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Association of VEGF-A Splice Variant mRNA Expression With Outcome in Bevacizumab-Treated Patients With Metastatic Breast Cancer.

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Abstract

BACKGROUND:

The prognostic utility of vascular endothelial growth factor A (VEGF-A) splice variants in patients with advanced breast cancer treated with bevacizumab has not been studied.

PATIENTS AND METHODS:

A total of 111 patients with metastatic breast cancer treated with weekly docetaxel or ixabepilone without bevacizumab (cohort A) and 100 treated with weekly paclitaxel and bevacizumab (cohort B) were studied. Formalin-fixed tumors were macrodissected for reverse transcription quantitative polymerase chain reaction relative quantification of VEGF-A165, -189, and -206 isoforms spliced at exon 8 proximal splice site (VEGF-Axxxa) and at exon 8 distal splice site (VEGF-Axxxb).

RESULTS:

For high VEGF-Axxxa, the hazard ratios (HRs) for progression were 1.08 (P = .71) in non-bevacizumab-treated patients (cohort A) and 0.66 (P = .22) in bevacizumab-treated patients (cohort B), and the HRs for death were 1.45 (P = .13) and 0.50 (P = .049), respectively. The interaction of VEGF-Axxxa with bevacizumab administration was significant (P = .011) for overall survival (OS). High tissue VEGF-Axxxb was not prognostic in cohort A but was predictive for bevacizumab benefit in cohort B (HR for progression, 0.57 [P = .04]; HR for death, 0.51 [P = .02]). Exploratory analyses done only in cohort B suggested that abundance of VEGFR1 messenger RNA (mRNA) in peripheral blood and low VEGFR2 mRNA in tissue correlated with poor outcome. In multivariate analysis, high tissue mRNA of angiogenic VEGF-Axxxa in the presence of bevacizumab therapy predicted for favorable progression-free survival (HR for progression, 0.39; P = .0227) and OS (HR for death, 0.32; P = .0140).

CONCLUSION:

Tissue mRNA expression of angiogenic VEGF-Axxxa isoforms was retrospectively associated with adverse prognosis in the absence of bevacizumab and with favorable outcome when bevacizumab was administered in patients with advanced breast cancer.