C-36

Grade Progression and Morphologic Transformation in Neuroendocrine Tumors: A Single-Institution Retrospective Analysis

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BACKGROUND

Well-differentiated neuroendocrine tumors (NETs) may undergo grade progression over time, often accompanied by increasing Ki-67 and worse outcomes. Rarely, these tumors transform into poorly differentiated, neuroendocrine carcinoma (NEC)-like phenotypes, but the clinicopathologic and molecular features of this process remain poorly defined.

METHODS

We queried our IRB approved institutional pathology database for patients with two tumor specimens obtained ≥12 months apart, at least one demonstrating grade 3 NET, NEC, or high-grade neuroendocrine neoplasm, with at least one specimen reviewed at our center. Patient demographics, clinical features such as tumor primary site, types of treatment, pathologic features such as tumor differentiation, Ki-67, mitoses, p53/RB status, next-generation sequencing (NGS) when available, and survival outcomes were abstracted. Overall survival (OS) was estimated by Kaplan-Meier methodology, measured from the date of grade change to death or last follow-up.

RESULTS

Paired specimens were available for review in 35 of 43 eligible patients. Primary tumor sites included pancreas in 28 patients (65.1%), small intestine in 11 (25.6%), and other sites in 4 (9.3%; lung n=2, rectum n=1, kidney n=1). Over a median interval of 62 months, median Ki-67 increased from 7.5% to 39.3% in the entire cohort. Most patients (37/43, 86.0%) retained well-differentiated morphology at progression, whereas 3 patients (7.0%) demonstrated poorly differentiated or NEC-like morphology and an additional 3 (7.0%) had ambiguous or indeterminate differentiation. Notably, all 6 patients with NEC-like or indeterminate transformation had pancreatic primaries and were characterized by higher Ki-67 indices (median 74.5%) and greater prior treatment exposure compared to those retaining well-differentiated morphology (median 3 prior systemic therapies vs 2). Next-generation sequencing at the time of grade change was available in 26 patients

(60.5%), revealing *TP53* mutations in 11 (42.3%) and *RB1* alterations in 2 (7.7%). MSI-high or high tumor mutational burden was identified in 4 patients (15.4%), all with pancreatic primaries. Therapies received prior to grade change included somatostatin analogs (38/43, 88.4%), radioligand therapy (24/43, 55.8%), and CAPTEM (16/43, 37.2%). The median number of therapies before grade change was three in both pancreatic and small intestinal NETs. Following grade progression or transformation, platinum-based chemotherapy (14/43, 32.6%) and immunotherapy (5/43, 11.6%) were used more frequently. Median overall survival from initiation of first therapy after grade change was 38.5 months.

CONCLUSIONS

Grade progression in NETs is characterized by marked increase in Ki-67, but most often retains well-differentiated morphology, supporting grade escalation and dedifferentiation as distinct biologic processes. True NEC-like transformation was uncommon, restricted to pancreatic primaries, and enriched for *TP53* alterations.

ABSTRACT ID #36633