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Biomarkers of benefit from cetuximab-based therapy in metastatic colorectal cancer: interaction of EGFR ligand expression with RAS/RAF, PIK3CA genotypes.

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Source

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Abstract

BACKGROUND:

More than half of patients with KRAS-wild type advanced colorectal cancer (CRC) fail anti-EGFR monoclonal antibodies. We studied EGFR-axis messenger RNA (mRNA) expression and RAS, RAF, PIK3CA mutations in order to identify additional biomarkers of cetuximab efficacy.

METHODS:

Previously genotyped (KRAS, NRAS, BRAF, PIK3CA mutations) formalin-fixed paraffin-embedded tumour biopsies of 226 cetuximab-treated CRC patients (1st to 3rd line therapy) were assessed for mRNA expression of epidermal growth factor receptor (EGFR) and its ligands EGF, Transofrming Growth Factor-a (TGFA), Amphiregulin (AREG) and Epiregulin (EREG) with real time quantitative PCR. Mutations were detected in 72 (31.9%) tumours for KRAS, in 6 (2.65%) for BRAF, in 7 (3.1%) for NRAS and in 37 (16.4%) for PIK3CA.

RESULTS:

Only PIK3CA mutations occasionally coexisted with other gene mutations. In univariate analysis, prognostic significance for survival (from metastases until death) was seen for BRAF mutations (Hazard Ratio HR 8.1, 95% CI 3.4-19), codon 12-only KRAS mutations (HR 1.62, 95% CI 1.1-2.4), high AREG mRNA expression only in KRAS wild type CRC (HR 0.47, 95% CI 0.3-0.7) and high EREG mRNA expression irrespective of KRAS mutation status (HR 0.45, 95% CI 0.28-0.7). EREG tumoural mRNA expression was significantly associated with a 2.26-fold increased likelihood of objective response to cetuximab therapy (RECIST 1.1). In multivariate analysis, favourable predictive factors were high AREG mRNA in KRAS wild type tumours, high EREG mRNA, low Ephrin A2 receptor mRNA. Cetuximab-treated patients with AREG-low KRAS wild type CRC fared very poorly, their survival being similar to KRAS mutant CRC. Patients with KRAS codon 13 or other non-codon 12 mutations had a median survival (30 months, 95% CI 20-35) similar to that of patients with KRAS wild-type (median survival 29 months, 95% CI 25-35), in contrast to patients with KRAS codon 12 mutations who fared worse (median survival 19 months, 95% CI 15-26).

CONCLUSIONS:

BRAF and codon 12 KRAS mutations predict for adverse outcome of CRC patients receiving cetuximab. AREG mRNA reflects EGFR signalling in KRAS wild type tumours, predicting for cetuximab efficacy when high and failure when low. EREG may have a prognostic role independent of KRAS mutation.