PI3K-AKT-mTOR Pathway Disregulation and its Correlation with Clinical Outcome in Patients with Advanced Neuroendocrine Tumors Treated with Everolimus

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Background: Everolimus (Eve) has been approved in patients with advanced, progressive, well/moderately differentiated pancreatic-neuroendocrine-tumors (pNETs). To date no clear biomolecular predictive factors to Eve have been reported in NETs. This is a retrospective analysis to correlate some biomolecular factors and clinical outcomes in patients with advanced gastroenteropancreatic (GEP) NETs treated with Eve as compassionate use.

Methods: all patients received Eve 10 mg once daily per os until disease progression or unacceptable toxicity. Immunohistochemical 0-5 (<3 = negative, > 3 = positive) staining score was used for PTEN, pAKT, pmTOR, p70S6K, pS6K, p4-EBP1; PCR-based exons 7 and 9 PI3K mutations were evaluated.

Results: 36 patients with metastatic NETs histologically confirmed by two expert pathologists, M.B. and E.P. were included. The primary tumor was: pancreas in 21 patients (58%), ileum in 10 (28%), other in 5 (14%). More than 90% were pretreated. Ten patients were refractory (PFS < 6 months) and 15 long responders (PFS > 1 year) to Eve. Ki67 and pmTOR were available in 36/36 (100%) patients: Ki67 was ≤20% in 30 patients and >20% in 6. The median PFS was 11 months (95% C.I.: 6, 18) for all patients, 11 (95% C.I.: 6, 19) for pancreatic, and 12 (95% C.I.: 2.7, -) for ileal. Global overall survival was 42 months (20, N.R.). In the ≤20% Ki67 group there was a statistically significant correlation for 0 vs. >0 pmTOR, with PFS 8.9 vs. 18.7 months (p = 0.043). Whereas no significant correlation occurred for negative/positive pmTOR, PTEN, p4-EBP1. No PI3K mutations were detected.

Conclusion: We observed a statistically significant correlation between 0/>0 pmTOR and PFS in patients with ≤ 20% Ki67 metastatic NETs. These results warrant a prospective investigation in a homogenous NETs population, in order to validate the predictive value to Eve and a reproducible score.