Influence of biotransformation and transport to the effects of chemotherapy and prognosis of breast cancer

Abstract:

Introduction: The aim of this study was to evaluate the influence of biotransformation enzymes and enzymes of multidrug resistance for the prognosis and effects of chemotherapy of breast cancer patients. The first part dealed with the genetic factors and the influence of genetic polymorphisms in selected biotransformation genes and in *ABCB1* gene and their influence in the formation and prognosis of breast cancer. In the second part, the expression profiles of these genes were analyzed as potential prognostic and predictive properties of a treatment's outcome.

Materials and methods: Polymorphisms of biotransformation genes were determined using real-time PCR and polymorphisms of *ABCB1* gene were determined using NanoChip Assay, which was performed in our cooperated department. In both cases, the polymorphisms were detected in DNA obtained from the blood of patients. The expression of genes was determined using quantitative real-time PCR in paired tumor and adjacent non-tumor tissue of breast cancer samples. The expression of NQO1 and p53 protein was assesed by immunohistochemistry in the tumor breast tissues.

Results: The frequencies of the studied SNPs did not differ from the previous published results, however SNP *SOD3* rs1799895 was interesting because only ancestral allele were found. In the first study significant association for gene *NQO1* were found, but there were not confirmed by validation study or subsequent extended study. The significant association was found for *NQO2* Leu allele of SNP rs1143684, which was associated with lower stadium of disease and with better prognosis of disease. *SOD2* genotype Ala/Ala of SNP rs4880 was associated with worse PFS in the treatment of cyclophoshamide without hormonal therapy outcome. Also significant association with PFS and *SOD3* SNP rs699473 was found, where worse PFS was related to presence of non-ancestral allele and hormonal treatment outcome (tamoxifen or aromatase inhibitor). For gene *ABCB1* significant association was found between non-ancestral allele of SNPs rs1128503 and rs1045642 and ER expression, which was not more often found in tumor tissues samples. In expression study of CYPs the highest expression was found for gene *CYP1B1*.

Conclusions: Our results from first two studies suggested the importance of including of validation sets into the performed studies or the verification of the results on the larger number of samples, which were initially performed on a small number of samples. According

to our studies of biotransformation enzymes (especially genes *CYP2E1* and *CYP1B1*) and enzymes modifying oxidative stress (especially genes *SOD2* and *SOD3*) seem to be promising prognostic markers in the future targeted therapy of breast carcinomas. The most interesting polymorphisms in ABCB1 seem to be SNPs in exon 12 and 26 for the next study of the resistence of breast cancer.