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Title: Role of Inflammation in Waldenstrom Macroglobulinemia: Insights from a Multicenter Study

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Introduction

Waldenstrom Macroglobulinemia (WM) is a chronic B-cell lymphoproliferative neoplasm treated with chemo-immunotherapy (CIT) and Bruton's tyrosine kinase inhibitors (BTKi). Recently, two French teams (Elessa et al., BJH 2023 and Forgeard et al., Haematologica 2023) reported large WM cohorts associated with elevated CRP, called inflammatory WM (iWM). Two different cutoffs of CRP (5/20mg/L) were proposed, and disparate associations were found (e.g., survival, genomics). This project aims to define the inflammatory form and assess the impact of inflammation on outcomes in WM.

Methods

Data compilation from the two retrospective studies (Saint Louis and Pitié-Salpêtrière Hospitals) was performed with the inclusion of a third center (Necker Hospital). Inflammatory status based on repeated CRP measures was evaluated in the last 6 months before initiating the first treatment. Bulk DNA from blood and bone marrow (BM) samples were analyzed in six French centers (Saint Louis, Lille, Cochin, Pitié-Salpêtrière, Necker and Henri-Mondor). Next-generation sequencing (NGS) was performed on blood (n=77) or BM samples (n=30) in three centers (Saint Louis, Cochin and Lille).

Results

Of 639 WM patients from the multi-centric cohort, 457 (72%) required treatments for symptomatic WM, including 176 with CRP < 5 mg/L (41%), 120 with CRP between 5 and 20 mg/L (26%), and 165 with CRP ≥ 20 mg/L (33%). Between the groups, no difference was observed for demographic or clinical presentation. There was no correlation with tumor burden (IgM peak or lymphocytic-plasma cell infiltration in BM). By contrast, the prevalence of 6q deletion increased with CRP levels ($p<0.001$), while a reverse effect was observed for *CXCR4* mutations ($p=0.02$). Concerning outcome, WM patients with CRP ≥ 20 mg/L had a shorter time to next treatment (TTNT) after CIT than patients with CRP < 20 mg/L (median: 1.5 years vs. 5 years, $p<0.001$), but longer TTNT after BTKi (median: 4 years vs 3 years, $p=0.008$). Based on these results and the absence of TTNT with CRP at 5 mg/L, inflammatory WM (iWM) was defined as CRP ≥ 20 mg/L. Owing to the known relation between clonal hematopoiesis (CH) and inflammation, we addressed the prevalence of CH in iWM by performing NGS in 46 patients with iWM and in 61 non-iWM. CH was more prevalent in iWM than non-iWM (67% vs. 28%, $p<0.001$). CH presence seems not to be associated with del6q ($p=0.71$). CRP levels in WM increased in patients with both del6q and CH in comparison with the 3 other combinations of del6q/CH ($p=0.005$, Figure).

Conclusion

The inflammatory form of WM defined by CRP ≥ 20 mg/L represents 30% of the symptomatic patients and is associated with distinct outcomes after CIT and BTKi. It might rely on intrinsic factors, including the 6q deletion detected in 50% of iWM, as well as extrinsic factors, as suggested by the association with clonal hematopoiesis involving the myeloid compartment, and both may act synergistically. Further analyses at the single cell level before and after BTKi are ongoing to delineate better and characterize the inflammatory form of WM.

Figure. Relation between CRP, del6q and/or CH presence (size of dots for VAF of mutation) in WM patients. One point represents one patient. CH and 6q deletion were associated with increased CRP levels. The association of both is associated with the highest CRP level.