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Management of Burkitt's lymphoma involving the central nervous system[1]

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Summary

The clinical features and pathogenesis of CNS involvement in Burkitt's lymphoma have been reviewed, with an emphasis on the relevant therapeutic approaches. Certain 'prophylactic' measures have been suggested and several are currently undergoing clinical trial. These include the use of CCNU, a nitrosourea which effectively crosses the blood-brain barrier, and the use of craniospinal irradiation early in the course of treatment. Malignant pleocytosis can be palliated by the use of intrathecal chemotherapy, but malignant cells in peripheral nerves or deep in the sulci of the brain parenchyma will be relatively inaccessible to drugs in the circulating cerebrospinal fluid (CSF). A bilateral approach (i.e. simultaneous systemic plus intrathecal chemotherapy) may kill cells lodged in this anatomic sanctuary, and the increased use of cytotoxic drugs crossing the blood-brain barrier may facilitate this approach.

Résumé

L'auteur passe en revue les traits cliniques et la pathogénèse de l'action du CNS dans le lymphome de Burkitt, en mettant l'accent sur la therapeutique appropriée. Il suggère certaines mesures 'prophylactiques', dont quelques unes sont en ce moment soumises à une epicure clinique. Parmi celles-ce figure l'emploi du CCNU, un nitrosourea qui traverse effectivement la barrière sang-cerveau, et l'emploi de l'irradiation cranio-spinale, tôt dans le cours du traitement. Par l'usage de la chemotherapie intrathecale on peut pallier à la pleocytose maligne, mais les cellules malignes dans les nerfs peripheriques, ou dans les profondeurs des sillons du parenchyme cervical seront relativement inaccessibles à l'action des remedes dans le CSF. Un mode d'action bilateral (c.a.d. une chemotherapie simultanement systemique et intrathecale) pourrait détruire les cellules logées dans ce sanctuaire anatomique, et un emploi intensif des remedes cytotoxiques qui traversent les barrières sang–cerveau pourrait facilitates ce mode d'action.

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Introduction

Involvement of the central nervous system (CNS) in Burkitt's lymphoma remains a major therapeutic challenge in a neoplasm potentially curable by cytotoxic drugs (Ziegler *et al.*, 1970a). The prognosis in patients developing CNS involvement is considerably less favourable than in patients free from this complication (Ziegler *et al.*, 1970b), although it is not altogether clear at the present time whether neurologic involvement *per se* is directly responsible for decreased survival. Tumour cells lodged in the meninges, brain parenchyma and possibly peripheral nerves appear to be relatively inaccessible to most cytotoxic drugs administered systematically. Intrathecal chemotherapy sometimes eliminates malignant pleocytosis, but frequently affords only a temporary reduction of tumour cells in the cerebrospinal fluid (CSF). This paper deals with the clinical recognition, pathogenesis, and management of CNS involvement, derived from experience with 150 patients with Burkitt's lymphoma seen over a period of 4 years.

Clinical features and pathogenesis

The neurologic manifestations of Burkitt's lymphoma have been well-characterized in a number of clinical and pathological studies in Africa (Cockshott & Evans, 1963; Janota, 1966; Clifford *et al.*, 1967;, Wright 1967; Frank, 1968; Odeku & Osuntokan

1968; Ziegler *et al.*, 1970a; Ziegler & Bluming, 1971). Presenting features commonly include paraplegia (10–15%) and less commonly cranial or peripheral neuropathy which is usually associated with the finding of lymphoma cells in the CSF. Diffuse involvement of the meninges with numerous tumour cells in the CSF is usually associated with meningismus, and signs and symptoms of raised intracranial pressure. Malignant pleocytosis however is often detected by routine lumbar punctures in the absence of neurological symptoms or signs. Relapses manifested by malignant cells in the spinal fluid often in the absence of tumour elsewhere, usually occur within 10 weeks of initial therapy and are associated with a poor prognosis.

The pathogenesis of paraplegia appears to be more complex than simply extradural compression and spinal cord block. Some patients for example present with flaccid paraplegia of rather sudden onset, associated with poor sphincter control. Sensory manifestations are often lacking, and spinal myelography may reveal no abnormality. At autopsy, findings suggestive of spinal cord ischaemia or infarction are present. Other patients, presenting with paraplegia accompanied by sensory abnormalities may show filling defects or complete spinal cord block on myelography. Thus, ischaemia of the cord, due presumably to pressure on blood vessels by tumours, and/or actual dural invasion by tumour appear to be responsible for the myelopathy associated with Burkitt's lymphoma (Wright, 1964; Janota, 1966; Ziegler *et al.* 1970b).

The pathogenesis of malignant pleocytosis is speculative at present, but most evidence points to direct spread rather than blood-borne metastasis (Ziegler *et al.*, 1970b). It has been postulated that tumour cells gain access to the meninges and spinal fluid by early involvement of cranial and peripheral nerves, followed by gradual retrograde migration to the dura-arachnoid. Malignant cells lodged in peripheral (particularly cranial) nerves may escape the effects of cytotoxic drugs (and immunological attack), and maintain a proliferative advantage during clinical remission. Such a reservoir of cells in peripheral nerves, with access to the subarachnoid space could continuously 'seed' the CSF with malignant cells and infiltrate other cranial nerves and neural structures.

Treatment

The treatment of paraplegia in Burkitt's lymphoma is chemotherapy, and should be considered as a medial emergency. A lumbar puncture should be performed, and as the protein content may be considerably elevated and the CSF pressure low, gentle suction on the spinal needle with a syringe may be necessary to collect adequate CSF for examination. CSF should be collected in heparin, and CSF pressure, total and differential cell counts, glucose, and protein evaluated with the spinal needle left in place. Myodil radiographic contrast can be instilled through the spinal needle at this time for subsequent myelography. Although malignant pleocytosis is not commonly found in paraplegic patients (less than one-third in our series) intrathecal chemotherapy (see below) should also be initiated through the spinal needle if this finding is present. At the same time, systemic chemotherapy using intravenous cyclophosphamide, 40 mg/kg, should be administered in a single dose, and repeated following recovery of the white blood count. The results of such treatment can often be dramatic. We have observed children who presented with dense flaccid paraplegia demonstrating full recovery of neurologic function within 2 weeks. The longer neurologic disability has been present, however, the less likelihood of functional recovery.

The optimal management of malignant pleocytosis in Burkitt's lymphoma remains a therapeutic dilemma. This complication, noted in up to 40% of patients in the Kampala series, is associated with early relapse, development of drug-resistance, and a poor prognosis. The results of a variety of treatment trials using intrathecal (IT) methotrexate (MTX) and/or cytosine arabinoside (ARA-C) have been recently published (Ziegler & Bluming, 1971). The initial CSF response following IT chemotherapy was complete in nearly every patient with dramatic reduction of the malignant cell count within 1 week of treatment. Both MTX and ARA-C were effective in killing lymphoma cells in the CSF, but recurrences were common with both agents, and drug-resistance ultimately developed. Intensive regimens (e.g. daily IT treatment for 10 days) did not improve results over weekly or 4-daily schedules using either agent.

New therapeutic approaches

In order to design improved therapeutic regimens for the management of malignant pleocytosis in Burkitt's lymphoma, it is first necessary to clearly define the present therapeutic problems. These lie in two broad

areas: (1) the prevention of early CNS relapse and (2) the permanent eradication of malignant cells from the CNS.

Prevention of CNS relapse will require drugs which will adequately penetrate neutral tissue and destroy the cells lodged within. The present first-line drugs effective in Burkitt's lymphoma (alkylating agents) fail to cross lipid barriers to any appreciable extent and newer effective agents which have this property must be sought.

A controlled trial of 'prophylactic' IT chemotherapy to prevent the development of malignant pleocytosis was unsuccessful. Ten patients and ten controls were evaluated and the frequency of subsequent CNS relapse was similar in both groups (Ziegler & Bluming, 1971). This result may not be unexpected if peripheral nerves containing tumour are 'seeding' the CSF: these structures will not be affected by drugs administered intrathecally.

Current efforts to prevent CNS relapse in patients free of overt CNS involvement at the time of presentation include the administration of a new chemotherapeutic agent, CCNU, (*cis*-chloroethylnitrosourea) a drug with a wide range of antitumour activity (Hansen *et al.*, 1971), which has the added advantage of lipid solubility. An analogue of this agent, BCNU, has been shown effective in Burkitt's lymphoma (Clifford *et al.*, 1967), and CCNU is considered to be more potent. A trial evaluation of this drug is in progress, according to the study design noted in Fig. 1. Although it is too early to evaluate the results, a preliminary analysis shows that two of five patients in the CCNU-treated group and two of five patients in the untreated group have developed CNS relapse (malignant pleocytosis). The median observation time in these patients is only 4 months, however, and further study will be required before any conclusion can be drawn.

Another approach to the prevention of CNS involvement is the prophylactic irradiation of the cranio-spinal axis. This approach has been evaluated in patients with acute leukaemia, and the results are convincingly favourable (Aur *et al.*, 1971). Of forty-five patients so treated, only three developed malignant pleocytosis, compared to twenty-three of forty-five untreated controls. Preliminary studies in the Kenyatta National Hospital Radiotherapy Centre in Nairobi, Kenya have shown that cranio-spinal irradiation has therapeutic benefit in patients with CNS Burkitt's lymphoma (T. Norin, personal communication). A collaborative controlled study of the prophylactic value of cranio-spinal irradiation will soon be underway.

Intrathecal chemotherapy is the major form of treatment of malignant pleocytosis at present. Unfortunately this approach is rarely curative since the distribution of drug within the CNS is limited, and malignant cells undoubtedly lie in neural structures remote from the CSF. Simultaneous systemic and intrathecal chemotherapy is perhaps the best approach to this pharmaco-anatomic problem. The ideal agents, as mentioned above, are those which are both effective against Burkitt lymphoma cells and which readily penetrate neural tissue.

In addition to the route of drug administration, the schedule of drug should be adjusted to the kinetics of

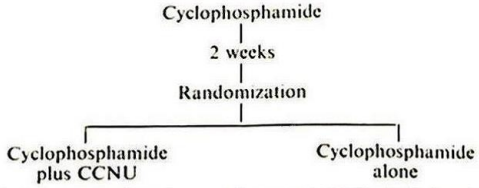

FIG. 1. Treatment of patients with stages I-III Burkitt's lymphoma.

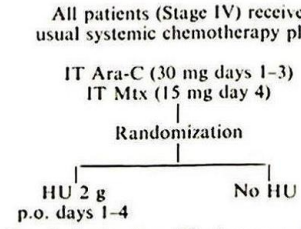

FIG. 2. Evaluation of hydroxyurea (HU).

the tumour cell population. Current evidence points to a cell doubling time of about 24 h in Burkitt's lymphoma, and the growth fraction is estimated to approach 100% (Iversen *et al.*, 1972). Therefore, continuous administration of cytotoxic drugs for several cell doubling times should, theoretically at least, destroy all tumour cells.

TABLE 1. Analysis of sixteen long-term survivors with CNS involvement

	No. patients
Stage:	
I-III	10
IV	6
Chemotherapy:	
CTX	9
TRIKE	7
IT therapy:	
Cycle	5
MTX	9
ARA-C	2
Neuropathy	8
Malignant cells only	8
Survival (median)	21 months (12–48)

CTX, cyclophosphamide; TRIKE, code name for a sequential systemic chemotherapeutic regimen consisting of cyclophosphamide, methotrexate, vincristine, and cytosine arabinoside. For details see Ziegler *et al.* (1970a); Cycle, IT. MTX 15 mg alternating every fourth day with IT. ARA-C for two cycles; MTX, methotrexate; ARA-C, cytosine arabinoside.

We recently obtained evidence that the cycle-active drug hydroxyurea (HU) was effective in Burkitt's lymphoma. As this compound crosses the blood-brain barrier it seemed logical to evaluate its role in the management of malignant pleocytosis. The study design for this trial is outlined in Fig. 2, and has been underway for 10 months at the Lymphoma Treatment Centre. Although twelve patients have entered the trial, sufficient time has not elapsed to enable conclusions to be drawn regarding the adjunctive effect of HU with IT chemotherapy.

The outlook for patients with malignant cells in the CSF is not entirely gloomy. In a series of sixty-three patients presenting with, or developing, malignant pleocytosis, sixteen have survived free of all tumour for 1 year or longer. An analysis of these patients appears in Table 1. No common features of these patients could be detected which might have predicted a good prognosis, however, and the explanation for why these few patients should survive remains obscure.

In conclusion, a concentrated and controlled therapeutic effort is needed in patients with Burkitt's lymphoma to prevent, and to eradicate involvement of the CNS. This goal can be best achieved through careful clinical trials in centres where Burkitt's lymphoma is frequently seen, and depends to a large extent upon the referral of patients to these centres, as well as close collaboration between the various investigators involved in the study. Further information is needed regarding the pathogenesis of CNS involvement, the pharmacology of cytotoxic drugs in relationship to the blood-brain barrier, and the kinetic behaviour of tumour cells in the CNS.

Acknowledgments

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