Prognostic Discrimination Among Younger Patients With Chronic Granulocytic Leukemia: Relevance to Bone Marrow Transplantation

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To obtain information relevant to the question of bone marrow transplantation, we examined the prognostic significance of disease features recorded at the time of diagnosis among 625 patients, aged 5 to 45, with Philadelphia chromosome-positive, nonblastic chronic granulocytic leukemia. The actuarial death rate for this population was 5% during the first year after diagnosis, 12% during the second year, and averaged 22.5% per year during the next eight years. Multivariable regression analysis of features recorded in nearly all cases indicated that sex, spleen size, hematocrit, platelet count, and percentage of circulating blasts were significant prognostic indicators. Analyses of additional data available in 113 to 421 cases suggested that serum lactic dehydrogenase activity, percentage of blasts in marrow, nucleated RBCs in blood, and percentage of basophils plus eosinophils might also provide useful prognostic information. A Cox model, generated with five variables representing features recorded regularly (the first five listed), permitted segregation of these patients into three groups with significantly different survival patterns. The high-risk group exhibited an actuarial mortality of 30% during the first two years after diagnosis and an annual risk of 30% thereafter. In contrast, the most favorable group had a two-year actuarial mortality of 5% and an average risk thereafter of 17% per year, with a median survival of 5½ years. We conclude that it should be possible to classify potential candidates for bone marrow transplantation according to risk with conventional therapy. Such information may be useful in making decisions regarding early or deferred marrow transplantation.

IN A REVIEW OF DATA from six European and American series of patients with chronic granulocytic leukemia (CGL), our group concluded that patients with Philadelphia (Ph') chromosome-positive, nonblastic CGL could be segregated into populations with significantly different survival patterns, on the basis of findings at the time of diagnosis.1 We identified several disease features with prognostic significance and reported that a Cox model generated with four variables representing percentages of circulating blasts, spleen size, platelet count, and age provided a useful representation of risk status in this patient population.

One of the potential applications of a prognostic classification of CGL is in the selection of patients for hazardous therapeutic procedures, such as allogeneic bone marrow transplantation. Bone marrow transplantation is the only therapy presently available that offers a hope of cure in CGL. It is most effective when it is performed during the chronic stage of CGL, rather than after progression to "accelerated" or blastic disease.2,3 However, even among selected patients in the chronic stage, it is currently associated with an early mortality of approximately 30%. This hazard would be acceptable for a patient in a high-risk category, in substantial danger of blastic transformation and death within two years. On the other hand, transplantation might well be deferred in the case of a newly diagnosed patient with a favorable near-term outlook, in the expectation that its risk will be reduced within the next few years.

Bone marrow transplantation is a therapeutic option that, at present, is only available for younger patients with CGL. Therefore, to be directly applicable to making decisions regarding transplantation, a prognostic model should be generated from a younger patient population than that used for the analyses in our earlier report. Several additional groups have joined the International CGL Prognosis Study since it was organized, and we now have approximately 1,500 patients with Ph' chromosome-positive CGL registered in our files. This has made it possible to undertake analysis of prognostic features in a relatively large population of younger patients, who would be representative of candidates for bone marrow transplantation.

PATIENTS AND METHODS

This report is based on data submitted by cooperating investigators for 625 patients with nonblastic Ph' chromosome-positive CGL, 5 to 45 years old at the time of diagnosis. Analysis was limited to patients diagnosed before 1981 in order to provide a minimum follow-up of three years. Patients found to have karyotypic abnormalities in addition to the Ph' chromosome, or significant marrow fibrosis (ie, evident without special stains and graded as more than "slight") were excluded because the effects of these unfavorable features do not meet a basic requirement for Cox model analysis; the relative risk associated with these findings is not stable over time.4

The techniques of data collection and processing used by our group, and the characteristics of the six series of patients constituting the original data base (from the Roswell Park Memorial Institute, University of Bologna, Italian Cooperative CML Study Group, Memorial Sloan-Kettering Cancer Center, University of Barcelona, and Duke University) were described previously.1 The additional series represented in the present report are:

- The Medical Research Council's trial of splenectomy in Ph' chromosome-positive CGL.3 These patients were entered into a
randomized trial of early splenectomy between September 1972 and March 1979. All patients received antileukemic therapy with busulfan in a standardized manner.

b. Previously untreated patients seen at the National Cancer Institute, US Public Health Service, before 1976. Most patients were treated with busulfan, but some received dibromomannitol as part of a randomized trial comparing these two agents.

c. University of Ulm. These patients were diagnosed during the period from 1968 to 1980, and almost all were treated with busulfan in a conventional manner.

d. Edouard Herriot Hospital, Claude Bernard University, Lyon, France. These patients were diagnosed during the period from 1974 to 1980. Treatment varied, but most patients received busulfan or hydroxyurea.

e. Finsen Institute, Copenhagen. These patients were diagnosed during the period from 1968 to 1980. Most received conventional therapy with busulfan.

Survival estimates were obtained by the Kaplan-Meier product-limit method. Prognostic factor relationships were determined using Cox's proportional hazard model for covariant analysis of censored survival data. Breslow's approximation to the risk set permutations on tied data was used.

RESULTS

The patient population consisted of 376 males (60%) and 249 females (40%). There were 25 children and adolescents under age 16 (4%), 249 patients aged 16 to 30 (40%), and 351 patients aged 31 to 45 (56%). Of the 625 patients, 80% have died of leukemia, 2% have died of other causes, 15% were alive at the last reporting date, and 3% have been lost to follow-up. The actuarial survival curve for this population is shown in Fig 1. It is essentially linear after the second year, on this semilogarithmic plot, indicating a constant risk of death during the succeeding years. The probability of death during the first year after diagnosis was 5%, and during the second year, 12%. Annual risk during the next eight years fluctuated between 19% and 25%, averaging 22.5% per year. Median survival was 50.5 months.

Sex and age of all patients were known. Information regarding spleen and liver size, hematocrit, WBC count, platelet count, and percentage of blasts in peripheral blood at the time of diagnosis was available in almost all cases. Other relevant data were available in 18% to 67% of cases. Evaluation of the prognostic significance of various disease features was performed in a manner similar to that described in our previous report. Univariate and multivariable regression analyses of the significance of the eight features listed earlier were performed, using both stepwise and simultaneous techniques of regression analysis. There were some quantitative differences in the results when the different techniques of regression analysis and different numbers of variables were used, but the overall findings were consistent. These are shown in the upper portion of Table I. Sex, spleen size, hematocrit, platelet count, and percentage of circulating blasts were identified as significant prognostic indicators. As we had observed before, results of univariate analysis sometimes differed markedly from those recorded in multivariable regressions.

To evaluate the disease features recorded in only part of the patient population, separate analyses were performed for each feature, restricted to the patients for whom the appropriate information was available, and adding that feature as a sixth variable in regression analysis to sex, spleen size, hematocrit, platelet count, and percentage of circulating blasts. The results are shown in the lower portion of Table 1. In these analyses, involving fewer patients and varying representation of the individual series in our cooperative study, results were much less consistent with respect to the five core variables. Although each of these features appeared as a statistically significant prognostic indicator in at least one of the seven regression analyses, none was found significant in all, and only two (spleen size and percentage of

Table 1. Prognostic Significance of Findings at Diagnosis Among 625 Patients 5 to 45 Years Old

<table>
<thead>
<tr>
<th>Feature (Direction of Worse Prognosis)</th>
<th>No. of Patients Studied (No. of Series)</th>
<th>Prognostic Significance, ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features recorded in 95% to 100% of cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>625 (11)</td>
<td>.09 .01</td>
</tr>
<tr>
<td>Age (higher)</td>
<td>625 (11)</td>
<td>.8 .06</td>
</tr>
<tr>
<td>Spleen (larger)</td>
<td>594 (11)</td>
<td>&lt;.00001 .001</td>
</tr>
<tr>
<td>Liver (larger)</td>
<td>592 (11)</td>
<td>.02 .6</td>
</tr>
<tr>
<td>Hematocrit (lower)</td>
<td>608 (11)</td>
<td>.0001 .02</td>
</tr>
<tr>
<td>WBC count (higher)</td>
<td>613 (11)</td>
<td>.0002 .3</td>
</tr>
<tr>
<td>Platelets (higher)</td>
<td>594 (11)</td>
<td>.04 .001</td>
</tr>
<tr>
<td>Blasts in blood (higher)</td>
<td>594 (11)</td>
<td>.0004 .03</td>
</tr>
<tr>
<td><strong>Features recorded in 18% to 67% of cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophils + eosinophils</td>
<td>421 (9)</td>
<td>.1 .05</td>
</tr>
<tr>
<td>Symptoms</td>
<td>321 (9)</td>
<td>.4 .9</td>
</tr>
<tr>
<td>Leukocyte alkaline phosphatase (abnormal)</td>
<td>307 (9)</td>
<td>.1 .3</td>
</tr>
<tr>
<td>Serum SGOT (abnormal)</td>
<td>191 (7)</td>
<td>.3 .2</td>
</tr>
<tr>
<td>Serum LDH (more than twice normal)</td>
<td>190 (7)</td>
<td>&lt;.0001 .0002</td>
</tr>
<tr>
<td>Blasts in marrow (higher)</td>
<td>174 (7)</td>
<td>.0002 .01</td>
</tr>
<tr>
<td>Nucleated RBCs in blood (≥ 1%)</td>
<td>113 (7)</td>
<td>.002 .01</td>
</tr>
</tbody>
</table>

Fig 1. Actuarial survival curve for the study population of 625 patients. Percentage surviving is plotted on a logarithmic scale. The survival plot becomes linear after the second year, indicating a constant annual risk of death thereafter.
circulating blasts) achieved definite or borderline significance in most.

A Cox model generated with five variables, representing sex, spleen size, platelet count, hematocrit, and percentage of circulating blasts, provided a satisfactory representation of risk status in this population of patients (Fig 2). Survival curves for the low-risk group and the high-risk group diverged progressively with time, and there was approximately a twofold difference in median survival between these two groups (67 v 35 months). The high-risk group of 168 patients (27% of the population) had a two-year actuarial survival of 70% and a subsequent probability of death of approximately 30% per year. In contrast, the low-risk group had a two-year survival of 91% and a subsequent risk of approximately 17% per year. The intermediate group also had a relatively favorable course, initially. The low-risk and intermediate groups together, accounting for three fourths of the patient population, had an actuarial survival of 89% at two years and 74% at three years.

To determine whether this prognostic model would provide consistent results in diverse patient populations, we examined its ability to discriminate between high- and low-risk groups within individual series included in this study. Four institutions contributing fewer than 40 patients each (for a total of 96 patients) were excluded from consideration because the subgroups in different risk categories were too small for meaningful analysis. The seven remaining series, contributing 44 to 127 patients to the study population, included three from the United States, two from Italy, one from England, and one from Spain. Both conventional and investigational treatments were represented; the latter included two controlled trials of early splenectomy, trials of combination chemotherapy, and an immunotherapy trial. In each of these seven series, the actuarial survival of patients with relative risk below 0.8 was compared with that of patients with relative risk greater than 1.2. In one of the American series, no difference in survival was seen. In the other six series, survival in these two risk categories differed significantly (P = .005 to P = .04). Figure 3 presents survival curves from the series in which discrimination failed, from another American institution, and from two of the European series. In the series that showed no prognostic discrimination, this appeared to be due principally to the relatively poor survival of the 17 patients with low relative risk scores (median, 3.1 years). In the other three series, median survival of patients in the low-risk category ranged from 6.2 to 6.7 years.

**DISCUSSION**

The results of this study are generally similar to those reported previously. Exclusion of patients over age 45 has provided a population with a somewhat more favorable outlook; median survival exceeds four years, and the actuarial death rate during the linear portion of the survival curve averages 22.5%, rather than the 25% we recorded among patients of all ages.

In our previous study, dealing with patients up to age 84, multivariable regression analysis indicated that age was a highly significant prognostic feature (P < .001) but that sex was not (P = .05). Loss of significance for age, after exclusion of older patients, is not surprising. The increase in significance of sex is consistent with observations in other areas of medicine, that advantages of female over male sex are most evident at premenopausal ages. Other features previously identified as significant prognostic indicators—spleen size, platelet count, percentage of circulating blasts, percentage of eosinophils and basophils, percentage of blasts in marrow, and serum lactic dehydrogenase (LDH) activity—were also found significant in the present study (Table 1), although there were some shifts in their apparent

**Fig 2.** Actuarial survival of patients in low-, high-, and intermediate-risk groups, according to a Cox model with five variables, generated from the study population of 625 patients. Relative risk was calculated from the following formula:

\[
\lambda(t) / \lambda_0(t) = \exp(0.0255\text{ (Spleen)} + 8.14) + 0.0324\text{ (Blasts)} - 2.22 + 0.1026\left(\frac{\text{Platelets}}{700}\right)^2 - 0.627 - 0.0173\text{ (Hct)} - 34.2 - 0.2882\text{ (Sex)} - 1.40.
\]

(Platelets: 10^9/L. Sex: Male = 1.0, female = 2.0).

**Fig 3.** Actuarial survival of patients with low and high relative risks, in two American series (including the only series in which prognostic discrimination was not seen), an Italian series, and an English series. Relative risk values as in Fig 2.
relative importance. The appearance of hematocrit as a feature with significant prognostic import in the current analyses constitutes the only major discordance between the two studies. Previously, although hematocrit was highly significant on univariate analysis, it was found to be insignificant on multivariable regression.

Our previous evaluation of serum LDH activity was equivocal, as its significance appeared to depend largely on data from a single institution. In the current study, however, with additional data from other centers, this doubt is resolved; regression analysis excluding data from that institution (not shown in Table 1) showed that this feature retained prognostic significance ($P = .002$). Nucleated RBCs in peripheral blood were not recorded in our original files. After one of our member groups called attention to this feature, however, it was added to the database. The current analysis provides additional evidence that circulating immature erythrocytes constitute an unfavorable prognostic sign.

We had previously concluded that these prognostic indicators were identifying differences in the “aggressiveness” of CGL among different patients and not simply earlier or later disease.

Patients in a favorable prognostic group still had a relatively low annual risk of death five or more years after diagnosis, when their disease should have been “advanced,” whereas patients in an unfavorable group reached a high mortality within two years of diagnosis. A similar pattern is evident in the present study (Fig 2). In reviewing the disease features with prognostic significance, one might generalize that a pattern of relatively uncomplicated overproduction of neutrophilic granulocytes in the bone marrow is associated with a good prognosis, whereas major abnormalities involving other cell lines (marked thrombocytosis, defects in erythropoiesis, nucleated RBCs in peripheral blood, prominent basophilia or eosinophilia) or other tissues (massive splenomegaly, other extramedullary involvement) indicate more aggressive disease. Defective maturation in the granulocytic pathway (increased percentage of blasts in blood or marrow) would be expected to be an unfavorable sign. This simplistic description does not explain why sex and age should have prognostic significance; one can only conclude that these host factors somehow affect the rate of disease progression in CGL, as they do in a number of other neoplasms. More puzzling is why serum LDH activity should be so significant a prognostic discriminator. This has also been found to have predictive value in other types of neoplasia, including acute myeloblastic leukemia, non-Hodgkin’s lymphoma and carcinoma of the prostate. We are not aware of any studies of pathogenetic mechanisms that might explain the prognostic significance of serum LDH in neoplasms of diverse origin.

A Cox model generated with variables representing disease features found to have prognostic significance on regression analysis permitted segregation of the patient population into three groups with significantly different survival patterns (Fig 2). In this younger population, both the low-risk group and the high-risk group had about a 12% better survival than we found previously, using the same hazard ratio boundaries. Again, there was approximately a twofold difference in median survival between these two groups and almost a twofold difference in annual death rates after the second year.

This prognostic model provided consistent results in six of the seven individual series in which it could be tested. The single exception was in one of the three American series. Thus, it does not appear that such differences as may exist among populations in Italy, Spain, England, and the eastern United States—or the differences in treatment schedules used at most of the cooperating centers—affected the validity of the model. We do not yet have an explanation for its failure in one series (Fig 3). This comparison involved the smallest number of patients among the seven series we examined, and the negative result might have been due to a chance aggregation of “unlucky” patients in what should have been a favorable group. However, we plan to examine data from that series in more detail, to determine whether there are any other factors that might explain this aberrant result.

Bone marrow transplantation is the only treatment currently available for CGL that offers the possibility of cure. Except when the donor is an identical twin, however, the procedure is presently associated with substantial hazards. In reaching a decision regarding allogeneic transplantation, the possibility of long-term survival must be balanced against the certainty of immediate severe morbidity and a considerable risk of early death. With conventional antileukemic therapy, on the other hand, a patient may expect to be asymptomatic and fully functional for a number of years, although anticipating an eventually fatal outcome.

Because of the risks associated with allogeneic bone marrow transplantation, some investigators proposed deferring the procedure until the disease had progressed beyond the stable, chronic stage, to a point at which the patient’s near-term outlook with conventional therapy would be poor. Unfortunately, however, experience has shown that both the fatal complications associated with the transplant procedure and the leukemia relapse rate are substantially higher when marrow transplantation is performed during accelerated or blastic disease. It is clear that the procedure is most effective when it is performed during the chronic stage. This creates a difficult dilemma for those involved in making the decision regarding marrow transplantation.

The possibility of a more precise estimation of a patient’s risk with conventional therapy may make the decision regarding marrow transplantation a less difficult one. Up to 45 years of age, prognosis with conventional therapy is not significantly affected by age. However, the risk of bone marrow transplantation varies considerably. A recent report from the International Bone Marrow Transplant Registry indicated that among patients transplanted during the chronic stage, one-year survival of those 25 to 42 years old was approximately 50%, whereas among those less than 25 years of age, it was 80%. These facts permit refinement of risk comparisons and may simplify the decision-making process in some cases. For example, for a 20-year-old patient in a high-risk category according to prognostic features (eg, 30% risk of death from leukemia within two years), early transplantation would seem an appropriate choice. On the other hand, for a newly diagnosed 37-year-old patient with a
relative risk below 0.8 and only a 9% probability of death from leukemia during the next two years, deferral of a procedure currently associated with a 50% risk would appear to be the wiser decision. Rapid progress is being made in reducing the morbidity and mortality of allogeneic bone marrow transplantation, and one may anticipate that it will become considerably less hazardous within the next few years.

Strictly speaking, the information needed for a decision regarding transplantation is not the risk of death during a particular time period, but rather the risk of disease transformation. Our files do not contain dates of transformation, but this risk can be approximated by a small adjustment of the survival curves presented in Fig 2. Because the median time from disease transformation to death is quite short,19,25 such adjustment would only involve shifting the curves by a few months for patients with recently diagnosed disease. In considering risks during the linear portions of these survival curves, no adjustment would be necessary. (The risks of disease transformation during the first and second years are somewhat higher than the risks of death during those years, but these risks become equal thereafter.)

A recent report from a major transplant center16 has disturbing implications for the line of reasoning presented above. These investigators found that transplant-related mortality in the chronic stage of CGL correlated with the duration of disease before transplantation. If such a relationship is confirmed and shown to be due to duration of disease per se rather than to confounding variables such as cumulative effects of treatment with busulfan, it will make selection of an optimal time for transplantation more difficult than we have suggested. It is hoped that this question will be resolved within the next year or two.

The Cox model used to calculate the relative risks for the survival curves in Fig 2 was generated with variables representing five disease features for which information was available in almost all cases. It is likely that risk estimates may be improved by inclusion of additional parameters that appear to have independent prognostic associations. Regression analyses in the present study, using data from 18% to 67% of the cases, suggest that percentage of bone marrow blasts, serum LDH activity, nucleated RBCs in peripheral blood, and percentage of basophils plus eosinophils should be considered for inclusion in expanded prognostic models. These features were previously reported to provide significant prognostic information in independent studies by members of our group.5,6,11 More precise definition of the prognostic implications of additional karyotypic abnormalities14 and of myelofibrosis would also be desirable.

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