Summary

Title: Study of new prognostic markers in patients with chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemic disorder of adults in Western hemisphere. It is characterized by clonal proliferation and accumulation of morphologically mature lymphocytes in bone marrow, peripheral blood and lymphatic tissues. Clinical course of CLL is extremely heterogeneous with some patients living for decades without need of therapy while others succumbing to the disease within several years. Thus, there has been great interest in identifying prognostic markers that could be used to distinguish patients with an aggressive form of CLL, because they might benefit from early intervention.

The process of angiogenesis has been shown to be crucial for growth and metastasizing ability of solid tumors. Angiogenesis in "liquid" tumors was supposed to be less important, nevertheless numerous recent studies have shown enhanced angiogenesis in many hematological malignancies including CLL. Elevated levels of circulating angiogenic cytokines and increased expression of genes encoding angiogenic factors have been reported in recent years in patients with chronic lymphocytic leukemia (CLL) but data regarding their prognostic and predictive significance are still limited.

Therefore, in the present main study based upon our prior pilot results, we measured mRNA expressions of angiopoietin-2 (Ang-2), fibroblast growth factor-2 (FGF-2) and endoglin (CD105) by reverse transcription quantitative PCR in purified $CD19^+$ cells from 97 untreated CLL patients (median age, 63 years; males, 67%; Rai 0/I+II/III+IV stages, 29/55/16%; unmutated variable region of immunoglobulin heavy chain (IGHV) genes, 59 %) and evaluated their possible association with established prognostic factors and clinical course of the disease. Higher expression of Ang-2 was significantly associated with unmutated IGHV genes ($n = 80$, $p = 0.0023$) and time to first treatment ($n = 97$, $p = 0.0437$). Higher CD105 expression was significantly associated with unmutated IGHV ($n = 80$, $p < 0.001$), high ZAP-70 expression ($n = 70$, $p = 0.0076$), Rai stage I-IV ($n = 97$, $p < 0.001$), progressive clinical course of CLL ($n = 97$, $p = 0.0003$), shorter time to first treatment ($n = 97$, $p < 0.001$) and shorter overall survival ($n = 97$, $p = 0.0260$). Expression of FGF-2 was not significantly associated with any of the prognostic markers.

These results indicate that elevated expression of Ang-2 and in particular CD105 by CLL cells is associated with unfavorable prognostic features and clinical outcome. Expression of both cytokines by malignant lymphocytes appears to play an important role in biology and progression of CLL; thus angiogenic molecules seem to be promising prognostic markers in CLL.