PHARMACOGENETIC BIOMARKERS FOR PREDISPOSITION TO TOXICITY WITH IRINOTECAN OR OXALIPLATIN-CONTAINING REGIMES IN COLORECTAL CANCER PATIENTS

P. Garcia Alfonso1, A. Muñoz Martin1, M. Blanco Codesido1, S. Custodio Cabello1, A. Ruperez Blanco1, D. Lopez-Trabada Ataz1, M. Martin Jimenez2, M. Cortejoso-Fernández2, I. García-García2, L. Manrique-Rodríguez2, A. López-Fernández2

1Hospital General Universitario Gregorio Marañón C/ Doctor Esquerdo, Madrid, Spain Medical Oncology Service and 2Hospital General Universitario Gregorio Marañón C/ Doctor Esquerdo, Madrid, Spain Pharmacy Service

PURPOSE: Chemotherapeutic regimes containing 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), and capecitabine and oxaliplatin (XELOX) or irinotecan (XELIRI) are the most common first-line-treatments for metastatic colorectal cancer (CRC). This combination of drugs has improved prognosis of the disease, however, toxicity is also increased. The purpose was to analyze associations between severe-adverse-reactions to oxaliplatin or irinotecan-containing-regimes and polymorphisms in genes of related metabolic-pathways.

METHODS: Retrospective study with 162 CRC patients treated with oxaliplatin (106pats) or irinotecan-containing-regimes (56 patients). It was approved by EC for Clinical Research and all patients signed IC for pharmacogenetic study. Following genotypes were determined: XRCC1 (rs25487), ERCC2 (rs13181), ERCC1 (rs11615), GSTP1 (rs1695), GSTT1 (copy number variation), EGFR (rs4559542), UGT1A (rs8175347and rs10929302) and ABCB1 (rs1128503, rs2032582 and rs1045642). Clinical data (age, sex, treatment & toxicity) and genotype of the selected single nucleotide polymorphisms (SNPs) or copy number variant (CNV) were registered. Toxicity grade ≥3 was considered severe (except hand-foot syndrome ≥2), based on CTCAE. Linear by linear association chi-square-test (SPSS v.18.0.) was used to study associations between polymorphisms and severe-toxicity. Multivariate-analysis including sex and PS was also conducted p<0.05 was considered significant.

RESULTS: Mean age patients included (64years), male (58.6%) univariate-analysis statistically significant associations were obtained between polymorphism ERCC2 and diarrhea and gastrointestinal toxicity; ERCC1 and mucositis; ABCB1 (rs1128503) and hand-foot syndrome, asthenia and other toxicities; ABCB1 (rs2032582) and asthenia; ABCB1 (rs1045642) and diarrhea; and GSTT1 and asthenia. Multivariate-analysis statistically significant associations were obtained in patients treated with an irinotecan-containing-regime between rs1128503 (ABCB1 1236) and CNV of GSTT1 with asthenia (CCvsCT/TT:OR, 0.043; 95%CI, 0.004-0.444; p=0.008 and OR, 0.046; 95%CI, 0.003-0.684; p=0.025, respectively), rs1045642 (ABCB1 3435) with diarrhea (CCvsCT/TT:OR, 0.162; 95% CI, 0.031-0.844; p=0.031) and rs1128503 (ABCB1 1236) with other toxicities (CCvsCT/TT:OR, 0.182; 95%CI, 0.045-0.742; p=0.017). Patients treated with oxaliplatin-containing-regimes the association between rs11615 (ERCC1) with neutropenia was confirmed (CCvsCT/TT:OR, 0.203; 95% CI, 0.060-0.683; p=0.010).

CONCLUSION: Results could help oncologists reduce adverse-reactions associated to irinotecan & oxaliplatin-containing regimes by giving patients the best option. Potential clinical applications and benefits to therapy prescribed by oncologists to CRC patients could improve patients’ QoL. Bigger cohorts are needed to verify associations obtained between polymorphisms ERCC2, ERCC1, ABCB1 and CNV in GSTT1 and development of toxicity.