Genetic determinants of response to FAC chemotherapy in breast cancer patients

Karolina Tęcza, Jolanta Pamuła-Piłat, Joanna Łanuszewska, Ewa Grzybowska

Center for Translational Research and Molecular Biology of Cancer, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

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 abilities to metabolize and remove drugs from the system. The factors that can influence the drug's therapeutic potential are reduced transport of drugs into tumor cells, overexpression of efflux transporters and modified DNA repair systems which remove drug-induced damage.

Primary endpoint of our study was to identify the genetic and clinical determinants of non-responsiveness to FAC chemotherapy in breast cancer patients. The analyses were conducted in the group of 324 women from the Silesian voivodeship diagnosed with breast cancer. Genes and their polymorphic variants were selected on the basis of analyses of their known or potential role in transport and metabolism pathways of all three FAC drugs, as well as in DNA damage repair systems. The genotyping was performed for 22 genetic variants in 17 genes- *ABCB1*, *ABCC2*, *ABCG2*, *ATM*, *MTHFR*, *DPYD*, *GSTT1*, *GSTM1*, *GSTP1*, *CYP1B1*, *CYP2C19*, *TYMS*, *ERCC1*, *ERCC2*, *XRCC1*, *TP53*, *SLC22A16*.

The results revealed that the presence of preexisted metastases and the variants c.-24C>T (rs717620) in *ABCC2* gene, p.Lys751Gln (rs13181) in *ERCC2* gene and p.Ser893Ala/Thr (rs2032582) in *ABCB1* gene were the independent prognostic factors of treatment responsiveness. Cumulative analysis shown that the growing number of high-risk genotypes is reflected in gradual increase in risk of non-responsiveness to treatment- from OR 2,68 (95% CI 1,37-5,23; p=0,004) for presence of two genotypes to OR 9,93 (95% CI 1,28-77,25; p=0,027) for carriers of all three negative genotypes. The growing number of unfavorable genotypes was also reflected in shortening of treatment failure-free survival from 54,4 months or carriers of one variant, to 51,5 and 34,9 months for the carriers of two and three genotypes, respectively. Furthermore, the division of patients based on the number of unfavorable genotypes revealed the subgroup of triple negative breast cancers, carriers of all three high-risk genotypes, that harbor an extremely high risk of FAC treatment non-responsiveness (OR 34,0; 95% CI 1,20-967,50; p=0,028).

Our results emphasize, that for the desired treatment outcome the activity of export systems though the ABC transporters and capability to repair drugs' caused DNA damage are essential. The worst prognosis observed for the carriers of all three unfavorable genotypes could be therefore an effect of, from the one hand the more efficient drugs and their metabolites efflux, and from the other hand improved DNA repair.

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