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EGFR gene gain and PTEN protein expression are favorable prognostic factors in patients with KRAS wild-type metastatic colorectal cancer treated with cetuximab.

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Abstract

INTRODUCTION:

Cetuximab is a monoclonal epidermal growth factor receptor (EGFR)-targeting antibody, used in the treatment of colon cancer. KRAS mutation status is strongly predictive of cetuximab efficacy, but more predictive factors are needed for better patient selection. PTEN is a downstream inhibitor of the EGFR pathway and has been evaluated as a predictive factor of cetuximab efficacy in colorectal cancer.

PATIENTS AND METHODS:

Formalin-fixed paraffin-embedded tumor tissue samples were collected from 226 patients with advanced or metastatic colorectal cancer that had been treated with cetuximab. Clinical information was collected retrospectively from the patients' medical records. After central evaluation, 147 cases with adequate material were eligible for further evaluation. EGFR and PTEN status was evaluated with immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Data were associated with cetuximab treatment outcome. Additional analysis was performed with previously published data on PIK3CA, BRAF and KRAS mutation status and EGFR ligand amphiregulin (AREG) and epiregulin intratumoral mRNA expression levels. PIK3CA mutation status and PTEN protein expression were also analyzed as a single complex parameter, to evaluate the predictive value of PI3K/PTEN axis dysfunction as one entity.

RESULTS:

Analysis showed a borderline association of overall response rate (ORR) and time to progression (TTP) with EGFR protein overexpression by IHC ($p = 0.059$ and $p = 0.057$, respectively) and a positive association of EGFR gain by FISH (found in only five cases) with longer TTP ($p = 0.026$). No association was found between ORR or TTP and PTEN IHC or FISH status. Comparative analysis with previously published data showed that PTEN protein expression is associated with longer TTP in patients with wild-type (WT) KRAS ($p = 0.036$) and especially in the ones with elevated AREG levels ($p = 0.046$), as well as in patients with both KRAS and BRAF WT ($p = 0.019$). Patients with both PIK3CA WT and PTEN protein expression had significantly longer TTP ($p = 0.010$) versus all others, in the absence of BRAF and KRAS mutations, a finding which persisted in the KRAS WT/AREG high subgroup ($p = 0.046$).

CONCLUSIONS:

In this cetuximab-treated colorectal cancer population, EGFR gain was associated with better outcome and PTEN protein expression with longer TTP in KRAS WT, KRAS WT/AREG high and KRAS/BRAF WT subpopulations. Cetuximab efficacy is greater with intact and activated EGFR signaling, without activating mutations of KRAS/BRAF and in the presence of preserved PTEN inhibitory activity upon the PI3K/AKT pathway. These results reflect a solid biological rationale and warrant further evaluation of the predictive role of PTEN in prospective studies.