Effect of Circulating CCL3, Which Is Produced by Malignant Cells of Waldenström’s Macroglobulinemia, on Patients’ Survival

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Introduction

- C-C motif ligand 3 (CCL3) chemokine, previously known as macrophage inflammatory protein-1 alpha, is a member of the C-C chemokine family. CCL3 has chemotactic function against monocytes, macrophages, mast cells, T-lymphocytes, dendritic cells, eosinophils and natural killer cells.
- Circulating CCL3 is elevated in hematopoietic malignancies, including multiple myeloma and chronic lymphocytic leukemia (CLL). CLL cells produce CCL3 and a recent study has shown that circulating CCL3 is an independent prognostic factor for survival in CLL patients (Sivina et al, Blood 2011;117:1662-9).
- Waldenström’s macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by lymphoplasmacytic bone marrow infiltration along with an IgM monoclonal gammapathy.
- Our group has previously shown that malignant cells of WM patients 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.

Patients - Methods

- We studied 41 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, individuals who served as controls.
- Bone marrow biopsy sections of all patients at diagnosis were immunohistochemically 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.

Results

- In all WM cases, the whole number of the neoplastic cells, including CD20(+) /CD138(+) / MUM-1(-)/ IgM(+) B-lymphocytes (small lymphocytes, lymphoplasmacytoid lymphocytes and rare immunoblasts, Fig.1) as well as CD20(+) /CD138(+) / MUM-1(+)/ IgM(kappa)(+) plasma cells (Fig.2) revealed strong cytoplasmic positivity for CCL3.

![H&E, CD20, CCL3, CD138, MUM1, IgM, CIGM](image)

- 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; Fig.3).
- Elevated circulating CCL3 correlated with high serum beta2-microglobulin levels (r=0.385, p=0.019), but there were no strong correlations between CCL3 levels and ISSWM stage, serum LDH, serum albumin, serum IgM levels or age.

- The median survival of all patients has not been reached yet, while the 3-year probability of survival was 77%.
- The 3-year probability of survival for low-, intermediate- and high-risk patients per ISSWM was 100%, 77% and 38%, respectively (p=0.018).
- We then evaluated the effect of circulating CCL3 on patients’ survival using as a cut-off value the level of 54 pg/ml, which was the highest CCL3 value of our control group. The median survival for WM patients with CCL3 levels ≥54 pg/ml was 67 weeks, while it has not been reached for patients with CCL3 levels <54 pg/ml (p=0.093; Fig.4).

Conclusions

- Our results suggest that CCL3 is produced by WM cells and its high circulating levels are associated with a clear trend for inferior survival.
- 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.

The authors have no relevant conflicts to disclose for this abstract.