

## biomarkers

### 100P 5-fluorouracil degradation rate as a predictive toxicity biomarker in early stage gastrointestinal cancer

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**Background:** Prediction and early management of severe toxicity might avoid both therapy's interruption and the benefit loss of adjuvant chemotherapy. However, predictive toxicity biomarkers are not yet available. The aim of this study was to investigate whether polymorphisms of different genes involved in fluoropyrimidine metabolism and 5-fluorouracil (5-FU) degradation rate were associated with clinical outcome of oral fluoropyrimidine-based adjuvant chemotherapy in patients with early stage GI cancer.

**Methods:** Genotyping of DPYD IVS14 IVS 14 + 1 G > A, MTHFR C677T and A1298C SNPs were performed by pyro-sequencing technology. PCR analysis was used for genotyping TYMS-TSER. Using PBMC cells, we also evaluated the 5-FU degradation

rate, which determines the amount of drug consumed by cells in a time unit. Patients were categorized in two groups according to their value of 5-FU degradation rate: below the 5th centile (poor metabolism - PM) or above the 95th centile (ultra-rapid metabolism - UM) and within 5-95th centile (0.85-2.2 ng/ml/10<sup>6</sup> cells/min).

**Results:** One hundred forty-two patients with early stage colon (39%), rectal (28%), stomach (20%) and pancreatic (13%) cancer, treated with 5FU-based adjuvant monochemotherapy, were included in this retrospective analysis. Forty-three per cent of patients had a lymphnode-positive disease, and 37% received concomitant radiotherapy. Most of patients had an ECOG PS = 0-1. Seventy-four and 20% of the patients suffered from at least one G1-4 and G3-4 adverse events (12 hematologic, 24 GI, 12 HFS), respectively. Sixteen (11%) patients resulted abnormal 5-FU metabolizers. At a multivariate logistic regression analysis, an altered 5-FU degradation rate (<0.86>2.10) resulted significantly associated with both G1-4 hematologic (OR = 2.99, 95% CI 0.98-9.12, P = 0.05) and all grade 3-4 adverse events (OR = 4.39, 95% CI 1.40-13.80, P = 0.01). No correlation was reported between toxicity and each tested gene polymorphism.

**Conclusions:** Our study showed a statistically significant association between 5-FU degradation rate and both G1-4 hematologic and all G3-4 toxicities. Therefore, the 5FU-degradation rate may be considered as a putative, predictive biomarker of fluoropyrimidine-related toxicity.

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