



Clinical features and outcome of familial chronic lymphocytic leukemia

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The prognostic impact of the presence of a familial trait was analyzed in 1449 patient with chronic lymphocytic leukemia (CLL). A family history of hematologic malignancy (HM) was identified in 181 cases (12.5%) and recorded more frequently among female than male patients (HM: $p < 0.05$; CLL: $p < 0.05$). The relative was affected by CLL in 89 cases (6%). Familial and sporadic cases showed non-statistically different proportions of advanced stages (10.8 vs 7.1%) and patients requiring therapy (55 vs 60%) and a similar survival probability at 10 years (67 vs 66%). These data suggest that in CLL the presence of a familial trait does not imply an adverse prognosis.

Key words: chronic lymphocytic leukemia, familial, prognosis.

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Chronic lymphocytic leukemia (CLL) is the form of leukemia in which familial aggregation has been described more frequently and quantified by multiple reports of familial clustering, case-control and cohort-studies.^{1,2} Moreover, using flow cytometric analysis the presence of either a CD5⁺ or a CLL-like phenotypic B-cell population has been detected more frequently in the peripheral blood of healthy, first degree relatives from selected families with two or more members affected by CLL compared to healthy individuals.³⁻⁵ Despite the large number of studies aimed at assessing the disease risk among relatives of CLL patients, there is very scanty information about other clinical features and outcome of familial CLL cases.⁶

This study was carried in order to evaluate whether patients with familial and sporadic CLL had the same clinical features and whether the presence of a family history of hematologic malignancy had a prognostic impact on survival.

Design and Methods

Patients

Between 1984 and 2000, the family histories of 1449 patients with CLL, all diagnosed and followed at the Institute of Hematology of the University "La Sapienza" of Rome, were analyzed. The median follow-up of patients was 54 months (range 12-216 months). The diagnosis of CLL was based on

standard morphologic and immunologic criteria. Stage was assessed according to the classification of Rai⁷ and treatment was given in the presence of advanced or progressive disease.

Family history

All patients included in this study were asked whether their living or dead first-degree relatives (parents, siblings, children) and second-degree relatives (grand-parents, uncles/aunts, cousins, nephews/nieces) were or had been affected by a hematologic malignancy: CLL, non-Hodgkin's lymphoma, Hodgkin's disease, myeloma, acute lymphoid leukemia, chronic myeloid leukemia, or acute myeloid leukemia. In the presence of a relative affected by a hematologic malignancy, all attempts were made to validate the diagnosis and clinical documentation (medical records, death certificates) was required. When the available medical documentation reported the affected relative as dead because of a not better defined leukemia, the case was recorded as affected by a fatal leukemia. Prior to the interview about their family history, patients gave their consent. This study was approved by the local Ethics Committee and carried out in accordance with the Good Clinical Practice precepts and Italian privacy laws.

Statistical analysis

The clinical features (age, gender, Rai's stage, treatment requirement, Richter's syndrome, second malignancy, acute leukemia,

Table 1. Distribution of the familial cases of CLL.

Types of HM which affected relatives	No. of CLL pts with a relative affected by HM (%)	No. of male CLL pts with a relative affected by HM (%)	No. of female CLL pts with a relative affected by HM (%)	p value
181/1449	92/848 (12.5)	89/601 (11)	<0.05 (15)	
Lymphoproliferative disorders	128 (9.0)	63 (7.4)	65 (11)	0.05
CLL	89 (6.0)	41 (5)	48 (8)	<.05
NHL ¹	21 (1.5)	12 (1.4)	9 (0.6)	ns
ALL	11 (0.7)	7 (0.8)	4 (0.66)	ns
HD	7 (0.5)	3 (0.35)	4 (0.66)	ns
Myeloproliferative disorders	15 (1.0)	8 (0.9)	7 (1.16)	ns
AML	10 (0.7)	6 (0.7)	4 (0.66)	ns
CML	5 (0.3)	2 (0.23)	3 (0.5)	ns
Fatal leukemia	38 (2.6)	21 (2.5)	17 (3)	ns

HM: hematologic malignancy; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; ALL: acute lymphoblastic leukemia; HD: Hodgkin's disease; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ns: not significant. ¹Only one case of a relative affected by multiple myeloma was recorded and this case was included in the subgroup of non-Hodgkin's lymphoma.

autoimmune disease) and survival probability of the group of patients without a familial history of hematologic malignancy, defined as sporadic patients, the group of patients with a relative affected by a hematologic malignancy, defined as familial patients and the subgroup of familial patients with a first-degree relative affected by CLL were analyzed and compared.

The corrected chi-squared test was applied to compare groups. Survival curves were calculated according to Kaplan and Meier⁸ and compared with the log-rank test.⁹ A Cox multiple regression model was applied¹⁰ to define the relative significance on survival probability of different variables including age, gender, stage according to Rai's classification (0+I vs II vs III+IV), treatment requirement and presence of a family history of hematologic malignancy and CLL.

Results and Discussion

Prevalence of familial cases of CLL

One hundred and eighty-one of the 1449 CLL patients (12.5%) reported having one or more relatives affected by a hematologic malignancy, which was a lymphoproliferative disease in 128 cases (9%) and CLL in 89 (6%) (Table 1). The proportion of female CLL patients with a familial history of hematologic malignancy, lymphoproliferative disease and CLL was significantly higher than that recorded in males (hematologic malignancy, $p < 0.05$; lymphoproliferative disease, $p = 0.05$; CLL, $p < 0.05$) (Table 1).

Affected relatives

A cumulative number of 230 affected relatives, 161 first-degree and 69 second-degree relatives, was recorded. When the total number of 10,145 first-degree relatives was considered, the rate of first-degree relatives with a hematologic malignancy was 1.6%, with a lymphoproliferative disease 1.15% and with CLL 0.8%. Fifteen parent/child pairs affected by CLL were recorded. In all cases but one, the age of the parent at diagnosis was older than that of his/her respective child, with a median difference of 22 years (range: -44 - +7).

Comparison between the clinical characteristics of familial and sporadic cases of CLL

Age, stage and treatment requirement

Female familial patients were younger at the diagnosis of CLL than were female sporadic cases, while no significant differences of age emerged between sporadic and familial cases in male patients (Table 2). A lower, though not significantly, rate of cases with advanced III-IV Rai's stage was observed among familial cases (Table 2). However, the proportion of patients requiring therapy was not different between the familial and the sporadic cases (Table 2).

Survival probability

No significant differences emerged when the survival probability curves of the two groups of familial patients were compared to the survival probability curve of the patients with sporadic CLL (% actuarial survival probability at 10 years: sporadic cases, 67%; patients with a family history of hematologic malignancy, 66%; patients with a family history of CLL, 61%; p : not significant) (Table 2 and Figure 1). Only male patients with a family history of CLL showed a lower survival probability compared to male sporadic cases although this difference was not statistically significant, ($p = 0.08$) (Table 2).

By multiple regression analysis, several variables emerged as independent prognostic parameters for the survival probability of the 1449 CLL patients included in this study. Significant and independent factors with an adverse effect on survival were: male gender ($p < 0.005$), older age ($p = 0.001$), advanced Rai's stage ($p < 0.00001$) and treatment requirement ($p < 0.00001$), while the presence of a family history of hematologic malignancies (first model) and of CLL (second model) showed no significant effect on survival.

Second malignancies, Richter's syndrome, acute myeloid leukemia and autoimmune hemolytic anemia

While no differences in the rate and distribution patterns of second tumors were observed between male sporadic and male familial cases, female patients with a positive family history showed a higher rate of second

Table 2. Comparison between the characteristics of familial and sporadic CLL patients.

	Patients with sporadic CLL			Patients with familial CLL with a relative affected by a HM			Patients with familial CLL with a first-degree relative affected by CLL		
	All (1268)	Male (756)	Female (512)	All (181)	Male (92)	Female (89)	All (81)	Male (39)	Female (42)
Median age, years	64 (28-91)	63 (35-91)	66 (28-89)	62 (31-91) p<0.001	60 (31-84) p=ns	64 (40-91) p<0.001	63 (31-91) p=ns	60 (31-86) p=ns	64 (47-91) p<0.05
% Rai stage III-IV	10.8%	11.2%	10.1%	7.1% p=ns	7.6% p=ns	6.7% p=ns	4.9% p=ns	7.7% p=ns	2.4% p=ns
% of patients requiring therapy	54.6%	58.6%	48.8%	60.4% p	62% p=ns	59% p=ns	52% p=ns	64% p=ns	40% p=ns
% actuarial survival probability at 10 years	67%	64%	71%	66% p=ns	59% p=ns	74% p=ns	61% p=ns	45% p=0.08	74% p=ns

HM: hematologic malignancy; CLL: chronic lymphocytic leukemia; ns: not significant.

malignancies compared to that in female sporadic patients (15.7% vs 7.4%; $p<0.05$). In particular, significantly higher rates of breast cancer (7% vs 2.3%; $p=0.05$) and skin cancer (3.4% vs 0.4%; $p<0.05$) were recorded. No relationship between the presence of a family history of hematologic malignancy and the proportion of cases with Richter’s syndrome, acute myeloid leukemia and autoimmune hemolytic anemia was observed.

Overall, 12.5% of 1449 CLL patients had one or more relatives affected by a hematologic malignancy. In 9% of the cases, the relative was affected by a lymphoproliferative disease, which was CLL in 6% of the entire case series. These data are in line with those reported by Yuille *et al.*¹

The estimated prevalence of first-degree relative with overt, clinical evidence of lymphoproliferative disease or CLL, respectively 1.6% and 0.8%, is lower than what could have been expected based on the subclinical evidence of a monoclonal CD5⁺ or CLL-like phenotypic B-cell population which has been detected in the peripheral blood of 13.5-18% of healthy relatives included in multiply affected families.³⁻⁵ As observed in Utah registries,¹¹ a higher proportion of female than male patients had a family history of CLL. Since CLL is more frequently diagnosed in males, it could be assumed that affected females might have greater or more penetrant inherited gene(s) predisposing to the occurrence of CLL than males. On this basis, females affected by CLL and their relatives could share the same strong inherited liability and this could explain the higher proportion of familial cases among female CLL patients than among male ones. This is a typical characteristic of some diseases, such as pyloric stenosis, characterized by an

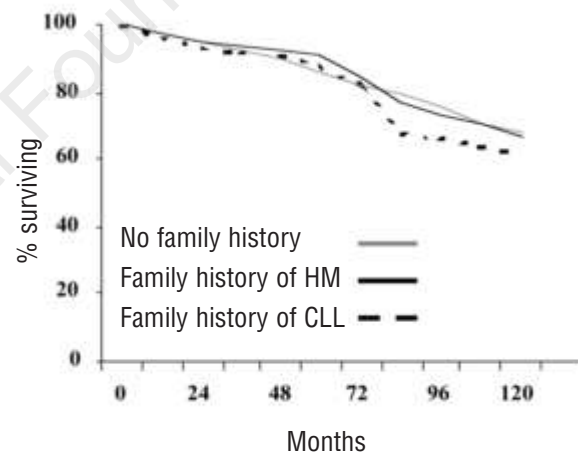


Figure 1. Actuarial survival probability according to the family history.

unequal sex incidence and in which relatives of a patient of a sex in which the condition is less common have a higher risk of developing the same disease.¹² In our study, no differences in survival probability emerged from comparing the survival curves of sporadic and familial CLL cases. The multivariate analysis also confirmed the lack of a prognostic effect associated with a family history.

While elevated levels of B-lymphocyte stimulator, a member of the tumor necrosis factor family with a role in the growth and survival of malignant B cells, have been found more frequently in familial CLL cases than in sporadic cases,¹³ no other biological features or a specific genetic profile with prognostic significance have been related to familial cases.¹⁴ These findings and the

results of the present study suggest that the features of familial cases are not substantially different from those of sporadic cases.

As reported by Ishibe *et al.*⁶ among 73 familial cases of CLL, patients with familial disease had a higher rate of second malignancies. However, in our study a higher rate of second tumors was recorded only among females with familial disease. The increased rate of second malignancies, a classic feature of many familial cancers, could reflect the presence of a common inherited alteration which could, particularly in females, predispose to the development of CLL, as well as other malignancies. In conclusion, our results indicate that a familial trait was significantly more common among female patients and was not associated with an adverse prognosis. This suggests that if an inherited gene predispos-

ing to the occurrence of familial CLL or lymphoproliferative diseases exists, it could play a role in promoting the development of the disease, while it is probably independent of other genetic factors involved in the proliferation pattern of leukemic cells leading to disease progression.

FRM: research design, clinical management of patients, analysis and interpretation of data, wrote the paper; EG, MG: clinical management of patients, collection, and analysis of data; VV: data collection; DG, IS: data interpretation, data analysis; AG: diagnostic work-up of patients included in the study; AP: discussion of results; RF: discussion of results and critical review of the paper.

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References

1. Yuille MR, Matutes E, Marossy A, Hilditch B, Catovsky D, Houlston RS. Familial chronic lymphocytic leukaemia: a survey and review of published studies. *Br J Haematol* 2000; 109:794-9.
2. Goldin LR, Pfeiffer RM, Li X, Hemminki K. Familial risk of lymphoproliferative tumors in families of patients with chronic lymphocytic leukemia: results from the Swedish Family-Cancer Database. *Blood* 2004; 104:1850-4.
3. Rawstron A, Hillmen P, Houlston R. Clonal lymphocytes in persons without known chronic lymphocytic leukemia (CLL): Implications of recent findings in family members of CLL patients. *Semin Hematol* 2004;41:192-200.
4. Marti GE, Carter P, Abbasi F, Washington GC, Jain N, Zenger VE, et al. B-cell monoclonal lymphocytosis and B-cell abnormalities in the setting of familial B-cell chronic lymphocytic leukemia. *Cytometry* 2003;52:1-12.
5. Marti GE, Rawstron AC, Ghia P, Hillmen P, Houlston RS, Kay N, et al. on behalf of The International Familial CLL Consortium. Diagnostic criteria for monoclonal B-cell lymphocytosis (MBL). *Br J Haematol* 2005;130:325-32.
6. Ishibe N, Sgambati MT, Fontaine L, et al. Clinical characteristics of familial B-CLL in the National Cancer Institute Familial Registry. *Leuk Lymphoma* 2001;42:99-108.
7. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternak BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34.
8. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Ass* 1958;53:447-58.
9. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Analyses and examples. *Br J Cancer* 1977;35:1-39.
10. Cox DR. Regression models and life tables. *J R Stat Soc* 1972;34:187-220.
11. Cannon-Albright LA, Thomas A, Goldgar DE, et al. Familiarity of cancer in Utah. *Cancer Res* 1994;54:2378-85.
12. Harper PS. Practical genetic counselling. Butterworth-Heinemann, Oxford, 1998.
13. Novak AJ, Grote DM, Ziesmer SC, Kline MP, Manske MK, Slager S, et al. Elevated serum B-lymphocyte stimulator levels in patients with familial lymphoproliferative disorders *J Clin Oncol* 2006;24:983-7.
14. Houlston RS, Sellick G, Yuille M, Matutes E, Catovsky D. Causation of chronic lymphocytic leukemia- insights from familial disease. *Leuk Res* 2003; 27:871-6.