Staging of Chronic Lymphocytic Leukemia

By Michele Baccarani, Michele Cavo, Marco Gabbi, Franco Lauria, and Sante Tura

One-hundred and eighty-eight patients with chronic lymphocytic leukemia were analyzed for prognosis based on Rai’s staging system. It was found that stages I and II were not homogeneous as to prognosis. Stage II patients presenting with isolated splenomegaly had a long survival and were pooled with stage 0 patients (low risk group, 30% of cases, relative death rate 0.24, median survival > 10 yr). Stages I and II patients with a lymphocyte count higher than \(40 \times 10^9/\text{liter}\) had a short survival and were pooled with stages III and IV patients (high risk group, 39% of cases, relative death rate 1.91, median survival 3.3 yr). Stages I and II patients with a lymphocyte count lower than \(40 \times 10^9/\text{liter}\) made up an intermediate or standard risk group (31% of cases, relative death rate 1.00, median survival 6.2 yr). This modified staging system applied successfully to both old and young patients (more and less than 60 yr old, respectively).

A SIMPLE STAGING SYSTEM of chronic lymphocytic leukemia (CLL) was proposed by Rai et al. in 1975 and was confirmed subsequently by several other investigators. Rai’s system allowed the identification of a low risk group (stage 0), a high risk group (stages III and IV), and a group with intermediate or standard prognosis (stages I and II).

In an attempt to improve and refine that staging classification, we reviewed a series of 188 CLL patients. It was confirmed that Rai’s definition of stage 0 and stages III and IV identified accurately patients at a low and a high risk of death, respectively. In contrast, it was found that stages I and II patients, who accounted for 50% of cases in all series studied so far, were heterogeneous as to prognosis. Stage II patients with isolated splenomegaly had a prognosis as good as stage 0 patients, while stages I and II patients with a high lymphocyte count (>40 \(\times 10^9/\text{liter}\)) had a prognosis as poor as stages III and IV patients.

MATERIALS AND METHODS

Two-hundred and sixty consecutive patients with CLL were referred to this Institute between January 1966 and June 1979. Seventy-two patients (28%) were excluded from the study, either because they had been diagnosed as having CLL more than 2 yr ago (17 cases) or because of prior antileukemic therapy (53 cases). The remaining 188 patients, all previously untreated, were included in the study. In 61 of them, or 32%, a diagnosis of CLL had been made elsewhere less than 2 yr ago (median 5 mo). Evidence of CLL was based either on blood counts or on lymphadenomegaly. For these 61 patients, the information on clinical and hematologic features at diagnosis was not complete. Therefore, the stage of these patients was determined based on the features recorded on first examination at this Institute, and survival was calculated from then on. Median age at diagnosis was 64 yr, with 14 patients (7%) less than 50 yr old, and 53 patients (28%) more than 70 yr old. There were 123 males (65%), and 65 females (35%).

The diagnosis of CLL was based on a peripheral blood lymphocyte count higher than \(5 \times 10^9/\text{liter}\) and on marrow lymphocyte infiltration over 40%. Seventy of 188 cases presented with a lymphocyte count between 5 and \(15 \times 10^9/\text{liter}\). In all of them, the diagnosis of CLL was unequivocally confirmed either by the demonstration of the disease or by the demonstration that more than 50% of blood lymphocytes were B cells with monoclonal surface immunoglobulins.

This was shown by direct immunofluorescence study after incubation with rabbit anti-human immunoglobulin and anti-light-chain antiserum. Patients with prolymphocytic leukemia, hairy cell leukemia, and so-called lymphosarcoma-cell leukemia were not included in this study.

No patient had received prior therapy for CLL. After diagnosis, the guidelines for therapy were essentially the same in all cases, although treatment was not given according to rigid protocols. Patients without symptoms and with a relatively small tumor burden were not treated until evolution to a more aggressive disease. First choice treatment was chlorambucil, usually associated with low dose corticosteroids. Other treatment included higher corticosteroid doses, cyclophosphamide, and radiation.

The study was based on the original Rai’s classification (Table 1). The data were analyzed to establish whether other clinical or hematologic features may be of value to refine Rai’s system. Such features were age, sex, isolated splenomegaly, peripheral blood lymphocyte count, absolute granulocyte count, immunoglobulin level (as measured by radial immunodiffusion), and marrow lymphocyte infiltration (estimated on fine-needle aspirate).

All patients were regularly followed until June 1980. By that date, 83 patients (44%) were dead—leukemia, infection, and/or other leukemia-related complications 58 cases; cardiovascular disease 15 cases; chronic liver disease 3 cases; second malignancy (carcinoma) 5 cases; myasthenia gravis 1 case; and complications after cholecystectomy 1 case. Median duration of follow-up was 40 mo for all cases and 43 mo for living patients.

Statistical Procedures

Survival was calculated by life-table analysis from date of diagnosis (127 cases) or date of first examination at this Institute (61 cases) to date of death or to June 1980. All deaths, whatever the cause, were included in the calculation. The test for trend and the test for heterogeneity by the logrank method, with two-tailed chi-square values, were used throughout, whenever appropriate. Both tests were
calculated by dividing the number of deaths on each day of the
son of the number of deaths observed
extensively described by Peto Ct al.'7 They are based on the compari-
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tion of death in that group (i.e., the interval from
to risk of death. By the way, E depends also on the time
exposure on that day, and adding all E values up to get the total extent of
period by the proportion of patients in each group remaining at risk
with the extent of exposure to risk of death (E) in that group. E is

group.

diagnosis to death) and the length of patients' follow-ups in that

extensively described by Peto et al.17 They are based on the compari-
son of the number of deaths observed (O) in each group of patients,
with the extent of exposure to risk of death (E) in that group. E is
calculated by dividing the number of deaths on each day of the period
by the proportion of patients in each group remaining at risk
on that day, and adding all E values up to get the total extent of
exposure to risk of death. By the way, E depends also on the time
distribution of each death in that group (i.e., the interval from
diagnosis to death) and the length of patients' follow-ups in that
group.

RESULTS

Life-table analysis of all 188 patients is summarized in Table 2. Median survival, in that series, was 6 yr.

Survival according to Rai's staging classification is shown in Fig. 1. The median was not reached in stage
0, was 5.4 and 6.0 yr in stages I and II, respectively, and was 2.6 and 3.0 yr in stages III and IV, respectively.

Sex, marrow lymphocyte infiltration, immunoglobulin level, and absolute granulocyte count had no signifi-
cant influence on prognosis and could not be used to refine Rai's staging system.

Stage 0 patients could not be subdivided further, as the
observed number of deaths (7 of 50) was small.

Stages III and IV patients were also homogeneous as to prognosis. In particular, patients presenting with
anemia and thrombocytopenia did not fare worse than patients presenting with anemia or thrombocytopenia
alone. It may be interesting to note that anemia and/or

Table 1. Stage Classification According to Rai et al.'

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| 0     | Blood and marrow lymphocytosis (absolute peripheral blood lymphocyte count ≥ 15 x 10⁹/liter, with 40% or more lympho-
cytes in the marrow). |
| I     | Blood and marrow lymphocytosis with lymph node enlargement. |
| II    | Blood and marrow lymphocytosis with splenomegaly and/or hepatomegaly (with or without lymph node enlargement). |
| III   | Blood and marrow lymphocytosis with Hb lower than 11 g/dl (excluding autoimmune hemolytic anemia) (with or without
lymph node, spleen, or liver enlargement). |
| IV    | Blood and marrow lymphocytosis with platelet count lower than 100 x 10⁹/liter (with or without lymph node, spleen, and
liver enlargement, and independently of Hb concentration). |

In this study, patients with 5 to 15 x 10⁹ lymphocytes/l were also included (see text).

palpable tumor mass. Only 5 of 49 stages III and IV patients had no organomegaly. All lymph nodes were
enlarged in 26 cases, 2 lymph node groups in 10 cases, and 1 lymph node group in the remaining 8 cases.
Twenty-nine patients had splenomegaly and 12 patients had hepatomegaly.

Six of 39 (15%) stage II patients had presented with
isolated splenomegaly. All 6 patients were alive and
well 3.3–7.3 yr after diagnosis. Therefore, as previously observed,²¹¹ patients with isolated spleno-
megaly fared better than patients with associated hepato-
megaly or lymph node enlargement.

Table 3 shows that the peripheral blood lymphocyte
count at diagnosis was negatively related to prognosis.
By inspection of the data and by trial and error, the
best cut-off point for lymphocyte count was identified
at a value of 40 x 10⁹/liter (Fig. 2). In all 5 stages it
was checked as to whether patients with a lymphocyte
count higher than 40 x 10⁹/liter had a worse prognosis.
In stage 0, only 5 patients had a lymphocyte count
over 40. In stages III and IV, 21 of 49 patients had a
lymphocyte count over 40, but their survival was
identical to that of patients with a lymphocyte count
lower than 40 (chi-square 0.94). In contrast, in stages I
and II, the 24 patients with a lymphocyte count higher

Table 2. Life-Table Analysis of All 188 Patients

<table>
<thead>
<tr>
<th>Years After Diagnosis</th>
<th>No. at Risk</th>
<th>Actuarial Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>188</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>175</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
<td>84%</td>
</tr>
<tr>
<td>3</td>
<td>107</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>57%</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>39%</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>29%</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>29%</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>23%</td>
</tr>
</tbody>
</table>

Fig. 1. Life-table analysis according to original Rai's staging
system.¹ Chi-square for trend.
Table 3. Relationship of Absolute Blood Lymphocyte Count to Survival

<table>
<thead>
<tr>
<th>Absolute Peripheral Blood Lymphocyte Count</th>
<th>No. of Patients</th>
<th>O</th>
<th>E</th>
<th>O/E</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20 x 10⁹/liter</td>
<td>90</td>
<td>31</td>
<td>42.32</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-40 x 10⁹/liter</td>
<td>46</td>
<td>20</td>
<td>23.04</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-60 x 10⁹/liter</td>
<td>15</td>
<td>9</td>
<td>4.61</td>
<td>1.95 10.02 &lt;0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-100 x 10⁹/liter</td>
<td>15</td>
<td>9</td>
<td>5.51</td>
<td>1.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 x 10⁹/liter</td>
<td>22</td>
<td>14</td>
<td>7.52</td>
<td>1.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O, Observed number of deaths; E, extent of exposure to risk of death; O/E, relative death rate.

χ² for trend.

Table 4. Test for a Trend in Prognosis. After Separation of Stages I and II into 3 Substages

<table>
<thead>
<tr>
<th>Substage</th>
<th>No. of Patients</th>
<th>O</th>
<th>E</th>
<th>O/E</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>7</td>
<td>25.17</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binet's II</td>
<td>6</td>
<td>0</td>
<td>3.57</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I + II Ly ≤ 40 x 10⁹/liter</td>
<td>59</td>
<td>31</td>
<td>30.82</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I + II Ly &gt; 40 x 10⁹/liter</td>
<td>24</td>
<td>15</td>
<td>7.40</td>
<td>2.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>8</td>
<td>6.21</td>
<td>1.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>32</td>
<td>22</td>
<td>9.82</td>
<td>2.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ² = 34.02, p < 0.0005

O, Observed number of deaths; E, extent of exposure to risk of death; O/E, relative death rate; Ly, absolute peripheral blood lymphocyte count.

than 40 x 10⁹/liter had a survival significantly shorter than the others (chi-square 7.33, p < 0.01).

Therefore, taking into account the values of isolated splenomegaly and lymphocyte count, patients could be divided into 6 substages, as shown in Table 4. Figure 3 shows life-table analysis of each substage. Stage 0 may be pooled with Binet's stage II (low risk group). Stages I and II, with more than 40 x 10⁹ lymphocytes/liter, may be pooled with stages III and IV (high risk group).

Then, only stages I and II patients presenting with a lymphocyte count lower than 40 x 10⁹/liter were left in the intermediate or standard risk group.

This modified staging system was compared with the original Rai's classification (Table 5 and Fig. 4). Both systems allowed a sharp separation in 3 prognostic groups. However, it was shown that with Rai's original classification, the intermediate risk group was unduly large (89 of 188 cases or 47%), as it included also a small group of 6 patients whose risk of death was actually low, and a larger group of 24 patients whose risk of death was actually high. In the modified system, the intermediate risk group was reduced to 59 cases, or 31%.

The relationship of age to prognostic groups and survival is shown in Table 6. Median survival of patients less than 60 yr old was 7.5 yr versus 5.0 yr for patients older than 60 (p < 0.02). However, this difference was mainly due to a higher proportion of old patients in the high risk group (42% versus 34%). Figure 5 shows the results of the application of this modified staging system to patients less than 60 yr old (68 cases) and to patients older than 60 (120 cases). The difference among prognostic groups was even more significant in the former than in the latter.

DISCUSSION

The recognition of the prognostic value of clinical and laboratory features and the identification of groups of patients with a different death rate is essential for the management of cancer and leukemia and...
for comparison of the results of different treatments. A staging classification is particularly required in CLL, because of the broad variations in the course of the disease and in the length of survival.1,3,8,19

The purpose of this study was to contribute to the staging classification of CLL based on the system proposed by Rai et al. It was felt that an independent approach, different from that of Rai et al., would be unnecessary, since Rai’s classification was based on simple clinical and laboratory features and gained general agreement by confirmation in several studies.2,7,10,20 As suggested also by Rai et al.,1 we included patients presenting with a lymphocyte count lower than 15 \times 10^9/liter whose diagnosis of CLL was unequivocal. Since the proportion of these patients was remarkable (70 of 188 or 37%), their possible influence was unequivocal. Since the proportion of these patients was evaluated (70 of 188 or 37%), their possible influence on the length of survival should not be overlooked. However, they were distributed over all stages (41% were in stage 0, 40% were in stages I and II, and 19% were in stages III and IV). They met all the requirements for the diagnosis of CLL,1,6,19,21,22 and their exclusion would not have been justified.

This study confirmed that patients presenting without organomegaly, anemia, and thrombocytopenia (stage 0) had the lowest death rate. In this series, median survival of stage 0 patients was not reached, and the actuarial proportion of patients surviving at 10 yr was as high as 79%. The observed number of deaths was so low (7 of 50) as to preclude any further analysis of the stage. Moreover, all deaths in that stage were apparently unrelated to leukemia (cardiovascular disease in 3 cases, chronic liver disease in 2 cases, myasthenia gravis in 1 case, and complications after cholecystectomy in 1 case). It was also confirmed that patients presenting with anemia (stage III) or thrombocytopenia (stage IV) had the highest death rate, with median survivals of 2.6 and 3.0 yr, respectively. Stages III and IV patients made up a group very homogeneous as to prognosis and could not be subdivided further according to any of the features that were analyzed. It was important to notice that almost all stages III and IV patients (44 of 49 or 90%) had lymphadenomegaly and/or splenomegaly and/or hepatomegaly. This finding confirmed prior observations that anemia and thrombocytopenia are related to the leukemic cell mass.1,23

Stages I and II patients accounted for 50% of all cases and had the same length of survival, as was also seen in most series studied so far.1,3,4,7,10,20,24 The analysis of that group showed that it was not homogeneous as to prognosis, as also previously noticed by others.24 According to prior reports2,3,7,9,11,18,22,23 and to the principles of Rai’s staging system that was based on the progressive accumulation of leukemic cells,1,22 it was expected that absolute lymphocyte count was related to prognosis. This expectation was confirmed by the test for trend extended to the whole series (Table 3), which suggested an optimal cut-off point at a value of 40 \times 10^9/liter. Selecting and fixing a cut-off point out of a linear series of data is, by necessity, open to criticism and may be troublesome. However, the value found in this study was only slightly different from that found by Binet et al.2 and by Phillips et al.3 (50 \times 10^9/liter) and allows the division of stages I and II patients...
Table 6. Relationship of Age to Stage Distribution and Survival

<table>
<thead>
<tr>
<th>Prognostic Group</th>
<th>Stage</th>
<th>No. and Proportion of Patients</th>
<th>Median Survival (yr)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rai's modified classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>O + Binet's II</td>
<td>&lt;60 yr 31% &gt;60 yr 29%</td>
<td>&gt;10.0 &gt;10.0 2.17 &lt;0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>I + II Ly ≤ 40 x 10⁹/liter</td>
<td>&lt;60 yr 35% &gt;60 yr 29%</td>
<td>7.6 4.3 4.79 &lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>I + II Ly &gt; 40 x 10⁹/liter + III + IV</td>
<td>&lt;60 yr 34% &gt;60 yr 42%</td>
<td>4.2 3.0 0.06 &lt;0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>68</td>
<td>120</td>
<td>7.5 5.0 6.37 &lt;0.02</td>
<td></td>
</tr>
</tbody>
</table>

χ² for heterogeneity.

into 2 substages that were significantly different as to survival.

Moreover, among stages I and II patients, it was possible to identify and separate a third small substage that included patients with isolated splenomegaly. These patients had a prognosis as good as stage 0 patients. Only 1 of them was splenectomized (at diagnosis). Three of them were started on intermittent low doses of chlorambucil 1–4 yr after diagnosis, and the remaining 3 patients are currently untreated. The relationship of isolated splenomegaly to good prognosis was not clear, but it confirmed prior observation by Binet and coworkers.21

We conclude that Rai's stages I and II include patients with a different prognosis, and we propose the original Rai's classification be modified by grouping stage 0 and stage II with isolated splenomegaly (Binet's stage II) in a low risk group. Stages I and II with a lymphocyte count higher than 40 x 10⁹/liter, stage III, and stage IV made up the high risk group. The intermediate or standard risk group was limited to stages I and II with a lymphocyte count lower than 40 x 10⁹/liter. We suggest that substage identification within each major prognostic group should be maintained so as to retain the nomenclature that was proposed by Rai et al.1 and that was used subsequently by several other investigators.2,10,23,24 Moreover, different substages within the same prognostic group may require different treatment. For example, high risk patients with a lymphocyte count greater than 40 x 10⁹/liter may be better candidates for more intensive therapy than high risk patients presenting with thrombocytopenia.

It should not be overlooked that other features may be useful for staging CLL2,3,4,8,10,11,24,25 and that different prognostic classifications may be developed. Very recently, a simplified alternate system was proposed by Binet et al.,7 who showed that prognosis of patients in Rai's stages 0, I, and II was influenced by the number of enlarged "lymph node groups" (cervical, axillary, inguinal, whether unilateral or bilateral, spleen, and liver). These criteria proved to be valid also in this series: among Rai's stages 0, I, and II, the relative death rate of patients presenting with 0–2 enlarged "lymph node groups" was 0.71 versus 1.69 of patients presenting with 3–5 enlarged "lymph node groups" (chi-square 10.33, p < 0.005). However, this difference was mainly due to Rai's stage 0 patients. When the calculation was limited to Rai's stages I and II, the relative death rate became closer (0.80 and 1.22, respectively, chi-square 1.93, p < 0.20). Although the classification proposed by Binet et al.7 was recommended by an International Workshop on CLL,26 Rai's staging system, with the appropriate modifications, may continue to serve as a basis for the determination of prognosis of CLL.

The influence of age on prognosis was either affirmed or denied by prior studies,3 and in some series, it was shown that after correction by stage, age was no longer statistically significant as a prognostic indicator.1,3 Yet, it is important to recognize that age has a primary importance in the management of CLL, independent of any other factor. Many patients are old or very old, but several patients develop CLL during fully active adult life. Moreover, the intensity and duration of treatment must take into account age-related problems. This modified staging classification applied successfully also to young patients (less than 60 yr old) and may well provide a useful guideline to their treatment.
REFERENCES

Staging of chronic lymphocytic leukemia

M Baccarani, M Cavo, M Gobbi, F Lauria and S Tura