COST-EVALUATION OF FLUOROPYRIMIDINES-RELATED TOXICITIES ASSOCIATED WITH DPYD FOUR-SNPS PANEL IN PATIENTS GENOTYPE

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Fluoropyrimidines (FL) (i.e. 5-fluorouracil, capecitabine, and tegafur) still represent the backbone of many combination regimens in the treatment of solid tumors but their efficacy in some cases (10-26%) is endangered by severe and life-threatening toxicities. Adverse events burden both patients' quality of life and cancer care costs for healthcare system. We already demonstrated that up-front DPYD three-SNPs panel (rs3918290, rs55886062 and rs67376798) genetic test can foresee severe or lethal (≥G3) FL-related toxicities with 99% specificity (Toffoli et al, 2015). Regardless, the test sensitivity remains low.

Aim of this study was to increase the pharmacogenetic test sensitivity by adding the DPYD-1236G>A/HapB3 (rs56038477) (four-SNPs panel) deleterious variant to the panel and to highlight differences in the toxicity-management cost per patient consistently with patients DPYD genotype.

Eligibility criteria were solid cancer diagnosis, Fl-based treatment, availability of biological sample and of detailed toxicity data. Only toxicity data the physician agreed to be chemotherapy-related were recorded at each cycle of the entire period of chemotherapy, until treatment discontinuation for any reason, and classified as stated in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) v. 3.0. For this analysis, patient clinical records were reviewed to evaluate all interventions performed to manage chemotherapy-related toxicities. The toxicity-management costs are based on the DRG-based reimbursement data of case-mix index and length of hospitalization at CRO-Aviano. All patients have been genotyped for DPYD*2A, DPYD*13, DPYD-2846, DPYD-1236; costs will be stratified accordingly.

578 patients were considered eligible for the analysis. 76 patients treated in FL-monotherapy regimen and 502 in FL-combination regimen. Of those 206 developed at least one severe grade 3 to 5 toxicity event during the treatment (119/578 hematological vs 133/578 non-hematological toxicity) with 4 toxic deaths. Conforming to the three-SNPs panel, 18 out of 569 (3.2%) patients presented at least one DPYD variant allele, 24 additional patients presented at least one variant allele for DPYD-1236G>A SNP. The association between DPYD genotype and toxicity occurrence was assessed. In agreement with the three-SNPs panel, 11 out of 18 patients (61.1%) with at least one variant allele developed grade 3 to 5 toxicity of any kind, vs 195 out of 551 (35.4%) without any variant alleles (OR, 2.87; 95%CI 1.09-7.52; p=0.0428 by Fisher's Exact test). Contrariwise, according to the four-SNPs panel 22 out of 44 patients (91.7%) with at least one variant allele developed toxicity vs 183 out of 526 (34.8%) without any variant allele (OR, 2.06; 95% CI 1.10-3.88; p=0.0292 by Fisher's Exact test).

The four-SNPs panel increased the sensitivity of the test from 5.3 (three-SNPs panel), to 10.7 maintaining the specificity above 95%. The association between DPYD genotype and toxicity

management costs was assessed. The predicted mean of toxicity management costs calculated by generalized linear model ranged from 830€ (95% CI, 789-871), in patients carrying no variant allele, to 1734€ (95% CI, 1358-2111) in patients carrying only DPYD-1236G>A, to 5693€ (95%CI, 3321-8064) in patients carrying at least one variant allele in the three-SNPs panel ($p<0.001$ by ANOVA test).

Our data demonstrate that by adding the DPYD-1236G>A genotyping test to the SIF-AIOM panel allows the identification of a doubled number of individual at risk of severe toxicity. The toxicity management costs are significantly different according to DPYD genotype. Pharmacogenetics could play a key role in intercepting high-cost outlier cases embodied by different genotypes as our group recently demonstrated (Roncato et al, 2017). The implementation of pharmacogenetic profiling could be helpful in the delivery of a more precise and efficient care that can be ultimately functional to save costs.

Toffoli et al, 2015. Int J Cancer. 2015 Dec 15;137(12):2971-80

Roncato et al, 2017. Clin Pharmacol Ther. 2017 Jan 11