ABSTRACT

Colorectal cancer is one of the most common cancer in this country and abroad. A major problem in the treatment of this disease is interindividual variability in response to treatment, since a large proportion of patients show resistance or adverse toxicity to the drug. The cause of this variability can be an individual's genetic makeup. From this perspective a need to find molecular markers for prognosis of the disease and markers through which we can predict response to therapy is growing.

The main aim of this study was to find differences in gene expression between healthy and tumor tissue from patients well and poorly responding to treatment based on 5-fluorouracil and compare the results to clinical data. This study aimed to evaluate gene expression of 14 potential molecular markers involved in 5-FU pathways involving metabolism, transport, and objectives of the drug.

Patients selection for the study was based on 5-FU regimens treatement. Expression was evaluated in two independent sets consisting of patients with indicated palliative or adjuvant chemotherapy. For each patient malignant and paired nonmalignant tumor tissue was available. Gene expression in these samples was measured using real-time RT-PCR with relative quantification using the preamplified cDNA.

In the first phase the gene expression was evaluated by a group of patients indicated for palliative treatment. Significant differences in gene expression between tumors and healthy tissues of patients showed a total of 6 genes. These genes were subsequently validated on an independent set of patients treated with adjuvant chemotherapy. Validation study confirmed the results from the first phase. Among the genes with lower expression in the tumor were catabolic genes DPYD and UPB1 as well as activation gene UCK1. Significantly elevated levels in tumor versus healthy tissue showed PPAT, SLC29A1 and RRM2 genes involved in metabolic tracks leading to the active metabolites 5-FU. Clear identification of the gene with a predictive function of therapy in this study unfortunately failed. As the most important in relation to the clinical data PPAT and UCK2 genes were identified whose increased expression correlated with a worse prognosis.

This study provided a view at gene expression profiles of metabolism and transport of 5-FU on patients with colorectal carcinoma. In this work I have identified potential prognostic markers of this serious illness but not predictive. The results of study could contribute to establishment of markers for individual treatment and thus increase its efficiency.