**Streszczenie w języku angielskim**

Proteasomes are multisubunit enzyme complexes that play very important role in oncogenic transformation by degradation of damaged intracellular proteins. Therefore, the level of their concentration and activity are increased in patients with malignant diseases, especially in the case of multiple myeloma. The major breakthrough in the treatment of multiple myeloma was the application of first generation selective reversible proteasome inhibitor (PI) – Bortezomib. Its anticancer activity depends on inhibiting the activity of the transcription factor NF-κB, accumulation of misfolded or damaged proteins, which in turn results in caspase activation and cell death. Proteasome inhibitors are new, special class of drugs, which have some different mechanisms of action compared to older drugs. Additionally, they have a stronger effect on cancer cells than normal cells, sensitise them to chemotherapeutics and overcome the multidrug resistance.

 This research was performed to evaluate proteasome concentration and ChT-L activity in newly diagnosed patients with multiple myeloma, and to determine the usefulness of these parameters in monitoring of treatment of patients.

 This two-stage study based on the same methodology. The proteasome ChT-L activity was assessed through ongoing monitoring of the production of AMC, which comes from degradation of fluorogenic peptide (AMC-substrate) by ChT-L activity of the proteasome. Proteasome concentration was measured by commercial ELISA kit (*Enzo Life Sciences*).

 The aim of the first experiment was to determine which material (plasma or serum) is better for measuring ChT-L activity and proteasome concentration. Seventy plasma and serum samples drawn from multiple myeloma patients and 31 samples of plasma and serum from healthy volunteers were included in this study. In the multiple myeloma patients, the median of proteasome ChT-L activity and concentration was significantly higher in plasma compared to serum. We also observed that the plasma proteasome ChT-L activity correlated positively and significantly with the concentration of β2-M, total calcium, and with LDH activity. Additionally, we noticed that plasma proteasome concentration correlated positively and significantly with concentration of serum protein, creatinine, β2-M, total calcium, and LDH activity.

The purpose of the next stage of this experiment was to evaluate the usefulness of measuring proteasome parameters in monitoring of treatment of multiple myeloma patients.
A total of 78 patients with newly diagnosed multiple myeloma were included in this study. Their blood samples were available for collection right before the chemotherapy, after its third cycle, and at the end of the treatment. Twenty-six patients were qualified for the CTD scheme of therapy and 52 patients for the therapy with PI – bortezomib. In the group of patients who respond to the PI therapy (CR+VGPR+PR), the values of proteasome ChT-L activity and proteasome concentration at the third cycle and at the end of chemotherapy were significantly lower than the baseline. The meaningful decrease in activity, but not in concentration, was shown also in our CTD responders. In the group of patients treated by PI, who did not achieve remission (patients with SD and PD) after the chemotherapy, we demonstrated that the median of proteasome ChT-L activity after third cycle of treatment was evaluated above 20% compared to the baseline and grew to the end of therapy. However, we observed only slight increase in the proteasome concentration. On the other hand, in the CTD non-responders group of patients at the end of the therapy, the analysis showed only modest increase in the activity and concentration compared to the baseline values, standing at the limit of significance.

 The study also revealed that pre-treatment values of proteasome ChT-L activity predicted better response to chemotherapy, and the patients who achieved at least PR had
a significantly higher baseline value compared to non-responders, regardless of the used scheme of chemotherapy. Additionally, the analysis performed by the Kaplan-Meier method shows that only patients treated by PI with a baseline value of proteasome ChT-L activity higher than the median, had a significantly longer PFS compared to subjects with value lower than the median.

 The data presented in this study show that measuring plasma proteasome ChT-L activity can be employed in monitoring of treatment and prediction of progression free survival in patients with newly diagnosed multiple myeloma. Moreover, it can be also used as a biomarker for predicting clinical response to treatment in these patients.