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Abstract Title: Tumor Associated Macrophages' cytokines; CD163, CCL4, CCL2 and IL-10 as possible new biomarkers in Waldenstrom's Macroglobulinemia with emphasis on AWM.

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## **Tumor Associated Macrophages' cytokines; CD163, CCL4, CCL2 and IL-10 as possible new biomarkers in Waldenstrom's Macroglobulinemia with emphasis on AWM.**

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### **Background:**

Tumor associated macrophages (TAMs) constitute a major part of the bone marrow microenvironment and play a pivotal role in growth of various hematologic malignancies. Cytokines secreted by TAMs, such as hemoglobin scavenger receptor CD163, along with TAMs' chemoattractant cytokines, such as Monocyte Chemoattractant Protein-1 (MCP-1/CCL2), Macrophage Inflammatory Protein (MIP-1b/CCL4) and Interleukin-10 (IL-10), can be detected in their soluble forms and reflect their burden. Interaction between these cytokines and their levels correlate with disease progression, mainly in solid tumors. The availability of new prognostic markers is important to discriminate in the heterogenous WM patients group, the subgroups at risk to present with an aggressive disease and those although asymptomatic at diagnosis, that might need treatment in the near future {Asymptomatic WM (AWM)}.

### **Aims:**

In our study, we aimed to investigate the clinical utility of the TAMs-associated cytokines in patients with WM.

### **Methods:**

204 patients were included of whom 82 had WM, 88 had AWM, 14 had IgM-MGUS and 20 had LPL. We defined AWM as patients receiving treatment at least 6 months after the initial diagnosis. Clinical and laboratory characteristics were reviewed, after patients' informed consent form. Their median age was 66.5 years (33-92 years), 56% were men and 44% women. Serum sCD163, IL10, CCL4 and CCL2 were tested in frozen sera collected at patients' diagnosis in 75, 72, 64 and 61 patients respectively, and in healthy individuals (HI). Measurements were performed by ELISA (Duo-Set R&D Quantiquine) according to the manufacturer's instructions. Median value of variables was used as the cut off point. Median time to treatment (TTT) was 6 months (0-452) and median overall survival (OS) was 75 months (0-452). Statistical analysis was performed with the SPSS v.26 software.

### **Results:**

Median sCD163 was 28163 pg/ml (16696 - 97286) in patients with WM and 27368 (25410-51319) pg/ml in patients with LPL, which was statistically significant compared to 26821 (14281-97280) pg/ml in patients with IgM-MGUS and 26826 pg/ml (11831- 97286) in HI. Median IL10 was 22 pg/mL (0-49439 pg/mL) in HI, and 284 pg/ml (0- 98850) in patients. Median CCL2 was 347.5 pg/ml (291-1829) in HI and 497,45 pg/ml (6,64-1713,11) in patients, and median CCL4 was 202 pg/ml (185,53-578,61) in HI and 278,61 (0-2462) in patients.

Shorter TTT was observed in AWM patients with CCL4 above median ( $p = 0,018$ ) (Figure 1). Decreased OS was observed in AWM patients with a ratio of CCL4/IL10 above median ( $p = 0,05$ ) (Figure 2). AWM patients with CCL2 above median had a strong tendency for decreased OS ( $p=0,08$ ) (Figure 3). A statistically significant decreased OS ( $p=0,033$ ) (Figure 4) was observed in all WM patients with CCL2 values above median.

#### Summary/Conclusion:

Our findings reveal that TAMs' burden is elevated in patients diagnosed with WM, as reflected by sCD163. TAMs-related cytokines could predict TTT and OS in AWM and are indicators of OS in all WM patients, supporting that cells of the monocyte-macrophage lineage may play a role in disease pathophysiology. sCD163, IL10 CCL2 and CCL4 could eventually prove to be significant biomarkers in WM.

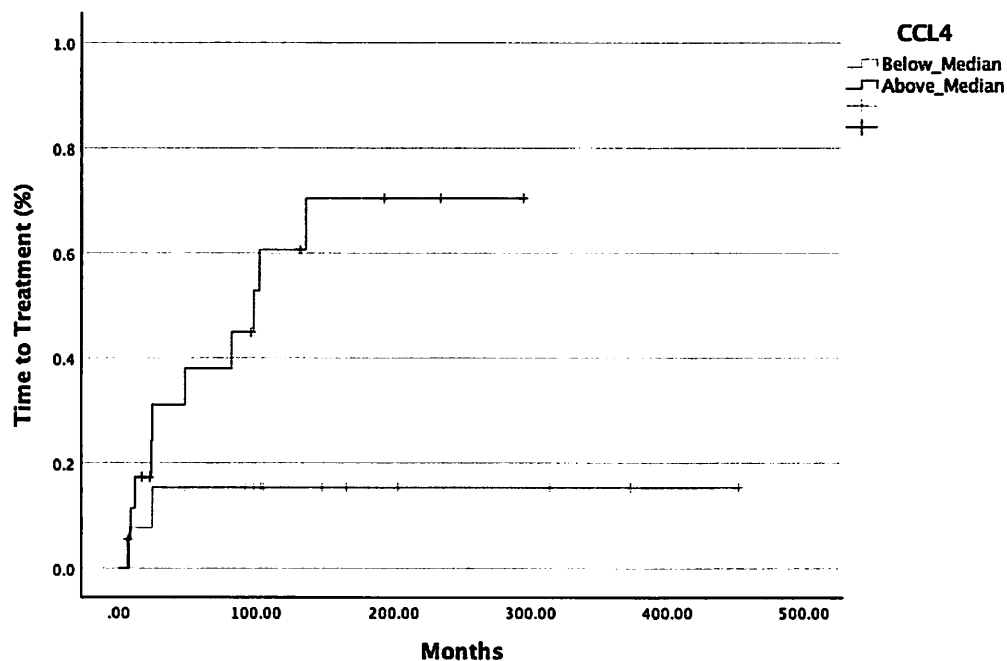


Figure 1: Shorter TTT in AWM patients with CCL4 above the median ( $p=0.018$ ).

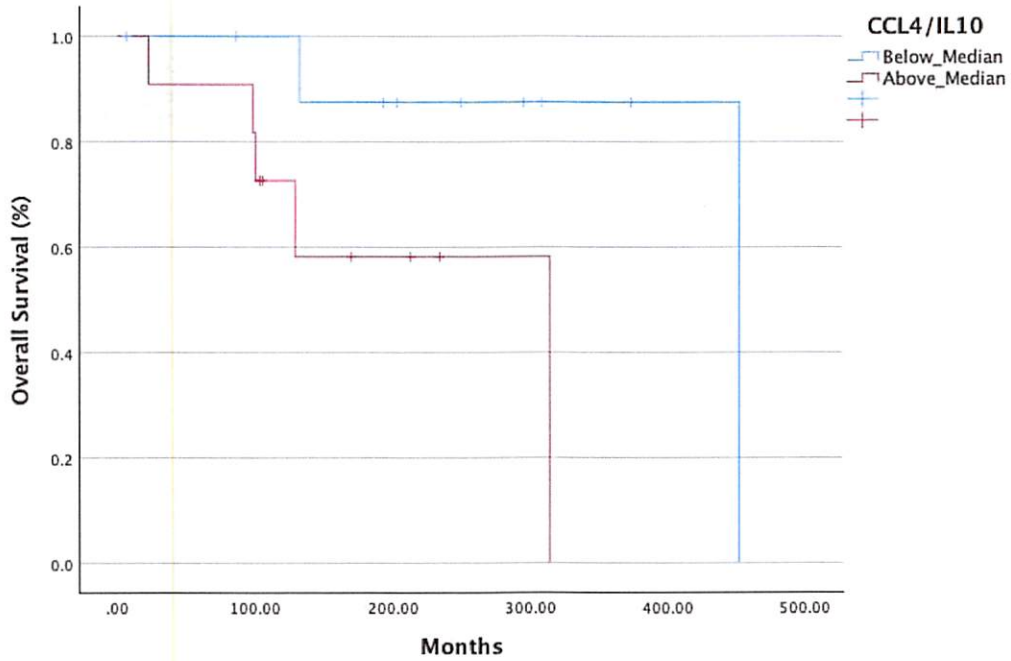


Figure 2: Decreased OS in AWM patients with a ratio of CCL4/IL10 above the median ( $p=0.05$ ).

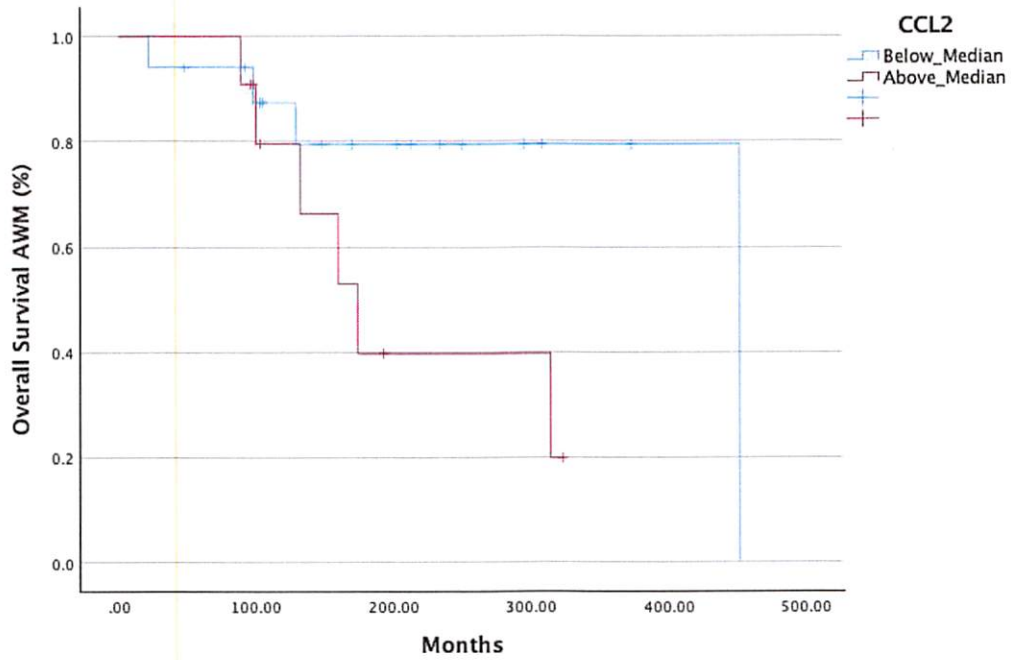


Figure 3: Decreased OS in AWM patients with CCL2 above the median ( $p=0.08$ ).

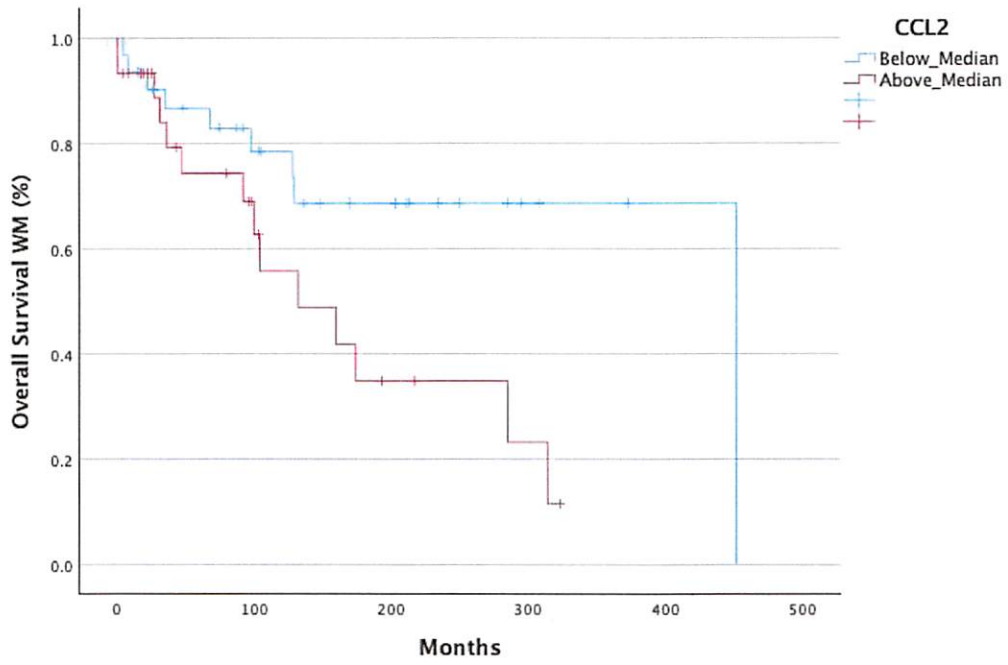


Figure 4: Decreased OS in all WM patients with a ratio of CCL2 above the median ( $p=0.033$ ).