Acute Leukaemia 1959-64: Factors Affecting Prognosis

R. M. HARDISTY and MORWENNA M. TILL

From the Department of Haematology, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London W.C.1

In any series of children with acute leukaemia receiving similar care and treatment, a wide variation in survival is seen, from days or weeks up to a few years—occasionally even 5 years or more (Burchenal, 1965, 1966). Although it is now well recognized that patients with acute lymphoblastic leukaemia usually respond much better to treatment than those with other cytological types, the relation of other factors to the prognosis of individual cases is less clearly established. We have reviewed some of the presenting clinical and haematological features of a series of leukaemic children seen during a 6-year period, in order to try and determine whether any of these features may be of prognostic value, in relation to either the incidence or duration of first remission or the total length of survival. Since the patients were not all treated in a uniform manner, no strict comparisons between matched groups can be made, and we have therefore not attempted to analyse our findings statistically. Careful inspection of our data, however, suggests that the effect of treatment on prognosis was independent of the other variables which we consider.

Criteria of Remission and Relapse

During most of the period under review, relatively few patients had bone-marrow examinations to confirm that a complete remission had been achieved. In most cases, therefore, the criteria for remission were confined to the clinical findings and the peripheral blood count: patients were considered to be in remission when they were symptom-free and had no abnormal clinical signs attributable to the disease, and when the blood count showed no blasts, at least 1500 neutrophils per c.mm., and platelets above 100,000 per c.mm. In those cases in which the bone-marrow was examined to confirm remission, the upper limit of normal for blasts in the marrow was taken as 10%. Relapse was confirmed in every case by the presence of more than 10% of blasts in the marrow unless the blasts in the peripheral blood exceeded 1000 per

c.mm. In cases where relapse was proved at an out-patient attendance but symptoms of ill health had started at some definite date between out-patient visits, the date of onset of these symptoms was taken as the date of relapse.

Because of the difficulty in establishing an exact date for the beginning of a remission, the time from the start of treatment until the first relapse was calculated in each case, thus including the time taken for induction as well as the actual duration of the subsequent remission.

Clinical and Cytological Types

During the six-year period 1959-64 the diagnosis of acute leukaemia was made in 88 children who were subsequently treated at The Hospital for Sick Children, Great Ormond Street. All were under 12 years of age at the time of diagnosis. In most cases the cytological type was assessed on the basis of Romanowsky staining only, but in some the cytological diagnosis was confirmed by cytochemical methods carried out by Dr. F. G. J. Hayhoe. Among the 88 children, 7 were myeloblastic, 4 were myelomonocytic, and one was eosinophilic in type. The survival curve of these 12 children as a group can be seen in Fig. 1, in comparison to that of the 76 children with acute lymphoblastic leukaemia; the corresponding remission rates and median times to first relapse and to death are shown in Table I.

The lymphoblastic group includes 7 patients who presented with clinical evidence of mediastinal lymph node enlargement at the time of diagnosis, whose data are also shown separately in Fig. 1 and Table I. Although lymphoblastic leukaemia carries a better prognosis than the other cytological types, it can be seen that the subgroup with 'mediastinal' lymphoblastic leukaemia did worse.

Some of the findings in the 'mediastinal' cases are summarized in Table II, which shows that 4 children presented with superior vena caval obstruction. 2 had symptoms of 4 months' duration resulting from the presence of nasopharyngeal tumours, and one other had a respiratory infection; these three also had clinical and radiological signs

FIG. 1.—Survival curves. ----, whole series (88); —, acute lymphoblastic leukaemia (76); ····, 'mediastinal' group (7); - · - ·, acute non-lymphoblastic leukaemia (12).

TABLE I
Prognosis According to Type of Leukaemia

Type	Number of Cases	Remission Rate (%)	Median Time to First Relapse* (wk.)	Median Survival† (wk.)
Acute lymphoblastic				
'Mediastinal'	7	71	13	22
Others	69	86	30	62
Total	76	84	27	60
Other cytological types	12	42	27	28
All cases	88	79	27	54

* For patients achieving remission.

† For all patients.

TABLE II
'Mediastinal' Type of Acute Lymphoblastic Leukaemia: Clinical and Haematological Features

Case No.	Age at Diagnosis (yr.)	Sex	Clinical Presentation	Spleen	Liver	Hb (g./100 ml.)	Total WBC $\times 10^3$ /c.mm.	Blasts $\times 10^3$ /c.mm.	Platelets $\times 10^3$ /c.mm.	Marrow Blasts (%)	Treatment*	Survival: Diagnosis till Death (wk.)
1	3	M	Ethmoidal tumour	0	++	7.5	29.0	10.8	145	90	P.MP.	1
2	3	M	Superior vena cava obstruction	0	0	12.4	15.2	0	348	46	P.MP.Mx.RT.	14
3	5	M	Upper respiratory tract infection	++	++	11.9	245.0	215.0	113	—	P.MP.Mx.	17
4	7	M	Nasopharyngeal tumour	+	+	6.1	8.1	4.0	124	58	P.MP.TEM.	20
5	5	F	Superior vena cava obstruction	+	0	10.3	6.7	0.067	217	11	P.MP.Mx.V. Chl.RT.	31
6	6	F	Superior vena cava obstruction	++	++	8.7	111.0	84.0	160	82	P.MP.Mx.V.C. RT	32
7	6	M	Superior vena cava obstruction	++	+	10.1	35.0	21.0	115	95	P.MP.Mx.V.C.	60

* P., prednisone; MP., 6-mercaptopurine; Mx., methotrexate; TEM., triethylenemelamine; Chl., chlorambucil; C., cyclophosphamide; V., vincristine; RT., local radiotherapy.

FIG. 2.—Survival according to time of diagnosis. ---, patients diagnosed in 1959-60 (22); —, 1961-62 (22); ·····, 1963-64 (32). [The graphs are derived from the cases of acute lymphoblastic leukaemia in this and all subsequent figures.]

of mediastinal enlargement at the time of diagnosis of leukaemia, though their presenting symptoms were not directly attributable to this. 6 of the 7 children also had lymph node enlargement in other areas (particularly the neck), and, paradoxically, those with the most widespread involvement responded best to treatment. All had platelet counts of more than 100,000 per c.mm. and neutrophil counts above 1000 per c.mm. Severe anaemia was not a common feature. In all 6 cases in which Romanowsky-stained marrow preparations were examined an excess of blast cells was present; these marrows could not be distinguished from those of the 69 other cases of lymphoblastic leukaemia on cytological grounds.

The response to treatment of the 7 'mediastinal' patients was poor and though the 6 who survived more than 48 hours from the start of treatment all showed some response to prednisone and 6-mercaptopurine initially, attempts at maintenance with either 6-mercaptopurine or methotrexate were unsuccessful, relapse occurring in each case shortly after withdrawal of the prednisone. Similarly, radiotherapy in 4 of the patients resulted in some regression of the tumour in the irradiated area but in none was this complete; in the 2 patients who received vincristine in adequate dosage, the response appeared to be as good as that obtained with prednisone. In each case relapse was associated with increase in size of mediastinal or cervical nodes together with the appearance of blasts in the peripheral blood, but the disease progressively became more widespread and the mediastinal lesion was

never again as prominent a clinical feature as it had been at the time of onset of the disease.

None of the other 69 patients with lymphoblastic leukaemia had clinical evidence of mediastinal node enlargement at diagnosis. Chest x-ray films in 29 of these were normal; the possibility that minor degrees of mediastinal enlargement were present in some of the remainder cannot be excluded. Nevertheless, in view of the similarity of their presenting features and of their poor response to treatment, it seems reasonable to regard the 7 proven 'mediastinal' cases as a distinct subgroup of acute lymphoblastic leukaemia. The following analysis of various factors affecting prognosis in acute lymphoblastic leukaemia is based on all 76 cases, including the mediastinal group.

Acute Lymphoblastic Leukaemia

Effect of changing methods of treatment.

It was to be expected that the availability of new drugs and the introduction of new methods of treatment within the six-year period would extend the median survival rate. That this was so can be seen in Fig. 2 which shows the survival curves for patients with acute lymphoblastic leukaemia in three groups, according to the 2-year period in which the diagnosis was made. The median survival increased from 40 weeks for patients diagnosed in 1959-60 to 60 weeks in the next 2-year period, and 68 weeks in the last. The proportion of patients achieving a first remission also increased from each period to the next, as did the median duration of first remissions (Table III).

TABLE III
Prognosis of Lymphoblastic Leukaemia According to Date of Diagnosis

Year of Diagnosis	No. of Cases	Remission Rate (%)	Median Time to First Relapse* (wk.)	Median Survival† (wk.)
1959-60	22	73	20	40
1961-62	22	86	30	60
1963-64	32	91	34	68

* For patients achieving remission.

† For all patients.

Adrenocortical steroids, 6-mercaptopurine, and methotrexate were available throughout the period but were used variously, both as regards dosage and length of maintenance. Vincristine was introduced in September 1962, cyclophosphamide was used from April 1964, and Rubidomycin from September 1966.

Before 1962 the patients were treated and followed up independently by a number of paediatricians. In 1962 it was decided that, though the patients should remain nominally under the care of the various paediatricians, the out-patient follow-up could be simplified and co-ordinated by the provision of a haematology clinic designed for the purpose. This clinic was arranged so that every patient had

blood taken for haemoglobin estimation, platelet count, and total and differential leucocyte counts on arrival, before being weighed and measured; the results were available to the haematologist about 45 minutes later when he examined the patient. Every patient was seen at least once in four weeks and the management of the children became more uniform. All patients from this time received maintenance treatment with an antimetabolite, prolonged treatment with steroids was avoided, and the dosage of drugs, calculated on a weight basis, was standardized. The treatment régimes, however, were by no means uniform, as some followed the specifications of various clinical trials and others were designed to fit individual requirements.

Clinical features at onset. In Table IV the cases of lymphoblastic leukaemia have been grouped according to their clinical and haematological features at the time of diagnosis; for each group, the remission rate, median time to first relapse, and median total survival time are shown.

Sex. The remission rate and median time to first relapse were slightly better in girls than in boys, but the median survival was similar for both sexes (Table IV). Amongst the longer survivors, there was a slightly higher proportion of girls than might have been expected: though the series included 45

TABLE IV
Prognosis of Lymphoblastic Leukaemia According to Presenting Clinical and Haematological Features

Feature	Subgroup	No. of Cases	Remission Rate (%)	Median Time* to first Relapse (wk.)	Median† Survival (wk.)
Age (yr.)	<3	22	73	24	32
	3+	54	89	28	64
Sex	Boys	45	80	24	60
	Girls	31	90	32	58
Spleen size	Impalpable or tip only	36	83	39	80
	More than tip	40	85	22	42
Liver size	Not enlarged	18	78	36	84
	Enlarged	58	86	24	54
Lymph nodes	Not enlarged	19	84	56	85
	Enlarged	55	84	22	46
Total leucocytes (per c.mm.)	<20,000	45	87	38	74
	20,000+	31	81	15	34
Blasts (per c.mm.)	<10,000	45	87	37	70
	10,000+	29	83	17	42
Neutrophils (per c.mm.)	<1,000	38	89	37	84
	1,000+	35	80	18	32
Platelets (per c.mm.)	<100,000	53	85	26	58
	100,000+	22	82	32	72
	100,000+‡	15	87	42	86

* For patients achieving remission.

† For all patients.

‡ Excluding 'mediastinal' cases.

FIG. 3.—Survival according to age. ----, under 3 years (22); —, 3–4 years (26); ····, 5 years and over (28).

boys and 31 girls, 8 girls and 7 boys were alive at 2 years and 5 of each sex at 3 years.

Age. On the whole the older children responded more favourably than the younger ones, the remission rate, remission duration, and survival being poorer in children under the age of 3 years at the time of diagnosis (Table IV, Fig. 3).

Infiltration of organs. Clinical enlargement of spleen, liver, and peripheral lymph nodes was without apparent effect on the rate of remission, but those patients with significant clinical involvement of each of these organs had a shorter median time to first relapse and median survival than the remainder (Table IV, Fig. 4, 5, and 6). As might be expected, two or more of these organs were

often clinically enlarged in the same patient, so that there was considerable overlap, for instance, between the groups of patients classified as having liver and lymph node enlargement, respectively. The correlation between these three parameters is shown in Table V, from which it can be seen, for example, that of the 55 patients with lymph node enlargement, 44 also had an enlarged liver and 32 had marked splenomegaly; similarly, the great majority of those patients in whom more than the tip of the spleen was palpable also had enlarged lymph nodes and liver. It follows that the apparently unfavourable prognostic effect of clinical enlargement of liver, spleen, and lymph nodes was probably due to a similar subdivision of cases in each instance:

FIG. 4.—Survival according to spleen size. ----, impalpable (16); —, tip palpable (20); ····, more than tip palpable (40).

FIG. 5.—Survival according to liver size. —, not enlarged (18); ----, enlarged (58).

FIG. 6.—Survival according to clinical involvement of peripheral lymph nodes. —, not enlarged (19); ----, enlarged (55).

TABLE V
Correlation of Clinical Features

		Liver		Lymph Nodes*	
		Not Enlarged	Enlarged	Not Enlarged	Enlarged
Spleen	Impalpable or tip only	15	21	12	23
	More than tip	3	37	7	32
Lymph nodes* .. .	Not enlarged	7	12	—	—
	Enlarged	11	44	—	—

* State of lymph nodes not recorded in 2 cases.

FIG. 7.—Survival according to total leucocyte count. —, less than 20,000 per c.mm. (45); ····, 20,000 per c.mm. and above (31).

FIG. 8.—Survival according to total blast cell count in peripheral blood. —, less than 10,000 per c.mm. (45); ····, 10,000 per c.mm. and above (29).

generalized organ enlargement, rather than involvement of any particular organ, appears to be the relevant prognostic feature.

Peripheral blood counts. The cases were divided into 5 groups according to the level of the initial total leucocyte count, and survival curves were constructed for each group. These revealed that the level which gave the clearest separation from the point of view of prognosis was 20,000 per c.mm.—a finding in agreement with that of Zuelzer (1964). The median duration of remission and

survival for patients with counts above and below this figure is shown in Table IV, and the full survival curves for the two groups in Fig. 7.

Similar grouping of the 74 cases for which the total pretreatment blast cell count was available showed that those with less than 10,000 blasts per c.mm. of peripheral blood had a better prognosis than those with more than this (Table IV, Fig. 8). There was very close correlation between this grouping and that according to the total leucocyte count: of 45 patients with less than 10,000 blasts per c.mm., 42 had less than 20,000 total leucocytes

TABLE VI
Distribution of Clinical and Haematological Features
by 2-year Periods

Unfavourable Prognostic Feature	Percentage of Patients Showing Each Feature			
	1959-60 (22 cases)	1961-62 (22 cases)	1963-64 (32 cases)	All years (76 cases)
Age <3 years ..	27	36	25	29
Spleen enlarged > tip ..	55	41	59	53
Liver enlarged ..	73	82	75	76
Nodes enlarged ..	77	77	72	75
Total leucocytes >20,000/c.mm.	41	36	44	41
Total blasts >10,000/c.mm.	41	36	44	41
Platelets* <100,000/c.mm.	90	81	68	78
'Mediastinal' onset ..	9	5	13	9

* Excluding 'mediastinal' cases.

per c.mm., while 27 of the 29 patients with at least 10,000 blasts per c.mm. had a total of more than 20,000 total leucocytes per c.mm.

About half the patients had less than 1000 neutrophils per c.mm. at the time of diagnosis; paradoxically this group did better than those with higher neutrophil counts (Table IV), chiefly because of a higher early death rate amongst the latter group which included a higher proportion of patients aged less than 3 years, and all those with the 'mediastinal' type of disease. We can think of no logical reason why a low neutrophil count should be a favourable prognostic feature *per se*, but our findings at least show no reason for regarding it as an adverse feature.

It was thought that a platelet count above 100,000 per c.mm. at the time of diagnosis might prove to be a favourable factor; however, since the 7 'mediastinal' cases, which have been found to have an inherently bad prognosis, all had high initial platelet counts, this association only became apparent when the 69 non-mediastinal cases were considered separately (Table IV).

Discussion

The improvement in remission rate and duration, and in total survivals, from each 2-year period to the next, might have been due to an uneven distribution in time of cases with unfavourable prognostic features. The proportion of cases of acute lymphoblastic leukaemia with each such feature was therefore calculated for each 2-year period; the distribution is shown in Table VI. It can be seen that the only adverse feature showing a marked fall in incidence from the first to the last period was thrombocytopenia. This difference between the groups was not sufficient to account on its own for

the improvement in prognosis, and it seems reasonable to attribute most of this to the steady improvement in treatment during the period. It should also be noted that the effect of most of the features listed was on duration of remission and survival only, whereas the improvement during the 6-year period was also reflected in the remission rate.

The two groups of patients with the most unfavourable prognosis were those with the 'mediastinal' variety of lymphoblastic leukaemia and those with cytological types other than lymphoblastic. In the latter group, this was due chiefly to a poor remission rate; the median duration of remissions, once achieved, was the same as in the lymphoblastic leukaemias. In the 'mediastinal' group, on the other hand, the remission rate approached that of the whole series, but remissions were short-lived.

Taking the acute lymphoblastic leukaemias as a whole, it is clear that extensive infiltration of organs at the time of diagnosis, and the presence of large numbers of leukaemic cells in the peripheral blood, were both adverse prognostic features. The effect in each case was on the duration of remission rather than on the remission rate. The close correlation between involvement of liver, spleen, and lymph nodes has already been pointed out; there was a similar association between the number of blasts in the peripheral blood at diagnosis and the degree of organ involvement. Thus, of 36 patients in whom not more than the tip of the spleen was palpable, 32 had less than 10,000 blasts per c.mm., while of 38 with greater splenic enlargement than this, 25 had more than 10,000 blasts per c.mm. The most obvious interpretation of these findings is that organ enlargement and blast count both reflect the extent to which the disease has progressed by the time of diagnosis, and hence, perhaps, the rate of proliferation of the leukaemic cells; and that a higher rate of proliferation tends to lead to earlier relapse. A similar association between total leucocyte count and over-all survival has been noted on several previous occasions (Haut, Altman, Wintrobe, and Cartwright, 1959; Zuelzer and Flatz, 1960; Zuelzer, 1964), and Hardisty and Norman (1967) have observed a similar inverse relation between the number of blasts in the CSF of children with meningeal leukaemia and the length of time until the next episode of meningeal involvement. They also found that patients with high peripheral blood blast counts at diagnosis tended to have high CSF counts when meningeal leukaemia developed, again suggesting a rapid rate of proliferation for the particular leukaemic cell line.

This explanation might be held to imply a characteristic rate of increase of the total leukaemic

cell population for any given patient. The work of Mauer, Lampkin, and Saunders (1966) and Foadi, Cooper, and Hardisty (1967) shows that the proportion of leukaemic cells undergoing division may vary widely throughout the course of the disease, being higher at the time of relapse than at diagnosis. This finding is not incompatible, however, with the concept of a wide variation between patients in the intrinsic rate of increase of leukaemic tissue during the proliferative stages of the disease.

Whatever the explanation, attention to these clinical and haematological features at the time of diagnosis may enable one to make a somewhat more accurate prognosis than is usually thought possible. As a final illustration of this, only 1 of the 10 patients in the series who survived over 3 years had more than the tip of the spleen palpable on first examination (in contrast to 53% of the whole series), and only 2 of the 10 had more than 10,000 blasts per c.mm. (as compared with 41% of the whole series); all 10 were aged over 3 years at diagnosis, and the incidence of hepatomegaly and of thrombocytopenia amongst them was only half that of the whole series. The longest survivor, a girl who lived for 8 years, had only 1 'unfavourable' feature out of all 7 considered in Table IV, as did two other girls, the only patients still in their first remission after more than 3 years. A fourth girl, diagnosed in 1957 and therefore not part of the present series, who is still alive and well without evidence of leukaemia 10 years later, also had only 1 unfavourable feature out of the 7. It thus appears to be amongst those patients with minimal evidence of disease at the time of diagnosis that such long survivors tend chiefly to be found.

Summary

Of 88 cases of acute leukaemia diagnosed during the years 1959-64, 76 were lymphoblastic, 7 myeloblastic, 4 myelomonocytic, and 1 eosinophilic in type. 7 of the acute lymphoblastic group

presented with mediastinal lymph node enlargement; these had a poorer prognosis than the remainder, and are discussed in some detail.

The remission rate, time to first relapse, and total survival of the 76 cases of acute lymphoblastic leukaemia have been analysed according to the year of diagnosis and in relation to various clinical and haematological features. Extensive infiltration of organs at the time of diagnosis, and the presence of large numbers of leukaemic cells in the peripheral blood, appeared to be adverse prognostic features. Patients aged over 3 years at diagnosis did better than younger ones, and those without significant thrombocytopenia had a longer course than the remainder. The significance of these findings is discussed.

We wish to thank the physicians, past and present, to The Hospital for Sick Children, who have allowed us to study their patients and participate in their management. This work was supported by a grant from the Leukaemia Research Fund.

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