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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

INTRACLONAL DIVERSIFICATION IN IMMUNOGLOBULIN LIGHT CHAIN GENES REFINES PROGNOSTICATION IN EARLY-STAGE CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: The mutational status of immunoglobulin heavy chain variable region (IGHV) genes represents one of the most robust biomarkers in chronic lymphocytic leukemia (CLL). Recently, the 99% identity cut-off for light chain genes further refined the prognostic value of IGHV. Intraclonal diversification (ID), characterized by the accumulation of somatic hypermutation (SHM) within immunoglobulin genes, affects IGHV genes and identifies a subset of mutated CLL patients with high-ID levels and improved clinical outcome (Vit et al., *Leukemia*. 2025). ID may also extend to light chain genes, but its impact on a large consecutive cohort of CLL patients has not yet been reported.

Methods:A total of 665 CLL patients were investigated for ID levels in both heavy and light chain genes using an amplicon-based next-generation sequencing. SHMs were assessed within FR1–FR3 regions of the V domain and the inverse Simpson Index (iSI) was applied to quantify ID.

Results: A total of 610 patients were analyzed for IGHV ID and 493 patients were analyzed for light chain ID. Patient characteristics were consistent with a real-world cohort of unselected, consecutive CLL. The median follow-up was 11.8 years. Considering the mutational status of both heavy and light chain genes, varying levels of iSI were observed across mutated and unmutated cases. U-IGHV patients exhibited significantly higher iSI levels than M-IGHV patients (p<0.001), whereas unmutated light chain genes (U-light) showed significantly lower iSI levels compared to mutated genes (M-light; p=0.004). No difference in iSI levels was seen between kappa and lambda expressing patients (p=0.9). Among patients with paired heavy and light chain iSI data (N=449), light chain genes displayed significantly lower levels than their IGHV counterparts (p<0.001), with median iSI of 1.007 and 1.58, respectively (Figure 1A). Using the maxstat test, the optimal iSI cut-off to predict time to first treatment (TTFT) for light chain ID (N=352 Binet A patients) was 1.007 (Figure1B). Light chain high-ID patients (≥1.007; N=193) experienced significantly longer TTFT than low-ID patients (<1.007; N=159)(p=0.001) (Figure 1C). Light chain high-ID patients inversely correlated with del(11q) (p=0.02), *TP53* aberrations (p=0.01), and lymphocyte count >15000/µL (p=0.03)(Figure 1D). In a multivariate analysis adjusted for IGHV and light chain mutational status, light chain high-ID patients maintained an independent association with longer TTFT (HR=0.57;CI=0.38-0.86;p=0.008) in early stage Binet A CLL (Figure 1E). Incorporating high-ID with the light chain mutational status, U-light chain high-ID patients (N=45) experienced longer TTFT compared to U-light chain low-ID patients (N=6;p=0.03) (Fig.1F). Conversely, high-ID did not further refine the outcome of M-light CLL patients.

Conclusion:These findings highlight the first evidence that intraclonal diversification in IG light chain genes may provide additional prognostic value to early-stage CLL patients.

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