Poster #: LB07

XXI IWCLL International Workshop on CLL

Risk Stratification in Chronic Lymphocytic Leukemia by IgHV Status and Mutational Co-Occurrence Profiling

Emilia Jaskuła[1,2], Anna Sobczyńska-Konefał [1,2], Wojciech Szlasa[2,3], Monika Kisielewska [2,3], Robert Mroczek[1], Marta Szyca-Śmieszniak [1,2], Monika Mordak-Domagała [2], Jacek Kwiatkowski [2], Katarzyna Tatara [2], Agnieszka Kuś [2], Mateusz Sawicki [2], Izabela Dereń-Wagemann [2], Mariola Sędzimirska [2], Marzena Wojtaszewska [4], Lidia Karabon [1], Monika Jasek [1], Jarosław Dybko[2,5]

1. Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wrocław, Poland
2. Lower Silesian Center for Oncology, Pulmonology and Hematology in Wrocław, Wrocław, Poland
3. Department of Molecular and Cellular Biology, Faculty of Pharmacy, Wrocław Medical University, Wrocław, Poland
4. Department of Hematology, University Hospital in Rzeszow, Poland
5. Department of Oncology and Hematology, Wrocław University of Science and Technology, Wrocław, Poland

OBJECTIVES

- Describe the molecular landscape of 215 consecutive CLL patients (IGHV/BCR, cytogenetics, 16-gene panel).
- Compare U-CLL vs M-CLL in repertoire, mutation burden, and frequencies of key lesions.
- Quantify the impact of IGHV and selected lesions on TTFT and TTST (KM/log-rank/Cox).
- Evaluate whether composite hubs—DNA-damage (ATM+del11q) and BCR-driven (U-CLL with NOTCH1/BRIC3/BRAF/BTK)—add prognostic value beyond single lesions.

CONCLUSIONS

- IGHV status remains the dominant prognostic anchor in our cohort, separating time to first and second treatment with large effect sizes;
- U-CLL shows earlier treatment need than M-CLL.U-CLL carries a higher mutation burden and is enriched for adverse lesions (notably del(11q)/ATM and NOTCH1), whereas M-CLL is characterised by more frequent del(13q) and a broader, less restricted BCR repertoire.
- Among single alterations, ATM, NOTCH1, and BTK consistently shorten TTFT; TP53 disruption (mutation and/or del(17p)) worsens PFS/TTST; XPO1 mutations identify a particularly high-risk subgroup with very short TTST.
- Taken together, routine IGHV typing plus a compact genomic panel (TP53/disruption, ATM/del11q, NOTCH1, BTK, XPO1) provides actionable risk stratification at diagnosis and can guide monitoring intensity and treatment sequencing; prospective validation is warranted.

Polish Academy of Sciences — Hirszfeld Institute of Immunology and Experimental Therapy

DCOPiH — Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii

Leczymy wiedzą i sercem

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) remains biologically heterogeneous, with outcomes that hinge on B-cell receptor (BCR) biology and the integrity of DNA-damage response pathways. Somatic hypermutation of IGHV is an established anchor of risk: unmutated IGHV (U-CLL) typically signals earlier treatment need, whereas mutated IGHV indicates a more indolent course. Additional lesions - including ATM/del(11q), TP53aberration (mutation and/or del(17p)), and BCR-pathway alterations such as NOTCH1 or BTK - further modulate prognosis and may interact with modern targeted regimens. Against this backdrop, we profiled a contemporary, consecutively accrued single-centre cohort to quantify the clinical impact of single lesions and composite genomic “hubs”, using time to first treatment (TTFT) and time to second treatment (TTST) as pragmatic endpoints.

METHODS

We analysed a cohort of 215 consecutive patients diagnosed with chronic lymphocytic leukaemia (CLL) between 2003 and 2025 at the Lower Silesian Centre for Oncology, Pulmonology and Haematology. The median age at diagnosis was 68 years, and 55% of patients were male. The IGHV mutation status was assessed using NGS (LymphoTrack® Dx IGHV Leader Somatic Hypermutation Assay, Invivoscribe) in 202 patients. Among them, 57.4% were classified as unmutated, 35.8% as mutated, and 6.9% as borderline. In a subset of 98 patients, an NGS panel (SureSeq CLL, OGT) covering 16 genes was performed with a variant allele frequency (VAF) threshold of ≥2%. Cytogenetic aberrations were assessed FISH. Deletion 11q (ATM) was detected in 21.6% of patients, Deletion 17p (TP53) in 10.3%,and deletion 13q in 59.5%, trisomy 12 was present in 8.7 % of cases. TP 53 mutation was detected in 18.2% of patients. At the time of data collection, 34.4% of patients remained in a ‘watch and wait’ strategy. Among those who received treatment, the most frequently used regimens included: Obinutuzumab with Venetoclax (19.5%), immunochemotherapy (8.4%), and combinations of Ibrutinib with Venetoclax (7.4%). Other treatments included Zanubrutinib, Acalabrutinib, chemotherapy, and combinations of BTK inhibitors, BCL2 inhibitors, and monoclonal antibodies, reflecting the evolving therapeutic landscape in CLL management. Time to first treatment (TTFT) and time to second treatment (TT2T) were analysed as indicators of progression-free survival (PFS).

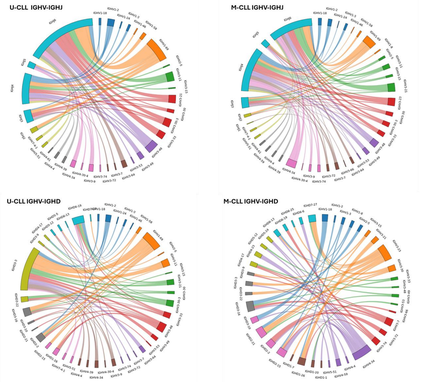
RESULTS

Comparison of IGHV recombination patterns revealed that U-CLL displayed a biased repertoire dominated by IGHV1-69 and IGHV3-21, with preferential pairing to IGHJ6/IGHJ4 and IGHD3 family members, reflecting stereotyped subsets. In contrast, M-CLL showed a broader and more diverse usage of IGHV (notably IGHV3-23, IGHV4-34, IGHV3-30) and IGHD2/IGHD6 segments, with more evenly distributed IGHJ usage, underscoring a less restricted BCR architecture (Figure 1).

IGHV multiclonality occurred in 27 patients (13.2%) - 13 with two productive IGHV and the rest productive+unproductive. Most IGHV were unassigned (176; 81.9%); among assigned, subset #2/IGHV3-21 was most frequent (6; 2.8%, aggressive irrespective of SHM), followed by #1 (5; 2.3%) and #6 (3; 1.4%); others each <1%.

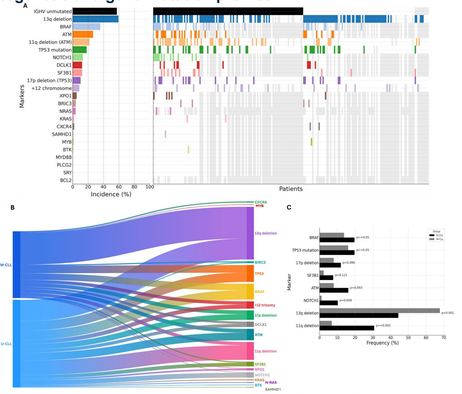
U-CLL patients demonstrated a significantly higher overall mutation burden compared to M-CLL patients (1.86 vs 1.43 mutations per patient, p=0.018, Figure 2). The most striking differences were observed in cytogenetic aberrations: 11q deletion was significantly more frequent in U-CLL patients (30.8% vs 6.9%, p<0.001, OR=0.17, Figure 2 D), while 13q deletion predominated in M-CLL patients (67.8% vs 44.4%, p=0.001, OR=2.63). Among gene mutations, NOTCH1 alterations were significantly more prevalent in U-CLL (10.3% vs 1.1%, p=0.008, OR=0.10, Figure 2 D). Several mutations showed trends toward higher frequency in U-CLL without reaching statistical significance, including ATM (16.2% vs 8.0%, p=0.093), SF3B1 (7.7% vs 2.3%, p=0.121), and 17p deletion (12.0% vs 8.0%, p=0.486). TP53 mutations and BRAF alterations were observed at similar frequencies in both groups (19.7% vs 16.1% and 19.7% vs 13.8%, respectively, both p>0.05). Notably, KRAS and NRAS mutations were exclusively detected in U-CLL patients (1.7% each), while CXCR4 and MYB alterations were found only in M-CLL patients (2.3% and 1.1%, respectively), though these differences did not reach statistical significance due to low frequencies. No mutations in BTK or SAMHD1 were detected in M-CLL patients, with minimal presence in U-CLL (0.9% each).

Figure 1. IGHV–IGHJ and IGHV–IGHD gene pairing patterns in U-CLL and M-CLL



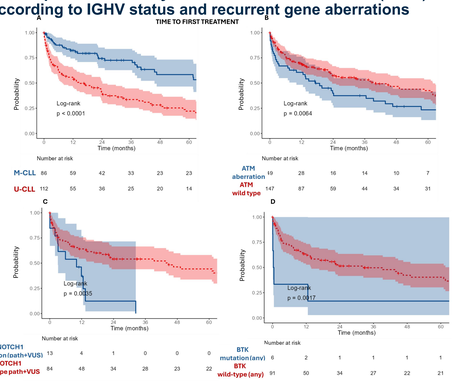
Chord diagrams showing IGHV–IGHJ (top) and IGHV–IGHD (bottom) gene pairings. U-CLL displays biased, restricted usage, while M-CLL shows a more diverse repertoire.

Figure 2. Genomic landscape of U-CLL versus M-CLL with emphasis on cytogenetic and gene mutation profiles



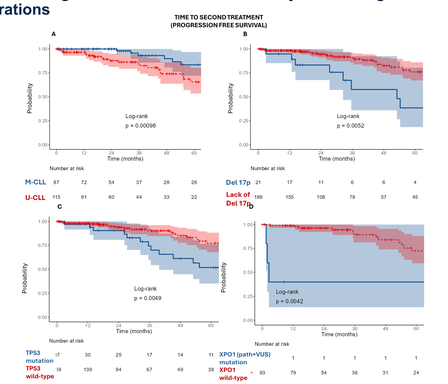
A) Oncoprint shows incidence and distribution of recurrent alterations by IGHV status.(B) Sankey diagram illustrates flow from IGHV subgroups to key mutations.(C) Horizontal barplot highlights enrichment of 11q deletion and NOTCH1 in U-CLL, while 13q deletion is more frequent in M-CLL.

Figure 3. Kaplan–Meier analysis of time to first treatment (TTFT) in CLL according to IGHV status and recurrent gene aberrations



Kaplan–Meier curves of TTFT. Unmutated IGHV, ATM aberrations, and NOTCH1 or BTK mutations were each associated with significantly shorter TTFT compared to their respective wild-type groups.

Figure 4. Progression-free survival in CLL by IGHV and gene aberrations



Kaplan–Meier curves of PFS. Unmutated IGHV, del(17p), TP53 mutations, and XPO1 mutations were each associated with significantly shorter PFS compared to wild-type patients.

RESULTS

IgHV status proved to be the strongest prognostic factor, with median TTFT of 69 months in mutated versus 15 months in unmutated cases (HR = 2.67; p < 0.001; Figure 3A), and TTST of 102 months versus not reached (HR = 3.23; p < 0.001; Figure 4A). ATM aberrations shortened TTFT to 14.7 versus 40 months (HR = 1.67; p = 0.007; Figure 3B), while NOTCH1 (10.1 vs. 45 months; HR = 2.70; p = 0.003; Figure 3C) and BTK mutations (0.4 vs. 32 months; HR = 3.57; p = 0.0017; Figure 3D) conferred particularly adverse outcomes. For PFS, 17p (TP53) deletion reduced median survival to 53 versus 137.9 months (HR = 2.63; p = 0.007; Figure 2B), TP53 mutations to 63.6 versus 151.6 months (Figure 4C), and TP53 aberrations overall to 63.6 versus 151.6 months (HR = 2.17; p = 0.009). Strikingly, XPO1 mutations were associated with dismal TTST of 2.5 versus 106.6 months (HR = 4.35; p = 0.008; Figure 4D).

Extending these single-lesion signals, composite genetic hubs were highly informative.

Patients in the DNA-damage hub (ATM mutation with del(11q)) had markedly shorter intervals: TTFT HR = 3.92 (95% CI 2.08–7.36; p≈5.2×10⁻⁶) and TTST HR = 7.79 (2.16–28.08; p≈2.2×10⁻⁴) versus the favourable reference (M-CLL with isolated del(13q)). The BCR-driven hub (U-CLL with NOTCH1/BRIC3/BRAF/BTK) was likewise adverse for TTFT HR = 3.86 (1.90–7.85; p≈5.8×10⁻⁵) and for TTST HR = 4.73 (1.17–19.09; p≈0.016), with clearly separated Kaplan–Meier curves. Within IGHV strata, NOTCH1 remained independently detrimental in U-CLL (TTFT HR = 2.09, 1.01–4.35; p = 0.047), whereas SF3B1 associated with shorter TTFT in M-CLL (HR = 6.88, 1.33–35.68; p = 0.022). TP53 disruption (mutation and/or del17p) showed the expected direction toward shorter TTST but did not reach significance in this cohort (wide CIs reflecting few second-line events). Collectively, the favourable subgroup (M-CLL with isolated del(13q)) retained the longest TTFT/TTST and served as a robust clinical reference throughout analyses.

CLL Risk Stratification - Summary

IGHV as Prognostic Anchor
U-CLL → earlier treatment (shorter TTFT/TTST)
M-CLL → delayed treatment need

U-CLL vs M-CLL - Molecular Landscape
U-CLL: higher mutation burden; enriched del(11q)/ATM, NOTCH1
M-CLL: more frequent del(13q); broader BCR repertoire

Key Single Alterations
ATM, NOTCH1, BTK → shorten TTFT
TP53 disruption (mut and/or del17p) → worse PFS/TTST
XPO1 → very short TTST

Actionable Diagnostic Panel
IGHV + TP53/disruption ATM/del11q, NOTCH1, BTK, XPO1
Guides monitoring & sequencing

ACKNOWLEDGMENTS

Supported by DWD/6/0422/2022 grant