5-1-2018

Acquired Resistance Mutations to EGFR Treatment in Non-Small Cell Lung Cancer

Benjamen Schoenberg
Thomas Jefferson University

Gregory Omerza, PhD
Thomas Jefferson University

Acquired Resistance Mutations to EGFR Treatment in Non-Small Cell Lung Cancer

Benjamen Schoenberg and Gregory Omerza
Clinical Genomic and Molecular Pathology Laboratory, Thomas Jefferson University Hospital

Non-small cell lung cancer (NSCLC) is currently the number one cause of cancer death in the United States for both men and women.[1] Mutations in the epidermal growth factor receptor (EGFR) gene are detected in approximately 30% of individuals with advanced NSCLC in Asia and 10-15% in Western countries.[2] For patients harboring activating EGFR mutations, treatment includes the use of first or second-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as afatinib, gefitinib, or erlotinib.

The purpose of this case study is to review the pathophysiology of the progression of NSCLC in a 63-year-old non-smoking Caucasian woman. The patient presented with worsening back pain for four months, sudden onset of lower extremity weakness, and unintentional 20-pound weight loss. Imaging revealed spinal cord compression, a right upper lung mass with hilar adenopathy, multiple vertebral metastases, adrenal lesions, and a mass in the left lobe of the liver. Transbronchial biopsy of the lung mass in the patient confirmed NSCLC of the adenocarcinoma type. Next Generation Sequencing (NGS) identified an L858R mutation in exon 21 of EGFR, which results in activation of the tyrosine kinase (TK) domain of the EGFR protein product, without the need for ligand binding and a decreased binding affinity for ATP. The patient began daily erlotinib therapy with subsequent regression of disease at four months follow-up. After 12 months on erlotinib the patient developed radiographic progression with a T790M mutation in exon 20, the most common resistance mutation secondary to treatment with first generation TKIs. The patient was subsequently started on the third-generation TKI, osimertinib. After 12 months of treatment the patient developed the EGFR C797S tertiary mutation leading to osimertinib resistance and further progression of the disease.

According to clinical guidelines, all patients with non-squamous NSCLC should be tested for mutations in EGFR. This case study serves as evidence that constant monitoring of EGFR positive patients is essential, as there are multiple ways in which cells develop resistance to TKI treatment.[3]

Works Cited

1. Cancer Prevalence Worldwide. *Global Cancer Observatory*, World Health Organization, gco.iarc.fr/today/fact-sheets-cancers?cancer=29&type=0&sex=0.
2. Midha, Anita, et al. EGFR Mutation Incidence in Non-Small-Cell Lung Cancer of Adenocarcinoma Histology: a Systematic Review and Global Map by Ethnicity (MutMapII). *American Journal of Cancer Research*, 2015.
3. Marhetti, Antonia, et al. EGFR Mutations in Non–Small-Cell Lung Cancer: Analysis of a Large Series of Cases and Development of a Rapid and Sensitive Method for Diagnostic Screening With Potential Implications on Pharmacologic Treatment." *Journal of Clinical Oncology*, 2005.