

CXCR4 mutations and outcomes after first-line therapy in Waldenström macroglobulinemia

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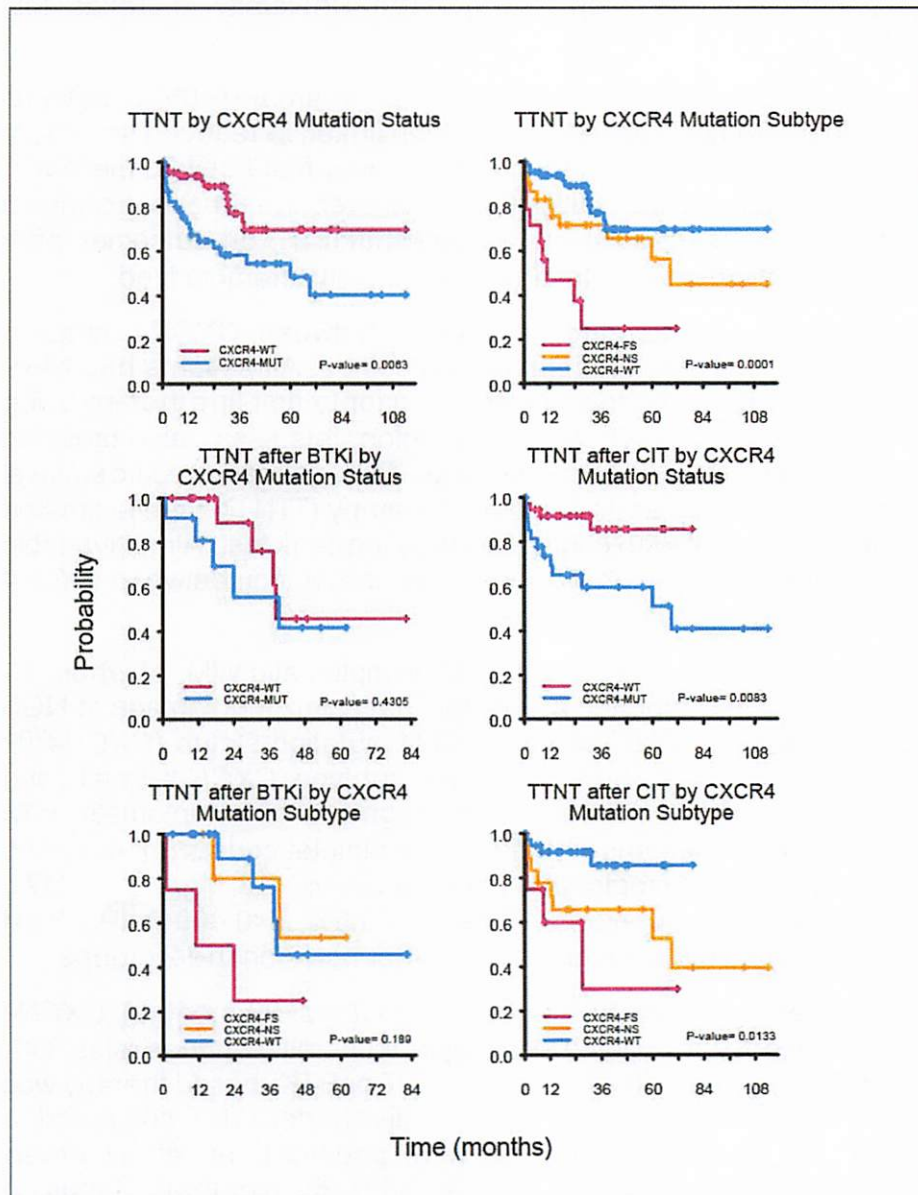
INTRODUCTION: Somatic mutations affecting *CXCR4* occur in around 40% of patients with Waldenström macroglobulinemia (WM) and have been linked to reduced sensitivity to BTK inhibitor (BTKi)-based therapy and inferior outcome after first-line treatment with Bendamustine-Rituximab chemoimmunotherapy (CIT). However, the prognostic impact of *CXCR4* mutation subtypes (nonsense (NS) and frameshift (FS)) on outcomes after first-line treatment for symptomatic disease remains incompletely characterized.

METHODS: We retrospectively analyzed the association between *CXCR4* mutation status and type with treatment response and survival outcomes. All patients had next-generation sequencing (NGS) of bone marrow specimens prior to first-line therapy using an assay with > 250x coverage of the *CXCR4* coding region; this assay also provided mutation statuses of *MYD88* and *TP53*. Overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), and time to next therapy (TTNT) were estimated using the Kaplan-Meier method, with group comparisons by log-rank test. A multivariable Cox proportional hazards model evaluated the independent association between *CXCR4* and TTNT, adjusting for other significant covariates.

RESULTS: The study cohort included 116 patients with symptomatic WM, of whom 63 (54%) were male and 107 (93%) self-reported as White/Caucasian. Median age at NGS testing was 68 years. Patients were stratified by *CXCR4* mutation status (*CXCR4*^{Wild-type}(WT), n=68 and *CXCR4*^{mutated}(MUT), n=48) and by mutation subtype (*CXCR4*^{FS}, n=16 and *CXCR4*^{NS}, n=31). Significant baseline differences at diagnosis of symptomatic WM between *CXCR4*^{MUT} and *CXCR4*^{WT} patients included lower platelet counts (median 185 vs. 234×10⁹/L, p=0.0002), lower β2-microglobulin (median 3.4 vs. 3.8 mg/L, p=0.017), and higher co-occurrence of *MYD88* mutations (100% vs. 73.5%, p<0.0001); IPSSWM and MSS-WM risk score categories did not significantly differ between the 2 groups.

Median follow-up after NGS test date was 47 months (95% CI: 42~99 months). *CXCR4* mutation status was not significantly associated with major or overall response rates, OS, CSS or PFS after first-line therapy, regardless of whether CIT or BTKi-based therapy was used. However, *CXCR4*^{MUT} was associated with significantly shorter TTNT compared to *CXCR4*^{WT} (median TTNT 60 months vs. not reached; p=0.006), an effect driven predominantly by *CXCR4*^{FS} (median TTNT 11 vs. *CXCR4*^{NS} (69 months)). Subgroup analyses revealed that these TTNT differences were observed with first-line CIT but not BTKi-based therapy. On multivariable analysis with *TP53* mutation status and DLBCL transformation, *CXCR4* mutation status remained independently associated with shorter TTNT (HR 2.56, 95% CI 1.25–5.27, p=0.011).

CONCLUSIONS: *CXCR4* mutations in WM are associated with a distinct baseline biological profile including lower platelet counts and lower $\beta 2$ -microglobulin but do not appear to compromise depth of response or overall/cancer-specific survival after first-line therapy. However, *CXCR4* mutations, particularly frameshift subtype, are independently associated with earlier need for next-line therapy, suggesting a shorter remission after first-line CIT but not BTKi-based regimens. These findings support incorporating *CXCR4* mutation status into risk stratification for treatment sequencing and surveillance planning and warrant prospective validation in larger multi-center cohorts.



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