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Prognosis of acute lymphoblastic leukaemia in Ibadan, Nigeria

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Summary

Patients with acute lymphoblastic leukaemia (ALL) seen in University College Hospital, Ibadan, Nigeria, still have low rates of complete remission and relatively short survival. Yet the overall prognosis was expected to have improved because the proportions of adults, males and people of low socio-economic class among the patients have decreased steadily over the past three decades. Possible causes of the persistent poor performance were sought for in 30 new ALL patients seen in the hospital over a period of 2 years and 9 months. Unfavourable prognostic factors, lack of standard cytotoxic drugs, inadequate supportive care and absence of modern facilities for therapy combined to make their disease outcome worse than expected.

Résumé

Les patients avec leucémie lymphocytoire aiguë (ALL) qu'on a vus à UCH Ibadan, Nigéria, ont rarement des rémissions complètes, et souvent une survivance relativement courte. Mais on attendait que le prognosis global soit améliorer parce que les proportions des adultes, des mâles, et des gens de classe socio-économique basse parmi les malades ont diminué fermement pendant les trois dernières périodes de dix ans. On a cherché des causes possibles pour la piètre marche continue parmi trente nouveaux malades vus à l'hôpital pendant une période de 2 ans et 9 mois. Des facteurs prognostiques défavorables, la manque des drogues cytotoxiques, la manque de soutien adéquat, et l'absence des facilités modernes pour la thérapie joignaient leurs forces afin d'empirer la santé des sujets.

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Introduction

Previous workers have reported the generally unfavourable outcome of acute lymphoblastic leukaemia (ALL) among patients seen in University College Hospital, Ibadan, Nigeria [1–5]. In the past 30 years the modal age group of these patients has changed from 10–15 years to 0–5 years, the male:female ratio has decreased from 3.5:1 to 1.4:1, and the proportion of individuals from the low socio-economic class has reduced from 64 to 22%. An improvement in overall prognosis would normally be expected to follow the above epidemiological changes, but this was not observed.

Determinants of disease outcome were therefore analysed in ALL patients seen in the hospital over the last 33 months to find out why their performance has not improved.

Subjects and methods

Data were obtained from the records of 30 newly diagnosed ALL patients seen in University College Hospital, Ibadan, from 15 January 1987 to 14 October 1989. Diagnosis was, in most cases, made from clinical features, haemogram and bone marrow cytology. Periodic acid-Schiff (PAS) and Sudan block B staining of the blood or bone marrow cells were used for definitive diagnosis in some subjects. Combination of cytology and cytochemistry was adequate to establish diagnosis in all cases.

Prognostic factors, treatment administered

and disease outcome were determined in the subjects. In 25 of them, serum concentrations of immunoglobulins G, M and A were measured by the single radial immunodiffusion method of Mancini *et al.* [7]. Serum immune complex levels were quantified in the same subjects by the polyethylene glycol precipitation method of Haskova *et al.* [8]. Blood cell counts were done by standard methods [9]. The French–American–British (FAB) morphological classification of the leukaemic cells [10] was done by a panel of haematologists. The socio-economic class of the subjects (or their parents in the case of children) was determined using criteria defined by Williams [5]. Central nervous system involvement was diagnosed if a subject had neurological features or leukaemic cells in the cerebrospinal fluid.

The COAP i.v. regimen used for remission induction consisted of i.v. cyclophosphamide 650 mg/m^2 on days 1 and 8, i.v. vincristine 1.4 mg/m^2 (up to a maximum of 2 mg) on days 1, 8, 15 and 22, subcut cytosine arabinose 100 mg/m^2 daily for 7 days, i.t. cytosine arabinose 50 mg/m^2 on days 1 and every 5th day for six doses and oral prednisolone 40 mg/m^2 for 28 days. Oral allopurinol 100 mg t.d.s. was given to prevent hyperuricaemia.

At the end of 28 days, response to therapy was assessed. Complete remission (CR) was defined as the disappearance of all clinical and laboratory features of the disease.

Subjects who had significant improvement in their disease features, e.g. anaemia, leucocytosis, lymphadenopathy and hepatosplenomegaly, but still had blast cells in the peripheral blood or more than 5% blasts in the bone marrow were classified as having partial remission (PR). Those who did not show appreciable improvement or whose disease worsened progressively were deemed to have shown no remission (NR).

If complete remission occurred, maintenance therapy was started with oral methotrexate 20 mg/m^2 weekly and 6-mercaptopurine 50 mg/m^2 daily so long as blood cell counts were adequate. Subjects with partial or no remission were given a second course of COAP. Those who relapsed had the same COAP regime for re-induction of remission. Packed erythrocyte and platelet concentrate transfusion as well as antibiotic therapy were given when necessary and available.

Results

Thirty ALL subjects were seen, the youngest was aged 10 months, the oldest 55 years. Their mean age was 17.4 years. Fourteen (47%) of them were children aged 12 years or less. There were 17 males and 13 females, giving a male:female ratio of 1.3:1. Table 1 shows the frequencies of various prognostic factors [10–13] among the ALL subjects.

Treatment and outcome

The outcome of treatment varied according to the completeness of cytotoxic drug administration (Table 2). Survival was defined for dead subjects as time from the onset of illness to death. For the living, it was the period from the onset of illness to the time of reporting.

Of the nine subjects who had all cytotoxic drugs, five were alive for periods ranging from 6 months to 2½ years, three are still in remission and two in relapse. The mean survival of the five subjects was 1 year and 2 months. In contrast, only two of the 15 who had partial treatment are alive after 1 year and none of them are in remission. No subject survived for more than 10 months without chemotherapy. The mean period of complete remission for the six subjects who achieved it was 4 months.

Adequate supportive care (particularly platelet concentrate transfusion) was not always available. Thrombocytopenic bleeding was the immediate cause of death in 10 subjects.

Discussion

Acute lymphoblastic leukaemia is not common in Ibadan. The estimated incidence is 3.7/million/year [5]. This is mainly why it took almost 3 years to see 30 ALL patients in a teaching hospital to which they are usually referred. The stated incidence implies that statistically significant observations can be made in this environment on a relatively small number of ALL patients.

Table 1 shows that the majority of ALL patients seen in UCH, Ibadan, during the period of study had had prognostic factors at presentation. Williams had shown that ALL patients seen in the same hospital had a high proportion of T-cell leukaemia, low proportion of

Table 1. Prognostic factors in ALL subjects

Prognostic factor	No. of subjects	Percentage
Age (years)		
2–7: Good	7	23
<2 and >7: Bad	23	77
Sex		
Female: Good	13	43
Male: Bad	17	57
Leucocyte count		
Normal: Good	5	17
$<2.6 \times 10^9$/l: Bad	1	3
$>10.2 \times 10^9$/l: Bad	13	43
$\geq 100 \times 10^9$/l: Very bad	11	37
CNS involvement		
Absent: Good	25	83
Present: Bad	5	17
FAB morphology		
L_1: Good	9	30
L_2: Bad	14	47
L_3: Very bad	4	13
Not certain	3	10
Serum immunoglobulin level		
Normal: Good	14	56
Low: Bad	11	44
Serum immune complex level		
Low: Good	4	15
High: Bad	21	85
Socio-economic class		
1–2: Good	15	50
3–5: Bad	11	37
Not clear	4	13

Normal leucocyte count in Ibadan = 2.6×10^9/l–10.2×10^9/l [14].

Table 2. Chemotherapy and outcome in ALL subjects

Treatment	No. of subjects	CR	PR	NR	Survival (months) Range	Mean
All drugs	9	6	3	0	2–30	10
Some drugs	15	0	12	3	1–9	4.6
No drugs	6	0	0	6	0.2–10	3.8
Total	30	6	15	9	0.2–30	6

common-ALL and low PAS-positivity of their leukaemic cells [1,5]. These features are associated with bad prognosis [10,15]. In our study, four (13%) of the subjects had the L3 morphological variant which has the worst prognosis. This percentage is significantly higher than the 1% generally stated for this rare B-cell type [16]. The socio-economic class of a patient affects the outcome of disease in various ways. Those from the lower classes are more likely to be malnourished and therefore immunodeficient [17,18]. They are unable to afford cytotoxic drugs and other treatment facilities. Patients from the lower socio-economic classes are less likely to have the L_1 morphological variant which has the best prognosis. Of the nine subjects who had the L_1 morphological variant, six (67%) were of high socio-economic class (1 and 2), and three (33%) of the lower classes (3 and 4). None were in class 5. In contrast, three (75%) of the four subjects with the L_3 variant which has the worst prognosis came from classes 3 and 4. The remaining one was of class 2. About half of the subjects in this study came from outside the high socio-economic class. There is no doubt that the bad prognostic factors seen in the majority of the subjects contributed substantially to the overall unfavourable outcome of their disease.

However, the effect of the bad prognostic factors was worsened by suboptimal therapy. The treatment regimen used was dictated mainly by the availability of cytotoxic drugs. Those who achieved complete remission did not have consolidation therapy with L-asparaginase and doxorubicin because the drugs were not available. The cost of available chemotherapeutic agents kept them beyond the reach of most subjects. Free dispensation or subsidized purchase of cytotoxic drugs was not always possible. Supportive treatment like transfusion of platelet concentrate could not always be given when needed. Facilities for treatment in sterile chambers and bone marrow transplantation are lacking. That 67% of the subjects who had all cytotoxic drugs achieved complete remission suggests that inadequate treatment contributed in no small measure to the low overall rate of complete remission (25%). The commonest immediate cause of death was haemorrhage due to thrombocytopenia — a condition preventable by adequate transfusion of platelet concentrate.

Patients with ALL seen in UCH, Ibadan, present with poor prognostic factors. However, the outcome of their illness is generally poor because of a combined effect of unfavourable prognostic factors and suboptimal therapy.

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