Haemoglobin and prognosis in childhood acute lymphoblastic leukaemia

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SUMMARY Two hundred and nine children presenting consecutively with acute lymphoblastic leukaemia to a regional paediatric oncology unit were investigated to determine the prognostic significance of various factors at diagnosis. There was a strong positive correlation between the pretreatment haemoglobin level and the percentage of bone marrow blast cells in S phase of the cell cycle as assessed by flow cytometry. Patients with T- and B-cell leukaemia had significantly higher haemoglobin levels than non-B non-T patients. In patients with total white cell counts $<20 \times 10^9/l$, aged <13 years, and no mediastinal mass, there was no association of haemoglobin with length of first remission. However, among those with white blood counts $>20 \pm 10^9/l$ there was a strong positive trend towards shorter remission with higher haemoglobin levels. Children with high white blood counts at diagnosis and low haemoglobin levels may have a better prognosis than predicted by the white blood count alone.

There have been few attempts to relate the haemoglobin (Hb) level at diagnosis of childhood acute lymphoblastic leukaemia (ALL) to the eventual outcome of the disease. In cases in which this factor has been studied it has not generally been in groups comprising children alone,^{1,2} or such study has produced inconsistent results.³⁻⁶ We thus decided to look at a consecutive unselected group of children to determine the relationship between haemoglobin and prognosis of the disease.

Patients and methods. The Royal Manchester Children's Hospital, Paediatric Oncology Unit serves a large area of the North West of England and takes an unselected population.⁷ Two hundred and nine patients who presented consecutively during a 6-year period to October 1977 were studied. ALL was diagnosed using the criteria of Hayhoe *et al.*⁸ Blasts always constituted more than 30% of marrow cells.

Thirty-two prognostic factors present at diagnosis were investigated and the findings with some of them have been reported elsewhere.⁹⁻¹⁴ Each factor was analysed for its effect on duration of first remission because the prognosis is known to be poor after relapse.¹⁵ Remission curves were calculated by the life table method and compared by the log

rank test.¹⁶ These tests were (1) a test for heterogeneity between the groups, and (2) a test for trend.

The first test determines whether there is a significant difference between the groups, irrespective of the order in which they were numbered; the second test takes into account the order of the groups (from low to high Hb for instance).

The curve for each subgroup of patients was summarised by calculating the relative relapse rate. This is defined as the ratio of the number of relapses in the subgroup during the period of follow-up related to the number expected, on the assumption that prognosis was the same in all subgroups. Thus, a relapse rate greater than unity would indicate a fairly poor prognosis and a relapse rate less than unity a fairly good one.

A Hb level was obtained on all patients before transfusion and before starting treatment using a Coulter haemoglobinometer.¹⁷ All patients were treated subsequently with a standard induction protocol for ALL together with cranial irradiation, intrathecal methotrexate, and 4-drug maintenance, generally according to the current UK Medical Research Council protocol. Maintenance therapy was continued for 3 years after the disease had been diagnosed.

Results

Twenty-three per cent of patients had Hb levels <5 g/dl; 40% were between 5 and 7.4 g/dl; 30% were between 7.5 and 10.9 g/dl; 7% were >11 g/dl (Table). There was a strong positive correlation between Hb level and percentage of blasts in S phase of cell cycle ($r = 0.36$; $P < 0.02$; $n = 42$).

The mean Hb level was 6.0 g/dl in 68 children with non-B, non-T cell leukaemia, and 7.9 g/dl in 11 patients with T- or B-cell leukaemia. This difference was statistically significant ($P < 0.01$).

Table Haemoglobin level compared with length of first remission in childhood acute lymphoblastic leukaemia

Groups	Hb (g/dl)	No of patients	Relative relapse rate	P for trend
Total	<5	49	0.82	0.052
	5-7.4	83	0.91	
	7.5-10.9	63	1.20	
	>11	14	1.45	
Good prognosis	<5	29	0.89	0.7
	5-7.4	59	0.92	
	7.5-10.9	41	1.30	
	>11	6	0.52	
Poor prognosis	<5	20	0.61	0.002*
	5-7.4	24	1.11	
	7.5-10.9	22	1.08	
	>11	8	2.88	

Patients in whom prognosis is good are not black, have WBC $<20 \times 10^9/l$, are aged <13 years, and have no mediastinal mass. Patients in whom prognosis is poor have at least one of the above features.

*Statistically significant value.

A strong statistically significant trend towards shorter remission time with higher haemoglobin level is present in patients for whom prognosis is poor but not in 'good risk' children.

Fig. 1 Haemoglobin level compared with length of first remission for patients with acute lymphoblastic leukaemia. Trend towards poorer prognosis with increasing haemoglobin levels just fails to reach statistical significance ($P = 0.052$)

When all patients were analysed together there was a trend towards longer first remission times with lower haemoglobin which just failed to reach statistical significance ($P = 0.052$; Table; Fig. 1). When patients with traditional good risk features were analysed separately (white blood count (WBC) $<20 \times 10^9/l$, no mediastinal mass, aged <13 years, and not black) the Hb level had no influence on prognosis ($P = 0.7$) (Fig. 2). However, in patients with poor risk features a higher Hb level was strongly correlated with shorter remission times ($P = 0.002$) (Fig. 3). The median length of first

Fig. 2 Haemoglobin level compared with length of first remission for patients with good prognosis. No statistically significant effect ($P = 0.7$).

Fig. 3 Haemoglobin level for patients with poor prognosis. There is a statistically significant trend to shorter duration of first remission with higher haemoglobin ($P = 0.002$). The median lengths of first remission for haemoglobin levels of <5 , 5-11, and >11 g/dl are 18, 9, and 4 months respectively.

remission for poor risk patients with haemoglobin levels of <5 g/dl, 5–10·9 g/dl, and >11 g/dl were 18, 9, and 4 months respectively.

Discussion

The percentage of patients with low Hb (<5 g/dl), intermediate levels (5–10 g/dl), and high (>10 g/dl) are similar to other series—that is 23, 62, and 15% respectively.⁵

A small series of 6 children and 61 adults treated between 1957 and 1964 described by Gunz and Burns in 1965¹ was the first report relating Hb levels to prognosis. Their finding was that lower levels conferred a worse outlook for the disease. The study of Zippin *et al.*² showed an improvement in median survival time with increasing Hb up to a level of 9 g/dl above which the prognosis was worse. A similar result was shown by George *et al.*⁵ but this trend was thought not to be statistically significant. Simone⁴ failed to demonstrate any significance for this factor, although there was a trend towards worse survival over 8 g/dl. However, Lonsdale *et al.*³ found a poor prognosis in patients with high Hb levels which was confirmed in the recent report of Miller *et al.*⁶ in which an association of high Hb level with high WBC negates some of its independent influence on prognosis in a multivariate analysis. Our results provide an explanation for the inability of some studies to demonstrate a statistically significant effect on prognosis. This effect is confined to patients with other poor risk factors and analysis of a complete group of children will blur its significance.

The reason why a high Hb level confers a poor outlook can be found in its association with the pretreatment proliferative activity of bone marrow blast cells and, to a lesser extent, with T-cell type of disease. We showed previously¹⁴ that a higher percentage of blasts in S phase of cell cycle carries a poor prognosis, and that T-cell disease is associated with a higher percentage of cells in S phase. It would thus seem reasonable to assume that the group of patients with high WBC and high Hb levels have a rapidly multiplying malignancy, and they present before the Hb has time to fall.

About one-quarter of patients with traditional poor risk factors have Hb levels <5 g/dl and they may be expected to do appreciably better than poor risk patients with higher Hb levels. This group may achieve a median length of first remission of 18 months with a 25% 5-year disease-free survival. In our series all patients with a WBC of $>20 \times 10^9/l$ and Hb of >7·5 g/dl had relapsed by 22 months and all had died by 3 years. This group of about 15% overall clearly responds poorly to current treatment

and would be suitable for consideration of novel approaches to treatment.

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