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Stage IV non-Hodgkin's Lymphoma in Children

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Abstract—*Twenty-five children with previously untreated stage IV non-Hodgkin's lymphoma (NHL) were studied. At the time of evaluation 16 patients were disease-free (64%), with a median observation time of 23 months. Intensive chemotherapy for childhood NHL provides a better outlook for these patients, including those who would be considered high-risk acute lymphoblastic leukemia (ALL).*

INTRODUCTION

THE OUTCOME of non-Hodgkin's lymphoma (NHL) has improved significantly during the last decade as a result of utilizing the principles of therapy which have been used in acute lymphoblastic leukemia (ALL). The prognosis seems to have improved even further as a result of more aggressive chemotherapy protocols in more recent years. The Sloan-Kettering Cancer Center, using the LSA_2-L_2 protocol [1], reported disease-free actuarial survivals of 64 and 65% in two groups of patients with stage IV disease, with median observation times of 48+ and 37+ months.

In spite of the advances in immunological, cytochemical and cytometric techniques, the controversy in differentiating acute lymphoblastic leukemia from stage IV NHL with bone marrow involvement is still unsolved [2, 3]. An arbitrary limit of less than 25% lymphoblasts in the bone marrow has been suggested to be in favor of diagnosis of NHL [4]. Nevertheless, the outcome of those patients diagnosed as ALL, with features such as bulky disease, partial bone marrow involvement, normal hemoglobin, T or B surface markers and higher ages, were dismal when classical ALL protocols were utilized [5].

In this study, patients with these criteria were treated as NHL stage IV regardless of the histopathology.

MATERIALS AND METHODS

Twenty-five consecutive patients with previously untreated NHL, diagnosed and treated in Istanbul Academy Vakif Gureba Hospital, Turkey and King Faisal University, Saudi Arabia from January 1980 to September 1983, were studied. There were 17 Turkish, seven Saudi and one Lebanese children in the study group. All patients had bulky disease at presentation, and the diagnosis was confirmed by tissue biopsy. A modified Rappaport classification was used for histopathological classification [6]. All patients had bone marrow or central nervous system (CNS) involvement at the time of diagnosis.

Criteria used to diagnose the stage IV NHL and differentiate from ALL were obtained by modification of criteria described by Wollner *et al.* [1, 7]: (1) lymph node involvement greater than 3 cm in diameter in one or more regions with partial (less than 25%) or total bone marrow involvement; (2) mediastinal involvement plus partial or total bone marrow involvement; (3) extranodal NHL by the primary site involvement such as gastrointestinal tract, nasopharynx, ovary, bone, etc., with partial or total bone marrow involvement; and (4) any of the above without bone marrow involvement but with CNS involvement.

Bone marrow blast morphology was evaluated according to the French-American-British (FAB) classification [8].

All patients received the same treatment, consisting of vincristine, prednisone, cyclophosphamide, L-asparaginase, intrathecal methotrexate and intermediate-dose methotrexate during the induction and consolidation, and vincristine, prednisone, cyclophosphamide, methotrexate and 6-mercaptopurine for the maintenance therapy for 24 months (Table 1).

No debulking surgery was attempted except in two cases of Burkitt's lymphoma without CNS involvement. In one of these patients approximately 50% of the tumor could be removed, while the other had more than 90% removal of tumor.

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RESULTS

Table 2 shows the patient population, histological subtype, bone marrow involvement, FAB classification of bone marrow blasts, initial white blood cell count, primary involvement site and survival of the 25 patients under study. There were 16 boys and nine girls in the study group (male:female = 1.8:1). Mean and median ages were 7 yr.

Histologically, all patients were classified as diffuse NHL. There were three histiocytic (H), seven lymphoblastic convoluted (LC), five lymphoblastic non-convoluted (LNC), four undifferentiated Burkitt's (UB) and six undifferentiated non-Burkitt's (UNB) lymphoma. Twenty-two patients had bone marrow involvement: 14 with greater than 25% and eight with less than 25% blasts in the bone marrow. All patients with greater than 25% involvement had circulating blasts in the peripheral blood, while only two of the eight patients with less than 25% had blasts in the periphery.

Table 1. Treatment scheme for children with non-Hodgkin's lymphoma

Induction and consolidation (week)											Maintenance (week)									
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21...104
V	V	V	V				V		V			V				V				
C	C	C	C									C				C				
	m	m	m	m		M		M		M		m	m	m	m	m				
				Asp.																
				P				P		P			P				P			
												**********								

V = vincristine, 1.5 mg/m² i.v.; C = cyclophosphamide, 400 mg/m² i.v.; m = methotrexate, 15 mg/m² i.t.; P = prednisone, 40 mg/m²/day p.o.; Asp. = L-asparaginase, 1000 u/kg/day i.v. for 10 days; M = methotrexate, 500 mg/m² i.v. infusion in 24 hr + 15 mg/m² i.t.; m = methotrexate, 15 mg/m²/week p.o. for 2 yr; ** = 6-mercaptopurine, 75 mg/m²/day p.o. for 2 yr.

Table 2. Clinical & laboratory characteristics of 25 children with stage IV non-Hodgkin's lymphoma

Patient No.	Age	Sex	Histologic type	Bone marrow >25%	FAB type	WBCs >20,000	Primary involvement	Survival (months)
1	6	F	H	-	L_1	-	IA	35+
2	5	M	H	-	L_1	-	IA	37+
3	9	F	LC	+	L_2	+	PA	7*
4	10	F	LC	(CNS)	-	+	M+PN	6*
5	5	M	UB	(CNS)	-	-	IA	4*
6	8	M	LNC	+	L_1	+	PN	25+
7	6	M	UB	-	L_3	+	IA	8*
8	8	F	LC	+	L_1	+	PN	25+
9	12	M	LC	+	L_2	+	M+PN	12*
10	5	F	UB	-	L_3	-	IA	16+
11	6	M	UNB	-	L_1	-	IA	23+
12	7	M	LC	+	L_2	+	PN	15*
13	4	F	H	-	L_1	-	IA	31+
14	3	F	LC	-	L_1	-	IA	33+
15	6	M	UB	(CNS)	$-_1$	-	IA	6*
16	7	M	LNC	+	L_1	-	PN	19+
17	11	M	UNB	+	L_1	+	PN	12*
18	11	M	LNC	+	L_1	-	IA	23+
19	7	M	UNB	+	L_1	-	IA	21+
20	8	M	LNC	+	L_1	+	M+PN	9*
21	7	M	LNC	+	L_1	-	PN	29+
22	4	F	LC	-	L_1	-	PN	25+
23	7	M	UNB	+	L_1	+	PN	19+
24	8	M	UNB	+	L_1	+	PN	19+
25	5	F	UNB	+	L_1	+	PN	16+

* = expired; IA = intra-abdominal; PN = peripheral nodal; M = mediastinal; H = histiocytic; LC = lymphoblastic convoluted; LNC = lymphoblastic non-convoluted; UB = undifferentiated Burkitt's; UNB = undifferentiated non-Burkitt's.

Three patients with L_2 FAB classification were histologically LC type, and all died at 7, 12 and 15 months following diagnosis. Two of the patients with UB had L_3 FAB classification. The remaining 20 patients were classified as FAB-L_1.

Three patients, one with LC and two with UB, had CNS involvement at the time of diagnosis. One other patient with UNB developed CNS involvement during the course of his disease, 12 months after the diagnosis.

Twelve of the 25 patients (48%) had initial WBCs greater than 20,000/mm^3 at the time of diagnosis. Seven of the nine patients who died had initial WBCs of greater than 20,000/mm^3.

Primary sites of involvement were: 11 intra-abdominal (IA) (44%), 11 peripheral nodal (PN) (44%) and three peripheral nodal plus mediastinal (PN + M) (12%).

Histological subtypes of patients with partial bone marrow involvement were: H = 3, LC = 3, UB = 4, UNB = 1. Bone marrow involvement greater than 25% were histologically distributed as: LC = 4, LNC = 5, UNB = 5. While it is worth noting that all patients with UB had less than 25% bone marrow involvement, the number of patients with different histological subtypes was too small for a meaningful statistical evaluation of its relation to the degree of bone marrow involvement.

Survival

Twenty of 25 patients (80%) achieved complete response (complete disappearance of bulky tumor and M_1 bone marrow).

At the time of evaluation, nine patients had relapsed and died 4, 6, 6, 7, 8, 9, 12, 12 and 15 months following diagnosis. Of these patients, five (5/14) had greater than 25% of bone marrow involvement, three had no involvement of the bone marrow but CNS involvement and one (1/8) had less than 25% involvement.

Three patients with CNS involvement at the time of diagnosis and three other patients with mediastinal mass were among those who had expired. Histological subtypes of the expired patients were: LC = 4, LNC = 1, UB = 3 and UNB = 1.

Partial regression followed by a local recurrence occurred in three patients with UB lymphoma.

Thirteen patients would have been considered 'poor prognostic ALL' by initial WBC count and/or lymph node involvement. Five of the deaths were among these 13 patients, at 7, 9, 12, 12 and 15 months after diagnosis. The remaining eight patients (62%) are alive 16–29 months (mean 22+) after the diagnosis. Sixteen of the 25 patients (64%) are disease-free, with a median observation time of 23+ months, and eight of these patients are off chemotherapy (Fig. 1).

Toxicity

Toxicities, in general, were within the acceptable range, and most of them could be managed in the outpatient setting with dose modification and oral hydration. None of the deaths were attributed to drug toxicity.

All patients developed neutropenia of less than 2000/mm^3 during the induction therapy. Two patients developed septicemia (*Streptococcus pneumococcus* and *Staphylococcus aureus*) in the third week of therapy but recovered completely following the appropriate treatment. The majority of patients (15/20) required progressive decrease in the cyclophosphamide dose after 6 months of maintenance therapy because of persistent neutropenia. In seven of the 14 patients who were followed beyond 12 months, cyclophosphamide had to be discontinued completely.

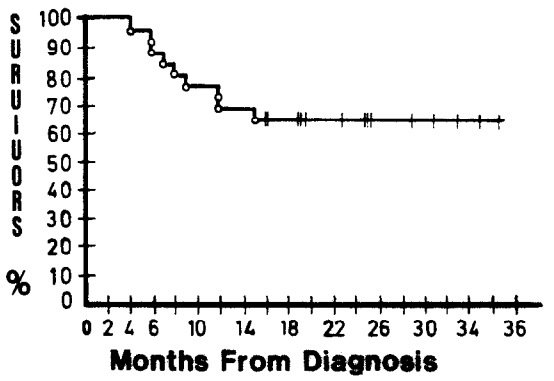

Fig. 1. Survival of children with stage IV non-Hodgkin's lymphoma.

DISCUSSION

Prognosis in childhood NHL has shown dramatic improvement during recent years. This improvement has been attributed to the intensive multi-agent chemotherapy with radiation to the bulky tumor [9, 10]. In a randomized trial, Murphy [11] was not able to demonstrate the therapeutic advantage of including radiation in the treatment. In our group of patients who were treated with chemotherapy alone, local recurrence occurred in only three of the patients who had histological subtype UB. The overall survival of 62% seems comparable to other series where the radiation was utilized. Considering the long-term hazards of irradiation, the efficacy of this mode of treatment in advanced NHL must be clarified in a larger group of patients by a randomized study.

The controversy in distinguishing NHL with bone marrow involvement from high-risk ALL

seems to be approaching a new stage since the use of intensive multi-agent chemotherapy by Wollner *et al.* [10]. With the conventional ALL chemotherapy, long-term survival of patients with 'high-risk ALL' has been less than 20% [12, 13]. However, in a recent study utilizing the LSA_2-L_2 protocol [1], the survival increased to 73% in this group of patients. In our study group, 13 patients that could be considered 'high-risk ALL' showed a disease-free survival of 62% after a follow-up ranging from 16 to 29 months. Even more interesting is the clinical behavior of these patients: they resemble more NHL than ALL in terms of very few or no relapses occurring after 18 months of disease-free survival. In our group of patients the latest relapse occurred at 14 months following the diagnosis. Nevertheless, a longer follow-up is necessary to assess this behavior.

It was not possible to correlate partial or complete bone marrow involvement to the histological subtypes in our small group of patients. However, there were five deaths among 14 patients with complete bone marrow involvement. These results seem to be different to those in a previous report [1]; however, the numbers are too small in our group for a conclusive evaluation.

In our group of patients the unfavorable prognosis signs were CNS involvement and L_2 bone marrow: all six patients with these features were dead 4-15 months following the diagnosis.

Intra-adbominal tumor as the primary site of involvement in our series of stage IV patients was 44% (11/25), in contrast to 14% in Sloan-Kettering stage IV patients [1]. When we reviewed all our patients with different stages of NHL, we found out that 70% had intra-abdominal tumor as the primary site of involvement. This finding correlates well with a previous report from Saudi Arabia in which intra-abdominal involvement was reported to be 79% [14]. In a review of a large series of NHL of all stages [15], intra-abdominal presentation was found in 35% of American children with non-Hodgkin's lymphoma. Intra-abdominal presentation of NHL seems to be less frequent in advanced stage NHL in both Middle East and Western populations. However, this presentation is more common in the Middle East when all stages are combined. The etiology of this geographic difference remains unsolved.

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