MTHFR-1298A>C is a predictor of survival in stage II/III colorectal cancer treated with adjuvant fluoropyrimidine chemotherapy with or without oxaliplatin

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Adjuvant treatment based on fluoropyrimidines (FL) alone or in association with oxaliplatin (OXA) improves both disease free (DFS) and overall survival (OS) in stage II/III colorectal cancer (CRC). However, response to anticancer drugs may be strongly affected by interpatient genetic variability and a certain percentage of patients do not take advantage of the treatment. The definition of validated prognostic biomarkers of the therapeutic outcome would spare therapy related morbidity in patients with a good prognosis. The aim of this study was to compare and cross-validate the impact of a set of FL-related polymorphisms on 5-year DFS in two groups of CRC patients treated with adjuvant FL with or without OXA. We analysed a set of 22 polymorphisms in 9 FL-related genes in 262 CRC patients. Genomic DNA was extracted from peripheral blood or from normal colonic mucosa obtained from CRC patients at surgery. Polymorphisms were analyzed by Pyrosequencing, TaqMan Allelic discrimination or RLFP method**.** We found a concordant effect in the two groups of patients for *MTHFR*-1298A>C (rs1801131) polymorphism. Carriers of *MTHFR*-1298CC genotype had a worse DFS in both groups (HR=3.48, 95%CI 1.01-11.96 in FL alone; HR=3.13, 95%CI 1.23-7.97 in FL+OXA). A concordant effect was observed also on patients overall survival. We computed a clinical score related to DFS including rs1801131, disease stage, sex, and tumor location, where rs1801131 is the most detrimental factor. In conclusion *MTHFR*-1298A>C is a strong prognostic factor for DFS in stage II/III CRC patients treated with a FL-based treatment and could be used as an useful additional criteria for the choice of the proper adjuvant regimen.