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Monoclonal Gammopathy Defines a Distinct Clinical in Chronic Lymphocytic Leukemia Across Therapeutic Eras

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OBJECTIVES

- We leveraged a largest known retrospective cohort of 2075 CLL patients (1999-2024).
- We discovered that the presence of an IgM-MG identifies a clinically and genetically distinct subgroup of CLL patients

CONCLUSIONS

- Monoclonal gammopathy in CLL is more than an epiphenomenon. It appears to be interwoven with the molecular and immunologic pathways of disease aggressiveness and treatment resistance.
- IgM-type MG-positive CLL patients are diagnosed at later clinical stages and exhibit distinct IGHV mutation statuses and IGHV segment usage.
- IgM-type MG often denotes a clone with intrinsic survival advantages that diminish dependence on BTK signaling, thereby contributing to resistance to BTK inhibitors.
- IFE detection is a simple, accessible, and cost-effective assay that may serve as a clinically relevant biomarker for disease stratification in CLL. Its routine use could enhance risk assessment by identifying biologically aggressive subgroups, thereby supporting more personalized therapeutic strategies. Given the suboptimal response to targeted therapies observed in patients with IgM-MG, alternative or combinatorial treatment approaches are urgently needed to improve outcomes in this high-risk population.

INTRODUCTION

- Approximately 10-20% of chronic lymphocytic leukemia (CLL) patients present with monoclonal immunoglobulinopathy (M-protein) at diagnosis, while 20-50% exhibit hypogammaglobulinemia (hypo-γ). However, the prognostic implications of M-protein and hypo-γ remain inconclusive, especially in the context of targeted therapies. There is a paucity of research on whether immunoglobulin levels guide treatment decisions.

METHODS

- We conducted a retrospective analysis of 2,075 CLL patients diagnosed at our institution from January 2000 to January 2024. All the patients had their serum immunoglobulin levels tested at diagnosis, with 1,223 undergoing immunofixation electrophoresis. We collected baseline clinical data, including cytogenetic abnormalities and IGHV mutation status.

RESULTS

- In this retrospective analysis of 2,075 CLL patients (1999–2024), MG was detected in 18.47% cases, with IgM (8.18%), IgG (8.09%), light-chain (1.14%) and IgA (1.06%) subtypes demonstrating divergent clinicogenomic profiles. Patients with IgA-MG were older at diagnosis, whereas those with IgG-MG had younger age and a higher frequency of mutated IGHV. In contrast, IgM-MG was associated with unmutated IGHV, elevated LDH and β2-microglobulin, and higher frequencies of TP53 aberrations and enrichment of MYD88, BIRC3, DDX3X mutations. IgG-MG was associated with shorter time to first treatment (TTFT) only, whereas IgM-MG correlated with significantly inferior TTFT, progression-free survival (PFS), and overall survival (OS). Subgroup analyses revealed that the adverse prognostic impact of MG was pronounced in IGHV-mutated CLL but attenuated in unmutated cases. Prognostic discrimination by the CLL-IPI remained robust regardless of MG status. Notably, patients with IgM-MG did not experience significant survival benefit from targeted therapy compared with conventional regimens.

Figure 1. Distribution of different subtypes of MG

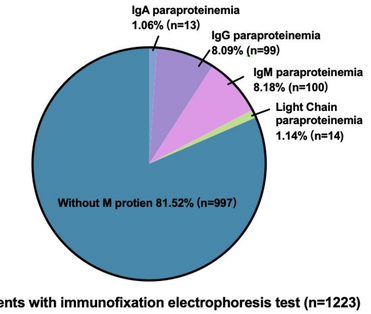


Figure 2. Proportion of patients with mutated IGHV in different MG group.

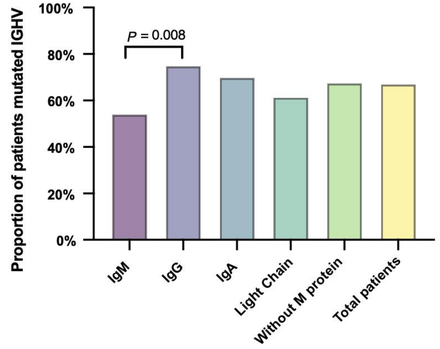


Figure 3. Mutation rates in patients with different types of paraproteinemia.

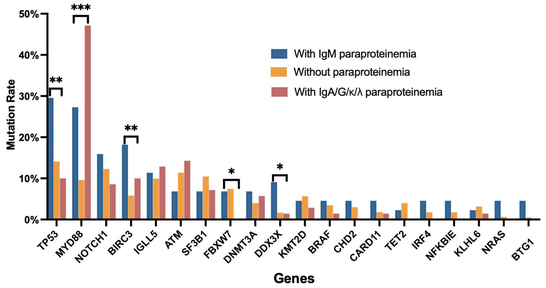


Figure 4. Survival analysis of monoclonal gammopathy-Positive and -Negative CLL Patients

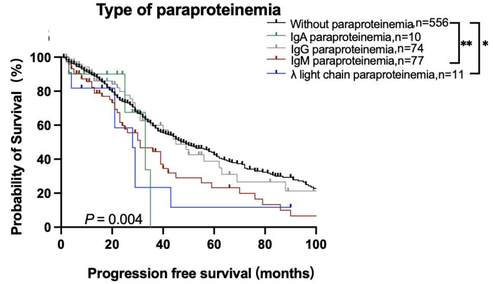


Figure 5. Survival curve of based on first-line treatment subgroups.

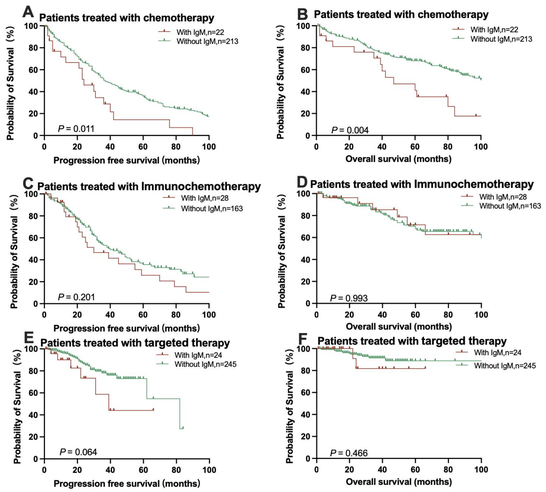
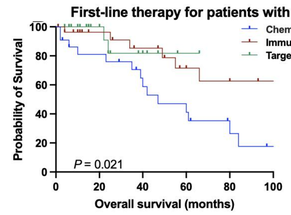


Figure 6. Survival curves according to different treatment regimens in patient with IgM MG



- IgM-MG did not significantly affect PFS or OS in patients receiving immunochemotherapy but was associated with shorter survival in patients treated with traditional chemotherapy.
- In patients receiving targeted therapy as first-line treatment, those with IgM-MG showed a trend toward inferior PFS compared to IgM-MG-negative counterparts, though this difference approached but did not reach statistical significance