

## gastrointestinal tumours, colorectal

### 586P 5-fluorouracil degradation rate (5-FU-DR) as a new toxicity predictive biomarker for adjuvant FOLFOX in colorectal cancer (CRC) patients

C.E. Onesti<sup>1</sup>, A. Botticelli<sup>1</sup>, F. Mazzuca<sup>1</sup>, A. Milano<sup>1</sup>, A. Romiti<sup>1</sup>, M. Roberto<sup>1</sup>, R. Falcone<sup>1</sup>, M. Occhipinti<sup>1</sup>, F.R. Di Pietro<sup>1</sup>, L. Lionetto<sup>2</sup>, M. Simmaco<sup>3</sup>, P. Marchetti<sup>1</sup>

<sup>1</sup>Medical Oncology, Azienda Ospedaliera St. Andrea - Roma, Rome, Italy,

<sup>2</sup>Advanced Molecular Diagnostic Unit, Istituto Dermopatico dell'Immacolata, Rome, Italy,

<sup>3</sup>Advanced Molecular Diagnostic Unit, Sapienza – Università di Roma, Rome, Italy

**Background:** FOLFOX (5-FU, Oxaliplatin and Leucovorin) is the most effective treatment for CRC patients in adjuvant setting. However, the toxicity can lead to reduction, delay or discontinuation of treatment. DPD is the key enzyme involved in 5-FU catabolism and 5-FU-DR is a phenotypic parameter, reflecting the entire metabolism of 5-FU. We investigated the association between 5-FU-DR and genetic polymorphisms of TSER, DPYD, MTHFR and with toxicity in CRC patients treated with adjuvant FOLFOX.

**Methods:** We collected 126 blood samples before starting treatment. 5-FU-DR was determined by measuring the decrease of a fixed amount of 5-FU added to a solution of

Peripheral Blood Mononuclear Cells after 2 hours of incubation. Patients were classified as: poor metabolizers (PM: 5-FU-DR  $\leq$  0.85 ng/ml/10<sup>6</sup>cells/min); normal metabolizers (NM: 0.85 < 5-FU-DR < 2.2 ng/ml/10<sup>6</sup>cells/min); ultra-rapid metabolizers (UM: 5-FU-DR  $\geq$  2.2 ng/ml/10<sup>6</sup>cells/min). DNA pyrosequencing was used to detect gene polymorphisms of MTHFR, DPYD and TSER. Toxicities were classified according to CTCAE v 4.0. Statistical analysis was performed with SPSS2 software. Pearson's Chi Square test was used to correlate gene polymorphisms and 5-FU-DR with toxicities.

**Results:** We analyzed 126 resected CRC patients (91 M, 35 F; median age 65 y, range 36-81 y), receiving adjuvant FOLFOX. 7 patients were PM, 116 NM and 3 UM. Median 5-FU-DR was 1.495 ng/ml/10<sup>6</sup>cells/min (range 0.42-2.29). G3-4 toxicities were observed in 22.2% of the cases: 59.3% hematological, 29.6% gastrointestinal, 7.4% neurological and 3.7% others. A higher G3-4 toxicity incidence was observed in PM and UM than in NM group (71.4% and 33.3% respectively vs 19%; p = 0.05). PM and UM required more frequently dose reduction due to toxicity (71.4% and 66.6% vs 31%; p = 0.04). One case of DPYD heterozygous mutated was detected and it was associated with 5-FU-DR PM (p = 0.04) and G4 hematological toxicity (p = 0.06). No statistically significant associations between toxicities and TSER (p = 0.2), MTHFR C677T (p = 0.5) and MTHFR A1298C (p = 0.8) were observed.

**Conclusions:** 5-FU-DR seems to predict toxicity in resected CRC patients treated with 5-FU. Larger and perspective studies are required to implement this results.

**Legal entity responsible for the study:** N/A

**Funding:** University of Rome "Sapienza"

**Disclosure:** All authors have declared no conflicts of interest.