Introduction: Tumor O6-methylguanine-methyltransferase (MGMT) reverses temozolomide-induced DNA injury, and low MGMT tumor expression has been shown as a predictor of response to temozolomide in glioblastoma. C/T therapy induces partial responses in up to 70% of pts with grade 1-2 pancreatic NEN (1), but the role of MGMT expression as a predictor is unclear. We evaluated MGMT expression by IHC as a prognostic and predictive biomarker for pts with aNEN of all grades and primary sites treated with C/T.

Methods: A retrospective review was carried out at Ohio State University of 29 pts with aNEN receiving C/T therapy from 2009 to 2013 and evaluable for RECIST response. MGMT expression was assessed when available by IHC on pre-treatment tumor samples to test the hypothesis that low MGMT expression (<10%) predicts response to C/T therapy vs high levels (≥10%).

Results: Of 29 pts, primary tumor site was pancreas in 18 pts, and non-pancreas in 11 pts. Progression-free survival (PFS), overall survival (OS), and best overall response data are outlined in Tables 1 and 2, respectively. Partial response (PR) rate was 50% in pts with pancreas primary vs 18% for non-pancreas primary. High PRs were observed in pts with grade 3 NEN (57%). Median PFS in the MGMT-low group was 16.6 months vs 9.5 months in the MGMT-high group (p=0.19). Median OS in the MGMT low group was 42.9 months vs 18.1 months in the MGMT-high group (p=0.16). There was a trend toward higher rate of PR (63%) in pts whose tumors had low levels of MGMT expression compared to those with high levels (17%) (p=0.10).

Conclusion: We observed a trend towards increased PR, median PFS, and median OS in aNEN pts whose tumors had low MGMT protein expression by IHC. The small sample size likely limited the statistical significance of the data. Results of this trial serve as strong rationale for future prospective trials to clarify role of MGMT expression in choosing C/T therapy for pts with NEC.

Objectives

• To determine whether MGMT expression by IHC can be used to predict response to treatment in patients with aNEN treated with C/T combination therapy
• To determine best overall response rate, PFS, and OS for patients with aNEN treated with C/T combination therapy
• To assess response rates among patients not previously evaluated with this regimen, including patients with NECs of non-pancreatic origin as well as patients with high grade tumors.

Background

Neuroendocrine neoplasms (NENs) are a diverse group of tumors than range from the fast growing small cell lung cancer to the slower growing well-differentiated gastroenteropancreatic NENs. Treatment options are limited and palliative in nature for patients with all types of metastatic NEN. C/T therapy has been evaluated in patients with well-differentiated pancreatic NENs (1-4), however little data is available to guide treatment for pancreatic and non-pancreatic NENs. MGMT deficiency has been evaluated in patients receiving temozolomide therapy (5-6), but its role in the use of C/T combination therapy is unclear.

Methods

A retrospective review was carried out of 29 patients who were treated with combination capecitabine and temozolomide for metastatic neuroendocrine carcinoma between 2009 and 2013 and evaluable for RECIST response, including 18 (62%) pancreatic and 11 (38%) non-pancreatic NEN. Patients were included regardless of prior therapies, including prior chemotherapy regimens and targeted therapies. Treatment regimen consisted of capecitabine 1500 mg/m2/day in a 2-week cycle.

Results

Figure 1: MGMT IHC. MGMT IHC was available for 20 patients. Representative slides are presented in the figure, demonstrating low (A), intermediate (B), and high (C) MGMT expression by IHC. Thresholds for expression were set as <10% for low, 10-49% for intermediate, and ≥50% for high MGMT expression.

Table 1: Progression free survival (PFS) and overall survival (OS). Median PFS and OS in the entire cohort, and compared by MGMT expression and WHO tumor grade. WHO tumor grade and Ki-76% was available for 27 patients.

Table 2: Overall response rates by MGMT expression and WHO tumor grade. A higher response rate was observed among patients with low MGMT expression by IHC.

Conclusions

• We observed a trend towards increased PR, median PFS, and median OS in aNEN pts whose tumors had low MGMT protein expression by IHC.
• We observed increased two year survival rates of patients with low MGMT expression compared to intermediate or high expression.
• C/T therapy showed activity in patients with poorly differentiated tumors as well as tumors of pancreatic and non-pancreatic origin.
• Results of this trial serve as strong rationale for future prospective trials to clarify role of MGMT IHC expression in choosing C/T therapy for pts with NEC.

References


Figure 3: Waterfall plot. Maximum percent change from baseline in the sum of the diameters of target lesions, by Ki-67% and MGMT IHC low (L) or intermediate/high (H). Patients with well-differentiated tumor histology but unknown Ki-67% were marked with (*).