Characteristics of the Terminal Phase of Chronic Granulocytic Leukemia

By Arthur Karanas and Richard T. Silver

ALTHOUGH SEVERAL FORMS of therapy result in the temporary clinical and hematologic improvement of patients with chronic granulocytic leukemia, their disease eventually becomes refractory to treatment with all agents. The final phase of this illness is frequently characterized in whole or in part by progressive anemia, a rising white blood cell count, thrombocytopenia, an increasing number of immature granulocytes in the peripheral blood and bone marrow, fever, and an enlarging liver and spleen.

Evaluation of chemotherapeutic drugs for treating the terminal phase of this disease requires better definition of its clinical and hematologic characteristics. If the characteristics at its onset could be established, new therapeutic agents might be introduced in sufficient time for these agents to be beneficial before the patient dies.

In this paper, we analyze the terminal phase of chronic granulocytic leukemia in a group of patients seen at The New York Hospital, our aim being to establish criteria for characterizing the onset of this phase of the disease. Determination of critical values of certain parameters made it possible to establish two sets of criteria, each of which identified a group of individuals, 75 percent of whom subsequently died within 6 months. Information pertaining to the course of the illness will also be discussed.

MATERIALS AND METHODS

Patients Studied

The records of all patients with an index diagnosis of chronic granulocytic leukemia seen at The New York Hospital—Cornell Medical Center from January 1949 to December 1964 were reviewed. The criteria for diagnosis were typical peripheral blood and bone marrow findings accompanied by characteristic clinical manifestations.

There were 75 patients with chronic granulocytic leukemia whose entire illness was closely followed at The New York Hospital. At the termination of the study (December 31,
1964), 67 patients had died and 8 were alive. The mean age at the time of diagnosis for the group of 75 patients was 49.9 years and ranged from 14 to 92 years. There was a preponderance of women (1.3 to 1). The mean age of the 67 dead patients was 50.1 years, and for the 8 living patients, 48.4 years.

**Modalities of Therapy**

The forms of therapy used included radiation to the spleen, p32, urethane, busulfan, Fowler’s solution, nitrogen mustard, triethylene melamine, hydroxyurea, 6-mercaptopurine, methotrexate, cortisone, prednisone, and related drugs.

**Methods Used for Characterizing the Terminal Phase**

After an initial review of the charts, we decided that the most available and pertinent information applicable to the determination of the onset of the terminal phase included, at least, the clinical status of the patient and abnormal values singly or in combination of hemoglobin concentration, white blood cell count, platelet count, per cent myeloblasts and promyelocytes in the peripheral blood, body temperature, and spleen size. It became apparent that the degree of splenomegaly was recorded too infrequently and too inaccurately for this measurement to be used as a meaningful parameter in subsequent analysis.

Two methods were used to determine the onset of the terminal phase of the illness. The first was based upon a retrospective review of each patient’s record. The period of “remission” preceding the terminal phase was based upon a good performance status, freedom from symptoms, and general well-being as evaluated by the patient’s physician. The onset of the terminal phase was marked by obvious deterioration in performance and the occurrence of symptoms irrespective of whether or not abnormalities developed in any particular laboratory parameter. Our aim was to find a complex of symptoms and laboratory values which characterized the onset of the terminal phase but which were not present during the preceding “remission.”

The second method was based upon a set of criteria which was evolved empirically by varying values of the previously mentioned clinical and hematologic parameters in order that death in less than 6 months could be predicted for at least 75 per cent of the identified group of patients. Thus, these criteria were independent of subjective fixing of the onset of the terminal phase.

**Results**

**Characteristics of the Onset of the Terminal Phase (O.T.P.) of Chronic Granulocytic Leukemia Based upon Retrospective Chart Analysis**

There were 39 records from which detailed sequential data could be obtained before and after the time estimated to be the onset of the terminal phase. All of these patients had died of leukemia.

Considerable variability in the hemoglobin concentrations and in the white blood cell counts in the periods considered “remission” and the “onset of the terminal phase” precluded an initial definition of abnormal hemoglobin concentration or abnormal white blood cell count. As a means for establishing an estimate of an “abnormal” hemoglobin concentration or white blood cell count, a method known as “cut-off point analysis” was used. In this method, numeric values of hemoglobin concentrations or white blood cell counts, or their logarithms, are plotted against normal equivalent deviates. The “cut-off point” refers to a value found by the intersection of two lines, one which represents the values in “remission” and the other the values at the O.T.P. The point of intersection of the two lines yielded a hemoglobin concentration of 10.5 Gm. per cent (Fig. 1). The mean values in “remission” and at the onset of the term-
Fig. 1.—Cut-off point analysis of hemoglobin values in the remission phase and at the O.T.P.

...
Fig. 2.—Cut-off point analysis of white blood cell counts in the remission phase and at the O.T.P.

peripheral blood. With treatment, the per cent of immature cells fell into the range of 20 per cent or less, and remained there until the onset of the terminal phase. When the per cent of immature cells subsequently exceeded 30 per cent, the patient's life span was brief. A figure of 30 per cent myeloblasts and promyelocytes was thus used as the initial value for indicating the onset of the terminal phase.

Analogous to other studies, fever of undetermined origin was defined as a rectal temperature of 38.5 C. or higher for 5 consecutive days without
Table 1.—Frequency of Abnormality of Five Parameters in Thirty-Nine Patients at the Onset of the Terminal Phase (O.T.P.) and in the Preceding Period of Remission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Remission</th>
<th>O.T.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Pts. %</td>
<td>No. Pts. %</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, Gm. per cent</td>
<td>&lt;10.5</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>White blood cells/mm.³</td>
<td>&gt;30,000</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>72</td>
</tr>
<tr>
<td>Platelets/mm.³</td>
<td>&lt;100,000</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>49</td>
</tr>
<tr>
<td>Myeloblasts and promyelocytes</td>
<td>≥30%</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Fever of undetermined origin</td>
<td>≥38.5 C. x 5 days</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>49</td>
</tr>
</tbody>
</table>

demonstrable infection and without temporal relation to a blood transfusion.

The frequency of abnormality of the five parameters at the onset of the terminal phase and in the preceding period of “remission” is shown in Table 1. At the onset of the terminal phase, 87 per cent of the patients had a hemoglobin less than 10.5 Gm. per cent, 72 per cent had a white blood cell count greater than 30,000/mm.³, 49 per cent had a platelet count less than 100,000/mm.³, 36 per cent had a myeloblast and promyelocyte count ≥30 per cent, and 49 per cent had fever of undetermined origin. In the preceding period of “remission,” 87 per cent of the patients had a hemoglobin greater than 10.5 Gm. per cent, 62 per cent of the patients had a white cell count less than 30,000/mm.³, 90 per cent had a platelet count greater than 100,000/mm.³, and no patient had a myeloblast and promyelocyte count ≥30 per cent, or fever of undetermined origin.

The frequency of the various combinations of abnormalities at the onset of the terminal phase and in the preceding period of clinical “remission” as defined for the 39 patients is shown in Table 2. In “remission,” nearly half (19) had no abnormality of any of the five parameters. The remaining had either an abnormality of hemoglobin concentration, white blood cell count, or platelet count, or a combination of no more than 2 of these 3 parameters.

When the triple combination of abnormal hemoglobin concentration, white blood cell count, and platelet count developed, the onset of the terminal phase was signified in the 5 patients in whom this occurred. Similarly, unexplained fever and a myeloblast and promyelocyte count equal to or greater than 30 per cent were not found in the period preceding the onset of the terminal phase, and their occurrence with or without other abnormalities always signified the onset of the terminal phase.

Nine of the 39 patients deteriorated clinically in association with either an abnormal hemoglobin concentration and white blood cell count (8 patients), or an abnormal hemoglobin concentration and platelet count (1 patient). Neither of these 2 combinations was sufficient to definitively identify the O.T.P. because 3 patients had had similar laboratory findings in the preceding period of “remission.” Seven of these patients, however, subsequently developed within a median interval of three and a half months either fever of un-
Table 2.—Frequency of Abnormalities or Combination of Abnormalities at the Onset of the Terminal Phase (O.T.P.) and in the Preceding Period of Remission in Thirty-Nine Patients

<table>
<thead>
<tr>
<th></th>
<th>Hb Only</th>
<th>Pl Only</th>
<th>Bl</th>
<th>WBC Hb</th>
<th>Fev Hb</th>
<th>Pl WBC Hb</th>
<th>Fev WBC Hb</th>
<th>Pl Bl Hb</th>
<th>Bl WBC Hb</th>
<th>Fev Bl Hb</th>
<th>Fev Bl WBC Hb</th>
<th>WBC Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Pts</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hb</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>13</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Pl</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>None</td>
<td>19</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Hb</td>
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<td>WBC</td>
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<td>Pl</td>
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</tbody>
</table>

**Key:**

Hb = Hemoglobin concentration
Bl = Myeloblast and promyelocyte count
Pl = Platelet count
WBC = White blood cell count
Fev = Fever of undetermined origin

determined origin, an increased number of myeloblasts and promyelocytes in the peripheral blood, or thrombocytopenia. The remaining two did not.

In summary, the characteristics which heralded the onset of the terminal phase that were not present in the preceding clinical “remission” phase were:

**Set I**

1. Fever of undetermined origin (temperature ≥38.5 C. for five consecutive days).

or

2. Myeloblasts and promyelocytes in the peripheral blood equal to or greater than 30 per cent.

or

3. Hemoglobin < 10.5 Gm. per cent, white blood cell count > 30,000/mm.³ and platelet count < 100,000/mm.³ occurring together.

These criteria, derived from the data obtained from the subgroup of 39 patients, were then applied to all 67 dead patients to insure that they were equally applicable to the whole group.

The O.T.P. was identified in 54 patients (81 per cent). The survival of these patients once they met the criteria establishing the onset of the terminal phase is shown in Figure 3. Of the patients who were identified at the O.T.P., one-
Table 3.—Number of Patients with Heralding Characteristics at the Onset of the Terminal Phase as Determined by Retrospective Chart Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>12</td>
</tr>
<tr>
<td>(2)</td>
<td>20</td>
</tr>
<tr>
<td>(3)</td>
<td>5</td>
</tr>
<tr>
<td>(1) + (2)</td>
<td>7</td>
</tr>
<tr>
<td>(1) + (3)</td>
<td>5</td>
</tr>
<tr>
<td>(2) + (3)</td>
<td>2</td>
</tr>
<tr>
<td>(1) + (2) + (3)</td>
<td>3</td>
</tr>
</tbody>
</table>

Key: Characteristics
(1) Myeloblasts and promyelocytes ≥ 30%
(2) Fever of undetermined origin (Temp ≥ 38.5 C.) for five or more days
(3) Anemia: hemoglobin < 10.5 Gm. %
Leukocytosis: white blood cell count > 30,000/mm.³
Thrombocytopenia: platelets < 100,000/mm.³

half (57 per cent) died within one month, 87 per cent by 6 months, and nearly all (96 per cent) by 12 months.

Each of the 54 patients in whom the onset of the terminal phase was identified manifested one or more heralding characteristics with the frequency shown in Table 3. The most common heralding characteristics were myeloblasts and promyelocytes ≥30 per cent, fever of undetermined origin, or both. Each or both of these 2 criteria occurred in 49 of 54 patients (91 per cent).

Characteristics of the Last Six Months of Life as Determined by Variable Value Analysis

We considered a reasonable statistic target a set of criteria which identified a group of patients, 75 per cent of whom subsequently died within 6 months. This set was obtained empirically by varying values of hemoglobin concentration, white blood cell count, platelet count, per cent myeloblasts and promyelocytes, and duration of fever. If less than 75 per cent of this group of patients died within 6 months, a trial set of criteria was judged inadequate. The set of criteria was improved, for example, by lowering the hemoglobin concentration criterion, or raising the white blood cell count criterion, etc., until the target was reached wherein 75 per cent of the patients who were identified died within 6 months.

Thirty per cent or more myeloblasts and promyelocytes in the peripheral blood predicted death within six months in 18 patients. This characteristic was not present in any relapse before the terminal phase. On the other hand, abnormalities of the other four parameters were found before as well as during the last six months of life. Therefore, in the absence of a myeloblast and promyelocyte count equal to or greater than 30 per cent, it was necessary to introduce factors relating to duration of disease and/or response to previous therapy in order to increase the likelihood that an abnormal finding pertaining to hemo-
globin concentration, white blood cell count, platelet count, or fever heralded the final six months of life and not a relapse which could respond to conventional therapy.

Of the many combinations tried, the following predicted death within six months for 75 per cent of the identified group of patients:

**Set 2**

A. Myeloblasts and promyelocytes in the peripheral blood \( \geq 30 \) per cent. or

B. One of the following conditions occurring after either completion of two courses* of therapy or twelve months after diagnosis. The conditions were:

1. Myeloblasts and promyelocytes in the peripheral blood \( \geq 20 \) per cent but \(< 30 \) per cent.

2. Hemoglobin \(< 9 \) Gm. per cent in the absence of hemorrhage.

3. A decrease in platelets below 100,000/mm.\(^3\) from above 100,000/mm.\(^3\) during treatment, not related to drug toxicity.

4. An increase of the white blood cell count after a course of treatment either to 50,000/mm.\(^3\) or more than double the count at the start of treatment.

5. Two weeks of fever (\( \geq 38.5 \) C.) unassociated with demonstrable infection.

*A course of therapy was considered the administration of sufficient radiotherapy or chemotherapy which resulted in clinical remission."
Table 4.—Number of Patients with Heralding Characteristics at the Onset of the Terminal Phase as Determined by Variable Value Analysis

<table>
<thead>
<tr>
<th>Total Number of patients</th>
<th>67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not identified</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Patients identified</td>
<td>56 (84%)</td>
</tr>
</tbody>
</table>

Characteristics

| (A) with or without other conditions | 18 (32%) |
| (B) with the following conditions   | 38 (68%) |
| (1)                                  | 4 |
| (1) + (3)                            | 3 |
| (1) + (2) + (5)                      | 1 |
| (2)                                  | 11 |
| (2) + (3)                            | 1 |
| (2) + (5)                            | 2 |
| (3)                                  | 1 |
| (3) + (5)                            | 1 |
| (4)                                  | 4 |
| (5)                                  | 10 |

Key: Characteristics

(A) Myeloblasts and promyelocytes in the peripheral blood ≥30%

(B) Completion of two courses of conventional treatment OR survival twelve months after diagnosis and one of the following conditions:
1. Myeloblasts and promyelocytes in the peripheral blood ≥20% but <30%.
2. Hemoglobin less than 9 Gm. % in the absence of hemorrhage.
3. Platelet fall to below 100,000/mm.³ from above 100,000/mm.³ excluding drug toxicity.
4. An increase of the white blood cell count after a course of treatment to either 50,000/mm.³ or more than double the count at the start of treatment.
5. Two weeks of fever (≥38.5 C.) unassociated with demonstrable infection.

Of the group of 67 dead patients, 56 (84 per cent) were identified. The survival of these patients once they met the criteria of Set 2 is shown in Figure 3. Of the patients who were identified in the terminal phase, 38 per cent died within one month, 75 per cent by six months, and 89 per cent by twelve months.

Each of the 56 patients in whom the onset of the terminal phase was identified manifested one or more heralding characteristics with the frequency shown in Table 4. The most common heralding characteristics in Set 2 were myeloblasts and promyelocytes in the peripheral blood ≥30 per cent, fever of undetermined origin, and anemia, each occurring alone or together with other abnormalities in 47 of 56 patients (84 per cent).

Comparison of Criteria of Set 1 and Set 2

Both sets identified approximately the same number of patients (Set 1, 54 patients, Set II, 56 patients). Of the 13 patients in whom the onset of the terminal phase was not identified by Set 1, 4 died of a cause which appeared directly related to leukemia. In these 4 patients, sufficient data had not been collected before death for the onset of the terminal phase to be characterized. The other 9 patients died because of concurrent illness while in hematologic remission.
Table 5.—Causes of Death in 67 Patients with Chronic Granulocytic Leukemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Cases</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Death directly related to leukemia</td>
<td>39</td>
<td>58.2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage and infection</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery thromboses</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2. Cause of death related to leukemia and concurrent illness</td>
<td>11</td>
<td>16.4</td>
</tr>
<tr>
<td>Probable drug toxicity</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Probable radiation toxicity</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure and pneumonia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bronchial obstruction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3. Death related to concurrent illness while patient was in hematologic remission</td>
<td>10</td>
<td>15.0</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Serum hepatitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Death following tooth extraction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diabetic acidosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Recurrent ulcer and hemorrhage</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute febrile illness of unknown cause</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. Cause of death unknown</td>
<td>7</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Of the 11 patients not identified by the criteria of Set 2, 2 died of a cause directly related to leukemia. Again sufficient data had not been collected before death for the onset of the terminal phase to be characterized. Of the remaining 9 patients, 7 died in hematologic remission of concurrent illness, and 2 with a hypoplastic marrow, one following radiotherapy, and one following chemotherapy. These two patients were not identified by the criteria of Set 2 because they died in less than one year after diagnosis and before two courses of therapy could be completed.

Both sets of criteria incorrectly identified a few patients who died in hematologic remission. Set 1 identified one such patient. This patient was known to have malignant melanoma. Anemia, an elevated white blood cell count, and thrombocytopenia occurred 2 months prior to death. The patient was treated with radiation to the spleen. The white blood cell and platelet counts returned to normal but anemia persisted. At autopsy, there was no splenomegaly and the bone marrow did not show granulocytic hyperplasia. Widespread melanoma was observed in all organs and in the bone marrow.

Set 2 incorrectly identified 3 patients. All 3 were identified because of anemia, which in all instances was probably related to other conditions. The first patient had metastatic melanoma, and the second, gastrointestinal bleeding from a duodenal ulcer. The third patient died of uremia secondary to chronic pyelonephritis and prostatic hypertrophy.

Causes of Death

The major causes of death of the 67 patients were grouped into four categories (Table 5).
Incidence and Occurrence of Fever of Undetermined Origin

Because of the previous importance attributed to fever of undetermined origin in the natural history of both acute and chronic leukemia, we examined this abnormality in our patients.

Fever of undetermined origin was common for it had been present in 42 of the 67 dead patients during some portion of their illness (Table 6). Most frequently it occurred in the last quarter of the disease, at the onset of the
terminal phase, and during the last 6 months of life, three periods which often coincided. It rarely occurred earlier.

Fever of undetermined origin did not always signify a “myeloblastic crisis.” A myeloblast and promyelocyte count greater than 30 per cent was found in only 10 (31 per cent) of the 32 patients with fever at the onset of the terminal phase.

Fever of undetermined origin has not been present as yet in any of the living patients, all of whom are in remission.

**Survival Data**

The average survival time* from diagnosis for the entire group of 75 patients was 24.2 months. The average elapsed time between the onset of symptoms and diagnosis was 3.5 months. The survival time of the 67 dead patients from diagnosis ranged from 3 days to 96 months. The 8 living patients had survived 15 to 84 months at the termination of the study.

**DISCUSSION**

The patients in this study had clinical and hematologic characteristics similar to those previously reported. The age at the time of diagnosis, the decade in which the disease appeared most frequently, the time elapsing between onset of symptoms and diagnosis, and the causes of death were similar to those in other series."10-30"

The object of this study was to establish criteria which would predict the onset of the terminal phase of chronic granulocytic leukemia. It has been suggested that this phase is equivalent to myeloblastic transformation. As defined by our criteria, 56 per cent of the patients were in a blast crisis at the time of death. In other series, the per cent of patients undergoing a blast crisis has ranged from 13 to 80 per cent."2,19,21-28" This variation can be related not only to the different criteria used to define a blast crisis but also to the particular time in the terminal phase when the blood was examined. We emphasize that less than half of our patients were in a blast crisis at the onset of the terminal phase as we defined it and thus, they entered it for reasons other than an increased number of myeloblasts and promyelocytes in the peripheral blood. Hence, although “myeloblastic transformation” is relatively common in end-stage chronic granulocytic leukemia, not all patients enter the terminal phase of the illness with this morphologic blood picture. Therefore, criteria for predicting the onset of the terminal phase must account for the deterioration in the clinical course of patients who initially do not have the laboratory findings indicative of a blast crisis.

Studies of the blast crisis, both ours and those of others, have been based on peripheral blood findings. Since it is known that changes in the marrow may antecede those in the peripheral blood, the bone marrow must be examined by aspiration and biopsy technics in prospective studies. Biopsy is particularly im-

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*Average survival time is equivalent to the antilogarithm of the average of the logarithms of the survival times.*"8,9"
important when the marrow contains many primitive cells which adhere to each other and are difficult to aspirate.

The two sets of criteria, derived by different means, identified approximately the same number of patients entering the terminal phase of their illness. Thereafter, the survival times of the patients in the two groups were about equal. Both sets failed to identify approximately the same number of patients because sufficient data was not available or because the patients were in hematologic remission at the time of death. Set 2 also failed to identify 2 patients who died of complications of therapy. Both sets incorrectly identified patients because of anemia secondary to a cause other than leukemia.

Certain advantages and disadvantages are inherent in both sets. In Set 1, the onset of the terminal phase is independent of a time element pertaining to the patient's illness. Thus, the criteria of Set 1 can identify patients whose course is rapid, yet who do not enter the terminal phase of their illness in a myeloblastic crisis. Such patients may not be identified in Set 2, since according to the time criterion of this set, 12 months or 2 courses of therapy must elapse after diagnosis. This occurred in 2 patients.

On the other hand, the larger number of criteria of Set 2 as compared to Set 1 places less emphasis on any one. This reduces the likelihood that a single abnormal value prematurely represents the terminal phase of the disease. In addition, the criteria in Set 2 identify patients approximately one month earlier than does Set 1. This may be of importance when new agents are used in this rapidly progressive phase of the disease. For these reasons, the second set of criteria was selected initially for use and evaluation by Acute Leukemia Cooperative Group B.31

It is emphasized that both sets of criteria were based upon a particular group of patients evaluated retrospectively, and this has limitations. Drawing from such a group experience to formulate individual predictions is difficult and is less desirable than predictions based upon specific changes in a given patient. Furthermore, the significance of an absolute change in any one laboratory parameter may vary in different stages of the illness.

Thus, whether or not the criteria presented will be applicable to patients studied prospectively must be confirmed in subsequent clinical practice. In addition, other clinical and laboratory criteria to be developed may be more pertinent. These include, for example, change in spleen size19 and values of leukocyte alkaline phosphatase and serum vitamin B12. Nevertheless, the criteria presented offer a reasonable starting point for those interested in the treatment of the resistant stage of chronic granulocytic leukemia.

The average survival time from diagnosis for our group of patients was 24.2 months. It differed from other series in which survival times have ranged from 11.7 months to 52 months.9,16-20 Clearly, meaningful survival-time data and information pertaining to the natural history of chronic granulocytic leukemia will be obtained only in prospective studies employing both accepted diagnostic criteria and standards for classification and relatively uniform criteria for evaluating the response to therapy. Such guidelines have been proposed.72
SUMMARY

Data obtained retrospectively from a group of patients with chronic granulocytic leukemia provided the basis for characterizing the onset of the terminal phase of chronic granulocytic leukemia. Such characterization permits an opportunity to introduce in sufficient time new therapeutic agents for the treatment of a phase of a disease which heretofore has been refractory to conventional therapy. The suggested criteria marking the onset of the terminal phase may require revision as more information is systematically collected in the future.

SUMMARIO IN INTERLINGUA

Datos retrospectivemente obtenite ab un gruppo de patientes con chronic leuceniia granulocytic esseva utilisate como base pro le characterisation del declaration del phase terminal de ille condition. Un tal characterisation provide le possibilitate de introducer in bon tempore nove agentes therapeutic pro le tractamento de un phase del morbo le qual in le passato esseva refractori a terapias conventional. Le suggestionate criterios indicante le declaration del phase terminal va possibilemente requirer modificationes in tanto que nove informationes es colligite in le futuro.

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