

Impact of tumor angiogenic profile on the outcome of patients with metastatic breast carcinoma treated with weekly docetaxel. A Hellenic Cooperative Oncology Group (HeCOG) study.

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Abstract

BACKGROUND:

Metronomic taxane administration has putative antiangiogenic properties. Herein, we examined the baseline tumor angiogenic profile of patients with metastatic breast carcinoma (MBC) in a prospective-retrospective translational research study. The interplay between the angiogenic factors expressed in the tumors and their prognostic value in MBC were investigated.

PATIENTS AND METHODS:

Tumor tissues from patients with MBC treated with weekly docetaxel (n=159) were examined by immunohistochemistry for VEGF-A, VEGF-C, VEGFR-1, VEGFR-2, VEGFR-3 and osteopontin (OPN) and by mRNA analysis for expression of VEGF-A, VEGF_{xxx}a, VEGF_{xxx}b, VEGF-C, thrombospondin-1 (THBS-1), hypoxia-inducible factor-1 α (HIF-1 α) and von Hippel-Lindau (VHL) genes. Associations between these parameters and outcome were statistically analyzed.

RESULTS:

Statistically significant correlations were identified between almost all biomarkers examined in continuous form, particularly at the mRNA level: VEGF-A with VEGF_{xxx}a ($\rho=0.70$); VEGF-C with VEGF_{xxx}a, VEGF_{xxx}b and VHL ($\rho=0.51, 0.60$ and 0.44 respectively); HIF-1 α with VEGF-C and THBS1 ($\rho=0.48$ and 0.45). High VEGF-A mRNA was associated with worse survival ($p=0.0279$) and marginally with progression free survival (PFS). Intratumoral co-expression of VEGFR-1 and VEGFR-2 proteins was associated with more favorable survival ($p=0.0337$). In multivariate analysis, only high VEGF-A mRNA levels retained their prognostic role for worse PFS and survival (PFS: HR=2.34, 95% CI=1.25-4.40, $p=0.0080$; survival: HR=3.15, 95% CI=1.48-6.72, $p=0.0029$).

CONCLUSIONS:

In MBC, this study confirms the adverse prognostic effect of high intratumoral VEGF-A mRNA and reveals the combined VEGFR-1/VEGFR-2 protein expression as a potentially favorable prognosticator, which merits further evaluation in larger studies.