and crizotinib for tumors with rearrangement of *ALK*. Both drugs are generically called tyrosine kinase inhibitor (TKI). There has been an enormous interest in the mechanisms that lead to activation and deactivation of tyrosine kinases in tumor biology because of the importance of this pathway in regulating cell growth, signaling, and division. Receptor tyrosine kinases form a complex signaling network and can amplify the signal by a ligand through intercommunicating pathways. In the case of *EGFR*, the signal can be mediated through the *RAS/RAF/MEK* and *PIK3CA/AKT/mTOR* pathways,[5] thereby offering multiple targets for drug interventions. All established and experimental drugs for target therapy in lung cancer are directed through these "switch on" pathways, also called oncogene addiction. There is no established targetable therapy for tumors with a mutation in a tumor suppressor gene or another distinct oncogenic mechanism.

EGFR Mutations

The concept of targeted therapy in lung cancer was propelled by the discovery of activating mutations in the tyrosine kinase domain of *EGFR* as the basis for the observed response in patients treated with TKI.[6-8] *EGFR* mutations are seen in approximately 20% of patients with lung adenocarcinoma. The mutation is more prevalent in nonsmokers and in the Asian population, where it has been reported as high as 60%.[9] Most of mutations in *EGFR* are seen in exomes 18 to 21 of the kinase domain. However, not all identifiable mutations are associated with response to TKI, and indeed there are mutations associated with resistance or insensitivity to the drugs.[10]

The two most common *EGFR* mutations in pulmonary adenocarcinoma are in-frame deletions in exon 19 (E746-A750 15-base-pair deletion) and the point mutation replacing leucine with arginine at codon 858 in exon 21 (L858R). These two mutations are responsible for 90% of the *EGFR* mutations in lung adenocarcinoma.[10] Other less-frequent mutations include in-frame deletions in exon 19 or point mutations in exon 18 and 21 (Fig 1).[10] Mutations characterized by insertions in exon 20 are associated with lack of sensitivity to TKI.[11,12]

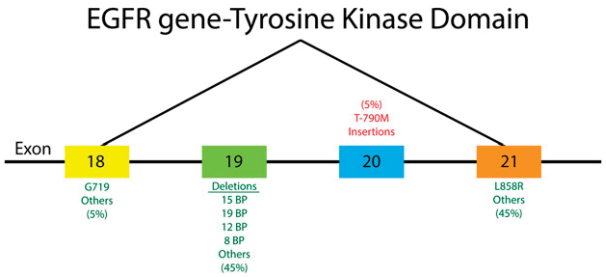

Figure 1 – *Simplified scheme of main mutations in the tyrosine kinase domain of* EGFR. *Sensitizing mutations are marked in green. Mutations associated with resistance to tyrosine kinase inhibitor (TKI) are indicated in red. The most common mutations are 15-BP deletion in exon 19 and point mutation (L858R) in exon 21. These two mutations represent almost 90% of all sensitizing mutation to TKI. Insertions in exon 20 are associated with resistance and are estimated to be the third most common mutation in the gene. BP = base pair; EGFR = epidermal growth factor receptor.*

Exon 20 insertions may be the third most common mutation in the gene after exon 19 in-frame deletions and L858R.[11] Computational analysis suggests that insertions in exon 20 cause structural changes in the epidermal growth factor receptor (EGFR) protein, thus preventing binding of TKI.[11] T790M is a point mutation (threonime-790 to methionine) in exon 20 that is associated with acquired resistance to TKI[12-14]; this mutation is often seen in tumors that were rebiopsied after TKI failed.[14] However, this mutation can be seen in untreated tumors, where it is associated with short-term response to TKI.[12,13]

Recently, a group of multidisciplinary investigators including pathologists, clinicians, and molecular pathologists published guidelines for molecular testing in lung cancer[15] and emphasized that priority should be given to the molecular alterations that have approved targeted therapy, namely EGFR and anaplastic lymphoma kinase (ALK). The recommendation also suggests that a test that can identify all possible mutations in the gene should be used, thus ensuring that all possible sensitizing mutations are identified. Currently, the diagnosis of EGFR mutations and ALK rearrangement requires different techniques to identify insertions, deletions, point mutations, and, in the case of ALK, a fluorescence in situ hybridization (FISH) test. Thus, there is great need for a comprehensive technique that can accomplish all these alterations in a single test.

ALK Rearrangement and ROS-1 Fusion

In 2007, a novel driver mutation, *EML4-ALK* fusion gene, was identified in approximately 5%[16] of patients with lung adenocarcinoma.[16] This mutation is the result of an inversion of the short arm of chromosome 2 involving 2p21 and 2p23, leading to the fusion of N-terminal