Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer.

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Source

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Abstract

BACKGROUND:

Somatic mutations of the k-RAS oncogene have been assessed as a mechanism of de-novo resistance to epidermal growth factor receptor (EGFR) tyrosine-kinase inhibition in patients with non-small-cell lung cancer (NSCLC), and to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer (mCRC). The aim of this systematic review and meta-analysis was to assess if k-RAS mutations represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in mCRC and NSCLC.

METHODS:

We systematically identified articles pertaining to k-RAS mutational status in patients with NSCLC treated with tyrosine-kinase inhibitors (TKI), and patients with mCRC treated with any anti-EGFR-based regimens. Eligible studies had to report complete responses (CR) and partial responses (PR), stratified by k-RAS mutational status. Potential between-study heterogeneity was accommodated by use of random-effects models for bivariable meta-analysis of sensitivity and specificity (the primary endpoints). The positive and negative likelihood ratios (+LR and -LR, respectively) of k-RAS mutations for predicting an absence of response were considered as secondary endpoints and were calculated by use of pooled estimates for sensitivity and specificity.

FINDINGS:

Of 252 retrieved manuscripts, 17 were deemed eligible for the NSCLC meta-analysis (165 of 1008 patients with mutated k-RAS). The presence of k-RAS mutations was significantly associated with an absence of response to TKIs (sensitivity=0.21 [95% CI 0.16-0.28], specificity=0.94 [0.89-0.97]; +LR=3.52; -LR=0.84). Of 68 retrieved manuscripts reporting on anti-EGFR monoclonal-antibody-based treatment of mCRC, eight studies were deemed eligible for the final analysis (306 of 817 patients with mutated k-RAS). The presence of k-RAS mutations was significantly associated with an absence of response to anti-EGFR monoclonal-antibody-based treatments (sensitivity=0.47 [0.43-0.52]; specificity=0.93 [0.83-0.97]; +LR=6.82; -LR=0.57).

INTERPRETATION:

This analysis provides empirical evidence that k-RAS mutations are highly specific negative predictors of response (de-novo resistance) to single-agent EGFR TKIs in advanced NSCLC; and similarly to anti-EGFR monoclonal antibodies alone or in combination with chemotherapy in patients with mCRC. The low sensitivity and relatively high -LR of k-RAS mutations for determining non-responsiveness clearly shows that additional mechanisms of resistance to EGFR inhibitors exist.