A possible association between *DPYD**2A and the onset of severe toxicity in patients treated with fluoropyrimidine: preliminary results and possible clinical implications

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BACKGROUND: 5-Fluorouracil (5-FU) and its pro-drug Capecitabine (CAPE) are widely used in the treatment of many malignancies, but approximately 10% of the patients suffer from severe or lethal fluoropyrimidines (FL)-induced toxicity. This may lead to a prolonged hospitalization period for recovery, and undesired treatment delays.
More than 80% of 5-FU is rapidly degraded and excreted in the urine.
Dihydropyrimidine dehydrogenase (DPYD) is the rate-limiting enzyme of the FL catabolic pathway. DPYD is subject to a wide inter-individual variability resulting in a range of enzymatic deficiencies that span from partial to complete loss of enzyme activity. The reasons for this deficiency can be various but it is clear that it is partly linked to DPYD genetic polymorphism.
*DPYD**2A (rs3918290) polymorphism consists of a G to A transition that lies in an exon/intron splice site leading to the omission of the exon 14 presumably resulting in a catalytically inactive enzyme. This rare polymorphism (allele frequency of about 1% in Caucasian population) is one of the most studied for its possible correlation with the onset of FL-related severe toxicities but it is also one of the most controversial because its phenotypic effect is not clear.

AIMS: The aim of our project is to study a possible association between *DPYD**2A polymorphism and the onset of early and severe toxicity in patients treated with FL-based regimens.

METHODS: We analyzed *DPYD**2A in 632 patients with mainly gastro-intestinal solid tumors treated with different FL-based regimens (86,4% 5-FU and 13,6% Capecitabine)
The study end-point was grade 4 toxicity (any toxicities except asthenia and cardiotoxicity) or toxic death according to NCI-CTC guide-lines v3. We considered only toxicities developed during the first 3 cycles of therapy in patients who have not been previously treated with FL.
All the patients recruited were screened for *DPYD**2A using Taqman or Pyrosequencing assays on genomic DNA extracted from peripheral blood cells.

RESULTS: Of the 632 patients 51 (8,0%) developed severe toxicities according to the above specified criteria. 10 out of 51 patients with severe toxicity (19.6%) had an heterozygous genotype for *DPYD**2A, whereas only 4 *DPYD**2A heterozygous genotype carriers were found among 581 (0.7%) patients with toxicities of a grade lower than 4 ($P<0.0001$; OR=28.48; 95% CI: 8.624 to 94.052).
In the present study, 71.4% of the patients heterozygotes for *DPYD**2A polymorphism (10/14) developed grade ≥4 toxicity (one toxic death), as compared to 6.6% of the wild-type genotype carriers (41/618).

CONCLUSIONS: Our study suggests that *DPYD**2A polymorphism can be a good predictor of the onset of severe and life-threatening FL-related toxicity, and a *DPYD**2A screening should be considered before FL-based treatment in order to reduce the therapy-related complications