Genetic variation of response to chemotherapy treatment of breast cancer.

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Background: The differences in patients' response to the same medication are one of the major problems in breast cancer treatment. Chemotherapy resistance makes a significant clinical problem due to shortened survival, decreased quality of life, prolongation of treatment.
Materials and Methods: In this study we evaluated the genetic and clinical risk factors of FAC chemotherapy-related response and adverse effects in the group of 324 breast cancer patients. Selected genes and their polymorphisms were involved in FAC drugs transport (*ABCB1, ABCC2, ABCG2,SLC22A16*), metabolism (*ALDH3A1, CBR1, CYP1B1, CYP2C19, DPYD, GSTM1, GSTP1, GSTT1, MTHFR,TYMS*), DNA damage recognition, repair and cell cycle control (*ATM, ERCC1, ERCC2, TP53, XRCC1*).
We analyzed also 33 polymorphisms in 3'UTRs of ADME genes in *ABCA1, ABCC4, ABCC1, ABCB1, ABCC5, SLC22A16, (Transporters), RALBP1, AKR1C3, ALDH5A1, CBR1, CYP1A2, CYP2E1, CYP1B1, NOS3, SULT4A1, UGT2B15, UGT2B4, DPYD (Drug metabolizers), GSTM3, ERCC1, ERCC4 (DNA repair), NR1/2, PGR (Nuclear Receptors)* in 305 the same breast cancer women treated with FAC regime. Germline DNA samples were examined by RFLP-PCR and sequencing.
Clinical endpoints of this study were: overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS) and overall response defined as treatment failure-free survival (TFFS).
Results: We showed that the response to treatment depended of the variability in genes engaged in drugs' transport (ABCC2c.-24C>T, ABCB1p.Ser893Ala/Thr) and in DNA repair machinery (ERCC2p.Lys751Gln). Furthermore, the growing number of high-risk genotypes was reflected in gradual increase in risk of the non-responsiveness to treatment- from OR 2.68 for presence of two genotypes to OR 9.93 for carriers of all three negative genotypes in the group of all patients. Similar gene-dosage effect was observed in the subgroup of TNBCs. In the 3'UTRs of ADME genes analysis in the cumulative model, the presence of growing number of high-risk factors was reflected in the increasing risk of death, from HR 4,40 p=0,015 for the three unfavorable factors to HR 10,88 p<0,00001 for the carriers of all six of them.
Conclusions: The germline variants commonly present in the population are important factors determining the response to treatment. We observed the effect of the accumulation of genetic and clinical factors on poor survival prognosis and overall treatment response. Study indicates the associations between overall survival and response and genetic polymorphisms in genes engaged in doxorubicin transport. Our results demonstrate also that the outcome of cancer treatment is the effect of many clinical and genetic factors. We observed also the over representation of triple negative breast cancer (TNBC) patients among the carriers of all unfavorable polymorphic variants. This study implicates that selection of patients based on the cumulative unfavorable models may be helpful in predicting prognosis in regard to death, progression or recurrence.
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