Phase II Multicenter Study of Brief Single-Agent Methotrexate Followed by Irradiation in Primary CNS Lymphoma

By P. O’Brien, D. Roos, G. Pratt, K. Liew, M. Barton, M. Poulsen, I. Olver, and G. Trotter

**Purpose:** To assess, in a multi-institutional setting, the impact on relapse, survival, and toxicity of adding two cycles of intravenous methotrexate to cranial irradiation for immunocompetent patients with primary CNS lymphoma.

**Patients and Methods:** Forty-six patients with a median age of 58 years and Eastern Cooperative Oncology Group performance status 0 to 3 were entered onto this phase II study. The protocol consisted of methotrexate 1 g/m² on days 1 and 8 followed by cranial irradiation on day 15. A whole-brain dose of 45 Gy was followed by a boost of 5.4 Gy. Intrathecal chemotherapy and spinal irradiation were given only to patients for whom cytologic examination of CSF was positive for CNS lymphoma. The median follow-up time was 36 months, with a minimum potential follow-up of 12 months.

**Results:** Median survival was 33 months, with 2-year probability of survival 62% ± 15% (95% confidence interval). Twenty patients have relapsed. The predominant site of relapse was the brain. Neither performance status nor age was found to influence survival. Six patients developed a dementing illness at a median of 16 months after treatment, and three of these died as a consequence.

**Conclusion:** A brief course of intravenous methotrexate before cranial irradiation is associated with 2-year and median survival rates superior to those reported for radiotherapy alone and similar to more intensive combined-modality regimens. Neurotoxicity remains an important competing risk for these patients.


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vomiting, and dexamethasone before radiotherapy. \(^{17,18}\) The inability of CHOP regimens to improve survival significantly has been attributed to poor blood-brain barrier (BBB) penetration. This may be particularly true outside the immediate region of tumor involvement, where theoretically BBB integrity is greater. \(^{27}\) One of the most widely quoted series is that from the Memorial Sloan-Kettering Cancer Center.\(^{15}\) Researchers there used preirradiation methotrexate, with intrathecal therapy in all patients, followed by radiotherapy and high-dose cytarabine (Ara-C) to complete treatment. Although this produced impressive survival in comparison with radiotherapy alone, there was a cost in terms of neurotoxicity. Ten (32%) of 31 patients developed a dementia-ataxia syndrome that required institutional care. This complication was significantly more common in patients more than 60 years old.\(^{15}\)

Our group sought to investigate the potential advantages of adding a brief course of intravenous (IV) methotrexate to cerebral irradiation, without routine use of CSF prophylaxis or postirradiation Ara-C. We hypothesized that this protocol would provide better survival than radiotherapy alone, similar to the Memorial Sloan-Kettering series, and that it would result in less treatment-related neurotoxicity. This represents one of the first multi-institutional studies of a methotrexate-only combined-modality regimen and expands on a preliminary report.\(^{28}\)

**PATIENTS AND METHODS**

**Eligibility and Assessment**

Under the auspices of the Trans-Tasman Radiation Oncology Group, 46 patients were entered onto this phase II study from 12 centers in Australia and New Zealand between 1991 and 1997. From 1994, members of the Australasian Radiation Oncology Lymphoma Group also contributed to the study. Patients were registered with the Trans-Tasman Radiation Oncology Group central trials office, at which time eligibility was confirmed. No further information was sought on patients who were not registered because they were deemed ineligible either at the time of attempted registration or by the participating institutions. Considering the incidence of PCNSL and the populations served by the participating institutions, it is unlikely that the study group was selected according to factors other than the predefined eligibility criteria.

Patients were considered eligible if histologic examination confirmed PCNSL, if serologic examination revealed no human immunodeficiency virus, and if their Eastern Cooperative Oncology Group performance status (ECOG) was 0 to 3.\(^{29}\) Adequate baseline hematologic, renal, and hepatic function was required with granulocyte counts greater than \(1,500 \times 10^9\) platelet counts greater than \(100,000 \times 10^9/L\), serum creatinine levels less than 0.15 mmol/L, and serum bilirubin and AST levels less than two times the upper limit of normal. All patients were required to give informed consent, and the protocol was approved by the ethics committee of each institution.

Primary radiologic assessment was made using either computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain. A CSF cytologic examination was required, but if raised intracranial pressure prevented a lumbar puncture, it could be delayed until the intracranial pressure had lessened. Only if the cytologic examination of CSF revealed clear evidence of malignant lymphocytes was the CSF considered to be involved. Immunohistochemical studies were not required, although they are standard practice in most centers. More sophisticated analysis, such as polymerase chain reaction for immunoglobulin gene rearrangements, was not performed on CSF. Abnormalities in protein and glucose levels were not considered diagnostic of CSF involvement. Staging investigations to assess the potential presence of lymphoma outside the CNS included CT of the thorax, abdomen, and pelvis, bone marrow trephine and biopsy, and ophtalmologic slit-lamp examination.

**Protocol Treatment**

Methotrexate 1 g/m\(^2\) was given as an IV infusion during a 6-hour period on days 1 and 8. Leucovorin, 15 mg orally every 6 hours for 72 hours, was started 24 hours after the methotrexate infusion was begun. If nausea or vomiting occurred during or after methotrexate, then leucovorin was given intravenously until oral medication could be tolerated. The patient was hydrated before and after infusion as part of the protocol to maintain urinary pH at less than 7, using sodium bicarbonate.

Intrathecal chemotherapy was given only to patients whose cytologic CSF studies were positive. Sixty milligrams of Ara-C was given twice weekly for 3 weeks starting on day 1 or as soon as possible after diagnosis of CSF involvement. Weekly Ara-C continued for three doses after clearance of the CSF.

The dose of dexamethasone was not specified because most patients were referred for management after dexamethasone had been started by the neurosurgical team. The protocol suggested that the dosage of dexamethasone be kept to the minimum required to manage the patient without producing deterioration in focal neurologic signs or symptoms of raised intracranial pressure. It was suggested that low-dose dexamethasone be continued throughout radiotherapy and that every attempt be made to withdraw corticosteroids at the completion of treatment.

Radiotherapy started on day 15. All patients were treated using an immobilization shell with customized shielding. Phase I of treatment was delivered to a volume including the whole brain (specifically denoted to include the optic nerve and cribriform plate) to the inferior border of the foramen magnum or the inferior border of the body of C2 (depending on individual center preference). A dose of 45 Gy prescribed to the midplane at the central axis of the treatment volume in 25 fractions was required to be delivered using opposed lateral fields; all fields were treated daily and were given five fractions per week. There was an option for reduction of the field from C2 to the inferior border of the foramen magnum at 39.6 Gy in patients with reduced separation and hence a high dose to the cervical spine at this level. Phase II of radiotherapy delivered another 5.4 Gy to the isocenter in three fractions of 1.8 Gy to a volume that depended on the number of sites of initial involvement in the brain. If there were one or two sites, the phase II volume included the prechemotherapy disease, defined as contrast-enhancing tumor (but not edema) with a 1-cm margin as encompassed by the 95% isodose contour. With two sites the boost could be delivered as a single volume or as two separate volumes. If there were more than two sites of disease, then the whole brain volume given in phase I was taken to a total dose of 50.4 Gy. Spinal irradiation was only given to patients with spinal cord involvement or whose cytologic examination of CSF was positive. A total of 36 Gy was delivered to the posterior aspect of the cord in 24 fractions for 5 weeks at 1.5
Gy/fraction. The field extended from the lower border of the cranial field at C2 to S3.

Follow-Up and Response Assessment

After patients completed all treatment, they were observed monthly for 2 months, then every 4 months with a CT or MRI of the brain to be performed 6 to 8 weeks after completion of radiotherapy. Additional follow-up scans were performed yearly or more often if clinically indicated.

Response was based on the following criteria: Complete response referred to the absence of any tumor enhancement on the posttreatment contrast CT scan. The patient was required to be off all dexamethasone. Partial response referred to a reduction in at least 50% of the contrast-enhancing CT volume, which is the sum of the products of all the maximum diameters of the measured lesion or lesions. Stable disease indicated objective regression of the measured contrast-enhancing CT volume, less than required to meet the criteria for partial response or less than a 25% increase in the measurable lesion. Progressive disease referred to an increase in the sum of the products in the maximum diameters by 25% or more. Acute toxicity was graded according to World Health Organization criteria.30

Statistics

The initial accrual target of this phase II study was 30 patients. Historic data at that time indicated 2-year survival probability after radiotherapy alone was 20% to 30%. However, it became apparent that the 95% confidence intervals (CIs) for the survival calculation at 2 years would not be sufficiently narrow to support the hypothesis of a significant improvement over historic controls treated with radiotherapy alone. It was therefore decided to continue accrual until the 95% CIs around the survival estimate at 2 years were 15% or less. It was also decided that in view of potential neuropsychiatric sequelae from treatment, at least 20 patients should have uncensored follow-up of 2 years or more. Survival and progression-free survival were estimated using the product limit method of Kaplan-Meier and calculated from the date of the start of chemotherapy. The log-rank test was used to compare survival outcomes among subgroups. Survival was measured until the date of death or last follow-up, and progression-free survival was until the date of progression or last follow-up.

RESULTS

Patients

Forty-six patients were entered onto the study between 1991 and 1997. Table 1 lists the characteristics of the patients. The median age was 58 years (range, 25 to 76 years), and 48% had an ECOG performance status of 0 or 1. Diagnosis was made by open biopsy in 43.5%, stereotactic biopsy in 43.5%, and excision biopsy in 13% of cases. Most patients had diffuse large-cell subtype (working formulation), although in 25% of cases it was impossible to subcategorize the lymphoma. In one case the immunophenotype was T-cell. The median follow-up was 36 months, and the minimum potential follow-up was 12 months. No patient was lost to follow-up.

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Protocol Compliance

In five cases, staging was incomplete because of CSF cytology not being performed (four cases) and the omission of slit-lamp examination (one case). Forty-five of the 46 patients received two doses of IV methotrexate as stipulated in the protocol. In all but four cases these were delivered 7 days apart, with the others given on day 8. One patient did not receive a second dose of methotrexate because of progression of neurologic symptoms. One of the three patients whose cytologic examination of CSF was positive did not receive intrathecal Ara-C or spinal irradiation.

Forty-five of the 46 patients proceeded to radiotherapy after chemotherapy. In one case fatal neutropenic sepsis occurred after the second dose of methotrexate and before the start of radiotherapy. Thirty-seven patients received 50.4 Gy, with four patients each receiving 54 Gy and 45 Gy. The median duration of radiotherapy was 39 days (range, 36 to 51 days). For the 44 patients who received two doses of methotrexate, radiotherapy was started no more than 10 days later in 41 (93%) and on days 11, 16, and 18 in the remaining three.
Response and Survival

One patient who died after a septic episode subsequent to chemotherapy and six patients who underwent complete surgical excision of their tumors were not assessable for response (as evaluated 6 weeks after completing all treatment). Of the remaining 39 patients, 32 (82%) had a complete response, five (13%) had a partial response, and one each had stable and progressive disease. The median survival for the entire group was 33 months, with a 2-year probability of survival of 62% ± 5% (95% CI) (Fig 1). Three patients were alive 48 months or more after treatment. Two died at 79 and 83 months, respectively; in both cases the cause of death was recurrent PCNSL. One of these recurrences was in brain and the other was extranodal (muscle). In total, 20 patients developed progressive disease at a median time of 17 months after starting treatment (range, 1 to 60 months). Fourteen patients progressed or relapsed in the brain, which was the predominant site. The other sites of progression were the spinal cord (two patients), eye (one patient), and CSF (two patients); systemic disease developed in four patients (three of these disease sites were extranodal—two in muscle and one in skin). None of the patients who relapsed in the CSF or the spinal cord was positive for CSF involvement at the time of diagnosis. Of the three patients with positive CSF involvement, one relapsed in brain in the high-dose radiotherapy volume. Progression-free survival at 2 years was 65% ± 15% (95% CI) (Fig 2).

Five patients died from causes other than recurrent or progressive PCNSL. Three of these had late neuropsychiatric sequelae. Another patient, who had an ECOG performance status of 3 at the time of diagnosis but did not improve functionally despite a radiologic complete response, committed suicide 12 months after treatment. The fifth patient, who also had an ECOG status of 3, had a partial response to treatment but died from pneumonia 7 weeks later.

Neither performance status, age, nor presence of focal versus multifocal disease was found to affect survival. The 2-year probability of survival for patients with an ECOG status of 0 to 1 was 66% versus 58% for those with an ECOG status of 2 to 3 (P = .47). Many groups have found increasing age to be of prognostic significance. There was no difference in survival for patients older than 60 years of age. Probability of 2-year survival was 57% for patients younger than 60 years versus 69% for those 60 years or older (P = .94)

Patients responding to treatment and not progressing within 6 months were evaluated for any change in performance status. Forty-eight percent and 55% of patients had improved performance status at 2 and 6 months after treatment. Fourteen percent had deteriorated at 2 months despite response of their disease.

Toxicity

Acute toxicity during treatment was generally minimal (Table 2). However, one death was due to neutropenic sepsis after the second dose of methotrexate. Most patients developed alopecia, which was only partially reversible.

Six patients developed a dementing disease, consistent with a late neurotoxic effect of treatment. In all six cases, repeat MRI or CT failed to show recurrent PCNSL, and in most cases revealed the characteristic features of late radiation injury, with cortical thinning, ventricular enlargement, and white matter changes. The age of the patients at the time of treatment ranged from 52 to 73 years (median, 61 years), with a time to onset of 12 to 30 months (median, 16 months). Four of these six patients have required...
institutional care and three have died. Another patient was thought to have developed late neuropsychiatric sequelae with typical MRI appearances but at autopsy was found to have diffuse infiltration of the brain with PCNSL. The Kaplan-Meier estimate of probability of neurotoxicity was 22% at 30 months (Fig 3).

DISCUSSION

Progress in the treatment of PCNSL has been slower than that in nodal and other selected extranodal lymphomas because of its rarity, which makes large-scale randomized studies difficult. Improvements in survival outcome using a combined-modality approach have been pioneered mostly in single-institution studies.15,16,19,20 These studies have all used methotrexate alone or in combination with other chemotherapeutic agents followed by radiotherapy. Thus far, two multi-institutional studies could not reproduce the improvements in survival using combined-modality regimens, but this may relate to the selection of chemotherapy using CHOP or cyclophosphamide, doxorubicin, vincristine, and dexamethasone.17,18 Our study allows some assessment of the potential gains from adding a simple regimen of two cycles of IV methotrexate to cerebral irradiation in a multi-institutional setting. The median survival of 33 months was superior to all prospective studies of radiotherapy alone. Selection criteria are unlikely to explain these results, as 52% of patients had an ECOG status of 2 or 3 and the median age was 58 years. The 2-year probability of survival was 62%, and three patients were alive and disease-free 4 or more years after treatment. Interestingly, two patients relapsed 5 years after treatment, one in the brain and the other in an extranodal site. The Memorial Sloan-Kettering series reports relapse as late as 51 months after combined-modality therapy.15 Longer follow-up will allow a more accurate estimate of the risk of late relapse.

Unlike other combined-modality studies, older patients did not have poorer survival prospects than their younger counterparts.15,17-20 Of the patients 60 years of age or older, 45% had an ECOG status of 0 or 1, and 40% had focal disease. This is not different from the group as a whole and does not suggest an influence of selection factors. The number of patients is small; therefore multivariate modeling may be unreliable. Even so, analysis using the Cox proportional hazards model does not suggest age, performance status, or focality to be of prognostic significance (data not shown). It may be that the efficacy of the regimen combined with its simplicity and lack of acute toxicity allows patients to complete treatment and hence is associated with a better chance of long-term survival. The ability to get most patients through the acute effects of any protocol is important in extrapolating its use to patients outside the controlled environment of a phase II study. This is particularly true in PCNSL, where up to 50% of patients are more than 60 years of age and often have worse performance status than patients with systemic non-Hodgkin’s lymphoma.

Age may be important not only in terms of acute tolerance but also in potential risk of late neurotoxicity. Thus far, six patients have developed late neurotoxicity, which presented as a dementing process. Once established, this process has been progressive and irreversible; most of these patients had required institutional care. Neither baseline nor prospective neuropsychiatric evaluation was a requirement of the protocol, so the number of cases identified may represent a minimal estimate. Kaplan-Meier estimates are often used to quantify the risk of neuropsychiatric sequelae, but this method may overestimate the real risk in such small studies.31 Nevertheless, this debilitating consequence of treatment is distressing to patients and their families.

Different approaches are being taken in an effort to minimize late neurotoxicity, including the omission of radiotherapy. The use of chemotherapy alone in PCNSL has involved variations in the agents and dose-intensity, up to and including the use of autologous bone marrow transplantation.21-24,32,33 An impressive median survival of 44
months has been obtained using BBB disruption with combination chemotherapy based around methotrexate.21 Again, this was a single-institution study and the intensive nature of the regimen limits its widespread applicability. Preliminary results are promising in a relatively small number of cases using other methotrexate-based regimens.23,24 The longer-term results of these and other ongoing studies are awaited with interest, in terms not only of efficacy but also of long-term toxicity. Acute toxicity needs to be considered in debilitated patients. Treatment-related deaths while using chemotherapy alone have been as high as 10%.32 Neurotoxic effects are not limited to studies using radiation. In one prospective study of chemotherapy alone, with a median follow-up of 3.3 years, three of 14 patients developed severe leukoencephalopathy.33 As a proportion, this is similar to our combined-modality series. The other approach being taken is to intensify chemotherapy and decrease the dose of irradiation, often excluding elderly patients, in an effort to avoid neurotoxicity. Eventually, a randomized study will be required to establish a gold standard for efficacy and toxicity. In all likelihood this will need to be an international effort. The incidence of PCNSL in the immunocompetent population has risen during the last 20 years, but this disease remains relatively uncommon, and it took 7 years to accrue 46 cases in this study of patients from Australia and New Zealand.3

The combination of methotrexate and irradiation is clearly implicated in the development of late neurotoxicity, but the disease process itself may also play a part. Primary CNS lymphoma has a predisposition for perivascular infiltration, which may contribute to the marked breakdown in the BBB. The importance of BBB integrity has been stressed in the study of late radiation injury of the CNS.34 Although the late morphologic effects of irradiation on the brain are well documented, debate continues about the relative contributions of vascular and direct neural injury, particularly when leukoencephalopathy rather than necrosis is the end point of interest.35 Some evidence suggests that the pathogenesis of intellectual impairment relates to vascular injury in the hippocampal region.36 The cause-and-effect issue remains unresolved by animal models, with changes seen in microvasculature, neuropil, neuronal bodies, and astrocytes.37 Radiation effects on vascular tissue, particularly endothelial cells and smooth muscle cells, may be mediated in part by a procoagulant environment.38,39 It remains to be seen whether developments in the therapy of vascular disorders with morphologic effects similar to those of radiation hold any promise in reducing this serious treatment effect.40 Because it is believed that the leptomeninges and CSF are predominant sites of relapse, it has been common to recommend that all patients receive intrathecal chemotherapy.41 There is a legitimate concern that the interaction between intrathecal methotrexate and cranial irradiation increases the risk of late cerebral injury.42 The BBB is disrupted in the presence of PCNSL and it is likely that cytotoxic levels of methotrexate will occur in the CSF after doses as low as 1 g/m² are given intravenously.43,44 Only two patients in our series suffered CSF relapse, so intrathecal therapy can probably be avoided in most patients, reserving it for those with CSF involvement at the time of diagnosis, provided adequate doses of IV methotrexate are used. Similarly, it is unlikely that spinal irradiation has a role other than in the rare patient with spinal cord involvement at the time of diagnosis.

Our group is still wrestling with an appropriate follow-up to this phase II study. Two recent randomized studies in localized intermediate-grade non-Hodgkin’s lymphoma provide persuasive evidence of an advantage for combined-modality therapy over chemotherapy alone.45,46 One of the attractive aspects of our regimen was its ease of deliverability in elderly patients, who are often debilitated by the disease. Major questions still exist as to the best drugs, doses, and timing for combined-modality regimens, and whether radiotherapy doses can be kept below 40 Gy. Our strategy is to maximize the potential efficacy of chemotherapy given before BBB repair and reduce the dose of radiotherapy. Although anthracyclines have some penetration in the presence of BBB disruption, this is likely to be limited, as evidenced by studies using CHOP. Liposomal daunorubicin may provide a method of using an anthracycline with activity in non-Hodgkin’s lymphoma and improved tumor uptake and endothelial penetration in the setting of BBB disruption.47,48 Pharmacokinetic studies in patients with astrocytomas treated with liposomal daunorubicin indicate prolonged intratumor levels of the active metabolite daunorubicinol.49 Methotrexate remains the most important single agent because of its BBB penetration and activity. By increasing the total dose of methotrexate and combining it with an active anthracycline before radiotherapy, we hope to produce a therapeutic advantage. This multi-institutional study has shown that in a phase II setting, methotrexate given immediately before irradiation seems to improve median survival outcome for patients with PCNSL. Neuropsychiatric sequelae remain an important competing risk for these patients. The challenge is to maintain or improve survival while minimizing this risk.
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REFERENCES


