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A study of gene expression markers for predictive significance for bevacizumab benefit in patients with metastatic colon cancer: a translational research study of the Hellenic Cooperative Oncology Group (HeCOG).

Pentheroudakis G[1], Kotoula V, Fountzilas E, Kouvatseas G, Basdanis G, Xanthakis I, Makatsoris T, Charalambous E, Papamichael D, Samantas E, Papakostas P, Bafaloukos D, Razis E, Christodoulou C, Varthalitis I, Pavlidis N, Fountzilas G.

Abstract

BACKGROUND:

Bevacizumab, an antibody neutralizing Vascular Endothelial Growth Factor (VEGF), is licensed for the management of patients with advanced colon cancer. However, tumor biomarkers identifying the molecular tumor subsets most amenable to angiogenesis modulation are lacking.

METHODS:

We profiled expession of 24526 genes by means of whole genome 24 K DASL (c-DNA-mediated, Annealing, Selection and Ligation) arrays, (Illumina, CA) in 16 bevacizumab-treated patients with advanced colon cancer (Test set). Genes with correlation to 8-month Progression-free status were studied by means of qPCR in two independent colon cancer cohorts: 49 patients treated with bevacizumab + chemotherapy (Bevacizumab qPCR set) and 72 patients treated with chemotherapy only (Control qPCR set). Endpoints were best tumor response before metastasectomy (ORR) and progression-free survival (PFS).

RESULTS:

Five genes were significantly correlated to 8-month progression-free status in the Test set: overexpression of KLF12 and downregulation of AGR2, ALDH6A1, MCM5, TFF2. In the two independent datasets, irinotecan- or oxaliplatin-based chemotherapy was administered as first-line treatment and metastasectomies were subsequently applied in 8-14% of patients. No prognostically significant gene classifier encompassing all five genes could be validated in the Bevacizumab or Control qPCR sets. The complex gene expression profile of all-low tumor (ALDH6A1 + TFF2 + MCM5) was strongly associated with ORR in the Bevacizumab qPCR set (ORR 85.7%, p = 0.007), but not in the Control set (ORR 36.4%, p = 0.747). The Odds Ratio for response for the all-low tumor (ALDH6A1 + TFF2 + MCM5) profile versus any other ALDH6A1 + TFF2 + MCM5 profile was 15 (p = 0.018) in the Bevacizumab qPCR set but only 0.72 (p = 0.63) in the Control set. The tumor expression profile of (KLF12-high + TFF2-low) was significantly associated with PFS only in the Bevacizumab qPCR set: bevacizumab-treated patients with (KLF12-high + TFF2-low) tumors had superior PFS (median 14 months, 95% CI 2-21) compared to patients with any other (KLF12 + TFF2) expression profile (median PFS 7 months, 95% CI 5-10, p = 0.021). The Hazard Ratio for disease progression for (KLF12-high + TFF2-low) versus any other KLF12 + TFF2 expression profile was 2.92 (p = 0.03) in the Validation and 1.29 (p = 0.39) in the Control set.

CONCLUSIONS:

Our «three-stage» hypothesis-generating study failed to validate the prognostic significance of a five-gene classifier in mCRC patients. Exploratory analyses suggest two gene signatures that are potentially associated with bevazicumab benefit in patients with advanced colon cancer.