Alterations in gene expression induced by oxaliplatin based chemotherapy on peripheral leukocytes: implications for long term survivors

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Introduction

Anticancer chemotherapy drugs target genetic material of tumours and normal cells. These effects on normal cells can induce genotoxicity and could have implications for long-term survivors.
Colorectal cancer represents the third most frequently diagnosed malignancy in the world and a considerable number of patients will receive adjuvant oxaliplatin based chemotherapy. Oxaliplatin produces long term side effects, like peripheral neuropathy, liver injury and thrombocytopenia.
Since a considerable number of patients with colorectal cancer treated with adjuvant oxaliplatin based chemotherapy will be cured, we designed the following study to search the effects of oxaliplatin based chemotherapy on gene expression of peripheral leukocytes with the following aims: 1) to assess the effects of the therapy on gene expression; 2) to determine if there are target genes for the drugs, and 3) to search for molecular markers of toxicity.

Patients and Methods

Peripheral leukocytes from patients with colon adenocarcinoma patients previously and after three FOLFOX- or CAPEOX-cycles were isolated with Ficoll-Hypaque gradient.
We isolated mRNA from leukocytes from 27 patients in both situations, prior- and post- three cycles treatment and differential transcriptome was analyzed.

Results

We choose the genes that were at least ten times over- or down-expressed. We found over-expression in the following genes: breast cancer anti-estrogen resistance 1 (BCAR1); bone morphogenetic protein receptor, type IB (BMPR1B); cystathionine-beta-synthase (CBS); cerebellar degeneration-related protein 2-like (CDR2L); collagen, type IV, alpha 2 (COL4A2); collagen, type VII, alpha 1 (COL7A1); elastin (ELN); keratin 8 (KRT8); melanoma antigen family C, 1 (MAGEC1); premelanosome protein (PMEL), and peroxisome proliferator-activated receptor gamma (PPARG).
The down-expressed genes were: cholesterol 25-hydroxylase (CH25H); granulocyte colony stimulating factor 3 (CSF3); GDNF family receptor alpha 1 (GFRA1); gap junction protein, beta 2, 26kDa (GJB2); interleukin 1, alpha (IL1A); interleukin 8 (CXCL8); inhibin, beta A (INHBA); RASD family, member 2 (RASD2); sarcoglycan, alpha (SGCA); solute carrier family 1 (glial high affinity glutamate transporter), member 3 (SLC1A3); superoxide dismutase 2, mitochondrial (SOD2), and tubulin tyrosine ligase-like family, member 10 (TTLL10).

Conclusions

Several genes alter their expression after oxaliplatin-based chemotherapy (FOLFOX or CAPEOX). These changes can be related to the effect of drugs on DNA or as a reaction of the cells to chemotherapy. Now, we are following the evolution of the patients and studying possible associations between alterations in the expression of certain genes with the development of neuropathy and sinusoidal obstruction syndrome of the liver.