

Prognostic Significance of CDKN1B (p27) Expression in Gastroenteropancreatic Neuroendocrine Tumors

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Background: CDKN1B is a cyclin dependent kinase inhibitor that has been implicated in regulating tumor growth; loss of CDKN1B expression has been associated with poor prognosis in various human malignancies. Somatic mutations in *CDKN1B* have been reported in a subset (8%) of small intestinal NETs (SINETS). However, the clinical significance of expression and mutation of *CDKN1B* in patients with gastroenteropancreatic neuroendocrine tumors (GEP NETs) has not been defined.

Methods: We evaluated CDKN1B expression in 144 patients with GEP NETs and correlated expression levels with mutational status and with overall survival after adjusting for other clinical prognostic variables using Cox proportional hazards regression models. Immunohistochemical expression was scored according to the percentage of tumor nuclei expressing CDKN1B protein.

Results: Reduced expression (nuclear staining < 50%) of CDKN1B was detected in 18% (26/144) primary GEP NETs (19 /111 SINETS, 3/19 pancreatic NETs, and 4/15 other GEP NETs; respectively). Among 111 primary SI NETs, low expression of CDKN1B was associated with shorter overall survival (OS) (multivariate HR 2.72, p=0.017). In the cohort of patients with metastatic SINETS (n=75), low expression of CDKN1B was also associated with shorter OS (multivariate HR 2.87, p=0.016). Mutational status had previously been determined in 45 primary SINETS; of these, 5/45 had *CDKN1B* mutations. We did not observe a clear correlation between reduced CDKN1B expression and mutation of *CDKN1B*. However, mutation of *CDKN1B* (observed in 4/34 patients with metastatic SINETS) was potentially associated with worse OS (multivariate HR 3.48, p=0.065) in patients with metastatic SINETS.

Conclusion: Low expression, and potentially mutation, of CDKN1B appears to be associated with poor prognosis in gastroenteropancreatic neuroendocrine tumors.