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Capecitabine Plus Temozolomide (CAP-TEM) in Patients with Advanced Neuroendocrine Tumors (NETs): An Italian Multicenter Retrospective Analysis

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Background: A combination of capecitabine (CAP) and temozolomide (TEM) has been successfully used as first-line treatment in low-grade pancreatic neuroendocrine tumors (pNETs). We reviewed activity and toxicity of the same regimen in patients with advanced NETs with different primary and grading.

Methods: Clinical data of patients who had received oral CAP 1500 mg/m2/day over 14 days bid plus oral TEM 150-200 mg/m2/day on days 10-14 of each 28-day cycle, were retrospectively reviewed. The methylenguanilmetiltransferase (MGMT) methylation-status (MGMT-gene $\geq$5% = responders) and TS-polymorphisms (2R/2R, 2R/3R = responders, 3R/3R = non-responders) in tumor-tissue/peripheral-blood were evaluated by pyrosequencing.

Results: Since March 2012, 26 patients were selected. The primary tumor was: pancreas in 13 patients (50%), gastrointestinal (GI) in 3 (11%), unknown in 2 (8%), lung in 8 (31%). According to 2010 WHO classification, Ki67 was 3-20% (G2) in 42% patients, >20% (G3) in 23% with two "low G3" (Ki67 21-30%), and unknown in 4%. Among lung: 8% typical and 23% atypical (Travis' classification). 73% patients (19/26) were progressive on different therapies: peptide-receptor-radiotherapy (58%), everolimus (26%). Partial-response (PR) occurred in 15% (4/26) of patients (95% CI: 4-35), stable-disease (SD) in 65% (17/26) (95% CI: 44-83) mainly pNET. The two "low G3" responded. Disease control rate (PR+SD): 80% (95% CI: 60-93). Median TTP: 8 months (95% CI: 0.46-N.E.). Thrombocytopenia was the most frequent grade 3 toxicity, always temporary. All 4 PR patients had genotype 2R/3R-2R/2R investigated for the 28 base-pair (bp) variable number of tandem repeats (VNTR) in the 5'UTR of the TS-gene, and MGMT-gene inactivation by epigenetic silencing.

Conclusions: This analysis suggests that CAP-TEM chemotherapy could be active and well tolerated in pre-treated patients with advanced NETs of different origins and grading. This warrants a prospective investigation in a more homogeneous population (G2 and "low-G3" GEP NETs or lung carcinoids), in order to validate the predictive value of MGMT methylation-status and TS-polymorphisms.