The Significance of Bone Marrow Lymphocytosis of Acute Leukemia Patients in Remission

By Roland T. Skeel, Edward S. Henderson and John M. Bennett

Bone marrow lymphocytosis (BML) occurring during remission of acute leukemia is commonly believed to be a poor prognostic sign that may presage early subsequent relapse. In 1956, the Clinical Studies Panel of the Cancer Chemotherapy National Service Center published its criteria for the evaluation of response to treatment in acute leukemia. They recommended that patients having significant BML be excluded from the excellent response category. Inclusion in the excellent response category required that the total number of lymphocytes be less than 10 per cent of the marrow population in adults and less than 20 per cent in children. Other groups have been less stringent, but many have followed the spirit of this recommendation.

In our routine examination of bone marrows from patients with acute leukemia, we observed that several patients recurrently had 30 to 60 per cent lymphocytosis during long remissions. On the other hand, there were also patients in whom it appeared that relapse occurred shortly after significant lymphocytosis. Because our impressions were based on anecdotal information, a retrospective study was undertaken to determine the significance of BML during remission of acute leukemia.

Materials and Methods

There were 99 patients on the Leukemia Service with acute lymphocytic leukemia (ALL) or acute granulocytic leukemia (AGL) who had 3 or more bone marrow examinations in 1965. Seventy-four of the 79 with ALL and 17 of the 20 with AGL were in remission at some time during 1965 and constituted the study group. The patients in each disease category were evaluated separately. The bulk of this paper will deal with our findings in the patients with ALL in whom the significance of BML is most apparent.

Bone marrow reports on all of the patients were reviewed to determine peak lymphocytosis of the remissions observed in 1965. If a patient had more than one remission period in 1965, the remission exhibiting the highest lymphocytosis in that year was selected for analysis. If a patient had less than 15 per cent lymphocytes throughout 1965, his first remission that year was studied.

Because of the possibility that interpretation of the bone marrows by several different observers might confound the results, one of us (J.M.B.) reviewed a significant sample of the bone marrow slides from one third of the patients studied. In doing 500...
For the purposes of this study, a patient was considered to be in remission if he had less than 5 per cent "blasts," which includes normal appearing lymphoblasts or myeloblasts and morphologically abnormal cells, in a bone marrow that was considered adequate for evaluation. Patients in remission routinely had bone marrow examination performed monthly, patients in relapse every 1 to 2 weeks. Both clot sections and particle smears were studied at each time the marrow was taken.

Patient charts were then reviewed for significant clinical data. We were particularly interested in the length of remissions and survival, but also noted the presence of extramedullary leukemia, infection, and medication current at the time of lymphocytosis.

**RESULTS**

**Acute Lymphocytic Leukemia**

Figure 1 shows the distribution of the patients according to peak BML for the remissions studied. As can be seen from the graph, lymphocytosis was not at all uncommon, the majority of the patients having 20 per cent or more lymphocytes at some time during the remissions studied. In comparing the remission lengths of the patients with varying degrees of peak
lymphocytosis, it was noted as shown in Figure 2, that those patients with less than 20 per cent lymphocytes had considerably shorter remissions than those patients with 20 per cent or more lymphocytes during remission.

The patients were then divided into two groups for further analysis: Group I containing 14 patients with less than 20 per cent bone marrow lymphocytes and Group II 60 patients with 20 per cent or more bone marrow lymphocytes. The median duration of remission of Group I was 3 months, while the median duration of remission of Group II was 14 months. The curves in Figure 3 depict the difference between the remission durations of the patients in Groups I and II. On the ordinate is the per cent of patients in remission for the length of time indicated on the abscissa. The upper boundary of the shaded area is drawn assuming that all the patients who had not yet relapsed as of September 1, 1967, will continue in remission indefinitely; the lower line assumes that they all relapsed September 1, 1967. The line in the center of the shaded area is the life table estimate of remission durations. As can be seen, the median is not affected by these estimates, though there are a significant number of patients in Group II with extended remissions. The difference in the remission durations between Groups I and II is statistically significant as determined by a median test ($P < 0.001$, two-sided).

The survival curves (Figure 4) of these two groups of patients illustrate
Fig. 3.—Remission duration curves for patients with and without significant bone marrow lymphocytosis. The difference between the remission durations of Groups I and II are highly significant ($P < 0.001$).

the difference in the median survivals between the two groups, and further show the extended survival of a significant number of patients. The median survival of Group I is 21 months, the minimum median survival of Group II is 34 months and the life table estimate of this group is over 36 months. The differences in the survivals between Groups I and II are also statistically significant as determined by rank sum analysis ($P < 0.05$, two-sided).

Since in the 74 patients studied, children tended to have higher degrees of peak lymphocytosis, and young children tend to respond better to chemotherapy of acute leukemia than do adults, we were concerned that the results might be due to a difference in age distribution between Groups I and II. However, the median ages at diagnosis were nearly identical for both groups: 6 years for Group I and 5 years 8 months for Group II. The age effect was further examined by looking only at the 52 children under the age of 10. This comparison showed that significant lymphocytosis was still associated with longer remissions and survivals, essentially the same as for the entire group. Thus, it appears that bone marrow lymphocytosis of 20 per cent or above at any time during remission of ALL has a definite association with longer remissions and survival, and that it is not dependent upon age.

The antileukemic therapy in the two groups was similar, with most patients initially receiving combination chemotherapy with vincristine, prednisone, methotrexate, and 6-mercaptopurine. However, since the patients in Group I
Fig. 4.—Survival curves for patients with and without significant lymphocytosis. The difference between the survivals of Groups I and II is significant (P < 0.05).

were diagnosed and admitted on the average five months earlier than the patients in Group II, more of the patients in Group II received their initial chemotherapy according to a later more effective combination of these drugs (POMP [4]). We, therefore, looked only at the patients in both groups who initially were treated with POMP. The 7 patients on this protocol in Group I had a median remission duration of 2 months and a median survival of 13 months, while the 41 patients in Group II initially treated by this protocol had a median remission duration of 12 months and a median survival of 28 months. Thus, even for this smaller population of patients the difference between Groups I and II persists.

The incidence of extramedullary leukemia as evidenced by enlarged liver or spleen, meningeal leukemia or other known organ infiltration was essentially the same for both groups. There was moderately increased infection in the patients with less lymphocytosis but the difference was not statistically significant (Table 1).

Acute Granulocytic Leukemia

There were 9 patients with AGL who had less than 20 per cent bone marrow lymphocytes (Group III) and 8 patients who had 20 per cent or more bone marrow lymphocytes (Group IV) during remission. The median remission duration of Groups III and IV were 3.5 months and 6.5 months respectively, and the median survivals 21 months and 26.5 months (Table 2). The
Table 1.—Relative Incidence of Infection and Extramedullary Leukemia in ALL and AML in Groups with and without BML. (Differences are not significant.)

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 20% BML</td>
<td>≥ 20% BML</td>
<td>&lt; 20% BML</td>
<td>≥ 20% BML</td>
</tr>
<tr>
<td>Infection</td>
<td>6/14</td>
<td>13/60</td>
<td>3/9</td>
<td>1/8</td>
</tr>
<tr>
<td>Extramedullary Leukemia</td>
<td>6/14</td>
<td>21/60</td>
<td>3/9</td>
<td>3/8</td>
</tr>
</tbody>
</table>

differences are not statistically significant. There were, likewise, no significant differences in the incidence of infection, extramedullary leukemia, or medication between Groups III and IV (Table 1).

**Discussion**

To our knowledge, a study of BML during remission of acute leukemia has not been carried out previously. In normal patients, there is a wide range of reported percentages of bone marrow lymphocytes. Healthy children 2 to 20 years old have median values for bone marrow lymphocytes of 13–19 per cent with a range of 5–26 per cent. Although normal adults on the average have about 15 per cent bone marrow lymphocytes, means between 3 and 25 per cent have been reported. Thus, it can be seen that the per cent of bone marrow lymphocytes in many of our patients in Groups II and IV is still within accepted normal ranges of bone marrow lymphocytosis.

We are unable to determine from this study whether BML reflects a variant of ALL or AGL, altered host defenses or a different response to antileukemic therapy. As noted in the results, some of the patients in Group I were diagnosed and treated several months earlier and did not receive therapy identical with the majority of patients in Group II. Thus, the exact relationship between drugs, remission duration, survival and BML is not yet completely clear. More extensive studies are necessary to evaluate the effect of various drugs, dosage schedules, and routes of administration.

The findings of this study would indicate, however, that those patients who are able to muster 20 per cent or more lymphocytes at any time in their remission do better than those who never achieve this level. Certainly lymphocytosis 20 per cent or more is not an ominous sign of impending relapse in ALL or AGL, and its presence should not exclude a patient from complete remission status. The occurrence of longer remissions and survivals in the group with lymphocytosis in ALL may, in fact, indicate an important relationship between this type of cellular response and successful control of the leukemic illness.

Table 2.—Median Remission Duration and Survival for all patients with AGL

<table>
<thead>
<tr>
<th></th>
<th>Group III</th>
<th>Group IV</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 20% lymphocytes</td>
<td>≥ 20% lymphocytes</td>
</tr>
<tr>
<td>Remission</td>
<td>3.5 mos.</td>
<td>6.5 mos. (p &gt; 0.05)</td>
</tr>
<tr>
<td>Survival</td>
<td>21 mos.</td>
<td>26.5 mos. (p &gt; 0.05)</td>
</tr>
</tbody>
</table>
Summary

Bone marrow lymphocytosis (BML) 20 per cent or greater occurring during remission of acute leukemia has been looked upon in the past as an unfavorable sign that may presage early subsequent relapse. Seventy-four patients with acute lymphocytic leukemia were studied to evaluate the significance of BML in remission. It was found that 14 patients with less than 20 per cent bone marrow lymphocytes at any time in remission had a median remission duration of 3 months and a median survival of 21 months, while 60 patients with 20 per cent or more bone marrow lymphocytes at any time in remission had a median remission duration of 14 months and a median survival time of 34 months. Patients with AGL and lymphocytosis had remissions and survivals not significantly longer than those without lymphocytosis. It is concluded that there is no justification for excluding a patient from complete remission status because of bone marrow lymphocytosis.

Summary in Interlingua

Lymphocytosis del medulla ossee (LMO) amontante a 20 pro cento o plus, occurrente durante un remission de leucemia acute esseva reguardate in le passato como un signo disfavorabile annunciante un precoce recidiva subsequente. Esseva studiate 74 patientes con acute leucemia lymphocytic pro evalutar le signification de LMO durante le remission. Esseva trovate que 14 patientes con minus que 20 pro cento de lymphocytos in le medulla ossee a transverso le integre tempore de remission habeva un duration median de ille remission de 3 menses e un longevitate median de 21 menses, durante que 60 patientes con 20 pro cento o plus de lymphocytos in le medulla ossee a un tempore o un altere durante le remission habeva un duration median de ille remission de 14 menses e un longevitate median de 34 menses. Patientes con acute leucemia granulocytic e lymphocytosis habeva remissiones e tempores de superviventia non significativemente plus longe que patientes sin lymphocytosis. Es concludite que il non es justificate excluder un patiente ab le stato de remission complete a causa de un lymphocytosis del medulla ossee.

Acknowledgment

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References

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