CONCISE REPORT

Left Shift in the Peripheral Blood Count at Diagnosis in Acute Lymphocytic Leukemia is Significantly Correlated With Duration of Complete Remission

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The prognostic significance of a left shift in the peripheral blood at the time of diagnosis of acute lymphocytic leukemia was investigated by a retrospective analysis of 109 patients treated on the same protocol in a single institution. Left shift was defined as the presence of 1% or more of metamyelocytes, myelocytes, or promyelocytes. All peripheral blood films were checked at the time of diagnosis by one of the authors. It was found that the duration of complete remission at 92 mo was 74% in patients with left shift and 42% in those without left shift ($p < 0.05$, log-rank test). By Cox regression analysis, only the total white cell count ($p < 0.001$) and the presence or absence of left shift ($p < 0.01$) were independently significant in determining the proportion of patients in complete remission. Patients with a left shift had a significantly higher granulocyte count at diagnosis ($p < 0.05$). We postulate that left shift in the peripheral blood count at the time of diagnosis may be an indirect measure of the total leukemia cell load. It is a new prognostic factor of significance in determining the likely outcome of the disease.

ACUTE LYMPHOCYTIC LEUKEMIA (ALL) in childhood is usually accompanied by neutropenia at diagnosis. This is associated with defective granulocyte-macrophage colony (CFU-C) growth in bone marrow culture. Careful examination of the peripheral blood smear shows immature granulocytic series (left shift) in some patients. The significance of this finding is unknown, and there has been no comment on its relationship to the outcome of the disease in the literature. We have investigated this question by means of retrospective analysis of 109 children with ALL treated on the same protocol in a single institution.

MATERIALS AND METHODS

The records of all patients included in a study of the role of intermittent chemotherapy and immunotherapy in maintenance of remission in childhood ALL were examined. This study was initiated in 1975 and closed in 1979. Details of the protocol and results of the study have been published. The peripheral blood smears of all patients in this study were initially examined by staff of the Haematology Laboratory and finally checked at the time of diagnosis by one of the coauthors (G.P.T.). The diagnosis of ALL was confirmed by a bone marrow aspirate, with morphological and cytochemical features generally accepted as diagnostic of ALL. A FAB classification of the bone marrow smears was not performed in this group of patients.

All patients with a white cell count of less than $30 \times 10^9$/liter were induced with vincristine (VCR) and prednisolone, followed by consolidation with l-asparaginase and cytosine arabinoside. Patients with a white cell count more than $30 \times 10^9$/liter were induced with combination chemotherapy using cytosine arabinoside, l-asparaginase, and cyclophosphamide. Presymptomatic central nervous system (CNS) therapy was given to all patients using cranial irradiation at a dose of 24 Gy and intrathecal injections with methotrexate at a dose of 12 mg/sq m given weekly for 4 wk. All patients received maintenance chemotherapy with intermittent courses of 6-mercaptopurine (6-MP) and methotrexate (MTX), with monthly injections of VCR for a period of 3 yr. Patients were randomized to receive bacillus Calmette-Guérin (BCG) inoculation during the rest period between courses of maintenance chemotherapy.

At the time of this analysis, 61 of the patients had discontinued treatment, 38 had died, and 10 were continuing therapy. A left shift (LS) was defined as the presence of 1% or more of metamyelocytes, myelocytes, or promyelocytes on the differential count of at least 100 cells performed by different observers on at least two occasions. The absence of LS was defined as a differential count consisting only of lymphoblasts, lymphocytes, and/or polymorphonuclear leukocytes. Bone marrow and blood smears were stained with Wright’s stain.

Life table plots were calculated by the Kaplan-Meier method. The test of life table differences was determined by the method of Peto et al. The Cox regression model for life table data was used for the multivariate analysis to assess the role of prognostic factors and their interrelationships. The prognostic factors studied were percent bone marrow infiltration; total white cell count; hemoglobin; enlargement of liver and spleen; sex; age; therapeutic protocol; presence or absence of LS; the degree of LS, and granulocyte count. The chi-squared test was used to examine the significance of the granulocyte counts in patients with or without LS.

RESULTS

Of the 109 patients, 66 were male and 43 female, and their ages ranged from 1 to 15 yr. LS at diagnosis was found in 47 patients, of whom 44 showed 1%–3% LS and 3 showed 4%–9% LS. By Cox regression analysis, only the total white cell count ($p < 0.001$) and the presence or absence of LS ($p < 0.01$) were independently significant in determining the duration of complete remission (CR). There was no significant...
FAVORABLE EFFECT OF LEFT SHIFT IN ALL  

relationship between the degree of LS and the total white cell count or the absolute granulocyte count. Nor was there any correlation between the degree of LS and the percent bone marrow infiltration. The granulocyte count at diagnosis was significantly higher in patients with LS ($p < 0.05$).

The duration of CR from the time of diagnosis of patients with and without LS is shown in Fig. 1. At 92 mo, 74% of patients with LS remained in CR, while in those without LS, 42% were in CR ($p < 0.05$, log-rank test). There was a plateau in the CR of patients with LS from 18 mo, while in patients without LS a plateau was apparent only after 54 mo.

DISCUSSION

In our institution, the peripheral blood smears of patients suspected to have leukemia are always carefully examined, and at least two, 100-cell differential counts are performed, as it is on this basis that decisions are made regarding isolation nursing procedures. Since this is a retrospective analysis of the reports of these differential counts, it is most unlikely that the observed difference in CR rates could represent observer bias. Although the number of patients analyzed is relatively small compared with intergroup studies, this study has the advantage in that all the peripheral blood smears were examined in the same laboratory and checked at the time of diagnosis by the same hematologist.

There is considerable debate regarding the mechanism responsible for depression of granulopoiesis in ALL. Mechanisms that have been suggested include crowding and replacement of normal stem cells by leukemia cells;\textsuperscript{1,2} decreased production of granulocyte-macrophage colony-stimulating activity;\textsuperscript{1,2} stem cell competition;\textsuperscript{9,10} and the possible presence of inhibitors to granulocyte production produced by leukemia cells.\textsuperscript{11}

The presence of LS in the peripheral blood in some patients with ALL may imply that these patients have less suppression of granulopoiesis, possibly due to a lower leukemia cell load. Alternatively, these patients may have an alteration in the mechanism of cell release from the bone marrow into the peripheral blood. This seems unlikely, as one would expect that the altered release mechanism would make it possible for leukemic lymphoblasts also to enter the peripheral blood more readily. Since there was no correlation between the degree of LS and the total white cell count, such an explanation appears unlikely. It is also possible that LS may reflect extramedullary hemopoiesis. Autopsy findings in newly diagnosed patients with ALL do not show extensive extramedullary hemopoiesis.\textsuperscript{12,13} It would therefore appear more likely that LS reflects lesser suppression of granulopoiesis due to a lower total leukemia cell load. This is supported by a significantly higher granulocyte count in patients with LS and the observation that there was a plateau in the CR of patients with LS after 18 mo, while in those without LS, a plateau only became apparent after 54 mo. The type of chemotherapy employed in ALL eradicates low rather than high leukemia cell numbers. The absence of a significant correlation between the degree of LS and the granulocyte count at diagnosis may in part be due to the small numbers of patients and clustering of 44 in the group with only 1%–3% LS. If our hypothesis is correct, then LS may be an indirect measure of the total leukemia cell load. While at present the explana-
tion for our findings remains speculative, there is no
doubt that LS at diagnosis should be considered as a
new laboratory feature distinguishing prognostic
groups in childhood ALL.

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