[ABSTRACT WM3.7]

Serum concentrations of angiogenic cytokines in Waldenstrom's Macroglobulinemia: the ratio of angiopoietin-1 to angiopoietin-2 and angiogenin correlate with disease severity

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Introduction: Angiogenesis represents an essential step of disease progression in several hematological malignancies. Microvessel density is increased in 30% of patients with Waldenstrom s macroglobulinemia (WM), but there is very limited information for the role of angiogenic cytokines in WM. The aim of this study was to evaluate the serum levels of different angiogenic cytokines in WM and explore possible correlations with clinical data. Patients & Methods: We studied 78 serum samples from 56 WM patients (38M/18F; median age: 71 years) in different phases of their disease. Twenty-four patients were evaluated prior any kind of treatment: 21 symptomatic before therapy administration and 3 asymptomatic who did not need therapy. Twenty patients were studied during active disease after treatment (refractory/relapsed WM) and 12 patients during remission after response to previous therapy. Furthermore, 11 patients with IgM-MGUS and 30 healthy controls were also studied. Serum concentrations of VEGF, angiogenin, angiopoietin-1 (Ang-1), Ang-2 and basic fibroblast growth factor (bFGF) were measured using an ELISA methodology (R&D Systems, Minneapolis, MN, USA) as well as serum levels of VEGF-A (Diaclone SAS, Besancon, France). Results: All patients had elevated values of VEGF, VEGF-A, angiogenin, Ang-2, and bFGF compared with controls ($p<0.001$). The ratio of Ang-1/Ang-2 was reduced in WM ($p<0.001$) but not in IgM-MGUS patients. Angiogenin levels correlated with disease status: continuous elevation from healthy subjects (mean±SD: 239.5±58.4 ng/mL) to IgM-MGUS (312.9±86.8 ng/mL), asymptomatic WM (340.1±52.2 ng/mL) and symptomatic, untreated patients (552.3±268.9 ng/mL, $p<0.001$); then reduced in patients at remission (369.9±219.9 ng/mL, $p=0.03$) and increased again in relapsed/refractory disease (458.7±162 ng/mL, $p=0.04$). Angiogenin correlated with serum albumin ($r=-0.392$, $p=0.001$). WM patients with lymphadenopathy had reduced levels of Ang-1/Ang-2 ratio compared with WM with no lymphadenopathy (2.5±0.5 vs. 9.4±7.6, $p<0.01$). Furthermore, the ratio of Ang-1 to Ang-2 correlated with beta2-microglobulin ($r=-0.572$, $p<0.0001$), hemoglobin ($r=0.33$, $p=0.01$) and albumin ($r=0.276$, $p=0.049$). Finally, a positive correlation was observed between VEGF-A and beta2-microglobulin ($r=0.284$, $p=0.03$). Conclusion: We showed, for the first time in the literature, that patients with WM have increased serum levels of angiogenin, VEGF, VEGF-A, bFGF and reduced values of Ang-1/Ang-2 ratio, which seems to be implicated in WM severity. The confirmation of our results will give the potential for using angiogenin for the follow-up of WM patients and targeting angiogenic molecules for the development of novel anti-WM agents.