Mechanisms of resistance to epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced non-small-cell lung cancer: clinical and molecular considerations.

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Source

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Abstract

Non-Small-Cell Lung Cancer (NSCLC) with somatic mutations of the epidermal growth factor receptor (EGFR) is anticipated to respond to small-molecule tyrosine kinase inhibitors (TKIs) of the EGFR tyrosine kinase. There are, however, patients with EGFR mutated tumors who do not demonstrate tumor response. The most widely accepted mechanism of 'de novo' (inherent) resistance to these TKIs involves mutations of the KRAS gene. KRAS is a downstream mediator of EGFR-induced cell signaling, such mutations appear to be mutually exclusive from EGFR mutations in lung cancer. The first molecular modifier of resistance identified in patients who developed resistance (termed 'acquired resistance') to TK inhibition was a new acquired somatic EGFR mutation (T790M). Today there is an ever-growing series of molecular events that have recently come to the forefront to explain other instances of TKI resistance not attributable to T790M or KRAS. These include a number of molecules that interact with EGFR or form part of its downstream signaling pathway such as HER-2, IGFR-1, MET and B-RAF. Considering that the majority of studies carried out to date with respect to the identification of resistant clones have not used highly sensitive techniques (e.g. allelic discrimination to identify somatic mutations), coupled with the relatively low number of studies examining multiple molecular markers and the accepted molecular heterogeneity of NSCLC raise question as to the existence of 'acquired' versus 'de-novo' resistance. By examining the current knowledge base with respect to mechanisms of resistance to EGFR TKIs in NSCLC, we explore whether 'acquired' resistance is 'de-novo' resistance in disguise, and discuss the promises and limitations of molecular stratification with respect to strategies incorporating TKIs in the treatment of NSCLC.