

Outcome of patients with primary central nervous system lymphoma treated outside clinical trials

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ABSTRACT

Reports on the outcome of patients with primary central nervous system lymphoma (PCNSL) are mainly based on results obtained in the context of clinical trials. However, due to poor performance status and cognitive impairment, most patients are actually treated outside clinical studies. The aim of this retrospective study was to get more insight into the outcome of HIV-negative PCNSL patients, treated between 2000-2010 in two hospitals (one academic centre and one categorical cancer centre).

Fifty-two patients were identified. Eight patients were treated with corticosteroids only. Sixteen patients received high-dose methotrexate (MTX)-based chemotherapy, ten received radiotherapy and 18 patients were treated with a combination of MTX-based chemotherapy and radiotherapy. At a median follow-up of 63.1 months, the median overall survival for all patients was 24.4 months (95% CI: 11.5-39.8 months), with an event-free survival of 14 months (95% CI: 7.3-24.4 months). Causes of death were progressive PCNSL in 29 patients, MTX toxicity in four patients and epileptic seizures in one patient. These results are comparable with the outcome of prospective clinical trials in this disease, which still has a relatively poor prognosis.

KEYWORDS

High dose MTX, primary central nervous system lymphoma, radiotherapy, retrospective study, survival, toxicity

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an extranodal lymphoma that involves the brain parenchyma, spinal cord, eyes, cranial nerves and/or meninges. PCNSL accounts for approximately 4% of newly diagnosed central nervous system tumours. Ninety-five percent are diffuse large B-cell lymphomas (DLBCL).¹ The incidence of PCNSL is 4.7 cases per million person-years.² The only established risk factor for PCNSL is acquired or congenital immunodeficiency.³ Treatment options for PCNSL include corticosteroids, chemotherapy and radiotherapy. Surgical therapy other than a diagnostic biopsy is not recommended.⁴ Current knowledge and guidelines are mainly based on results obtained from small clinical trials. However, because of poor performance status and cognitive impairment, most patients are actually treated outside prospective studies.

We therefore performed a retrospective analysis of HIV-negative patients with a PCNSL treated outside clinical trials, to obtain more insight into the nature, clinical course and outcome of this disease in comparison to results obtained in the context of prospective clinical trials.

PATIENTS AND METHODS

This is a retrospective study of all HIV-negative patients ≥ 18 years with PCNSL diagnosed between 2000 and 2010 who were treated outside prospective clinical studies in the

Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (a comprehensive cancer centre) and the Academic Medical Centre in Amsterdam. HIV-positive patients were excluded from this study because the course of their disease can differ from that of HIV-negative patients with PCNSL. The data were retrieved from the registries of both hospitals. The following items were collected: age, sex, World Health Organisation performance status (PS), comorbidities, presence of immune deficiencies other than HIV infection, presenting symptoms, pathology, treatment, response, duration of response, acute and late toxicities, recurrence-free survival, overall survival and event-free survival (RFS, OS, EFS) and cause of death. The PCNSL prognostic score at presentation was calculated based on the following parameters: age (≤ 60 vs. > 60 years), PS (0 to 1 vs. 2 to 4), serum lactate dehydrogenase (LDH) level (normal vs. elevated), cerebrospinal fluid (CSF) protein concentration (normal vs. elevated) and involvement of the deep regions of the brain (no vs. yes).⁵ RFS was only considered for patients with a response to chemotherapy and/or radiotherapy, and was defined as the time from diagnosis to date of recurrence or death, whichever occurred first. OS was defined as time from diagnosis to death (irrespective of cause) and EFS was defined as time from diagnosis to any disease failure for all patients. For patients still alive without disease failure at the time of analysis and for patients lost to follow-up, the date of last contact in the hospital was chosen to measure duration of response and the calculation of OS, RFS and EFS.

The date of histological confirmation was defined as the date of diagnosis. In the absence of pathology results, the date of diagnostic MRI or CT scan imaging was chosen as the date of diagnosis.

The study was approved by the Ethics Committees of both hospitals.

RESULTS

Patient characteristics

The main baseline characteristics are summarised in *table 1*. Fifty-two patients were identified with a median age of 64.5 years. Thirty-two patients had comorbidities which, however, did not influence the treatment choice. Two patients were considered to be immune compromised, one patient due to chronic use of prednisolone for 15 years for arteriitis temporalis, the other patient because of treatment with mycophenolate mofetil for several years following a liver transplantation for cryptogenic cirrhosis of the liver. In eight patients neither histological nor cytological confirmation of the PCNSL diagnosis could be obtained. In those patients the diagnosis was based on clinical presentation and MRI imaging of the brain. In five patients the diagnosis was based on the combination of the presence of a monoclonal B-cell population in the CSF

Table 1. Patient characteristics

Characteristics	Percentage, number of patients
Total	52
Male	52% (27) [#]
Age (years)	
Median	64.5
Range	43-83
40-49	7.5% (4)
50-59	27% (14)
60-69	37% (19)
70-79	21% (11)
80-83	7.5% (4)
Performance status	
0-1	44% (23)
2	19% (10)
3	29% (15)
4	7.5% (4)
PCNSL Prognostic score	
Complete	48% (25)
0-2	19% (10)
≥ 3	29% (15)
Incomplete*	52% (27)
0-2	33% (17)
≥ 3	19% (10)

*No cerebrospinal fluid data: n=25; serum LDH level unknown: n=2; #absolute numbers between brackets.

and MRI imaging. One patient died before a histological diagnosis could be made, but the presence of PCNSL was confirmed by autopsy. The reasons for failure to obtain histological confirmation of the PCNSL lesions were: poor PS, risk of severe neurological deficit by biopsy, no lumbar puncture performed because of the risk of cerebral herniation. All patients with histological verification had a diffuse large B-cell lymphoma.

In *table 2* presenting symptoms are summarised. The main focal neurological deficits were: hemiparesis, gait abnormalities, motor and sensory aphasia, dysphasia and hemianopsia. Cognitive dysfunction included, but was not limited to: memory impairment, disorientation, confusion, bradyphrenia and mutism.

The sites of tumour localisation are summarised in *table 3*. The most likely reasons for not participating in a clinical trial were: no histological confirmation in 14 patients, poor performance status and cognitive impairment in 24 patients, no ongoing clinical trial available at the time of diagnosis in 14 patients.

PCNSL prognostic score

The PCNSL prognostic score of the patients is summarised in *table 1*. In 27 patients (52%), no complete PCNSL

Table 2. Presenting symptoms

Presenting symptoms	Percentage of patients
Total	52
Focal neurological deficit	77% (40) [#]
Cognitive dysfunction	50% (26)
Decreased consciousness	36.5% (19)
Epilepsy	32.5% (17)
Headache	29% (15)
Behavioural changes	27% (14)
Gait abnormalities	23% (12)
Nausea/vomitus	21% (11)

#: absolute numbers between brackets.

Table 3. Location of tumour

Location	Percentage of patients
Total	52
Number of sites involved	
Single	56% (29) [#]
Multiple	44% (23)
Location	
Supratentorial	85% (43)
Infratentorial	4% (2)
Both supra- and infratentorial	11.5% (6)
Leptomeningeal involvement	11.5% (6)
Ocular involvement	2% (1)

#: absolute numbers between brackets.

prognostic score could be calculated mainly due to lack of CSF data (25 patients). In two patients the serum LDH level was unknown.

Median time between symptoms and other parameters

The median time between the first neurological symptoms and diagnosis was 1.5 months (range 0-34 months). Treatment was started within a median time of two weeks (range 0-20 weeks) from diagnosis. The median time from diagnosis to death for patients receiving any kind of treatment was 7.0 months (range 0.25-78 months). The median time between diagnosis and relapse was 11.5 months (range 0.5-76 months) for responding patients.

Treatment and response

All patients were treated with corticosteroids (dexamethasone or prednisolone) in variable doses and during variable time periods. Thirty-two patients (62%) had a clinical response to corticosteroids. Seven patients (13%) received no further chemotherapy or radiotherapy due to poor PS and rapid deterioration despite treatment with corticosteroids. The median time to death for those patients was 26 days (range 0-35 days). One patient who achieved a complete remission (CR) after treatment with dexamethasone for 97 days (starting dose 4.5 mg twice

daily) received no further treatment and is still alive 126 months after diagnosis. In this patient, the diagnosis was based on the presence of a monoclonal B cell population in the CSF in combination with MRI imaging showing tumour involvement of the right frontotemporal region, basal ganglia, thalamus and mesencephalon.

Thirty-four patients (65%) received high-dose MTX-based chemotherapy. Fourteen patients (27%) were treated according to the schedule of the EORTC 26952 study (MTX, CCNU, procarbazine and prednisolone, for the complete schedule see Hoang-Xuan *et al.*⁶), nine patients (17%) according to the MBVP (MTX, BCNU, teniposide=Vumon[®], prednisolone) schedule of the EORTC 20962 study (for the complete schedule see Poortmans *et al.*⁷), seven patients (13%) according to the Berlin protocol⁴ with monotherapy high-dose MTX (≥ 1 g/m² per cycle) and four patients were treated according to the standard arm of the HOVON 105 study (two MBVP cycles, followed by one cycle of high-dose cytarabine (8 g/m² in total). High-dose MTX was given as a three-hour infusion. The treatment choice was based on previous experience with the above-mentioned studies and the hospital site.

Fifteen patients received high-dose MTX-based chemotherapy alone. Five of these patients achieved a CR, two a partial remission (PR), four had progressive disease (PD) and four patients were not evaluable for response because of lethal MTX toxicity. The median duration of response was 20 months (range 1-86 months).

Nineteen patients received radiotherapy after MTX (median radiation dose 34 Gy, range 8-50.4 Gy). In 13 patients radiotherapy was given as consolidation therapy according to the EORTC 20962 and HOVON 105 protocol. Eleven patients achieved a CR and two patients a PR. The median duration of response was 13 months (range 1-114 months). One patient developed an intraocular lymphoma localisation after one month. He received intraocular treatment with MTX. This patient is still in continuous complete remission (CCR) three years after treatment.

In six patients radiotherapy was given because of progressive disease shortly after or during chemotherapy. Two patients achieved a CR, one patient a PR and three patients had PD. The median duration of response was two months (range 1-28 months).

Ten patients received radiotherapy only, with a median dose of 34.5 Gy (range 20-50 Gy). Four patients achieved a CR, four a PR, one had PD and one patient was not evaluable because of loss to follow-up. The median duration of response was 20 months (range 1-31 months). Five patients received cranial irradiation for recurrence, with a median time interval of 14 months after the last cycle of chemotherapy (range 4-27 months). The median survival after irradiation was eight months (range 2-22 months).

Acute toxicities

We used the Common Terminology Criteria for Adverse Events (CTCAE) version 4 to classify side effects of the different treatments.⁸ The toxicities are likely to have been recorded incompletely due to the retrospective nature of the study.

One patient suffered from CTCAE grade 3 side effects due to treatment with corticosteroids: osteoporosis with thoracic vertebral fracture and avascular femoral head necrosis. One patient suffered from aggravation of a schizophrenic disorder while using corticosteroids.

Seven patients who received chemotherapy suffered from toxicities grade ≥ 3 : anaphylactic reaction to teniposide with hypotension and fever (1), deep vein thrombosis (1), pneumonia with respiratory failure (1), aspiration pneumonia resulting in death (2), pneumonitis probably due to MTX resulting in death (1), pulmonary embolism and pneumonia with sepsis resulting in death (1).

None of the patients suffered from any acute toxicity grade ≥ 3 following cranial irradiation.

Late toxicities and chronic symptoms

Late toxicities defined as occurring beyond 90 days after the end of therapy were not systematically recorded in the patient charts. Cognitive impairment, gait disturbances, fatigue and focal neurological deficits were spontaneously reported as chronic symptoms in 13 patients (median age 56 years, range 44-82 years), of whom one was treated with cranial irradiation only, nine were treated with chemotherapy and radiotherapy and three received chemotherapy only. The median time to follow-up (after treatment) of these patients was 54 months.

Survival

With a median follow-up of 63.1 months, 34 patients have died: 29 due to PCNSL (15 at initial diagnosis and 14 at relapse). As noted above, four patients died of treatment-related toxicity. One patient died due to an epileptic seizure while in CR. Four patients were lost to follow-up at 4, 18, 21 and 22 months after diagnosis. The patient in whom the diagnosis was confirmed by autopsy was excluded from the survival analyses.

The median RFS for the 32 responding patients was 23.8 months (95% CI: 15.9 - not applicable). The two-year RFS was 47.9% (95% CI: 32.3-71.0%) and the five-year RFS was 34.3% (95% CI: 19.8-59.4%). The median OS for all patients was 24.4 months (95% CI: 11.5-39.8 months), with a two-year OS of 53.7% (95% CI: 41.3-69.7%) and a five-year OS of 28.7% (95% CI: 17.4-47.1%). The median EFS for all patients was 14 months (95% CI: 7.3-24.4%). The two-year EFS was 34.0% (95% CI: 22.7-51.0%) and the five-year EFS was 23.0% (95% CI: 13.2-40.3%) (figure 1a-c).

Figure 1a. Overall survival

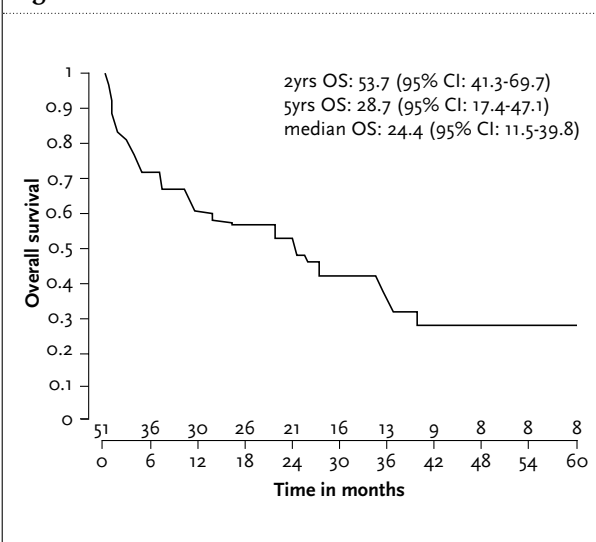


Figure 1b. Event-free survival

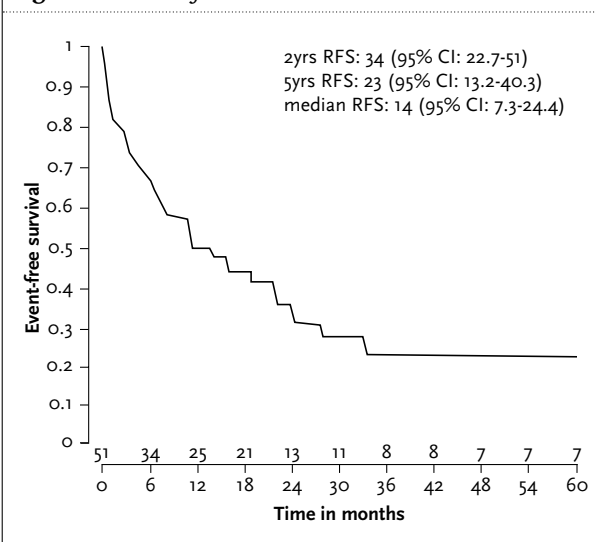
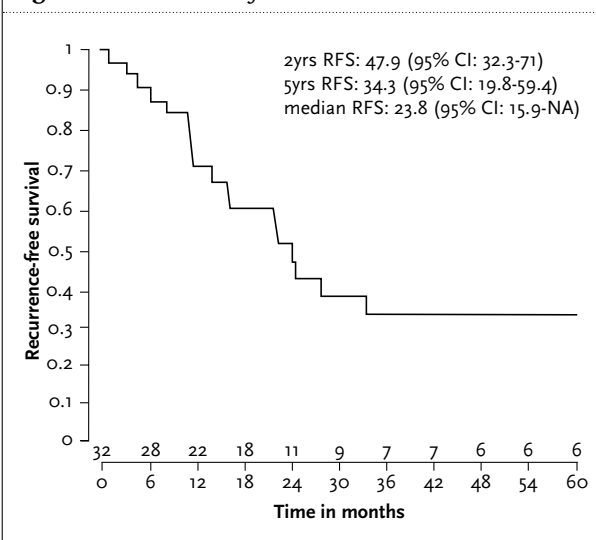


Figure 1c. Recurrence-free survival



DISCUSSION

Important issues regarding the treatment of PCNSL include the selection of therapy for each specific patient, the optimal dosage and schedule of (often MTX based) chemotherapy, the role of (consolidation) radiotherapy and the role of rituximab. These questions will hopefully be resolved by prospective trials, but many patients are actually treated outside clinical studies. The majority of the patients (73%) in this retrospective series could not enter a prospective clinical trial, either because of cognitive impairment, poor performance status and/or inability to obtain histological confirmation of the PCNSL diagnosis. In 27% of the cases no trials were available at the time of diagnosis.

The pretreatment characteristics of the patients included in our analysis are in line with those published in prospective series.^{4,6,7,9,10} The median overall survival of our patients (65% >60 years) was 24.4 months (95% CI: 11.5-39.8 months). Especially elderly patients with PCNSL have a poor prognosis: the median overall survival as published in the EORTC 26952 study including 50 patients older than 60 years was only 14.3 months.⁶ This was confirmed in a German PCNSL study, with a median survival of only 12.5 months in patients aged 70 years or more.¹¹ The best median overall survival for patients with PCNSL reported thus far (46 months) was found in the EORTC 20962 study.⁷ In this trial, however, 42 of the 52 patients included were younger than 60 years, the majority had a good performance status, and most patients were able to receive both chemotherapy and radiotherapy as first-line treatment, which may explain their better overall survival. Of the 14 patients in our series who are currently still alive without disease, 11 patients had a PCNSL prognostic score of ≤ 2 .² This confirms the experience that PCNSL patients in good clinical condition at the start of treatment have the best chance of being cured with MTX-based chemotherapy, which is considered to be the cornerstone of the treatment for PCNSL.²

Both dose and infusion rate are important when using MTX. A dose of ≥ 3 g/m² given as a short-lasting infusion as done in our series can reach tumouricidal levels in the CSF¹² whereas doses up to 8 g/m² delivered in a 24-hour continuous infusion do not.¹³ MTX can be used either as monotherapy or in combination with other cytostatic drugs, such as high-dose cytarabine.²

Four of the 34 patients treated with MTX in our series, however, died due to treatment-related complications. All four patients had a PCNSL score of > 2 . Also in the EORTC 20962 study, the treatment-related mortality was 10%.⁷ Therefore, high-dose MTX should be used in selected patients and under carefully controlled circumstances. Five of the 15 patients who were treated with MTX-based chemotherapy alone achieved a CR, three of whom

relapsed within two years. In the study by Birnbaum *et al.* 31% of the patients achieving a CR after MTX-based chemotherapy suffered from an early relapse.¹⁴ These patients have a dismal prognosis and the question is whether consolidation RT after MTX-based therapy can improve these results.

The study by Thiel *et al.*, in which complete responders were randomised between radiotherapy or no further treatment and the partial responders to radiotherapy or high-dose cytarabine, showed that the administration of radiotherapy had no impact on overall survival but a tendency to improve progression-free survival at the expense of more neurotoxicity in the irradiated patients.⁴ In our study, radiotherapy only was chosen in ten patients who were not able to tolerate high-dose MTX according to the opinion of the treating physician. Despite the fact that treatment with radiotherapy alone can cause long-lasting remissions, it seldom induces cure.² Radiotherapy, given as salvage therapy in chemotherapy refractory or relapsing patients, is a good palliative treatment but responses are not long lasting as also demonstrated in our series. The results of second-line chemotherapy are also disappointing.^{15,16}

Corticosteroids given as monotherapy can induce transient responses in 70% of patients.¹⁷ In our series, one cytologically confirmed PCNSL patient receiving monotherapy with corticosteroids is still alive without disease at 126 months after diagnosis. As corticosteroids can cause reduction or disappearance of the lesions within days to weeks, it can delay histological confirmation of the diagnosis and further treatment.^{17,18} The disappearance of cerebral lesions following treatment with corticosteroids cannot, however, be used as confirmation of the PCNSL diagnosis, since 50% of patients responding to steroids have an alternative diagnosis.¹⁸

The inability to obtain CSF in 25 out of our 52 patients indicates that protein content of the CSF is a less usable prognostic factor, which corresponds to the results obtained by Ferreri *et al.*⁵ In this study, a complete PCNSL score could be obtained in only 105 of the 378 patients. The Memorial Sloan Kettering prognostic score based on age (<50 years) and performance score (Karnofsky index >70%) can be applied to all PCNSL patients,⁹ but the value is questionable since most patients are in fact >50 years of age.²

In the majority of the patients, recurrence of PCNSL usually develops within two years after the end of first-line treatment.^{19,20} Late recurrences (>5 years after diagnosis) occur in 3-8% of the patients.^{19,20} In our study one patient developed a late relapse 76 months after diagnosis.

The present study has several limitations which are inherent to a retrospective analysis. For instance, several patients are lost to follow-up and (late) toxicities were not consistently reported. In most studies, including

ours, a systematic evaluation of cognitive functions was not performed at the start of treatment or thereafter. This makes it difficult to discern whether the impaired neurological status often reported after the treatment for PCNSL is caused by the PCNSL itself, by pre-existing cognitive function impairment not related to PCNSL, or by the treatment.

In conclusion, the treatment and management of patients with PCNSL clearly requires improvement, especially for elderly patients and for those presenting with a PCNSL prognostic score >2, who have a poor prognosis due to lower response rates to treatment as well as higher toxicity following treatment with high-dose MTX. Also salvage therapy is less effective and less well tolerated in this patient population.^{2,11,15,16} Prospective clinical trials and a centrally based registry including histological data on PCNSL patients might enhance our knowledge about this rare disease. Despite the fact that the majority of our patients could not enter a trial because they did not meet all inclusion criteria, their outcome is similar to patients treated in prospective trials. Less strict inclusion criteria could enhance the participation of more patients in trials which can lead to a more accurate estimation of the value of a given treatment in the whole patient population. Currently, the role of rituximab, radiotherapy and the value of high-dose chemotherapy followed by autologous stem cell transplantation in the treatment of PCNSL are being investigated in several clinical trials.^{10,21-23} In addition, more targeted treatment targeting deregulated signalling pathways in this type of disease is being explored.²

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