to the ABC transporter family, is lung resistance-related protein (LRP).
Since MDR requires one or combination of these genes expression, clinically relevant gene expression thresholds have been established and sequential samples from individual patients have been obtained for correlating MDR gene expression with the clinical course of disease. Studies in breast cancers, showed that expression of some of these genes correlates with poor response to chemotherapy.
In this presentation, I will provide an overview of the data (including ours) regarding the role of these genes in mediating drug resistance in breast cancer. In addition, I will briefly explain some of the strategies employed to overcome drug resistance in cancer cells.

P29

Hypothesis on targeted modification on human individual radiosensitivity as a new method of anti-cancer protection

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Goals: To represent and substantiate the hypothesis on targeted modification on human individual radiosensitivity on the genetic level. This is explained by the investigations which revealed that the formation of chromosomal aberrations in cell population is potentially an oncogenic event. Therefore, an increased individual radiosensitivity in comparison with mean population level value is the factor of radiogenic cancer and development of the risk. New candidate genes of human individual radiosensitivity connected with the formation of radiosensitive cell phenotype (BRCA1, BRCA2, XRCC1 etc.) are known today.
Methods: Analysis of chromosomes aberrations in culture of human lymphocytes, G2-radiosensitivity assay.
Results: The basis of the presented hypothesis is the position that targeted modification of individual radiosensitivity of human organism consists of the formation of normal mean population values of radiation effects and reactions. The proposed approach to modification on human individual radiosensitivity radically differs from the traditional 'radioresistance increasing', which assumes increased intensity of repair and other radioprotection systems functioning leading to their exhaustion in conditions of long-term irradiation and modification of individual radiation reactions. Pathology status is determined as the deviation from norm (increasing and reduction of parameter value is mean). Thus it is expedient to modify hypo- and hypersensitivity of human cells, tissues and organism in case of radiation therapy, the strategy of which is directed to maximal lesion (deviation) of tumor cells and protection of surrounding normal tissues.
Conclusions: The proposed hypothesis on targeted modification on human individual radiosensitivity is aimed at lowering the level of cancerogenic risk. The suggested method would increase an efficiency of the primary prevention of the development of the radiogenic cancer.

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The experimental proof of the usage of radioprotector inosine for cancer prevention

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Goals: To study the modification effect of inosine on the frequency of the radiation-induced cytogenetic effects in human somatic cells.
Methods: The irradiation of lymphocytes in vitro received from healthy donors had been done on therapeutic apparatus "Rockus" (with ^{60}Co source) in range 0.1–1.0 Gy. The metaphase analysis of chromosome aberrations had been carried out with group kariotyping. The inosine was added to the cell culture in the concentration of 0.01 mg/mL of blood 30 min before the irradiation.
Results: The highest radioprotective effect of inosine is observed when the cell culture is irradiated in the range between 0.1–0.2–0.3 Gy. The level of chromosome aberration decreases from 6.06±0.6; 7.06±1.6; 7.76±1.0 to 1.6±0.1; 2.6±0.4; 2.2±0.6 respectively and reaches the meanings of spontaneous level of genetic damages of human's cells. During this the coefficient of modification equals to 2.7–3.8. With a further increase in radiation up to 1.0 Gy, the radioprotective effect of inosine decreases and the coefficient of modification equals to 1.2. Under the effect of inosine the dose curve built on the basis of group-average frequency of chromosome aberration, is situated below the caliber curve with the same plateau in the range 0.1–0.3 Gy, which has been observed under the single radiation. Since the process of reparation always takes place with the usage of energy, inosine, which stimulates the processes of renovation in a genetic material of cells, thus decreases the level of chromosome aberrations, that mirror genome instability and may cause the development of radiation cancerogenesis.
Conclusions: The protective effect of inosine has been established on the genetic level of human somatic cells by using small doses of radiation. Inosine does not affect an abnormal form of the 'dose–effect' curve. Obtained data regarding inosine effect on human genome stability should be taken into account for a primary prevention of the development of radiogenic tumors as a remote negative effect of Chernobyl accident.

P31

Cardioprotection during cancer chemotherapy with the use of natural antioxidants: review of literature and results of own studies

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Cardiotoxicity is a frequent side effect occurring during cancer chemotherapy, often responsible for long term heart failure in surviving cancer patients. The abnormalities range from small changes in blood pressure and arrhythmias to cardiomyopathy. This type of toxicity has been most widely investigated in the case of anthracyclines, doxorubicin (DOX) in particular, the effective anticancer drugs whose clinical use is limited by cumulative dose-dependent injury to cardiac tissue, often jeopardizing patients' life despite successful cancer eradication. Though best described for DOX, cardiotoxicity as a side effect has been observed during chemotherapy with majority of antineoplastic agents displaying different mechanisms of action: mitoxantrone (cardiomyopathy), fluorouracil (myocardial infraction), cyclophosphamide and vinca alkaloids (cardiac necrosis), trastuzumab (cardiac disfunction), imatinib mesylate (congestive heart failure).
The cardiotoxicity of anthracyclines, at least in part, is attributed to their ability to redox cycle with molecular oxygen leading to the formation of superoxide radical that initiates cascade of reactive oxygen and nitrogen species. It has therefore been suggested that some phytochemicals with high antioxidant potential, when administered together with DOX (and perhaps other antitumor agents), could decrease the toxic side effects of chemotherapy and reduce the risk of heart failure. Cardioprotective properties have been shown for preparations obtained from such foods as grapes, garlic, tomato, spinach, as well as for melatonin (a hormone synthesized by the pineal gland, but also present in many edible plants), chalcones (precursors of all known

flavonoids), some herbal dietary supplements and vitamins A, C, and E. However, in the majority of these studies natural antioxidants were administered i.v., thus in a way typical for pharmacological approach. In contrast, our studies were designed so as to represent truly nutritional approach in which animals undergoing chemotherapy were fed the diet enriched in a particular food item – red beetroot (*Beta vulgaris*) juice (RBJ).

In these experiments, we checked whether the dietary intervention with RBJ might have any impact on therapeutic efficacy of DOX. For this purpose, leukaemia L1210 bearing mice were treated with DOX and fed RBJ ad libitum (instead of water) for 7 or 14 days. DOX was very effective in prolonging survival time of leukaemia bearing mice (ILS about 400%). However, only in groups receiving DOX in combination with RBJ total cures were observed. These were not sporadic events but concerned about 50% of animals.

In accompanying experiments, healthy or leukaemia L1210 bearing mice were fed RBJ ad libitum instead of water for 7 days and then were treated with DOX applied in different schemes. Control mice received water to drink. From control and treated mice, bloods and hearts were collected and analysed for various markers of oxidative insult. In mice fed with RBJ prior to DOX treatment, the damage of DNA in cardiomyocytes was clearly decreased indicating marked protection offered by the employed dietary intervention. As RBJ on its own had no antitumor effect, one can speculate that the improved outcome of chemotherapy resulted from reduced cardiotoxicity.

Our research suggests then that appropriately designed dietary intervention may offer very considerable benefits to cancer patients.

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The role of the anti-hyperglycemic metformin, a potential chemopreventive agent, in regulating tumour angiogenesis

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Metformin is a biguanide drug used as a first-line therapy for the management of type 2 diabetes. It has been shown to decrease hyperglycemia primarily by suppressing hepatic gluconeogenesis and consequent glucose release from liver. Moreover, metformin increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Prospective studies unveil a possible role for metformin in preventing cardiovascular diabetic complication and cancer risk. Metformin is known to work in part through activation of AMP-activated protein kinase (AMPK). AMPK is involved in cancer cell growth and metabolism by modulation of gene expression and translation. It has been observed that metformin activates AMPK in human umbilical vein endothelial cells (HUVEC). Endothelial cells are part of the tumor microenvironment system, and play a key role in the inflammation-driven tumor angiogenesis and metastatisation. New blood vessel formation is fundamental to allow tumor feeding and modification in vessel permeability and physiology is required for tumor dissemination. Here we show an overview of the general metformin mechanisms of action. We carried out HUVEC morfogenesis assay in matrigel in presence of metformin. We found that the compound affects normal tube formation. Moreover we assessed the effect of metformin on cell viability by a crystal violet assay in presence of different doses of the drug. We also observed that this compound affected endothelial cell proliferation and migration. Our preliminary results highlight a potential role for metformin as angiogenic-modulating agent for new therapeutic approaches.

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Chemopreventive strategies for cardiotoxicity induced by anticancer drugs

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The use of chemotherapeutic agents, radiation therapy, and molecular targeted therapies are all approaches that can injure the cardiovascular system both at a central level by deteriorating the heart function, and in the periphery by enhancing hemodynamic flow alterations and thrombotic events often latently present in oncology patients. Cancer patients showing signs of cardiovascular disease induced by the antineoplastic therapy are currently treated for the specific disease. Moving towards a protective chemoprevention approach, several drugs may be useful to flank chemotherapy to reduce cardiotoxicity without losing, and possibly even enhancing, anti-tumor activity. Most of these are still at an experimental stage, however some could easily be considered for clinical trials. Antioxidants such as the glutathione (GSH) precursor and analogue N-acetyl-L-cysteine can be given to patients at relatively high levels with an excellent toxicity profile. Numerous antioxidants and free radical scavengers found in dietary components such polyphenols and flavonoids, vitamins, micronutrients, enzymes and hormones, such as selenium, zinc, coenzyme Q10 and melatonin also show promise. Several plant derivatives such as Gingko biloba, grape seed extracts as well as polyphenols previously investigated for their anti-angiogenic, anti-inflammatory and anti-cancer activities (Epigallocatechin-3-gallate (EGCG) from green tea, resveratrol from red wine, and curcumin from curry) have been found to have cardioprotective activity in experimental studies. Since damage to the endothelium appears to underlie the cardiotoxicity of a variety of chemotherapeutic drugs, agents that prevent endothelial cell apoptosis should provide protective effects. Interestingly, investigation of some anti-angiogenesis compounds, in particular those that target the NF-κB pathway, have also been found to render endothelial cells more resistant to apoptosis induced by external stimuli. These include NAC and deguelin, while xanthohumol and triterpenoids did not perturb endothelial cell viability in vitro. The concept is that these agents force the endothelial cell into a quiescent state that leads to increased resistance to apoptosis.