A Note on the Relationship Between Bone Marrow Lymphocytosis and Remission Duration in Acute Leukemia

By Norman Breslow and Richard Zandstra

In a sample of 148 children with acute leukemia a positive correlation was found between the duration of remission and the highest percentage bone marrow lymphocyte count observed during remission; a negative correlation was found between remission duration and the average lymphocyte count. The first finding is probably a statistical artifact, while the second supports the view that bone marrow lymphocytosis occurring repeatedly during remission may be a poor prognostic sign.

A recent article has called into question the criteria for the evaluation of response to treatment in acute leukemia which were originally proposed by the Clinical Studies Panel of the Cancer Chemotherapy National Service Center. The article reported that children with acute leukemia whose bone marrow lymphocyte count (BMLC) remain below 20 per cent throughout remission tended to have shorter remissions than those patients whose BMLC exceeded the 20 per cent level at least once. Such a finding would seem to be at odds with the criterion that patients with significant bone marrow lymphocytosis be excluded from the excellent response category. However, it is in all likelihood due to a statistical artifact, which will be illustrated below with another set of data.

Methods

A retrospective survey was made of the records of all patients who entered a cooperative clinical trial conducted by Children's Cancer Study Group A during the years 1963-64. Results of this trial were published previously. Only complete records of patients with a diagnosis of acute lymphatic leukemia were included in the analysis, leaving a final sample of 148. A patient would enter the trial at the beginning of his initial remission, having attained an M1 bone marrow rating, i.e., less than 6 per cent blasts. Bone marrow examinations were performed every six weeks during remission and the BMLC recorded along with other measurements. Remission duration was defined as time elapsed until the marrow showed greater than 25 per cent blasts, the percentage associated with an M3 rating. (The choice of a single M3 marrow as an endpoint differs slightly from the endpoint of two consecutive M2 or M3 marrows, which was used in the previous study. It was felt that the M3 endpoint was more appropriate for the present series since several children had two consecutive M2 marrows followed by a long period of complete remission.) Twenty-four patients were recorded as still being in remission, and 33 as still living, at the time of their last examination before the data were compiled.

From each patient's record were computed the values of the variables under study:

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Fig. 1 — Remission duration curves for three groups of patients defined according to their maximum percentage bone marrow lymphocyte count (BMLC) during remission (upper chart), and for three groups defined according to the average of their counts during remission (lower chart).

remission duration, survival duration, maximum BMLC, and average (i.e., arithmetic mean) BMLC. Patients were then divided into three groups of roughly equal size on the basis of their maximum BMLC, and life-table estimates of remission duration curves computed separately for each group. These three groups were: LO 0–24 per cent maximum BMLC, 43 cases; MED 25–34 per cent maximum BMLC, 56 cases; HI 35–65 per cent maximum BMLC, 49 cases. The same methodology was used to determine the effect of the average BMLC on remission duration. In this case the three groups were: LO 0–14 per cent average BMLC, 51 cases; MED 15–19 per cent average BMLC, 51 cases; HI 20–45 per cent average BMLC, 46 cases.

RESULTS

Figure 1 shows the remission duration curves for each of the three groups defined according to maximum BMLC and for the three groups defined by average BMLC. It is apparent that remission duration decreases with decreasing maximum BMLC. The median remission duration for the group with HI maximum BMLC is 14 months, while for the group with LO maximum BMLC it is only 6 months. This confirms the results of the previous study. However, in the case of average BMLC, the results are just the opposite. Remission duration decreases, with increasing average BMLC. The median remission duration for the group with HI average BMLC is 8 months, while for the group with LO average BMLC it is 18 months. An analysis based on survival curves, rather than remission duration curves, yielded equivalent results: the maximum BMLC is positively correlated with length of
survival, while the average BMLC is negatively correlated with the length of survival. All these results are "highly statistically significant" as evaluated by a generalized Kruskal-Wallis test.

**DISCUSSION**

The results for maximum BMLC can be explained in terms of the normal variation of a patient's BMLC over a period of time. For these patients it was not uncommon that the BMLC vary from 10 to 25 to 15 per cent in the course of three successive examinations. Many factors may have contributed to this variation. The patients in this particular trial were subjected to an extremely variable chemotherapeutic regimen, including periods of steroid treatment, with as many as five different drugs being used one at a time. There may be normal variations in a patient's bone marrow over time due to changes in disease status, regardless of the chemotherapy. And finally, though perhaps of lesser importance, are the variations associated with any clinical or laboratory measuring technique. Hence, the larger the number of observations made on any one patient, the greater is the likelihood that one of them will exceed any preassigned level merely by chance. Those patients with longer records will tend to have higher maxima or, conversely, those with high maxima will generally have the longer records. The same phenomenon is true of other measurements which vary with time; for instance the maximum daily rainfall for a 10-year period will generally exceed that for a 1-year period, even if the average rainfall is the same. In cases where such variation is large, as it is here, caution must be used when dealing with maxima.

Use of the average BMLC, though not ideal, is less liable to this type of difficulty since averaging tends to reduce, rather than emphasize, the effect of random variation. For a patient to have a high average BMLC means that he must have sustained a high BMLC over some period of time, rather than on just one "chance" occasion. Thus the finding that children having a higher average BMLC tended to have a shorter remission duration cannot be dismissed so easily as an artifact and warrants greater attention. It suggests that a pattern involving repeated marrow lymphocytosis may be a poor prognostic sign. Although this finding would seem to support the accepted response enitenia, the exact nature of such a pattern is certainly not yet clear. Statistical methods need to be employed which can consider the entire time-series of BMLC observations in its relation to remission duration so that the effects of trends and cyclic variation in the lymphocyte counts, as well as the concurrent variation of therapy over time, can be analyzed. While one can say that a single episode of bone marrow lymphocytosis in an otherwise normal record does not necessarily presage immediate relapse, it would be desirable to say with some precision what two, three, or four such episodes might mean for the future course of a patient's disease.

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