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Neoadjuvant Capecitabine/ Temozolomide for Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors

Malcolm Squires[1]; Patrick Worth[2]; Bhavana Konda[3]; Manisha Shah[1]; Mary Dillhoff[1]; Sherif Abdel-Misih[1]; Timothy Pawlik[1]; Carl Schmidt[1]; George Poultsides[2]; Jordan Cloyd[1]

[1]The Ohio State University; [2]Stanford University; [3]The Ohio State University Comprehensive Cancer Center

BACKGROUND: Recent evidence has demonstrated the efficacy of the chemotherapy regimen capecitabine and temozolomide (CAPTEM) in the treatment of metastatic well-differentiated pancreatic neuroendocrine tumors (PNETs). However, the role of CAPTEM in the neoadjuvant setting has not been established.

METHODS: All patients with locally advanced or resectable metastatic PNETs who received CAPTEM with neoadjuvant intent between 2009-2017 at 2 high-volume academic centers were retrospectively reviewed. Radiographic response was assessed according to RECIST 1.1 criteria and predictors of response were measured by logistic regression.

RESULTS: Thirty patients with either locally advanced PNET (n=10) or pancreatic neuroendocrine hepatic metastases (n=20) underwent neoadjuvant CAPTEM therapy, receiving a median of 4 cycles (IQR, 3-8 cycles). Overall, 13 patients (43%) exhibited a partial response (PR) whereas 16 (54%) had stable disease and 1 patient (3%) developed progressive disease. Twenty-six (87%) patients underwent resection (pancreatectomy [n=12], combined pancreatectomy and liver resection [n=8], or major hepatectomy alone [n=6]); 3 (18%) declined surgery despite experiencing a PR, and 1 (3%) underwent an aborted pancreatoduodenectomy due to cirrhosis. Median PNET primary tumor size on

final pathology was 5.5cm (IQR, 3.3-9.3cm), and the median Ki-67 index was 3.5% (IQR, 1-8%). Rates of PR were similar (p=0.24) across WHO tumor grades (Table 1): Grade 1 (58%), Grade 2 (31%), and Grade 3 (40%). At a median follow-up of 49 months for the cohort, the median progression-free survival for all patients was 28.2 months, and the 5-year overall survival was 63%. A decrease of >50% in the pre-treatment serum value of the tumor markers pancreatic polypeptide or pancreastatin was associated with PR (p=0.02), while Ki-67 and tumor grade were not significantly associated with radiographic response.

CONCLUSION: Neoadjuvant CAPTEM is associated with a favorable radiographic response rate for locally advanced or metastatic PNET and may facilitate the selection of patients appropriate for surgical resection.

Table 1. Objective radiographic response rates (RECIST 1.1) stratified by WHO Grade

	PR	SD	PD
All patients (n=30)	13 (43%)	16 (53%)	1 (3%)
WHO Grade 1 (n=12)	7 (58%)	5 (42%)	0
WHO Grade 2 (n=13)	4 (31%)	9 (69%)	0
WHO Grade 3 (n=5)	2 (40%)	2 (40%)	1 (20%)