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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.

Table 2. Comparison of the clinical and pathological characteristics of patient groups

	Group A RT alone (n = 6)	Group B Combined therapy (n = 7)
Sex		
Males	3	3
Females	3	4
Age		
<30	0	1
30–60	4	5
>60	2	1
Karnofsky score		
<40	1	1
40–60	2	3
>60	3	3
Size of lesions		
≤5 cm	3	3
>5 cm	3	4
Number of lesions		
Solitary	4	5
Multiple	2	2
Histotype (WF)		
Intermediate-grade	4	4
High-grade	2	2
Not specified	0	1

Table 3. Group A—RT alone: treatment, objective response (OR), disease-free survival (DFS) and survival (Sv)

No.	WBRT (Gy)	Boost (Gy)	OR	DFS (months)	Sv (months)	Cause of death
1	45	–	CR	8.7	21	NHL progression
2	2	–	NV	NV	4	Progressive coma
3	6	–	NV	NV	4	Pulmonary embolism
4	45	10.8	CR	9	14	NHL progression
5	45	–	CR	8.4	21	NHL progression
6	45	14.4	CR	8	20	NHL progression

NV, not valuable ; CR, complete remission.

methotrexate (MTX) and concomitant intravenous chemotherapy followed by 39.6 Gy to the whole brain and 26.4 Gy to the spinal cord. Disease-free survival was measured from the data of the assessment of CR. Survival was calculated from the date of diagnosis.

RESULTS

Group A

4 patients that received an adequate target dose were assessable for response. They achieved CR with clinical improvement, but relapsed within 9 months of the assessment of CR (Table 3). The site of relapse was invariably the brain. Of 2 patients that received a boost, one relapsed within the boosted area. After recurrence, a further transient response was observed in 2 cases with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) orally and intrathecal MTX and cytarabine (ARA-C). All these patients died from neural lymphomatous progression within 21 months of histological diagnosis.

Group B

All patients were evaluable for response. The results are reported in Table 4. Three patients treated with WBRT followed by chemotherapy achieved CR. Two (nos 7 and 9) relapsed in the brain after 7 months, and died within 15 months of diagnosis. In these patients, no response was obtained with further salvage treatment (CCNU orally, intrathecal chemotherapy). The third patient (no. 8) died of pulmonary embolism while disease-free after 8 months from diagnosis.

3 of the 4 patients treated with preradiation chemotherapy achieved CR. The remaining patient (no. 10) had a PR, but had local progression that was unsuccessfully treated with WBRT (45 Gy) and a boost (6 Gy) to the bulky area. The patient died 11 months after diagnosis. Patient 11 achieved CR but relapsed after 12 months; he had a CR with 3 courses of PEI regimen followed by radiotherapy and is alive and disease-free 42 months after diagnosis.

The remaining 2 patients (nos 12 and 13), who received chemotherapy followed by radiotherapy, both had a CR and are alive and disease-free after 45 and 34 months, respectively. 2 of the 6 patients treated with a boost to the bulky lesion relapsed. One patient relapsed within the boosted area and the other outside this.

While no patient is alive from Group A, 3 patients from Group B are alive and disease-free; all were treated with a preradiation methotrexate-containing chemotherapy without evidence of neurological toxicity.

DISCUSSION

PCNSL is a very aggressive neoplasm with a poor prognosis. Conventional treatment, i.e. WBRT and corticosteroids, obtains a high CR rate, but most patients relapse within 1 year from the start of treatment [1, 6, 9, 10, 12, 13, 22]. Moreover, surgery does not improve survival [1, 19, 23], producing an important and definitive neurological sequelae. Optimal management has not yet been defined.

Although the optimal radiation dose is still to be determined [3, 10, 11], more than 40 Gy seems to be an adequate dose of WBRT, having a favourable impact on survival [10, 11, 23]. Previous reports suggest that a dose–response relationship may exist [4, 10, 13], and a statistically significant improvement in survival time with a total target dose >50 Gy has been reported [4, 13]. In the current series, radiotherapy was homogeneous and adequate as for field and dose. Our results confirm that radiation therapy alone is insufficient to improve local control in patients with PCNSL. In agreement with a previous report [19], brain recurrences in patients treated with WBRT plus boost occurred with similar frequency within (2/5) and outside (3/5) the boosted zone. Outcome with radiotherapy alone was similar to those previously reported, while the role of a boost to the bulky lesion remains unclear.

The prophylactic and therapeutic role of spinal cord irradiation (SCI) is not well defined, but is known to be highly toxic. It seems probable that intrathecal chemotherapy effectively treats meningeal lymphoma. In the current series, one patient with postive CSF cytology received 26.4 Gy to the spinal cord without late neurotoxicity. The patient is alive and disease-free after 45 months from clinical diagnosis. However,

Table 4. Group B—combined therapy: treatment, objective response (OR), disease-free survival (DFS) and survival (Sv)

No.	Sequence of treatment		OR	DFS (months)	Sv (months)	Cause of death
7	45 + 14.4 Gy	VEPA	CR	7.5	15	NHL progression
8	45 + 14.4 Gy	CHOP	CR	NV	8	Pulmonary embolism
9	45 + 14.4 Gy	VEPA	CR	7.2	15	NHL progression
10	CEOP	45 + 6 Gy	PR	NV	11	NHL progression
11	M-BACOD	45 + 6 Gy	CR	12	42*	
12	VEPA	39.6 Gy	CR	42*	45*	
13	M-BACOD	45 + 6 Gy	CR	30*	34*	

PR, partial remission; CR, complete response; NV, not valuable.
* Disease-free survivors.

contemporaneous intrathecal chemotherapy does not allow any conclusion regarding the therapeutic activity of SCI to be drawn.

Good results from combined modality therapy for systemic NHL suggest a potential benefit of chemotherapy in the treatment of PCNSL. Since PCNSL is a rare neoplasm, data from combined therapy is scarce. Few prospective studies have been conducted, while retrospective studies include a small number of cases treated heterogeneously. Nevertheless, favourable results have been obtained with high-dose methotrexate (HD-MTX) [13, 24], postradiation PVC (procarbazine, vincristine, CCNU) [25] or VEPA regimens [18], intravenous HD-MTX and intrathecal MTX before WBRT with further systemic high-dose cytarabine (HD-ARA-C) [19]. Moreover, some retrospective studies, which compared radiotherapy alone with combined therapy, concluded that chemotherapy may improve disease-free survival (DFS) and overall survival (OS) [25–28]. Although it is difficult to draw firm conclusions based on a small series, our experience suggests an important role for chemotherapy in the treatment of PCNSL. In fact, the patients treated with a combined therapy had longer DFS and OS.

Although, in the current series, all patients except one, treated with an adequate dose of either chemotherapy or radiotherapy, reached CR, those treated with radiotherapy alone or post-irradiation chemotherapy relapsed within 9 months. In contrast, preradiation chemotherapy improved DFS and OS. In fact, the only 3 long-term survivors of the current series were treated with chemotherapy followed by radiotherapy. An improved outcome with this sequence of treatment was also observed by other authors. Hochberg and associates [2] and Gabbai and associates [24] reported a median survival of 42 and 27+ months, respectively, in patients treated with HD-MTX, either alone or in combination with the CHOD regimen (cyclophosphamide, doxorubicin, vincristine, prednisolone). DeAngelis and associates [19] found a prolonged progression-free period (median, 51 months) in 31 patients treated with HD-MTX followed by radiotherapy and HD-ARA-C. Only Brada and associates [16] reported a negative effect of preradiation chemotherapy on survival, with a median OS of 14 months in 10 patients treated with MACOP-B regimen (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), and 16 months for a historical group of 25 patients treated with radiotherapy alone.

However, postradiation chemotherapy has been successfully employed by several authors. Shibamoto and colleagues [18], using VEPA regimen, found a significant difference of survival as compared to the patients treated with radiotherapy alone. In their series of 30 patients, 14 received combined therapy and achieved a 2-year survival of 45%, while 75% of patients treated with radiotherapy alone died within 14 months from the start of treatment. Notably, only 9 of the 16 patients from the group treated with radiotherapy alone received more than 45 Gy, while 4 patients were irradiated using an involved field. In agreement with current opinion, 10 patients from the control group received inadequate radiotherapy, while all 14 patients treated with VEPA regimen were adequately treated. Pollack and associates [23] described a favourable impact of postradiation chemotherapy on survival in 27 patients in comparison with radiotherapy alone. However, the control patients were irradiated heterogeneously, and half received less than 40 Gy WBRT, while 10 underwent a total target dose which could be considered inadequate.

The usefulness of initial chemotherapy could be valuable considering the characteristics of the blood–brain barrier (BBB) in the PCNSL. Initially, as evidenced by the tomographic enhancement, the BBB of PCNSL areas is impaired and drugs may reach the lymphomatous cells. With the response, the lymphomatous masses regress and BBB progressively returns to normal (within 3–4 weeks [16]), hampering further response.

Since BBB is not homogeneously impaired, an initial administration of agents that permeate normal BBB is necessary. MTX seems to be the most active agent in the treatment of PCNSL. In fact, DeAngelis and associates [19], as described above, found a significantly longer DFS (median, 51 months) in a series of 31 patients treated with HD-MTX followed by radiotherapy and HD-ARA-C, compared with 16 patients treated with radiotherapy alone. In the current series, the 3 long-term survivors received an initial MTX-containing chemotherapy, either by systemic or intrathecal route, while the fourth patient, treated with initial chemotherapy not containing MTX, died after 11 months.

BBB disruption, either by mannitol [29] or intra-arterial chemotherapy [20], is cumbersome and associated with severe morbidity and mortality near 20% [20]. Moreover, a high recurrence rate has been observed, and only less than 15% of patients survived over 2 years after diagnosis [20].

The response to initial treatment should not be considered as a prognostic factor for survival, since all patients from both groups reached CR but only 3 are still alive. Late neurological toxicity associated with combined therapy has been reported in 11.5% of 1-year survivors, and consisted of dementia, ataxia and

deteriorating cognitive function [19]. None of the long-term survivors in our series showed symptoms of neurotoxicity after a follow-up of 34–45 months. Elderly subjects [19] and patients treated with WBRT contemporaneously to MTX-containing chemotherapy may be particularly vulnerable. Our survivors were younger than 50 years and MTX was administered before radiotherapy, which, at least experimentally, reduced the risk of leucoencephalopathy [30].

Although the small number of patients does not allow statistically significant conclusions, the survival of patients treated with preradiation chemotherapy is longer than any median survival reported with radiotherapy alone [1, 3–5, 10, 11], which suggests a considerable impact of chemotherapy on treatment outcome.

In conclusion, any immunocompetent patient with PCNSL may be considered for initial chemotherapy with efficacious agents against systemic NHL that permeate the normal BBB, followed by WBRT. The benefit of radiation boost, SCI, contemporaneous intrathecal chemotherapy and high-dose chemotherapy remains undefined.

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