Do Biologic Parameters Affect the Time to First Treatment of Clinical Monoclonal B-Cell Lymphocytosis and Chronic Lymphocytic Leukemia Rai Stage 0? Results of a Prospective Analysis

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Abstract

We investigated the clinical relevance of classic and new prognostic markers, immunoglobulin heavy-chain variable (IGHV) gene mutational status, and chromosomal abnormalities in clinical monoclonal B lymphocytosis (cMBL) compared with chronic lymphocytic leukemia (CLL), Rai stage 0. In our prospective patient cohort, we have confirmed that IGHV mutation status appeared to be the best predictor of the time to first treatment in patients with cMBL/CLL Rai stage 0. In addition, when associated with the B-cell count, IGHV mutational status might help to better stratify patients into more precise subgroups.

Background: We investigated the clinical relevance of classic and new prognostic markers, immunoglobulin heavy-chain variable (IGHV) gene mutational status, and chromosomal abnormalities in clinical monoclonal B lymphocytosis (cMBL) compared with chronic lymphocytic leukemia (CLL) Rai stage 0. **Patients and Methods:** We analyzed the clinical outcomes in terms of the time to the first treatment (TTFT) of a prospective cohort, including 125 patients with cMBL and 197 patients with CLL Rai stage 0. **Results:** In the overall patient population, prognostic parameters such as IGHV gene mutational status ($P < .0001$), CD38 expression ($P < .0001$), 70-kDa zeta-associated protein (ZAP-70) expression ($P < .0001$), and cytogenetic abnormalities ($P = .01$) predicted for TTFT on univariate analysis. IGHV gene identity was significant on multivariate analysis ($P < .0001$), regardless of the B-cell cutoff (5.0 or 10×10^9 B cells/L). A prognostic stratification using the combination of IGHV mutational status and absolute B-cell lymphocytosis identified 3 different groups that were significantly different with respect to the TTFT ($P < .0001$). **Conclusion:** In the present series of patients with cMBL and CLL Rai stage 0, we have confirmed that IGHV mutation status appeared to be the best predictor of TTFT. In addition, when associated with the B-cell count, IGHV mutational status might help to better stratify patients into more precise subgroups.

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Introduction

The World Health Organization classification and International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria have defined monoclonal B-cell lymphocytosis (MBL) as a clonal B-cell expansion in which the B-cell count is $< 5 \times 10^9$/L and no symptoms or signs of lymphoproliferative disorder are detected.[1-3] The term "MBL" encompasses, however, an array of entities with a different likelihood of representing a true pre-leukemic condition.[4] Accordingly, MBL is now usually subdivided

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into 2 categories: clinical MBL (cMBL) and population-screening MBL.[5,6] They have different immunoglobulin heavy chain variable (IGHV) gene repertoires and frequencies of B-cell receptor stereotypy.[7] In contrast, the results of recent studies have suggested that the immunogenetic characteristics and clinically relevant parameters of cMBL and chronic lymphocytic leukemia (CLL), Rai stage 0, are similar.[4-6,8-12]

From a clinical standpoint, cMBL is a combination of stable and progressive conditions.[13] Similarly, CLL Rai stage 0 includes patients with mild lymphocytosis that persists and is stable over the time and patients experiencing early progression needing treatment.[14] However, the studies that evaluated the effect of genetic or molecular features on the clinical outcome of either cMBL or CLL Rai stage 0 has yielded inconclusive results.[4,5,10,12,15]

In a prospective, multicenter cohort, we have confirmed that IGHV gene mutation status might contribute to improved prognostic stratification of patients with cMBL or CLL Rai stage 0. In addition, when associated with the B-cell count, IGHV mutational status might help to better stratify patients into more precise subgroups.

Patients and Methods

Patients

Suitable for the present analysis were 322 patients with newly diagnosed, Rai stage 0 CLL, aged < 70 years old, from several institutions, who were prospectively registered within 12 months of diagnosis in a national database (O-CLL1 protocol; clinicaltrial.gov identifier NCT00917540). All patients had an absolute lymphocyte count of $\geq 5.0 \times 10^9$/L at diagnosis and thus fulfilled both 1988 and 1996 National Cancer Institute (NCI)-sponsored Working Group (WG) guideline criteria for CLL.[16,17]

Using the criteria from the 2008 NCI-sponsored workshop,[3] the 322 patients with CLL in Rai stage 0 could be further subdivided into cMBL (125 patients with B lymphocytes in the peripheral blood between 0.5×10^9/L and $< 5.0 \times 10^9$/L) and Rai stage 0 CLL (197 patients with B lymphocytes in the peripheral blood $\geq 5.0 \times 10^9$/L). The diagnosis was confirmed using flow cytometry (CD5+/SmIg weak) by the biologic review committee according to flow cytometry analysis centralized at the National Institute of Cancer Laboratory in Genoa. Determination of CD38 and ZAP-70 expression and immunoglobulin variable region heavy chain (IgVH) mutational status was also performed.

The patients were evaluated for either traditional clinical and laboratory prognostic factors or newer prognostic factors, including IGHV mutation status, chromosome abnormalities using fluorescence in situ hybridization (FISH) analysis, and CD38 and 70-kDa zeta-associated protein (ZAP-70) expression.[18,19] Evaluations of IGHV mutation status, CD38 (glycoprotein) expression, and ZAP-70 expression by flow cytometry were centralized at the National Institute of Cancer Laboratory in Genoa. The study of chromosome abnormalities by FISH analysis was centralized at the Research Center for the Study of Leukemia, Institute for Cancer Research and Treatment Foundation at the University of Milan.[20]

Information regarding the traditional prognostic factors and clinical and laboratory variables, including sex, age, Rai stage, hemoglobin level, platelet count, β2-microglobulin, and lactate

Figure 1 Time to First Treatment (TTFT) for Patients With Clinical Monoclonal B Lymphocytosis (cMBL), Patients With Rai Stage 0 Chronic Lymphocytic Leukemia (CLL) With B-Cell Counts Between 5.0 and 11.9 × 10^9/L, and Patients With Rai Stage 0 CLL With a B-Cell Count of ≥ 12.0 × 10^9/L. (Lower Right Corner) Hazard Ratios, Which Refer to the Comparison Between cMBL and Low-count, Rai Stage 0 CLL With B-Cell Counts Between 5.0 and 11.9 × 10^9/L and cMBL and Rai Stage 0 CLL With B-Cell Counts ≥ 12.0 × 10^9/L