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CEREBROSPINAL IRRADIATION OF BURKITT'S LYMPHOMA

Failure in preventing central nervous system relapse

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Involvement of the central nervous system is a prominent clinical feature of Burkitt's lymphoma, appearing as either paraplegia, cranial nerve palsy, altered sensorium or asymptomatic malignant pleocytosis in the cerebrospinal fluid (ZIEGLER et coll. 1970). It may be present on admission, but frequently it is an accompanying complication of early relapse (ZIEGLER et coll. 1972).

The management of the central nervous disease remains the most challenging aspect of the treatment of Burkitt's lymphoma. Several attempts have been made at the Lymphoma Treatment Centre, Kampala, to prevent the development of this complication. These include short-term prophylactic intrathecal therapy, and oral administration of lipid-soluble agents which cross the blood-brain-barrier, namely hydroxyurea and (1-(2-chlorethyl)-3-cyclohexyl-1-nitrosourea) (CCNU). Intrathecal prophylaxis proved to be ineffective (ZIEGLER & BLUMING 1971) whilst CCNU, although inducing a delay in the appearance of central nervous manifestations, did not decrease their frequency, and it was associated with an increased death rate from resistant tumour (ZIEGLER et coll. 1975). The CCNU trial was therefore abandoned.

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Table 1

Treatment in the two groups

	Age (years)		Sex		Induction therapy	
	Median	Range	Male	Female	CTX	COM
Irradiation	8	4–14	6	5	3	8
No irradiation	5	4–14	6	5	5	6

Hydroxyurea was not associated with any adverse side effects, but it did not confer any beneficial effects on its recipients (unpublished data).

Cerebrospinal irradiation has been shown to be effective in preventing central nervous relapse in children with acute lymphoblastic leukemia (AUR et coll. 1972, HURSTU et coll. 1973). An attempt was therefore made to combine this type of irradiation with systemic chemotherapy in Burkitt's lymphoma with the hope that it would delay or prevent the development of central nervous disease. The result of a randomized clinical trial of cerebrospinal irradiation versus no further therapy is now reported.

Material and Methods

The material consisted of all patients with histologic or cytologic diagnosis of Burkitt's lymphoma who were free of central nervous involvement on admission and at the time they attained complete remission. Remission induction was achieved using either cyclophosphamide alone (CTX) or a combination of cyclophosphamide, oncovin and methotrexate (COM) as previously described (OLWENY et coll. 1976). Those patients who were free of both systemic disease and involvement of the central nervous system were further randomized by stage and induction regimen to receive or not to receive irradiation. The staging system used was based on the staging criteria proposed by ZIEGLER & MAGRATH (1974), and the randomization was performed by previously prepared cards.

Those randomized to be irradiated were sent to the Kenyatta National Hospital, Nairobi, where radiation therapy was given with a ^{60}Co unit (Siemens Gammatron). The brain was irradiated from two opposing lateral ports and the spinal cord from two portals with floating border. The treatment was given over 2 periods of 5 days each, commencing on a Monday and ending on a Friday, and separated by a weekend, during which radiation therapy was not given. Each of the daily doses was superfractionated (3 treatments at 4 hourly intervals) as previously described (NORIN et coll. 1971). The calculated tumour dose of the brain and of the spine was 20 to 24 Gy (0.7 to 0.75 Gy per fraction).

All patients were closely followed up and the cerebrospinal fluid was examined every 2 weeks for 6 months and then monthly up to 12 months. Special attention was paid to malignant pleocytosis and protein concentration. The same method of ex-

Table 2

Relapse frequencies in relation to induction regimens

Induction	Irradiation			No irradiation		
	Relapse	No relapse	Total	Relapse	No relapse	Total
CTX	0	3	3	2	3	5
COM	6	2	8	2	4	6
Total	6	5	11	4	7	11

amination has been used at the Lymphoma Treatment Centre since 1968 (SKEEL et coll. 1968). Whenever any doubt existed, a cytocentrifuge specimen stained with Wright's stain was examined. Patients who relapsed received further courses of COM systemically plus intrathecal cytosine arabinoside (30 mg daily for 3 days) and methotrexate (15 mg) on the fourth day. Elliot's B-solution was used as diluent for all intrathecal administrations. Tests of significance were done using Fisher's exact test (for one tail).

Results

Twenty-five patients fulfilled the criteria set forth, but in 2 malignant pleocytosis in the cerebrospinal fluid developed before they could travel to Nairobi (while awaiting appointment date), and the parents of one other child refused to participate. Thus, 22 patients remained, 11 were irradiated and 11 were controls.

The 2 groups were comparable with respect to age, sex and induction regimens (Table 1). Ten patients have relapsed, in 8 (80 %) of these as an asymptomatic malignant pleocytosis. In the remaining 2 patients there were cranial nerve palsies and recurrent jaw tumours in addition to the pleocytosis. These 2 patients had received CTX only as the inductive regimen. The relapse frequency in relation to the induction regimens appear in Table 2. Eight of 14 (57 %) COM induced patients have relapsed as compared with 2 of 8 (25 %) CTX induced patients. The differences in relation to the induction regimens are not significant ($p = 0.204$). Six of 11 (54 %) irradiated patients have relapsed as compared with 4 of 11 (36 %) in the control group (Table 2). The median follow up periods are $21\frac{1}{2}$ months (range 3 to 35) and 19 months (range 3 to 36) for the irradiated and the control groups, respectively. No significant difference exists between the relapse frequencies in relation to stage of disease. Most relapses occurred in patients with stages AR and D (Table 3).

Two patients in the irradiated group are known to be dead, a third is lost to follow up and is presumably dead. All these 3 had died at home with features suggestive of raised intracranial pressure, namely severe headache and vomiting. In the control group one patient died at home of unknown cause and 2 are alive but with active central nervous disease. The median survival period is 24 months (range 3 to 36) for the irradiated group of patients and 19 months (range 3 to 37) for the control group.

Table 3

Relapse frequency in relation to stage of disease

Stage	Irradiation				No irradiation			
	Relapse				Relapse			
	None	One	Two	Total	None	One	Two	Total
A	3	—	—	3	2	—	—	2
AR	1	2	1	4	2	—	1	3
B	—	1	—	1	—	—	1	1
C	1	—	—	1	2	1	1	4
D	—	2	—	2	1	—	—	1
Total	5	5	1	11	7	1	3	11

Two patients were found to have malignant cerebrospinal pleocytosis soon after completing irradiation. The mean cell count at the time of relapse for the 6 irradiated patients was 34 (range 4 to 82), and for the 4 non-irradiated patients 22 (range 15 to 30) cells. The corresponding mean protein concentration at the time of relapse for the 6 irradiated patients was 63.3 mg% (range 10 to 100). Excluding the 2 patients with malignant pleocytosis upon completion of the irradiation the mean cell count in the remaining 4 relapsing patients was 1.5 (range 0 to 4); it rose to 13 (range 4 to 27) when relapse occurred. The protein concentration for these 4 patients soon after completion of irradiation was 15 mg% (range 10 to 30); it rose to a mean of 45 mg% (range 10 to 100) at the time of relapse. None of the 4 control patients who relapsed had elevated protein concentration but their mean cell count rose from a mean of 3 (range 0 to 9) to a mean count of 22 cells (range 15 to 30).

Relapsing patients were treated with intrathecal sequential cytosine arabinoside and methotrexate, and 5 of 10 patients attained complete remission with a median duration of 26 months (range 16 to 28). Of the 5 patients who failed to achieve remission, 2 are dead, one is lost to follow up and presumably dead while 2 are alive but with persistent disease of the central nervous system.

The adverse side effects included alopecia, nausea and vomiting in all patients irradiated. Leucopenia was mild except in one patient with a WBC of 400/mm^3 following the irradiation. No patient has developed a second malignancy. The post-irradiation syndrome characterized by fever and fatigue was not observed in any case.

Discussion

Following the development of effective chemotherapy for remission induction in acute lymphoblastic leukemia, a new phenomenon emerged, i.e. involvement of the central nervous system. Children in complete hematologic remission frequently

developed symptoms and signs of meningitis and were found to have leukemic cells in the cerebrospinal fluid. The same situation has developed in Burkitt's lymphoma. Effective inductive regimen is now available and remissions are terminated by relapse of the central nervous system.

Unlike acute leukemia where cerebrospinal irradiation early during complete remission prevents relapse, this type of irradiation does not prevent or even delay central nervous relapse in Burkitt's lymphoma. The cause of the failure is not well understood but several possibilities may be discussed. First, little is known about kinetics of malignant cells in the central nervous system, although it is suggested that these cell kinetics may be similar to those of Burkitt's lymphoma, cells from peripheral sites (IVERSEN et coll. 1974). It is possible that in certain instances the cell doubling time as well as the growth fraction may not be comparable to that of peripheral tumours. The probably altered kinetics may partly explain the poor response.

Secondly, the majority of the 10 relapsing patients in the present material (5 of 6 in the irradiated and 3 of 4 in the control group) had advanced disease on admission. Before surgery, 2 of 7 stage AR patients had stage C and the remaining 5 had stage D. Stages C and D usually have disseminated disease. It is possible that some of these patients had foci of malignant cells in the central nervous system at the time of irradiation. This could have been the situation especially in 2 patients who were found to have malignant pleocytosis at the completion of irradiation. If this is the case, then 24 Gy may not have been adequate to control already established involvement of the central nervous system as was observed in leukemic patients (HURSTU et coll. 1973). This dose was, however, found to be sufficient in inducing remissions of systemic Burkitt's tumour (NORIN & ONYANGO, to be published). This observation suggests that there may well be differences between systemic disease and central nervous tumour and such differences may be based on kinetics of tumour growth.

Soon after irradiation immature, blast-like basophilic cells have been observed in some leukemic children (GARWICZ et coll. 1975). It may be said that blast-like cells could have been induced by the irradiation in some of the present patients as well and were mistaken for lymphoma cells. However, this is unlikely because careful cytocentrifuge cytology was performed in the 6 irradiated patients at the time of relapse, and in 4 of 6 irradiated patients the cerebrospinal fluid was normal upon completion of the irradiation but malignant cells were detected 5 to 30 weeks later. In one of these a second relapse occurred after 14 weeks. Furthermore, in the post-irradiation syndrome described by GARWICZ et coll., those patients who developed blast-like cells in the cerebrospinal fluid, maintained normal total cell count and protein concentration. In the present patients both the total cell count and protein concentration were clearly elevated. Admittedly in 2 patients the malignant pleocytosis was detected soon after their return from Nairobi, but in both the pleocytosis persisted till their death 3 and 8 months later, respectively. Although a similar rise in the cell count occurred in the non-irradiated patients at the time of relapse no concomitant rise in the protein concentration was found in these 4 patients. The

explanation for the disparity is not clear, but is possible that the irradiation per se may be responsible for the elevation in the protein concentration.

COM-treated patients tend to relapse with central nervous disease only while CTX-treated patients relapse with both systemic disease and central nervous tumour (OLWENY et coll. 1976). This observation may explain the slight over-representation of the COM-treated among the relapsing patients. The duration of the remission and the survival period is similar for the irradiated and the control groups.

In conclusion, prophylactic irradiation of the central nervous system has not conferred any benefit to children with Burkitt's lymphoma.

The data on each individual child may be obtained on request from the Uganda Cancer Institute.

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SUMMARY

Twenty-two patients with Burkitt's lymphoma in complete remission induced by either cyclophosphamide or a combination of cyclophosphamide, oncovin and methotrexate were randomized to receive or not to receive prophylactic cerebrospinal irradiation. Six of 11 irradiated patients relapsed with tumour of the central nervous system as compared to 4 of 11 controls. Relapse frequency appeared to be related to stage of disease on admission. It is concluded that irradiation does not prevent relapse.

ZUSAMMENFASSUNG

Zweiundzwanzig Patienten mit Burkitts Lymphom mit einer vollständigen Remission, entweder durch Cyklophosphamid oder eine Kombination von Cyklophosphamid, Oncovin und Methotrexate erzielt, wurden in eine Gruppe mit und eine Gruppe ohne prophylaktische Bestrahlung von Gehirn und Rückenmark eingeteilt. Sechs von 11 bestrahlten Patienten hatten ein Rezidiv mit einem Tumor des zentralen Nervensystems verglichen mit 4 von 11 Kontrollen. Die Rezidivfrequenz scheint zum Stadium der Erkrankung bei der Einweisung relatiert zu sein. Es wird festgestellt, dass Bestrahlung nicht ein Rezidiv verhindert.

RÉSUMÉ

Vingt-deux malades atteints de lymphome de Burkitt en rémission complète induite soit par le cyclophosphamide soit par une association de cyclophosphamide, d'oncovin et de méthotrexate ont été randomisés pour recevoir ou ne pas recevoir une irradiation prophylactique cérébro-spinale. Six des 11 patients irradiés ont fait une récidive avec une tumeur du système nerveux central; il y a eu 4 récidives sur 11 sujets non irradiés. La fréquence des récidives paraît en rapport avec le stade de l'affection au moment de l'admission. Les auteurs concluent que l'irradiation n'empêche pas la récidive.

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