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POSTER ABSTRACTS

1. The Effect of PJ-34 and Ionizing Radiation on Viability of MDA-MB-231 Human Triple Negative Breast Cancer Cell Line | *Best Poster Award Received*

Agnė Bartnykaitė[1], Rasa Ugenskienė[1,2], Arturas Inčiūra[3], Elona Juozaitytė[3]
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Background and Objectives
Radiation therapy plays an important role in the treatment of breast cancer but sometimes its effect is limited by the radioresistance of cancer cells. Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in many cellular processes, especially, DNA repair. Various PARP inhibitors have been demonstrated to exhibit anti cancer activity as a single agent and in combination with chemotherapeutic agents or radiation therapy. PJ-34, one of the PARP inhibitors, has been shown to sensitize other types of tumor to chemotherapy and radiotherapy. However, the analysis has never been done on MDA-MB-231 human triple negative breast cancer cells in combination with ionizing radiation. Thus, the aim of the study was to analyze the combined effect of PJ-34 and ionizing radiation on proliferation of MDA-MB-231 cells.

Material and Method
Human triple negative breast cancer cell line MDA-MB-231 was used for the study. Cells were grown as monolayers in Dulbecco's Modified Eagle's medium (DMEM; Sigma-Aldrich) supplemented with 10% fetal bovine serum (Gibco), 100 U/mL penicillin with 100 µg/mL streptomycin (Gibco) and 2 mM L-glutamine (Gibco) at 37°C in humidified 5% CO2. PJ-34 solution was purchased from SigmaAldrich, and frozen at −80°C in small quantities to prevent freeze-thaw cycles. Working solutions were prepared before each experiment. Cells were treated with different concentrations of PJ-34 one hour before irradiation. Cell irradiations were performed with the single dose of 1, 2, and 4 Gy, using a medical Clinac 2100C/D linear accelerator. Cells were irradiated with the drug present in the medium and were immediately returned to the incubator. The effect on MDA-MB-231 breast cancer cells was evaluated by MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) cell proliferation assay 71 hours after the irradiation.

Results
We examined the effect of PARP inhibitor PJ-34 and ionizing radiation on proliferation of MDA-MB-231 triple negative breast cancer cells using MTT assay. The results demonstrated that PJ-34 alone affects cells viability in a dose-dependent manner and the significant decrease was observed after the treatment with concentrations of 10 and 30 µM. Ionizing radiation alone also significantly reduced cell viability, however, the results following the radiation with 1 and 2 Gy were very similar. For the combined effect analysis, cells were treated with PJ-34 and exposed to a single radiation dose of 1, 2 or 4 Gy. MTT assay revealed that the combination therapy of 10 and 30 µM PJ-34 and radiation (1, 2 and 4 Gy) produced a significant decrease in MDA-MB-231 viability in a dose-dependent manner in comparison to radiation alone.

Conclusions and Recommendations
Overall, the current findings suggest that PJ-34 improved the response to ionizing radiation on MDA-MB-231 cells by increasing the inhibition of cell proliferation. It can be concluded that PJ-34 acts as a radiosensitizer and requires further study to elucidate the molecular mechanisms responsible for the sensitizing effect.

Acknowledgments
This work was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no 730983 (INSPIRE).

2. The Investigation of TP53 rs1042522 and BBC3 rs2032809 Polymorphisms and Their Association with Early-Stage Breast Cancer | *Best Poster Award Received*

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Background and Objectives

Breast cancer is one of the most common cancers among women worldwide. Apoptosis-related genes TP53 and BBC3 are known to play an important role in the pathogenesis of breast cancer. Studies showed that SNPs, located in genes that are involved in the regulation of apoptosis, can cause dysregulation of essential cellular processes resulting in uncontrolled cell growth. However, the roles of polymorphisms in TP53 and BBC3 genes have not been fully defined. Therefore, this study aimed to analyze the association between TP53 rs1042522 and BBC3 rs2032809 polymorphisms and breast cancer clinicopathological features and their prognostic value in breast cancer patients.

Material and Method

Lithuanian women with early-stage breast cancer were enrolled in this study (n = 171). The study group consisted of patients aged between 30 and 75 years. For SNP analysis genomic DNA was extracted from peripheral blood. TP53 rs1042522 and BBC3 rs2032809 polymorphisms were analyzed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The age at the time of diagnosis, pathological tumor size (pT), differentiation degree (G), estrogen (ER) and progesterone (PR) receptors status, human epidermal growth factor receptor 2 (HER2) status, pathological lymph node status (pN), disease progression, metastasis and death were considered as clinicopathological features. The data was collected from medical records. SPSS was used to perform statistical data analysis. The study was approved by Kaunas Regional Biomedical Research Ethical Committee (protocols No. BE-2-10 and No. P1-BE-2-10/2014).

Results

In our study TP53 rs1042522 polymorphism did not show any statistically significant associations with clinicopathological features. Meanwhile, significant associations were identified between BBC3 rs2032809 and the age at the time of diagnosis (P = 0.009), presence of disease progression (P = 0.001), development of metastasis (P = 0.003) and patients' mortality (P = 0.001). Logistic regression showed that AG and GG genotypes were significantly associated with older age at the time of diagnosis (>50 years) (OR = 4.808, 95% CI 1.348-17.144, P = 0.015; OR = 6.552, 95% CI 1.758-24.415, P = 0.005, respectively) compared to the patients with AA genotype. Moreover, the AG genotype showed higher risk for presence of disease progression (OR = 7.892, 95% CI 2.178-28.593, P = 0.002), metastasis (OR = 5.917, 95% CI 1.622-21.593, P = 0.007) and death (OR = 17.100, 95% CI 2.178-134.257, P = 0.007) in comparison to AA genotype. In the survival analysis our findings also revealed that patients with AG genotype were more likely to have a shorter OS (HR = 14.523, 95% CI 1.943-108.546, P = 0.009), PFS (HR = 7.078, 95% CI 2.130-23.521, P = 0.001) and MFS (HR = 5.535, 95% CI 1.646-18.610, P = 0.006) than those with AA genotype.

Conclusions and Recommendations

In conclusion, our study showed that BBC3 rs2032809 polymorphism is associated with disease progression, development of metastasis and patient survival in early-stage breast cancer.

3. The Interface Between Fatty Acid Composition of Platelet Membrane and Platelet-Leukocyte Aggregates Formation During Stress

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Background and Objectives

Platelet-leukocyte aggregates (PLAs) are associated with a range of acute and chronic thrombo-inflammatory conditions. Platelet phospholipid membrane is also extremely susceptible to peroxidation, so prolonged stress has a

synergistic effect on above mentioned injuries. Therefore, the aim of our study was to evaluate the interface between platelet phospholipid membrane fatty acids (FAs) composition and formation of PLAs under psychological stress.

Material and Method
In this study ten Wistar rats were on a diet with extra omega (ω) 9 FA for a month. Half of the time subjects underwent psychological stress. Then the same rats were on a diet with extra ω3 and ω6 FAs for the next four weeks with a fortnight stress as well. FA methyl esters of platelet phospholipid membrane of ten rodents were identified by gas chromatography/mass spectrometry while PLAs were analyzed by whole blood flow cytometry. The composition of platelet phospholipid membrane FAs was compared to the percentage of PLAs' formation of test animals during stress and stress-free periods.

Results
The total sums in percentage of saturated FAs and ω3 FAs separately were statistically significantly higher in platelet phospholipid membrane of rats consuming extra ω3/ω6 FAs than extra ω9 FA in stress-free period (median: 82.12 vs 76.77, p=0.009766; 3.745 vs 1.705, p=0.04883). Whereas the level of monounsaturated FAs was lower (median: 9.145 vs 14.53, p=0.01367). The percentage of platelet and monocyte aggregates' formation was statistically significantly higher in ω3/ω6 FAs stress-free group than in ω9 FA stress group of our study laboratory animals (median: 2.65 vs 1.25, p=0.001953).

Conclusions and Recommendations
After a period of stressful conditions, platelets may increase synthesis and incorporation of polyunsaturated FAs in platelet phospholipid membrane and that could potentially influence platelet activation in the future.

4. Association Analysis of ABCB1, ABCC1 and ABCC2 Genetic Variants with Pathomorphological Parameters and Clinical Course of Breast Cancer

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Background and Objectives
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. The objectives of the study were three: to identify breast cancer patients genotypes and alleles frequency of ABCB1 (rs1128503, rs1045642), ABCC1 (rs4148350, rs3743527) and ABCC2 (rs717620, rs8187710) genes; to analyze the correlations of the identified variants with the clinical and morphological characteristics of the breast cancer tumor; to investigate the association of ABCB1, ABCC1 and ABCC2 genes polymorphisms with the course of the disease.

Material and Method
Three genes of the ABC family and their polymorphisms were investigated in this work: ABCB1 (rs1128503, rs1045642), ABCC1 (rs4148350, rs3743527) and ABCC2 (rs717620, rs8187710). DNA was isolated from 171 patients (lithuanian women with stage I-II breast cancer) peripheral blood leukocytes. Genotyping of the studied polymorphisms was performed using the real-time polymerase chain reaction method and the distribution of genotypes and alleles were analyzed. Association analysis were performed between ABCB1, ABCC1, ABCC2 genes and pathomorphological parameters and the course of breast cancer.

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. There were no associations between ABCB1 (rs1128503), ABCC1 (rs4148350, rs3743527) and ABCC2 (rs717620, rs8187710) genes polymorphisms and pathomorphological parameters of breast cancer. Statistically significant correlations with overall and progression-free survival were obtained with rs1128503 and rs1045642 polymorphisms of the ABCB1 gene.

Conclusions and Recommendations
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.

5. Influence of IL-6 and IL-1β Gene Polymorphisms on Clinical and Morphological Characteristics of Cervical Tumors and Patient Survival

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Background and Objectives
Cervical cancer is 4th most common cancer in women worldwide. The main causative factor of this disease is human papilloma virus (HPV). In developed countries, where regular checkups, vaccination programs and various other preventative measures are a standard of care, the rate of cervical cancer was reduced by half in the last 30 years. Despite that, the disease still remains a significant issue. It is known that chronic inflammation has an important role in carcinogenesis processes. IL-6 and IL-1β are important cytokines partaking major roles in inflammatory process. Studies show a significant correlation between polymorphisms in IL-6 and IL-1β genes and increased risk of various cancers. Objective of this study was to evaluate 4 polymorphism (IL-6 gene rs1800795 and rs1800797, IL-1β gene rs1143634 and rs16944) genotype and allele frequencies and their correlation with clinical and morphological cervical tumor characteristics and survival in Lithuanian cervical cancer patient group.

Material and Method
A total of 172 patients (mean age 55 years) with cervical cancer diagnosis were enrolled in the study, which was approved by Kaunas Regional Biomedical Research Ethical Committee (BE-210 and BE-2-10/2014). DNA for SNP analysis was extracted from peripheral blood leukocytes. Real Time-PCR (RT-PCR) method was used for SNP analysis. All clinical and morphological patient data was obtained from medical records by oncologists in Lithuanian University of Health Sciences Kaunas Clinics. Every participant signed informed consent forms. Study data included age at diagnosis, tumor staging based on TNM and FIGO classification, histological type, tumor grade (G1 and G2, G3), progress and death. Associations between SNPs and patient clinical characteristics and disease outcome were evaluated. Statistical analysis was performed using SPSS program.

Results
The results of analysis showed that rs1800797 polymorphism of IL-6 gene was associated with disease progress to local lymph nodes. Our data indicated that GG genotype carriers, compared to AA genotype carriers, had 3.24 times higher probability of developing metastases to local lymph nodes (OR 3.243 CI 1.378-7.583, p=0.007). We also found a borderline significant link between IL-1β rs16944 polymorphism G allele and overall survival (OR 0.386 CI 0.148-1.007, p=0.052). rs1800795 polymorphism of IL-6 gene and rs1143634 of IL-1β had no significant correlations with tumor clinical and morphological characteristics.

Conclusions and Recommendations
Our study suggests that there is a correlation between IL-6 and IL-1β gene polymorphisms and cervical cancer morphology. However, to confirm the significant correlations, a bigger study with more participants is required. Moreover, new parameters, such as gene-environment and gene-gene interactions should be involved in future studies for more precise results.

6. JAK2 GGCC (46/1) Haplotype and its Relationship with Other Mutations and Clinical Characteristics in Patients with Chronic Myeloproliferative Diseases

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Background and Objectives

Chronic myeloproliferative diseases are group of blood diseases which have an increased number of blood cells in the peripheral blood. JAK2 positive chronic myeloproliferative diseases include essential thrombocytaemiaosis, polycythemia vera, and primary myelofibrosis. The association of the JAK2 GGCC (46/1) haplotype with JAK2 V617F is also disscused in the literature. Various studies suggest that the JAK2 GGCC (46/1) haplotype is inherited, associated with a more aggressive course of the disease and a lower likelihood of remission. This study will investigate patients with chronic myeloproliferative diseases, the frequency of JAK2 mutation and the association with the JAK2 GGCC 46/1 haplotype. The detected results will be compared with the data found in the scientific literature.

Objectives:

1. To determine the frequency of JAK2 GGCC (46/1) haplotype JAK2 rs10974944 (C / G) single nucleotide polymorphism in patients with chronic myeloproliferative diseases.
2. To investigate the frequency of JAK2 V617F mutation and its association with JAK2 GGCC (46/1) haplotype JAK2 rs10974944 (C / G) single nucleotide polymorphism.
3. To evaluate the association of JAK2 GGCC (46/1) haplotype JAK2 rs10974944 (C / G) single nucleotide polymorphism with CALR mutation in chronic myeloproliferative diseases.

Material and Method

A retrospective study has included 104 patients with chronic myeloproliferative diseases who was diagnosed and treated in the LSMU KK Oncology and Hematology clinic from 2001. January to 2019 December. Analysis of the medical records of patients with MPN will be done and clinical, laboratory data, information on advanced arterial and venous thrombosis, and JAK2 V617F mutation status will be collected. Patients with MPN will undergo a molecular genetic study of the rs10974944 (C/G) 46/1 haplotype. Data collection and statistical analysis will be performed using Excel and SPSS 23.0. The difference between the study groups is considered statistically significant if p was <0.05

Results

Samples from 104 patients with LMPL were examined. The most common LMPLs were: 53.8% ET, 39.6% PV, 6.6% MF. The JAK2 V617F mutation was detected in 69.8% of patients. The genotypes of Haplotype 46/1 JAK2 rs10974944 (C / G) VNP were distributed as follows: 24.5% were CC, 52.8% were GC (heterozygous) and 22.6% were GG (homozygous). CALR was studied in 13.2% of patients, of whom 8.5% were found. Overall, venous or arterial thrombosis was detected in 46.2% of patients, and both arterial and venous thrombosis were detected in 3.8% of patients. Thrombosis prior to diagnosis of MPL was detected in 57.4% of all thrombotic patients. Following diagnosis of MPL, thrombosis occurred in 27.7% of patients. Arterial hypertension occurred in 49.1% of patients. Diabetes mellitus occurred in 10.4% of patients. Data on ischemic heart disease were collected from 75.5% of patients studied, of whom 19.8% had IHD. There was a statistically significant difference between the diagnoses of ET, MF, PV comparing the groups of JAK2 positive and negative patients. The duration of disease was statistically significantly longer in the group of JAK2 mutations (141.01 months ± 54.66) than in the group of JAK2-negative (122.28 months ± 44.55) patients. The GG genotype of haplotype 46/1 JAK2 rs10974944 was statistically significantly higher in the JAK2-positive group compared to the JAK2-negative group. In the group of patients with JAK2 V617F mutation, statistically significantly higher LEU (1.32 109 / l;), RBC (0.57 1012 / l;), higher HT (5.1 l / l), lower MPV (0.68 fl), MCV (4.8 fl), and MCH (1.97 pg) compared with the group of patients without the JAK2 V617F mutation. Haplotype 46/1 JAK2 rs10974944 (C / G) VNP GG and CG genotypes were identified in 75.5% of patients. Patients in the G allele group were statistically significantly older than those in the CC genotype group. Disease duration was statistically significantly longer in the G allele group than in the CC genotype group. The JAK2 V617F mutation was detected statistically significantly more frequently in the G allele group than in the CC genotype group. Patients with the GG genotype had a longer duration of disease than those with the GC / CC genotype (140.82 ± 49.72 months and 118.54 ± 57.43 months). The incidence of JAK2 V617F mutation was statistically significantly higher in the GG genotype group than in the CG / CC genotype group (91.7% and 61.4%). The number of monocytes and MPV in patients with the GG genotype were statistically significantly lower than those with lower activity haplotype 46/1 JAK2 rs10974944 genotypes, respectively.

Conclusions and Recommendations
1. In our research 75.5 percent. of subjects we identified with haplotype 46/1 JAK2 rs10974944 VNP.
2. In patients with chronic myeloproliferative diseases, we determined the frequency of JAK2 V617F mutation and its relationship with haplotype JAK2 rs10974944 VNP.
3. No association was found between the haplotype JAK2 rs10974944 VNP and CALR mutation in patients with chronic myeloproliferative diseases.

7. Patients with AML on Programmed Polychemotherapy with Secondary Immunodeficiency Syndrome: The Role of Functional Hypogammaglobulinemia

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Background and Objectives
The initial stages of the disease (screening and induction therapy) are very often accompanied by the development of infections complications in adult patients with acute leukemia. It is known that the main position in the development of the secondary immunodeficiency syndrome is occupied by the insufficiency of cellular immunity as a result of replacement of hematopoiesis by blast cells. And there is no sufficient assessment of the role of humoral immunity (functional hypogammaglobulinemia) in the development of infections episodes.

Material and Method
The study included 7 adult patients with AML in attack 1 who received specific treatment: induction chemotherapy course under the "7 + 3". The intervention group (infectious episodes during cytopenia) and the control group were matched by demographics, clinical characteristics and laboratory tests were not statistically different ($p > 0.05$). For the primary outcome in the analysis, the decrease in the level of immunoglobulin G (IgG) from screening indicators was taken.

Results
Among total study subjects, 4 patients experienced infectious episodes during cytopenia. The average value of the level of IgG at the screening stage in the group with the development of infectious episodes 12.49 [95% Cl: 9.6 – 15.4] vs infection-free group – 8.48 [95% Cl: 5.26 – 11.7]. The average value of the level of IgG during cytopenia in the group with the development of infectious episodes 8.43 [95% Cl: 5.63 – 11.2] vs infection-free group – 9.31 [95% Cl: 6.08 – 12.5]. In the comparison group, the IgG level was statistically significantly reduced during the period of cytopenia against the background of an infectious episode in comparison with the initial values in screening – lower than in the control group (delta IgG level 4.08 vs delta IgG level 0.83; $p = 0.01$).

Conclusions and Recommendations
The suppression of humoral immunity takes place (violation of the functional activity of gammaglobulins). Which plays a significant role in the development of infections episodes in patients with acute myeloid leukemia. As a result, replacement therapy with immunoglobulin at the stages of induction therapy can be a predictive prevention of infectious episodes.

8. Determination of the Risks of Clinical Variants Occurrence of the COVID-19 Course and Complications in Pediatric Cancer Patients

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Background and Objectives
The SARS-CoV-2 pandemic is a significant problem for oncologists, since COVID-19 disease has several clinical courses and is generally the biggest threat to patients with decreased immune reactivity, which the cancer patients are. There is still little information in the literature on the SARS-CoV-2 infection effect on various types of oncological pathologies in children, therefore, the purpose of the planned research is:

- research of the oncological pathology structure in pediatric patients of hematological hospitals with COVID-19;
- determination of the clinical variants of the COVID-19 course, complications of the disease and risks of their occurrence in patients with pediatric cancer, depending on the malignant process that may arise as a result of the SARS-CoV-2 infection.

Material and Method

Multicenter prospective research was carried out as a result of which 46 patients at pediatric oncohematological departments of Ukraine were supervised. The selection criteria for the research were: confirmed diagnosis of oncological disease, patient's age <18, with positive SARS-CoV-2 PCR test. Exclusion criteria from the research: follow-up duration for pediatric cancer is more than 5 years; bone marrow transplantation carried out in the case history.

According to the clinical course of COVID-19 patients from the researched group were stratified as asymptomatic course, the mild course, moderate to severe COVID-19 course were stratified. For the purpose to identify the risks of developing one of the clinical variants of the COVID-19 disease course among patients with pediatric cancer, they were divided into subgroups: patients with the haematopoietic and lymphoid malignancies and cancer patients with solid tumors. The χ^2 criteria was used to determine the differences between groups of children. Statistically significant difference was considered at the p value of ≤ 0.05. Statistical calculations were carried out using the STATA 16.1 software license package.

Results

The research group included 46 patients with pediatric cancer, 1 patient of which died due to the development of complications against the background of severe course of COVID-19, and 2 patients died due to the progression of the underlying prior disease. Thus, the overall survival in the research group is 93.5%; the mortality in this group was 6.5%; the case fatality rate from COVID-19 among patients with pediatric cancer was 2.2%. The research group included 89.1% of patients had haematopoietic and lymphoid malignancies: B-ALL – 58.7%; T-ALL – 2.2%; AML – 15.2%, 13% of patients with lymphomas and 10.9% of patients had solid tumors (neuroblastoma, rhabdomyosarcoma, CNS tumor, thymic carcinoma).

According to the clinical course of COVID-19, the following variants of the course of the disease have been identified: asymptomatic course - 19.6% (n = 9); 52.2% of patients had mild course; 28.3% of children had a moderate and severe course of COVID-19.

Speaking about complications resulting from SARS-CoV-2 infection, we found that behavioral disorders were the most frequent in the research group, reflected by emotional lability and aggressive behavior (39.1% of the researched, n = 18); as well as sleep disorders, which were diagnosed in 32.6% of patients (n = 15). Blood coagulation system disorders also took place in the research group. Thus, 8 patients (17.4%) had subcutaneous hemorrhage, 3 patients (6.5%) had bleeding, including with the development of disseminated intravascular coagulation, for one patient it ended fatally. Deep vein thrombosis of the lower extremities was diagnosed in 3 patients.

There was no statistically significant difference found in the developing risk of moderate to severe COVID-19 course between the available hematologic cancer and solid tumor in patient ($p = 0.439$), as well as risk of asymptomatic ($p = 0.248$) or mild course ($p = 0.147$) was not found. Similarly, there was no statistically significant difference found in the developing risk of complications from the clinical course of the disease.

Conclusions and Recommendations

According to our research, it was found that presence of tumor with the haematopoietic and lymphoid malignancies in pediatric oncological patients is not a risk factor for severe or mild course of COVID-19 disease and does not differ from the COVID-19 course in patients with solid tumors. The risk of complications arising in case of SARS-CoV-2 infection if there is a tumor with the haematopoietic and lymphoid malignancies is also not greater than in such children with solid tumors.

Further research of the features of the clinical course of the COVID-19 disease in pediatric cancer patients will allow to research the risks of particular clinical variant of COVID-19 in more details, which makes it possible to predict and prevent changes in treatment tactics (postponement of therapy and support therapy correction in connection with the variant of the clinical course or COVID-19 complication).

9. Radiosensitization Effect of Resveratrol on Breast Cancer Cells

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Background and objectives

Radiotherapy is an important and effective treatment strategy for breast cancer although it is sometimes limited by radio-resistance and radiotoxicity. Thus, the identification of a radiosensitizer with a high benefit to risk ratio is needed. One of these is resveratrol (RSV). Resveratrol is a polyphenol produced by several plants, including grapes, red wine, berries and peanuts and is a phytoestrogen that possesses antioxidant, anti-inflammatory, cardioprotective, and anti-cancer properties. Studies with this substance show its ability to inhibit the expression of cancer-specific genes, induce changes in the cell cycle, and activate apoptosis. Therefore, we decided to investigate the in vitro effects of RSV on cellular radiosensitivity and to analyze the expression changes of apoptosis-related gene BCL-2.

Material and Method

Cell culture. MCF7 and MDA-MB-231 breast cancer cell lines were purchased from CLS Cell Line Service (Germany). Cells were grown in DMEM medium supplemented with 10% FBS, 1% glutamine and 100 IU/ml penicillin-streptomycin solution at 370C, humidified and filled with 5% CO2air conditions.

MTT assay. The anti-proliferative effect of resveratrol against breast cancer cells was determined using the colorimetric MTT assay. The cells were seeded on 96-well culture plates with DMEM medium at a density of 4x103 cells per well. Following incubation for 24 h at 37˚C, the cells were treated with different concentrations of RSV (0, 10, 25, 40, 50, 80, 100, 150 and 200 µM) for 24, 48 and 72 h. Subsequently, 10 µl MTT was separately added to each well, and the cells were cultured at 37˚C for an additional 3 h. Finally, 100 µl SDS (10%) was separately added to each well and the optical density (OD) was determined at 570 nm using a microplate reader (Thermo Scientific Multiskan Sky).

Irradiation (IR). Cells were seeded into culture plates, incubated overnight, treated with resveratrol as described above. After 24 h the media was removed and replaced with fresh resveratrol-free culture medium. Cells were irradiated with 2 or 10 Gy using high energy X-rays, which were generated using an X-rays instrument Clinac 2100C/D.

Apoptosis analysis. Cells (2×105 cells/well) in 6-well plates were treated as described above, trypsinized, stained according to the instructions of the apoptosis kit and were analyzed using a Guava Muse Cell Analyzer.

RT-PCR analysis. The gene expression of BCl-2 was quantitatively determined by real-time PCR. Total RNA was extracted using RNA isolation kit and one microgram of total RNA was reverse transcribed to cDNA using first strand cDNA synthesis kit.

Statistical analyses. All data are represented as the means ± SD. Statistical significance was determined using Student's t-tests. $P<0.05$ was considered to indicate a statistically significant result.

Results

We examined the effect of resveratrol on viability of two breast cancer cell lines: MDA-MB-231 and MCF-7. Our study suggests that the inhibition of cell viability was significantly increased in both cell lines in response to resveratrol in a dose-and time-dependent manner compared with the control group (0 µM RSV) ($P<0.05$). Inhibitory potency did not differ substantially between cell lines.

Further the radiosensitizing effect of resveratrol at different concentrations (25, 50, 80 µM) in 24 h cell cultures irradiated at 0, 2, and 10 Gy were evaluated. The combination of resveratrol and radiation (RSV+IR) treatment produced significantly greater antitumor effects on the breast cancer cells than either treatment alone.

To determine whether the RSV-induced inhibition of breast cancer cells growth was due to cell apoptosis, MDA-MB-231 and MCF-7 cells were stained with annexin V. Flow cytometry analysis showed that the apoptotic cell population increased in a dose-dependent manner in both cell lines. However, the combination of RSV+IR therapy activates cell apoptosis only in MDA-MB-231 cells. The percentage of cells undergoing apoptosis increased with radiation dose and resveratrol concentration. RT-PCR analysis showed that only in MDA-MB-231 cells combination of RSV+IR treatment showed significantly reduced BCL-2 gene expression than either treatment alone.

Conclusions and Recommendations
Our study results revealed that resveratrol is a potential radiosensitizer of breast cancer cells. We also demonstrated that the inhibitory effect of combination of RSV+IR on MDA-MB-231 cell growth was related to the induction of apoptosis and the expression reduction of apoptosis-related gene BCL-2.

10. The Investigation of Associations between Glutathione-S-Transferase Gene Polymorphisms and Cervical Cancer Prognosis

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Background and Objectives
Cervical cancer is one of the most common cancers among woman worldwide. Literature reviews suggest that specific genetic variants coding for enzymes could be responsible for increased diseases susceptibility and could modify the course of disease. Glutathione-S-Transferase, which is a detoxifying enzyme protecting human cells and DNA, is commonly suggested to influence cancer diseases. Null alleles mutations (GSTM1*0 and/or GSTT1*0 alleles) result in complete absence of the enzymes leading to a disabled detoxification of toxins and carcinogenic waste. Therefore, we aimed to identify the distribution of genetic GSTM1 null and GSTT1 null polymorphism among cervical cancer patients and find possible correlations of these mutations with clinicopathological characteristics and disease prognosis.

Material and Method
Our study involved 172 women from Lithuania with cervical cancer. The mean age of participant was 55 years (between 22 and 82 years). Genomic DNA for GST analysis was extracted from blood leukocytes. Multiplex PCR was used to detect GSTM1 and GSTT1 null genotypes. Relationships between genotypes and cervical cancer clinicopathological features were estimated by Pearson‘s Chi-square/ Independent T test. Clinicopathological factors evaluated included TNM status (T, lymph node involvement, metastasis), tumor grade, the fact of cancer progression and death. Odds ratio was calculated by Logistic Regression. Survival prognosis was estimated by Kaplan-Meier and Cox Regression methods. SPSS was used to perform statistical data analysis. The data was collected from medical records. Kaunas Regional Biomedical Research Ethical Committee approved the study (protocols No. BEC-MF-397 and No. SPBT-15).

Results
The distribution of studied genotypes was as follows: GSTM1 null - 44.1%, GSTT1 null – 6.9%, GSTM1 null and GSTT1 null – 6.4%, others – 42.6%. Carriers of combined GSTT1 and GSTM1 deletion had a significant correlation with the fact of cervical cancer progression ($P = 0.026$). The determined association cannot be used as a prognostic indicator for disease progression since logistic regression method could neither confirm nor deny the odds ratio for this relationship. GSTT1, yet non-significant, showed a borderline value ($P = 0.061$) related to progression of cancer. No other significant relations with clinicopathological features of cervical cancer were found. GSTM1 null and GSTT1 null variants did not affect our patients´ survival prognosis when analyzing OS and PFS.

Conclusions and Recommendations
Carriers of combined GSTT1 null and GSTM1 null had a significant correlation with the fact of cervical cancer progression. However, more detailed studies on larger cohort are recommended to confirm our findings. For more precise results gene-environmental and gene-gene interactions should be included in cervical cancer analysis.

11. The Clonal Hematopoiesis of Indeterminate Potential is a Risk Factor of Cardiovascular Complication in Patients of Older Age

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Background and objectives
Despite controversial values of different new thrombosis predictors, the "classical" triggers of them, such as diabetes mellitus, hyperlipidemia or dyslipidemia, smoking, obesity and family anamnesis, are still most powerful risk factors.

However, according to the last data, the clonal hematopoiesis of indeterminate potential (CHIP) is an independent risk factor of cardiovascular complications (CVC) such as myocardial infarction or coronary stenosis (CS).

Material and Method
In the study we included 243 patients with median age of 67.0 (25-percentile and 75-percentile (PL) = 57.0 and 76.0, accordingly). The main group included 157 patients, who had CVC and who were performed percutaneous coronary intervention (PCI) because of CS, the comparison group created 86 subjects, who had CVD without CVC and whom PCI was not performed. In the main group the median age was higher (67.0; 25 and 75- PL = 49.0 and 88.0 accordingly), than in the control group (65.0; 25 and 75-PL = 48.0 and 78.0 accordingly) (Z = 3.0; p = 0.002). To assess CHIP we tested DNMTA3A (R882), IDH1 (R132), IDH2 (R140 and R172), NPM1 in exon 12 (4 bp insertion), SRSF2 (P95) by real-time polymerase chain reaction (PCR) with melting curve analysis and JAK2 V617F was determined by PCR and gel electrophoresis. DNA was obtained from peripheral blood mononuclear cells. Comparison between categorical indices was made using two-tiled Fisher's test. The degree of correlation between categorical indices was expressed as relative risk (RR) with corresponding confident intervals (CI). The presence of significant discrepancies was assumed in cases of the error probability below 0.05.

Results
In the general cohort of patients, the CHIP was found in 30 of 243 patients (12.24%). The DNMTA3A (R882) mutation was detected in 20 (64.51 %), JAK2 V617F – in 6 (19.35 %), NPM1 in exon 12 – in 3 (9.67 %), IDH2 (R140 and R172) – in 2 (6.45 %) subjects. The SRSF2 (P95) mutation was not detected in any case. The frequency of DNMTA3A (R882) mutation was higher, than JAK2 V617F (p=0.007), NPM1 in exon 12 (p=0.004) and IDH2 (R140 and R172) (p=0.001) mutations.

In patients 60 years of age and older CHIP was detected in 15.11 % (26 from 172) cases, and in persons, who were younger, than this age's limit – in 5.63 % (4 from 71) (p=0.052). The age of 60 years increased the risk of CHIP by factor of 1.2 (95 % CI = 1.0-1.5).

In the main group, one of the markers of CHIP was found in 16.02 % of patients (25 out of 156 cases), in the control group – in 6.97 % of cases (6 from 86) (p = 0.046). It was estimated that the relative risk of CVC associated with CHIP was equal 1.3 (95 % CI = 1.0-1.6). The DNMTA3A (R882) mutation was found more frequent in the group with CVC on the level of statistical significance (17 out of 165 vs 3 out of 86; p=0.051), compared to the control group. The difference of the frequency of JAK2 V617F mutation (5 from 156 vs 1 from 86; p = 0.426), NPM1 mutation in exon 12 (3 from 156 vs 0 from 86; p = 0.554) and IDH2 (R140 and R172) (2 from 156 vs 0 from 86; p = 0.539) mutation was not detected between the main and control groups.

Conclusions and Recommendations
The most often mutation in patients with CHIP was DNMTA3A (R882) which was found in 64.51 % of cases. The JAK2 V617F mutation was detected in 19.35 %, NPM1 in exon 12 – in 9.67 %, and IDH2 (R140 and R172) – in 6.45 % subjects. The CHIP more often was found in the group with CVC (16.02 % vs 6.97 %). CHIP carriers are characterized by 1.2 times increased CVC risk in persons older than 60.

12. Case of BRCA1 Gene Germline Mutation in Patient with Neuroendocrine Tumor

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Introduction and Aim
Neuroendocrine tumors are a rare type of cancer, which arise from the endocrine and central nervous systems. It is estimated that they make up 0.5 % of all cancers and have a prevalence of 35 cases out of 100 000 per year. Because of the diffuse endocrine system, they may arise from multiple sites like the digestive tract (stomach, small intestines, etc.), endocrine glands, skin, etc. Research shows that about 10 percent of gastrointestinal tumors have a germline mutation in hereditary cancer genes, mostly in MEN1, RET, VHL, NF1. In rare cases there might be other causative variants in cancer predisposition genes. Here we report a case of neuroendocrine tumor which might be associated with a BRCA1 gene pathogenic variant.

Case Report
66 years of age female patient was referred to a clinical geneticist due to a family history of cancer: the patient has a daughter with the BRCA1 mutation and 2 primary breast cancers at 35 and 39 years of age, also the patients sister had breast cancer at 37, mother had pancreatic cancer at 38, mother's sister had breast cancer at 50 and her pedigrees also BRCA1/2 spectrum cancers (ovarian, gastric, lung cancers). Patient herself was diagnosed with invasive ductal breast cancer at 52 years of age. She was treated with chemotherapy and mastectomy. At 66 years of age, she was diagnosed with a gastrointestinal intermediate grade neuroendocrine tumour as there were several nodes detected during the patients liver ultrasound and computer tomography which were later confirmed by performing a biopsy. A targeted genetic test for familial BRCA1 gene variant NM_007294.4:c.5173_5176delGAAA was performed which was positive. This variant causes a frameshift and is expected to cause loss of protein function by nonsense mediated decay or by truncating the protein. This variant has multiple entries in ClinVar database as pathogenic and is also reported in various affected patient cases.

Discussion
BRCA1 gene pathogenic variants are well known to increase the risk of various cancers such as breast, ovarian, prostate, pancreatic, skin and others. In our patient's family the BRCA1 variant discussed earlier is highly penetrant as multiple family members are affected. Our patient' s case is unique as not only breast cancer but also a neuroendocrine tumor has developed. Larouche V. et al. (2019) study found 26 cases of such co‐occurrence of breast cancer and neuroendocrine tumors, of which 9 were genetically studied but no BRCA1/2 gene mutations were found. Howover, PALB2, APC, and NTHL1 genes pathogenic variants were detected. Scarpa E. et al. (2017) studied pancreatic neuroendocrine tumors and on rare cases found BRCA2 germline pathogenic variants and pathogenic variants in other DNA repair genes such as MUTYH and CHEK2. In two published cases (Erdrich J. et al. 2018; Zhu M. et al 2020) there were BRCA1 germline frameshift variants. This shows an increasing amount of evidence that pathogenic variants in DNA repair mechanism genes are important in neuroendocrine tumors development. BRCA1 pathogenic variants are very rare in neuroendocrine tumor patients and there is a possibility that these variants occurrence is not increased in neuroendocrine tumor patients.

Conclusions
Expanding neuroendocrine tumor patient genetic testing to also test for pathogenic variants in DNA repair mechanism genes may be needed.

13. Fanconi Anaemia with Biallelic BRCA2 Variants Presented as Paediatric Cancer: Two Case Reports
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Introduction and Aim
Fanconi anemia (FA, MIM 227650) is a rare autosomal recessive condition affecting ∼1 in 300 000 children. Aetiology of FA is genetically heterogenous and biallelic mutations in BRCA2 gene are detected in ~3% of cases (FA group D1). FA is characterized by variable congenital abnormalities, short stature, bone marrow failure, hypersensitivity to DNA crosslinking agents, and a predisposition to malignancies. We report two paediatric Fanconi anaemia cases where biallelic mutations in BRCA2 gene were detected.

Case Report
The first patient is a girl who was diagnosed with grade IV medulublastoma at 8 years old. Initially the surgery was performed and then the patient treatment was continued with radiation therapy (54 Gy) and chemotherapy. Family history - maternal grandmother died due to breast cancer before 50 years old. For patient testing "Onco-GeneSG®" gene panel analysis was performed and homozygous BRCA2 pathogenic variant NM_000059.3:c.658_659delGT, p.(Val220IlefsTer4) was detected. Patient inherited these variants from both parents.

The second patient is a boy who was diagnosed with nephroblastoma (Wilms tumour) at 5 years of age. Skin pigmentation abnormality was noticed: several café au lait spots and one melanocytic nevus on the truncus. The patient was treated with four courses of chemotherapy by UMBRELLA (2016 y.) protocol, which was followed by surgery. The treatment was continued with postoperative chemotherapy. Family history - maternal grandmother was diagnosed with breast cancer at 50 years old and paternal grandmother died due to ovary cancer. "Onco-GeneSG®" gene panel testing was performed and compound heterozygous BRCA2 variant was found:

NM_000059.3:c.658_659delGT, p.(Val220IlefsTer4) and NM_000059.3:c.3847_3848del, p.(Val1283fs). The genetic testing showed that both parents are heterozygous for BRCA2 pathogenic variant.

Discussion
Biallelic pathogenic variants in BRCA2 are associated with early-onset acute leukemia and solid tumors the cumulative probability of any malignancy is 97% by age six, including acute myeloid leukaemia, medulloblastoma, and Wilms tumor. The 1st patient is slightly older than the average reported. Experience with chemotherapy regimens for malignancy in FA patients is quite limited. Severe toxicity, including bone marrow aplasia without hematologic recovery, severe mucositis, and severe pulmonary and renal toxicities have been reported. Use of radiation therapy has been reported in patients with FA without immediate toxicity, however, this needs careful consideration due to baseline increased risk of other malignancies. Patients with biallelic pathogenic variants in BRCA2 should be carefully monitored for the other malignacies (hemathological and solid tumors).

It is known that heterozygous pathogenic variants in BRCA2 confer an increased risk of breast and ovarian cancer (84% and 27%, respectively by age 70) in women, as well as breast and prostate cancer in men. Genetic counselling and genetic testing should be provided for parents and siblings of the patient.

Conclusions
Genetic testing is especially important in the cases of paediatric cancer. If biallelic pathogenic variants in BRCA2 gene is detected there should be considerations regarding the treatment and follow up regimens. Moreover, it is importatn to provide proper genetic counselling for the family of the patient.

14. Immunophenotypic Markers of Blast Cells in Patients with High-Risk Myelodysplastic Syndrome
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Background and Objectives
Genetic disorders leading to the formation of a tumor clone contribute to the formation of an aberrant immunophenotype that differs from the antigenic profile of normal cells.

The aberrant myeloid stem cell immunophenotype in MDS may be associated with recurrent genetic abnormalities. Taking into account the spectrum of cytogenetic abnormalities in MDS, the identification of the antigenic profile of blast cells of myeloid origin associated with cytogenetic abnormalities will help to determine their prognostic significance, as well as to make a decision in the choice of therapy taking into account risk factors.

The aim of the study was to identify immunophenotic markers of blast cells in patients with high-risk myelodysplastic syndrome

Material and Method
The study included 54 patients diagnosed with MDS. When assessing the immunophenotypic profile of the analyzed 54 patients with MDS, it was found that the expression of CD38 was detected in 24 patients, of which 15 people (62.5%) were diagnosed with RAEB-II. High expression of CD25 on the surface of blast cells was detected in 6 patients, of which 4 were newly diagnosed RAEB-II.

High-risk cytogenetic markers in the study group of 52 patients were determined with the following frequency: 1 patient with TP53 gene mutation, 6 patients with structural changes in chromosome 7 (11.5%) and 9 patients with ≥3 complex aberrations (17.3%).

The analysis of the obtained data was performed using the program Statistica 8.

Results and discussion
We assessed the overall survival and the time to transformation into acute leukemia in patients with MDS, taking into account the immunophenotypic (CD25, CD38) and cytogenetic (chromosome 7 anomaly and complex aberrations) markers identified in our study, determined at the time of diagnosis (Table 1).

Table 1. – Comparative characteristics of overall survival and time to transformation into acute leukemia in patients with MDS of various prognostic scales, taking into account immunophenotypic and cytogenetic markers.

Markers	Overall survival (days)	Time to transformation (days)
Expression CD25 No expression of CD25	250 530	75 340
	p=0,04	p=0,035
Expression CD38 No expression of CD38	430 600	200 -
	p=0,38	p=0,035
Chromosome 7 anomaly	285	208
	p=0,38	p=0,044
Complex aberrations (≥3)	353	199
	p=0,19	p=0,18

Conclusions and Recommendations

According to our data, the median time to transformation (TTT) was 894 days (median overall survival (OS) is 1131 days).

Patients with MDS received a variety of therapies prior to transformation, including hypomethylating agents and low-dose chemotherapy.

The median TTT in the group of patients with MDS in the expression of CD25 is characterized by a 4.5-fold shorter time to transformation (75 days vs. 340).

The median OS in the group of patients with MDS with CD25 expression was 530 days versus 340 days in the group of patients without CD25 expression (p=0,04).

The TTT of patients with MDS was assessed similarly, taking into account the expression of CD38. The median TTT in the MDS group with CD38 patients was 200 days.

The median OS in the group of patients with MDS with CD38 expression characterized by a shorter period and accelerates the poor prognosis in comparison with the group of patients without CD38 expression (430 days vs. 600 days).

Thus, according to the presented calculations, the presence of expression of CD25 and CD38 on blast cells confirms the high risk of transformation into acute leukemia and shortening of the overall survival of patients.

15. Combined (Endovascular and Radiation Therapy) Treatment of Aggressive Large Plasmacytoma with Multiple Myeloma

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Introduction and Aim

Multiple myeloma is a mature B-cell neoplasm that accounts for 13% of all hematologic malignancies and has an age-adjusted incidence rate of nearly 6 per 100 000 persons per year. Multiple myeloma is defined by the presence of ≥10% of clonal plasma cells in the bone marrow (or a biopsy-proven extramedullary plasmacytoma) and by the evidence of end-organ damage attributed to the plasma cells disorder (hypercalcemia, renal insufficiency, anemia, and bone lesions). For most myeloma patients, the plasma cells proliferation is restricted to the bone marrow. However, a subset of multiple myeloma patients develops extramedullary myeloma, defined by the presence of clonal plasma cells outside the bone marrow.

Case Report

A 65-year-old woman was diagnosed with IgG-lambda multiple myeloma in 2020. At this time, she presented with symptomatic myeloma-related bone lesions, and a bone marrow aspirate confirmed the presence of 99.3% clonal plasma cells. The International Scoring System (ISS) score was high (III). The first line of therapy consisted of 5 cycles of bortezomib-dexamethasone. The patient achieved a partial response (PR) after the completion of therapy.

Three months after the last course of chemotherapy, patient was diagnosed with biopsy-proven extramedullary plasmacytoma of the left shoulder. CT scan revealed formation measuring 127x110x45mm. And one month later patient was administered to the emergency department with massive bleeding from arterial branches feeding the tumor of the left shoulder. To stop the bleeding arteriography with embolization of the arteries of the upper extremities was performed. The patient then started irradiation therapy (33 Gray) in order to reduce the size of the

tumor. Control CT scan revealed decreasing size of tumor compared to the previous study to 12x39x32 mm. The patient continued to receive bortezomib-dexamethasone therapy.

Discussion
Extramedullary myeloma is associated with an adverse prognosis in newly diagnosed and in relapsing multiple myeloma patients. To the best of our knowledge, no prospective therapeutic studies have been specifically dedicated to extramedullary myeloma patients. Radiotherapy of a soft-tissue plasmacytoma should be considered to improve local disease control and analgesia. Some authors recommend the combination of radiotherapy and IT chemotherapy. Innovative approaches using molecular targeted therapies or immune therapies (chimeric antigen receptor T cells) have recently shown promising results in a limited number of relapsed patients with extramedullary myeloma. Nevertheless, the outcome of extramedullary myeloma patients remains exceedingly poor, and innovative strategies are warranted.

Conclusions
The management of extramedullary myeloma is particularly challenging, and important questions relating to its definition, diagnosis, and treatment exist.

16. DNA Methyltransferase *DNMT1* Rs2228611 and Rs2228612 Polymorphisms and Their Effect on Breast Cancer Pathomorphological Characteristics and Patient Prognosis

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Background and Objectives
Breast cancer is the most frequently cancer and the leading cause of cancer related death among women worldwide. The number of new cases and mortality is expected to grow rapidly with population growth. Furthermore, populations adopt lifestyle behaviors that are known to increase cancer risk, such as smoking, physical inactivity, excess body weight and poor diet, different reproductive patterns and et. There is still a need of biomarkers, which could be used for disease phenotype prognostification and for evaluation of the disease outcomes.

Epigenetic regulation plays a major role in supervising the cellular RNA expression patterns, which are important for the normal biological functions in multicellular organisms. DNA methylation is one of epigenetic modification, it has a role in genomic imprinting, X chromosome inactivation, regulation of gene expression and tumorigenesis. DNA methyltransferases (DNMTs) have key role in establishing and maintaining DNA methylation patterns. Abnormal DNA methylation patterns are present in the process of malignant transformation. The aim of this study was to identify DNA sequence variation in DNMT1 and to analyse their effect on tumor phenotype and breast cancer patient prognosis.

Material and Method
In this study there were 100 participators with breast cancer. The study research protocol was approved by Kaunas Regional Biomedical Research Ethical Committee (protocol number BE-2-10 and BE-2-10/2014). Patient peripheral blood samples were used for genomic DNA extraction. The patient's clinical information was collected from medical documentation. Polymerase chain reaction restriction fragment length polymorphism analysis (PCR-RFLP) was performed for rs2228611 and rs2228612 polymorphism testing. Afterwards the associations between analyzed SNPs and tumor pathomorphological parameters and the cause of the disease was investigated. The statistical data analysis was performed with SPSS program.

Results
Two polymorphisms were analyzed in our study, DNMT1 rs2228612 and rs2228611. In the rs2228612 polymorphism analysis, the A allele (94.6%) was more frequent than the G allele (5.4%). The distribution of genotypes was as followed: AA - 89.1% and AG - 10.9%. In rs2228611 polymorphism the A and G alleles had almost the same frequencies: A allele - 49%, G allele- 51%. The distribution of genotypes was as followed: AA - 24.3%, AG - 49.5%, GG - 26.2%.

In the association analysis it was determined that patients with DNMT1 (rs2228611) polymorphism AG and GG genotypes had lower probability of tumor vascular infiltration than patients with AA genotype. In DNMT1 (rs2228612) polymorphism analysis the association between G allele and lymph node status was observed. The non-

carriers of G allele were 5.3 times more likely to have positive lymph nodes than the carriers of G allele. None of the polymorphisms showed any significant association with overall survival (OS), progression-free survival (PFS) and metastasis-free survival (MFS).

Conclusions and Recommendations
Our results suggest that DNMT1 rs2228612 and rs2228611 polymorphisms are important for breast cancer development and tumor spread. More research on the subject is needed as it can provide us with additional information on prognostic and predictive value of studied polymorphisms for more individualized patient approach.

17. *HSPA1A* Rs1043618 and Rs562047 Polymorphism Analysis and the Assessment of Their Effect on Tumor Pathomorphological Parameters and Breast Cancer Patient Prognosis

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Background and Objectives
Breast cancer became the most common cancer in women worldwide. There is a number of studies aiming to analyze different genetic variants and their effect on cancer phenotype and prognosis. Recently Heat shock proteins (HSPs) attracted scientific attention. HSPs participate in protein folding under stressors such as hypoxia, heat shock, and degradation process. HSPs also play a role across various types of cancers as they are implicated in cancer-related activities such as cell proliferation and metastasis. HSPs overexpression has been observed in various cancers such as ovarian, gastric, breast, colon, lung, and prostate cancers, however the data concerning germline HSP and carcinogenesis is limited. The aim of this study was to analyze the contribution of HSPA1A rs1043618 and rs562047 polymorphisms to tumor phenotype and breast cancer patient prognosis.

Material and Method
This is a retrospective study, involving 100 breast cancer patients. The study research protocol was approved by Kaunas Regional Biomedical Research Ethical Committee (protocol number BE-2-10 and BE-2-10/2014). Patient blood samples, acquired by clinicians in a time-frame from 2014-2016, were utilized for the genomic DNA extraction. rs1043618 and rs562047 polymorphisms were analyzed with polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. Patient clinical information (the age at diagnosis, pT, pN, G, ER, PR, HER2, disease outcome parameters (PFS, MFS and OS)) was collected from clinical records. The statistical analysis was performed using IBM "SPSS".

Results
In our study the distribution of tumor pathomorphological parameters was as follows: estrogen-positive (57%), progesterone positive (48%), HER2 overexpression 28% of tumors. Approximately half of the studied BC patients (46%) had positive lymph nodes. The majority (71%) of the tumors were well to moderate differentiated (G1 and G2), and most of them were classified as T1 (66%). During a follow-up period, 26% of patients experienced distinct organ metastasis, 31% – local progress, 22% - deaths. The median follow-up of patients was 115 months.

In our study, two polymorphisms in HSPA1A rs1043618, rs562047 genes were analyzed. In the rs1043618 polymorphism analysis, the C allele (66%) was more frequent than the G allele (34%). The distribution of genotypes was as follows: GG- 7%, CG- 54%, CC- 39%. In rs562047 analysis C allele (83.5%) was more common than the G allele (16.5%). The distribution of genotypes was as follows: GG - 4%, CG - 25%, CC - 71%. The frequencies of genotypes in HSPA1A rs1043618, rs562047 were according to the Hardy-Weinberg equilibrium.

The association between the selected SNP's (genotype and allele model) and tumor pathomorphological characteristics (ER, PR, HER2 status, G, T, N, L, V) was investigated. The association analysis was performed using Chi-square or Fisher's tests however the results were non-significant in both genotype and allelic model. In further association analysis, the univariate logistic regression was implemented. There was no significant links determined between the analyzed rs1043618 and rs562047 polymorphisms (genotype and allelic model) and tumor pathomorphological characteristics.

As far as survival analysis is concerned, the possible associations between HSPA1A rs1043618 and rs562047 polymorphisms and BC patient survival were assessed using Kaplan-Meier analysis (Log Rank test). No significant link between these SNP and PFS, MFS and OS were determined in both the genotype and allelic model.

Conclusions and Recommendations
The data indicate that rs1043618 and rs562047 polymorphisms in HSPA1A are not significantly related to tumor phenotypes and disease outcomes in this breast cancer patient group. For more precise analysis, studies, involving larger patient groups and implementing more advanced techniques in genetic testing, are suggested.

18. Optimization of an Electroporation Protocol Using Acute Myeloid Leukemia Cell Line as a Model: Role of the Pulse Strength, Duration and Concentration of Plasmid | *Best Poster Award Received*

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Background and Objectives
Transfer of biomacromolecules, such as mRNA, DNA or proteins, into cells is essential for cellular manipulation, genome editing or medical applications. Non-adherent cells are difficult to transfect with standard chemical-mediated delivery methods. Therefore, electroporation (EP) is becoming the most commonly used strategy to introduce a molecule of interest into suspension cell lines. It is well known that particular care must be taken with the viability of the transfected cells, since parameters, which increase transfection efficiency result in higher cell death rates.

In this work, we describe the methodologies that we have developed for optimization of EP settings to balance the highest possible transfection efficiency with robust UT-7 (acute myeloid leukemia) cell line viability and growth post-electroporation.

Material and Method
The UT-7 human cell line was purchased from the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany). Cell line authentication was done by DSMZ. These cells were used for square-wave electroporation experiments in which the following parameters were tested systematically: pulse strength, duration and different concentrations of the plasmid DNA.

The pEGFP (3400 bp) plasmid encoding a green fluorescent protein was used as an indicator for the assessment of transfection efficiency. Cells were transfected with pEGFP by EP at various conditions using the EP system BTX T820 (Harvard Apparatus). The transfection efficiency was determined by the counting pEGFP positive cells 48 h after transfection. Additionally, cells were observed with propidium iodide viability assay 48 h post-transfection for discrimination between live/dead transfected cells. Fluorescence of the cells was analysed with BD Accuri C6 (USA) flow cytometer.

Results
Firstly, different EP conditions were assessed, including variations in pulse strength (1200, 1400, 1600, 1800 V/cm) and pulse duration (100, 250, 500 and 750 µs). The entire experiment was performed in laboratory-made EP buffer containing 100 µg/ml final concentration of pEGFP plasmid. One high voltage electric pulse was applied. The best results were obtained applying 1200 V/cm pulse with duration of 500 µs and yielded 11 ± 1.61% pEGFP-positive live cells with total 42.3 ± 5.4 % viable cells in the sample compared to untreated cells. Further increase of pulse strength or pulse duration resulted in decrease of overall cell viability and amount of transfected viable cells. The intensity of fluorescence under these conditions was 19 % lower compared to that at 1400 V/cm 750 µs pulse where only 3.6 ± 0.5 % pEGFP-positive live cells with total 11.11 ± 1.2 % of viable cells were obtained.

Furthermore, various plasmid concentrations (20, 50, 100, 200 µg/ml) were used for transfection using 1200 or 1400 V/cm 250 µs pulse. The optimal plasmid amount with respect to viability and pEGFP-positive live cells was 200 µg/ml when a single pulse of 1400 V/cm for 250 µs was used.

Conclusions and Recommendations
Transfection efficiency in difficult to transfect myeloid non-adherent cells like UT-7 can be improved by testing and adjusting various electroporation parameters. The use of optimal pulse strength, electric pulse duration and concentration of plasmid greatly determines the transfection efficiency. This study demonstrates that electroporation can be a competitive transfection tool for difficult to transfect cell lines compared to conventional plasmid delivery methods.

19. Analysis of *PROS1*, *EPCR* and *PROC* Single Nucleotide Polymorphisms in Patients with Myeloproliferative Neoplasms

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Background and Objectives
Patients with Philadelphia-negative (Ph-) myeloproliferative neoplasms: primary myelofibrosis (PMF), essential thrombocythemia (ET) and polycythemia vera (PV); often encounter thrombotic events and other disease complications. It was suggested that the genetic variants that are responsible for blood coagulation play causal role in the development of thrombosis. In this work, we evaluated the effect of single nucleotide polymorphisms (SNPs) in PROS1, EPCR, PROC genes and the risk of developing thrombosis as well as clinical characteristics in patients with myeloproliferative disorders.

Material and Method
In the present study, we performed the analysis for PROS1 g.66847T>C, EPCR c.4678G>C, EPCR c.6936A>G, PROC c.565C>T polymorphisms for patients with myeloproliferative neoplasms. The study included 88 patients who were diagnosed with ET, PV or PMF between 2000 and 2014 at the Department of Hematology of the Institute of Oncology, the Lithuanian University of Health Sciences, Kaunas, Lithuania. Medical information was collected such as the patient's age, sex, history of arterial or venous thrombosis, mean platelet volume, platelet count.

Venous blood samples were collected in vacutainers with EDTA as anticoagulant. Genomic DNA was extracted from peripheral blood leukocytes using a commercially available DNA extraction kit, according to the instructions provided by the manufacturer (Thermo Fisher Scientific Baltics, Vilnius, Lithuania). Genomic variants in all of the cases were detected by employing a polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method.

Results
After genotyping 88 patients with Ph- myeloproliferative neoplasms, regression analysis revealed that the carriers of PROS1 66847 TC (p=0.007; OR 0.063; 95% CI 0.008 – 0.471), EPCR 4678 GC (p<0.001; OR 0.226; 95% CI 0.099 – 0.513), EPCR 6936 AG (p<0.001; OR 0.171; 95% CI 0.077 – 0.381) or GG (p=0.017; OR 0.083; 95% CI 0.011 – 0.641), PROC 565 CT (p=0.003; OR 0.158; 95% CI 0.047 – 0.534) or TT (p=0.009; OR 0.067; 95% CI 0.009 – 0.505), genotypes were associated with a lower risk of developing venous thrombosis. Furthermore, EPCR 6936 AG genotype could be considered as a protective factor against arterial thrombosis (p=0.026; OR 0.515; 95% CI 0.287 – 0.925). Logistic regression analysis showed that there is a lower chance of developing venous thrombosis for carriers of the PROC 565 CT genotype (p=0.003; OR 0.158; 95% CI 0.047 – 0.534) and 565 TT genotype (p=0.009; OR 0.067; 95% CI 0.009 – 0.505). Occurrence of thrombosis overall is lower for those who have 565 TT genotype by 0.357-fold (p=0.048; OR 0.357; 95% CI 0.129 – 0.992). The carriers of 565 CT (p=0.034; OR 0.389; 95% CI 0.162 – 0.931) and 565 TT (p=0.019; OR 0.267; 95% CI 0.089 – 0.803) genotypes had lower chance of decreased mean platelet volume.

Conclusions and Recommendations
It can be concluded that PROS1, EPCR and PROC single nucleotide polymorphisms may be associated with thrombotic events. However, more research is needed, since there are many conflicting results published regarding the complexity of the possible interactions between these genetic variants and predisposition to thrombotic events.

20. Analysis of *SIPA1* and *RRP1B* Gene Variants and Their Association with the Course of Cervical Cancer

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Background and Objectives

The signal induced proliferation associated gene 1 (SIPA1) is a gene that modifies the onset of metastases, that activates GTPases (proteins that catalyze the hydrolysis of guanosine triphosphate), is involved in mitogen-induced cell cycle regulation, may enhance or stop cell cycle progression and plays an important role in regulating cell adhesion. Ribosomal RNA processing 1 homolog B (Rrp1b) interacts with SIPA1 and thus contributes to the regulation of the metastatic process. According to the literature, relationships between single nucleotide polymorphisms (SNPs) of these genes and tumor spread to regional lymph nodes in other oncological diseases have been identified, but their significance for cervical cancer as one of the most common oncological diseases progression is still poorly understood.

We performed a study to investigate the distribution of SIPA1 gene functional polymorphisms (rs746429, rs931127) and RRP1B gene polymorphism (rs9306160) in a group of patients with cervical cancer. Then we analyzed the correlations between genotypes and alleles with tumor pathomorphological parameters and course of the disease.

Material and Method

172 patients with cervical cancer were enrolled in the retrospective study. Subjects were recruited from October 2014 to August 2020. Clinical data on patients and peritheral blood sample were collected. Genomic DNA was extracted from leucocytes. Molecular genetic studies were performed using the real time polymerase chain reaction method. The obtained SNPs were used in further statistical analysis in genotype and allelic models. The statistical analysis was performed using SPSS. The associations between the genotypes and alleles with tumor characteristics were assessed using Pearson's Chi-square or Fisher's Exact tests. Univariate and multivariate analysis to present odds ratios with 95% confidence intervals (CIs) and p-values were calculated with logistic regression. Differences in PFS and OS were assessed using hazard ratios (HRs) from univariate and multivariate Cox proportionate hazard models. p-value of <0.05 was considered statistically significant for all analysis.

Results

172 patients (mean (+/- SD age, 55.4 (+/- 13.5), 71.5% ≤50 years) were involved in the study. 91.3% of patients had squamose cell carcinoma histopatology type, adenocarcinoma accounted for 8.7% of cases. The majority of patients had T1-2 tumors (63.4%) and 36.6% were T3-4. Less than half (44.8%) of patients had positive lymph nodes. Metastases were found in the small group of cases (5.8%). A large part (73.3%) of tumors were well or moderate differentiated (G1 or G2). The distribution of genotypes was according to the Hardy-Weinberg equilibrium. The distribution of rs746429 genotypes was as follows: GG-26.2%, AG-51.7%, AA-22.1%. Data showed that rs746429 AG genotype compared to GG genotype decreased risk for bad differentiated (G3) tumors (OR = 0.329, 95% CI: 0.147-0.736, p = 0.007). Patients with A allele were less likely to have G3 cancer (OR = 0.424, 95% CI: 0.205-0.880, p = 0.021). AG genotype reduced the chance of having a worse prognosis (T3-4 and G3) cancer (OR = 0.255, 95% CI: 0.088-0.739, p = 0.012). Carrying the A allele statistically significantly reduced the chance of having T3-4 and G3 cancer (OR = 0.296, 95% CI: 0.114-0.769, p = 0.012). In case of rs931127, no significant link between genotypes or alleles and tumor phenotype or patient survival (PFS or OS) was detected. Rs9306160 genotypes are distributed as follows: CC-32.5%, TC-54.4%, TT-13.1%. Borderline significant association detected between TT genotype and metastases. Patients with TT genotype compared to CC genotype are more likely to have chance for metastases (OR = 5.889, 95% CI: 0.993-34.906, p = 0.051). In a multivariate analysis this association remained significant when the adjustment for age of patients was done (OR = 6.356, 95% CI: 1.046-38.619, p = 0.045). C allele was significantly associated with decreased risk for metastases (OR = 0.194, 95% CI: 0.057-0.661, p = 0.009). In cox regression analysis no significant link between genotypes or alleles and PFS was detected. There was significant link between genotypes and OS (Log Rank, p = 0.048). Patients with TT genotype had shorter OS than CT genotype holders (Log Rank, p = 0.012), but in a multivariate cox regression analysis no significant link between genotypes or alleles and OS was detected when the adjustment for tumor T, N, G and age of patients were done.

Conclusions and Recommendations

Our study suggests that SNPs rs746429, Rs9306160 may have the potential to be markers contributing to the assessment of the cervical cancer phenotypes and survival prognosis.

CONTENT

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