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Comparison of Well-differentiated Gastroenteropancreatic Grade 3 Neuroendocrine Tumors (G3NETs): De Novo and In The Setting of Apparent Grade Progression Over Time

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BACKGROUND

G3NETs demonstrate variable clinical behavior (Ki-67>20-100%). Treatment extrapolated from grade 1/2 (G1/2) NETs and neuroendocrine carcinomas depending on clinicopathologic features. Therapy for treatment-emergent G3NETs remains especially ill-defined.

METHODS

Retrospective chart review of patients with de novo G3NETs or progressing from low-to-high grade (L-H) (G1/2 at diagnosis and G3 >=3 months later). Treatment patterns compared by Pearson chi-squared tests among patients with complete treatment information. Overall survival (OS) from stage IV G3NETs diagnosis estimated by Kaplan-Meier.

RESULTS

N=50 patients with G3NETs: 18% nonwhite, 46% female, median age at G3 62 (29-81). Primary site: pancreas 60%, other gastrointestinal 22%, unknown 18%. Median follow-up from stage IV G3 48 months (mo). *De novo* G3NETs in 38% (19/50) with median Ki-67 30% (range 21-70%), Ki-67<=55% in 79%. Among these, 89% (17/19) stage IV and 11% (2/19) locoregional at diagnosis (treated surgically before developing metastases). Median OS was 35 mo (95% CI 20-54).

L-H G3NETs in 62% (31/50): median Ki-67 at G3 diagnosis 38% (21-75%), Ki-67<=55% in 87%. Among these, 77% (24/31) stage IV at G1/G2 diagnosis. Median time to L-H 58 mo (range 3-391 mo); 97% (30/31) stage IV. Therapy prior to G3 diagnosis: SSA 81%, surgery 48%, liver-directed therapy (LDT) 41%, cytotoxic chemotherapy (CC) 39%, radiation 32%, peptide receptor radionuclide therapy (PRRT) 29%, and targeted agents (e.g. everolimus, sunitinib) 26%. Median OS 16 mo (95% CI 9-22). Treatment for advanced G3 listed in Table 1.

Table 1: First-line (1L) and second-line (2L) treatment for metastatic G3NETs (N=44)

	De novo G3NETs (N=19)	L-H G3NETs (N=25)		
	1L,N(%)	2L,N(%)	1L,N(%)	2L,N(%)
SSA^	**9(47)**	0	**1(4)**	0
Cisplatin/carboplatin-based	8(42)	3(16)	4(16)	2(8)
Other CC*/Immunotherapy	0	7(37)	4(16)	5(20)
Everolimus	0	0	0	2(8)
PRRT	0	1(5)	2(8)	1(4)
Radiation	0	1(5)	2(8%)	3(12)
LDT	0	3(16)	6(24)	4(16)
Surgery (primary or metastasis)	2(11)	2(11)	6(24)	2(8)

*capecitabine/temozolomide, FOLFOX

^Pearson chi-squared test indicated significant differences in 1L ($p<0.001$)

CONCLUSIONS

Higher prevalence of L-H compared to *de novo* G3NETs was observed at our institution. While there is extensive overlap, *de novo* G3NETs more commonly treated with SSA. Further research is needed to compare the outcomes and molecular underpinnings of apparent de novo G3NETs vs L-H, and the impact of primary tumor site, Ki67, and prior therapy. Understanding these differences will help elucidate whether these subtypes are truly distinct entities (with one being treatment-emergent) or simply reflect the natural history of the disease and intrapatient heterogeneity.

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