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Quantitative MYD88 L265P Monitoring by ddPCR Reveals Clinically Relevant Discordance with IgM in Waldenström Macroglobulinemia

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Background

Serum IgM remains the cornerstone biomarker for response assessment in Waldenström macroglobulinemia (WM), as reflected in IWWM-11 criteria. However, IgM reflects secretory activity rather than direct tumor burden and may not fully capture disease biology. We evaluated whether quantitative MYD88 L265P mutation burden in bone marrow (BM) and peripheral blood (PB) by droplet digital PCR (ddPCR) correlates with marrow infiltration and whether it aligns with IgM-based response assessment.

Methods

Fifteen consecutive MYD88 L265P - mutated WM patients were serially monitored. Mutation burden in BM and PB circulating tumor DNA (ctDNA) was quantified by ddPCR at baseline and during therapy. Marrow tumor infiltration was independently assessed by flow cytometry and histopathology. Correlations between mutation burden, IgM, M-protein, and marrow involvement were analyzed. Discordance was defined as non-parallel kinetics between IgM response and molecular mutation burden.

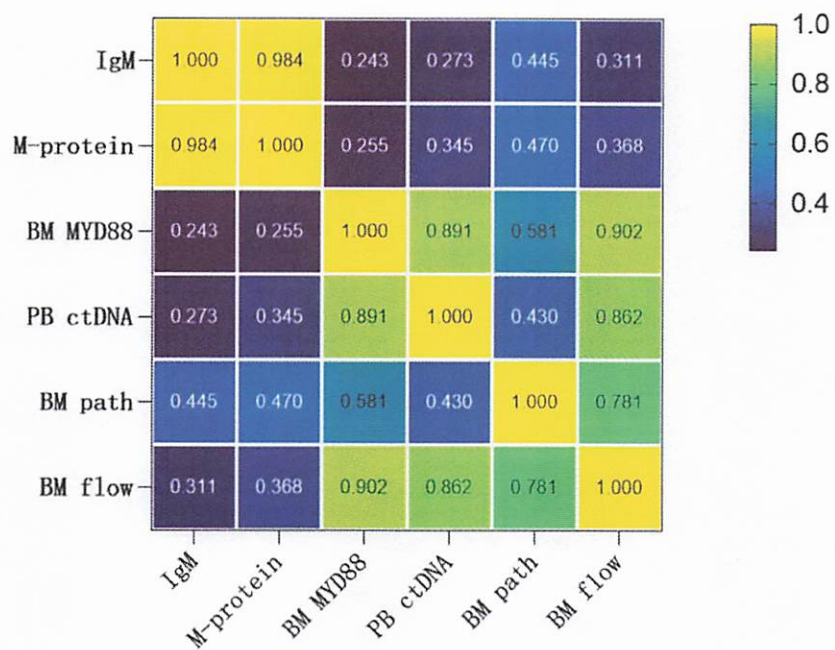
Results

Median baseline IgM was 24.9 g/L. ddPCR demonstrated a strong correlation between BM MYD88 mutation burden and flow cytometry - measured lymphoplasmacytic infiltration ($r = 0.902$, $P < 0.01$), as well as between PB ctDNA burden and flow cytometry infiltration ($r = 0.862$, $P < 0.01$). In contrast, neither BM nor PB mutation burden correlated significantly with serum IgM or M-protein levels.

Longitudinal analysis revealed discordance between IgM kinetics and molecular mutation burden in 5/15 patients (33%). Notably, 3 patients achieved biochemical partial response or very good partial response by IgM criteria despite persistent or minimally reduced molecular burden, while 2 patients demonstrated substantial molecular decline without proportional IgM reduction. In several cases, molecular dynamics more closely paralleled changes in marrow infiltration than IgM levels. This discordance in biomarker assessments is commonly identified in patients with multiple extramedullary lesions, disease transformation, BTKi rebound after drug discontinuation, or oligosecretory phenotype.

Conclusions

Quantitative MYD88 L265P assessment by ddPCR strongly correlates with marrow tumor infiltration but not with serum IgM dynamics. Nearly one-third of patients demonstrated discordance between biochemical and molecular response parameters. These findings suggest that IgM and molecular tumor burden represent biologically distinct dimensions of disease activity in WM. Integration of molecular monitoring may refine response evaluation and warrants prospective validation within future IWWM response frameworks.



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