Summary

Background Incidence of malignant melanoma (MM) is rising worldwide. This tumour is immunogenic and angiogenic. Vascular endothelial growth factor (VEGF), interferons and matrix metalloproteinases (MMPs) are natural agents with important role both in immunosuppression/stimulation, and angiogenesis. Interestingly, evidence is currently emerging that activation of angiogenesis leads to immunosuppression both at the local and systemic levels. These are very complex and interconnected processes. Mortality of MM is high and depends very much on early detection. Plateau phase on mortality curves we´ve seen recently in developed countries thanks to early diagnosis, public awareness of skin pigment lesions, emphasis on primary and secondary prevention, and also thanks to new potent drugs. Cornerstone of treatment in MM is surgery, if the tumour is diagnosed early. We can find surgery sufficient and safe only if the tumour hasn´t reached angiogenic switch and vertical growing yet. We cannot exclude trend to create metastasis in tumours with Breslow more than 1mm. The same we can say about ulcerated tumours or nodal metastasis. Patients after surgery for MM stage IIB, IIC and III according to AJCC are thought to be high risk. Their risk of recurrence and death is 35-40%. Loco-regional recurrence after previous surgery has prognosis even worse. These are clinical the stages in which adjuvant oncologic treatment is found to be appropriate. The question is what is the right choice of adjuvant treatment.

Aim In this study, our aim was to establish interferon alpha-2b as an anti-angiogenic agent and show the complexity of angiogenesis and immunomodulation through the serum levels of VEGF and MMP-8 in high-risk resected MM before and after adjuvant therapy with high-dose interferon alpha-2b (HDI). Clinical outcomes of patients were also evaluated.

Material and methods We prospectively measured serum levels of VEGF and MMP-8 by ELISA in 29 patients with high-risk resected MM receiving adjuvant HDI. Blood samples were collected before and within one week after the end of the treatment.

Results To see the results clearly, we divided patients into two groups. The first group of patients, whose VEGF serum level decreased after HDI (66%), showed long-term complete remission. The mean VEGF serum level in these patients decreased from 779.4 pg/ml to 446.2 pg/ml. This downward trend in VEGF was statistically significant. The second group of patients who did not show a decrease in VEGF serum level after HDI (34%) and they had no clinical benefit from the treatment. The mean VEGF serum levels in second group was 408 pg/ml before the treatment and 500 pg/ml after HDI. Results for MMP-8 were ambivalent. Metabolism of interferons is too fast to be administrated according to measured levels.

Conclusion Non-specific immunotherapy HDI reduces angiogenesis. Our results are in line with the current research view of complexity of angiogenesis and immunomodulation/suppression. Non-specific immunotherapy HDI disrupts the immunosuppressive effect of angiogenesis on development of immune response against tumours and supports antitumour response in both direct and indirect way. The interference of HDI with activation of angiogenesis and tumour progression can explain good clinical outcomes of patients with decrease in serum VEGF. The outcomes of MMP-8 are inconclusive, its role remains unclear, and MMP-8 does not seem to work as tumour suppressor.