

## posters

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### 5-Fluorouracil Degradation Rate in Patients with Recurrent Gastrointestinal Cancer Treated with Metronomic Capecitabine

M. Roberto<sup>1</sup>, A. Romiti<sup>1</sup>, L. Lionetto<sup>2</sup>, C. D'Antonio<sup>1</sup>, C. Onesti<sup>3</sup>, A. Botticelli<sup>3</sup>, A. Milano<sup>1</sup>, R. Falcone<sup>3</sup>, M. Occhipinti<sup>3</sup>, F. Mazzuca<sup>3</sup>, M. Simmaco<sup>4</sup>, P. Marchetti<sup>1</sup>

<sup>1</sup>La Sapienza University, Sant'Andrea Hospital, Rome, Italy

<sup>2</sup>Istituto Dermatologico dell'Immacolata, Rome, Italy

<sup>3</sup>University La Sapienza, Sant'Andrea Hospital, Rome, Italy

<sup>4</sup>University La Sapienza, Rome, Italy

**Introduction:** 5-Fluorouracil (5-FU) is the milestone chemotherapeutic drug for the treatment of the gastrointestinal tract (GI) tumours. Dihydropyrimidine dehydrogenase (DPD) is the key enzyme involved in 5-FU catabolism. DPD deficiency may often subtend the development of severe toxicities in patients treated with a fluoropyrimidine-based chemotherapy. The degradation rate of 5-FU is a phenotypic marker of the 5-FU metabolism. We have recently described a correlation between DPD gene (DPYD) polymorphism and 5-FU degradation rate [1]. Moreover, patients with altered 5-FU degradation rate showed high prevalence of severe toxicities after a fluoropyrimidine-based chemotherapy [2]. Thus, 5-FU degradation rate has been suggested as a putative biomarker of 5-FU fluorouracil toxicity. In detail, patients with a value below the 5th centile (poor metabolism - PM) or above the 95th centile (ultra-rapid metabolism - UM) experienced a higher incidence of grade 3-4 toxicity compared with those patients whose 5-FU degradation rate was within 5-95th centile

(0.85-2.2 ng/ml/10<sup>6</sup> cells/min). Data about 5-FU degradation rate and outcome of metronomic capecitabine (mCAP) in patients with GI cancer are still lacking. The aim of the study was to explore the relationship between the 5-FU degradation rate and toxicity of low dose capecitabine in pretreated patients with GI cancer.

**Methods:** Eighty-four patients with recurrent GI cancer treated with mCAP (1500 mg per day) (48 male, 36 female; median age: 69 years, range: 30-85; 41 colon cancer, 16 rectum, 13 gastric and 14 pancreatic adenocarcinoma) were included in this analysis. Patients had performed the 5-FU degradation rate before starting the treatment. 5-FU degradation rate was assessed with a high-performance liquid chromatography-tandem mass spectrometry instrument as previously reported [3]. Freshly prepared peripheral blood mononuclear cells (2.5-3.5 x10<sup>6</sup> Cells) are incubated at 37°C, shaking, with a known amount of 5-FU. Cell aliquots are drawn at time 0, 1 and 2 h, lysed and centrifuged, and the concentration of 5-FU in the supernatants is quantified. The 5-FU degradation rate was expressed as ng FU ml<sup>-1</sup> per 10<sup>6</sup> cells per min and reported as mean ± SD.

**Results:** Seventy-six patients had completed at least one cycle of mCAP and were evaluable for toxicity. No grade 3-4 toxicity was reported. Twenty-seven patients (36%) had, at least, a grade 1-2 toxicity: 18 (23.6%) gastrointestinal, 6 (7.9%) haematological, 12 (15.8%) hand-foot-syndrome. Overall, the mean value of 5-FU degradation rate was 1.6 ± 0.3 ng/ml/10<sup>6</sup> cells/min. According to the above-defined range of 5-FU degradation rate, 3 patients resulted in PM and 2 UM. Two out 5 (40%) PM/UM patients showed grade 1-2 toxicities (1 anemia, 1 diarrhea) compared with 36% of normal metabolizers patients (p = 0.65).

**Conclusion:** mCAP showed a good toxicity profile in pretreated patients with GI cancer. On account of the lack of severe toxicity, a relationship between the 5-FU degradation rate and the occurrence of adverse events could not be observed. Further predictive biomarker for mCAP toxicity should be explored.