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Survivin and DLL-3 as predictors of survival in low-grade neuroendocrine tumor patients

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BACKGROUND

Neuroendocrine tumors (NETs) are increasing in incidence, but treatment options are limited. Emphasis on novel targeted agents and somatostatin receptor directed therapies is needed. To this end, we explored the expression of anti-apoptosis protein – survivin, and notch pathway regulator - DLL-3 in NETs as there are now agents to target these proteins in other clinical settings (glioblastoma multiforme and small cell lung cancer). They are being explored in high grade neuroendocrine carcinomas, but have not yet been well elucidated in low grade NETs as potential targets. We studied these biomarkers and correlated them with survival outcomes.

METHODS

With IRB approval, grade 1 and 2 NET patients who received chemotherapy: Temozolomide-based therapies, Everolimus, somatostatin analogous (SSAs) or Peptide Receptor Radionuclide Therapy (PRRT) and had survival follow-up of 3 years or longer were included. Their retrospectively banked tissue samples were stained for expression of survivin and DLL-3 using standardized methods. Correlation with 3-year overall survival (OS) was done in blinded fashion.

RESULTS

Twenty-five patients with NETs were included. Median age at diagnosis was 63.8 years (range: 46.1-79.7) and 52% were female. Primary tumor sites were lung (n=3), unknown (n=1) and gastrointestinal (GI) (n= 21). Survivin and DLL3 status was available for 24 and 20 patients respectively (missing cases had insufficient tumor cells for staining). Four patients had positive survivin staining: pancreas (n=2), colorectal (n=1), GI (n=1). Two patients had positive DLL3 expression: pancreas (n=1), lung (n=1). No patients were positive for both. The 3-year OS rate in survivin positive patients was lower than survivin negative patients [0.50 (95% CI 0.06- 0.84) vs 0.71 (95% CI 0.44- 0.87)], but this didn't reach significance. The 3-year OS rate for the two DLL3 positive patients was higher than that of the 18 DLL3 negative patients. [1.00 (95% CI 1.00-1.00) vs 0.82 (95% CI 0.54-0.94)]

Table 1: 3-year OS rates by survivin, DLL-3 and treatment regimen:

		3-yr OS Rate (95% CI)
Total		0.68 (0.43, 0.83)
Survivin	Negative (n= 20)	0.71 (0.44, 0.87)
	Positive (n =4)	0.50 (0.06, 0.84)
DLL3	Negative (n=18)	0.82 (0.54, 0.94)
	Positive (n=2)	1.00 (1.00, 1.00)
Chemo	Temozolomide + Capecitabine (n=14)	0.74 (0.38, 0.91)
	Temozolomide (n=1)	1.00 (1.00, 1.00)
	Everolimus (n=6)	0.67 (0.19, 0.90)
	None (n=4)	0.38 (0.01, 0.81)
Hormone	None (n=5)	0.75 (0.13, 0.96)
	Lanreotide (n=8)	0.50 (0.11, 0.80)
	Octreotide (n=1)	1.00 (1.00, 1.00)
	Sandostatin (n=11)	0.73 (0.37, 0.90)

CONCLUSIONS

Survivin and DLL3 can be therapeutic targets in NETs. Survivin positivity is more frequent in NECs, but can also be seen in low grade NETs and is correlated with lower 3-year OS. Larger studies are needed to explore therapeutic response to currently approved agents in these subsets.

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