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


CRD summary
The authors concluded that k-RAS mutations were highly specific negative predictors of response to epidermal growth factor receptor-targeted treatments for non small cell lung cancer or metastatic colorectal cancer. A lack of high-quality studies and methodological weaknesses (particularly a lack of information about study validity), means the conclusions may need to be interpreted with a degree of caution.

Authors' objectives
To assess the value of somatic k-RAS mutations in predicting non-responsiveness to epidermal growth factor receptor (EGFR)-targeted agents in advanced non small cell lung cancer (NSCLC) and metastatic colorectal cancer (mCRC).

Searching
MEDLINE via PubMed (to June 2008) and The Cochrane Library (Issue 2, 2008) were searched. Search terms were reported. Relevant journals were handsearched, as were the reference lists of articles retrieved and relevant reviews. Experts in the field were consulted. The search was restricted to published studies and for NSCLC studies was restricted to those published in 2004 or later.

Study selection
Phase II or III randomised controlled trials (RCTs), single-arm non-randomised studies, prospective and retrospective studies of anti-EGFR targeted agents (used alone or in combination with other agents) for treating NSCLC and mCRC were eligible for inclusion. Studies were required to report complete response and partial response rates stratified by k-RAS oncogene mutational status. Case reports (studies that reported on five or fewer patients) were excluded.

Most of the NSCLC and all the mCRC studies included previously treated patients. All participants in the NSCLC studies were of white or Asian ethnicity. Specific techniques used for mutation analysis varied across studies, but in all cases involved analysing codons 12 and 13 for k-RAS mutations. The primary endpoints of the review were the sensitivity and specificity of k-RAS mutations for predicting no response to anti-tyrosine-kinase inhibition in NSCLC patients or to anti-EGFR monoclonal antibodies (of any type) in mCRC patients. Positive and negative likelihood ratios were secondary endpoints. Response criteria varied across studies, as did the monoclonal antibody and chemotherapy treatments used.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors stated that they conformed to published guidelines on meta-analysis and conducted subgroup analysis that compared studies that were potentially biased against non-biased studies. The criteria used to assess validity were not described and the authors did not state how the assessment was performed.

Data extraction
Data were extracted linking k-RAS mutations to treatment outcome. Possible outcomes were no response (stable disease or progressive disease) and response (partial or complete). A true positive test was defined as a patient with a k-RAS mutation that showed no response and a true negative test was defined as a patient with wild type (non-mutant) k-RAS that showed a response. For each study, the sensitivity and specificity of k-RAS mutations were calculated.

Data were extracted independently by two reviewers; discrepancies were resolved by consensus with a third author. Additional data were requested from study authors, if required.
Methods of synthesis
Studies were combined by a bivariate approach, whereby random effects models were used to account for potential heterogeneity between studies, which incorporated the potential association between sensitivity and specificity. As specificity was equal to one in most studies, it was used as a fixed effect in the model, and a value of 0.5 was included for false-negatives (which would otherwise be zero). Forest plots were generated. The results of individual studies were plotted within a receiver operating characteristic (ROC) plane. Likelihood ratios (LRs) were calculated from the pooled estimates for sensitivity and specificity. Subgroup analyses were conducted to investigate the effects of demographic, clinical and methodological differences between the studies.

Results of the review
Twenty-five studies were included in the review (n=1825): 17 of NSCLC (n=1008, range 15 to 138), all of which were retrospective; and eight of mCRC (n=817, range 20 to 376), of which two were prospective.

Sensitivity and specificity of k-RAS mutations for predicting no response: In the NSCLC studies, pooled sensitivity was 0.21 (95% CI: 0.16 to 0.28) and specificity was 0.94 (95% CI: 0.89 to 0.97); positive LR was 3.52 and negative LR was 0.84. In the mCRC studies, pooled sensitivity was 0.47 (95% CI: 0.43 to 0.52) and specificity was 0.93 (95%CI: 0.83 to 0.97); positive LR was 6.82 and negative LR was 0.57. Plots of the ROC plane showed specificities equal or very close to one for all studies and sensitivities that ranged from 0.05 to 0.42 for NSCLC and from 0.40 to 0.60 for mCRC.

Subgroup analyses did not significantly change the results, except that in mCRC studies specificity was significantly higher (p=0.02) when non-sequencing rather than sequencing methods of mutation detection were used.

Authors’ conclusions
K-RAS mutations were highly specific negative predictors of response to EGFR-targeted treatments for NSCLC or mCRC.

CRD commentary
The objectives and inclusion criteria of the review were clear and some relevant sources were searched for studies, but the search included a very limited number of databases and was restricted to published articles. This meant that some studies may have been missed and the review was prone to publication bias. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer extract data, but it was unclear how study selection was conducted and it did not appear that study validity was assessed. Appropriate statistical techniques appeared to be used to combine the data and investigate differences between the studies, although it appear that statistical heterogeneity was not formally assessed. The authors discussed possible limitations of the review (such as lack of prospective studies or individual patient data) and heterogeneity between the studies. Lack of high-quality studies and methodological weaknesses in the review, in particular a lack of information about study validity, means that the authors’ conclusions may need to be interpreted with a degree of caution.

Implications of the review for practice and research
Practice: The authors stated that k-RAS mutations predicted the absence of response to widely used anti-EGFR strategies in NSCLC and mCRC, but that the absence of such mutations did not guarantee an improved likelihood of response in either patient group.

Research: The authors stated that a large co-operative prospective study was needed to address the prognostic and predictive role of k-RAS mutations in predicting the efficacy of EGFR-targeted therapies in lung or colorectal cancer, including its use in first-line and adjuvant settings. The predictive role of k-RAS mutations in other cancers (for example, pancreatic cancer) warranted further investigation. Further research was also needed to check whether there was a difference between white and Asian people in sensitivity to k-RAS mutations, explore whether non-sequencing methods of mutation detection were superior and explore additional mechanisms of resistance to EGFR inhibitors.

Funding
No external funding.
Bibliographic details
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.
Lancet Oncology 2008; 9(10): 962-972

PubMedID
18804418

DOI
10.1016/S1470-2045(08)70206-7

Original Paper URL
http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(08)70206-7/fulltext

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /therapeutic use; Antineoplastic Agents /therapeutic use; Carcinoma, Non-Small-Cell Lung
/drug therapy /genetics; Colonic Neoplasms /drug therapy /genetics /secondary; Drug Resistance, Neoplasm /genetics;
Genes, ras; Genetic Markers; Humans; Likelihood Functions; Lung Neoplasms /drug therapy /genetics; Mutation;
Prognosis; Protein Kinase Inhibitors /therapeutic use; Receptor, Epidermal Growth Factor /antagonists & inhibitors

AccessionNumber
12009102448

Date bibliographic record published
07/04/2009

Date abstract record published
21/10/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.