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Prognostic significance of B7H3, DLL3, and survivin expression in neuroendocrine neoplasms

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BACKGROUND

B7-H3, DLL3, and survivin are emerging therapeutic targets in neuroendocrine neoplasms (NENs), but their prognostic significance remains unclear. We evaluated their expression in NENs and their association with survival and tumor grade.

METHODS

We analyzed 42 patients with NENs who underwent IHC staining for B7-H3, DLL3, and survivin. Tumors were classified according to the WHO 2019/2022 grading system (G1-G3). B7-H3 and DLL3 were evaluated using exploratory thresholds due to lack of validated cut-offs (1-50% for B7-H3; 1% and 50% for DLL3), while survivin positivity was defined as ≥1%. Because isolated B7-H3 expression was common whereas DLL3 and survivin were less frequent and associated with worse disease, patients were stratified into three groups based on 1% positivity: Group 1 (all biomarkers negative), Group 2 (B7-H3-positive only), and Group 3 (other biomarker combinations). OS and PFS were analyzed using Kaplan-Meier methods and Cox proportional hazards models. Multivariable analyses adjusted for primary tumor site, stage, prior chemotherapy and radiation. Associations with tumor grade were evaluated using proportional odds models.

RESULTS

Gastrointestinal tumors comprised 62% of cases, 36% had stage III-IV disease, and 48.8% had grade 3 disease. Median follow-up was 106 months. B7-H3 positivity was in 64% of tumors at the 1% cutoff and 33% at 50%, while DLL3 and survivin positivity were 27% and 26%, respectively. Survivin positivity was associated with worse OS (HR 2.82, p=0.041), while DLL3 (HR 2.39, p=0.057) and B7-H3 > 50% (HR 2.70, p=0.073) showed trends toward worse OS. Compared with Group 1, Group 2 had worse OS (HR 6.54, 95% CI 1.17-36.5, p=0.032) and PFS (HR 12.8, 95% CI 1.60-103, p=0.016). Group 3 (17 patients, 40.5%) had the worst outcomes (OS HR 19.3, 95% CI 4.17-88.9, p<0.001; PFS HR 26.8, 95% CI 4.13-174, p<0.001). Grade 3 disease occurred in 76.5% of Group 3. Within Group 3, patients positive for all 3 biomarkers were more likely to have grade 3 disease. Higher B7-H3 and survivin expression correlated with higher tumor grade (p=0.008 and p=0.047, respectively).

CONCLUSIONS

Combined B7-H3, DLL3, and survivin expression identified patients with worse survival after adjusting for clinicopathologic factors, while higher B7-H3 and survivin expression correlated with higher tumor grade. These findings support their potential as prognostic biomarkers and as candidates for targeted therapies. Prospective validation in larger cohorts is warranted to establish NEN-specific cutoffs, characterize expression heterogeneity, and determine prognostic value across disease stages.

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