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gastrointestinal (colorectal) cancers

D23 Pharmacogenomic evaluation of single nucleotide polymorphisms associated with oxaliplatin-induced peripheral neuropathy: a preliminary study

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Background: Oxaliplatin-based chemotherapy is a standard treatment for metastatic colorectal cancer (mCRC). Chronic peripheral neuropathy often limits its prolonged use in responding patients. Single nucleotide polymorphisms (SNPs) in genes involved in drug transport may play a role in this toxicity. In this study, we evaluated the clinical usefulness of a pharmacogenetic panel testing of 4 SNPs in predicting the likelihood of adverse events for mCRC patients receiving oxaliplatin.

Materials and methods: Germline DNA was available from 95 mCRC patients who received oxaliplatin between 2007 and 2016. SNPs were determined by Real-Time PCR. We evaluated variants in SLC31A1 (rs10981694 T > G), ABCC224 (rs717620 C > T), ABCC2 4544 (rs8187710 G > A)) and ABCG2 (rs2231142 G > T) genes to assess their association with grade 2-3 neurotoxicity and other AEs.

Results: A strong correlation was found between incidence of neurotoxicity and oxaliplatin cumulative dose (odds ratio (OR) 2.09, 95% CI 1.30,3.33, p = 0.002). For each SNPs analyzed, the percentage of patients who developed OXPN was higher among carriers of at least one polymorphic allele and those without, although this difference was not statistically significant (SLC31A1: 35.7% v 28.3% (p = 0.476), ABCC224: 37.5% v 26.9% (p = 0.348), ABCC2 4544: 35.2% v 29.4% (p = 0.772) and ABCG2: 38.8% v 28.5% (p = 0.405)). At the univariate analysis performed using logistic models, there were no significant associations between SNPs (considered as dominant model, one or two polymorphic alleles versus none) and incidence of OXPN, even if the ORs were always >1. At the multivariate analysis using a "random forest" model, significance was obtained for the ABCC224 (p = 0,010), ABCC2 4544 (p = 0,013) and GSTP1 (p = 0,058) polymorphisms. However, by entering the cumulative dose variant in the model, all polymorphisms lost significance (p = 0,178, p = 0,201, p = 0,161, respectively). By using a predictive score, presence of SNPs in ≥2 genes was associated with increased risk of OXPN and maintained significance at multivariable analysis including oxaliplatin cumulative dose (OR = 2.12; 95%CI, 1.32-3.39; p = 0.002).

Conclusions: Assessment of SNPs of genes involved in oxaliplatin transport is a promising strategy. To overcome the masking effect of the cumulative dose, we consider necessary a further validation of our analysis on a larger sample size.