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TP53 Mutation Portends a Worse Overall Survival in Patients with Advanced Grade 3 Well-Differentiated Neuroendocrine Tumors

Nancy Joseph[1], Alan Paciorek[2], Bryan Khuong Le[3], Farhana Moon[3], Li Zhang[2], Emily Bergsland[4].

[1]Department of Pathology, University of California San Francisco, San Francisco, CA, USA; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [3]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA.

BACKGROUND

The well-differentiated grade 3 neuroendocrine tumor (G3NET) category was introduced in the 2017 WHO classification as a new category of high-grade neuroendocrine neoplasm (NEN). G3NET is thought to have worse overall survival (OS) than lower grade NET, but better OS than poorly differentiated neuroendocrine carcinoma (NEC). However, challenges in pathologic diagnosis and changes in terminology have limited our understanding of the G3NET category. We compared outcomes in patients with metastatic and high grade gastroenteropancreatic NEN and assessed whether specific mutations had an impact on outcomes.

METHODS

We performed an IRB-approved retrospective chart review of 134 patients with high grade metastatic NEN, formal pathology review at UCSF, and tumor DNA sequencing performed in the context of clinical care. Pathology reports and clinical histories were re-reviewed by a single pathologist and cases were best re-classified as NEC, NET or ambiguous G3NEN. OS, defined from the time of high grade and metastatic NEN diagnosis to death or last follow-up, is measured using Kaplan-Meier methods, and log-rank test is used to compare across G3NET, NEC, and ambiguous G3NEN.

RESULTS

Of the 134 patients, 56 (42%) had NEC, 33 (25%) had G3NET, and 45 (34%) had ambiguous NENs. The median age was 61 and 41% were female, with no differences in NEC versus G3NET versus ambiguous G3NEN. Site of origin was pancreas (n=46, 34%), colorectum (n=30, 22%), other gastrointestinal (n=24, 18%) and unknown (n=34, 25%). The most common recurrently altered genes in NEC were *TP53* (75%), *RB1* (39%), *KRAS* (29%), *APC* (25%), *MYC* (11%), and *CDKN2A* (9%). G3NET demonstrated frequent alterations in *MEN1* (49%), *DAXX* (21%), *ATRX* (9%), *TSC1* or *TSC2* (18%) *SETD2* (18%), *CDKN2A* (18%), and *TP53* (21%). Ambiguous G3NEN had frequent alterations in *TP53* (53%), *RB1* (31%), *CDKN2A* (29%), *APC* (18%), *MEN1* (13%), *KRAS* (9%), and *ARID1A* (9%). Median OS among G3NET (20 months, 95% CI 10-not calculable), NEC (17 months; 95% CI 10-21), and ambiguous G3NEN (15 months, 95% CI 12-40) was not statistically different (log-rank p=0.411).

However, patients with G3NET harboring mutation in TP53 had significantly worse OS (6 months, 95% CI 2-NC) than those without mutation in *TP53* (25 months, 95% CI 16-NC; p=0.021).

CONCLUSIONS

There is potential to use *TP53* mutation status for prognosis of advanced G3NET. Validation of these findings in a larger cohort is needed. Ongoing work is focused on investigating the prognostic value of other mutated genes in this cohort of high grade NEN.

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