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Prognostic Significance of VEGFC and VEGFR1 mRNA Expression According to HER2 Status in Breast Cancer: A Study of Primary Tumors from Patients with High-risk Early Breast Cancer Participating in a Randomized Hellenic Cooperative Oncology Group Trial.

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Abstract

BACKGROUND:

Vascular endothelial growth factor C (VEGFC) and vascular endothelial growth factor receptor 1 (VEGFR1) mRNA overexpression has recently been shown to have strong predictive and prognostic value in patients with high-risk early breast cancer undergoing adjuvant chemotherapy. The present study evaluated associations of VEGFC and VEGFR1 with human epidermal growth factor receptor 2 (HER2) and their prognostic value dependent on HER2 status.

PATIENTS AND METHODS:

RNA was isolated from 298 formalin-fixed paraffin-embedded tumor tissue samples from the HeCOG 10/97 (HE10/97) trial, evaluating adjuvant dose-dense sequential chemotherapy with epirubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil therapy with or without paclitaxel (E-T-CMF vs. E-CMF). A fully-automated method based on magnetic beads was applied for RNA extraction, followed by one-step quantitative reverse transcription-polymerase chain reaction.

RESULTS:

At 13.3 years of median follow-up, 116 patients (38.9%) had experienced relapse and 115 (38.6%) had died. There were strong associations between VEGFC/VEGFR1 mRNA expression and HER2 and estrogen receptor/progesterone receptor status. In multivariate analysis, both VEGFC and VEGFR1 were found to be associated with risk for death or relapse, but such associations depended on HER2 status and treatment group. High VEGFC was a negative prognostic factor for disease-free survival [hazard ratio (HR)=1.79, 95% confidence interval (CI)=1.05-3.05, Wald's p=0.032], with a trend for overall survival (HR=1.80, 95% CI=0.94-3.47, p=0.078) in patients treated with E-CMF adjusted for clinicopathological characteristics, while high VEGFR1 was associated with increased risk for death, yet non significantly in patients with HER2-negative disease (HR=1.51, 95% CI=0.82-2.77, p=0.18), regardless of treatment.

CONCLUSION:

VEGFC and VEGFR1 mRNA overexpression is of prognostic value, dependent on HER2 status, in patients with high-risk early breast cancer undergoing adjuvant treatment. Among HER2-negative cases, these angiogenic markers could identify more aggressive tumors with worse prognosis. Further studies are warranted to validate VEGFC and VEGFR1 as potential biomarkers in adjuvant therapy and their use in identifying sub-groups that could benefit from anti-VEGF strategies.