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Childhood non-Hodgkin's lymphoma in Egypt: preliminary results of treatment with a new ifosfamide-containing regimen

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Summary. Pediatric non-Hodgkin's lymphoma (NHL) constitutes 16% of pediatric malignancies reported to the National Cancer Institute (NCI) in Cairo. Since July 1985, we have treated 39 previously untreated pediatric NHL cases younger than 16 years of age (mean, 7.6 years) with a new protocol consisting of alternating cycles: regimen A comprised cyclophosphamide, high-dose ara-C, Adriamycin and vincristine; regimen B consisted of ifosfamide, methotrexate and VP16, with intrathecal methotrexate. Diagnoses included 20 abdominal masses, 16 peripheral lymphadenopathies and 6 bony lesions. Histopathology according to the working formulation revealed 21 cases of small non-cleaved lymphoma, 6 lymphoblastic, 5 large-cell and 7 unclassified diffuse lymphomas. Responses were complete in 31 cases (82%) and partial in 4 cases (10%), and no response was obtained in 4 cases (8%). Overall survival was 82% in limited disease and 60% in extensive disease at 28+ months. This short-term ifosfamide-containing regimen proved its efficacy, with results matching those of other regimens used in the United States and Europe.

Introduction

In patients younger than 16 years of age, childhood cancer represents 7.2%–8.5% of all malignancies in Egypt [1, 2]. Malignant lymphomas, including 16% non-Hodgkin's lymphoma (NHL), account for 50% of the childhood cancers reported to the National Cancer Institute (NCI) in Cairo; leukemias anount to 40% and solid tumours, 10% [5, 7]. In a study of 298 cases of pediatric NHL compiled between January 1975 and December 1984, there was a boy-to-girl ratio of 3:1 and a mean age of 8.2 years. Histopathology according to the working formulation showed that 7.8% were low-grade malignancies, 60% were intermediate-grade and 32.2%, high-grade. At initial presentation, 46.3% of the cancers were nodal and 53.7% were extra-nodal, the majority of the latter occurring in the gastro-intestinal tract (74.5%). In all, 35% of the patients had B symptoms. Staging according to the Murphy system [12] revealed that 42.5% of cases were stages I and II and 57.5% were stages III and IV. All patients were treated by chemotherapy, surgery being used for de-bulking large abdominal masses or for abdominal emergencies; radiotherapy was used for large mediastinal masses and/or cranial irradiation [7].

The objective of the present study was to determine the feasibility and efficacy of an intensive, short-term chemotherapy protocol for the treatment of childhood NHL. In our center we have previously used the St. Jude protocol for the treatment of childhood NHL [12], but the duration of this regimen (2 years) increases the overall cost of treatment and risk of infection; furthermore, patients from low socioeconomic classes are less likely to comply with the regimen. We incorporated ifosfamide and VP16 into the regimen since these drugs are known to be effective against lymphoma [4, 6], and we anticipated a population of patients with a generally higher tumour burden than usually found in Europe or the United States.

Materials and methods

The study was carried out between July 1985 and December 1986 in 39 consecutive patients with NHL who reported to the pediatric unit of the Medical Oncology Department, NCI, Cairo. Every patient was subjected to a thorough clinical examination, complete blood count, bilateral iliac-crest bone-marrow biopsies, determinations of sedimentation rate and serum uric acid, a liver biopsy, liver function tests (SGOT, alkaline phosphatase and serum bilirubin), renal function tests (serum creatinine and blood urea) and a CSF examination, as well as a chest X-ray, abdominal sonography and X-rays of other bones, if needed; computerized axial tomography (CAT) was carried out in a few cases. Laparotomy was done in patients with an abdominal or pelvic mass and for abdominal emergencies such as intussusception and/or intestinal obstruction. Diagnosis was established by tissue biopsy, and histo-pathological diagnosis was done according to the working formulation. Staging was carried out according to the Murphy staging system [12].

There were 32 boys and 7 girls, for a ratio of 4:1, and the age range was 10 months to 16 years, with a mean age of 7.6 years. In all, 26 patients were stage III, 10 were stage II, 2 were stage I and 1 was stage IV. The sites involved are shown in Table 1. Abdominal tumours occurred in 20 cases, including involvement of the small intestine (particularly the terminal ileum and ileo-cecal region) as well as the colon and mesenteric lymph nodes. Peripheral lymph-

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Table 1. Involved sites in 39 patients with non-Hodgkin's lymphoma

	Number
All abdomen	20
Peripheral lymphadenopathy	16
Mediastinal	6
Jaw	3
Other bone	3
Nasopharynx	1
CNS	1

adenopathy, mainly cervical, was encountered in 16 cases, and a mediastinal mass was detected in 6 cases. Bones involved included the jaw in 3 cases and other bones in another 3 cases. The nasopharynx was involved in 1 case and the CNS (CSF malignant pleocytosis), in 1 case. A total of 21 cases were histologically classified as small, non-cleaved lymphomas; there were 6 lymphoblastic, 5 large-cell and 7 unclassified, diffuse lymphomas.

Once disease had been diagnosed and staged, treatment was commenced following a regimen of alternating cycles (A and B) containing different drugs. Patients were classified as low risk if all of an abdominal tumour was resected or there was a single extra-abdominal site of involvement other than the mediastinum. All other patients were classified as high risk. The low-risk group received four alternating cycles of therapy: A, B, A and B. The high-risk group received eight alternating cycles of therapy: A, B, A, B, A, B, A and B. Intrathecal (i.t.) therapy was given for the only first two cycles in low-risk patients and for the first four cycles in high-risk patients (Tables 2, 3). Blood counts were checked every 3 weeks and subsequent cycles were initiated as soon as the neutrophil count reached $\geqslant 1{,}000/mm^3$ and the platelet count was $\geqslant 100{,}000/mm^3$.

Surgical resection of intra-abdominal masses was attempted with the objective of completely removing the disease. For the initiation of therapy all patients were hospitalized, well hydrated, alkalinized, given allopurinol and treated with diuretics when necessary to maintain a good urinary output. Broad-spectrum parenteral antibiotics were used empirically for the management of febrile episodes associated with leucopenia, and daily oral trimethoprin (150 mg/m^2) was used prophylactically against *Pneumocystis carinii*. Packed RBC transfusions were used to correct severe anemia and platelet concentrates, for control of bleeding episodes.

After the patients had recovered from each cycle, response was assessed by physical examination, blood counts, examination of marrow aspirates and CSF, and repetition of initially positive staging studies. A complete response was defined as the disappearance of all evidence of tumour and a partial response, as a 50%–99% reduction of all tumour mass; a relapse was defined as the reappearance of lymphoma at any site. The disease-free interval was measured from the start of treatment to the date of relapse or of the last follow-up.

Table 2. Chemotherapy regimen A[a]

Cyclophosphamide	800 mg/m^2 i.v. on day 1, 200 mg/m^2 i.v. on days 2–4 (15-min infusion)		
Vincristine	1.4 mg/m^2 on days 1, 8, 15 (push injection)		
Adriamycin	20.0 mg/m^2 on days 1, 2 (push injection)		
Ara-C[b]:			
1st cycle	0.5 g/m^2 i.v. on day 1 at 0 and 12 h	}	each Ara-C dose infused over 3 h
2nd cycle	1.0 g/m^2 i.v. on day 1 at 0 and 12 h	}	
3rd cycle	2.0 g/m^2 i.v. on day 1 at 0 and 12 h	}	
Ara-C i.t. on day 4	$\geqslant$3 years	70 mg	
	2 years	50 mg	
	1 year	30 mg	
	<1 year	20 mg	
MTX i.t. on days 8, 12	$\geqslant$3 years	12 mg	
	2 years	10 mg	
	1 year	8 mg	
	<1 year	6 mg	

[a] Blood count to be checked three times/week; each cycle to be started at a neutrophil count of $\geq 1{,}000/mm^3$ and a platelet count of $\geq 100{,}000/mm^3$

[b] Ara-C dose on each cycle not to be escalated if neutropenia (<500 neutrophils) lasted larger than 5 days on the previous cycle

Table 3. Chemotherapy regimen B[a]

Ifosfamide[b]	1,200 mg/m^2 i.v. daily, days 1–5 (30-min infusion)
VP16	60 mg/m^2 i.v. daily, days 1–3 (1-h infusion)
Methotrexate	15 mg/m^2 i.v. daily, days 1–3 (push injection)
Vincristine	1.4 mg/m^2 (push injection)
Ara-C i.t.	dose as for regimen A, days 1, 4
MTX i.t.	dose as for regimen A, days 8, 12

[a] Blood count to be checked three times/week; each cycle to be started at a neutrophil count of $\geq 1{,}000/mm^3$ and a platelet count of $\geq 100{,}000/mm^3$

[b] Mesna 400 mg/m^2 i.v. prior to ifosfamide and 400 mg/m^2 every 4 h × 3 doses after each dose of ifosfamide

Results

Responses were complete (CR) in 31 cases (82%) and partial (PR) in 4 (10%). There was no response (NR) in three cases (8%), and early death occurred within 1 week in one patient. The PR and NR patients were designated as treatment failures (TF). Amongst the 31 complete responders, there were 11/12 patients (91.67%) with limited disease (stages I and II) and 20/26 cases (77%) of extensive disease (stages III and IV). In patients with limited disease who attained CR, one patient died after 2 months, one relapsed after 10 months and nine are still alive, resulting in an overall survival of 82% at 28+ months (Fig. 1). In patients with extensive disease who achieved CR, 2 died after 2 months, 6 relapsed and 12 are still alive, for an overall survival of 60% at 28+ months (Fig. 1).

All patients with diffuse large-cell, diffuse lymphoblastic and diffuse, unclassified lymphoma achieved CR, as opposed to CR in 14/21 cases (66.7%) of diffuse, small, non-cleaved lymphoma. None of the latter has yet relapsed (28+ months), although 5/6 cases of lymphoblastic lymphoma, 1 patient with large-cell lymphoma and 1 with undifferentiated lymphoma suffered relapses. All relapses occurred within 2–10 months after the achievement of CR, except one who relapsed at 21 months. Of 39 patients 13 died, 1 during the 1st week of therapy, 3 while in CR, 1 of generalized herpes simplex and 2 of pneumonia. Another 6 patients died of progressive disease; they included

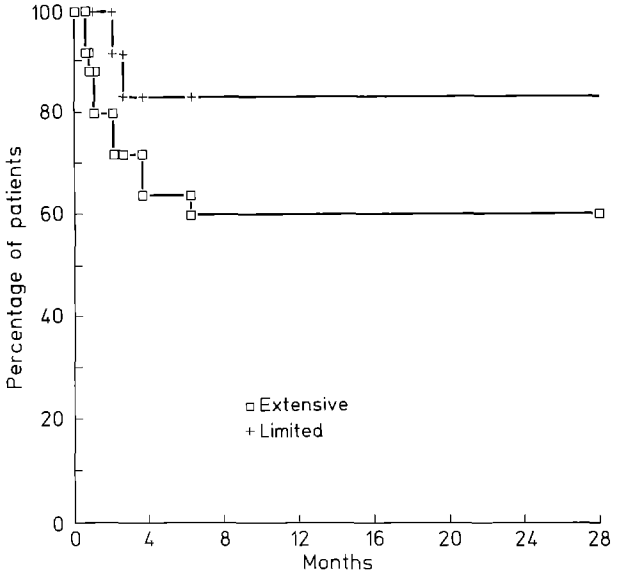

Fig. 1. Overall survival in patients with extensive vs limited disease

2 who relapsed after achieving CR and 4 who were in PR. The three non-responders died of abdominal fistulae during the first few months of therapy.

The overall survival of the 39 patients was 66% (Fig. 2); treatment was well tolerated by all patients. Toxicities in all of the 195 cycles given to the patients included grade 3 alopecia, grade 3 nausea and vomiting and grades 2 and 3 mucositis. Hematological toxicities occurred as grades 2 and 3 anemia in 90% of the cycles, grades 2 and 3 leucopenia in 70% of the cycles and grades 1 and 2 thrombocytopenia in 90% of the cases. Dysuria and microscopic hematuria were encountered in 6% of regimen A cycles containing cyclophosphamide, whereas only one case of hemorrhagic cystitis was observed in regimen B cycles containing ifosfamide and mesna. No neurotoxicity was detected. We noticed that the toxicities were more frequent with regimen A than with regimen B.

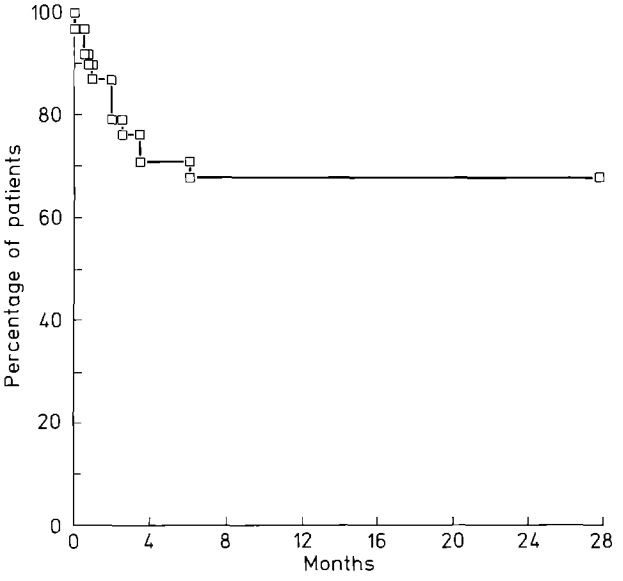

Fig. 2. Overall survival in all patients

Discussion

The prognosis for children with NHL has dramatically improved in the past decade. A review of the literature in 1963 [9] revealed that < 10% of children with NHL became long-term survivors. Subsequent reviews [10] showed that by the 1970s, 30% of children achieved long-term survival. Subsequently aggressive chemotherapy with cranial irradiation and maintenance chemotherapy have increased the remission rate to 60%–90% and long-term survival to 50%–80%. Since few relapses occur in these children beyond 12 months after the initiation of therapy, current studies are exploring a stategy of intensive, short-term chemotherapy.

The present study was designed to test the feasibility of such an intensive, short-term treatment protocol. We included ifosfamide and VP16 since both are known to be effective against NHL. Our preliminary results demonstrate that this protocol can be successfully conducted, that the toxicity is acceptable and that the results of treatment with ifosfamide- and VP16-containing regimens are similar to those of intensive chemotherapy protocols currently used in other centers [13]. If the incidence of complications due to a high tumour burden (usually encountered in the present studies) were reduced, the results would appear to be comparable with those of the best available protocols. Therefore, our future attempts will focus on decreasing the incidence of death due to complications from post-surgical tumour treatment as well as possibly shortening or further simplifying such treatment.

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