Clinical validity of *UGT1A1*28* genotyping in the management of metastatic colorectal cancer patients: the CRO translational experience

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Irinotecan is used as standard of care in many chemotherapeutic regimens. The risk of severe toxicity remains, for the vast majority of patients, unpredictable. It has been reported that cancer patients with the longer TA promoter repeat in the *UGT1A1* gene (the *UGT1A1*28* allele) are at increased risk of severe toxicity when treated with irinotecan. The drug label has been revised by FDA to include the *UGT1A1*28* homozygosity as a risk factor for severe toxicity.

We have previously demonstrated that the inherited genetic variability in UGT1A genes family has an important role in the outcome of an irinotecan containing regimen (FOLFIRI: irinotecan, 5-fluorouracil and leucovorin) used as first-line treatment in 250 metastatic colorectal cancer (CRC) patients (Toffoli J Clin Oncol 2006; Cecchin J Clin Oncol 2009). Specifically, patients with the UGT1A1*28 variant experienced increased exposure to the cytotoxic SN-38 metabolite with higher risk of severe toxicity but with an higher response rate. We subsequently reported the clinical validity of UGT1A1*28 polymorphism in a phase Ib pharmacogenetic study aimed to define the maximum tolerated dose (MTD) of irinotecan according to UGT1A1*28 polymorphism in first-line FOLFIRI therapy. Irinotecan MTD in wild type and heterozygous UGT1A1* 28 patients, was higher than the standard dose (180 mg/m^2). Patients treated at higher doses (310 mg/m^2 for *1/*28 and 370 mg/m2 for *1/*1) seemed to respond better to treatment, as suggested by our previous data (Toffoli J Clin Oncol 2010).

A further validation is being carried on in an independent set of patients. A phase Ib study is aimed to define Irinotecan MTD in first-line treated metastatic CRC patients treated with FOLFIRI plus bevacizumab, according to UGT1A1*28 polymorphisms. The study is on-going but up to now MTD is 260 mg/m2 in the *1/*28 cohort and at least 310 mg/m2 in the *1/*1 cohort.

In conclusion our clinical experience with the use of UGT1A1*28 as a pharmacogenetic marker for irinotecan dosing in FOLFIRI first-line treated metastatic CRC patients pointed out that: 1. *28/*28 patients are more prone to acute grade 3-4 hematological toxicity; 2. *28/*28 patients are also good therapy responders; 3. *1/*1 and *1/*28 patients resulted under-dosed according to current protocols and the use of higher doses seems to improve their tumor response; the effect of UGT1A1*28 on patients prognosis (Time To Progression and Overall Survival) is still unclear; the predictive value of UGT1A1*28 on FOLFIRI outcome could be increased by the definition of the entire UGT1A patient haplotype. On these bases UGT1A1*28-based irinotecan dosing in CRC patients undergoing FOLFIRI treatment should be taken into account.