Slow Disappearance of Peripheral Blast Cells: An Independent Risk Factor Indicating Poor Prognosis in Children With Acute Lymphoblastic Leukemia

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The aim of this study was to find out whether the time required for disappearance of peripheral blast cells, or blast clearance, could be used to identify patients with a slow response to treatment associated with a poor prognosis of acute lymphoblastic leukemia (ALL). Our series consisted of 158 children with newly diagnosed ALL. The mean follow-up time was 69 months (range 22 to 140 months). Blast clearance was significantly associated with length of event-free survival. Only two of nine children with blast clearance ≥2 weeks and 4 of 11 children with blast clearance of 11 to 13 days were in remission at the time of analysis as compared with 86 of 138 of the children with more rapid blast clearance. The respective 5-year event-free survivals were 17%, 36%, and 60% (P < .003). Multivariate analysis showed that the relative risk of death or relapse in patients with blast clearance of >10 days was 5.2-fold (95% confidence limits 2.1 to 13.1) as compared with the others (P < .001). Our results indicate that patients with a slow response to treatment can be identified by simple differential peripheral cell counts during the early induction phase well before or even instead of performance of a more invasive bone marrow aspiration.

MORE THAN 20 factors have been reported to influence the prognosis of children with acute lymphoblastic leukemia (ALL).1-3 Children who respond slowly to induction therapy, however, ie, who have M2 bone marrow morphology at day 14, have a poor prognosis despite other possible favorable characteristics.4,5 These patients appear to form a special group that should be identified and perhaps treated differently.

The response to therapy can be assessed in different ways. Bone marrow examination is an invasive procedure that cannot be performed often. Assessment of the patient’s general condition may be clinically helpful, but lacks accuracy and specificity. The response could also be judged from the decrease in total peripheral WBC count and, for example, the time of occurrence of the nadir of leukopenia.

We have studied whether it is possible to combine the precision of bone marrow examination with the simplicity of WBC determination by counting the blast cells in the peripheral blood. The disappearance of blast cells from the peripheral blood, or blast clearance, was used as a criterion to identify patients with a slow response and to assess the relative risk of death or relapse in individual patients.

PATIENTS AND METHODS

All 173 children who presented with newly diagnosed ALL at the Children’s Hospital, University of Helsinki, during the 10-year period from 1975 to 1984, were at first included in the study. Six of these patients had Down syndrome and nine patients from the earliest study years had not had differential WBC performed regularly (ie, every second or third day) during the course of induction therapy. These 15 patients were excluded from the analysis. Thus, 158 patients remained for the final analyses. The median age of these patients was 4.8 years, with a range from 2 months to 15 years. The numbers of boys and girls were 77 and 81, respectively.

Blast clearance was defined as the time interval from diagnosis to the day when no blast cells could be detected in the differential count of 200 peripheral WBCs. Because differential counts were done every second or third day, this estimation is reasonably accurate with this reservation: If the patient had no peripheral blast cells at diagnosis, blast clearance was recorded as 0.

The diagnosis of ALL was based on bone marrow aspirates in all cases and, in addition, bone marrow biopsies, and surface marker and karyotype analyses were performed in 150, 98, and 72 cases, respectively, to support the classification of ALL. The therapeutic regimens used were the routine Scandinavian protocols.6,7 The agents used during induction therapy were prednisone, vincristine, L-asparaginase, intrathecal methotrexate, and additional doxorubicin in some patients.

Patients were followed at least once a month throughout the treatment period and once or twice a year after discontinuation of therapy. Two patients were lost to follow-up because of emigration; both were in primary remission lasting 7 and 36 months, respectively. The closing date of follow-up was October 31, 1986. The mean follow-up time was 69 months (range 22 to 140 months).

Statistical analyses were performed using the BMDP statistical software package.8 Groups were compared with likelihood ratio chi-square (G²) test or Student’s t test. Differences in survival were analyzed with Mantel-Cox’s test; survival curves were constructed by the product-limit method. All deaths during induction, relapses, and deaths during complete remission were considered failures. The results remained essentially unchanged if the eight patients who died during the induction phase were excluded from the analyses. The independence of prognostic factors was assessed with Cox’s proportional hazards model. The risk ratio was calculated as exp(coefficient) and the 95% confidence limits as exp(coefficient ± 1.96 SE).

RESULTS

The median value of blast clearance was 6 days, with a range from 0 to 38 days. In the majority of patients (113 of 158) blast clearance took ≤1 week. In nine children, ≥2 weeks elapsed before all peripheral blasts had disappeared. Eight patients (5.1%) died during the induction phase before verification of bone marrow remission was possible. At the time of death, however, none of them had any blast cells left in the peripheral blood. Blast clearance in these eight patients was 5, 5, 6, 7, 9, 9, 13, and 16 days, respectively.

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There were no differences in the prognoses of patients in blast clearance categories ≤10 days. The 5-year event-free survival for the 11 patients with blast clearance of 0 was 58%, and for the eight patients with blast clearance of 10 days it was 63%; however, the longest blast clearance values were associated with a poor prognosis. The 5-year event-free survivals for children with blast clearance ≤10 days (n = 138), 11 to 13 days (n = 11), and >13 days (n = 9) were 60%, 36%, and 17%, respectively (Fig 1). The overall differences in the length of event-free survival between these groups were statistically significant (P = .003). The average follow-up times for these three groups did not differ significantly from each other (70, 68, and 54 months, respectively).

Patients with long blast clearances tended to have higher WBCs than those of the other patients, more blast cells in the peripheral blood, and more often splenomegaly at time of diagnosis (Table 1). These associations were not, however, responsible for the prognostic effect of blast clearance. Multivariate analysis showed that blast clearance had an independent effect on prognosis even when WBC and all other factors presented in Table 1 were taken into account. The relative risk of death or relapse in patients with blast clearance >10 days was 5.2-fold (95% confidence limits 2.1 to 13.1) as compared with the other patients (P < .001). The other independent prognostic factors were age, WBC, initial central nervous system (CNS) leukemia, and platelet count (Table 2).

**DISCUSSION**

Our results indicate that blast clearance can be used as a criterion in identifying a subgroup of patients with poor prognosis. The risk of death or relapse is directly proportional to blast clearance, ie, the longer the blast clearance, the greater the risk. Only two of nine children with blast clearance ≥2 weeks and 4 of 11 children with blast clearance of 11 to 13 days were in remission at the time of analysis as compared with 86 of 138 of the other children. Thus, the minor irregularities in timing of the differential counts in this study do not seem to be of crucial importance. It is evident, however, that because of this bias no clear line can be drawn between patients with a favorable and unfavorable prognosis.

The value of bone marrow examination at day 14 for assessing prognosis is well established. However, there is no evidence that day 14 is the optimal point for evaluating the response. Clearly it would be inconvenient and even unethical to perform bone marrow examinations regularly at short intervals during the early induction phase. In contrast, peripheral differential counts can be repeated several times a week without any major disadvantages. We could demonstrate the existence of a group of patients who did not harbor any blast cells in the peripheral blood at day 14 but nevertheless had a poor prognosis because blast clearance had taken >10 days.

![Graph](https://via.placeholder.com/150)

**Fig 1.** The effect of blast clearance on the event-free survival of children with ALL (P = .003).
A left shift in the differential count at the time of diagnosis has been documented to be associated with a good prognosis in children with ALL.\textsuperscript{9} To our knowledge, however, no report exists on the prognostic value of serial differential counts during the early induction phase. The present data indicate that patients with a slow response and associated poor prognosis can be identified by simple differential peripheral cell counts during the early induction phase well before or even instead of performance of a more invasive bone marrow aspiration.

REFERENCES

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