PAPERS

The need for prophylactic treatment to the central nervous system in patients with aggressive non-Hodgkin's lymphoma

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Summary

During 2 years, 6 out of 34 patients presenting with newly diagnosed non-Hodgkin's lymphoma developed central nervous system (CNS) complications. All were male and had diffuse, undifferentiated lymphomas. In all 6 patients, CNS disease developed during, or shortly after, treatment. We suggest that a group at high risk from these complications can be identified and should be considered for a trial of prophylaxis.

KEY WORDS: lymphoma, central nervous system, treatment.

Introduction

Involvement of the central nervous system (CNS) in non-Hodgkin's lymphoma (NHL) is now more frequently recognized. In the majority of patients, it is diagnosed when there is advanced disease elsewhere (Young *et al.*, 1979), but in some it may be the first manifestation of the lymphoma (Littman and Wang, 1975; Venables *et al.*, 1980). In some patients, CNS disease may develop during or after treatment. Under these circumstances, the CNS acts as a sanctuary site inaccessible to most conventional chemotherapeutic agents.

In 34 consecutive newly diagnosed patients with non-Hodgkin's lymphoma in Nottingham, 6 developed CNS disease. All 6 were male and had diffuse undifferentiated lymphomas. All developed CNS disease during, or shortly after, concluding treatment with a modification of the CHOP regimen described originally by McKelvey *et al.* (1976) and used by the British National Lymphoma Investigation (BNLI) for the treatment of advanced high grade NHL. None of the cytotoxic drugs employed in this regimen crosses the blood-brain barrier and our experience of CNS relapse in the face of recent or continuing chemotherapy suggests there is a need for a controlled trial of additional treatment as

prophylaxis against CNS disease in such high risk patients.

Patients

The patients described were seen at University Hospital, Nottingham during 1980 and 1981. The clinical details are summarized in Tables 1 and 2. In 5 of the 6 patients, the diagnosis was established on lymph node biopsy, but in Case 5, it was made by histological examination of the testis after orchidectomy for painless swelling. Pathological material in 5 of the patients was examined additionally by the Pathology Panel of the British National Lymphoma Investigation (BNLI) and was classified accordingly (Jelliffe and Vaughan-Hudson, 1981).

All patients were staged according to the recommendations of the BNLI. Five patients had widespread disease with marrow involvement (Stage IV) on presentation. Case 3 was initially regarded as having limited mediastinal disease (Stage IIA) on the basis of a staging laparotomy. However, whilst undergoing radiotherapy, it became clear that the disease had rapidly disseminated with bone and marrow involvement. The cerebrospinal fluid (CSF) was examined routinely by cytocentrifugation on diagnosis in all patients, except Case 6, and was, at that time, within normal limits.

Chemotherapy with the modified CHOP regimen consisted of pulsed intravenous injections of cyclophosphamide 750 mg/m², adriamycin 25 mg/m² and vincristine 1.4 mg/m² given on days 1 and 8 with prednisone orally 40 mg/m² from day 1 to day 8 inclusive. (McKelvey *et al.*, 1976). Courses were given every 4 to 6 weeks depending on the peripheral blood counts to a minimum of 6 courses and at least 3 courses after complete remission.

In patients 1 and 3, CNS involvement appeared during treatment with CHOP at a time when there appeared to be remission of the disease elsewhere. In patients 2 and 5, CNS disease appeared shortly after the patients completed therapy with CHOP and had achieved clinical remission. In 2 patients (Cases 4

TABLE 1. Clinical details of 6 patients with non-Hodgkin's lymphoma and CNS involvement (see also Table 2)

Case	Age at diagnosis	Sex	Clinical presentation and staging after initial investigation	Histological diagnosis	Treatment	Duration from diagnosis to onset of neurological disease
1	59	M	Fever, abdominal mass and inguinal nodes Stage* IV B	Unclassified (BNLI)*	CHOP* × 3	3 months
2	64	M	Glands in neck Stage IV A	Undifferentiated large cell (lymphoid) (BNLI)	CHOP × 6	8 months
3	29	M	Glands in neck and mediastinum Stage II A (→ Stage IV A during treatment)	Undifferentiated large cell (lymphoid) (BNLI)	DXR to mediastinum. CHOP × 6	6 months
4	47	M	Glands in neck, fever Stage IV B	Unclassified (BNLI)	CHOP × 2	3 months
5	53	M	Testicular swelling, lung infiltration Stage IV A	Undifferentiated large cell (lymphoid) (BNLI)	CHOP × 6	8 months
6	66	M	Weakness, lymphadenopathy Stage IV B	Diffuse lymphocytic lymphoma	CHOP × 3	3 months

*See text for details.

and 6), CNS disease developed during early CHOP therapy.

No consistent regime of CNS therapy was given as patients had received variable amounts of chemotherapy at the stage of CNS involvement. Case 2 required urgent neurosurgery with ventricular shunting for his communicating hydrocephalus and was later treated with cranial irradiation and intra-thecal methotrexate. All other patients received intra-thecal methotrexate in dosages of 10–15 mg weekly up to 6 weeks. Additionally, Cases 3 and 5 received cranial irradiation (Table 2). Post-mortem examination in cases 1 and 5 revealed generalized relapse of the non-Hodgkin's lymphoma as well as extensive CNS disease.

Discussion

Our own experience in this 2-year period confirms recent suggestions that CNS involvement, particularly lymphomatous leptomeningitis in diffuse non-Hodgkin's lymphoma is becoming more common (Littman and Wang, 1975; Young *et al.*, 1979; Bunn *et al.*, 1976; Levitt *et al.*, 1980). Whilst part of this increase may be attributable to improvements in diagnosis, such as identification of malignant cells in the CSF after centrifugation and isotope and computer assisted tomographic (CAT) scanning, these are unlikely to be the sole determinant factors. Much of the increase is likely to be due to the emergence of new disease syndromes arising from intensive che-

motherapeutic regimes in patients with diffuse aggressive non-Hodgkin's lymphoma. Improved survival using combination chemotherapy, as typified by the CHOP regimen, has presumably extended survival only to allow the extension of disease to sanctuary sites such as the central nervous system.

Differences in histological nomenclature render direct comparisons with other studies difficult, but all reports confirm a much greater risk of CNS complications with diffuse histiocytic and diffuse undifferentiated lymphoma using the Rappoport classification. Using the BNLI nomenclature, 3 of our own patients have had undifferentiated large cell (lymphoid) disease and 2 others have had highly malignant diffuse lymphoid tumours which defied accurate classification. CNS disease is usually associated with bone marrow involvement though in a third of cases this may only be detected at post-mortem examination (Young *et al.*, 1979). In 5 of our own cases, lymphomatous infiltration of the bone marrow was seen at presentation. Law *et al.* (1975) have suggested that lymphoma with retroperitoneal involvement might have predilection for CNS relapse, as was the situation with Case 1. One of our patients (Case 5), had testicular swelling as an initial symptom and Wolley *et al.* (1976) proposed that that type of clinical presentation might predispose to CNS disease later.

The analogy between CNS involvement in diffuse non-Hodgkin's lymphoma and acute lymphoblastic leukaemia cannot be avoided and prompts the

TABLE 2. Clinical details of 6 patients with non-Hodgkin's lymphoma and CNS involvement—details of CNS disease

Case	Clinical features of CNS disease	Cerebrospinal fluid at onset of CNS symptoms					Treatment	Outcome
		Scan	Protein	Glucose	Cells/mm ³			
1	Drowsiness, dysphasia, hemiplegia, wasting of small muscles of hand	CAT scan—normal	3.0	—	376 Abnormal mononuclear cells with deeply cleft nuclei and nucleoli		IT MTX* ×4	Died 7 weeks after onset of CNS symptoms. Diffuse meningeal disease at autopsy
2	Drowsiness	CAT scan—obstructive hydrocephalus	1.0	7.1	41 lymphocytes of abnormal type		Ventricular shunt, cranial irradiation; IT MTX×4	Alive
3	Fits	Isotope scan—frontal lobe lesions	0.25	3.7	No excess of cells initially. Later cytopspin showed cells with cleft lobulated nuclei and prominent nucleoli		Cranial irradiation, IT MTX×6	Died 10 months after onset of CNS symptoms. No autopsy
4	Confusion, pains in limbs	Not performed	0.5	3.9	17 abnormal mono-nuclear cells of malignant type		IT MTX	Died 2 months after onset of CNS symptoms. No autopsy
5	Spastic paraparesis, bilateral deafness, blindness	Isotope scan—normal	4.0	1.0	18 (45%) bizarre neoplastic cells		Cranial irradiation, IT MTX×7	Died 10 months after onset of CNS disease. Diffuse infiltration of CNS with leptomeningitis at autopsy
6	III nerve palsy, sciatica	CAT scan—normal	0.6	3.6	Initially no excess, one month later malignant cells		IT MTX and Hydrocortisone ×2	Died 1 month after onset of CNS disease. No autopsy

*IT MTX = Intrathecal methotrexate × number of treatments.

suggestion that this is 'leukaemia revisited' (Bunn *et al.*, 1976). Certainly, in the absence of specific CNS prophylaxis in acute lymphoblastic leukaemia, a high proportion of patients develop infiltration of the meninges within 2 years. CNS prophylaxis with cranial irradiation and intra-thecal methotrexate has been clearly shown to improve the prognosis of acute lymphoblastic leukaemia in children (Working Party on Leukaemia in Childhood, 1973; Dritschilo *et al.*, 1976) and in adults (Lister *et al.*, 1978b).

A number of studies have suggested that a related approach ought to be of value in adult NHL. High doses of both methotrexate and cytosine arabinoside given by continuous intravenous infusion can achieve cytotoxic concentrations in the CSF (Tattersall *et al.*, 1975; Weinstein *et al.*, 1978). In the case of methotrexate, intravenous infusion has been shown to give a more uniform distribution in the CNS than intra-thecal administration (Shapiro, Young and Mehta, 1975). High dose methotrexate administered to patients with unfavourable NHL in relapse with CNS disease has produced appreciable improvement (Skarin *et al.*, 1977), but at present it is most unlikely that complete eradication can be achieved once overt CNS disease has developed (Schein *et al.*, 1976; Young *et al.*, 1979; Lister *et al.*, 1978a).

The addition of methotrexate to regimes such as BACOP/D (bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone or dexamethasone) in the initial treatment of patients with diffuse histiocytic or undifferentiated lymphomas has produced encouraging results with only one patient with CNS relapse in a series of 30 patients treated by Canellos, Lister and Skarin (1978). Also, the use of methotrexate and cytosine arabinoside may account for the lack of CNS relapses seen with the COMLA (cyclophosphamide, vincristine, methotrexate with leukovorin rescue and cytarabine) regimen (Sweet *et al.*, 1980). Combined cranial irradiation and intra-thecal methotrexate has been used after induction of systemic remission in aggressive NHL in adults (Lister *et al.*, 1978a) and has proved effective in children (Murphy and Hustu, 1980).

All the patients treated by these regimens had diffuse histiocytic or undifferentiated lymphomas and CNS disease in nodular lymphoma is rare. Our results support the suggestion of Young and his colleagues (1979) that CNS prophylaxis is only warranted in patients with advanced diffuse histiocytic or undifferentiated lymphomas. Results with the M-BACOP/D and COMLA regimes have highlighted the benefits that might accrue from the addition of methotrexate or cytosine arabinoside, but concurrent control groups have not been used for comparison.

Apart from its inadequacy with respect to CNS relapse, CHOP is an effective regime (McKelvey *et*

al., 1976; Armitage *et al.*, 1980) and is widely used for the treatment of advanced NHL. We suggest that a controlled trial to evaluate the efficacy of additional CNS prophylaxis with methotrexate and craniospinal irradiation would be ethical and timely.

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