Presenting Features and Prognosis of Chronic Lymphocytic Leukemia in Younger Adults


We have analyzed 117 younger patients with chronic lymphocytic leukemia (CLL) (mean age, 44.5 years; SD, 4.8; range, 19 to 49; male/female ratio, 2.08) with three main objectives: (1) to see whether these patients have distinctive presenting clinical features; (2) to investigate the impact of the disease on survival; and (3) to analyze whether already well-known prognostic factors are also useful when applied to these patients. As compared with an older age population (>50 years), there were no major differences in presenting features except for an increased proportion of males (2.08 vs 1.21; P < .025) and a higher hemoglobin level (13.47 ± 2.70 g/dL vs 12.84 ± 2.77 g/dL; P < .05) in the younger group. Median survival is 12.3 years (expected median from a control group, 31.2 years). Clinical stages, bone marrow patterns, blood lymphocyte counts, and its doubling time are all useful to separate different risk groups of patients. Whereas patients with favorable prognostic factors have a survival probability of about 80% 14 years after diagnosis, those with poor prognostic features have a median survival of less than 3 years. It is concluded that CLL in younger adults has no major distinctive presenting features and that known prognostic factors are useful to separate different risk groups of patients. These results should be of help in planning therapy for younger persons with CLL.

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CHRONIC LYMPHOCYTIC leukemia (CLL), the most frequent type of adult leukemia in Western countries, is characterized by the accumulation of relatively mature-appearing, immunologically incompetent lymphocytes, usually of B-cell phenotype, and by a highly variable clinical course. Current therapies for this disease are unsatisfactory and usually have a merely palliative effect.1,2

The prognostic heterogeneity of CLL patients has prompted studies to identify parameters useful in predicting survival and in planning therapy. Clinical stages,3 bone marrow histology,5,6 blood lymphocyte counts,7,8 and lymphocyte doubling time9,10 are reliable predictors of the patient outcome. Because CLL basically occurs in older persons, prognostic studies have been performed in cohorts of patients with a median age of over 60 years, with less than 10% of them being under 50 years of age.

There are no studies dealing with the presenting features and prognosis of large series of younger patients with well-documented CLL. The analysis of CLL in young persons, however, is important for several reasons: (1) the clinical characteristics of CLL in these patients have not been described; (2) it is not known whether the prognostic parameters identified so far for CLL also apply to younger patients, a poorer prognosis having being claimed for this latter group;11-14; (3) treatment strategies reasonable in older patients may not be so in younger persons; and (4) such analysis can be of help in identifying young patients with CLL as candidates to receive experimental treatment approaches (eg, bone marrow transplantation or high-dose chemotherapy plus hematopoietic growth factors).

Because CLL is very infrequent in relatively young persons, it would be very difficult for a single group to collect enough cases to meaningfully address the aforementioned issues. Therefore, the Spanish Cooperative Group for CLL undertook a multicentric study that is reported herein.

MATERIALS AND METHODS

Patients

One-hundred and seventeen patients with CLL from 14 different Spanish institutions were included in this study. These patients have been diagnosed from 1972 to 1990 and their median follow-up at the time of this report is 46.3 months.

Control Groups

Three hundred and sixty-two patients with CLL from the Postgraduate School of Hematology and the Spanish Cooperative Group series were used for comparative studies. Part of these series have been previously reported.15,16 A sex- and age-matched Spanish population was used to compare survival of CLL patients with normal persons.

Diagnosis

The diagnosis of the 117 patients included in this report was made according to the criteria recommended by the International Workshop on CLL.17 A review of peripheral blood smears, as well as bone marrow aspirate and/or biopsy, was performed to exclude lymphoproliferative disorders other than CLL. In 102 cases the diagnosis was confirmed by cell-surface marker analysis.

Staging Systems

Rai et al18 and Binet et al14 clinical staging systems were used. "Smoldering" CLL. "Smoldering" CLL is defined by all the following criteria: (1) Binet's stage A; (2) nondiffuse bone marrow pattern; (3) hemoglobin (Hb) ≥ 13 g/dL; (4) blood lymphocyte count less than 30 × 10⁹/L; and (5) doubling time greater than 12 months.19

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Other prognostic parameters. Other prognostic parameters analyzed were: (1) absolute lymphocyte count in peripheral blood; (2) lymphocyte doubling time, i.e., the period of time needed to double the initial lymphocyte count; and (3) bone marrow histologic patterns, i.e., diffuse and nondiffuse patterns. Lymphocyte doubling time was available in 36 cases, and bone marrow histology in 90.

Treatment

Most of the patients received therapeutic regimens that include alkylating agents (chlorambucil, cyclophosphamide) and prednisone.

Statistical Methods

Comparison between groups was performed by the corrected χ² test. Survival curves were obtained by the method of Kaplan and Meier and compared by the Breslow and Mantel-Cox tests. The expected survival of the control population was calculated from the age- and sex-specific death rates of the 1975-1976 Spanish life table, using a method detailed in the Survfit procedure (as estimated from projection studies, these life table data will remain valid until 1995). The observed/expected ratio correlates the actual number of observed deaths in the cohort studied with the number of deaths that could be expected in the control group. Relative median survival rates are obtained in the following manner: median observed/median expected × 100.

RESULTS

Patients Characteristics

Mean age of younger adults with CLL included in this study is 44.54 years (range, 20 to 49). The number of cases increased with age: one patient was less than 20 years old; one was between 20 and 30 years old; 16 were between 30 and 40 years old; and 99 (85%) were between 41 and 49 years old (Fig 1). Table 1 depicts the most important presenting features of both the younger age group (less than 50 years of age) and the older age group (50 or more years of age) used for comparative purposes. In the younger group there is a significant predominance of males (2.08 ± 1.21; P < .025), and the Hb level is slightly, albeit significantly, increased (13.47 ± 2.70 g/dL vs 12.84 ± 2.77 g/dL; P < .05). No differences are found in the initial lymphocyte and platelet counts.

Table 1. Clinical Features and Prognostic Stratification

<table>
<thead>
<tr>
<th></th>
<th>CLL &lt; 50 y (n = 117)</th>
<th>CLL ≥ 50 y (n = 362)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>44.54 (4.84)</td>
<td>67.12 (8.61)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>2.06</td>
<td>1.21</td>
<td>&lt; .025</td>
</tr>
<tr>
<td>Hb (g/dL) (mean ± SD)</td>
<td>13.47 (2.70)</td>
<td>12.84 (2.77)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Lymphocytes (×10⁹/L) (mean ± SD)</td>
<td>51.88 (58.32)</td>
<td>62.07 (81.02)</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets (×10⁹/L) (mean ± SD)</td>
<td>192.66 (91.99)</td>
<td>194.32 (90.56)</td>
<td>NS</td>
</tr>
<tr>
<td>Rai’s stages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>22.2%</td>
<td>32.0%</td>
<td>NS</td>
</tr>
<tr>
<td>I + II</td>
<td>59.8%</td>
<td>45.1%</td>
<td>NS</td>
</tr>
<tr>
<td>III + IV</td>
<td>18.0%</td>
<td>22.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Binet’s stages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>47.9%</td>
<td>49.7%</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>35.0%</td>
<td>29.4%</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>17.1%</td>
<td>20.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Bone marrow patterns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiffuse</td>
<td>64 (71.1%)</td>
<td>191 (69.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diffuse</td>
<td>26 (28.9%)</td>
<td>84 (30.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Doubling time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 mo</td>
<td>39 (69.6%)</td>
<td>64 (61.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>≤ 12 mo</td>
<td>17 (30.4%)</td>
<td>41 (39.0%)</td>
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</tbody>
</table>

Abbreviation: NS, not significant.

The distribution of clinical stages, bone marrow histologic patterns, and lymphocyte doubling time in both groups is also shown in Table 1. There are no significant differences in any of these parameters. Most of the patients in both groups have been diagnosed at early clinical stages (Binet’s A, Rai’s 0, I, II), have nondiffuse bone marrow histologies, and display stable lymphocyte counts. No sexual predominance was observed within any of the clinical stages, neither in the younger nor in the older groups of patients. The clinical characteristics of 18 patients less than 40 years old included in this series were not different from those of patients 40 to 49 years old (data not shown).

Survival Studies

At the time of this report, 36 patients have died. Median survival is 12.3 years. In Fig 2, the survival of young patients with CLL (median, 12.3 years) is compared with that of the control population (median, 31.2 years) (P < .001). In Fig 3, the same analysis is presented taking patients aged 50 or over into consideration. Again, patients with CLL had a life expectancy significantly shorter (median survival, 4.6 ± 12.3 years; P < .001). Although the absolute life expectancy is higher in the younger age group than in the older age group, it is noteworthy that there are no significant differences in the observed dead/expected (O/E) ratio of both groups (O/E = 36/19.5, ratio: 1.85; and O/E = 193/124.8, ratio: 1.55; respectively). Moreover, when considering the relative median survival rates, there are no differences either (younger patients, 39.4%; older patients, 37.4%).

Although females seem to live longer than males (median survival, not reached v 142 months) (Fig 4), the observed
difference is not statistically significant. The analysis of survival according to clinical stages (Rai's and Binet's systems), lymphocyte counts, bone marrow histology, and lymphocyte doubling time is shown in Figs 5 through 9, and are further detailed in Table 2. As can be observed, all these parameters discriminate different risk groups. Stage 0 (Rai) or A (Binet), a nondiffuse bone marrow pattern, a blood lymphocyte count equal or less than $50 \times 10^9/L$, and a long lymphocyte doubling time are all capable of identifying a population with a survival probability of about 80% 14 years after diagnosis. In contrast, patients with poor prognostic factors have a median survival probability of less than 3 years.

Twenty-six of 56 patients in stage A fulfilled criteria of "smoldering." Only one of these patients progressed and died 18 months after diagnosis, the remaining being alive 24 to 170 months after diagnosis with a projected survival probability of 85% at 14 years.

As for the small group of patients under 40 years of age, six of 18 have died (10 to 50 months after diagnosis) and 12 remain alive after 6 to 160 months of follow-up. The O/E dead ratio is not significantly different for patients less than
Montserrat et al. reported that the probability of survival for patients with CLL differed based on Binet's stages. The survival rates were as follows:

- Stage A: 0.90
- Stage B: 0.70
- Stage C: 0.50

Most patients (26 of 36) died of infectious complications, particularly pneumonia. In two patients, the cause of death was hemorrhage. Renal failure and a traffic accident accounted for one death each. In seven cases, the cause of death was unknown. One patient developed a second neoplasm (leiomyosarcoma), and three patients developed a large-cell lymphoma (Richter's syndrome).

Fig 6. CLL in younger patients. Survival according to Binet's stages.

Fig 7. CLL in younger patients. Survival according to blood lymphocyte counts.

Fig 8. CLL in younger patients. Survival according to bone marrow patterns.

Fig 9. CLL in younger patients. Survival according to lymphocyte doubling time.
CLL IN YOUNGER ADULTS

Table 2. Survival of Younger Patients With CLL According to Different Parameters and Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>Dead/Total</th>
<th>Median Survival (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>28/79</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>8/38</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 0</td>
<td>1/26</td>
<td>NR</td>
<td>&lt;.0001 (Breslow)</td>
</tr>
<tr>
<td>Stage I + II</td>
<td>19/70</td>
<td>149</td>
<td>&lt;.0001 (Mantel-Cox)</td>
</tr>
<tr>
<td>Stage III + IV</td>
<td>16/21</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Stage A</td>
<td>5/56</td>
<td>NR</td>
<td>&lt;.001 (Breslow)</td>
</tr>
<tr>
<td>Stage B</td>
<td>15/41</td>
<td>115</td>
<td>&lt;.001 (Mantel-Cox)</td>
</tr>
<tr>
<td>Stage C</td>
<td>16/20</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Blood lymphocytes ≤ 50 x 10⁹/L: 17/83 NR .002 (Breslow)
Blood lymphocytes > 50 x 10⁹/L: 19/34 58 .001 (Mantel-Cox)
Nondiffuse pattern: 10/64 NR <.0001 (Breslow)
Diffuse pattern: 17/26 51 <.0001 (Mantel-Cox)
Doubling time > 12 mo: 2/39 NR .0005 (Breslow)
Doubling time ≤ 12 mo: 7/17 98 .0004 (Mantel-Cox)

“Smoldering” CLL: 1/28 NR

Abbreviations: NR, not reached; NS, not significant.

DISCUSSION

In this study the presenting features and prognosis of a large series of previously untreated younger patients with CLL have been analyzed.

The increased male/female ratio in the younger group (2.08) was an unexpected finding. Interestingly, a similar trend has been observed in a large series of patients from the Medical Research Council, and an even more striking predominance of male patients was found in a small series (21 males of 22 cases) from the Eastern Cooperative Group. In contrast, Drancourt et al did not find such a male predominance among 24 patients less than 40 years of age (male/female ratio, 1.4). The reasons for these discrepancies are not clear.

As far as the clinical characteristics are concerned, it is noteworthy that the distribution of clinical stages and bone marrow histologic patterns (which reflect the tumor burden), and the lymphocyte doubling time (which accounts for the pace of the disease), are not different in either the younger or the older group. Similarly, the absolute number of lymphocytes in peripheral blood, another indicator of the tumor mass, is almost the same in both groups. The slightly increased Hb level in the younger group of patients is explained by the fact that male patients, predominating in this group, had higher levels of Hb (data not shown). We have not found among these patients the “tumoral forms,” associated with a poor outcome, described by others.

Survival and prognostic studies are of interest. Median survival of younger patients is greater than 12 years as compared with less than 4 years in the older group. In the few series from the literature from which the median survival of younger patients with CLL can be evaluated, the median survival rates are 12.3 years in 25 patients from the Rai's et al series and 8.5 years in 42 patients from the report by Lee et al. In contrast, the median survival in the series from De Rossi et al can be estimated to be between 6.2 and 7.5 years, and has not been reached in the series from Drancourt et al. Although not significant, there is a trend for a longer survival in females, a fact probably related to their longer life expectancy and that has been previously reported.

The impact of the disease on survival is best evaluated taking into account the O/E dead ratio and the relative median survival rate (O/E median survival). The O/E dead ratio is not significantly different in younger (1.85) and older age patients (1.55). As for the relative median survival rate, there are no differences either. In other words, although the absolute survival time is longer in younger patients, their relative survival is not different from that of the older patients. From the prognostic point of view, the most important prognostic parameters recognized so far, clinical stages, bone marrow histology, blood lymphocyte counts, and doubling time, are useful in predicting the outcome of the disease in younger patients. Moreover, the concept of “smoldering” CLL also applies to this population. These results are in contrast with those recently reported by De Rossi et al in a retrospective study of 133 younger adult patients. According to these authors, the only independent predictor of survival in younger patients with CLL is the percentage of lymphocytes in the bone marrow aspirate, and clinical stages are not adequate to establish the prognosis of these patients. Bone marrow histology and lymphocyte doubling time were not analyzed. However, in this study the diagnosis was confirmed by cell-surface markers in only a minority of patients. On the other hand, the finding of a follicular pattern in some cases in which a lymph node biopsy was performed raises the possibility, as the authors state, that patients with lymphoproliferative disorders other than CLL (namely, non-Hodgkin's lymphomas in leukemic phase) could be included in the analysis. Similar criticisms can be made regarding other smaller series previously published.

Our study demonstrates that: (1) as compared with older patients, younger persons with CLL have no distinctive presenting features; (2) the impact of CLL on survival is the same regardless of the patient's age; and (3) already known CLL prognostic factors are useful when applied to younger patients.

These results are of interest when considering treatment strategies in young adults with CLL. Although new drugs and strategies offer promise, the effect of standard treatments in CLL is usually merely palliative, with no long-lasting remissions of the disease. This effect is particularly inappropriate for younger patients, in whom the aim of treatment should be the curing of the disease. With this background, the issue of intensive therapies in CLL has been reasonably raised. Whether all younger patients with CLL should be offered intensive treatment approaches is an unresolved issue. Nowadays, blood cell counts are being
increasingly performed for a variety of reasons and immune-cell marker studies are becoming available to most laboratories. As a consequence, CLL is diagnosed more and more frequently at an early stage and in relatively younger persons. Therefore, the issue of the best possible treatment should be first investigated in patients with poor prognostic factors and failing standard therapies, age by itself being not a criterion. Finally, further studies will refine both the prognostic assessment of CLL in young persons as well as its optimal management.

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Presenting features and prognosis of chronic lymphocytic leukemia in younger adults [see comments]

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