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## Original Paper

# Primary Central Nervous System Lymphoma: Treatment with Chemotherapy and Radiotherapy

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**Between 1989 and 1993, 22 HIV negative patients with primary central nervous system lymphoma (PCNLS) were treated with three different regimens. In group A, 13 patients received preradiotherapy systemic and intrathecal methotrexate (MTX), radiotherapy (RT) and three courses of post-RT chemotherapy (CT) with thiotepa and procarbazine. In group B, 4 patients received a similar CT only after RT and without intrathecal MTX in 3/4 cases. In group C, 5 elderly patients received CT alone. In group A, 9/13 patients achieved response after pre-RT CT and 12/13 were in complete response (CR) after RT. After a median follow-up of 27 months, 8/13 (62%) patients are alive but 4 have leucoencephalopathy and cognitive dysfunction. In group B, all 4 patients were in CR after RT but the 3 patients who did not receive intrathecal MTX died within 10 months with meningeal recurrence. In group C, 4/5 patients had a response to CT. 2 patients died of recurrent tumour at 5 and 10 months, and 2 are living in CR 11+ and 21+ months after diagnosis, 1 after salvage CT. Combined treatment with RT and CT is useful in PCNSL but adequate treatment of the meninges is required. CT alone is sometimes of value in elderly patients in whom RT is not indicated.**

**Key words: primary central nervous system lymphoma, chemotherapy**
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## INTRODUCTION

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) is a rare neoplasm, accounting for approximately 0.70% of malignant lymphomas and 0.85–1.5% of primary intracranial tumours [1, 2]. Yet, its incidence is increasing not only in HIV positive patients, but also among immunocompetent patients [3]. Unlike brain tumours of glial origin, PCNSL is highly responsive to conventional treatment with whole-brain radiotherapy (WBRT) and corticosteroids. Unfortunately, the duration of response after WBRT is brief and median survival does not exceed 12–18 months in most published series [4, 5]. Recent evidence suggests that chemotherapy in combination with cranial irradiation at the time of initial treatment benefits patients, in terms of median survival and disease-free survival [1, 6, 7]. In this paper, we review our experience of chemotherapy in 22 immunocompetent patients with PCNSL.

## PATIENTS AND METHODS

We reviewed the records of 22 HIV negative patients suffering from PCNSL who were treated between 1989 and 1993. A pathological diagnosis was obtained in 19/22 patients (large cell, 7; large immunoblastic, 3; lymphoblastic, 2; small cell cleaved, 1; large but not otherwise classified, 6). Immunohistochemical studies performed in six tumours revealed B-lymphocyte lineage in all. In 3 patients, including 1 with a hyalitis, the diagnosis was based on magnetic resonance imaging (MRI) (see below). 11 patients had a solitary tumour (supratentorial in 8 and infratentorial in 3) and 11 had multifocal lesions. All patients underwent a staging evaluation that included lumbar puncture, abdominal chemotherapy (CT), bone marrow biopsy, an ophthalmologic examination including slit lamp, and HIV antibody titres. None of the patients had evidence of systemic disease. However, 4 had a uveitis and 2 had evidence of meningeal dissemination with malignant cells in the cerebrospinal fluid (CSF).

Three groups were defined according to the administered treatment.

Group A (pre- and postradiotherapy (RT) chemotherapy) consisted of 13 patients. There were 6 men and 7 women. The mean age was 62 years (range, 43–72). Median Karnofsky prior to treatment was 50. The diagnosis of PCNSL was established by pathological examination of a surgical specimen of the brain tumour in 11 and by a vitrectomy in 2. Chemotherapy consisted of pre-RT intravenous (i.v.) methotrexate (MTX) 1 g/m$^2$, given weekly for two doses along with six doses of intrathecal metho-

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trexate (administered through an Ommaya reservoir in 6 patients and by lumbar punctures in 7 patients) given on a twice weekly schedule with leucovorin rescue. MTX administration was followed within 2 weeks by a course of RT, delivering a dose of 3000–4000 cGy to the whole brain (WBRT) with a 1000–2000 cGy boost to the tumour bed. 3 weeks after completion of RT, patients received three courses of thiotepa and procarbazine. Each course consisted of thiotepa (40 mg/m$^2$ i.v. at day 1) and procarbazine (100 mg/m$^2$ orally (p.o.) days 1–15). The courses were repeated every 4 weeks. Patients also received prednisone, usually 80 mg/day, that was progressively tapered during RT. Eligibility requirements for chemotherapy included adequate bone marrow (WBC count >3400/mm$^3$, platelet count >130 000/mm$^3$, haemoglobin >10 g/dl), liver (serum bilirubin <1.5 mg/dl) and renal functions (serum creatinine level <1.5 mg/dl).

Group B (post-RT chemotherapy) consisted of 4 patients. There were 2 men and 2 women. The mean age was 56 (range, 46–63). Median Karnofsky prior to treatment was 40. The diagnosis of PCNSL was established by pathological examination of a surgical specimen of the brain tumour in 3 and by CSF examination in 1. By the decision of their physician, these patients were treated first with RT (3000–4000 Gy WBRT plus a 1500 cGy boost to the tumour bed in 2 patients). Chemotherapy was started 3 weeks after completion of RT and consisted of i.v. MTX 1 g/m$^2$, given weekly for two doses with leucovorin rescue. Intrathecal MTX was not administered in this group (because of the increased risk of leucoencephalopathy when intrathecal methotrexate is administered after RT) except in 1 patient. 2 days after the last infusion of MTX, patients were started on thiotepa and procarbazine (three courses with the same doses and schedules as used in group A). Patients also received prednisone, usually 80 mg/day, that was progressively tapered during RT.

Group C (chemotherapy alone) consisted of 5 patients. There was 1 man and 4 women. The mean age was 76 years (range, 69–85). Median Karnofsky prior to treatment was 50. The diagnosis of PCNSL was established by pathological examination of a surgical specimen of the brain tumour in 1 patient and by CSF examination in another. Another patient developed a left hyalitis, but a vitrectomy was not diagnostic. In 3 patients, the diagnosis was based on MRI (periventricular, poorly defined, multifocal and diffusely enhancing lesions) with tumour regression following a few days of corticosteroids. Chemotherapy consisted of MTX 1 g/m$^2$, given weekly for two doses along with six doses of intrathecal MTX (as in group A). The last MTX administration was followed 2 days later by the first of three courses of thiotepa and procarbazine administered with the same doses and schedules as in group A. Prednisone, 80 mg/day, was progressively tapered over 8 weeks.

Neurological status and tolerance was judged on clinical examinations, repeated at each course of treatment. Patients' blood counts, serum creatinine and SGOT (aminotransferase serum aspartate (AST)) were also examined and repeated every 6 weeks. Therapeutic effects were judged using Karnofsky performance status rating, and CT or MRI examinations repeated every 6 weeks. Patients were considered responders when they improved clinically and on CT scan. A complete response (CR) was defined as the disappearance of all enhancing tumours on consecutive CT scans at least 1 month apart, and a partial response (PR) consisted of a reduction of 50% of the largest cross-sectional area of contrast enhancement on CT scan. Stable disease was defined as a neurological stabilisation for at least 3 months, without change in corticosteroid dosage, and when the largest cross-sectional area of contrast enhancement on CT scan did not change more than 25%. Progression of the largest cross-sectional area of contrast enhancement on CT scan over 25%, or the appearance of new lesions was considered a treatment failure. Response of leptomeningeal tumour was assessed by CSF cytology and the patient's clinical course. Ocular disease was evaluated by repeated ophthalmologic examination. Any patient found to have ocular lymphoma (at diagnosis or at recurrence) received ocular RT (4000 cGy).

Median time to tumour progression (MTTP) was calculated from the date of diagnosis to the time of treatment failure. Survival duration was measured from date of diagnosis to date of death or last follow-up. WHO scale toxicity criteria were used, and toxicity grades were measured during each cycle, and reflected the most severe degree.

## RESULTS

### *Toxicity*

Tolerance was evaluated in 22 patients. Vomiting was prevented by administration of ondansetron before perfusion. Blood toxicity over grade I occurred in 6 patients (27%) and 3 patients developed grade III leucopenia or thrombopenia. There was no grade IV blood toxicity. None had renal or auditory toxicity. 4 patients developed systemic venous thrombosis of the lower extremities requiring anticoagulant therapy. There were two episodes of septic meningitis after intra-Ommaya MTX.

### *Therapeutic effects*

*Group A (pre- and post-RT chemotherapy).* An objective response to pre-RT chemotherapy (i.v. and intrathecal MTX and corticosteroids) was found in 9/13 patients (3 CR and 6 PR). Following RT, 12/13 patients were in CR and 1 patient in PR. The median time to tumour progression was 10 months. The main site of recurrence was ocular which occurred in 4 patients, while 3 had cerebral/meningeal relapse and 1 had testicular and peripheral nerves relapse.

After a median follow-up of 27 months (5–40 months), 8/13 (62%) patients are alive, 5 are free of recurrence and 3 had an ocular relapse which responded to ocular RT (Table 1). 5 patients have died; 1 had a testicular relapse and died from extensive peripheral nerve involvement (histologically documented by sural nerve biopsy) without evidence of cerebral/meningeal disease 37 months after diagnosis. One had only a PR after chemotherapy and RT and died of recurrent disease 9 months after diagnosis. 2 patients had a CR after treatment and died 12 and 40 months after diagnosis of recurrent cerebral/meningeal tumour (with ocular disease in 1). Finally, 1 patient had a CR after chemotherapy and RT for a cerebellar lymphoma; 1 year after RT she became progressively demented while CT and MRI showed the development of a severe leucoencephalopathy; she died in a nursing home 37 months after diagnosis without evidence of tumour relapse; autopsy was not obtained but she was presumed to have had treatment-induced dementia.

During the follow-up period, 4 patients developed progressive cognitive dysfunction in the absence of recurrent cerebral or meningeal tumour with a leucoencephalopathy on CT scan and MRI. In 2, a severe dementia was found and this was the presumed cause of death in the patient reported above.

*Group B (post-RT chemotherapy).* All 4 patients were in CR after RT when chemotherapy was started. However, the 3 patients who did not receive intrathecal MTX had early neuro-

*Table 1. Patients' characteristics: group A (pre- and post-RT chemotherapy)*

| No. | Age/Sex | KI | Symptoms | Response after treatment | Recurrence time (months) | Site of recurrence | Treatment at recurrence | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 65/F | 50 | L. hemiparesis, frontal Sd | CR | 9 | Ophthalmic | Ocular RT | 31+ |
| 2 | 64/M | 40 | Frontal Sd | CR | – | – | – | 5+ |
| 3 | 57/F | 50 | L. hemiparesis, HLH, R. cerebellar ataxia | CR | – | – | – | 34+ |
| 4 | 55/M | 60 | L. hemiparesis, diplopia | CR | 16 | Testicle and nerves | Cisplatin, VP16, Ara-C | 37 dead |
| 5 | 60/M | 50 | R. hemiparesis | CR | 2 | Ophthalmic | | 8+ |
| 6 | 43/F | 90 | ICH, ataxia | CR | 25 | Cerebral/meningeal | MTX,T, P, Cx, V | 40 dead |
| 7 | 70/F | 60 | ICH, L. hemiparesis and HLH | PR | 5 | Cerebral/meningeal | – | 9 dead |
| 8 | 68/F | 70 | ICH, cerebellar Sd | CR | – | – | – | 37 dead (dementia) |
| 9 | 62/M | 40 | Hyalitis, drowsiness, chorea | CR | – | – | – | 7+ |
| 10 | 62/M | 30 | Acute hydrocephalus | CR | – | – | – | 4+ |
| 11 | 72/F | 90 | L. hemiparesis | CR | 7 | Ophthalmic | Ocular RT | 25+ |
| 12 | 60/M | 50 | Frontal Sd | CR | – | – | – | 38+ |
| 13 | 65/F | 50 | L. hemiparesis and HLH | CR | 7 | Ophthalmic cerebral/ meningeal | Ocular RT, MTX | 12 dead |

L, left; R, right; Sd, syndrome; KI, Karnofsky index; HLH, homonymous hemianopia; ICH, intracranial hypertension; CR, complete response; PR, partial response; NR, no response; Ara-C, cytarabine; MTX, methotrexate; IT, intrathecal; T, thiotepa; P, procarbazine; PCV, procarbazine; Cx, cyclophosphamide; V, vinicristine; VP16, etoposide.

*Table 2. Patients' characteristics: group B (post-RT chemotherapy)*

| No. | Age/Sex | KI | Symptoms | Response after treatment | Recurrence time (months) | Site of recurrence | Treatment at recurrence | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 55/F | 50 | Drowsiness, L. hemiparesis | CR | 1 | Ophthalmic cerebral/ meningeal | – | 8 dead |
| 2 | 46/F | 40 | R. hemiparesis, dysphasia | CR | 4 | Meningeal | PCV | 4 dead |
| 3 | 61/M | 30 | R. hemiparesis, frontal Sd | CR | 10 | Cerebral/ meningeal | Corticosteroids | 10 dead |
| 4 | 63/M | 40 | L. hemiparesis, ataxia, confusion, diplopia | CR | – | – | – | 48+ |

See legend of Table 1 for definitions.

*Table 3. Patients' characteristics: group C (chemotherapy alone)*

| No. | Age/Sex | KI | Symptoms | Response after treatment | Recurrence time (months) | Site of recurrence | Treatment at recurrence | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 72/M | 30 | R. hemiparesis, confusion | PR | 5 | Cerebral | – | 10 dead |
| 2 | 75/F | 90 | ICH, dysphasia | NR | – | – | – | 5 dead |
| 3 | 69/F | 80 | L. cerebellar Sd, nystagmus, diplopia | CR | – | – | – | 11+ |
| 4 | 77/F | 30 | Confusion, L. hemiparesis | CR | 7 | Ophthalmic cerebral | Ocular RT IV+IT MTX | 21+ |
| 5 | 85/F | 50 | ICH, dysphasia, R. HLH | CR | – | – | – | 2 dead Lyell Sd |

See legend of Table 1 for definitions.

logical relapse and died 4, 8 and 10 months after diagnosis with extensive meningeal recurrence. The only patient who received intrathecal MTX post-RT is living 48+ months after diagnosis with moderate memory dysfunction and leucoencephalopathy on CT scan/MRI.

*Group C (chemotherapy alone).* An objective response to chemotherapy occurred in 4/5 patients (3 CR and 1 PR) while 1 patient did not respond. One patient (in complete response) died 1 month after the first cycle of chemotherapy from a Lyell syndrome, related to the prescription of trimethoprim-sulpha-

methoxazole to prevent pneumocystis pneumonia. 2 patients died of recurrent cerebral tumour 5 and 10 months after diagnosis. One patient (in CR after treatment) had ophthalmic and cerebral relapse 7 months after diagnosis. MTX i.v. (1 g/m$^2$) given weekly for two doses per month and intrathecal MTX (12 mg twice a month) was administered (eight courses) in combination with ocular RT, inducing a second CR with excellent quality of life. One patient is in CR 11 months after diagnosis.

## DISCUSSION

In PCNSL, several recent studies have shown increased median survival (27–45 months) with the combination of radiation and chemotherapy [1, 6, 8]. Despite the absence of a consistent chemotherapy regimen, a review of the literature shows that high-dose MTX (administered intra-arterially (i.a.)) [9] or i.v. [10–12] or combined treatment with an intermediate dose of systemic MTX (1 g/m$^2$) and intrathecal MTX were used before radiotherapy by almost all authors who reported increased survival [13–15]. The drugs that we used included intermediate doses of i.v. MTX (as well as intrathecal MTX in most patients) in combination with thiotepa and procarbazine. Thiotepa was chosen because its entry into the brain parenchyma and CSF is not restricted by the blood–brain barrier [16, 17]. Procarbazine was added since it has also shown efficiency in PCNSL [18].

In our 13 patients who received pre- and post-RT chemotherapy (group A), 8/13 (62%) are alive after a median follow-up of 27 months. This result is in contrast to the report of median survival of 10–18 months after RT alone [19, 20], and indicates that this combination regimen is useful in PCNSL [5, 21]. The median time to tumour progression was relatively low (10 months), a finding mostly due to a high rate of ocular relapse in patients who had no ocular involvement at the onset of disease. Ocular relapse responded well to a course of ocular RT [22, 23], but previous suggestions that whole-brain RT include the posterior poles of the eyes should be considered in future trials. Also of concern is our finding that 4/13 patients in group A developed progressive cognitive dysfunction with leucoencephalopathy in the absence of recurrent tumour. 2 were bedridden with severe dementia, and leucoencephalopathy was the presumed cause of death in 1. Combined treatment with methotrexate (i.v. and intrathecal) and radiotherapy appears to be the main cause of this encephalopathy [24–26], which is not prevented by the administration of MTX before RT.

Our results in the 4 patients who received chemotherapy immediately after RT (group B) were disappointing. Because of the major risk of inducing leucoencephalopathy when intrathecal MTX is administered after RT [20, 24, 25, 27], it was withdrawn in 3/4 patients while systemic MTX, procarbazine and thiotepa were administered with the same doses as in group A. Despite a complete response after RT, these 3 patients died within 10 months and all had extensive meningeal relapse. None had meningeal involvement at the onset of treatment. The fourth patient who had meningeal disease at the onset of treatment and who received post-RT intrathecal MTX survived and is in CR at 48+ months. These data emphasise the importance of appropriate treatment of the meninges in PCNSL [17, 28], and suggest that thiotepa alone does not adequately prevent meningeal relapse.

Finally, 5 patients received only chemotherapy (Group C). RT was not administered because the old age of these patients (mean age, 76 years) markedly increased the neurotoxic risk of RT [4, 20]. Our finding that 4/5 had an objective response to chemotherapy alone with a good tolerance is encouraging. Although the duration of response to chemotherapy was short lived in 2 patients, 2 are still in remission 11+ and 21+ months after diagnosis with a good quality of life. These data suggest that chemotherapy alone may be useful in elderly patients (> 70 years of age) in whom WBRT is not indicated.


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