# Fluoropyrimidine-related toxicity in gastrointestinal cancer patients. Assessment of risk factors.

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**Background**

Fluoropyrimidines (5-fluorouracil and capecitabine) represent the backbone of many chemotherapeutic regimens for the treatment of gastrointestinal cancers. However, a narrow therapeutic index characterizes these drugs. Major side effects are frequently observed, sometimes leading to patient death. Moreover, toxicity often implies treatment discontinuation or delayed drug administration.

A potential relationship between clinical and/or genetic characteristics and the development of side effects during fluoropyrimidine administration has been shown.

The aim of this study was the identification of clinical, pathological and pharmacogenetic factors related to the development of fluoropyrimidine-related toxicity in a retrospective cohort.

**Patients and methods**

157 patients affected by gastrointestinal neoplasms (colorectal and gastric cancers) treated with fluoropyrimidine-based chemotherapy (single agents or combinations mainly with platinums) were included. Fluoropyrimidine-related toxicity was evaluated by theNCICommonTerminologyCriteria for Adverse Events (NCI-CTCAE 4.03). Dihydropyrimidine dehydrogenase (*DYPD*) variants were analyzed by Sanger sequencing and TaqManallelicdiscrimination assay. Statistical correlations were performed by SPSS V.21 software. $P<0.05$ was considered statistically significant.

**Results**

The study of correlations between clinical, pathological factors and toxicity evidenced a relationship between development of toxicity (especially toxicity occurring during the first three cycles) and gender (greater in females vs males), chemotherapy regimen (greater in polychemotherapy vs monochemotherapy), and disease stage (greater in IV vs II-III stage).

Eighty-three patients (a cohort whose baseline characteristics were similar to those of the entire case series) were genotyped for *DYPD* polymorphisms, including three nonfunctional *DPYD* variants related to fluoropyrimidine toxicity (c.1905+1G>A, c.2846A>T and c.1679T>G) and the putative deleterious variant hapB3.

A statistically significant association was observed between gastrointestinal toxicity and *DPYD* c.1905+1G>A and c.2846A>T polymorphisms. In particular, these polymorphisms were associated with grade ≥2 toxicity ($p=0.004$ and $p=0.005$, respectively). *DPYD* c.1905+1G>A was also correlated with asthenia ($p=0.001$).

**Conclusions**

Our results confirm the role of clinical and pathological factors (e.g. gender, chemotherapeutic regimen, disease stage) in predicting the risk of fluoropyrimidine toxicity. These factors in addition to the genetic analysis of *DPYD* variants (e.g. c.1905+1G>A, c.2846A>T and c.1679T>G), could help in the development of a predictive algorithm of toxicity in patients with gastrointestinal cancer treated with fluoropyrimidine-based chemotherapy.