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#023 | A subgroup of patients with unmutated IgHV 1-69; 3-30; 1-02; 4-39 and high expression of activation-induced cytidine deaminase require earlier treatment.

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Abstract:

Chronic lymphocytic leukemia (CLL) is characterized by its clinical and molecular heterogeneity. The practical challenge presented by this diverse landscape is the difficulty in predicting leukemia progression. Despite extensive efforts employing various clinical and/or molecular prognostic tools, accurate prediction of disease progression remains elusive for a significant number of patients. Our group, along with others, described that activation-induced cytidine deaminase (AID) is abnormally expressed in the peripheral blood (PB) of patients with poor clinical outcomes, predominantly in unmutated cases (U-CLL). This enzyme is necessary to initiate somatic hypermutation (SHM) and class-switch recombination process in B- lymphocytes. Additionally, deamination of “off-target” genes by AID can result in oncogenic mutations or translocations. Nevertheless, the role of this enzyme in the origins and evolution of CLL as well as why AID is predominantly expressed in U-CLL, remains a topic of ongoing debate. Previous studies from our laboratory demonstrated the loss of superantigenic and polyreactive binding of B-cell receptor (BCR) following SHM, (Oppezzo et al., 2004 EJI). Furthermore, findings from (Hervé et al. 2005, JCI), provide evidence that both U-CLLs and M-CLLs may originate from self-reactive B cell precursors. Collectively, these studies highlight SHM as a pivotal process in the origins/development of B-cell lymphoid neoplasms by altering the original autoreactivity of the BCR. Based on this concept, we hypothesize that the absence of SHM in U-CLL may result in continuous BCR stimulation and constitutive AID expression, contributing to a poorer clinical outcome.In this work, we characterized CLL patients based on AID expression in PB, its association with immunoglobulin heavy chain gene (IgVH) status/use and disease progression, assessed as time to first treatment (TTFT). PB samples were collected from patients meeting the clinical/immunophenotypic criteria for CLL, following the iwCLL guidelines. The cohort included 279 patients from Uruguay and 33 from Argentina. Written informed consent was obtained, and the study was approved by the Institutional Ethics Committees of each institution. Peripheral blood mononuclear cells were isolated using Ficoll-Hypaque, and RNA extraction and cDNA synthesis performed. From 312 studied cases, 56% were Binet's stage A, 23% were stage B, and 21% were stage C. The IgHV gene status was mutated in 52% of cases, cytogenetic aberrations were observed in 70.5% of patients, including 13q14_deletion (36.5%), trisomy_12 (13%), 11q22_deletion (9.7%), and 17p_deletion (8.3%). The median age at diagnosis was 66 years old, and the median follow-up was 5 years. Our results identify a novel CLL subgroup characterized by clonal expression of an unmutated BCR with specific rearrangements (IgHV_1-02, 1-69, 3-30, 4-39), high expression of AID enzyme and earlier treatment. Moreover, our results suggest that AID expression in U-CLL could be linked with antigen restriction and clinical outcome. This subset constitutes approximately 38% of the U-CLL (15% of the total cohort) and can be identified in advance by integrating AID mRNA expression and IgVH profile assessment into routine testing. We propose a new and practical prognostic tool, assessed in PB, which enables the identification of a novel CLL entity requiring early treatment initiation, typically within the first year.