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Identification of Response Predictors to Capecitabine/Temozolomide in Metastatic Pancreatic Neuroendocrine Tumors

Mauro Cives[1]; Masoumeh Ghayouri[1]; Marjorie Brelsford[1]; Michael Black[1]; Anthony Rizzo[2]; Alan Meeker[2]; Jonathan Strosberg[1]

[1]H. Lee Moffitt Cancer Center and Research Institute, 33612 – Tampa, FL, USA
[2]Johns Hopkins University School of Medicine, 21231 – Baltimore, MD, USA

Background: Capecitabine and temozolomide (CAPTEM) are active in the treatment of metastatic pNETs, with response rates ranging from 30% to 70%. Several small retrospective series have suggested that MGMT deficiency may predict response to temozolomide, however expression of MGMT has not been validated as a predictive biomarker. Cytotoxic chemotherapy is thought to be most active in aggressive tumors, however the ki-67 index has not been formally evaluated as a predictive factor. It is unclear whether chromosomal instability (which correlates with alternate lengthening of telomeres) predicts response.

Methods: 143 patients with metastatic pNET who underwent treatment with CAPTEM were retrospectively evaluated for radiographic and biochemical response as well as survival outcomes. The predictive/prognostic role of tumor grade, ki-67% and MGMT by IHC as well as ALT activation by FISH was assessed on up to 128 evaluable archival specimens. Frequently altered genes in pNETs were also sequenced and their status was correlated to the radiographic response.

Results: Treatment with CAPTEM was associated with partial response and stable disease by RECIST 1.1 in 54% and 35% of patients respectively. On waterfall plot analysis, 78% of patients showed some degree of tumor shrinkage. Major reductions (>50%) in CgA levels were recorded in 61% of cases. After a median of 9 cycles of treatment and a follow-up duration ranging from 5.6 to 112.8 months, the median OS was 73.2 months (95% CI, 51.9-81.1 months), while the median PFS was 17 months (95% CI, 15-25 months). Response to CAPTEM was not significantly influenced by tumor grade (p=0.19), mitotic count (p=0.06) or ki67% (p=0.1). MGMT status (p=0.1) and ALT pathway activation (p=0.37) were not predictive of response. Low mitotic rate (p=0.007) and ALT-positive phenotype (p=0.02) were significant predictors of better prognosis.

Conclusions: CAPTEM is an effective treatment regimen in pNETs. MGMT status appears to have no correlation with response.

Table . Candidate biomarkers in pNETs.

Criteria of stratification	ORR (%)	*P*	PFS, 95% CI (months)	*P*	OS, 95% CI (months)	*p*	Major biochemical response (%)	*P*
Grade		.19		.83		.84		.7
1	65		16.8 (15.4-24.3)		72.1 (48.6-81.1)		64	
2	52		14.5 (10-14.5)		67.4 (35.2-73.2)		72	
3	69		24.6 (22.6-24.6)		76.2 (17.8-76.2)		78	
Mitotic count/10 HPF		.06		.58		.007		.03
<2	54		17.4 (15.4-24.3)		74.8 (36.4-81.1)		64	
2 <MC<20	50		16.8 (9.8-24.6)		73.2 (31.5-73.2)		74	
>20	50		NR		14.6 (11.4-14.6)		100	
Ki-67 labeling index		.10		.27		.61		.74
>3%	65		NR		35.2 (33.6-35.7)		90	
Between 3% and 20%	50		NR		73.2 (42.2-81.1)		67	
>20%	42		14.5 (10-24.6)		76.2 (17.9-76.2)		71	
MGMT status		.10		.25		.40		.66
MGMT-intact	65		16.8 (14.5-16.8)		NR		67	
MGMT-deficient	40		14.5 (6.2-14.5)		81.1 (73.2-81.1)		50	
ALT status		.37		.38		.02		.66
ALT-positive	63		NR		NR		77	
ALT-negative	47		14.5 (10.2-16.8)		36.4 (30.1-81.1)		70	
DAXX/ATRX status		.34		.35		.13		.27
Positive	52		16.3 (14.5-16.8)		48.7 (34.5-48.7)		53	
Negative	69		NR		NR		75	

HPF: High-powered field, NR: not reached.