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

C. J. HAWKEY
B.A., B.M., M.R.C.P.

P. J. TOGHILL
M.D., F.R.C.P.

University Hospital, Queen’s Medical Centre, Nottingham NG7 2UH

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 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)

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

*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 chemotherapeutic 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 predisposition 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>
<thead>
<tr>
<th>Case</th>
<th>Clinical features of CNS disease</th>
<th>Scan</th>
<th>Protein (g/l)</th>
<th>Glucose (mmol/l)</th>
<th>Cells/mm³</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drowsiness, dysphasia, hemiplegia, wasting of small muscles of hand</td>
<td>CAT scan—normal</td>
<td>3-0</td>
<td>—</td>
<td>376 Abnormal mononuclear cells with deeply clef nuclei and nucleoli</td>
<td>IT MTX* ×4</td>
<td>Died 7 weeks after onset of CNS symptoms. Diffuse meningeal disease at autopsy</td>
</tr>
<tr>
<td>2</td>
<td>Drowsiness</td>
<td>CAT scan—obstructive hydrocephalus</td>
<td>1-0</td>
<td>7-1</td>
<td>41 lymphocytes of abnormal type</td>
<td>Ventricular shunt, cranial irradiation; IT MTX ×4</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Fits</td>
<td>Isotope scan—frontal lobe lesions</td>
<td>0-25</td>
<td>3-7</td>
<td>No excess of cells initially. Later cytopsin showed cells with clef lobulated nuclei and prominent nucleoli</td>
<td>Cranial irradiation, IT MTX ×6</td>
<td>Died 10 months after onset of CNS symptoms. No autopsy</td>
</tr>
<tr>
<td>4</td>
<td>Confusion, pains in limbs</td>
<td>Not performed</td>
<td>0-5</td>
<td>3-9</td>
<td>17 abnormal mono-nuclear cells of malignant type</td>
<td>IT MTX</td>
<td>Died 2 months after onset of CNS symptoms. No autopsy</td>
</tr>
<tr>
<td>5</td>
<td>Spastic paraparesis, bilateral deafness, blindness</td>
<td>Isotope scan—normal</td>
<td>4-0</td>
<td>1-0</td>
<td>18 (45%) bizarre neoplastic cells</td>
<td>Cranial irradiation, IT MTX ×7</td>
<td>Died 10 days after onset of CNS disease. Diffuse infiltration of CNS with leptomeningitis at autopsy</td>
</tr>
<tr>
<td>6</td>
<td>Ill nerve palsy, sciatica</td>
<td>CAT scan—normal</td>
<td>0-6</td>
<td>3-6</td>
<td>Initially no excess, one month later malignant cells</td>
<td>IT MTX and Hydrocortisone ×2</td>
<td>Died 1 month after onset of CNS disease. No autopsy</td>
</tr>
</tbody>
</table>

*IT MTX = Intra-thecal 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.

References


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(Accepted 25 November 1982)
The need for prophylactic treatment to the central nervous system in patients with aggressive non-Hodgkin's lymphoma.

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*Postgrad Med J* 1983 59: 283-287
doi: 10.1136/pgmj.59.691.283

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