Lymphoproliferative Disorders

What is changing in the natural history of chronic lymphocytic leukemia?

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Background and Objectives. In the last few years there has been a trend towards an improvement in overall survival of patients with chronic lymphocytic leukemia (CLL). Studies based on tumor registries of the general population or including patients referred to hematologic institutions have analyzed reasons for these changes. However, results need to be validated on independent series.

Design and Methods. We retrospectively evaluated 518 CLL patients diagnosed at our institution between January 1970 and December 1998. In this cohort of patients we looked at characteristics affecting natural history such as age and sex distribution, stage at diagnosis, survival probability and impact of the disease status on the actuarial survival. Trends in these variables were analyzed after splitting the whole series into three groups according to the period in which the diagnosis was made. Group I consisted of 75 patients diagnosed between 1970 and 1979, group II consisted of 149 patients diagnosed in the period 1980-1989, group III was composed of 293 patients diagnosed between 1991 and 1998.

Results. Age and sex distribution did not reflect different periods of diagnosis. The proportion of patients in whom diagnosis was established in low clinical stage (stage A) was higher in the group III (72%) than in groups I or II (26.3% and 50.3%, respectively) ($p < 0.0001$). Differences in the stage distribution affected life-expectancy which was longer for patients diagnosed in the nineties (median survival, 93 months) than in those diagnosed in the eighties (median survival, 54 months) or in the seventies (median survival, 38 months) ($p < 0.0001$). Finally, survival analyses by stage showed an improvement of life-expectancy when dealing with patients of high risk category ($p = 0.005$).

Interpretation and Conclusions. CLL patients diagnosed in the last decade enjoy the best clinical outcome, mostly as a result of a greater proportion of patients in the low-risk clinical stage and a relatively longer survival of the high risk group. It is not clear whether these changes represent true modifications of the natural history of CLL. At the beginning of the third millennium CLL continues to be a fatal disease with a significant impact on life-expectancy.
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Over the last few decades we have been witnesses of important progresses in the knowledge about both the biology and therapy of CLL. Hallmarks of these progresses rely on the development of clinical staging systems and prognostic factors, increasing use of immunologic, cytogenetic and molecular techniques as well as on the introduction of new therapeutic approaches.[1] Furthermore, an increasing number of patients may be asymptomatic prior to an incidental diagnosis made from investigations for other medical reasons. All these factors have had a consistent impact on the survival changes observed in the more recently published CLL series in comparison to the older ones.[2,3] Studies derived from tumor registries of the general population or including patients referred to hematologic institutions have addressed such an issue.[4-7] However, the reasons for these changes are still matter of discussion. We would like to contribute to this debate by presenting our personal data collected over a 28-year period. For this purpose, factors affecting the natural history of the disease, such as sex and age distribution, clinical stage at presentation and survival, were evaluated. All analyses were carried out after splitting the patient cohort into three different groups according to the decade in which the diagnosis was established.

Design and Methods

By analysis of medical records 518 patients observed in the period 1970-1998 met diagnostic criteria of CLL.[8] The diagnosis of CLL relied solely on morphology for patients observed before 1978. Briefly, more than 15×10^9/L lymphocytes in peripheral blood (PB), bone marrow (BM) infiltration of 30% or more, and less than 10% atypical lymphocytes in either PB or BM were considered as diagnostic criteria. Starting from 1979 a B-cell phenotype was demonstrated by means of immunologic markers (i.e., Sm Ig, rosette-E). Immunophenotype studies based on monoclonal antibodies (Mo Abs) (i.e., CD3, CD5, CD20) introduced in 1983, were further expanded in terms of number of MoAbs utilized at the

end of 1988 when the first flow cytometer became available at our institution. The following data were registered: date of diagnosis, age, sex, clinical stage at the time of diagnosis, date and status (alive or dead) at the last follow-up. Trends of these variable were analyzed using appropriate statistical methods after splitting the patient cohort into three groups according to the period in which the diagnosis was made. Group I consisted of 75 patients diagnosed in the period 1970-1979, group II consisted of 149 patients in whom the diagnosis was established between 1980 and 1989, and group III was composed of 293 patients diagnosed between 1990 and 1998. All patients were staged according to the Binet staging which recognizes patients in low (stage A), intermediate (stage B) and high-risk stage (stage C).[9] As far as the timing of therapy is concerned, our policy remained unmodified over the time. Generally, stage C or symptomatic stage B patients received immediate treatment at the time of diagnosis. For stage A patients or asymptomatic stage B patients, treatment was deferred until signs of disease progression (i.e., from A or asymptomatic B to symptomatic B or C) were observed. An alkylating agent, usually chlorambucil, associated with low doses of corticosteroids was the up-front therapy. Only a few patients were included in clinical trials aimed at testing fludarabine versus chlorambucil as first-line therapy.

Non-parametric tests (Mann-Whitney, Chi-squared) were used to calculate differences between medians of continuous or discrete variables. Survival curves were plotted according to the Kaplan-Meier method and compared according to the log-rank test. All statistical analyses were performed using the statistical program GraphPAD Software 2.00 (GraphPAD Software Inc., San Diego, California, USA). Finally, survival of patients diagnosed in the period 1991-1998 was compared with that of an age- and sex-matched Calabrian population.[10] The expected survival of the control group was calculated from the age- and sex-specific death rates of the 1989-1993 life-table of the Calabrian population. The expected probability of survival for the age- and sex-matched population was obtained using the Survit procedure.[11]

Results

Comparison of male to female (M/F) ratio demonstrated a constant male predominance that is consistent with other published series (Table 1).[4,5,7] The same applied for the age at diagnosis. The median ages of patients diagnosed in the three different decades were virtually similar (group I, 67 years; group II, 66 years; group III, 68 years; $p = 0.304$)(Table 1). As a matter of fact incidence of either younger patients (i.e., less than 55 years old: group I, 12.9%; group II, 12%; group III, 9.7%; $p = 0.602$) or older patients (i.e., more than 70 years old: group I, 32.4%; group II, 35.6%; group III, 40.2%; $p = 0.376$) did not reflect the period of diagnosis. To obtain a historical perspective, survival curves were plotted according to the time of patients' diagnosis. Different patterns of survival were observed in the

Table 1. Sex, age and stage distribution of CLL patients stratified into 3 groups according to the period of diagnosis.

	Group I (n=76)	Group II (n=147)	Group III (n= 301)	p value
Sex				
M	51 (67.1%)	96 (65.3%)	182 (60.4%)	0.427
F	25 (32.8%)	51 (34.6%)	119 (39.5%)	
Age (yrs), median	67 (40-85)	66 (37-92)	68 (40-98)	0.304
Stage				
A	20 (26.3%)	74 (50.3%)	217 (72%)	
B	25 (32.8%)	33 (22.4%)	31 (10.2%)	< 0.0001
C	31 (40.7%)	40 (27.2%)	53 (17.6%)	

three decades; the median survival for patients diagnosed between 1970 and 1980 was 38 months, whereas it was 54 months for patients observed from 1980 through 1989 and 93 months for patients diagnosed between 1990 and 1998 (Chi-squared for trend= 23.13; d.f.=1; $p < 0.0001$) (Figure 1). We wondered whether these changes were merely due to differences of stage distribution or reflected modifications of natural history. An increased proportion of low-risk patients characterized the more recent series, and indeed patients diagnosed in Binet stage A accounted for 26.3% in group I, 50.3% in group II and 72% in group III (Table 1). Despite these differences in the stage distribution, survival curves plotted by Binet stage did not change as a function of time of diagnosis in either stage A or B patients (Figures 2 and 3). The same did not apply to patients belonging to the high-risk category (Binet stage C): in this subset of patients life-expectancy significantly increased in the last decade (Chi-squared for trend= 7.64; d.f.=1; $p = 0.005$) (Figure 4). It has been shown that differentiating CLL (i.e., tumor progression, infections) from non-CLL related (i.e., cardiovascular, metabolic, second epithelial neoplasms) deaths is remarkable only when dealing with patients with early disease.[12] As shown in Figures 5a and 5b separating CLL- and non-CLL-related deaths is especially relevant for Rai stage 0 patients.

Finally, we wondered whether the tendency towards an earlier diagnosis in the last few years might be the explanation for the life-expectancy of CLL patients approaching that of an age- and sex-matched population. We, therefore, compared survival of CLL patients diagnosed in the last decade with that of a healthy control population in the period 1989-1993. CLL was still, in the nineties, an uncurable disease affecting overall survival. This appears clear when comparing either low risk (stage A) or stage A' subgroup cases with healthy controls ($p < 0.001$)(Figure 6).
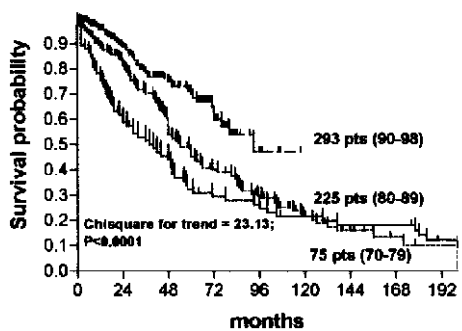
Figure 1. Survival of CLL patients stratified into three groups according to the period in which the diagnosis was established.
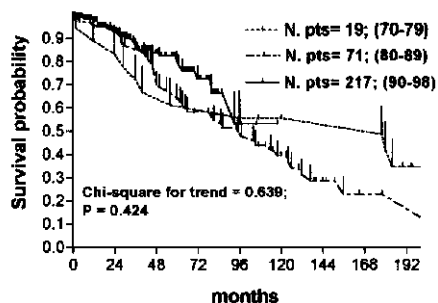

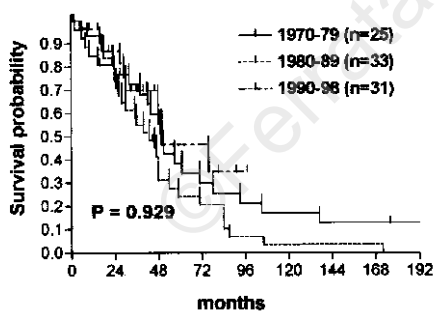**Figure 2. Survival of stage A CLL patients according to the period of diagnosis.**

Figure 3. Survival of stage B CLL patients according to the period of diagnosis.

Figure 4. Survival of stage C CLL patients according to the period of diagnosis.

Figure 5, A and B. Survival curves of Binet stage A and Rai stage 0 patients stratified according to the causes of death (CLL- and non-CLL-related).

Discussion

The diagnosis and treatment of CLL have changed substantially over the last 15 years.[1] In the past, CLL has been considered a disease of older individuals who eventually died of non-CLL-related causes.[12] Recently published studies cast considerable doubt on that thinking.[7] As advances in flow cytometry, cytogenetics, molecular biology, and treatment seem to improve clinical out-
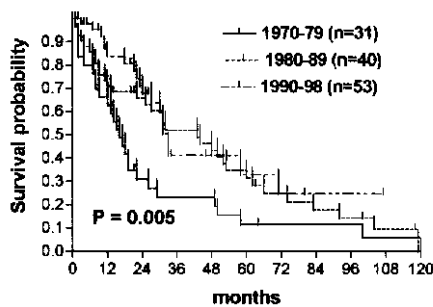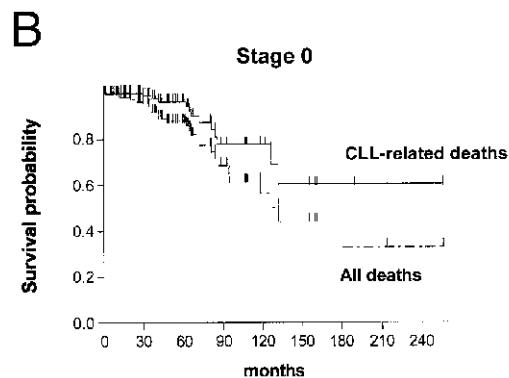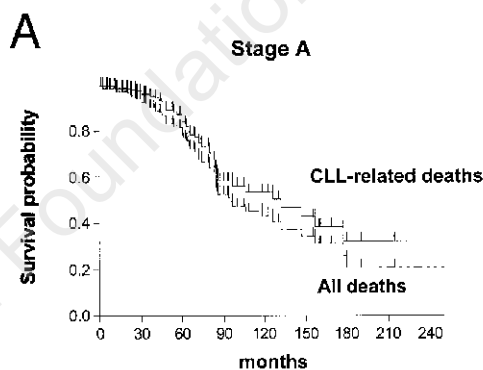
come of patients with CLL, a reappraisal of demographic and survival data appears critical. To obtain a historical perspective, Rozman *et al.*[5] compared two cohorts of CLL patients observed at a single hematology institution over a 30-year period. They concluded that the increasing survival of CLL patients at the present time reflects a combination of both artificial and true changes in the natural history of disease. Call *et al.*[4]
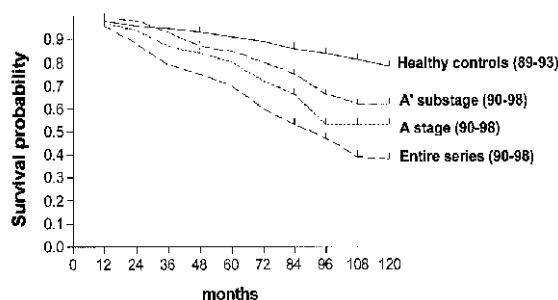
Figure 6. Comparison of survival of CLL patients (all stages, stage A, stage A') diagnosed in the last decade with that of an age- and sex-matched control population.

looked at records of CLL patients diagnosed in Olmsted County, Minnesota, from 1935 through 1989. The overall annual incidence rate of CLL per 100,000 population in Olmsted County increased from 2.6 in 1935 through 1944 to 5.4 in 1975 through 1984. They argued that the increased proportion of early diagnoses might account, at least in part, for the improvement in overall survival over time.

A survey carried out by the EUROCARE Working Group of seven hematologic malignancies diagnosed in Europe between 1985 and 1989 from 39 cancer registries in 17 countries compared survivals with those of patients diagnosed in the 1978-1979 period. The 5-year survival of CLL patients improved in 1987-1989; consequently, the relative risk (RR) of death for CLL was 0.65.[6] Case-mix age and gender characteristics, management and outcomes of patients diagnosed with CLL in United States over the last decade were recently published using the National Cancer Data Base.[7] The risk of developing CLL increases progressively with age without reaching a plateau and was about 3 times higher for older men than for older women. Also in this study, a trend toward earlier diagnosis was found.[7]

Longer survival and a higher proportion of patients presenting in early clinical stage characterize more recently diagnosed series in our study, too. However, our results deserve additional comments. For instance the very low incidence of stage A patients we observed in the seventies is not a common feature especially when results are compared with those of other published series of same period. It should be taken into account that the routine practice of performing white blood cell counts was relatively infrequent in those times in southern Italy where a health care program for the elderly was not developed. We do not have any apparent explanation for the increased incidence of stage C in comparison to stage B patients. Nonetheless, in a historical Spanish series, the stage B to stage C ratio approaches,[1] thus making our findings not completely surprising.[2] Interestingly, survival analysis by risk groups

clearly demonstrated survival changes only among the high-risk category. This pattern of survival only marginally reflects the impact of new therapies such as purine analogs whose activity in inducing an increased rate of response did not translate into an improvement of overall survival.[15] The prevention and treatment of both disease- and chemotherapy-related complications may perhaps account for the gain in overall survival of stage C patients in the last decade.[16,17]

It is generally believed that CLL is a relatively benign disorder with a very low impact on life expectancy. However, there are very little data that indicate how survival of patients with CLL compares with that of age- and gender-matched populations. Rozman et al.[5] reported that the observed-to-expected (O/E) survival was 0.26 between 1960 and 1979 and improved to 0.08 between 1980 and 1989. Nonethless, CLL remains a fatal disease. This is true also for patients with early disease whose prognosis is, on the other hand, heterogeneous. While there is clear evidence of a very good clinical prognosis for smoldering CLL, predicting the outcome of non-smoldering CLL is more difficult.[18-22]

In conclusion, the increased survival of patients with CLL in recent years is associated with an enlarging proportion of them receiving an earlier diagnosis. This trend may be related in part to extensive examinations of elderly patients because of improvements in health care programs for the elderly population. Other facts, such as the age-specific incidence rate of CLL should be considered in the context of a general population whose life-expectancy is increasing. Finally, as Rozman et al.[5] suggested, a combination of true and artificial changes in the natural history of CLL are going to modify our current approach to this disease.

Potential implications for clinical practice

Despite improvement in overall survival in the last decade CLL continues to be a fatal disease.
This concept also applies to patients in the low-risk group whose survival is not different from an age- and sex-matched control population.

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