Summary

Prognostic factors in chronic lymphocytic leukemia

Introduction: Search for new prognostic markers in order to improve prognostic accuracy and predict clinical outcome at the time of diagnosis has recently become one of the major trends in chronic lymphocytic leukemia (CLL). *Aims of the project*: Assessment of selected markers of apoptosis and angiogenesis and their potential as new prognostic factors and correlation with conventional and modern prognostic factors and clinical course. *Patients and Methods*: We evaluated serum levels of tumor necrosis factor alpha (TNF-α), transforming growth factor beta-1 (TGF-ß1) and fibroblast growth factor-2 (FGF-2) using comercially available enzyme-linked immunosorbent assay; furthemore, we quantified expression of type II receptor for transforming growth factor beta (TGFßRII) and type 2 receptor for FGF-2 (FGFR2) on CLL cells using flow cytometry analysis in 75 previously untreated patients with CLL (47 males and 28 females, median age, 65 years, range, 38-82) and healthy donors. *Results*: We found significantly elevated TNF-α in patients with CLL compared to the control group ($p<0.0001$); high expression of TNF-α was associated with unfavourable prognosis: significantly higher TNF-α was present in patients with Rai high-risk group compared to low- and intermediate-risk groups ($p = 0.0008$ and $p = 0.0097$), with high serum beta 2-microglobulin ($p = 0.045$), massive lymphadenopathy ($p = 0.0083$), unmutated genes for variable region of immunoglobulin heavy chain (IgVH) ($p = 0.041$) and unfavourable cytogenetic aberrations ($p = 0.0014$). In addition, patients with progressive CLL had significantly higher TNF-α than those with stable clinical course ($p = 0.0009$); time to treatment (TTT) was significantly shorter in patients with higher TNF-α ($p = 0.0049$). Higher TGF-ß1 concentrations were associated with favourable prognosis, i.e. with Rai low-risk group compared to high-risk group ($p = 0.011$), patients without massive lymphadenopathy ($p = 0.041$), patients with mutated IgVH ($p = 0.012$) and ZAP-70 negativity (zeta-associated protein of 70 kilodaltons) ($p = 0.044$). Patients with progressive CLL had significantly lower TGF-ß1 levels than those with stable course ($p = 0.0014$) and TTT was significantly longer in patients with higher TGF-ß1 ($p = 0.016$). Patients with Rai high-risk group had significantly lower TGFßRII expression than those with low-risk group ($p = 0.022$). Serum concentrations of FGF-2 were significantly higher in patients with CLL compared to the control group ($p < 0.0001$). FGFR2 expression was significantly lower in CLL compared to the control group ($p = 0.042$). The prognostic significance of FGF-2 and FGFR2 was not found. Significant and independent prognostic factors for overall survival were high serum concentrations of TNF-α and massive lymphadenopathy (evaluated by ultrasound) ($p = 0.036$ and $p = 0.047$). *Conclusions*: Based on our results, TNF-α and TGF-ß1 possess prognostic significance in CLL; further research in this direction may also be important therapeutically, because these signal pathways could serve as possible treatment targets. Low TGFßRII expression in advanced stages could contribute to resistance to anti-proliferative effect of TGF-ß and worse

prognosis. Massive lymphadenopathy proved to be a negative prognostic feature; therefore detection by ultrasound could be useful in daily clinical practice.