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The prognostic role of ephrin A2 and endothelial growth factor receptor pathway mediators in patients with advanced colorectal cancer treated with cetuximab.

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Abstract

BACKGROUND:

Patients with colorectal cancer (CRC) with wild-type KRAS mutations are often treated with the endothelial growth factor receptor (EGFR) monoclonal antibody cetuximab. Despite the presence of a specific molecular target, most patients still do not derive benefit from this biological treatment. Our study explores the role of ephrin A2 (EphA2) receptor expression and of EGFR pathway mediators as predictors of cetuximab benefit.

PATIENTS AND METHODS:

Formalin-fixed paraffin-embedded (FFPE) tumor biopsy samples from 226 cetuximab-treated patients with CRC were studied for mRNA expression of insulin growth factor binding protein 2 (IGFBP2), insulin growth factor receptor 1 (IGF1R), cMET, EphA2, human epidermal growth factor receptor 2 (HER2), HER3, and HER4 by means of TaqMan reverse-transcribed polymerase chain reaction (RT-PCR).

RESULTS:

Of the 226 patients evaluable for exploratory analysis, 222 had complete data from follow-up visits. The univariate analysis revealed the following significant adverse prognostic factors for risk of death: high EphA2 mRNA levels (hazard ratio [HR], 1.61; P = .015), high HER2 mRNA levels (HR, 1.51; P = .045), and high IGF1R mRNA levels (HR, 1.56; P = .021). Low EphA2 tumor expression was significantly associated with objective response to cetuximab therapy. In multivariate analysis of a broad biomarker panel, factors with independent prognostic value included EphA2 mRNA levels (HR, 1.67; P = .029), high amphiregulin (AREG) mRNA levels in KRAS wild-type tumors (HR, 0.17; P < .0001), and high epiregulin (EREG) mRNA levels (HR, 0.38; P = .006).

CONCLUSION:

High EphA2 receptor expression in CRC was associated with a worse outcome in patients treated with cetuximab-based therapy. Prospective validation in treated and control patients is required to dissect the predictive from prognostic role in advanced CRC.