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Acute Myelocytic Leukemia in Children

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Acute myelocytic leukemia (AML) comprises less than one third of childhood leukemia cases[1, 2] in our patients it accounts for 25 % of all the children with leukemia.

In acute lymphocytic leukemia (ALL) remission can be achieved in 90 % of all patients and in 50 % of these cases a five-year leukemia free survival is possible.[3] However, the remission rate and survival in AML is not as good as in ALL; until 1968 remission was obtained in 66 % of patients,[4] since then remission rates up to 70 % have been reported by combination drug therapy.[5] More recently, better results have been obtained by using cytosine arabinoside (Ara-C). Because few studies on small numbers of patients have been published on the effect of Ara-C in obtaining remission in childhood[6-8], we would like to report our results with Ara-C in children with AML since 1975.

Materials and Methods

Thirty-one children with newly-diagnosed AML, 19 boys and 12 girls with an age range of 4 to 16 years, were entered into this study between July, 1975 and February, 1978. Although during this period 54 patients were diagnosed as having AML, 8 of these patients died during the induction therapy, within two weeks, and the parents of 15 children refused the treatment for their children therefore the thirty-one previously untreated patients were treated according to the protocol outlined in Table I.

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TABLE I

OUTLINE OF THERAPY IN CHILDREN WITH AML

A- Remission Induction (4-8 weeks)			
Ara-C	3 mg/kg I.V. push	4 days/weekly	
VCR	0.05 mg/kg I.V.	1 day/weekly	for 2 weeks
Prednisone	1.5 mg/kg P.O.	daily	
Arc-C	3 mg/kg I.V. push	2 days/weekly	
VCR	0.05 mg/kg I.V.	1 day/weekly	for 6 weeks
B- If Remission Is Obtained*			
Prophylactic cranial irradiation** 2400 rads 6^0 Co 2 years		(2 1/2 weeks)	
C- Maintanance Therapy			
Ara-C	3 mg/kg I.V.	weekly	
Cyclo	7 mg/kg I.V.	weekly	
6MP	1.5 mg/kg P.O.	daily	

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

** Because of short duration of remission and survival it was given only to 17 patients, after that it was discontinued.

The diagnosis of AML was made by the examination of bone marrow aspirated, classification of morphological subtypes of AML was not done.

Results

Age and sex: There was no peak age among our patients as seen in ALL (Figure 1). The male to female ratio was 1.6.

Initial Clinical and Laboratory Findings: Initial leukocyte counts in 4 of the 31 patients were less than 5000/mm^3, in 19 patients less than 26000/mm^3 and in 8 patients ranged from 30,000 to 220,000/mm^3. The percentage of blasts in the peripheral blood at diagnosis ranged from 0 %-100 %. Auer bodies in bone marrow were seen in 9 patients (29 %). Thirty-five per cent of the children had no palpable liver, 65 % had no palpable spleen, and 29 % had neither palpable spleen nor liver. Exopththalmia was present in 6 patients (19 %), of whom 5 were boys. Gingival hypertrophy was seen in only two patients (6 %).

Prognostic Factors: To evaluate the effect of some of the initial clinical and laboratory findings on prognosis, we divided the patients into two groups. Group I consisted of 20 patients (64.5 %) who had achieved remission; Group II consisted of 11 patients (35 %) who could not be induced into remission (Table II, III). As seen in Table II and

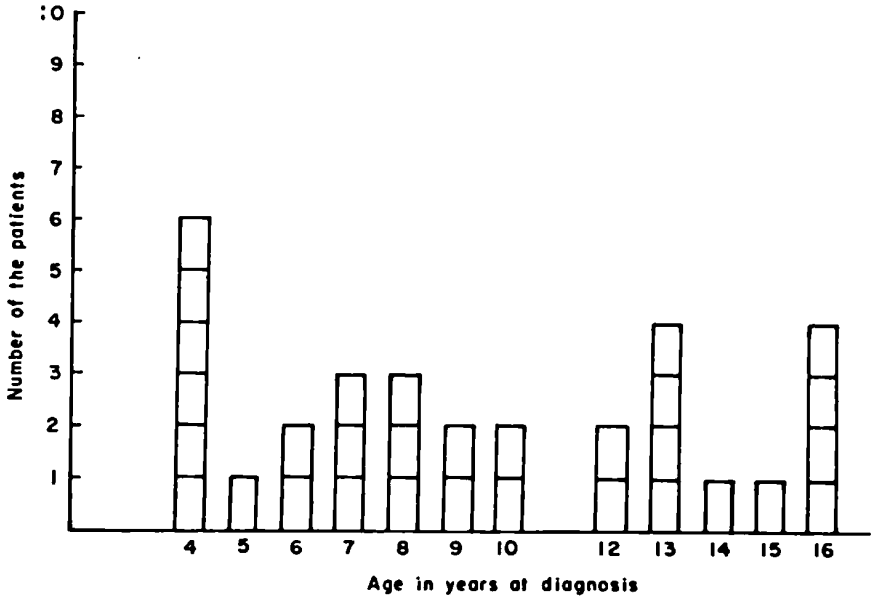

Figure 1
Age distribution of 31 children with AML.

TABLE II

SOME OF THE INITIAL CLINICAL AND LABORATORY FINDINGS IN 20 PATIENTS WITH AML WHO ACHIEVED REMISSION

No of patients	Age (yrs)	Sex	WBC/mm³	% of blasts in peripheral blood	Auer body	Liver (cm)	Spleen (cm)	Exophthalmia
1	16	M	49000	97	+	—	—	—
2	16	M	18200	68	—	—	—	—
3	7	F	2200	18	—	—	—	—
4	8	M	7030	9	—	—	—	+
5	8	M	13600	28	—	—	—	+
6	9	M	31800	5	—	—	—	—
7	13	F	2500	0	+	—	—	—
8	6	M	10000	73	+	1	—	+
9	16	F	3400	0	—	—	3	—
10	5	F	40000	28	—	2	—	+
11	4	M	20000	10	—	3	—	—
12	14	M	26000	85	—	6	6	+
13	9	F	84000	92	+	9	—	—
14	9	F	10000	53	—	5	4	—
15	10	F	6800	0	—	3	2	—
16	16	F	55300	95		6	7	—
17	12	F	9800	65		1	2	—
18	6	M	18000	74	—	8	7	—
19	12	M	8235	0	—	3	—	—
20	13	F	220000	100	—	4	—	—

III, although induction into remission was not affected by age, it seemed to be affected by sex. Eighty-three per cent of the females went into remission while only 52 % of the males went into remission, suggesting that the female sex may have better results in induction remission.

TABLE III

SOME OF THE INITIAL CLINICAL AND LABORATORY FINDIGNS IN 11 PATIENTS WITH AML WHO DID NOT ACHIEVE REMISSION

No of patients	Age (yes)	Sex	WBC/mm³	% of blasts in peripheral blood	Auer body	Liver (cm)	Spleen (cm)	Exophtalmia
1*	13	M	13600	28	+	—	5	—
2	8	M	10000	78	+	5	—	—
3	4	M	15426	100	+	4	3	—
4	4	M	9600	13	—	5	4	—
5	7	M	7000	39	—	2	—	—
6	7	M	18670	36	+	3	—	—
7	16	F	3250	7	—	—	—	—
8	4	M	31800	13	—	5	4	+
9*	4	F	56000	78	—	4	—	—
10*	10	M	23400	2	+	2	—	—
11	7	M	7000	28	—	—	—	—

* Patients who went into partial remission

Although a better survival has been reported[9] in children who had an initial WBC below 10,000/mm³ in our series of children, no prognostic significance of WBC counts below or above 10,000/mm³ was found. Auer bodies were observed in 4 patients in Group I and in 5 patients in Group II. Both liver and spleen were not palpable in 7 patients (35 %) in Group I and in 2 patient (18 %) in Group II. Exophthalmia was observed in 5 patients (35 %) in group I and in 1 patient (10 %) in Group II.

Complications: Since lumbar punctures were not performed routinely at the time of diagnosis, the exact incidence of central nervous system (CNS) infiltration is unknown. One patient out of 17 who had had prophylactic CNS therapy developed CNS infiltration, as did 2 patients who had not had prophylactic therapy. Bilateral mammary and parotis involvement was detected in a 16 year old girl while she was in relapse. Two patients developed zona zoster while they were in remission.

Response to Therapy: Complete remission was induced in 20 of 31 patients (64 %) and partial remission in 3 patients (10 %). The median duration of remission was 4 months with lenght of remission varying between 1.5 and 9 months. The median survival was 7.5 months with the lenght of survival varying from 5 to 12 months.

Discussion

Because of the low incidence and brief duration of remission in patients with AML, there has been constant striving to achieve better results using various metods of combined chemotherapy as shown in Table IV. Cytosine arabinoside has been used by a number of investigators in the treatment of AML in a small number of patients. More recently, Ara-C was used with infusion to synchronize leukemia cells in the DNA synthesis phase (S) of the mitotic cycle by Lampkin et al, and complete remission was reported in 12 out of 16 children with AML in 1976.[15] With the combination of Ara-C and vincristine, we obtained remission in 20 of 31 patients (64 %). Partial remission was seen in 10 % of all of our patients.

TABLE IV

EFFECTIVENESS OF COMBINATIONS OF DRUGS FOR REMISSION INDUCTION OF CHILDHOOD AML

Drugs	No of patients	CR*	References
MTX+Cyclo	2/10	20	10
VAMP	8/12	66	4
Ara-C+Cyclo	4/7	57	2
Ara-C+VCR+Cyclo	27/60	45	11
POMP	29/47	61.7	12
VCR+DNR+Pred	16/42	38	13
Pomp	5/5	100	14
PRAVD	5/9	55	14
Pomp-PRAVD	7/10	70	14
VCR+6MP+6-Azur+Pred	57/86	66	9
Ara-C+Pred	12/16	75	15
Ara-C+VCR+Pred	20/31	64.5	Our study

* CR = complete remission

Abbreviations: MTX=methotrexate ; Cyclo=cyclophosphamide; VAMP= Vincristine+Ara-C+MTX+6-mercaptopurine; VCR=vincristine; POMP=prednisolone+ VCR+MTX+6-MP; PRAVD=prednisolone+VCR+Ara-C+daunomycin; 6MP=6-mercaptopurine; 6-Azur=azauridine; Pred= prednisolone

A peak age distribution for childhood AML was not observed in our patients, confirming the observations of others.[9, 16, 17] Although the causes of the preponderance of males in acute leukemia is not known, the ratio of males to females among our patients was 1.6, which is in accordance with previous reports.[9, 17, 18]

The median survival of our patients was 8 months which was not significantly different from results by others. Although we gave prophylactic CNS therapy to half of our patients with the hope of achieving

better results, duration of remission was still short. For this reason we decided against continuing this prophylactic treatment. In one study, longer survival with initial leukocyte counts below 10,000/mm^3 was reported, but no relationship was found between survival and the percentage of blasts in peripheral blood and the presence of Auer bodies.[9] In our patients, some of the initial laboratory findings such as a WBC below or above 10,000/mm^3, percentage of blasts in peripheral blood, and Auer bodies were not related to prognosis.

Hepatosplenomegaly and exophthalmia at the time of diagnosis were signs of a poor prognosis in our series. Exophthalmia is one of the important clinical features in our patients which has rarely been seen in other countries. Although 83 % of our AML patients who had exophthalmia achieved remission, their duration of remission was very short (between 1.5 and 2.5 months), except for one boy whose leukemia started extramedullarily with the eye involvement 7 months before the diagnosis of AML. Because of the high incidence of exophthalmia as a presenting feature in acute myelocytic leukemia in Turkey[19] these children should specially be studied.

From our study, we assume that, to obtain a good remission rate in AML, the methods that we used (Ara-C in combination with Vincristine) is effective in children. However, short duration of remission and survival of these patients is far from successful maintanance therapy. It has been suggested that immunotherapy and splenectomy increase the survival time of AML patients, however, these results have not been proven.[20-22] Further investigation is needed to discover more ways to help patients with AML to survive longer.

Summary

Thirty-one children (4 to 16 years) newly diagnosed as having AML received combination chemotherapy (Ara-C and VCR) for remission induction. Twenty achieved complete remission, 3 had partial remission. A median duration of hematological remission was 4 months which is far from satisfactory. Exophthalmia and enlarged liver and spleen were signs indicating very poor prognosis in our patients.

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