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The prognostic and predictive value of mRNA expression of vascular endothelial growth factor family members in breast cancer: a study in primary tumors of high-risk early breast cancer patients participating in a randomized Hellenic Cooperative Oncology Group trial.

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Source

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Abstract

ABSTRACT:

INTRODUCTION: The main prognostic variables in early breast cancer are tumor size, histological grade, estrogen receptor/progesterone receptor (ER/PgR) status, number of positive nodes and human epidermal growth factor receptor 2 (HER2) status. The present study evaluated the prognostic and/or predictive value of vascular endothelial growth factor (VEGF) family members in high-risk early breast cancer patients treated with adjuvant chemo-hormonotherapy.

METHODS:

RNA was isolated from 308 formalin-fixed paraffin-embedded primary tumor samples from breast cancer patients enrolled in the HE10/97 trial, evaluating adjuvant dose-dense sequential chemotherapy with epirubicin followed by cyclophosphamide, methotrexate, fluorouracil (CMF) with or without paclitaxel (E-T-CMF versus E-CMF). A fully automated method based on magnetic beads was applied for RNA extraction, followed by one-step quantitative RT-PCR for mRNA analysis of VEGF-A, -B, -C and vascular endothelial growth factor receptor (VEGFR) 1, 2, 3.

RESULTS:

With a median follow-up of 8 years, 109 patients (35%) developed a relapse and 80 patients (26%) died. In high VEGF-C and VEGFR1 mRNA expressing tumors, ER/PgR-negative tumors (Fisher's exact test, P = 0.001 and P = 0.021, respectively) and HER2-positive tumors (P <0.001 and P = 0.028, respectively) were more frequent than in low VEGF-C and VEGFR1 expressing tumors, respectively. From the VEGF family members evaluated, high VEGFR1 mRNA expression (above the 75th percentile) emerged as a significant negative prognostic factor for overall survival (OS; hazard ratio (HR) = 1.60, 95% confidence interval (CI): 1.01 to 2.55, Wald's P = 0.047) and disease-free survival (DFS; HR = 1.67, 95% CI: 1.13 to 2.48, P = 0.010), when adjusting for treatment group. High VEGF-C mRNA expression was predictive for benefit from adjuvant treatment with paclitaxel (E-T-CMF arm) for OS (test for interaction, Wald's P = 0.038), while in multivariate analysis the interaction of VEGF-C with taxane treatment was significant for both OS (Wald's P = 0.019) and DFS (P = 0.041) and continuous VEGF-B mRNA expression values for OS (P = 0.019).

CONCLUSIONS:

The present study reports, for the first time, that VEGF-C mRNA overexpression, as assessed by qRT-PCR, has a strong predictive value in high-risk early breast cancer patients undergoing adjuvant paclitaxel-containing treatment. Further studies are warranted to validate the prognostic

and/or predictive value of VEGF-B, VEGF-C and VEGFR1 in patients treated with adjuvant therapies and to reveal which members of the VEGF family could possibly be useful markers in identifying patients who will benefit most from anti-VEGF strategies.

TRIAL REGISTRATION:

Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12611000506998.