Summary

Angiogenesis is currently considered a crucial process in the biology of malignant growth. While the role of angiogenesis is clear in solid tumors, much less knowledge exists about its significance in hematological malignancies. Chronic lymphocytic leukemia is the predominant leukemic disorder on the western hemisphere. It is typical of extremely heterogeneous clinical course with overall survival ranging from several months to dozens of years. Therefore, maximal efforts are devoted to best possible prognostication of newly diagnosed CLL patients.

The purpose of the thesis was to try to better characterize the exact role of angiogenesis on prognosis and its relationship to other prognostic parameters in CLL. Angiogenesis was quantified using two principal methods: concentrations of circulating angiogenic activators bFGF, VEGF, sCD105 and inhibitor endostatin in peripheral blood plasma were measured using commercially-available ELISA in untreated CLL patients (bFGF and VEGF, n=73; endostatin, n=62; sCD105, n=79). Bone marrow microvessel density (MVD) was analysed immunohistochemically in bone marrow biopsies from untreated CLL patients using monoclonal antibodies against CD34 (n=22) and von Willebrand factor (vWF, n=17). Angiogenic activators bFGF, VEGF, sCD105 and inhibitor endostatin were all significantly elevated in peripheral blood plasma of CLL patients. Levels of sCD105 were significantly elevated in patients with advanced clinical stages and with progressive disease; in addition, higher sCD105 correlated with shorter progression-free survival. bFGF concentrations were significantly higher in patients with mutated vs. unmutated IgVH genes while VEGF was elevated in patients with low ZAP-70 expression. In addition, levels of bFGF and VEGF significantly decreased after successful treatment based on fludarabine. With regard to bone marrow microvessel density, we have detected its elevation in CLL patients over controls but no association with classical or modern prognostic factors was found. Likewise, there was no correlation between microvessel density and circulating angiogenic cytokines. The values of MVD were significantly affected by choice of endothelial marker (significantly higher MVD using CD34 vs. vWF). In conclusion, our data indicate that angiogenesis may play an important role in CLL biology. Further studies using larger patient cohorts and longer follow-up are warranted in order to confirm our results and further contribute to better understanding of angiogenic processes and refined prognostication of individual patients in CLL.