The Role of CCL3 (MIP-1 alpha) in Waldenström's Macroglobulinemia

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C-C motif ligand 3 (CCL3) chemokine, previously known as macrophage inflammatory protein-1 alpha (MIP-1 alpha), is a member of the C-C chemokine family. CCL3 has chemotactic function against monocytes, macrophages, mast cells, and other cell types. Circulating CCL3 is elevated in hematopoietic malignancies, including multiple myeloma and chronic lymphocytic leukemia (CLL). CCL3 is produced by CLL cells and its circulating levels have independent prognostic value for survival in CLL patients (Sivina et al, Blood 2011;117:1662-9). Our group has shown that malignant cells of patients with Waldenström's macroglobulinemia (WM) also express CCL3 (Terpos et al, Clin Lymphoma Myeloma Leuk 2011;11:115-7). However, there is no information for the prognostic significance of CCL3 in WM.

To address this issue, we studied 55 newly-diagnosed patients with symptomatic WM who required therapy. Fifty-eight per cent were males and their median age was 66 years (range: 39-82 years). According to ISSWM, 22% were low risk, 60% were intermediate risk and 18% were high risk patients. Circulating CCL3 was evaluated using an ELISA methodology (R&D Systems, Minneapolis, MN, USA) in all patients and in 40 healthy, age- and gender-matched, controls. Bone marrow biopsy sections of all patients at diagnosis were immunochemically tested for the expression of CCL3 (using an anti-CCL3 monoclonal antibody by Santa Cruz Biotechnology, Santa Cruz, CA, USA), CD20, CD79a, CD138, MUM-1, as well as for mu, gamma, alpha heavy and kappa and lambda light immunoglobulin chains. The immunoreactivity of CCL3 was examined on the basis of positive lymphoplasmacytic and/or plasma cells with a cut-off value of >20% positive cells to be defined as positive expression.

Median circulating CCL3 levels were higher in WM patients 66 pg/ml (range 10.6-1627 pg/ml) compared to healthy controls (median 15.4 pg/ml, range: 1.4-54 pg/ml; p=0.01). In all WM cases, the whole number of the neoplastic cells, including CD20(+)/CD138(-)/MUM-1(-)/CIgM(kappa)(+) B-lymphocytes (small lymphocytes, lymphoplasmacytoid lymphocytes and rare immunoblasts) as well as CD20(-)/ CD138(+)/MUM-1(+)/CIgM(kappa)(+) plasma cells revealed strong cytoplasmic positivity for CCL3. Elevated circulating CCL3 correlated with high serum beta2-microglobulin levels (r=0.385, p=0.019), with ISSWM stage (p=0.016), and increased bone marrow microvessel density (r=0.25, p=0.041).

All patients received rituximab-based regimens as first line therapy and 67% of them achieved at least a minor response. With a median follow-up of 3 years, the median survival of all patients has not been reached yet, while the 3-year probability of survival was 75%. The 3-year probability of survival for low-, intermediate- and high-risk patients per ISSWM was 88%, 80% and 43%, respectively (p=0.045). We then evaluated the effect of circulating CCL-3 on patients' survival using as a cut-off value the median CCL3 level. Increased serum CCL3 predicted for shorter PFS (27.8 months versus not reached, p=0.048; Figure).

In conclusion our results suggest that CCL3 is produced by WM cells and its high circulating levers are associated with inferior PFS. These observations support a role of CCL3 in WM biology through interactions of the malignant clone with the marrow microenvironment and reveals CCL3 as a potential target for developing novel drugs against WM.

Progression free survival and CCL3 (MIP-1 alpha) serum levels in WM patients