MALIGNANT LYMPHOMA IN CHILDREN: UNIVERSITY HOSPITAL, KUALA LUMPUR 1967 — 1980

D Sinniah
B E Tan
H P Lin

SYNOPSIS

Malignant lymphoma constitutes the third most common childhood malignancy seen at the University Hospital, Kuala Lumpur and can be categorised into Hodgkin's disease and non-Hodgkin's lymphoma. Both diseases demonstrate a higher preference for Chinese males. The majority of patients presented with stage IV disease. High default rate and poor compliance to treatment were associated with poor overall cure rates but encouraging results have been obtained in those who adhered to therapy. There is an obvious need to educate the public on the improved outlook for childhood malignancies and for earlier referral to help reduce the higher mortality and morbidity associated with advanced disease.

INTRODUCTION

Malignant lymphoma is the third most common childhood cancer in the United States and can be categorised into Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The introduction of the MOPP regimen by De Vita et al (1) has revolutionised the treatment of HD and has not been surpassed by alternative programmes. The prognosis for NHL in children in the past has been dismal but more recent combination therapy protocols have produced very encouraging results (2, 3).

With improvements in socioeconomic conditions and control of infectious disease, malignancy is emerging as a major paediatric problem in West Malaysia (4). While limited epidemiological and clinical data are available for leukaemia and several solid tumours (4,5,6), there is no data on childhood lymphoma. Although a high prevalence of lymphoma has been described in parts of Africa (7) and India (8), the situation is Malaysia, where there is no comprehensive register of cancer cases and where only 32% of all deaths are medically certified, is not known.

This review of the epidemiology, clinical and pathological features and outcome of treatment in all cases of childhood HD and Non-HD lymphoma seen at the University Hospital (UH), Kuala Lumpur, over a 13 year period compares the frequency of this tumor with that of other countries.

MATERIAL AND METHOD

All cases of malignant lymphoma admitted to the Paediatric Unit, University Hospital, Kuala Lumpur, during the period 1967 through March 1980 were reviewed. The diagnosis was based on biopsy findings on relevant tissue. Two broad categories were recognised: Hodgkin's disease and non-Hodgkin's lymphoma. The histopathological typing of HD was based on the Rye modification of the classification of Lukes & Butler (9) into lymphocyte predomint (LP), nodular sclerosing (NS), mixed cellularity (MC) and lymphocyte depleted subtypes (LD).

Department of Paediatrics
Faculty of Medicine
University of Malaya
Kuala Lumpur

D Sinniah, MA, MD, FRACP, FRCPI, DCH.
Associate Professor

B E Tan, MBBS. Medical Officer

H P Lin, MBBS, FRACP, MRCP, DCH.
Associate Professor

NHL is usually typed according to Rappaport's classification into lymphocytic, histiocytic and diffuse or nodular histological patterns. The lymphocytic variety is further subdivided into poorly and well differentiated subtypes. There is in addition Burkitt's lymphoma and an unclassified group of lymphoma. The prognostic usefulness of this classification while demonstrable in adults has not been established in childhood where the majority of cases (97.2%) are of diffuse histological type (10) and distinguishing the rare child with nodular NHL is largely an academic exercise.

For staging the Ann Arbor System was used for HD (11) (Table I), and for NHL, the St. Judes Children's Research Hospital system (12) — see Table II. The distinction between NHL with marrow involvement and lymphomatous acute lymphatic leukaemia is ill defined due to common clinical features and probable similar pathogenesis. Analysis of immunological surface markers was not conducted to categorise the tumors. There was no standard treatment protocol and treatment was individualised along the same lines as for acute lymphoblastic leukemia in some of the recent cases.

The clinical details, treatment and outcome in our series were reviewed and compared with other countries. Complete remission was defined as complete disappearance of all evidence of disease and resolution of all symptoms and laboratory evidence of disease. Staging laparotomy was not performed routinely and was carried out in 3 cases of HD: in 1 as part of treatment for abdominal disease and in another with clinical stage II disease to determine the initial treatment plan and in the third as a diagnostic measure.

RESULTS

Epidemiology

During the index period, 350 cases of childhood malignancies, including leukaemia were admitted to the Unit. Lymphoma comprised 7.1% of these cases. HD accounted 14 cases and NHL for all cases, the latter included one case of Burkitt's lymphoma.

Table I. Staging Classification Proposed by Ann Arbor Conference

Stage	Description
I	Involvement of a single lymph node region or a single extra lymphatic organ or site (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm or localised involvement of an extra lymphatic organ and one or more lymph node regions (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm which may also be accompanied by a localised involvement of extra lymphatic organ (IIIE) or spleen (IIIS) or both (IIISE).
IV	Diffuse involvement of one or more extra lymphatic organs with or without associated lymph node enlargement. The reason for classifying the patient as stage IV should be identified by further defining the site by a symbol: A = asymptomatic; B = Fever, sweats, or weight loss, 10% of body weight.

Table II. Staging System for Childhood NHL (1)

Nodal	Stage	Extra Nodal
One site	I	Single site.
Two or more sites same sides diaphragm	II	Single tumour with regional nodes: 2 single tumours + regional nodes same side diaphragm.
		Primary gut tumour in ileocaecal area + associated mesenteric nodes
Two or more sites above and below diaphragm	III	Two or more sites above and below diaphragm
Primary intrathoracic tumours (mediastinal)		Primary intrathoracic tumours (mediastinal; pleural, thymic).
Extensive primary intraabdominal		Extensive primary intraabdominal.
Any of above with initial CNS and/or marrow involvement	IV	Any of above with initial CNS and/or marrow involvement

Hodgkin's Disease

These accounted for 4% of all malignancies in childhood. The 14 cases comprised 9 Chinese, 4 Indians and 1 Malay. There appears to be a lower incidence in Malays compared with the other races. There were 11 males and 3 females with a median age of 9 years and range 3 to 12 years. The male predominance observed here has also been noted in other series (13).

The presenting clinical signs are seen in Table III.

Table III. Presenting symptoms and signs in 14 patients with Hodgkin's disease

Symptoms	No. of patients	Signs	No. of patients
Fever	12	Hepatomegaly	9
Weight loss	7	Gen. Lymphadenopathy	9
Anorexia	4	Emaciation	6
Abdomen swelling	4	Abdominal mass	5
Neck swelling	4	Pallor	5
Lump in groin	2	Local lymphadenopathy	4
Cough	2	Splenomegaly	4
Vomiting, bone pains lethargy	1	Pleural effusion, oedema, ascites, jaundice, impetigo, clubbing	2
Sweating	1		1

The average duration of symptoms prior to diagnosis was 1.4 years and ranged from 3 months to 3 years. Six of the patients had symptoms for more than 2 years before admission. The commonest symptoms were fever, weight loss, glandular swelling and anorexia; the commonest signs were lymphadenopathy, hepatosplenomegaly and abdominal mass.

Pathological and Staging

Diagnosis of HD was based on biopsy of cervical nodes in 9 cases, abdominal nodes in 3 and axillary and inguinal nodes in one each respectively. Bone marrow infiltration was observed in 1 patient and reactive plasmacytosis with abnormal immunoglobulin production in another. Nine children had significant anemia (Hb < 10 g/dl), the mean Hb was 8 g/dl and ranged from 3.6 — 12.7 g/dl. Total white blood cell counts were normal and eosinophilia was not a prominent feature. The ESR ranged from 8-157 mm/hr. Liver function tests were abnormal in one case only. The histopathological typing and staging of the 14 children is seen in Tabe IV.

Table IV. Histopathological typing and staging of 14 cases of HD

Stage	Histopathological sub-type				
	LP	NS	MC	LD	Total
I	1	0	1	0	2
II	1	0	2	0	3
III	0	0	1	0	1
IV	1	0	6	1	8
Total	**3**	**0**	**10**	**1**	**14**

The majority had advanced disease at the time of diagnosis and the most common histological type was mixed cellularity followed by lymphocyte predominant disease.

Outcome of Treatment

Details of treatment and outcome in individual cases are shown in Table V. Eight of the 14 patients either refused treatment or did not return to complete therapy. Only 6 patients received an adequate trial of chemotherapy either alone or in conjunction with radiotherapy. One patient died of septicemia whilst in remission and another was lost to follow up 2 years after admission when the patient developed resistance to MOPP and ABVD regimes. The other 4 patients are alive and well at 3, 8, 8 and 8 years respectively. One child developed an extra pyramidal tract syndrome after 17 courses of MOPP (14).

Non-Hodgkin's Lymphoma

10 cases of NHL, excluding one child with Burkitts lymphoma reported previously by Sivanesan and Sinniah (15), were admitted during the index period and comprised 7 Chinese, 2 Malays, and 1 Indian. They included 8 males and 2 females with a median age of 2-3 years; ranging from 8 months to 11 years. Their presenting clinical signs are shown in Table VI. The average duration of symptoms varied from 3 days to 15 months. The commonest symptoms were fever, anorexia and neck swelling; the commonest signs were hepatomegaly, lymphadenopathy and splenomegaly. The clinical staging, treatment and outcome in the 10 patients are shown in Table VII.

All 4 children with mediastinal NHL were male, 3 had head/neck disease, 1 had abdominal NHL and in 2 cases the disease was too generalised to be certain of the site of origin of the malignancy.

Table V. Clinical staging and outcome of treatment in 14 cases of Hodgkin's disease in childhood.

Case No.	Age	Stage/cell type		Treatment	Outcome
1	9	I	LP	nil	AOR
2	4	IB	MC	nil	AOR
3	5	IIA	LP	Splenectomy, RT COP x 18 mos	A + W 8 yrs
4	5	IIA	MC	nil	AOR
5	5	IIA	MC	nil	AOR
6	9	IIIB	MC*	RT, MOPP x 6	A + W 3 yrs
7	11	IVB	MC	Mustine HCl — then pulmonary disease at 6 mos	LTFU
8	6	IVB	MC	VBL + CPM	AOR 6 mos.
9	12	IVB	MC	nil	AOR
10	12	IVB	LP*	nil	AOR
11	3	IVB	MC	MOPP x 17	A + W 8 yrs
12	9	IVB	LD	MOPP x 17	A + 8 yrs (EPTS)
13	12	IVB	MC*	MOPP x 4	died septicemia (8 mos) in remission
14	11	IVB	MC	MOPP x 6 ABVD x 6	resistant to MOPP LTFU at 2 yrs

* abdominal; AOR — went home at own risk against advise; A + W — alive and well; LTFU — lost to follow up; EPTS — extrapyramidal tract syndrome; VBL — vinblastin; CPM — cyclophosphamide; RE — radiotherapy.

Table VI. Presenting symptoms and signs in 10 patients with NHL

Symptoms	No. of cases	Signs	No. of cases
Fever	5	Lymphadenopathy	7
Anorexia	5	Hepatomegaly	7
Neck swelling	3	Splenomegaly	3
Bone pain	2	Pallor	2
Cough	2	Bruising	1
Vomiting	1		
Weight loss	1		

Outcome of Treatment

Five patients refused treatment or failed to return for follow up. One patient with stage III disease died within 3 weeks of hemothorax while another died nine months after radiotherapy. Only 3 patients received an adequate trial of chemotherapy. They include one who complied poorly to treatment and returned from a visit to China with CNS relapse. Another patient received COAP therapy followed by MOPP when he relapsed a year later. His disease con-

verted to ALL which was then treated with Memphis V protocol. He died of gastrointestinal bleeding. Only one patient is alive and well 1 year after completing 3 years of a modification of Memphis V protocol (16) for NHL.

Table VII. Clinical staging and outcome of treatment in 10 cases of NHL

Case No.	Stage	Treatment	Outcome
1	I (neck)	—	AOR
2	IV (mediastinal)	Memphis protocol Went to China returned with CNS relapse	Died at 7 mos
3	IV (mediastinal)	COAP x 6 relapsed then MOPP x 7 converted to ALL — Memphis protocol V.	Died of pneumonia and gastro-intestinal bleeding at 18 mos
4	IV (neck)	VCR + PNSL x 1	AOR
5	IV (generalised)	Memphis V protocol for 3 yrs	A + W, off therapy 1 year
6	IV (abdominal)	—	AOR died 2 mos.
7	IV (mediastinal with TI2 vertebral collapse)	Memphis V protocol	AOR 4 mos
8	IV (mediastinal)	PNSL	AOR 4 weeks.
9	III (generalised)	CPM daily	Died at 3 weeks of hemothorax.
10	III (neck)	RT	Died 9 mos

AOR — discharged against medical advise; A + W — alive and well
PNSL — prednisolone; CPM — cyclophosphamide; RT — radiotherapy;
VCR — vincristine; COAP — cyclophophamide + oncovin + cytosine arabinoside + prednisolone.

DISCUSSION

While the overall prevalence of lymphoma in childhood is highest in Nigeria and India, it appears to be lower in Kuala Lumpur as in Australia, USA and UK (Table VII).

The relative frequency of HD and NHL is almost equal in our series and both diseases show similar trends in racial and sex preferences. The higher incidence in Chinese is also observed in China. Children with HD tend to be older and usually have symptoms of longer duration than NHL.

Table VII. Prevalence of lymphoma in representative countries of the globe expressed as percent of all childhood malignancies

Site-or Type of malignancy	Australia (17)	USA (18)	UK (19)	Nigeria (7)	India (8)	China (19)	Korea (20)	Kuala Lumpur
Lymphoma	7	8	9	59	22	12	11	7 7
Hodgkin's Disease	2	4	4	4	9.8	—	1.3	4.6
L. Sarcoma/NHL	5	4	5	1.7	8.4	—	5.1	3 1
Burkitt's	—	—	—	52	—	—	—	1
Leukaemia	36	33 5	29	5	35	30	55	43.6
Brain tumor	19	16	17	2	11 6	20	1.4	9.2
Retinoblastoma	2	1	3	7	10	—	7	7 7
Teratoma	5	—	4	1.5	—	—	1	7 3
Wilms' tumor	7	5	5	6	5	?	5 1	5

The majority of our cases demonstrated MC type histology and none had NS and HD. The relative increase in frequency of MC has been observed in the younger patients in the USA (21).

Although previous studies have shown better prognosis for NS histology compared with MC this advantage has been eliminated by current therapy.

The majority of our patients presented with stage IV disease. Staging laparotomy was not done routinely and is now performed only if the results are likely to alter the initial treatment plan. Splenectomy was avoided in all cases except one as it is associated with 10% incidence of septicemia and meningitis (22). The relative importance of splenectomy may be reduced by the routine addition of chemotherapy.

Good response can be obtained in most cases of HD and NHL with current treatment protocols. Straus et al. (23) have obtained 100% response rate and 80% or better 4 year survival in patients with Stage IV HD. Our results in advanced HD have also been encouraging. The outlook for NHL has improved in recent years. Patients with lymphoblastic NHL do better with the LSA2-L2 regime (2,24) while those with non-lymphoblastic disease fare better with COPAD or COMP therapy (25).

The majority of our cases of HD and NHL presented with Stage IV disease and there was poor compliance to treatment. This was largely responsible for the relatively poor overall cure rates in our series. There is a definite need to educate the public about the improved prognosis in childhood malignancies to reduce the high default rate. Early referrals would help reduce the mortality and morbidity associated with the disease.

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