A Multivariate Analysis of Prognostic Factors in Chronic Myeloid Leukemia

By Francisco Cervantes and Ciril Rozman

The prognostic value of different clinical and laboratory findings at diagnosis of chronic myeloid leukemia (CML) was analyzed in a series of 121 cytogenetically studied patients. From the univariate and multivariate analysis of the whole series it was apparent that the minority of Ph'-negative patients (11.5%) could be considered as a poor prognosis group. The analysis was then restricted to the Ph'-positive patients. From a multivariate survival analysis (Cox's regression model) of the latter group the following poor prognosis factors emerged: splenomegaly, hepatomegaly, presence of erythroid precursors in peripheral blood, and bone marrow myeloblasts over 5%. From the contribution of each one of these factors to the regression model, a clinical staging of Ph'-positive CML was derived: stage I (low risk, 32% of patients), including patients with one or no factors; stage II (intermediate risk, 38%), including cases with two factors; and stage III (high risk, 30%), including patients with three or four factors. The difference in survival of the patients at different stages was highly significant ($p < 0.001$).

A NALYSIS OF PROGNOSTIC FACTORS has permitted the design of staging systems in several hematologic disorders, thus playing a major role in planning the treatment of such diseases. In most instances, chronic myeloid leukemia (CML) displays a typical biphasic course, with an initial, easily controllable, or "chronic" phase, which is followed after a median of about 3 yr by an acute or subacute terminal period, the so-called transformation or blastic phase. To date, no therapeutic approach has achieved a substantial delay in the universally fatal outcome of the disease. Because of this, interest in the last years has been focused on the study of prognostic factors in CML. It is well known that the minority of CML patients without the Philadelphia (Ph') chromosome show a poorer prognosis, with a more rapid evolution to the blastic phase than the Ph'-positive ones. This statement has led to the suggestion that Ph'-negative CML should be regarded as a distinct entity and be considered separately. Thus, a major criticism of most reports on prognostic factors in CML is the lack of karyotypic study in a high percentage of patients, as well as the mixture of Ph'-positive and Ph'-negative patients at the time of prognostic evaluation. Such facts make it difficult to compare survival results from different series. Recently, Tura et al. have proposed a staging system at diagnosis of CML based on a few simple clinical and hematologic features. However, a multivariate survival analysis in a large series of CML patients with chromosomal study has previously not been performed.

The primary aim of the present work was to analyze the prognostic significance of different features present at diagnosis in a series of 121 CML patients, all of whom had cytogenetic studies. In addition, it was attempted to derive a staging system from the results of such an analysis, as well as to ascertain the correlation of Tura et al.'s staging system in the present series.

MATERIALS AND METHODS

Patients and Diagnostic Criteria

Of 183 consecutive patients diagnosed as CML in a single institution over a period of 12 yr (1969–1981), cytogenetic study was available in 130 cases. None of the latter patients fulfilled the criteria of blastic phase (medullary or extramedullary) at presentation of CML and were consequently excluded from the survival analysis. Patients were considered as being in initial blastic phase when displaying one of the following features at diagnosis: (A) blasts $\geq 20\%$ in peripheral blood or bone marrow; (B) blasts plus promyelocytes $\geq 30\%$ in peripheral blood or $\geq 50\%$ in bone marrow; or (C) extramedullary blastic involvement (for instance, lymph node). The remaining 121 patients are the subject of the present report. There were 61 females and 60 males. Median age was 46 yr (range 8–89).

Diagnosis of CML was based on the conventional criteria: a typical peripheral blood and bone marrow picture in addition to a low leukocyte alkaline phosphatase (LAP) score. The Ph' chromosome was present in 107 cases (88.5%). Banding techniques were performed only since 1979.

All patients were uniformly treated with busulfan from diagnosis until the appearance of blastic phase. In 24 patients, additional courses of vincristine and 6-mercapropurine were given every 3 mo. Median survival of the series was 45.7 mo. At the time when the analysis was carried out (June 1981), 62 patients were dead, 52 alive, and 7 lost to follow-up some time after diagnosis (range 2–57 mo). Death was due to blastic transformation in over 90% of the cases. The remaining patients died from complications somehow related to CML: marrow aplasia (1 case), severe infection (3 cases), ictus cerebri and myocardial infarction (1 case each). Although it is difficult to ascertain the contribution of CML to the development of vascular injuries in elderly patients, it must be pointed out that in
both instances death from such a cause occurred coincidently with high leukocyte counts and/or high platelet count.

**Parameters Evaluated**

In each patient the following clinical, hematologic, and biochemical data at diagnosis were recorded and evaluated for prognosis: (1) clinical features such as age, sex, and spleen and liver size; (2) peripheral blood parameters such as hemoglobin concentration (Hb), platelet count, white blood cell count (WBC) with its differential, percentage of erythroid precursors in a 100-cell differential count, and erythrocyte sedimentation rate (ESR); (3) bone marrow features such as myeloid-erythroid (M/E) ratio, semiquantitative estimation of megakaryocytes, percentage of myeloblasts, myelocytes, and promyelocytes in a 500-cell differential count, presence or absence of the Ph' chromosome, as well as presence of Ph' mosaicism in the Ph'-positive patients; (4) serum biochemical data including uric acid, blood urea nitrogen (BUN), lactic dehydrogenase (LDH), alkaline phosphatase, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), iron, and vitamin B12 concentration.

**Statistical Methods**

Actuarial survival probability curves were plotted according to the method of Kaplan and Meier. Different curves were statistically compared using the log rank test. When needed, chi square for trend was computed.

The cut-off level of each parameter was selected by starting at its median value and then cutting at different levels, above and below, until significance was eventually obtained. In this way, some parameters (for instance, Hb) reached significance only at a value far from the median.

In order to identify the most significant prognostic factors, those features showing prognostic significance in the univariate study were included in a multiple regression analysis according to the model for censored survival developed by Cox. The variables for the whole series were defined as follows: Ph' chromosome (Ph'), positive = 1, negative = 0; spleen (S), palpable = 1, not palpable = 0; liver (L), palpable = 1, not palpable = 0; Hb <8.5 g/dl = 1, ≥8.5 g/dl = 0; blood basophils, over 8% = 1, ≤8% = 0; erythroid precursors in blood (EPB), present (≥1%) = 1, absent (<1%) = 0; marrow myeloblasts (MM), over 5% = 1, ≤5% = 0. In order to make the development of a staging system easier, a binary method for the variables (present versus absent) was preferred rather than working with continuous variables.

For the Ph'-positive group, the variables were defined in the same way but, logically, cytogenetic status was not entered in the regression model.

A stepwise forward selection procedure that inserts variables in turn until the regression is satisfactory was used. The 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, 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.

**RESULTS**

**Whole Series**

The univariate analysis demonstrated seven parameters to be associated with a poor prognosis: absence of the Ph' chromosome (p < 0.001, Fig. 1), bone marrow myeloblasts over 5% (p < 0.005), hepatomegaly (p < 0.005), splenomegaly (p < 0.01) (in both cases organomegaly was considered when the organ could be felt by palpation), presence (≥1%) of erythroid precursors in peripheral blood (p < 0.025), Hb lower than 8.5 g/dl (p < 0.025), and blood basophils higher than 8% (p < 0.05). The prognostic significance of spleen size was evaluated at different levels from the costal margin (>15 cm, >8 cm, >4 cm, palpable, not palpable). Although significance was reached at the cut-off level of 4 cm below the costal margin, a higher significance was achieved when comparison was made between palpable and not palpable spleen. Likewise, liver size was evaluated for prognosis at different cut-off levels (>6 cm below the costal margin, palpable, not palpable), significance being obtained only for a palpable liver.

Furthermore, the multivariate analysis confirmed the lack of the Ph' chromosome as the single most important prognostic factor in the whole series (p = 0.0008). In addition, three other parameters kept their prognostic value: a palpable spleen (p = 0.0009), bone marrow myeloblasts over 5% (p = 0.02), and presence of erythrocyte precursors in peripheral blood (p = 0.02). Ph'-negative patients, when compared with the Ph'-positive population, showed some differences in their clinical characteristics, such as male sex predominance (72% men versus 46% in the Ph'-positive group, p = 0.06) and older age (mean age 53 ± 19 yr versus 43 ± 17 yr in the Ph'+positive group, p = 0.06).
Table 1. Results of the Univariate Analysis in the Ph'-Positive Group

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Survival (mo)</th>
<th>O/E</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spleen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not palpable</td>
<td>23</td>
<td>71</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable</td>
<td>79</td>
<td>43</td>
<td>1.24</td>
<td>6.01</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not palpable</td>
<td>52</td>
<td>57</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable</td>
<td>48</td>
<td>36</td>
<td>1.47</td>
<td>6.40</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td><strong>Hb (g/dl)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;8.5</td>
<td>86</td>
<td>56</td>
<td>0.91</td>
<td>4.90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&lt;8.5</td>
<td>12</td>
<td>33</td>
<td>2.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erythroid precursors in blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>44</td>
<td>58</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (≥1%)</td>
<td>48</td>
<td>42</td>
<td>1.49</td>
<td>7.01</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Blood basophils</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8%</td>
<td>87</td>
<td>54</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8%</td>
<td>7</td>
<td>33</td>
<td>1.91</td>
<td>1.35</td>
<td>&lt;0.10</td>
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<tr>
<td><strong>Blood myeloblasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2%</td>
<td>50</td>
<td>57</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2%</td>
<td>44</td>
<td>42</td>
<td>1.16</td>
<td>1.01</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td><strong>Blood myeloblasts + promyelocytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5%</td>
<td>53</td>
<td>55</td>
<td>0.96</td>
<td>0.09</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>41</td>
<td>44</td>
<td>1.05</td>
<td></td>
<td></td>
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</table>

Ph'-Positive Patients

Once it was apparent that Ph'-negative patients could be considered a poor prognosis group by themselves, irrespective of the features present at diagnosis, the survival analysis was restricted to Ph'-positive patients. The univariate analysis in the latter group (Table 1) demonstrated five poor prognosis parameters; splenomegaly (S) (>4 cm below the costal margin, $p < 0.05$; palpable, $p < 0.025$, Fig. 2), hepatomegaly (L) (palpable, $p < 0.025$), Hb lower than 8.5 g/dl ($p < 0.05$), erythroid precursors in peripheral blood (EPB) (≥1%) ($p < 0.01$, Fig. 3) and bone marrow myeloblasts (MM) over 5% ($p < 0.005$). Table 1 also includes some of the information regarding features that did not reach statistical significance in the univariate analysis.

The results of the multivariate analysis as well as the frequency of the prognostic factors in the Ph'-positive group are presented in Table 2. When splenomegaly more than 4 cm below the costal margin was considered, significance in the multivariate analysis was borderline ($p = 0.1$), whereas a high significance was obtained for a palpable spleen ($p = 0.006$). Therefore, splenomegaly (S) was eventually considered in the multivariate analysis only when the spleen was palpable. As it can be seen, four variables entered the regression at the significant level. Utilizing these vari-

Table 2. Results of the Multivariate Analysis in the Ph'-Positive Group

<table>
<thead>
<tr>
<th></th>
<th>Level of Significance</th>
<th>Frequency in the Ph'-Positive Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>$p = 0.0064$</td>
<td>77%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>$p = 0.012$</td>
<td>48%</td>
</tr>
<tr>
<td>Erythroid precursors in blood</td>
<td>$p = 0.066$</td>
<td>52%</td>
</tr>
<tr>
<td>Marrow myeloblasts &gt; 5%</td>
<td>$p = 0.022$</td>
<td>17%</td>
</tr>
<tr>
<td>Hb &lt; 8.5 g/dl</td>
<td>$p = 0.38$</td>
<td>12%</td>
</tr>
</tbody>
</table>

Significance of entry of the variables analyzed by the regression model and frequency in the series.
ables, the following model for survival prediction was created: $\lambda(t)/\lambda_0(t) = \exp(0.73760(S - 0.77) + 0.52298(L - 0.48) + 0.88523(EPB - 0.52) + 1.04238(MM - 0.17))$ 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. All the patients were used for the multivariate analysis. In 85 of the 107 cases, the complete dataset was available. In the remaining patients the mean value in the series for the missing parameter was utilized, as suggested by Rosenman et al.23

**Staging System of Ph' Positive Patients**

A staging system was derived from the multivariate model as follows. For each patient the log of relative hazard rate ($\beta z$ in Cox’s notation) was computed. Figure 4 shows the scores obtained in this way for the Ph' positive patients. According to such a score, three subgroups without overlapping were observed: a low-risk group of patients, integrated by cases with none or only one of the poor prognosis factors; an intermediate-risk subgroup, which included patients showing two poor prognosis features; and a high-risk group of patients, including cases with three or four poor prognosis factors. The above three stages can be easily obtained by assigning 1 point to each prognostic factor. Thus, the low-risk group or stage I would include patients with a score of 0 or 1, the intermediate-risk group or stage II those patients with a score of 2, and the high-risk group or stage III those patients displaying a score of 3 or 4. Stage I includes 32%, stage II 38%, and stage III 30% of the Ph'-positive patients. The difference in survival of patients belonging to each one of the three groups was highly significant ($\chi^2 = 19.78, p < 0.001$, Fig. 5, Table 3). As can be seen, the O/E ratio was lower (stage I), equal (stage II), or higher (stage III) than 1. That is to say, survival of the intermediate-risk patients was similar (median survival 45 mo) to that of the whole population, whereas survivals of the low-risk and high-risk patients were longer or shorter (median survival 86 and 28 mo, respectively). At 5 yr from diagnosis, the survival probability is 70% for stage I patients, versus 30% and 15% for stage II and stage III patients, respectively. Among stage I patients, a comparison was made between those with a palpable spleen and the remaining (i.e., those with either no prognostic factor or one of the other factors), and no difference in survival was observed.

When the staging system proposed by Tura et al. was applied to the present series, there was no statistically significant difference between the 3 stages ($p > 0.10$) (Fig. 6).

**DISCUSSION**

The fatal outcome of CML has stimulated the analysis of prognostic factors in this disease.1-15 However, there is no agreement on the prognostic value of different findings at diagnosis, except for a single feature, i.e., Ph' negativity.3,5,15-17 The strongest prognostic factor in the present series, as confirmed by the multivariate analysis, was also the absence of Ph'.
Prognostic Factors

Spleen enlargement was a feature associated with a poor prognosis in our series, as confirmed by the multivariate analysis. An evident prognostic significance was observed for a palpable spleen, irrespective of the degree of enlargement. Although most patients in the present series displayed such a physical finding at diagnosis, as it is typical in CML, the minority of patients in whom the spleen was not sufficiently enlarged to be palpated enjoyed a better prognosis. A prognostic value for splenomegaly has been reported by some authors, but not by others. In our series, liver enlargement was also associated with a poor prognosis, in the univariate as well as in the multivariate analysis, confirming previously published results. Both spleen and liver enlargement reflect a high tumor burden. However, the lack of correlation with survival of other features indicating a great leukemic mass (for instance, a high leukocyte count, an increased M/E ratio, or high serum levels of vitamin B12 or uric acid) does not give support to such an interpretation of the possible mechanism of influence on prognosis of the former features. As pointed out by other workers, spleen and liver can be the source of more abnormal clones leading to the development of the blast crisis.

A parameter of clearly negative prognostic influence in our series was the presence of erythroid precursors in peripheral blood. This feature has previously not been evaluated for survival in CML, except by Jacquillat et al., who found a poor prognosis for percentages of myeloblasts + erythroid precursors in blood over 5%.

A bone marrow myeloblast percentage higher than 5% was another finding negatively related to survival in our patients. Although it could be argued that distribution of blasts in CML depends on the area in which the aspirate is carried out and, furthermore, that in general a good correlation exists with peripheral blood findings, the prognostic value of such a feature has also previously been reported by others.

A parameter that did not keep its prognostic value in the multivariate analysis was a low Hb. It has previously been reported as a poor prognosis factor by some authors.

Similarly, some authors have recognized marked blood basophilia as a poor prognosis factor in CML. Although an increased percentage of blood basophils was associated with a poor prognosis in the univariate analysis of our whole series, such a feature lost its prognostic value in the multivariate analysis and did not reach any prognostic significance even in the univariate analysis of the Ph'-positive patients. This fact could be explained through the smaller size of the latter population, which would probably account for decreasing the significance of a feature already of borderline prognostic value in the whole series.

There were other features which were not associated with a poor prognosis in the present series, in contrast with previous reports. This was the case of old age, male sex, low or high platelet counts, increased leukocyte counts, high percentages of myeloblasts or granulated precursors in peripheral blood, or high LDH serum levels. A good prognostic influence of Ph' mosaicism has also been reported by different authors. However, neither our results nor a recent report by Sokal give support to such a statement.
Staging System

The current trend in the elaboration of staging systems is to use a few easily available data. CML is not, however, the ideal disease for such an approach, because of the universally recognized discriminating prognostic importance of the chromosome study. Furthermore, the current trend in the treatment of CML is to apply aggressive, life-threatening therapies early after diagnosis in order to delay the development of the blast crisis. Such aggressive therapies are restricted to Ph'-positive patients. Thus, based on the latter fact, it appears a logical approach that a staging system of CML must be restricted to Ph'-positive cases in order to identify at diagnosis different prognosis groups of patients and restrict such aggressive modalities of therapy only to high or intermediate-risk patients.

Ideally, a staging system of CML should fulfill the following characteristics: (A) be based on a few easily available data, (B) each prognostic feature should account in proportion to its influence on prognosis, (C) be derived from multivariate statistical analyses in order to avoid redundant variables and select only the most important ones, (D) be reproducible in different series. When the staging system proposed by Tura et al. was applied to the present series, it failed in separating groups of patients with a different prognosis. This failure is not surprising, having taken into account that the prognostic factors obtained in Tura et al.'s series were very different from those of the present series. However, it must be pointed out that a comparison between both series does not seem appropriate, as Tura et al.'s series includes a mixture of Ph'-positive and Ph'-negative patients together with a fourth of patients without cytogenetic studies. The staging system derived from the present analysis isolates groups of patients with different survival probability in our series and satisfies the above conditions, A, B, and C. The reproducibility of such a staging system requires its further application to other series of patients.

Anyway, as the frequency of CML in the general population is very low, future progress in this field will probably be made through cooperative studies in order to collect a large number of patients with chromosome and other pertinent studies, in whom multivariate analysis could be performed.

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