Association Analysis of *ABCB1, ABCC1* and *ABCC2* Genetic Variants With Pathomorphological Parameters and Clinical Course of Breast cancer

6th Kaunas / Lithuania International
Hematology / Oncology Colloquium
28 May 2021

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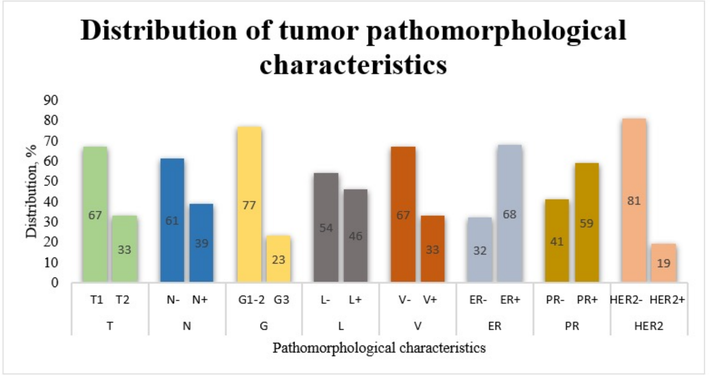
Objective

Breast cancer is the first of all oncological diseases in the world. Since it is multifactorial, driven by both genetic and environmental factors, it is extremely difficult to find effective diagnosis and treatment methods. Genes in the ABC family have been widely associated with the development of chemoresistance in certain anticancer drugs but in recent years, researchers have been trying to understand whether these genes can determine the development of breast cancer's pathomorphological parameters and disease course. Although there are not many studies yet and the findings are quite controversial, these genes could be used as prognostic factors in the study of breast cancer. The aim of this study was to perform genotyping of *ABCB1*, *ABCC1* and *ABCC2* genes variants in breast cancer patients and to determine a possible association with breast cancer pathomorphological parameters and the course of the disease.

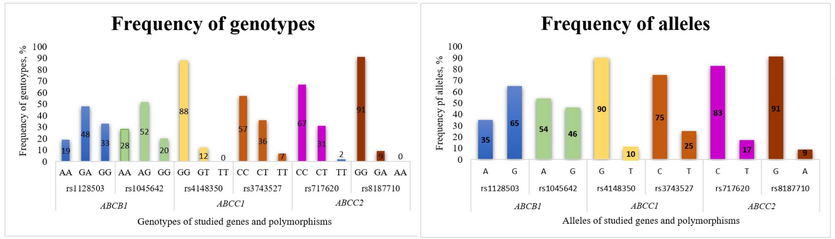
Methods

- Data of patients clinical and tumor pathomorphological parameters related to the course of the breast cancer were collected in the period of 2014-2019 from medical records by oncologists.
- DNA was isolated from 171 patients (lithuanian women with stage I-II breast cancer and mean age of 47,5 years) peripheral blood leukocytes.
- Genotyping of the studied polymorphisms was performed using the **real-time polymerase chain reaction** with Taqman genotyping assay and distribution of genotypes and alleles were analyzed.
- Statistical analysis were done with Rstudio program: association analysis were performed between *ABCB1*, *ABCC1*, *ABCC2* genes and pathomorphological parameters using Pearson's Chi-square test and odds ratios were calculated with univariate, multivariate logistic regression. Survival analysis were done with log-rank test and Kaplan-Meier method. The Hazard ratios were estimated with Cox proportional hazards univariate and multivariate models.



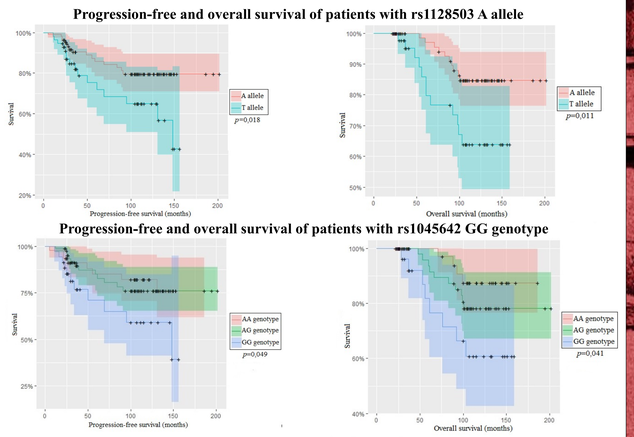
T- pathological tumor size (T1 <2; T2 2-5 cm), N – lymph node status (N- negative; N+ positive), G – tumor differentiation grade (G1-2 well-differentiated; G3 poorly differentiated), L – Lymph node infiltration (L- negative; L+ positive), V – vascular invasion (V- negative; V+ positive), ER – estrogen receptors (ER- negative; ER+ positive), PR – progesteron receptors (PR- negative; PR+ positive), HER2 – Human epidermal growth factor receptor 2 (HER- negative; HER+ positive)

Results



- Genotyping results revealed that rs1128503 and rs1045642 polymorphisms of *ABCB1* gene were predominantly heterozygous and alleles were evenly distributed. The wild-type allele and its homozygotes were predominant in the *ABCC1* and *ABCC2* genes polymorphisms. There were no or very few homozygotes for the mutated allele.

- In the association analysis a statistically **significant association was found between the GG genotype of the *ABCB1* gene rs1045642 polymorphism and poorly differentiated tumor (OR=0.167; 95% CI 0.028-1.003; *p*=0.050)**. There were no associations between *ABCB1* (rs1128503), *ABCC1* (rs4148350, rs3743527) and *ABCC2* (rs717620, rs8187710) genes polymorphisms and pathomorphological parameters of breast cancer.



- *rs1128503 A allele holders had longer progression-free (HR=0.463; 95% CI 0.219-0.981; p=0.044) and overall (HR=0.372; 95% CI 0.144-0.960; p=0.041) survival.*
- *Patients of rs1045642 GG genotype had shorter progression-free (HR=3.201; 95% CI 1.051-9.752; p=0.041) and overall (HR=9.633; 95% CI 1.544-6.456; p=0.015) survival.*

Conclusions

According to our data, studied polymorphisms of *ABCC1* and *ABCC2* genes have not revealed a prognostic value for breast cancer. On the contrary, our results suggest that rs1128503 and rs1045642 polymorphisms of *ABCB1* gene are important for breast cancer prognosis.

Key words

Breast cancer, ABCB1, ABCC1, ABCC2, association