C30

Tumor Expression of VEGFA and Its Receptors and Clinical Outcomes in Neuroendocrine Tumors

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Background: Clinical studies have suggested efficacy of VEGF pathway inhibitors in the treatment of advanced neuroendocrine tumors (NETs). We investigated the prognostic significance of immunohistochemical expression of VEGF pathway components in patients with NETs generally, and in a subset of patients treated with the VEGF inhibitor bevacizumab.

Methods: We evaluated expression of VEGFA, FLT1 (VEGFR1), and KDR (VEGFR2) in a cohort of archival NETs. We correlated expression levels with clinical outcomes after adjusting for other clinical prognostic variables.

Results: We evaluated 173 patients with the following clinical characteristics: small intestinal/pancreas/other: 112/19/42; M/F: 88/85; mean age 54.7 yrs; localized (Stage 1-3)/metastatic (stage 4): 95/78; MKI67 ≤2% / >2%: 95/78. Within 173 primary tumors, high expression of VEGFA was an adverse prognostic factor, and was associated with shorter overall survival (OS) (multivariate HR 2.14, p=0.03) whereas high expression of FLT1 was a favorable prognostic factor, and was associated with improved OS (multivariate HR 0.46, p=0.03). In the cohort of patients with metastatic small intestinal NETs (SINETs) (n=76), high expression of VEGFA was also associated with shorter OS (multivariate HR 3.13, p=0.013). We additionally investigated associations between VEGF pathway component expression and PFS in patients with SINETs treated with bevacizumab (n=19). Remarkably, in bevacizumab-treated patients, high expression of VEGFA was associated with improved PFS (multivariate HR 0.01, p= 0.018; median PFS: 12.6 months for VEGFA-high *v* 6.7 months for VEGFA-low). Conversely, high expression of FLT1 was associated with shorter PFS (multivariate HR 30.5, p= 0.016).

Conclusion: Consistent with their reported biologic effects, expression of VEGFA appears to be an adverse prognostic factor and expression of FLT1 a favorable prognostic factor in patients with NETs. In addition, VEGFA and FLT1 may be specifically associated with the treatment effect of bevacizumab in patients with advanced SINET. Confirmatory studies are warranted.