

Modulation of adverse effects of chemotherapy treatment of breast cancer by noncoding genetic variants in ADME genes.

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Chemotherapy toxicity is a significant clinical problem due to decreased quality of life, prolongation of treatment and reinforcement of negative emotions associated with therapy. Chemotherapeutic drugs used in breast cancer treatment often cause side effects and toxicity during and after chemotherapy. Pharmacogenetics studies showed that the genetic polymorphic variants of ADME (adsorption, distribution, metabolism, efflux) genes modified the adverse effects of chemotherapy.

The associations between 3'UTR genetic variants in ADME genes, clinical factors, and the risk of breast cancer chemotherapy toxicity we studied in 305 patients treated with FAC regimen. Those variants and factors were tested in relation to seven symptoms belonging to myelotoxicity (anemia, leukopenia, neutropenia), gastrointestinal side effects (vomiting, nausea), nephrotoxicity, and hepatotoxicity, occurring in overall, early, or recurrent settings. The cumulative risk of overall symptoms of anemia was connected with *AKR1C3* rs3209896 AG, *ERCC1* rs3212986 GT, and >6 cycles of chemotherapy; leukopenia was determined by *ABCC1* rs129081 allele G and *DPYD* rs291593 allele T; neutropenia risk was correlated with accumulation of genetic variants of *DPYD* rs291583 allele G, *ABCB1* rs17064 AT, and positive HER2 status. Risk of nephrotoxicity was determined by homozygote *DPYD* rs291593, homozygote *AKR1C3* rs3209896, postmenopausal age, and negative ER status. Increased risk of hepatotoxicity was connected with *NR1/2* rs3732359 allele G, postmenopausal age, and with present metastases. The risk of nausea and vomiting was linked to several genetic factors and premenopausal age. The conclusion was that chemotherapy tolerance emerges from the simultaneous interaction of many genetic and clinical factors.

The study highlights the importance of many factors from different regulatory levels and pathways of relationships leading to the manifestation of tolerance of breast cancer treatment. The SNPs selected for our analyses were located in the noncoding region of ADME genes and, with regard to main genetic principles, did not alter the protein synthesis. However, genetic variants located on the miRNA target side influence the expression of gene and regulation of mRNA degradation. It should be emphasized that in our study we paid attention to the multifactorial determination of the occurrence of side effects or the toxicity of therapy. It suggests that the phenotypic occurrence of a symptom is determined by the accumulation of clinical and genetic factors and the patient's condition. It suggests the potential correlations between SNPs in 3'UTR ADME genes, clinical factors, and modulation of breast cancer treatment-related toxicities. The study shows that chemotherapy tolerance emerges from the simultaneous interaction of many genetic and clinical factors. The good tolerance of treatment with favorable outcomes seems to be the result of a delicate balance between drugs' intake, excretion, metabolism rate, and innate patient, and also tumor, characteristics. Also, in the often-seen correlation of the given SNP with several toxic symptoms, the pleiotropic nature of genes involved in drugs' management is strongly emphasized.

The effect of therapy depends on the interaction of many factors: clinical stage, histological type and its accompanying biomarkers, and genetic and epigenetic factors. Common variants in the coding sequences of genes could affect protein function and modulate treatment outcomes in cancer patients. However, SNPs in noncoding regions (introns, 3'UTR, 5'UTR) of genes and regulatory factors may also participate in the response to therapy.