

# **Analysis of UGT1A1\*28 and DPYD\*2A polymorphisms in Sicilians patients with metastatic colorectal cancer treated with Irinotecan and 5-fluorouracil.**

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Irinotecan (CPT-11), in combination with 5-fluorouracil (5-FU) and leucovorin, is used in the treatment of metastatic colorectal cancer (mCRC). Its active metabolite SN-38 is extensively metabolized to the inactive glucuronide by several UDP-glucuronosyltransferase (UGT), which include UGT1A1, UGT1A6, UGT1A9 and UGT1A7. The main dose-limiting toxicities of CPT-11 are delayed diarrhea and neutropenia and polymorphisms of the UGT1A family members may determinate variability in the toxic response to the drug among the patients. The most common genetic variant described to date in the UGT1A1 gene is a dinucleotide repeat polymorphism in the TATA box region of the UGT1A1 promoter. The variant allele consists of seven TA repeats in the A(TA)<sub>n</sub>TAA motif (UGT1A1\*28), whereas six TA repeats characterize the common allele (UGT1A1\*1). The presence of UGT1A1\*28 was previously found to decrease UGT1A1 gene expression and to be associated with CPT-11-related toxicity.

Dihydropyrimidine dehydrogenase (DPYD) is the initial and rate-limiting enzyme in the catabolism of 5-FU. An uncommon variant (allelic frequency of 0,7%) of the DPYD gene, consisting of a G to A mutation in the splicing recognition sequence of intron 14 (IVS14+1G>A) of the DPYD encoding gene (DPYD\*2A), produces a non-functional enzyme due to skipping of exon 14 and in homozygosis is associated with a life-threatening toxicity of 5-FU.

The aim of our study was to examine both the allelic frequency and the influence on toxicity of UGT1A1\*28 and DPYD\*2A polymorphisms in 50 Sicilian patients with mCRC treated with CPT-11 and 5-FU. There are not data about the allelic frequency of these variants for Sicilian people.

The TA repeat promoter polymorphism UGT1A1\*28 was detected by PCR and automatic sequencing. The mutation in the DPYD gene introduces a restriction site and was detected by PCR-RFLP. Our results showed that 28% of the patients exhibited the UGT1A1\*28 polymorphism. Genotypes frequencies for UGT1A1\*1/\*1, UGT1A1\*1/\*28 and UGT1A1\*28/\*28 were 72% (36 patients), 16% (8 patients) and 12% (6 patients), respectively. The allelic frequencies of UGT1A1\*1 and UGT1A1\*28 were 80% and 20%, respectively. The frequency of the UGT1A1\*28 was lower than that of other Caucasian populations (38.7%). This result might depend on the limited number of patients studied till now or represent an own characteristic of a population made up mainly of Sicilians.

We examined the relationship between the genotypes and the toxicity of CPT-11 in the patients. Homozygous and heterozygous patients for the UGT1A1\*28 polymorphism showed a higher incidence of neutropenia (22%) compared to wild type patients (4%). A statistically significant (P = 0.026) higher incidence of diarrhea (grade 2-3) was observed in patients carrying a UGT1A1\*28 allele (55%) compared to UGT1A1\*1/\*1 patients (16%).

Accordingly to the rarity of the DPYD\*2A mutation, this polymorphism was not found in any of our patients. Clearly, these data exclude the occurrence in any patient of a 'Combined pharmacogenetic syndrome', consisting of a heterozygosity for both DPYD\*2A and UGT1A1\*28, which could cause very severe toxicity.

The present results confirm that screening for the UGT1A1\*28 allele may be effective in identifying patients at risk of CPT-11 toxicity. Possibly, however, other variant alleles of UGT1A (UGT1A6\*2, UGT1A7\*3 and UGT1A9\*22) might be taken into consideration to prevent severe adverse event following CPT-11 administration.