A multivariate survival analysis by means of Cox’s multiple regression model was performed on a series of 150 consecutive patients with chronic lymphocytic leukemia (CLL) from a single institution. In addition to the well-established clinical staging system that has been widely accepted, a marked prognostic value of the degree of absolute lymphocytosis emerged from this analysis. This was evident in the whole population as well as in low and intermediate risk groups of patients (Rai’s stages 0, I, and II and International Workshop on CLL stages A and B), pointing out that different subsets of patients can be isolated within these groups.

In chronic lymphocytic leukemia (CLL), a certain number of prognostic factors have been isolated. Some of them were grouped by Rai et al. in a clinical staging system that has been widely accepted and verified. However, some attempts to improve this classification have been carried out. Recently, an International Workshop on CLL has recommended a modified system for CLL staging, which although not considered as a final one, provides advantages in planning treatment and in research because clinical stages are limited to three. In this staging system, patients are classified depending on the presence or absence of anemia and/or thrombocytopenia (group C) and the number of “lymphoid” areas enlarged (groups A and B). The International Workshop on CLL has particularly encouraged the investigation of methods to predict within each of the A, B, and C groups subsets of patients who develop a progressive or aggressive clinical course as compared to patients whose clinical course is benign or stable.

The analysis of a series of 150 consecutive patients from our institution supports the new revised proposal for CLL staging. In addition, in the study of this series by means of a multiple regression model developed by Cox (1972), lymphocytosis has emerged as a useful parameter to subclassify “low” and “intermediate” CLL stages in both Rai’s and International Workshop on CLL staging systems. This article is a detailed account of this study.

MATERIALS AND METHODS

Patients and Diagnostic Criteria

One-hundred and fifty patients (83 males and 67 females) from a single institution were included in the study. Mean age was 61.3 yr (SD 11.1).

The diagnostic criteria for CLL were those usually recommended: (1) more than 15 x 10^9/liter lymphocytes in peripheral blood; (2) bone marrow infiltration by lymphocytes of 50% or more; (3) less than 10% atypical lymphocytes in either the peripheral blood or the bone marrow. Lymphosarcoma cell leukemia, prolymphocytic leukemia, and leukemic reticuloendotheliosis were excluded.

Most patients received no treatment or were treated with a single agent, either cyclophosphamide or chlorambucil. A few patients with an aggressive form of the disease received polychemotherapy (cyclophosphamide, vincristine, and prednisone).

Statistical Methods

Actuarial survival probability curves were plotted according to the method of Kaplan and Meier. Different curves were statistically compared by using the log-rank test. Chi square for trend was computed as recommended by Peto et al.

A multiple regression model for censored survival data developed by Cox was employed in order to identify the most significant prognostic factors. A stepwise forward selection procedure was used that inserts variables in turn until the regression is satisfactory.

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Submitted July 15, 1981; accepted December 30, 1981.

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0006-4971/82/5905-0022$01.00/0
Table 1. Variables Tested by Cox’s Multiple Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>In years</td>
<td>&gt;60 yr = 1</td>
</tr>
<tr>
<td>Sex</td>
<td>M = 1; F = 0</td>
<td>M = 1</td>
</tr>
<tr>
<td>Lymphadenopathy (number of areas involved)</td>
<td></td>
<td>3 or more areas = 1</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Absent = 0</td>
<td>present = 1</td>
</tr>
<tr>
<td></td>
<td>≤10 cm = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm = 2</td>
<td></td>
</tr>
<tr>
<td>Absolute lymphocyte count</td>
<td>in (10^3/\mu l)</td>
<td>&gt;50 (\times 10^3/\mu l) = 1</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>in g/dl</td>
<td>&lt;11 g/dl</td>
</tr>
<tr>
<td>Platelets</td>
<td>in (10^3/\mu l)</td>
<td>&lt;100 (\times 10^3/\mu l) = 1</td>
</tr>
</tbody>
</table>

order of insertion is determined by using the maximum log likelihood value as a measure of the importance of variables not yet in the regression equation. At each step the significance level is computed. As recommended by Kalbfleish and Prentice (1973), ties in uncensored and censored observation times were avoided as far as possible by expressing such times in days instead of in months of observation.

We included in this analysis only those variables that are easily obtainable from a simple clinical and hematologic examination. Among these, from a previous univariate analysis, the following ones emerged as the most interesting: age (>60 yr), lymphadenopathy (number of territories, considering each one, either right or left, of the following areas: latero-cervical-supraclavicular, axillar and inguinal, with a maximum of 6 areas involved), splenomegaly, absolute lymphocyte count, hemoglobin level, and platelet count. The model was tested twice by expressing the variables in two different ways (model A and B, Table 1). In order to isolate the most important prognostic factors in patients without anemia and thrombocytopenia, the same analysis was performed in such a restricted series (Rai’s stages 0, I, and II or IWCLL stages A and B).

RESULTS

The survival probability according to A, B, and C groups is shown in Fig. 1. As can be seen, there are clear-cut differences in the life expectancy for these groups of patients. However, the survival of group B is quite similar to the whole series of patients.

The results of the multivariate regression analysis are presented in the Table 2. When the complete series of 150 patients is examined, 3 variables enter the regression model at a significant level and an additional one at near significant level. Although the order of entering varies according to the way of expressing variables, in all instances the peripheral blood lymphocytosis is included among the significant ones. In model B, lymphocytosis shows a greater significance than anemia and thrombocytopenia.

When only the “low” and “intermediate” (Rai’s stages 0, I, and II or IWCLL stages A and B) risk groups of patients are analyzed, lymphocytosis emerges as the most significant prognostic factor. In model B, lymphadenopathy adds significantly to the regression model.

Utilizing the most significant factors predicting survival in the Cox’s regression analysis, the following models (A and B) for survival prediction based on this group of patients were created, where \(\lambda(t)\) is the hazard rate for survival at time \(t\) and \(\lambda_0(t)\) is the hazard computed at the average values of the factors in the model (Table 3). The ability of these models to predict survival compared to actual observed survival in this group of patients is shown in Table 4.

In order to investigate whether the introduction of this new prognostic variable could be useful, the survival was analyzed in the following way (Fig. 2): (A) Rai’s stage 0, (B) Rai’s stages I and/or II with ≤50 \(\times 10^9/\text{liter}\) lymphocytes, (C) Rai’s stages I and/or II with >50 \(\times 10^9/\text{liter}\) lymphocytes, and (D) Rai’s stages III and IV. The log-rank analysis of these survival curves is presented in Table 5. As can be seen, the 0/E ratio is either lower or higher than 1. In other words, all the stages designed in this way discriminate in respect to the whole population. In addition to the highly significant log-rank test (chi-square both for heterogeneity and for trend), a strongly significant
Table 2. Variables Entering the Regression at Significant or Nearly Significant Level

<table>
<thead>
<tr>
<th>Whole series (150 patients)</th>
<th>Model A</th>
<th>p</th>
<th>Model B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>0.00005</td>
<td>Lymphocytosis</td>
<td>0.000004</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>0.0047</td>
<td>Anemia</td>
<td>0.0001</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td>0.0294</td>
<td>Thrombocytopenia</td>
<td>0.0419</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td>0.1140</td>
<td>Splenomegaly</td>
<td>0.0613</td>
</tr>
<tr>
<td>Rai’s stages 0 + I + II (110 patients)</td>
<td>Lymphocytes</td>
<td>0.016</td>
<td>Lymphocytosis</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lymphadenopathy</td>
<td>0.0571</td>
</tr>
</tbody>
</table>

Table 3. Models for Survival Prediction

**Model A**

\[
\frac{\lambda(t)}{\lambda_0(t)} = \text{EXP} \left[ -0.18179(H - 12.73) + 0.00263(L - 67.1) - 0.00531(P - 165.68) + 0.28801(S - 0.71) \right]
\]

**Model B**

\[
\frac{\lambda(t)}{\lambda_0(t)} = \text{EXP} \left[ 1.12618(L - 0.35) + 0.97476(H - 0.23) + 0.85143(P - 0.13) + 0.58932(S - 0.46) \right]
\]

H, hemoglobin; L, lymphocytes; P, platelets; S, spleen.

Table 4. The Fit of the Probability Models

<table>
<thead>
<tr>
<th>Months</th>
<th>1</th>
<th>2</th>
<th>6</th>
<th>12</th>
<th>23</th>
<th>35</th>
<th>44</th>
<th>55.5</th>
<th>65</th>
<th>81</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed (Kaplan-Meier)</td>
<td>0.965</td>
<td>0.950</td>
<td>0.912</td>
<td>0.861</td>
<td>0.750</td>
<td>0.683</td>
<td>0.621</td>
<td>0.500</td>
<td>0.406</td>
<td>0.366</td>
<td>0.183</td>
</tr>
<tr>
<td>Predicted (model A)</td>
<td>0.977</td>
<td>0.968</td>
<td>0.940</td>
<td>0.900</td>
<td>0.802</td>
<td>0.727</td>
<td>0.651</td>
<td>0.509</td>
<td>0.393</td>
<td>0.338</td>
<td>0.108</td>
</tr>
<tr>
<td>Predicted (model B)</td>
<td>0.980</td>
<td>0.971</td>
<td>0.946</td>
<td>0.909</td>
<td>0.815</td>
<td>0.740</td>
<td>0.661</td>
<td>0.489</td>
<td>0.345</td>
<td>0.287</td>
<td>0.077</td>
</tr>
</tbody>
</table>

Fig. 2. Actuarial survival probability in CLL according to a modified version of Rai’s staging system in which lymphocytosis is the parameter used to subclassify I and II stages.
Table 5. Log-Rank Analysis of the Survival Curves

<table>
<thead>
<tr>
<th>Stage</th>
<th>Observed (Total)</th>
<th>Expected</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and/or II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ≤50 × 10^9/liter lymphocytes</td>
<td>13 (50)</td>
<td>22.39</td>
<td>0.58</td>
</tr>
<tr>
<td>Stage I and II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with &gt;50 × 10^9/liter lymphocytes</td>
<td>9 (20)</td>
<td>5.49</td>
<td>1.64</td>
</tr>
<tr>
<td>Stages III and/or IV</td>
<td>22 (40)</td>
<td>7.72</td>
<td>2.85</td>
</tr>
<tr>
<td>Total</td>
<td>48 (150)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ² for heterogeneity (3 df) = 38.28, p = 2.47 × 10⁻⁴.
χ² for trend (1 df) = 34.66, p = 3.93 × 10⁻⁵.

DISCUSSION

Though developed on an empirical basis, the Rai’s staging system has represented a major progress in prognosis of CLL, permitting the isolation of a “high risk” group (stages III and IV), a “low risk” group (stages 0 and I), and an “intermediate” group (stage II) of patients. However, a critical review demonstrates certain limitations of this system, namely, there are too many prognostic categories to be useful for therapeutic trials; static and progressive forms of the disease are not separated; and a considerable number of patients belong to stage II, showing a survival expectancy equal to the whole population of CLL patients. The new staging system (IWCLL) derived from a simultaneous multivariate survival analysis by Binet et al. (1981) represents further progress. In the work performed by these authors, the prognostic value of the number of involved lymphatic areas has been recognized. This staging system is reproducible, and it has been confirmed in large series of patients and endorsed by the International Workshop on CLL.

The need to isolate different subsets of patients within each prognostic group has been emphasized, since among them there can be patients with a more aggressive course and others with quiescent forms of the disease, probably not needing therapy.

To date, the prognostic value of lymphocytosis in CLL has been a controversial issue. Whereas some authors point out that a marked lymphocytosis means poor prognosis, others state that this feature is devoid of prognostic significance. From our study it is clearly evident that, in addition to anemia and thrombocytopenia, the degree of absolute peripheral lymphocytosis represents an important prognostic factor in CLL. This is true for the whole series, as well as for the patients of low and intermediate risk, who are usually more difficult to classify from the prognostic point of view. Interestingly, Cavo et al. have recently presented the analysis of their series in which lymphocytosis has also proved to be useful for subclassifying Rai's stages. It is not surprising at all that the lymphocytocumulative phenomenon, so characteristic of CLL, would be reliably expressed in peripheral blood. Therefore, the prognostic value of peripheral lymphocytosis in CLL should be taken into account and eventually incorporated into the CLL staging systems.

ACKNOWLEDGMENT

We express our gratitude to the Department of Biomathematics of the University of Texas Cancer Center for kindly supplying us with the computer program of Cox's multiple regression analysis.
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