

Genetic polymorphisms, response to treatment and adverse effects in breast cancer patients treated with FAC chemotherapy

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Clinical resistance to breast cancer chemotherapy is observed as incidences of disease progression, local recurrence, primary and secondary tumors at different locations, and cancer-related mortality. Apart from tumor-related factors, chemotherapy resistance is associated with patient's body ability to metabolize and remove drugs from the body. The factors that can influence therapeutic potential of drug are: its reduced transport into tumor cells, overexpression of efflux transporters and modified repair systems which remove drug – induced damage.

Chemotherapy toxicity is a significant clinical problem due to decreased quality of life, prolongation of treatment and reinforcement of negative emotions associated with therapy.

It is postulated that the variation, including single nucleotide polymorphisms in the phase I activations, phase II detoxification enzymes, and ABC membrane transporters, plays an important role in the efficacy and toxicities of chemotherapy.

These studies were done the group of 324 breast cancer patients treated with FAC regimen.

The response to treatment depended of the variability in genes engaged in drugs' transport ABCC2, ABCB1 and in DNA repair ERCC2. The growing number of high-risk genotypes was reflected in the gradual increase in the risk of non-responsiveness to treatment from OR 2,68 for the presence of two unfavorable genotypes to OR 9,93 for carriers of all three unfavorable genotypes in the group of all patients.

The novelty in our model is the overrepresentation of triple negative breast cancer (TNBC) patients among the carriers of all unfavorable polymorphic variants.

The multifactorial risk models that combine genetic risk modifiers and clinical characteristics were constructed for 12 toxic symptoms. For the carriers of multiple high risk factors the chance of developing given symptom was significantly elevated which proved the factor-dosage effect. We found the strongest associations between concurrent anemia, nephrotoxicity, early nausea and genetic polymorphisms in genes responsible for DNA repair, drugs metabolism and transport pathways.

An important role in controlling gene expression is played by untranslated regions (UTR). 3' untranslated regions (3'UTRs) can modify the gene expression by controlling mRNA nuclear transport, cytoplasmic localization and stability or by affecting the translational efficiency.

ALDH5A1 rs1054899, surgery and PGR status were connected with the lack of treatment response from HR 2,46 for one unfavorable factor to HR 54,17 for the accumulation of 3 unfavorable factors: one genetic and two clinical.

These studies show that polymorphic genetic variants in germline can modify the response of patients to treatment.