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Original Paper

Combined Therapy for Primary Central Nervous System Lymphoma in Immunocompetent Patients

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A retrospective series of 13 immunocompetent patients with histological diagnosis of primary central nervous system lymphoma (PCNSL) is presented. The series was divided into Group A, 6 patients treated with radiotherapy alone, and Group B, 7 patients treated with chemotherapy and radiotherapy. Clinicopathological patterns were similar for the two groups. In Group A, 4 patients achieved complete remission after radiotherapy (45–59.4 Gy) but relapsed within 9 months and died within 21 months of diagnosis. 4 Group B patients received chemotherapy followed by radiotherapy, and three who received a methotrexate-containing regimen are alive and disease-free at 34, 42 and 45 months, while the fourth died after 11 months. The other 3 subjects in this group were treated with radiotherapy followed by chemotherapy, and died within 15 months of diagnosis. Although radiotherapy is the standard treatment, chemotherapy has potentially an important role in the management of PCNSL. The sequence of combined treatment could be crucial to improvement of outcome.

Key words: primary central nervous system lymphoma, brain neoplasms, non-Hodgkin's lymphomas, chemotherapy, radiotherapy, combined modality therapy, blood–brain barrier
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INTRODUCTION

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) is an uncommon neoplasm (1% of brain tumours [1–5], 1% of all non-Hodgkin's lymphoma (NHL) [6] and 1.6% of extranodal NHL). In the past 15 years, the incidence has risen 3-fold in high-risk groups (immunocompromised, AIDS) [2] and in the general population [7]. PCNSL is characterised by symptoms caused by an intracranial mass with focal cerebral deficits in approximately 50% of cases [8]. Computerised tomography (CT) scan generally detects multiple masses in the paraventricular regions and basal ganglia. Although there are no histological differences between extranodal NHLs and PCNSL [9], the prognosis of the latter is very poor [3, 4] due to early recurrence in more than 90% of patients, with 5-year survival less than 5% [1–5, 10, 11]. The median survival for patients receiving only supportive care is 1.8–3.3 months [1, 6]. Surgery has not improved the survival of patients with PCNSL (0.9–5.5 months) [1, 4, 9]. The use of corticosteroids improves symptoms only transiently. Patients treated with radiotherapy alone have a median survival of 15 months [1, 6, 9, 10, 12, 13]. Despite the high complete response (CR) rate obtained with conventional treatment, i.e. whole brain radiotherapy (WBRT) and corticosteroids [1, 12], disease-free and overall survival are very poor [3, 4, 6, 10–12, 14, 15]. Favourable results of combined modality therapy for systemic NHLs suggest a potential benefit in PCNSL with the same approach. Although the role of chemotherapy in the multimodality treatment of PCNSL has not yet been defined [6, 9, 10, 15, 16], some authors have reported a significant improvement in therapeutic outcome with various schedules of chemotherapy [13, 17–20].

In this retrospective series, the results of combined therapy are compared with those obtained with radiotherapy alone. Moreover, potential improvement of the survival rate with chemotherapy as the initial step of the combined therapy is discussed.

PATIENTS AND METHODS

Patients' characteristics

From 1982 to 1992, 13 immunocompetent patients with histologically proven PCNSL were treated and evaluated. No evidence of extracranial NHL localisation was observed for any patient after a staging evaluation consisting of chest X-ray, whole body CT, liver function test, lymphography and bone marrow biopsy. Three other cases in which staging showed systemic dissemination were excluded from this analysis.

Initial evaluation of all patients included cranial CT with intravenous contrast infusion. Six patients underwent NMR,

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and 4 an angiographic evaluation. Cerebrospinal fluid (CSF) cytological examination was performed in 8 cases. The median age was 52 years (range 16–70 years). 6 patients were males and 7 females. Clinical features are summarised in Table 1. Clinical presentation with multiple symptoms or neural signs was usual. The average time from first symptom to diagnosis was shorter than 2 months (range: 5 days–12 months).

Radiological evaluation and pathology

CT evaluation detected multiple intracranial lesions in 4 cases. The most common location was deep temporal lobe (Table 1). One patient (no. 6) had posterior fossa lesions, and another (no. 12) had diffuse infiltration of several bilateral cranial nerves. This patient was the only one with a positive CSF cytological examination.

The histlogical samples were obtained by surgical resection in 9 cases, stereotactic biopsy in 3 and CSF cytology in the remaining patient. According to the Working Formulation, all but one neoplasm (no. 12) were intermediate- or high-grade lymphoma with a B-cell immunophenotype (Table 1).

Treatment

Patients were divided into two groups: Group A ($n = 6$) treated with radiotherapy alone and Group B ($n = 7$) with chemotherapy and radiotherapy. As shown in Table 2, there were no differences among the two groups for clinicopathological characteristics. All patients but one (no. 1: 10 MeV photons) were irradiated using 6 MeV photons with 180 cGy daily fractions, 5 days/week.

Group A patients received WBRT with or without boost to the primary tumour site. The total target dose for this group was 45–59.4 Gy (Table 3). In patient nos 2 and 3, irradiation was stopped early because of progressive coma and pulmonary embolism, respectively.

Patients in Group B received anthracycline-containing polichemotherapy (Table 4): VEPA regimen (vincristine, doxorubicin, cyclophosphamide, prednisolone) [18] for 4 or 5 courses ($n = 3$), CEOP (cyclophosphamide, epirubicin, vinicristine, prednisone) for 4 cycles ($n = 1$), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for 5 cycles ($n = 1$) and M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone) [21] for 4 courses ($n = 2$). Three patients (nos 7, 8 and 9) from this group were treated with postradiation chemotherapy. The remaining 4 patients were treated with chemotherapy followed by radiotherapy. Two of these were irradiated only after progression following CEOP chemotherapy (no. 10) or relapse (no. 11). Patient no. 11 underwent radiotherapy associated with the chemotherapy PEI (carboplatin, etoposide and ifosfamide) regimen after local relapse from M-BACOD chemotherapy.

Radiotherapy in all Group B patients except one consisted of WBRT with a boost to the bulky lesion (total target dose: 51–59.4 Gy). The remaining patient (no. 12), who had a positive CSF cytology examination, received eight doses of intrathecal

Table 1. Clinical presentation and histological diagnosis

Patient no.	Symptoms	Duration of symptoms	Site of involvement	No. of lesions	Method of diagnosis	CSF	Histotype-WF (Kiel)
1	Changes in personality, diplopia	3 w.	Basal ganglia	S	SB	neg	Diffuse large cell - G (Centroblastic)
2	Dysphasia, paresthesia, hemiplegia, headache	2 m.	Parietal lobe (L), basal ganglia	M	SB	NV	Convoluted cell - I (Lymphoblastic)
3	Seizures	2.5 m.	Frontal lobe (R), parietal lobe (R)	S	SR	NV	Diffuse small and large - F (Centroblastic–centrocytic diffuse)
4	Headache, amnesia, nausea, vomiting	2 m.	Temperal lobe (R)	S	SR	NV	Large-cell - H (Immunoblastic)
5	Hemiparesis	2.5 m.	Frontal lobe (R), parietal lobe (R)	S	SR	neg	Diffuse large cell - G (Centroblastic)
6	Cerebellar symptoms, diplopia	3 w.	Occipital lobe (L), Cerebellum (L)	M	SR	neg	Diffuse large cell - G (Centroblastic)
7	Seizures	3 w.	Temporal lobe (R)	S	SR	NV	Diffuse large cell - G (Centroblastic)
8	Headache, nausea, hemianopsia	2 w.	Temporal lobe (L), basal ganglia	M	SB	neg	Small non-cleaved - J (Burkitt's type)
9	Hemiplegia	3 w.	Frontal lobe (R)	S	SR	neg	Diffuse large cell - G (Centroblastic)
10	Headache, confusional syndrome	2 w.	Periventricular area	S	SR	NV	Diffuse large cell - G (Centroblastic)
11	Seizures	5 d.	Temporal lobe (L)	S	SR	neg	Diffuse large cell - G (Centroblastic)
12	Hemiplegia, headache, diplopia	12 m.	Periventricular area, basal ganglia, several cranial nerves	M	CCE	pos	Large-cell NOC (Unclassified)
13	Headache, changes in personality	10 d.	Temporal lobe (R)	S	SR	neg	Large-cell - H (Immunoblastic)

w, weeks; m, months; d, days; L, left; R, right; S, solitary lesion; M, multiple lesion; SB, stereotactic biopsy; SR, surgical resection; CCE, CSF cytological examination; NV, not valuable; neg, negative; pos, positive; NOC, not otherwise classified; WF, working formulation.