J Exp Clin Cancer Res. 2012 Sep 19;31(1):77. doi: 10.1186/1756-9966-31-77.

Molecular predictors of response to tyrosine kinase inhibitors in patients with Non-Small-Cell Lung Cancer.

Murray S, Karavasilis V, Bobos M, Razis E, Papadopoulos S, Christodoulou C, Kosmidis P, Fountzilas G.

Source

BioMarker Solutions Ltd, London, UK; & Department of Molecular Oncology, GeneKOR, Athens, Greece. smgenedb@gmail.com.

Abstract

ABSTRACT:

INTRODUCTION:

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have become a treatment option in non-small-cell lung cancer (NSCLC) patients. However, despite their use in this disease, a significant number of patients will eventually develop resistance and relapse. In this study, we aimed to characterize several molecular events involved in potential resistance mechanisms to anti-EGFR treatment and correlate our findings with clinical outcome.

MATERIAL AND METHODS:

The medical records of patients with NSCLC who received anti-EGFR TKIs in any line within the participating centers were reviewed and available paraffin embedded tissue was retrieved. Mutational analysis for EGFR, KRAS, BRAF and intron-exon 14 deletions of MET; FISH analysis for chromosomal gain or amplification for EGFR, MET and the deletion marker D7S486 were performed. Furthermore, the expression of EGFR and MET were analysed by immunohistochemistry. All results were correlated with treatment outcomes.

RESULTS:

Between 10/2001 and 12/2009 from an initial cohort of 72 treated patients, 59 cases (28 gefitinib/ 31 erlotinib) were included in the analysis. The majority had adenocarcinoma histology (68%), and received treatment in the second line setting (56%). Disease control rate (DCR) was 25.4% for all patients. EGFR and RAS mutational rates were 33% and 10% respectively, no other mutations were identified. High EGFR expressing tumors were found in 7 of 45 cases and pEGFR positivity (IHC) was found in 56% of the cases; MET expression was found in 48% of tumors. EGFR gene amplification was found in 4 cases, two cases showed high polysomy; overall, 13% cases were FISH positive for EGFR. High polysomy of MET gene was detected in 1/43 cases tested. D7S486 locus deletion was detected in 15/37 (40%) of cases. EGFR mutational status and gene gain were both associated with more favorable DCR. No other associations between examined biomarkers and DCR or survival were noted.

CONCLUSIONS:

EGFR mutational status is a predictor for disease control in patients with NSCLC treated with anti-EGFR TKIs. The predictive role of several other molecules involved in potential resistance to anti-EGFR TKIs is worthy of additional investigation.