

Abstract

Background: Malignant melanoma is one of the most malignant types of skin cancer. Incidences are on the rise worldwide and in the Czech Republic an increase of 5% in diagnosed cases is noted each year. Early detection and early surgical removal are associated with reduced mortality. The strong aggressiveness of this malignant disease is caused by its local invasive growth and tendency to metastasize early.

Aim of the study: The malignant melanoma is highly metabolically active tumor that releases a number of enzymes, cytokines, growth hormones and other molecules. The aim of this work was to determine the usability of preoperative and postoperative serum and plasma levels of biomarkers in primary diagnosis of tumor activity and in the postoperative follow-up care. These findings would be of clinical relevance for the patient's prognosis, modification of multimodal treatment and follow-up of patients with malignant melanoma.

Methods: We measured circulating levels of several biomarkers in a group of 77 patients with malignant melanoma and cohort of 34 patients without cancer as a control group. Using routine immunoassays and novel multiplex xMAP technology, we measured: thymidine kinase, tissue polypeptide specific antigen, protein S100A, osteoprotegerin, osteopontin, insulin-like growth factor 1 and 3, epidermal growth factor, interleukin -2, -6, -8, -10, vascular endothelial growth factor and basic fibroblast growth factor. Samples of peripheral blood were collected preoperatively (the day of surgery), 10 days after surgery and subsequently at 3-months intervals according to clinical examinations.

Results: We found statistically significant correlation of the concentration of the protein S100A serum with the tumor load, lymph node status and clinical prognostic information such as Breslow thickness, ulceration or tumor localization. Serum levels of tissue polypeptide specific antigen also correlated with tumor load and were increased in advanced melanoma compared to preoperative levels in primary melanoma. Differences in protein S100A and tissue polypeptide specific antigen profiles were determined between melanoma patients and healthy subjects. No other proliferative markers in our study reflected any association with studied variables. As for angiogenic factors reflected in the presented study, we found no relation between serum levels of vascular endothelial factor or basic fibroblast factor and studied parameters. Increasing osteopontin expression has been identified as a powerful predictor of sentinel lymph node involvement. Serum levels were correlated with lymph

node status and higher serum levels were observed in advanced melanoma compared to preoperative levels in primary melanoma. Differences in osteopontin and osteoprotegerin profiles were found to exist between melanoma patients and healthy subjects. Dynamic studies of serum levels of interleukins have shown that serum levels of interleukin-2 were correlated with sentinel lymph node positivity/negativity in preoperative levels and preoperative serum levels of interleukin-6 were correlated with Breslow thickness or tumor localization. Interleukin-8 has been found to be elevated in melanoma group compared to the healthy control group. Insulin-like growth factor reflected tumor load and was elevated in melanoma patients compared to healthy controls in our study. As for sensitivity and specificity of studied markers - the ROC curves did not highlight any acceptable concentration.

Conclusion: According to new and promising results in immunotherapy, we should aim our attention at increasing the accuracy of patient follow-up. Using biomarkers in primary diagnosis and then during follow-up, we can determine the biological activity of the tumor.