

IGHV1 status in chronic lymphocytic leukemia identify ethnic groups with an aggressive clinical course (Comment to Giudice ID, Foà R. *Haematologica*. 2019;104(2):219-221)

We have read with great interest the editorial by Del Giudice *et al.* concerning the history of immunoglobulin heavy chain variable region (*IGHV1*) mutations based on a prognostic approach in chronic lymphocytic leukemia (CLL) patients.¹ In their editorial the authors reviewed the importance of *IGHV1* mutations in CLL in the light of the results obtained by the ERIC group, published in the same issue of *Haematologica*.² They underlined that the *IGHV1* mutational status, additional to *TP53* deletions/mutations, is still the most robust prognostic biomarker. In fact, the patients harboring a high number of somatic mutations in the *IGHV1* usually have a better prognosis and a longer survival than those with an unmutated profile. In addition, the same authors state that these clinical-biological associations are present in all ethnic groups, although the biased ethnic and geographic variants of the clinical course and the *IGHV1* usage can vary across the population comparing the Caucasian with the Chinese population.³ We wish to point out, however, that a recently published paper by our group (Amato *et al.*)⁴ disclosed ethnic and geographic variations in the mutational status of *IGHV1* among different ethnic groups. In more detail, we observed in a double cohort study of CLL patients collected at two reference centres: one in Europe (Siena, Italy) and one in Africa (Dakar, Senegal) a strong predominance of the unmutated CLL (U-CLL) in the Senegalese cohort and a striking difference in the frequencies of the usage of *IGHV1*. In particular, we detected that *IGHV1* (*IGHV1-69*), *IGHD3*, and *IGHJ6* were significantly more frequent in Senegalese patients, whereas *IGHV3-30* was not only common among the Italian cohort but also limited to that cohort. Undoubtedly, our findings reflect an antigen selection process related to the ethnic, geographic and environmental background in which individuals live, providing a biological explanation for the earlier onset of the disease and the more aggressive clinical behavior of the Senegalese CLL patients compared to the Italian CLL patients.^{4,5,6,7} Furthermore, the interactions between the neoplastic lymphocytes responding to B- cell receptor stimulation and the microenvironment might play a key role in CLL pathogenesis.^{8,9} Indeed, U-CLL, the most common subtype in Africa, shows a more active BCR signalling pathway, whereas mutated CLL (M-CLL) is the most common subtype in Western countries.⁴ Thus, this mechanism may reflect not only intrinsic differences in clones but also different interactions with T cells, presumably in response to Toll-like receptor (TLR) stimulation which is characteristic of recurrent malaria infection.¹⁰ Further evidence is provided by the detection of a preferential usage of *IGHV1-69* in Senegalese patients which has been shown, similar to the vast majority of unmutated immunoglobulins, to be much more broadly active against bacteria.¹¹ This evidence

points out that chronic antigenic stimulation is a pivotal driver of malignant cells in the pathogenesis of African CLL. Despite the fact that *IGHV* usage and the frequency of BCR subsets can vary across populations with a different incidence of CLL (Caucasian versus Chinese and Caucasian versus African), the reliability of the *IGHV1* mutational status in predicting the prognosis remains undiscussed, even though *IGHV1* sequencing constitutes a valid guide for making the choice between chemoimmunotherapy and novel agents in all CLL patients requiring first-line treatment, in particular for those belonging to ethnic groups at risk. However, in the era of immunotherapy, innovative therapeutic approaches might overcome the prognostic impact of the *IGHV1* mutational profile on the basis of advancements in the understanding of the CLL pathology.

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References

- Giudice ID, Foà R. Another step forward in the 20-year history of *IGHV* mutations in chronic lymphocytic leukemia. *Haematologica*. 2019;104(2):219-221.
- Baliakas P, Moysiadis T, Hadzidimitriou A, et al. Tailored approaches grounded on immunogenetic features for refined prognostication in chronic lymphocytic leukemia. *Haematologica*. 2019;104(2):360-369.
- Marinelli M, Ilari C, Xia Y, et al. Immunoglobulin gene rearrangements in Chinese and Italian patients with chronic lymphocytic leukemia. *Oncotarget*. 2016;7(15):20520-20531.
- Amato T, Sall A, Dièye TN, et al. Preferential Usage of Specific Immunoglobulin Heavy Chain Variable Region Genes With Unmutated Profile and Advanced Stage at Presentation Are Common Features in Patients With Chronic Lymphocytic Leukemia From Senegal. *Am J Clin Pathol*. 2017;148(6):545-554.
- Mukiibi JM, Paul B, Nyirenda CM, et al. Chronic lymphocytic leukaemia (CLL) in central Africans. *Cent Afr J Med*. 2004;50:111-115.
- Salawu L, Bolarinwa RA, Durosinmi MA. Chronic lymphocytic leukaemia: a twenty-years experience and problems in Ile-Ife, South-Western Nigeria. *Afr Health Sci*. 2010;10:187-192.
- Sall A, Touré AO, Sall FB, et al. Characteristics of chronic lymphocytic leukemia in Senegal. *BMC Hematol*. 2016;16:10.
- Kostareli E, Gounari M, Agathangelidis A, et al. Immunoglobulin gene repertoire in chronic lymphocytic leukemia: insight into antigen selection and microenvironmental interactions. *Mediterr J Hematol Infect Dis*. 2012;4:e2012052.
- Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nat Rev Dis Primers*. 2017;3:16096.
- Tamani M, Laurenti L, Longo PG, et al. The proliferative response to cpG-ODN stimulation predicts PFS, TTT and OS in patients with chronic lymphocytic leukemia. *Leuk Res*. 2010;34(9):1189-1194.
- Hatzi K, CATERA R, ATANASIO CM, et al. Chronic lymphocytic leukemia immunoglobulins display bacterial reactivity that converges and diverges from auto-/poly-reactivity and *IGHV* mutation status. *Clin Immunol*. 2016;172:44-51.