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PROGNOSIS IN 262 TURKISH CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA*

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Following the introduction of the first effective chemotherapy in the late 1940's, children with acute lymphocytic leukemia (ALL) could still only survive for a few months[1]. Up until 1962, antileukemic agents were used only for palliation of the disease. Since then, by using a combination of various methods, fairly good results have been obtained. In recent years in developed countries, by using a combination of chemotherapeutics and central nervous system (CNS) prophylaxis, much better results have been obtained and ALL has become a curable disease[2]. As Turkey is a developing country, it is difficult to obtain drugs and to make the patients come for follow-up treatment, which adds to the problems of curing the disease. To the best of our knowledge, the results of treatment of a large number of patients with ALL have not been reported in developing countries. We would like to present our results in the treatment of 262 children with this disease.

Material and Methods

This study, carried out at the Hacettepe Children's Hospital, covers the 6-year period from October 1975 to October 1981. During this period a total of 477 patients with acute leukemia were examined. Three-hundred seventy (78%) of them were diagnosed as having ALL and the remaining 107 patients (22%) as having acute myelocytic leukemia (AML). For various reasons 108 children with ALL (29%) could not be given treatment (Table I). Therefore, the study group consisted of 262 children with ALL, 165 (63%) males and 97 (37%) females. The ages of the patients ranged between 2 months and 17 years with a median age of 5 years. The peak age distribution was between 4 and 7 years (Figure 1). Most of the patients had come from villages with poor socio-economic conditions.

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TABLE I

The Factors which Prevented 108 out of 370 Childen with Acute Lymphocytic Leukemia from Entering a Treatment Protocol

	No. of patients	% of 370 patients
Patients who did not accept the treatment	26	7
Patients who had received treatment previously in another hospital	23	6
Patients who stopped therapy within 4 weeks	42	11
Patients who died within 2 weeks	17	4.5
Total	108	29

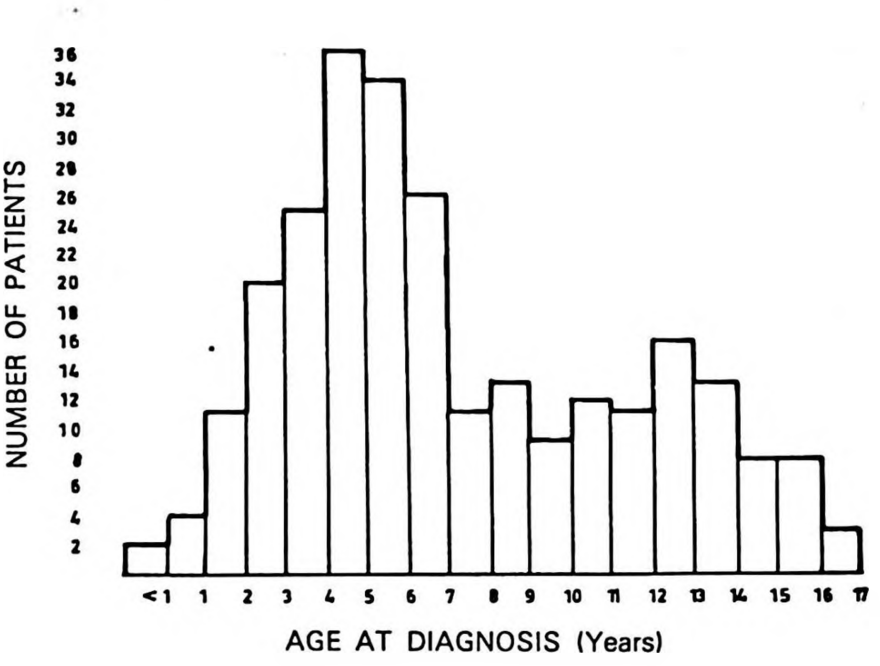

Figure 1

Age distribution of 262 children with acute lymphocytic leukemia.

The diagnosis of ALL was made by the examination of a Wright-stained bone marrow aspiration smear. CNS leukemia was diagnosed when leukemic blasts were seen in the CSF centrifugate prepared with Wright's stain.

In accordance with our treatment protocol, remission was induced by prednisolone (PRED) and vincristine (VCR). In treatment of high risk group patients (leukocytes $> 50{,}000/\mu l$, liver and spleen enlargement more than 6 cm and evidence of extramedullary infiltration such as CNS, mediastinal, testis, parotis, renal and L_3 type

ALL), cytoxan (Cyclo) and/or L-asparaginase were also combined when these were available. After obtaining remission, prophylactic cranial irradiation of 2400 rad and 5 doses of intrathecal (IT) methotrexate (MTX) were given. Maintenance treatment consisted of daily oral mercaptopurine (6-MP) and weekly MTX. The therapy given is summarized in Table II. During the last 2 years of the study 46 patients were given PRED together with MTX (IT) for CNS prophylaxis, and cytoxan was also added as a third agent for maintenance therapy.

Results

Initial laboratory and physical findings.

The initial hemoglobin (Hb) levels of the patients ranged from 2 to 13 gm/dl (mean 6.4 gm/dl). 89% of the patients had anemia for their age, and Hb level was less than 8 gm/dl in 73% of the children. The initial leukocyte counts were less than 4000 /μl in 12% of the patients, and leukocytosis was observed in 14% of them, counts being between 15,000 and 25,000/μl; 11% had leukocytosis over 100,000/μl, and pancytopenia was observed in 8% of the patients. Hepatosplenomegaly was observed in 85% of the patients being greater than 6 cm below the respective costal margins. Mediastinal lymph node enlargement was shown by x-ray in 33 of the patients (13%) and 3 of them had pleural effusion.

TABLE II

Outline of Therapy in Children with Acute Lymphocytic Leukemia

A — Remission induction (4 - 6 weeks)

PRED	2 mg/kg	PO daily
VCR	0.05 mg/kg	IV weekly

B — If remission is obtained*

Prophylactic cranial irradiation (2 ½ weeks) 2400 rad
(dosage for children over 2 years of age)
MTX 0.5 mg/kg IT x 5 doses
PRED**

C — Maintenance therapy

6-MP	1.5 mg/kg	PO daily
MTX	0.5 - 1 mg/kg	PO weekly

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* A bone marrow which has active hematopoiesis and less than 5% leukemic blast cells and less than 40% lymphocytes.

** During the last two years of study PRED was given (0.25 mg/kg IT) together with MTX (0.25 mg/kg IT).

The initial complaint in 3 children was parotis infiltration and in another 3, as reported previously[3], arthritis that simulated acute rheumatic fever. One patient was first seen because of renal failure due to marked hyperuricemia. Associated congenital disorders were observed in 3 children, two with Down's syndrome and one with Poland's syndrome.

Results of therapy.

Complete remission was obtained in 197 (75%) out of 262 patients who received a combination treatment of PRED+VCR. Furthermore, remission was obtained by the addition of a third or more agents in 29 children (11%), bringing the total remission rate up to 86% (Table III). Since 15 children (7%) out of the 226 patients who

TABLE III

Remission Induction in 262 Children with Acute Lymphocytic Leukemia

No of patients who achieved remission		Rate of remission %	Treatment
197		75	VCR + PRED
6	29		Ara-C
6			6-MP + MTX + Cyclo
5			Ara-C + Cyclo
4		11	Ara-C + MTX
6			L-Aspa + Cyclo
2			Cyclo
Total 226		86	

TABLE IV

Analysis of 226 Children with Acute Lymphocytic Leukemia who Achieved Remission

	No. of patients	%
Patients who came for follow-up treatment and received their therapy regularly	108	48
Patients who did not come to receive CNS prophylaxis	15	7
Patients who stopped their therapy after receiving CNS prophylaxis while they were in remission	103	45

achieved remission failed to come for follow-up treatment, cranial prophylaxis could be carried out on only 211 (93%) of the patients. However, 103 (45%) of the patients either did not keep their appointments or received irregular chemotheraphy and had to be dropped from the protocol (Table IV). The remaining 108 children (48%) received regular and continuous chemotherapy. Analysis of the treatment results is shown in Table V. Relapse occurred in 49 patients (45%) within 2 to 29 months with a mean duration of remission of 11.5 months in this group. This period was found to be much shorter in the high risk group with a duration of remission of 7.7 months (range between 2 and 13 months). Fifty-three children remained in remission during the period of study. Treatment could be discontinued in only 12 patients (11%) who have remained in initial remission for more than 3 years. Relapse occurred in one girl 9 months after cessation of therapy. Eleven patients are still in remission between 4 months and 2.5 years after discontinuation of therapy.

TABLE V

Analysis of 108 Children with Acute Lymphocytic Leukemia who Received Treatment Regularly

	No. of patients	%
Patients who are still in remission	53	49
Patients who died from infection while they were in remission	6	6
Patients who relapsed	49	45

Since cerebrospinal fluid examinations were not carried out routinely, it is not known whether or not there was a patient who had CNS infiltration at the time of diagnosis. However, 5 children (4.5%) who were given cranial prophylaxis and received their therapy regularly developed leukemic CNS infiltration. Four children (6.4%) out of 62 had CNS complications before 1979. During the last two years, when IT-MTX were given together with IT-PRED, only 1 patient (2%) out of 46 developed CNS infiltration. Leukemic CNS complication was also observed in 4 other patients who received CNS prophylaxis with irregular antileukemic therapy. One patient reported previously developed toxoplasmosis[4]. She is still in remission 2.5 years after cessation of therapy. Six children died from infections during remission (Table VI).

Discussion

The incidence of childhood ALL and AML varies in previously reported series[5,6]. In this study 78% of the patients had ALL and 22% had AML which corresponded to the incidence in some other large series[7,8]. Although there was no peak in age distribution in patients with AML[9], it was between 4 and 7 years of age in children with

TABLE VI

The Causes of Death in 6 Children with Acute Lymphocytic Leukemia During Remission

Case No.	Age (years), sex	Causes of death	Time of death after achieving remission (in months)
1	5 M	Hepatitis	17
2	7 M	Measles	1
3	5/12 M	Purulent meningitis	4
4	7 M	Sepsis (pyocyaneous)	4
5	15 F	" " ?	18
6	4.5 M	" " ?	2

ALL. Although peak incidence is generally seen at 4 years of age in these children, this was not evident in African children with ALL[10,11]. This was explained by the probable leukemia suppressive factors in an African child or underdiagnosis of the disease there[12]. The ratio of males to females in our patients with ALL was found to be 1.8:1. Male preponderance was also shown in other studies from our hospital[13,14]. The ratio of males to females was found to be 1.6:1 in children with AML[9]. However, the reasons why a preponderance of males are afflicted with acute leukemia are not known. The youngest patient in our study was a 2-month-old boy. Since the symptoms did not begin at birth and his general condition was surprisingly good with a negative family history of leukemia, we think that this is an acquired leukemia that started at an unusually early age. Although the prognosis is very poor at this age, our patient achieved remission within 6 weeks and remained in remission for 7 months. He later achieved a second and third remission; he is in relapse now at 1.5 years of age. During the treatment periods he showed no side effects to the antileukemic therapy, and he had no severe infection. He only developed measles without complications.

Although leukemic infiltration of mediastinal lymph nodes is usually seen in males over 5 years of age who have high WBC counts[15], in our series it was seen in 21 (13%) out of 165 male patients, 17 of whom were over 5 years of age. In 6 children (28%) WBC counts were found to be over 100,000/mm^3 and in one over 50,000/mm^3. Mediastinal involvement was also observed in 12 (12%) out of 97 girls. Eight of them were over 5 years of age and 6 (50%) had WBC counts of over 50,000/mm^3. The observation of about the same incidence of mediastinal involvement in both boys and girls was interesting. A detailed study of the membrane phenotypes in these girls could prove useful in understanding these findings.

It has been very well documented that CNS leukemia is seen more often in children with ALL than in children with AML if none has received prophylactic therapy[16]. In

our series, with preventive CNS treatment, only 5 patients developed leukemic CNS involvement. During the last 2 years, when IT-MTX was given together with IT-PRED, only 1 patient developed CNS infiltration. This combination seems to be more effective in prophylactic CNS therapy in our study. None of our patients developed severe complications of prophylactic CNS therapy. In very few patients chemical arachnoiditis, fever and pleocytosis developed. In one patient purulent meningitis was diagnosed after two doses of IT-MTX. With this exception, it was not necessary to stop therapy in any patients. However, more recently, in 3 children not in this group, paralysis of the legs was observed as a possible complication of this therapy.

Our treatment results are strikingly different from those results obtained in developed countries[2,17]. Using a combination of PRED+VCR, the rate of remission in western countries has been over 90% while in our studies it was only 75%. The discrepancy in the achievement of remission may be due to the large number of patients who had high risk factors in this series. Although an immunological classification of our patients could not be carried out in all cases, a small group was studied, showing that 33% of them had T cell leukemia[18], which was higher than in previously reported series[19]. The incidence of mediastinal leukemic infiltration was also found to be strikingly high compared with another large series on childhood leukemia[20].

The prognosis of our patients was also very disappointing. Despite use of the same chemotherapeutic regimen which has resulted in 5-year leukemia-free survival in 50% of childhood ALL in western countries[20,21], antileukemic therapy could be stopped in only 12 patients (11%) in our series. The mean duration of remission in all our patients was 17.6 months. In the high risk group it was 7.7 months. Since addition of a third agent, cytoxan, into the maintenance therapy did not affect the duration of remission, we have now decided to discontinue its use. The prognosis of our patients with AML was also very poor[9]. Since a great majority of our patients came from small villages where the socio-economic conditions of the inhabitants are generally very poor, the different findings in the prognosis of our patients may be due in part to their poor living standards. In fact, 7 out of 12 patients whose treatment could be discontinued came from a comparatively higher social class than the other patients with ALL. In our studies, 15 patients (7%) while in remission, and 103 children (45.5%) after being given CNS prophylaxis, out of a total of 226 children, discontinued their therapy or did not come for follow-up treatment. In another study from the Hacettepe Children's Hospital it was also observed that 60% of 96 patients with ALL had discontinued their antileukemic therapy while they were in remission[14]. This negligent care of the parents concerning their children with leukemia may also be an indication of the low social status of our patients. Therefore our conclusion is that poor social conditions should be considered as a poor prognostic factor in childhood leukemia as proposed previously[22,23].

Although some epidemiological differences in childhood leukemia have been indicated from developing countries, there is not enough documentation about the results of treatment[10-12,24]. However, because of poor socio-economic conditions, it seems to us that in developing countries it is much more difficult to achieve successful results in the treatment of childhood leukemia. We believe that through increased research and concern for those children who are afflicted with acute childhood leukemias it will be possible to change the present dire prognosis and increase the survival rate.

Summary

During the six years from October 1975 to October 1981, 370 children were diagnosed as having ALL at Hacettepe Children's Hospital. Two-hundred sixty-two children were able to enter treatment protocols. Complete remission was obtained in 226 children (86%). In 197 patients (75%) remission was obtained with a combination of PRED + VCR and in 29 patients (11%) by the addition of a third or more agents. One-hundred eighteen patients (52%) who did not keep their treatment appointments or receive irregular chemotherapy were dropped from the treatment protocol. The remaining 108 children received regular and continuous chemotherapy. Relapse occurred in 49 patients (45%) within 2 to 29 months (mean 11.5 months). Treatment could be discontinued in only 12 patients (11%) who remained in initial remission for 3 years. Relapse occurred in only one girl 9 months after cessation of therapy. In our series the CNS relapse rate was 4.5% in 108 patients who received cranial prophylaxis and regular chemotherapy.

The prognosis in our patients was considerably different from the results in developed countries. We come to the conclusion that poor socio-economic conditions should be considered as a poor prognostic factor in childhood leukemia.

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REFERENCES

1. Farber S, Diamond I, Mercer R, et al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl glutamic acid (aminopterin). *N Engl J Med* 238:787, 1948.
2. Sallan SE, Weinstein HJ, Nathan DG. The childhood leukemias. *J Pediatr* 99:676, 1981.

3. Gürgey A, Hiçsönmez G. Artrit ile gelen akut lösemiler. *Çocuk Sağlığı ve Hastalıkları Dergisi* 24: 57, 1981.

4. Hiçsönmez G, Kanra G, Gürsel T, et al. Acute lymphoblastic leukemia and toxoplasmosis. *Turk J Pediatr* 21:24, 1979.

5. Meighan SS. Leukemia in children. Incidence, clinical manifestations, and survival in an unselected series. *JAMA* 190:578, 1964.

6. Burgert EO Jr, Nieri RL, Mills SD, Kinman JW. Nonlymphocytic leukemia in childhood. *Mayo Clin Proc* 48:255, 1973.

7. Pierce MI, Borges WH, Heyn R, et al. Epidemiological factors and survival experience in 1770 children with acute leukemia. Treated by members of Children's Study Group A between 1957 and 1964. *Cancer* 23:1296, 1969.

8. Choi SI, Simone JV. Acute nonlymphocytic leukemia in 171 children. *Med Pediatr Oncol* 2:119, 1976.

9. Hiçsönmez G, Gürgey A, Suloğlu G, et al. Acute myelocytic leukemia in children. *Turk J Pediatr* 20:63, 1978.

10. Fraumeni JF Jr, Miller RW. Epidemiology of human leukemia: recent observations. *J Natl Cancer Inst* 38:593, 1967.

11. Davies JN. Leukemia in children in tropical Africa. *Lancet* 2:65, 1965.

12. Amsel S, Nabembezi JS. Two-year survey of hematologic malignancies in Uganda. *J Natl Cancer Inst* 52:1397, 1974.

13. Berkel İ. Çocuklarda akut lösemiler I. *Çocuk Sağlığı ve Hastalıkları Dergisi* 12:217, 1969.

14. Altay Ç, Yetgin S, Zamani VP, et al. 131 akut lenfoblastik lösemi vakasının analizi ve 96 hastanın kombine ilaç tedavisi ile santral sinir sisteminin methotraxate profilaksisine verdikleri cevap. *Çocuk Sağlığı ve Hastalıkları Dergisi* 22:40, 1979.

15. Sen L, Borella L. Clinical importance of lymphoblasts with T markers in childhood acute leukemia. *N Engl J Med* 292:828, 1975.

16. Price RA, Johnson WW. The central nervous system in childhood leukemia I. The arachnoid. *Cancer* 31:520, 1973.

17. George SL, Aur RJ, Mauer AM, Simone JV. A reappraisal of the results of stopping therapy in childhood leukemia. *N Engl J Med* 300:269, 1979.

18. Yeğin O, Sanal Ö, Ersoy F, et al. Çocukluk çağı akut lenfoblastik lösemi vakalarında lenfosit yüzey markerleri ve klinik önemi. *Çocuk Sağlığı ve Hastalıkları Dergisi* 21:199, 1978.

19. Altman A, Schwartz AD. *Malignant Diseases of Infancy, Childhood and Adolescence* (Vol 18). Philadelphia, London, Toronto: WB Saunders Co, 1978, p. 169.

20. Lampert F. Kombinations-chemotherapie und Hirnschädelbestrahlung bei 530 Kindern mit akuter lymphoblastischer Leukämie. *Dtsch Med Wochenschr* 102:917, 1977.

21. Simone JV, Aur RJ, Hustu HO, et al. Combined modality therapy of acute lymphocytic leukemia. *Cancer* 35:25, 1975.

22. Hann IM, Palmer MK, Morris-Jones PH, Evans DI. Childhood leukemia and social status. *Lancet* 2:1282, 1981.

23. Simone JV, Verzosa MS, Rudy JA. Initial features and prognosis in 363 children with acute lymphocytic leukemia. *Cancer* 36:2099, 1975.

24. Kasili EG, Taylor JR. Leukemia in Kenya. *East Afr Med J* 47:461, 1970.