Natural history of early chronic lymphocytic leukemia. A single institution study with emphasis on the impact of disease progression on overall survival

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ABSTRACT

Background and Objectives. Criteria for identifying patients with early chronic lymphocytic leukemia (CLL) who are likely to progress to a more advanced clinical stage rely on results of prospective clinical trials. It is not clear whether these same criteria apply to patients followed-up in the setting of clinical practice. With the aim of addressing this issue we investigated the clinical outcome of a series of patients with Binet stage A CLL.

Design and Methods. Two hundred and four Binet stage A CLL patients observed at a single institution over an 18-year period form the basis of this study. Different proposals for subclassifying Binet stage A were validated by using our patients as test-set cases.

Results. The survival of patients with early CLL (i.e., Binet stage A and Rai stage 0) was significantly different from that of an age- and sex-matched population. Three of 4 different criteria for subclassifying stage A (Rai substaging, Montserrat criteria, French Group proposal), when applied to our patients, gave similar results in terms of sample size, death rate and disease progression (DP) risk. The French Group proposal, based exclusively on blood counts and hemoglobin levels, was not effective in predicting the risk of DP. Forty-nine (23.5%) patients progressed to a more advanced clinical stage (30 to stage B and 19 to stage C); the risk of DP was 32.8% at 5 years and 49.6% at 10 years. When analyzed as a time-dependent variable (Mantel-Byar method), DP had a clear cut-impact on overall survival ($p < 0.0001$). Finally, outlook for survival of patients who experienced a change of clinical stage was similar to that of patients in that stage at the time of diagnosis.

Interpretation and Conclusions. As many patients are now being diagnosed while asymptomatic and at a younger age than previously, an accurate evaluation of prognosis is mandatory in early CLL. How prognostic information translates into a policy of early or delayed therapy is still unclear. Our results further support a conservative approach for CLL in early stage; patients who progress into a more advanced stage have similar survival to those in that stage at diagnosis.

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Key words: stage A CLL, smoldering CLL, disease progression

Several staging systems have been proposed for chronic lymphocytic leukemia (CLL). These systems identify three major subgroups and guide appropriate treatment decisions. However, the situation is more complex in patients diagnosed at an early stage of disease (i.e., Binet stage A, Rai stage 0), who account for up to 60% of all CLL patients. In this subset of patients none of the staging systems currently used can identify those patients who will have an indolent course and good prognosis as compared to those who will progress rapidly and finally die of their disease.

Several proposals have been made to identify criteria useful for the prognostic assessment of early CLL. It should, however, be emphasized that definitions of smoldering CLL rely on series of patients included in clinical trials. It is not, therefore, clear whether these criteria apply to patients followed-up in the setting of clinical practice. This is of particular importance considering that new prognostic factors, that in the future might assist identification of high-risk category of patients with early CLL, have been shown to be of independent prognostic value only in a small subgroup of studies.

We report the results of a retrospective study carried out on a series of 204 stage A CLL patients observed in a single institution over the last 18 years. The objective of this study was to validate proposals for defining smoldering CLL by using our patients as test-set cases. The natural history of stage A CLL was also investigated taking into account the behavior of patients after they had progressed to a more advanced clinical stage.

Design and Methods

Patients

Over the 1979-1997 period, 204 CLL patients fulfilling Binet stage A criteria were observed. There were 133 males and 71 females. Their median age was 65.4 years (range, 43-83 years). The cytomorphologic and immunologic criteria of CLL were those recommended by the revised guidelines of the National Cancer Institute (NCI). According to the Rai staging system, patients were distributed as follows: stage 0, 133; stage I-II, 67; stage III, 4. Bone marrow (BM) biopsies were performed at the time of
diagnosis in 140 (68.6%) diagnosed after 1986 and the pattern of BM infiltration was evaluated according to the criteria suggested by Rozman et al. In patients diagnosed in the period 1979-1985, who formed 31.3% of the overall series, the assessment of BM involvement relied on the percentage of lymphocyte infiltration (LI) on aspiration smears. The previously demonstrated correlation between the histopathologic pattern of BM infiltration and the percentage of LI by aspiration prompted us to arbitrarily consider for prognostic purpose LI > 80% equivalent to diffuse BM histology. Lymphocyte doubling time (LDT), assessed during the treatment-free period, was available for 156 out of the 204 (76.4%) patients.

All patients were treated according to conventionally accepted methods. Treatment indications included clear evidence of disease progression (DP) (i.e., from stage A to C or symptomatic B), a LDT < 6 months, appearance of B symptoms (i.e., fever, night sweats, or loss of weight not resulting from other causes), or autoimmune cytopenias. One hundred and forty-six patients (71.5%) did not receive any treatment for periods ranging from 1 to 155 months. An alkylating agent, usually chlorambucil, associated with low doses of steroids was the treatment chosen for the remaining 58 patients.

Statistical methods

Results were analyzed with the statistical program GraphPAD Software 2.00 (GraphPAD Software Inc, San Diego, CA, USA). Survival curves were plotted using Kaplan and Meier’s method and compared by the log-rank test. To determine the influence of DP on the patients’ survival, progression was analyzed as a time-dependent event according to Mantel and Byar’s method.

Finally, survival of either Binet stage A or Rai stage 0 patients was compared with that of an age- and sex-matched Calabrian population. The expected survival of the control population was calculated from the age- and sex-specific death rates of the 1989-1993 interval chosen for plotting the survival curves of the sex- and age-matched population. The comparison between a CLL patient series observed during a 18-year period (1979-1997) and a control population observed over a 4-year period (1989-1993) could introduce a bias. Although life-expectancy of patients with early CLL has not changed over the last 30 years (unpublished results and ref. #21), the life-expectancy of the sex- and age-matched population has increased in the last few years. However, the 1989-1993 interval chosen for plotting the survival curves of the sex- and age-matched population was close to the median year in which our CLL patients were diagnosed. This could reduce, at least in part, the bias created by comparing population samples observed in different periods. The expected probability of survival for the age- and sex-matched population was obtained using the Survit procedure.

Results

Survival of stage A patients

At the time of writing this report, 63 (30.8%) of the 204 stage A patients have died; actuarial median survival was 95 months. Death could be related to CLL (i.e., leukemia-progression, infections) in 50 patients (79.3%), whereas death in 10 patients was attributed to causes unrelated to CLL (i.e., second epithelial neoplasms, 7 (11.1%); cardiovascular and/or metabolic diseases, 3 (4.7%)). The cause of death was unknown in 3 patients (4.7%). CLL-unrelated deaths were equally distributed between patients with smoldering and non-smoldering CLL (p = 0.485).

Twenty-seven out of the 204 patients (13.2%) were younger than 55 years. Actuarial median survival of younger patients was longer than that of older ones [156 months versus 93 months; hazard ratio (HR), 2.215; 95% confidence interval (CI), 0.9932 to 4.438; p = 0.05].

Prognostic stratification of stage A patients

Different criteria for subclassifying stage A patients have been proposed recently (Table 1). Three of 4 methods apply to our patient series, thus providing reliable results in terms of sample size, survival rate and DP risk (Tables 2 and 3). The French Group proposal has the advantage of simplicity since it can be derived exclusively from the blood count without requiring BM evaluation or LDT. Furthermore, in our test-set series it included, in the so-called indolent category (A'), a consistent proportion of patients (150 out of 204 i.e. 73.4%). However, the discriminant prognostic power of this method was, at least partially, lower than others; furthermore it was unreliable

### Table 1. Different proposals for subclassifying stage A CLL.

<table>
<thead>
<tr>
<th>Rai et al.</th>
<th>Montserrat et al.</th>
<th>French group</th>
<th>French Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hb ≥ 11 g/dL</td>
<td>1. Stage A</td>
<td>1. Hb ≥ 12 g/dL</td>
<td>1. Hb ≥ 12 g/dL</td>
</tr>
<tr>
<td>2. PLT ≥ 100×10³/L</td>
<td>2. Non-diffuse BM histology</td>
<td>2. PB lymphocytes &lt; 30×10³/L</td>
<td>2. PB lymphocytes &lt; 30×10³/L</td>
</tr>
<tr>
<td>3. No involved areas</td>
<td>3. Hb ≥ 13 g/dL</td>
<td>3. BM lymphocytes &lt; 80%</td>
<td>3. BM lymphocytes &lt; 80%</td>
</tr>
<tr>
<td></td>
<td>4. PB lymphocytes &lt; 30×10³/L</td>
<td>5. LDT &gt; 12 months</td>
<td>4. Fewer than two areas involved</td>
</tr>
</tbody>
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We wondered whether features of smoldering CLL, (i.e., non-diffuse BM histology, LDT > 12 months, PB lymphocytosis < 30×10^9/L) could add prognostic information to the Rai staging system at early stages (Rai 0 to II). When the subgroup of patients in Rai stage 0 was further split according to the definition of smoldering CLL, a slightly better prognosis characterized patients belonging to the above mentioned subcategory (p = 0.05; RR, 1.404; 95% CI, 0.940-1.862). No risk stratification could be identified when a similar analysis was performed on patients in Rai I-II stage (p = 0.108; RR, 0.857; 95% CI, 0.406-1.308).

## Progression of disease
Forty-nine (23.5%) of the 204 patients progressed to a more advanced clinical stage (i.e., 30 from stage A to B and 19 from stage A to C). The risk of disease progression was 32.8% (SE, 4.7%) at 5 years and 49.6% (SE, 6.4%) at 10 years. More important was the fact that, when analyzed as a time-dependent variable, DP had a clear-cut impact on survival (p < 0.0001) (Figure 1).

The potential of aggressiveness of disease was reflected in the shorter life-expectancy of patients in both Binet stage A (p < 0.0001) and Rai stage 0 (p < 0.0001) in comparison to the sex- and age-matched population survival (Figure 2). Interestingly, differences between curves became more appreciable starting from the 5th year, when patients with early CLL experienced an increased rate of DP.

Finally, we tried to verify whether outlook for survival of patients who underwent disease progression was similar to that of patients in that stage at the time of diagnosis. For statistical comparison we used 91 patients in stage B and 53 in stage C diagnosed in the period ranging between 1979-1997. As shown, differences in survival time in any stage, whether the patients were diagnosed initially in that stage or they entered the stage during the evolution of their disease, were not significant (Figures 3 and 4).
Discussion
Recommendations for an appropriate approach to patients with early CLL derive mainly from patients included in clinical trials. It is not, therefore, completely clear whether these recommendations should be applied to patients followed-up in the setting of clinical practice. In this respect our results, although confirmatory in many aspects, have important clinical implications in day-to-day practice. Our results yield the following information relevant for physicians caring for patients with CLL:
1. survival of CLL patients with early stage disease (i.e., Binet stage A and Rai stage 0) is significantly shorter than that of an age- and sex-matched population;
2. DP is an event affecting overall survival;
3. three of 4 different proposals for subclassifying stage A provide similar results in terms of sample size, long-term survival and DP risk. The French Group method, based exclusively on blood count and hemoglobin levels, was not effective in predicting the risk of DP;
4. survival of patients who progress to a more advanced clinical stage, evaluated from the time of entry into a new stage, is similar to that of patients in that stage at diagnosis.

How these results translate into the timing of therapy is still a complex issue. In a recently published series of results of early versus delayed therapy it was shown that chlorambucil (CLB) can only delay DP but not affect survival. Furthermore, a recent meta-analysis of 2,048 patients with early stage disease, enrolled in 6 trials of immediate versus deferred chemotherapy (CLB or CLB plus prednisone), demonstrated that the 10-year survival was slightly although not significantly worse with immediate chemotherapy (44% versus 47% survival). These results support a conservative approach.
treatment strategy for patients with early CLL. Nonetheless, this strategy should be reconsidered as soon as results of trials based on newer chemotherapy agents become available.

Although CLL is the quintessential example of an indolent lymphoid neoplasia, about 33% of stage A patients progress to a more advanced clinical stage by 5 years and finally die of their disease. This is clearly reflected in the significantly shorter survival of patients with early stage CLL in comparison to that on an age- and sex-matched population. Interestingly, differences between survival curves become more appreciable starting from the 5th year, when both Rai stage 0 and Binet stage A patients showed an increased rate of DP.

Since adequate follow-up data were available, it was possible to assess survival duration starting from the time of entry into a new stage and to compare these results with those of patients in that stage at diagnosis. Survival in any stage, whether patients were diagnosed initially as being in that stage or they entered the stage during the course of their disease were not significantly different. Thus Rai’s pipeline-like concept, based on the assumption that the prognosis for a patient in a given stage is the same whether the patient is staged at the time of diagnosis or enters the stage by progression, is confirmed by the present study.1

In conclusion, prognostic assessment of patients with early CLL is still a complex issue. In order to improve the discriminant power of clinical parameters, several biological features including tumor cell proliferation, immunophenotype, adhesion molecule expression and release, karyotypic abnormalities and findings of increased angiogenesis have been investigated.13,22,26 However, many biological markers are based on time-consuming and non-standardized assays, therefore their extensive use in the day-to-day practice is not recommended or practical. In this setting proposals for subclassifying stage A patients can be used indifferently for prognostic purpose. Biological parameters should be incorporated into clinical prognostic models in order to identify subsets of patients, especially younger ones, with a clinically aggressive course of disease.

Contributions and Acknowledgments

SM was responsible for the conception of study, performed the statistical analysis and wrote the paper. In addition, SM and DL cared personally for most of the patients. AD was responsible for the immunophenotype studies. All authors gave their approval to the final version of paper.

Disclosures

Conflict of interest: none.
Redundant publications: no substantial overlapping with previous paper.

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References

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