

## **Associations between germline genetic polymorphisms and toxicity of breast cancer chemotherapy.**

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The chemotherapy toxicity is the major problem in breast cancer treatment. Lack of sensitivity to chemotherapy is most often associated with reduced transport of drugs into tumor cells, overexpression of transporter proteins that remove chemotherapeutic agents from the cells, high levels of repair of DNA damage caused by the drug. The study aimed to describe a relationship between the common germline genetic variants in genes coding for ADME targets and toxicity to FAC chemotherapy.

We analyzed genetic variations within 3'UTRs of ADME genes in breast cancer women treated with FAC regime. The impact of polymorphism on therapeutic toxicity was based on multivariate models based on 12 symptoms of toxicity.

The accumulation of adverse genetic and clinical factors increased the risk of adverse myeloid toxicity. The carriers of *AKRIC3* rs3209896 and *ERCC1* rs3212986 receiving more than six of chemotherapy cycles had a higher risk of overall anemia syndrome (OR 30.83; 5.22-181.97;  $p=0,0001$ ). In the cumulative analysis, we observed risk gradation of overall leucopenia from OR 2.33; 0,84-6,44;  $p=0,1$  in 1's factor's carriers (no statistically significant result) to OR 3.84; 1.37-10.76;  $p=0.01$  for carriers of both unfavorable factors *ABCC1* rs129081 and *DPYD* rs291593. The simultaneous presence of *ABCB1* rs17064, *DPYD* rs291583 and positive HER2 status increased the risk of overall neutropenia (OR 14.00; 1.38-142.44;  $p=0.002$ ). Furthermore, the carriers of *NRI2* rs3732359 at perimenopausal age with and presence of metastases had increased the risk of hepatotoxicity (OR 66.0; 4.54-959.22;  $p=0.001$ ). In our study carriers of *DPYD* rs291593, *AKRIC3* rs3209896 at perimenopausal age and with negative ER status had higher risk of chemotherapy-induced nephrotoxicity (OR 53.25; 5.85-484.25;  $p=0.0004$ ).

We observed the impact of the accumulation of genetic and clinical factors on the increased risk of chemotherapy toxic effects. The effect of the transmission of adverse genetic variants may be the decrease of chemotherapy tolerance or the risk of toxicity. Identifying genetic factors can lead to the implementation of an alternative diagnostic and therapeutic strategy.

This study was funded by the National Science Centre, Poland, grant No. 2016/21/D/NZ5/01913