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Central Nervous System Involvement in Non-Hodgkin's Lymphoma

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Abstract—*Fifty-eight Hong Kong Chinese patients with CNS lymphoma were reviewed (primary seven, secondary* 51*). The incidence of secondary CNS lymphoma in patients with non-Hodgkin's lymphoma was estimated to be* 9.4%*. The Working Formulation separated subtypes which had a special propensity to involve the CNS. Significant proportions of our patients with secondary CNS lymphoma had other features which were known to be associated with a high risk of CNS disease including stage IV* (48/51, 91.4%), *bone marrow* (26/51, 50.9%), *peripheral blood* (7.51, 13.7%), *nasal* (7/51, 13.7%), *orbital* (3/51, 5.9%), *testicular* (2/51, 3.9%) *and bulky retroperitoneal* (6/51, 11.8%) *disease.* 82% *of patients with secondary CNS lymphoma had concurrent systemic disease and a further* 12% *had systemic relapse shortly afterward. CNS lymphoma is associated with poor prognosis and only* 29% *and* 14% *of the patients with primary and secondary CNS lymphoma respectively survived beyond* 1 *year. Patients responding to therapy had significantly better survival.* 69.9% *of the deaths were related to progressive systemic disease.*

INTRODUCTION

THE central nervous system (CNS) is not uncommonly involved in patients with non-Hodgkin's lymphoma [1–9]. Despite recent advances in the therapy of lymphoma, the best management for patients with CNS lymphoma remains uncertain. The relative roles of surgery, radiotherapy, intrathecal and systemic chemotherapy still need to be defined. This paper presents a retrospective analysis of the clinical course and management of 58 Hong Kong Chinese patients with CNS lymphoma.

MATERIALS AND METHODS

The medical records of patients attending the lymphoma clinic, Queen Mary Hospital, Hong Kong, between January 1971 and June 1987 with a diagnosis of non-Hodgkin's lymphoma were reviewed. Patients were considered to have 'definite' CNS lymphoma if cerebrospinal fluid (CSF) cytology, autopsy or biopsy of CNS tissues showed malignant lymphoma. A diagnosis of 'probable' CNS lymphoma was made if patients met all of the following criteria: (a) known lymphoma outside CNS; (b) otherwise unexplained CNS symptoms or signs; (c) 'suspicious' CSF cytology or compatible structural abnormality documented by computerized axial tomography (CT) of the brain, myelography or cerebral angiography; (d) resolution or improvement of symptoms or signs associated with radiotherapy and/or chemotherapy [6].

The pathological materials were reviewed and classified according to the Working Formulation [10]. Immunohistochemical studies were performed on fresh tissue specimens obtained from 11 patients using methods previously reported [11]. Patients were staged according to the Ann Arbor Classification [12] and clinical staging procedures included complete physical examination, plain chest radiograph, full blood counts, blood biochemistry, iliac crest trephine biopsy and aspirate of bone marrow. Lymphogram and/or CT abdomen were performed. Percutaneous liver biopsy was done in selected patients.

The crude incidence of secondary CNS lymphoma for the Working Formulation histologic subgroups was estimated by the technique previously employed by the Stanford group [6]. The incidence of each histologic subgroup in this series of patients with secondary CNS lymphoma was compared with the incidence of the corresponding subgroup in a series of 234 consecutive Hong Kong Chinese patients with non-Hodgkin's lymphoma seen in the same clinic between 1975 and 1982 [13]. Twenty of these 234 patients (9.4%) developed secondary CNS lymphoma.

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Tumour responses were assessed using standard criteria [14]. The Kaplan–Meier product limit method was used to generate survival curves [15]. The survival time was measured from the date of diagnosis of CNS disease to the date of last follow up or the date of death. The log-rank procedure was used to compare survival curves.

RESULTS

Fifty-eight patients were found to have CNS lymphoma. Forty-eight of them were classified as definite and 10 as probable.

Patient characteristics and histology

Of the seven patients with primary CNS lymphoma, five were male and two female. Their median age was 63 years (range 39–74). There were one diffuse mixed small cleaved and large cell, one diffuse large cell, two diffuse immunoblastic, two diffuse small non-cleaved and one unclassified lymphomas. Fresh tissue was available for immunophenotyping in a case of diffuse immunoblastic lymphoma and was positive for B cell markers. One patient had a history of nasopharyngeal carcinoma which responded to a course of local radiotherapy given 2 years before the diagnosis of lymphoma. Another patient had Klinefelter's syndrome. Otherwise, none of them were immunocompromised. The sera of three patients were tested for HTLV-III antibody and all were negative.

Fifty-one patients had secondary CNS lymphoma. The diagnosis was definite in 41 cases (80.4%) and probable in 10 (19.6%). Thirty patients were male (58.8%) and 21 (41.2%) female. Their median age was 54 years (range 12–81). At first presentation, two (3.9%) patients had stage II, one (2%) stage III and the remaining 48 (94.1%) stage IV disease. Twenty-seven of them (52.9%) had B symptoms and nine (17.6%) bulky disease (tumour diameter greater than 10 cm: cervical one, mediastinal two, retroperitoneal six). The extent of disease on initial presentation is shown in Table 1 which also shows the additional disease sites involved at subsequent relapses or disease progression.

Table 2 shows the histologic subclassification of the 51 patients with secondary CNS lymphoma. For the 10 cases where fresh tissues were available for immuno-phenotyping, nine of them were positive for B cell markers (diffuse mixed two, diffuse large cell four, diffuse immunoblastic one, diffuse small non-cleaved cell two) and one case of lymphoblastic lymphoma was positive for T cell markers.

The probability of CNS lymphoma for a particular histologic subtype, $P(\text{CNS/H}) = P(\text{H/CNS}) \cdot P(\text{CNS})/P(\text{H})$. The incidence of CNS lymphoma in 234 consecutive Hong Kong Chinese patients with non-Hodgkin's lymphoma, $P(\text{CNS})$, was estimated to be $22/234 = 9.3\%$. $P(\text{H/CNS})$ is the incidence of a particular histologic subtype for the 51 patients with CNS lymphoma and $P(\text{H})$ is the incidence of a particular histologic subtype for the 234 Hong Kong Chinese patients with non-Hodgkin's lymphoma (Table 2).

Prior therapy

Thirty-five patients had received therapy for their lymphoma prior to the development of CNS disease.

Table 1. Extent of disease involvement of 51 patients with secondary CNS lymphoma on initial presentation and at subsequent relapses or disease progression

	Initial presentation	Relapse/progression	Total
Lymph node	43 (84.3%)	6 (11.8%)	49 (96.1%)
Bone marrow	22 (43.1%)	4 (7.8%)	26 (50.9%)
Spleen	18 (35.3%)	2 (3.9%)	20 (39.2%)
Liver	17 (33.3%)	2 (3.9%)	19 (37.2%)
Bone	7 (13.7%)	0 (0%)	7 (13.7%)
Nasal	7 (13.7%)	0 (0%)	7 (13.7%)
Peripheral blood	4 (7.8%)	3 (5.9%)	7 (13.7%)
Skin	4 (7.8%)	2 (3.9%)	6 (11.8%)
Stomach	6 (11.8%)	0 (0%)	6 (11.8%)
Small bowel	6 (11.8%)	0 (0%)	6 (11.8%)
Pleura	4 (7.8%)	1 (2%)	5 (9.8%)
Lung	5 (9.8%)	0 (0%)	5 (9.8%)
Kidney	2 (3.9%)	3 (5.9%)	5 (9.8%)
Pericardium	2 (3.9%)	2 (3.9%)	4 (7.8%)
Orbit	3 (5.9%)	0 (0%)	3 (5.9%)
Large bowel	2 (3.9%)	0 (0%)	2 (3.9%)
Testis	2 (3.9%)	0 (0%)	2 (3.9%)
Ovary	0 (0%)	1 (2%)	1 (2%)
Breast	1 (2%)	0 (0%)	1 (2%)
Vagina	1 (2%)	0 (0%)	1 (2%)

Table 2. Incidence of secondary CNS lymphoma by histology

Histology		Incidence of the histologic subtype for CNS lymphoma patients, P(H/CNS)	Incidence of the histologic subtype in 234 consecutive lymphoma patients, P(H)	Probability of CNS lymphoma, P(CNS/H)
I.	Low grade:			
	A. Diffuse small lymphocytic	0 (0%)	15 (6.4%)	0%
	B. Follicular small cleaved	0 (0%)	20 (8.6%)	0%
	C. Follicular mixed	0 (0%)	10 (4.3%)	0%
		0 (0%)	45 (19.3%)	0%
II.	Intermediate grade:			
	D. Follicular large cell	0 (0%)	1 (0.4%)	0%
	E. Diffuse small cleaved	2 (3.9%)	16 (6.8%)	5.4 ± 4.1%
	F. Diffuse mixed	9 (17.7%)	38 (16.2%)	10.3 ± 4.0%
	G. Diffuse large cell	16 (31.4%)	57 (24.4%)	12.1 ± 3.8%
		27 (52.9%)	112 (47.8%)	10.4 ± 2.6%
III.	High grade:			
	A. Diffuse immunoblastic	8 (15.7%)	25 (10.7%)	13.8 ± 5.9%
	I. Diffuse lymphoblastic	10 (19.6%)	20 (8.5%)	21.7 ± 8.9%
	J. Diffuse small non-cleaved cell	4 (7.8%)	4 (1.7%)	43.1 ± 31.1%
		22 (43.1%)	49 (20.9%)	19.4 ± 5.6%
IV.	Others and unclassified	2 (3.9%)	28 (12%)	3.1 ± 2.3%

*P(CNS/H) = P(H/CNS)· P(CNS)/P(H), where P(CNS) = 9.3% (22/234) was estimated from the overall incidence of CNS lymphoma in the 234 consecutive lymphoma patients. Standard error of the estimate is noted.

Thirty-three of them were given various regimes of chemotherapy: BACOP three, CHOP 21, COPP five, CVP two and PAC two [16–20]. Eight patients received local radiotherapy. A total of 20 patients achieved complete remission prior to CNS disease (median duration 14 months, range 3–36 months). No patient received CNS prophylaxis.

Status of systemic disease

The status of systemic disease at the time of CNS involvement of the 51 patients with secondary CNS lymphoma was: (1) refractory systemic disease not responding to therapy in 17 (33.3%); (2) simultaneous onset (within 1 month) of CNS and systemic disease 15 (29.4%); (3) simultaneous (within 1 month) CNS and systemic relapse after therapy in 10 (19.6%); (4) isolated CNS relapse or progression in nine (17.6%). For the 36 patients who did not have simultaneous onset of CNS and systemic lymphoma, the CNS disease developed at 2–127 months (median 11 months) from the time of initial diagnosis of lymphoma. For the nine patients with isolated CNS relapse or progression, six of them had systemic relapse or progression at intervals from 2 to 9 months (median 4 months) from the time of diagnosis of CNS disease. There was no apparent relationship between the status of systemic disease at the time of CNS involvement and the histology (Table 3).

CNS symptoms and signs

The symptoms and signs exhibited by the seven patients with primary and 51 secondary CNS lymphomas which were attributed to their CNS disease are shown in Table 4. Focal motor weakness and cranial nerve deficits were the most frequent presentations.

Diagnostic investigations and treatments

All seven patients with primary CNS lymphoma had parenchymal disease which involved the cerebral hemispheres. Seven patients had secondary extradural disease compressing the spinal cord and the remaining 44 had meningeal disease and/or parenchymal involvement. The results of the diagnostic investigations are summarized in Table 5. For the 30 patients with positive CSF cytology, their CSF showed a median leucocyte count of 32/mm^3 (range 1–120), mean protein level 0.891 g/l (range 0.42–2.14) and mean glucose level 2.1 mmol/l (range 1.7–4.2).

Six of the seven patients (86%) with primary CNS lymphoma were diagnosed by craniotomy and open biopsy. The remaining patient was diagnosed only at autopsy. Two patients had debulking operation and one of them required an insertion of ventriculo-atrial shunt for hydrocephalus. All six patients diagnosed during life received cranial irradiation but two of them died before completion. Only the two patients (29%) who received systemic

Table 3. Status of systemic disease at the time of CNS involvement

Histology	Refractory systemic disease	Simultaneous onset of systemic and CNS disease	Simultaneous CNS and systemic relapse	Isolated CNS relapse	
Intermediate grade:	9	6	6	6	27 (52.9%)
Diffuse small cleaved	1	1	0	0	2 (3.9%)
Diffuse mixed	3	2	2	2	9 (17.7%)
Diffuse large cell	5	3	4	4	16 (31.4%)
High grade:	7	8	4	3	22 (43.1%)
Diffuse immunoblastic	3	3	1	1	8 (15.7%)
Diffuse lymphoblastic	3	3	2	2	10 (19.6%)
Diffuse small non-cleaved	1	2	1	0	4 (7.8%)
Others and unclassified	1	1	0	0	2 (3.9%)
	17 (33.3%)	15 (29.4%)	10 (19.6%)	9 (17.6%)	51 (100%)

Table 4. Symptoms and signs of CNS lymphoma

	Primary CNS lymphoma ($n = 7$)	Secondary CNS lymphoma ($n = 51$)	Total ($n = 58$)
Focal motor weakness	5 (71.4%)	29 (56.9%)	34 (58.6%)
(a) paraparesis	0 (0%)	11 (21.6%)	11 (19.0%)
(b) hemiplegia	4 (57.1%)	6 (11.8%)	10 (17.2%)
(c) others	1 (14.3%)	12 (23.5%)	13 (22.4%)
Cranial nerves	1 (14.3%)	25 (49%)	26 (44.8%)
(a) II	0 (0%)	7 (13.7%)	7 (12.1%)
(b) III/IV/VI	1 (14.3 %)	20 (39.2%)	21 (36.2%)
(c) V	0 (0%)	6 (11.8%)	6 (10.3%)
(d) VII	0 (0%)	10 (19.6%)	10 (17.2%)
(e) IX/X/XII	0 (0%)	3 (5.9%)	3 (5.2%)
Headache	5 (71.4%)	11 (21.6%)	16 (30.8%)
Mental change	2 (28.6%)	14 (27.5%)	16 (30.8%)
Sensory abnormality	0 (0%)	14 (27.5%)	14 (24.1%)
Bladder/bowel	1 (14.3%)	6 (11.8%)	7 (12.1%)
Papilloedema	3 (42.9%)	3 (5.9%)	6 (10.3%)
Back pain	0 (0%)	5 (9.8%)	5 (8.6%)
Gait disturbance	0 (0%)	5 (9.8%)	5 (8.6%)
Vomiting	1 (14.3%)	2 (3.9%)	3 (5.2%)
Seizures	2 (28.6%)	1 (2%)	3 (5.2%)
Horner's syndrome	0 (0%)	2 (3.9%)	2 (3.4%)
No symptom	0 (0%)	2 (3.9%)	2 (3.4%)

chemotherapy plus radiotherapy achieved clinical remission. One of them received methotrexate 3 gm/m^2 intravenously (plus folinic acid rescue) for seven courses and Ara C 300 mg/m^2 intravenously for five courses resulting in clinical remission for 47 months but he subsequently died of systemic relapse at 54 months. The other patient receiving weekly Ara C 300 mg/m^2 intravenously and methotrexate 120 mg/m^2 intravenously (plus folinic acid rescue) remains in clinical remission to date at 4 months from the time of diagnosis.

Five of the seven (71%) patients with extradural disease had laminectomy and decompressive surgery was performed to relieve the spinal cord compression. Six patients (86%), including one who had no surgery, received local radiotherapy which was

Table 5. *Diagnostic investigations*

	CT scan brain*	Cerebral angiography*	Myelography*	CSF cytology*	Open biopsy*	Autopsy*	Diagnosis† Probable	Diagnosis† Definite
1. Primary CNS lymphoma (n = 7)	7/7	2/2	—	1/1	6/6	2/2	0	7
2. Secondary CNS lymphoma (n = 51)	11/22	—	8/15	29/46	8/8	5/5	10	41
(a) Extradural (n = 7)	3/3‡	—	7/7	0/7	5/5	1/1	1	6
(b) Meningeal and/or parenchymal (n = 44)	8/19	—	1/5	29/39	3/3	4/4	9	35

*No. of patients with positive test/No. of patients having the test.
†No. of patients.
‡CT scan of spine.

completed in all but one patient. Two (29%) patients also had intrathecal methotrexate and five (71%) systemic chemotherapy: PAC in two, CHOP in one, COMP in one and HOAP-Bleo in one [17, 20, 21, 24]. One patient with CNS disease diagnosed at autopsy received no therapy.

Of the 44 patients with meningeal and/or parenchymal involvement, 34 (77.3%) received local radiotherapy (cranial in 32, craniospinal in two); 25 (56.8%) intrathecal chemotherapy (17 methotrexate, eight methotrexate and Ara C); and 30 (68.2%) systemic chemotherapy: CHOP in six, HOAP-Bleo in four, COPP in four, COMLA in three, PAC in two, MACOP-B in two, COMP in one, methotrexate (300 and 100 mg/m^2) with folinic acid rescue in two and others in six [17, 18, 20–24]. All but two of the 34 patients receiving radiotherapy completed the radiotherapeutic treatment. An intraventricular reservoir was inserted in three patients for intraventricular therapy and they were free from complications. Five patients had no specific therapy.

The radiation doses and intrathecal schedules were not standardized.

Clinical response and survival

The overall survival of the seven patients with primary CNS lymphoma and the 51 patients with secondary CNS lymphoma, including the seven patients with extradural disease who survived 3, 3, 3, 4+, 5+, 10 and 14 months, is shown in Fig. 1. There was no significant difference in survival between the two groups. Five of the seven patients with primary CNS lymphoma died of progressive CNS disease and one died of massive cerebral infarction. The causes of death of 46 patients with secondary CNS lymphoma included: (1) progression of systemic lymphoma in 16 (34.8%); (2) progression of both CNS and systemic lymphoma

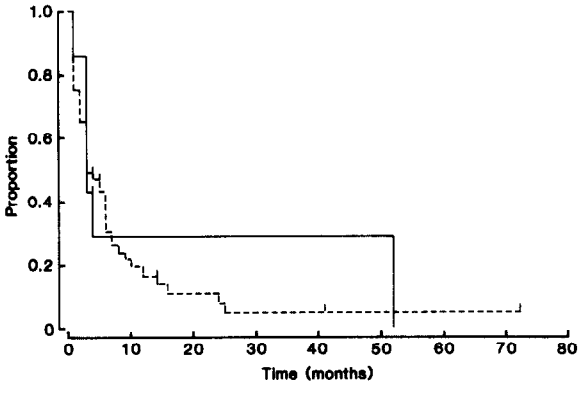

Fig. 1. *The overall survival curves of seven patients with primary* (——) *and* 51 *patients with secondary CNS lymphoma* (-----). *A similar median survival of* 3 *months was observed in both groups of patients.*

in 16 (34.8%); (3) progression of CNS lymphoma in seven (15.2%); (4) septicaemia in four (8.6%); (5) pneumonia in one (2.2%); (6) intracranial bleeding in one (2.2%) and (7) cerebral infarction in one (2.2%).

Complete remission was difficult to document in these patients. However, 18 patients with secondary CNS lymphoma achieved good clinical remission of their CNS disease, which was defined as complete resolution of the radiological and cytological evidence of CNS disease with some recovery of the neurological deficits, and the remissions lasted for 1–68+ months (median 4 months). The survival of this group of 18 patients was significantly better ($P < 0.01$) than that of the remaining 33 patients who had poor response (Fig. 2).

Other factors including sex, age, histologic subtypes, B symptoms, status of systemic disease, sites of CNS disease did not significantly affect the survival. However, the number of patients in each subgroup was small. The effects of various therapeutic strategies on survival could not be deter-

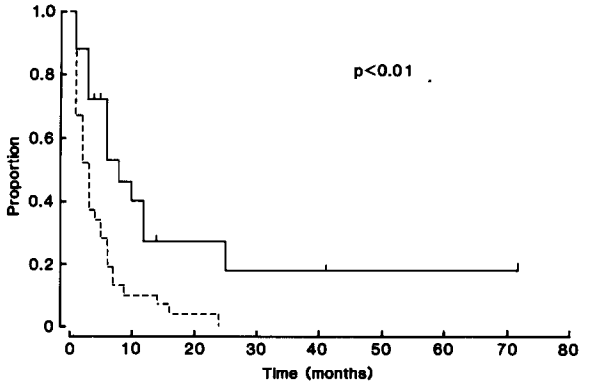

Fig. 2. The overall survival curves of 51 patients with secondary CNS lymphoma: 18 responders (——) versus 33 nonresponders (-----). The median survival of responders and nonresponders were 3 and 8 months respectively.

mined in this analysis because of the variety of treatment utilized.

DISCUSSION

Primary CNS lymphoma is uncommon and its association with immunosuppression, such as cardiac or renal transplantation, congenital immunodeficiency, rheumatoid arthritis, systemic lupus erythematosis and acquired immunodeficiency syndrome (AIDS) is well recognized [25–27]. None of our seven patients with primary CNS lymphoma was immunosuppressed and their survival was similar to that of patients with secondary CNS lymphoma (Fig. 1).

9.4% of our patients with non-Hodgkin's lymphoma developed secondary CNS disease. This is comparable to the figures of 7–29% reported in the literature [8, 28].

It is known that CNS involvement is unusual in nodular lymphoma (<2%) but is more common in diffuse histologic subtypes, particularly the lymphoblastic and undifferentiated lymphomas of the Rappaport Classification [6]. In this analysis, attempts were made to correlate the risk of CNS involvement with various histologic subtypes according to the Working Formulation which has recently gained wide acceptance [10]. There is a good correlation between the aggressiveness of the lymphoma and the risk of CNS involvement. It appears that the Working Formulation is discriminant in separating groups which have a special propensity to involve CNS. No patient with low grade lymphoma, which is uncommon in Hong Kong Chinese [13], developed CNS disease. On the other hand, high grade lymphoma especially the diffuse lymphoblastic and diffuse small non-cleaved cell types, had a very high incidence of CNS disease.

As only a small proportion of our patients in this analysis had fresh tissue specimens available for tumour marker analysis, the effect of immunophenotype on CNS involvement could not be ascertained. However, we have shown in a previous analysis that, unlike T-lymphoblastic lymphoma, peripheral T cell lymphoma does not appear to have a propensity to CNS disease [29].

Significant proportions of our patients with secondary CNS lymphoma had features which were known to be associated with a high risk of CNS disease. They included stage IV (48/51, 94.1%), bone marrow (26/51, 50.9%), peripheral blood (7/51, 13.7%), nasal (7/51, 13.7%), orbital (3/51, 5.9%), testicular (2/51, 3.9%) and bulky retroperitoneal disease (6/51, 11.8%) [5, 6].

CNS involvement should be suspected in any patient with lymphoma in whom CNS symptoms or signs develop. The important differential diagnosis is CNS infection. The diagnosis can be easily confirmed by positive CSF cytology in most cases, especially those with predominantly meningeal disease. For the other cases, while imaging techniques including CT scanning, angiography and myelography may outline the CNS lesions, surgical intervention is often necessary to obtain a tissue diagnosis. However, precise cytologic or histologic confirmation may not be possible in each and every case, and empiric therapy is often necessary [6]. It appears that primary CNS lymphoma was more often presenting as parenchymal lesion and meningeal involvement was more commonly seen in secondary CNS lymphoma (Table 5).

CNS lymphoma is associated with an extremely poor prognosis. Only 29% and 14% of our patients with primary and secondary lymphoma respectively survived beyond 1 year. The best management of CNS lymphoma remains to be determined. Since neurological dysfunction can progress rapidly and cause permanent damage, early diagnosis and prompt treatment are essential to provide good palliation [28]. Moreover, patients responding to therapy had significantly better survival (Fig. 2).

Patients with extradural compression of the spinal cord often require diagnostic surgery but the therapeutic value of laminectomy has not been firmly established. Although laminectomy is usually effective in decompressing the spinal cord, radiotherapy to the involved segment is often recommended [7, 28]. In our small series of such patients, their prognosis appears to be similar to that of the other patients with secondary CNS lymphoma.

For patients with meningeal and/or parenchymal CNS disease, intrathecal chemotherapy and radiotherapy are the mainstay of treatment. The benefit of giving chemotherapeutic agent through an intraventricular reservoir has not been resolved [6, 8].

There is increasing evidence suggesting that systemic chemotherapy with high dose methotrexate (with folinic acid rescue) and/or Ara C is useful in treating CNS lymphoma because of its good

penetration through the blood–brain barrier [6]. In addition, this approach has the advantage of treating the systemic disease at the same time as 82% of our patients with secondary CNS lymphoma had concurrent systemic disease and a further 12% had systemic relapse shortly afterward. 69.6% of their deaths were ultimately related to progressive systemic disease. This approach of using systemic moderate or high dose methotrexate and/or Ara C requires further evaluation to determine the optimal dose and timing of the treatment.

Prophylactic CNS treatment is effective in reducing the incidence of CNS involvement in childhood acute lymphoblastic leukemia [3]. A similar approach has also been advocated for lymphoma patients with a high risk of developing CNS disease including (a) high grade non-Hodgkin's lymphoma, especially diffuse lymphoblastic and diffuse small noncleaved cell types, or (b) bone marrow, nasal, orbital, testicular or bulky retroperitoneal disease [3, 5, 6, 9]. These patients are recommended to receive cranial radiotherapy and/or intrathecal methotrexate. The alternative approach is to incorporate moderate to high dose methotrexate and/or Ara C in the systemic regimes. The impact of CNS prophylaxis in non-Hodgkin's lymphoma appears to be small as the majority of patients developing CNS disease have progressive or relapsing systemic disease as their major cause of death [3]. The future probably depends on the development of more effective systemic chemotherapy regimes with CNS prophylaxis in selected high risk cases.

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