

Impact of *MYD88* and *CXCR4* Mutational Status on Clinical Phenotype and First-Line Treatment Outcomes in Patients with Waldenström Macroglobulinemia

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Introduction: Waldenström macroglobulinemia (WM) is characterized by somatic mutations in the *MYD88* (predominantly L265P) and *CXCR4* genes, which are present in over 90% and up to 40% of patients, respectively.

Methods: We analyzed 201 patients with available *MYD88* and 152 patients with *CXCR4* mutational status at diagnosis and their outcomes.

Results: 171/201 (85.1%) patients were *MYD88*-L265P mutated (*MY88mut*) and 30 (14.9%) wild-type. *MY88mut* had significantly higher baseline platelet count compared to wild-type (*MYD88wt*) (median 243.0[IQR 170.5–323.5] vs 195.5[122.8–256.5] $\times 10^9/L$, $p=0.023$). No other clinical or laboratory differences were noted ($p>0.05$). Overall Major Response Rate (MRR) was 61.4% (105/171) for *MYD88mut* versus 53.3% (16/30) for *MYD88wt* ($p=0.424$). The duration and the median time to response (DOR) did not differ between the two groups.

Among patients treated with frontline BTK inhibitors (BTKis), *MYD88mut* achieved a significantly higher MRR than *MYD88wt* (77.5% [31/40] vs 28.6% [2/7], $p=0.018$). Moreover, a trend for an increased median time-to-response was observed for *MYD88wt* treated with BTKis (7.3 months), compared to *MYD88mut* (1.0 months). Among *MYD88wt*, BTKis significantly improved response odds (aOR=2.50, $p=0.029$). In multivariable logistic regression adjusted for R-IPSSWM, neither frontline treatment regimen nor *MYD88mut* status were independently predictive of achieving a major response.

Among 152 patients with available *CXCR4* status, 38 (25.0%) were mutated (*CXCR4mut*) and 114 (75.0%) were wild-type (*CXCR4wt*). The S338X nonsense mutation was the most prevalent single alteration ($n=14$), followed by the synonymous I142I variant ($n=6$), while the remaining 20 patients presented with other missense and frameshift mutations. *CXCR4mut* patients had higher bone marrow infiltration at baseline compared to *CXCR4wt* (72.5% [56.2–80.0] vs 60.0% [35.0–80.0], $p=0.020$).

Among those with the S338X *CXCR4mut* overall MRR was 64.3% (9/14) compared to 61.6% (85/138) among others ($p=0.998$). The duration and time-to-response did not differ between the two groups. Moreover, there were no significant differences in MRR by treatment subgroup.

Among patients with MYD88 data, a total of 45 (22.1%) deaths and 74 (36.8%) relapse events were recorded over a median follow-up of 7.38 years (95%CI:5.57-8.87). No significant differences were observed in survival outcomes among *MYD88mut* vs *MYD88wt*. The 5- and 10-year cumulative incidence of WM-related mortality was 2.7% at both timepoints for *MYD88mut*, compared to 3.3% and 17.5% for *MYD88wt*, respectively. Cause-specific Cox regression analysis did not demonstrate any difference in the hazard of WM-related death between the two groups (HR=2.60; p=0.176).

Among patients with CXCR4 data, a total of 38 (25.0%) deaths and 57 (37.5%) relapse events were recorded over a median follow-up of 8.33 years (95%CI:6.98-9.57). No significant differences were observed in survival outcomes among *CXCR4wt* vs *CXCR4mut*. The 5- and 10-year cumulative incidence of WM-related mortality was 3.0% at both timepoints for *CXCR4mut*, compared to 2.7% and 8.2% for *CXCR4wt*, respectively. *CXCR4* mutational status did not significantly impact the hazard of WM-related death (HR=2.71; p=0.351).

Conclusion: Mutational profiling of MYD88 and CXCR4 is important in WM, as these genotypes translate into distinct clinical phenotypes and treatment outcomes, such as lower MRRs in *MYD88wt* patients receiving first-line treatment, especially with BTKis, and increased bone marrow infiltration in *CXCR4mut*.

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