B18

Expression of MTOR Pathway Components and Association with Clinical Outcomes in Neuroendocrine Tumors

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Background: Clinical studies have implicated the MTOR pathway in the regulation of neuroendocrine tumor growth. We investigated whether immunohistochemical expression of mTOR pathway components have prognostic significance in NET patients.

Methods: We evaluated expression of the mTOR pathway components PIK3CA, PIK3R1, PDPK1, AKT, p-AKT, TSC1, TSC2, MTOR, p-MTOR, p-RPS6KB1, p-RPS6, and p-EIF4EBP1, in a cohort of archival neuroendocrine tumors. We correlated expression levels with clinical outcomes, after adjusting for other clinical prognostic variables.

Results: We evaluated 196 cases with the following clinical characteristics: small bowel/pancreas/other: 125/19/52; M/F: 94/102, mean age 56 yrs, localized (Stage 1-3)/metastatic (stage 4): 96/95; Ki 67 ≤20%/>20%: 173/12. In the overall cohort, high expression of p-RPS6KB1, a downstream target of mTOR, was associated with both shorter DFS (HR 3.34, p=0.019) and OS (HR 2.80, p=0.02) in a multivariate analysis. In the subgroup of resected small bowel NET (n=47), high expression of mTOR was associated with shorter DFS in both univariate (HR 3.73, p=0.036) and multivariate (HR 11.7, p=0.016) analysis. In metastatic small bowel NET (n=76), univariate analysis revealed that high expression of mTOR (HR 2.48, p=0.029), p-RPS6 (HR 3.37, p=0.01 and p-EIF4EBP1 (HR 2.64, p=0.022) was associated with shorter OS. In multivariate analysis, high expression of p-RPS6KB1 (HR 3.02, p=0.03) and p-EIF4EBP1 (HR 2.77, p=0.037) was associated with shorter OS in metastatic pts.

Conclusion: Expression of MTOR and its downstream effectors, including p-RPS6KB1 and/or p-EIF4EBP1 appear to be associated with clinical outcomes in patients with NET. In addition to studies confirming these observations, specific studies investigating whether these markers may also be associated with response to MTOR inhibitors are warranted.