

SUMMARY

Plasma cell dyscrasias are a group of diseases whose common feature is production of a homogeneous protein known as monoclonal protein by a single clone of plasma cells. One of the more frequently observed diseases from this group is multiple myeloma (MM), a neoplasm associated with a clonal proliferation of plasma cells. Clinical course of MM varies considerably. The introduction of new drugs into the treatment standards caused an increase in the percentage of patients responding to treatment. Nevertheless, the disease is still considered incurable.

The development of symptomatic MM that requires treatment is preceded by the occurrence of a premalignant condition defined as monoclonal gammopathy of undetermined significance (MGUS). This condition is asymptomatic and often discovered incidentally during the diagnostic process of other diseases. Although occurrence of MGUS precedes development of plasma cell dyscrasia, its presence does not always determine the onset of the disease.

A relatively new field of science is metabolomics, which aims to characterize the metabolome, i.e. the complete set of metabolites or small molecule chemicals involved in biological processes occurring in the cell. Metabolomic studies are used in hemato-oncology to determine the usefulness of the method for earlier diagnosis of cancer, selection of patients for clinical trials, determination of biomarkers of response to treatment, as well as identification of potential markers of malignant transformation and aggressive course of the disease, which could play a role in qualifying patients for early treatment.

The aim of the study was to determine the metabolic profiles of patients with selected plasma cell dyscrasias: MGUS and multiple myeloma. An additional objective was to identify potential biomarkers of MGUS progression to MM.

A total of 100 people participated in the study. The study group consisted of patients of the Hematology Department of the University Clinical Hospital in Białystok with newly diagnosed MGUS (30 patients) and multiple myeloma (50 patients) at various stages of the disease during the collection of the material. Both groups were similar in terms of median age. The control was a group of healthy people matched in terms of sex and age - blood donors and volunteers (20 people).

The study design was to obtain a venous blood sample from fasting patients during routine morning diagnostic examinations. The obtained material, after initial processing, was evaluated using a liquid chromatograph coupled with a sensitive mass detector (LC-QTOF-MS) using a non-targeted analysis method (metabolomic fingerprinting).

After initial data processing by LC-MS, 751 metabolic features were obtained. Taking into account the experimental weight and obtained fragmentation spectra and comparing them to the molecular weights and reference spectra in Internet databases it was possible to identify 104 compounds that differentiated metabolomic profiles of patients in particular groups.

In the MGUS group, compared to the control group, an increase in the level of identified compounds from the group of carnitines and sphingomyelins (SM) and compounds such as bilirubin, carboxy-methyl-propyl-furanopropanoic acid, benzothiazolethion and piperine was observed. Compared to the control group, in the group of patients with MM, an increase in the level of carnitines, phosphatidylethanolamines (PE) and compounds such as bilirubin, carboxy-

methyl-propyl-furanopropanoic acid and benzothiazolethion was observed. In both groups (MGUS and MM) when compared with healthy study participants decreased levels of lysophosphatidylinositols (LPI), eicosapentaenoic acid (EPA), arachidonic acid and an inconclusive trend of changes in the levels of phosphatidylcholines (PC), lysophosphatidylcholines (LPC) and lysophosphatidylethanolamines (LPE) were observed. Additionally, unlike MGUS vs. control group, in the MM group there was a decrease in the level of SM. In the last comparison (MM vs. MGUS), a decrease in the level of carnitines, SM, LPI, LPC, PC, PE, bilirubin and EPA was found - the exceptions were PC (34:3), PE (16:0/18:2), LPE (16:0), the level of which increased among patients with MM compared to patients with MGUS.

The observed changes in the level of identified metabolites are associated with changes in the cellular metabolism of clonal plasma cells, for example with increased energy demand,

synthesis of cell membranes, activation of enzymes and production of pro-cancer metabolites or inflammatory processes that promote carcinogenesis and drug resistance of cancer cells.

The above study allowed to determine significant differences in metabolomic profiles in individual study groups (MGUS, MM, control group). This information can not only be used in the process of diagnosing and monitoring patients and their stratification, but also enable the identification of a group of patients with MGUS among whom early anti-cancer treatment should be considered as well as be used to determine new targets for drugs in MM therapy.