GENETIC MARKERS IN NUCLEAR RECEPTORS AND INFLAMMATION-RELATED GENES AS INDEPENDENT PREDICTORS OF OVERALL SURVIVAL IN METASTATIC COLORECTAL CANCER PATIENTS RECEIVING FIRST-LINE FOLFIRI TREATMENT

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Host genetic variations in the nuclear receptors (NRs) and immune-related factors were indicated to have a potential role in determining the tumor risk, prognosis, and response to treatment (De Mattia 2013, Cecchin 2016, De Mattia 2016). Pharmacogenomics was largely applied to the FOLFIRI-based colorectal cancer (CRC) treatment personalization. This work aimed to uncover novel genetic markers of prognostic significance in metastatic CRC (mCRC) patients treated by FOLFIRI regimen.

A panel of 246 tagging SNPs in 22 candidate genes encoding for transcriptional controllers, including NRs, and key pro-inflammatory cytokines was selected and analyzed in a Veracode (Illumina) platform (De Mattia 2017) on 247 mCRC patients (discovery set, DS) treated with FOLFIRI therapy, and followed up for at least 36 months after drug administration. The primary clinical end-point of the study was 3-years overall survival (OS). A validation set (VS) of 92 mCRC patients receiving FOLFIRI-based therapy was used for significant markers ($p<0.05$) replication. The effect of the validated SNPs on 3-years progression free survival (PFS) was also assessed.

Twenty-eight polymorphic variants were found to be significantly ($p<0.05$) associated with 3-years OS in the discovery set. The minor allele frequency (MAF) of these polymorphisms resulted in line with the data reported for the Caucasian population (http://www.ncbi.nlm.nih.gov/snp). Of the 28 markers emerged, the majority (n=21) were predictors of increased risk of mortality (HRs:1.40 to 37.9), while the remaining (n=7) were correlated to longer survival (HRs: 0.43 to 0.65). Three marker were successfully replicated in the validation cohort. Particularly, CHUK rs11595324 (dominant model - DS, HR:1.82 CI:1.04-3.19 P=0.0373; VS, HR: 4.05 CI:1.25-13.2, P= 0.0201) and NR1I2 (encode for PXR) rs1054190 (recessive model – DS, HR:6.78 CI:1.98-23.2 P=0.0023; VS, HR:3.56 CI:1.05-12.1 P=0.0418) were predictor of higher risk of mortality, while VDR rs7299460 (dominant model - DS, HR:0.61 CI:0.73-0.88 P=0.0076; VS, HR:0.57 CI:0.33-1.00 P= 0.0478) was associated to a longer patients OS. One of them, NR1I2 rs1054190, was highlighted to have a comparable effect on 3-years PFS in both discovery and validation set (recessive model – DS, HR:0.71 CI:0.55-0.96 P=0.0284; VS, HR:0.73 CI:0.46-1.16 P=0.1776).

PXR, VDR and CHUK protein have been reported to be implicated in the modulation of the clinical efficacy of chemotherapeutics, including irinotecan, as well as to impact the CRC proliferation, apoptosis and metastasis independently from xenobiotic enzyme regulation. Hence, it could be suggested that an altered expression of these factors due to genetic variations contribute to affect the patient survival through various complex mechanisms.

In conclusion, the present discovery/validation study demonstrated for the first time that some variants in transcriptional controller and related pathway could make a crucial contribution to predicting the patients survival after irinotecan therapy (FOLFIRI regimen) in mCRC patients. These findings could be used as an additional criterion to improve the clinical management of mCRC patients FOLFIRI-treated.

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