



The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Comparison of Familial Versus Sporadic Forms of Chronic Lymphocytic Leukemia: An Italian Multicenter Case-Control Study

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The incidence of monoclonal B-cell lymphocytosis (MBL) and chronic lymphocytic leukemia (CLL) in relatives of patients with CLL is 13-22% and 5-7% respectively. Studies on MBL have provided evidence of a more aggressive pattern of evolution in patients with a familial predisposition, even if in a real-life population study, familial CLL showed non-statistically different overall survival (OS) at 10 years. This retrospective and prospective multicenter case-control study aimed to compare the clinical features, molecular biomarkers, and patient outcomes in terms of time to first treatment (TTFT), time to next treatment (TTNT), and OS between familial and sporadic CLL patients.

Adult MBL/CLL patients from 18 Italian centers were included. The observational period was 1987-2021 for retrospective data, and 2022-2024 for prospective data. Familial CLL was defined as the presence of one or more first-degree relatives affected by MBL/CLL. For each patient with familial CLL, two patients with sporadic CLL matched for gender and age within 4 years were enrolled in the control cohort. Time-to-event outcomes were evaluated using the Kaplan-Meier method. TTFT was defined as time from diagnosis to treatment initiation. TTNT was defined as time from treatment initiation to the initiation of subsequent therapy or death.

Of the 480 enrolled patients, 160 had familial CLL, and 320 had sporadic CLL. Age at diagnosis and gender were matching criteria; therefore, for both cases and controls, 53.7% were male and 46.3% were female, and the median age at diagnosis was 63 years for familial CLL (interquartile range, IQR 52-68), 62 for sporadic CLL (IQR 52-69). Patients with familial CLL at diagnosis manifested more frequently with bulky lymph nodes >5 cm than sporadic CLL [7.2% (11/152) vs. 2.8% (8/290), respectively ($p=0.027$)]. No other clinical differences were detected between the two groups at diagnosis in terms of advanced Rai/Binet stage, splenomegaly, and hypogammaglobulinemia. No differences were either detected with respect to genetic features, such as del17p, del11q, tris12, del13q, TP53, NOTCH1, SF3B1, and BIRC3 mutations, except for IGHV mutational status. The IGHV gene was unmutated in 36.2% (77/213) of the controls versus 55.5% (61/110) of the cases ($p<0.001$). The median age at first treatment was 65 years in both groups (IQR 55-72) and TTFT was superimposable (median 35 months in both groups). Frontline treatment was required in 55.6% of familial CLL patients and 43.1% of sporadic CLL patients ($p=0.001$). Second-line treatment was required in 46.1% of familial CLL patients versus 29.6% of sporadic CLL patients ($p=0.034$). TTNT was shorter for patients with familial CLL [median TTNT of 60 months (95% CI: 42.9-77.1)] than for sporadic CLL [median TTNT of 94 months (95% CI: 43.7-144.3, $p=0.030$)]. Stratifying the patients by the treatment received, TTNT for familial cases was 33 months (95% CI: 0-70.2) for patients treated with chemotherapy (CT), 52 months (95% CI: 30.0-74.0) with chemoimmunotherapy (CIT), and 65 months with inhibitors; for sporadic controls, TTNT was 67 months (95% CI: 0-158.4) with CT ($p=0.86$), 94 months (95% CI: 64.7-123.2) with CIT ($p=0.018$) and median was not reached with inhibitors ($p=0.41$). OS at 5, 10, 15, and 20 years was 97.9%, 90.6%, 82.0%, and 68.6% for familial cases and 98.2%, 95.8%, 87.3%, and 75.4% for sporadic controls, respectively ($p=0.23$). Comparing OS through different "eras", 5-year OS did not differ between cases and controls neither in the "CT era" (1987-2009), in the "CIT era" (2010-2015) and in the "inhibitors era" (2016-2024). Secondary neoplasms occurred in 18.8% (30/160) of familial CLL patients and 15.9% (51/320) of sporadic CLL patients ($p=0.44$). Richter's transformation occurred in 2.0% of familial cases and 2.5% of familial controls ($p=0.74$).

In this multicenter case-control study, patients with familial CLL showed a more aggressive presentation at diagnosis, higher need for treatment, and shorter TTNT after frontline therapy than those with sporadic CLL, especially with CIT, while OS was similar. Whole-exome sequencing analysis to identify possible recurrent gene mutations in these patients is ongoing. Given the similar OS, screening for familial forms of CLL is not recommended, but familial predisposition should be investigated to provide optimal clinical care for these patients.

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