

Title:

Cytogenetic abnormalities in WM: a Hidden Driver of disease progression in Waldenström Macroglobulinemia (WM).

Authors :

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Background

Risk stratification in Waldenström macroglobulinemia (WM) relies mainly on clinical and laboratory parameters reflecting tumor burden. Although molecular alterations have improved our understanding of WM biology, the clinical significance of conventional cytogenetic abnormalities (CCAs) remains poorly defined. Thus, we investigated the prognostic impact of CCAs in patients with WM.

Patients and Methods

We retrospectively analyzed 50 patients diagnosed with WM between 1993 and 2026. Thirty-one patients had smoldering WM at diagnosis. Clinical and cytogenetic characteristics at diagnosis were collected after informed consent. Complex karyotype was defined as the presence of ≥ 3 independent CCAs. Time to treatment evolution (TTE) was defined; the interval from the diagnosis of smoldering WM to the development of symptomatic WM, overall survival (OS); the time from diagnosis to death or last follow-up. Statistical analysis was performed using SPSS version 29.

Results

Fifty patients with WM were included (30 males, 20 females), with a median age of 65 years (range, 40–91). Nineteen patients required therapy during follow-up, whereas 31 had smoldering WM at diagnosis. Of these, 12 never required treatment. Bone marrow infiltration >50% was present in 19 patients. Median OS was 62 months (range, 1–341), and median TTE was 26.6 months (range, 2–354).

Abnormal CCAs findings were identified in 13 patients (26%), including 6 patients with complex karyotype. The most frequently involved chromosomes were 1, 6, 9, 11, and 13, with recurrent abnormalities affecting 1q, 6q, 9p, 11q, and 13q regions. Structural abnormalities included der(1;2)(p10;q10), t(2;14)(p13;q32), der(7)t(5;7)(q23;q31), der(12)t(6;12)(p12;q15), der(16)t(12;16)(q21;q24), and t(1;4)(p13;q21).

Nearly all patients with abnormal karyotype eventually required treatment. CCAs were associated with markers of higher disease burden, including hemoglobin ≤ 11.5 g/dL ($r=0.345$, $p=0.014$), $\beta 2$ -microglobulin levels ($r=0.367$, $p=0.012$), C-reactive protein ($r=0.634$, $p=0.005$), free κ light chains ($r=0.376$, $p=0.011$), free λ light chains ($r=0.365$, $p=0.014$), free light chain ratio ($r=0.354$, $p=0.017$), and lymphadenopathy ($r=0.511$, $p=0.0001$). Patients with CCAs had significantly shorter TTE compared with those with normal cytogenetics ($p=0.031$), whereas no association with OS was observed ($p=0.535$).

In univariate Cox regression analysis, factors associated with shorter TTE included hemoglobin (HR=0.80, 95% CI: 0.70–1.00, $p=0.002$), $\beta 2$ -microglobulin (HR=1.3, 95% CI: 1.05–1.5, $p=0.027$), albumin (HR=0.40, 95% CI: 0.20–0.90, $p=0.026$), bone marrow infiltration (BMINF) (HR=2.5, 95% CI: 1.2–5.4, $p=0.014$), and CCAs (HR=2.07, 95% CI: 0.9–4.3, $p=0.04$).

To capture complementary biological aspects of WM, a risk model integrating BMINF and abnormal karyotype was developed. Patients with both BMINF >50% and abnormal karyotype received 2 points, patients with either factor; 1 point, and patients without either factor 0 points. This model identified distinct risk groups, with median TTE of 3, 50, and 190 months, respectively ($p=0.001$).

During follow-up, two patients with initially normal cytogenetics developed abnormalities at relapse; one acquired a complex karyotype and the other developed 46,XY,add(9)(p22),del(9)(p13). Both achieved remission with Bruton tyrosine kinase inhibitor therapy.

Conclusion

CCAs are present in approximately one-quarter of patients with WM and identify a subgroup with higher disease burden and earlier treatment requirement. Integration of abnormal karyotype with BMINF may refine risk stratification beyond standard parameters.

Figure 1. Time to evolution according to the presence of CCAs. Patients with CCAs had a shorter time to evolution (TTE) ($p=0.031$).

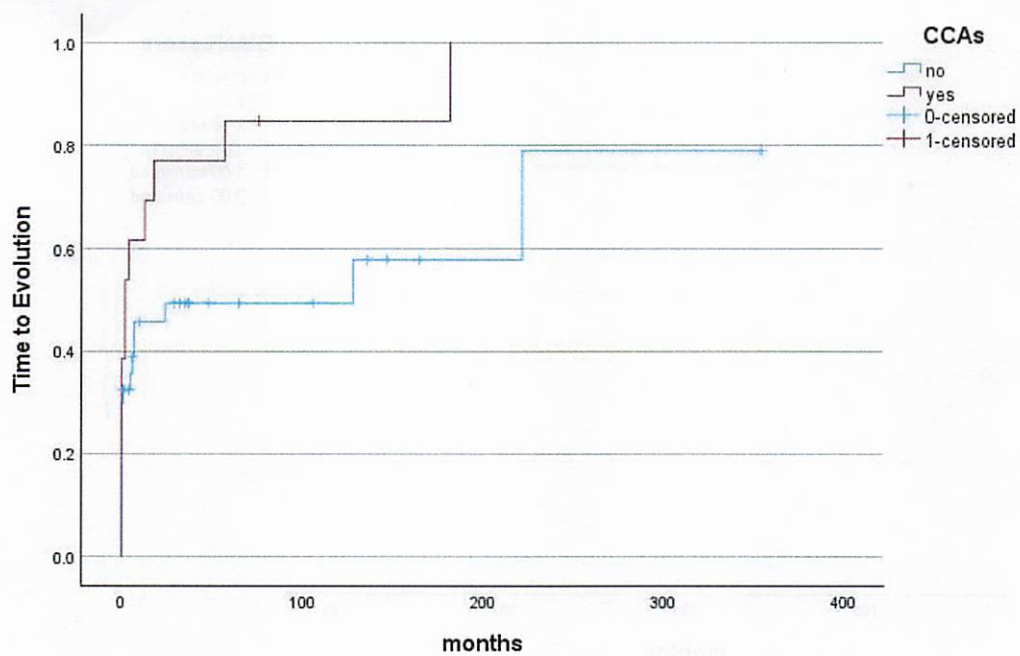
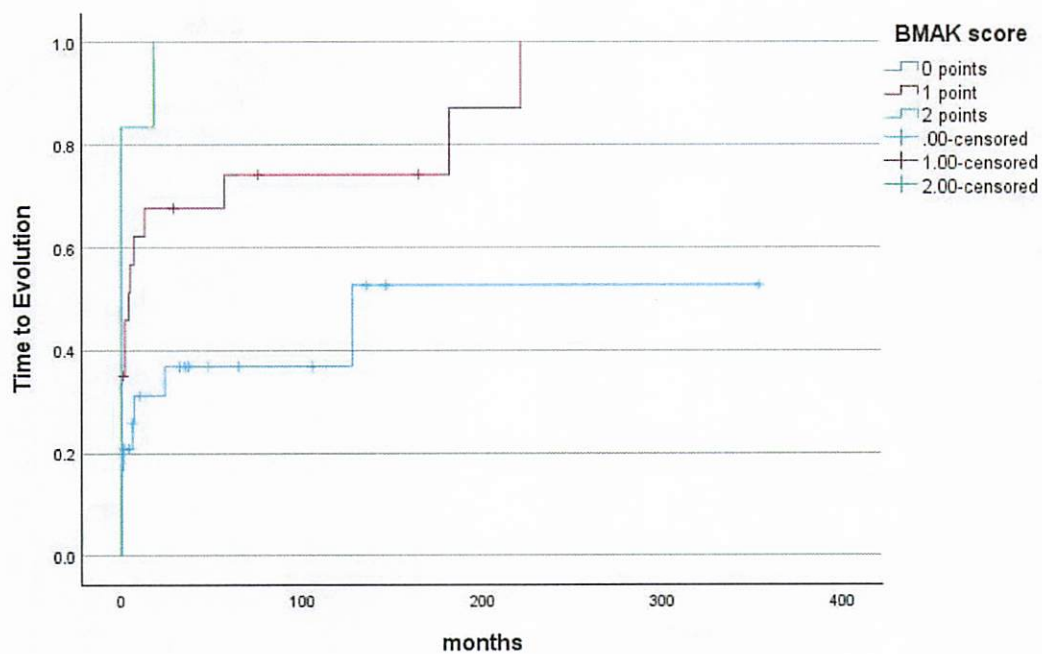


Figure 2. Risk model for WM progression. The model identified three distinct risk groups, with median times to evolution (TTE) of 3, 50, and 190 months, respectively ($p = 0.001$).



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Abstract Title: Cytogenetic abnormalities in Waldenström Macroglobulinemia (WM): a Hidden Driver of disease progression in WM.

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